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TRAUMATIC INJURY OF THE SUPERIOR MESENTERIC VESSELS

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Abstract

Background : *Superior mesenteric vessels injury is an uncommon and the majority of injuries occurred due to penetrating trauma. These injuries are devastating entity with mortality rates reported as high as 64%. Exsanguinating hemorrhage accounts for the majority of early deaths. The purpose of this study is to review our experience with superior mesenteric vessels injury, to analyze Fullen's anatomical zones for their predictive value and outcome for primary repair versus ligation.*

Patients and Methods : *This case series study was conducted in Emergency hospital at Mansoura University between January 2007 to January 2011, seven patients presented during this period by injury of superior mesenteric vessels. Operative findings analyzed included the presence of active hemorrhage, associated abdominal injuries; surgical procedure performed in addition general morbidity and mortality.*

Results : *The mechanism of injuries were blunt abdominal Trauma three patients (43%) (Motor accident and falling from height), penetrating injury four patients (57%) (Three stab wound & one gunshot wound). The mean age was 27.5 ± 14 years (range 18 - 72 years) and 6 patients (85.7%) were male and one patient (14.3%) was a female, There were associated intra-abdominal organ injuries in all patients with different combination (spleen in two patients, liver in three patients, colon in one patient, small bowel in two case, pancrease in two patients, kidney in one patient and stomach in one patient) . Three patients (43%) had combined SMA & SMV repair, one patient(14.3%) had repair of isolated SMA, one patient (14.3%) had ligation of both vessels , one patient (14.3%) had ligation of SMV and one patient (14.3%) had ligation of jejunal branches of SMA (Fullen's grade IV). Mortality rate was 43% (three*

patients, one patient died intraoperatively, another one died 12 hours postoperative and one patient died 8 days postoperative). Two patient (28.6%) needed for second look operation 2 days post operative one patient who had repair of SMA ; arterial thrombectomy was done to SMA and the other patient who had ligation of SMV and there was negative exploration just oedema in the intestine which treated conservatively by anticoagulant.

Conclusion: *Superior mesenteric vessels injuries are highly lethal injury, the time of surgical intervention, injury grade of SMA and associated injuries are predictive for mortality; Ligation appear to be safe and should be selected for haemodynamically unstable patients.*

Key words: *Superior mesenteric vessels injuries, penetrating trauma, blunt abdominal trauma, vascular repair.*

Introduction

Superior mesenteric vessels injury is an uncommon and the majority of injuries occurred due to penetrating trauma[1]. Penetrating trauma account for 67% of injuries and blunt trauma account for 33% of that injuries. [2]

Mesenteric injury after blunt abdominal trauma is rare and may be difficult to diagnose. However, the conse¬quences of missed injury are significant in the form of higher morbidity and mortality [3].

The incidence of blunt bowel and mesenteric injury has increased in recent years due to the high incidence of blunt abdominal trauma in the urbanized world. Thus growing number of patients with blunt abdominal injury is thought to be due to high-speed motor accidents and the use of seat belts [4]. The diagnosis of mesenteric injury represents a challenge to clini¬cians when faced with victims of blunt abdominal trauma and a correct and speed diagnosis is particu¬larly important because early surgical intervention significantly decreases morbidity and mortality of these patients [5].

The mechanism of the mesenteric injury in blunt abdominal trauma is direct crushing of the small bowel against the vertebral column [6]. Tearing and shearing

forces, especially seat belts in car accidents, applied to the abdomen, particularly at points of mesenteric attachment, can also be the mechanism. According to the surgical literature, proximal jejunum and distal ileum are more prone to injury from blunt trauma because of the short mesentery in these areas [2].

Injury to the superior mesenteric artery (SMA) is an uncommon and devastating entity with mortality rates reported as high as 64%. Exsanguinating hemorrhage accounts for the majority of early deaths. Late deaths usually occur secondary to sepsis, multiple systems organ failure (MSOF), and the sequelae of ischemic bowel in those who survive their initial surgical procedure [7].

Injuries to the superior mesenteric vein (SMV) are uncommon¬but devastating, incurring very high morbidity and mortality. The rarity of this injury prevents sur¬geons from developing significant experience with their management [8].

Outcome of superior mesenteric vessels injury has been correlated with the presence of shock upon admission, the number of associated injuries, the anatomic location of injury, the method of surgical repair and the presence of "black bowel" upon entering the abdominal cavity[9,10].

Diagnostic peritoneal lavage is used in the trauma setting for detecting intraperitoneal hemorrhage or ` intestinal content leakage, but it lacks sensitivity for detecting retroperitoneal injuries [6]. Alternatively, Focused Abdominal Sonography for Trauma (FAST) facilitates the detection of intraperitoneal free fluid in abdominal trauma. Computed Tomography (CT) scan was performed in stable patients with suspicious of injury or positive FAST [11].

Fullen and altemeier made the first attempt to classify SMA injuries in a series of eight patients. Their grading system was based on location of injury and degree of ischemia present [12] (Table 1).

The purpose of this study is to review our experience with superior mesenteric vessels inju-

ry, to analyze Fullen's anatomical zones for their predictive value and outcome for primary repair versus ligation

Patients and Methods

This case series study has conducted in Emergency hospital at Mansoura University from January 2007 to January 2011.

Seven patients presented during this period by injury of superior mesenteric vessels all patients presented at the emergency room and after initial evaluation and resuscitation underwent operative intervention.

Resuscitation included rapid infusion of warm fluids and blood.

Data Collected included, Demographics, mechanism of injury, haemodynamically instability (systolic blood pressure < 90 mm/Hg and pulse > 100).

In haemodynamically, unstable Traumatic patients, Diagnostic peritoneal large (DPL) or Focused Abdominal Sonography for Trauma (FAST) were performed in the Trauma room. The presence of free intraperitoneal fluid during the FAST was considered positive and the patient was a candidate for operative intervention.

Computed Tomography (CT) was done in three patients (stable patients with suspicious of intra-abdominal injury or a positive FAST).

Calculation of the Glasgow Coma Score (GCS).

Operative findings analyzed included the presence of active hemorrhage, associated abdominal injuries; surgical procedure performed in addition general morbidity and mortality.

Operative procedure included lateral arteriorrhophy (Three patient, two with saphenous patch and one direct repair), primary end-to-end anatomists (one patient) and venorrhaphy (three patients, all with saphenous patch). Three patients required combined vessel repair; one patient required ligation of superior mesenteric vein, one patient required ligation of jejunal branches of SMA (Fullen's grade IV) and one patient required ligation of both vein and

artery with bowel resection.

Second look operations were performed in two patients.

Superior mesenteric artery (SMA) injuries had been classified according to Fullen's classification.

Exposure of the superior mesenteric vessels through a Mattox maneuver (Medial visceral rotation) or exposure through the lesser sac.

Results

From January 2007 to May 2011, seven patients had superior mesenteric vessels injuries 4 patients had both SMA & SMV injuries, 2 patients had isolated SMA injury and one patient had isolated SMV injury.

The mechanism of injuries were blunt abdominal Trauma three patients (43%) (Motor accident and falling from height), penetrating injury four patients (57%) (Three stab wound & one gunshot wound).

- Four patients (57%) presented with hypovolemic shock in which resuscitation was done and FAST diagnosed intraperitoneal fluid and aspirate blood; all of these patients underwent rapid exploratory laboratory, three patients presented fully consciness without any signs of hypovolaimic shock in which CT was done then exploratory laporotomy was done.

- The mean age was 27.5 ± 14 years (range 18- 72 years) and six patients (85.7 %) were male and one patient (14.3 %) was a female (Table 2).

There were associated intra-abdominal organ injuries in all patients with different combination, spleen in two patients, liver in three patients, colon in one patient, small bowel in two case, pancrease in two patients, kidney in one patient and stomach in one patient (Table 3).

Surgical management included primary suture repair to SMA (arteriorrhaphy) in three patients, primary end-to-end anastomosis in one patient and venorrhaphy of SMV in three patients.

Three patients had combined SMA & SMV repair, one patient had ligation of both vessels, one patient had ligation of SMV and one patient had ligation of jejunal branches of SMA (grade IV) (Table 4,5).

Mortality rate was 43% (three patients out of seven patients) one patient died intraoperatively due to active bleeding after ligation of both SMA & SMV. Another one died 12 hours postoperative in ICU who had repair of both SMA & SMV due to irreversible shock and one patient died 8 days postoperative due to intra abdominal infection.

Two patient had second look operation 2 days post operative one patient who had repair of SMA, arterial thrombectomy was done to thromsed SMA and the other patient who had ligation of SMV and there was negative exploration just oedema in the intestine which treated conservatively by anticoagulant.(Continued venous drainage after ligation of SMV from the bowel is typically achieved via the inferior mesenteric vein, retro peritoneal perforators and Porto systemic collateral circulation [8].

Table 1 : Fullen's anatomic classification of superior Mesenteric artery injury by zone and by Grade

Zone	Segment of superior Mesenteric Artery	Grade	Ischemic Category	Bowel segments Affected
I	Trunk proximal to first major branch (inferior pancreaticoduidenal)	I	Maximal	Jejunum, ileum, right colon
II	Trunk between inferior pancreaticoduidenal and middle colic	II	Moderate	Major segment, small bowel and/or right colon
III	Trunk distal to middle colic	III	Minimal	Minor segment or segments, small bowel or right colon
IV	Segmental branches, Jejunal ileal or colic	IV	None	No ischemic bowel

Table 2: Demographics and mechanism of injury.

Age	**27.5 ± 14 years**
Sex Male	6 patients (85.7 %)
Female	One patient (14.3%)
Blunt trauma	3 patients (43%)
Penetrating trauma	4 patients (57 %)

Table 3: Mechanism of injury and associated intra-abdominal injuries.

Organ	**Mechanism of injury**	**Percentage**
Spleen	Blunt	2 patients (28.6%)
Liver	Blunt & penetrating	3 patients (43%)
Small bowel	Penetrating	Two patients (28.6%)
Colon	Penetrating	One patient (14.3%)
Pancrease	Penetrating & blunt	Two patients (28.6%)
Kidney	Blunt	One patient (14.3%)
Stomach	penetrating	One patient

Table 4: Injury and operative procedure

Site of injury	**Number of patients** (total 7 patients)	**Operative procedure**	
		Repair	ligation
Combined SMA and SMV	4	3	1
Isolated SMA	2	1	1
Isolated SMV	1	-	1

Table 5: Fullen's classification of arterial injury, Operative procedure and outcome

Grade	Number of patients	Operative procedure	Outcome
I	1	Ligation	Died Intraoperatively
II	2	Repair	One patient survive and one patient died 12 hours post operative
III	2	Repair	One patient survive and one patient died 8 days post operative
IV	1	Ligation	Survive

Discussion

Superior mesenteric vessels injuries is an uncommon but potentially lethal injury, their rarity prevent, surgeons from developing a significant experience with their management [13].

The majority of superior mesenteric vessels injuries reported in the literature occur from penetrating trauma however, it is occasionally associated with blunt trauma of the abdomen [14].

The abdomen is a frequent site of injuries during a motor-vehicle crash (MVC) which represents the primary cause of blunt trauma in developed countries. Isolated vascular injuries are rare but seem to be increasing as reported in several studies and are the stated cause in 5% to 15% of all blunt trauma[15]. The pathophysiology of the trauma can also be influenced by the type of motor vehicle and/or the type of security systems or restraints of the vehicle. The principles of the pathophysiology of these injuries were described by Vance[16] in 1923. Three mechanisms were categorized: (a) crushing force applied to the bowel against the spine; (b) shearing force of the bowel and mesentery along the lines of attachment; and (c) bursting force occurring secondary to increased intra¬luminal pressure.

The diagnosis of these potentially lethal injuries is based especially on clinical examination, FAST, or diagnostic peritoneal lavage[17]. When the general condition is not critical, Computed Tomography scan (Computed Tomography Angiography) can also help to obtain the diagnosis with a

high sensitivity and specificity of 88.3% and 94%, respectively, and an accuracy of 99.9%[18]. A delay in the diagnosis of these major intra-abdominal vascular injuries can result in higher mortality and morbidity related to shock. Emergency laparotomy is often the best approach for patients in shock or with unstable circulation.

Ulvestad[19] in 1954 reported the first case of an SMV injury in a patient that sustained an associated SMA injury; the SMV was ligated and the SMA was primarily repaired resulting in patient survival. Fullen, in his classical study, describing the anatomic zones and ischemia grades of superior mesenteric artery injuries, described only one patient with an associated SMV injury.

Courcy [20] in 1984 reported a series of 13 patients with combined SMA and SMV injuries, of which 12 patients incurred blunt SMV injuries. Asensio[8] in 2001 reported 35 patients with SMA injuries with 17 (49%) associated SMV injuries, of these patients, 8 (23%) sustained their injuries secondary to blunt trauma. In Asensio's [1] Multi-Institutional Study of 250 SMA injuries, 84 (34%) patients had associated SMV injuries. Blunt mech¬anism of injury accounted for 48% of these injuries.

In ours, study blunt abdominal trauma occurred in three patients (43%) while penetrating trauma occurred in four patients (57%).

In our study associated intra abdominal organs injury was present in all patients with different percentage, splenic injury present in two patients (28.6%) in which splenectomy was done in one patient and splenprrhophy in the other patient. hepatic tear occurred in three patients (43%) in with treated by hepatic sutures.

Small bowel injuries in two patients (28.6%) which treated by resection and anastomosis, colonic injury in the transverse colon in one patients (14.3%) which treated by transverse colostomy. pancreatic injury in two patients (28.6%) in which treated by distal pancreatectomy in one patient and the other patient treated by simple repair of the tear.

Huge renal tears occur in one patent (14.3%) treated by nephrectomy.

While stomach tear occurred in one patient (14.3%) and treated by suture of the gastric tear in two layers.

Asaylai et al [21] 2009 report associated intra-abdominal organ injures after blunt bowel and mesenteric injures were spleen 18.9% liver 15.7% pancrease 1.8% kidney 1%.;- These incidence is lower than our study due to type 2 error (small number of patients in our study). However, in Asensio et al [13] 2007 study reported the incidence of associated intraabdominal organ injuries with superior mesenteric venous injuries nearly equal to our study.

Mortality rate in our study was 43% (3 patients) one patient intraoperative due to active bleeding, one patient 12 hours post operative after ligation of both SMA & SMV due to irreversible shock and another patient died 8 days post operative due to intraabdominal sepsis. This mortality rate is less than which reported by Peter et al 1984 in which reported 57% mortality rate after superior mesenteric vessels injuries. While in Arensio et al[22] 2000 study, the mortality rate after SMA injury was 47.6% and SMV injury was 52.7%. but Sirinek and Levine reported 19% mortality rate [23].

There is limitation in this study the number of patients is small.

Conclusion

Superior mesenteric vessels injuries are highly lethal injury, the time of surgical intervention, injury grade of SMA and associated injuries are predictive for mortality; Ligation appear to be safe and should be selected for haemodynamically unstable patients.

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COMBINED EFFECT OF ANGIOTENSIN RECEPTOR BLOCKER, AND ANTIOXIDANTS ON RECOVERABILITY OF RENAL FUNCTIONS AFTER RELIEF OF PARTIAL URETERAL OBSTRUCTION OF SOLITARY KIDNEY

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Abstract

Objectives: *To evaluate the effect of a combination of angiotensin receptor blocker losartan, and antioxidant Ferulic acid on the recovery of renal function and renal damage after relief of partial ureteral obstruction (PUO) of a solitary kidney.* ***Methods:*** *thirty-two male mongrel dogs were classified into three groups: sham (8), control (12) and study (12). Right nephrectomy was done and dogs in the study and control groups were subjected to 4 weeks of PUO. Serum creatinine, creatinine clearance (CrCl), and renographic clearance (RC) were measured at baseline, 4 weeks of obstruction and 8 weeks after relief of obstruction. Markers of lipid peroxidation (malondialdehyde MDA), superoxide dismutase (SOD), and reduced glutathione (GSH), and immunostaining of markers of apoptosis (caspase 3 and Bcl2), cell proliferation (ki67) and interstitial fibrosis in the kidney were evaluated at the end of experiment.* ***Results:*** *a combination of losartan and FA enhanced the recovery of serum creatinine, CrCl and RC by an extra 30%, 30%, and 47% of the basal values at 8 weeks, after relief of 4 weeks obstruction, respectively. Also, this combination caused significant decrease in MDA, and significant increase in GSH and SOD. Moreover, this combination significantly reduced the interstitial fibrosis, and caspase 3 expression, and significantly increased the expression of Bcl2 and ki67 in kidney tissues at* 8^{th} *week after relief of obstruction.* ***Conclusion:*** *combination of losartan and FA enhances the recoverability of renal function and minimizes*

the renal damage through reduction of oxidative stress, tubular apoptosis and the interstitial fibrosis in the solitary kidney after relief of PUO.

Introduction

Obstructive uropathy is the eventual outcome of many urological disorders such as urinary stone and ureteric stricture. Ureteric obstruction (UO) is a common clinical finding in a solitary kidney[1]. The pathophysiology of renal damage in UO is complex and it was reported that the renal damage continues even after relief of UO2,[3]. Within the first week of induction of UO, a network of inflammatory, vasoactive and apoptotic processes results in the appearance of signs of tubular atrophy and features of tubulointerstitial fibrosis[4]. Ureteral obstruction triggers tubular cell death by apoptosis and necrosis[5], interstitial inflammatory infiltration[6], and progressive fibrosis with loss of renal parenchyma, myofibroblast activation and extracellular matrix deposition[7,8]. All these changes contribute to renal parenchymal damage leading to sustained decrease in renal function.

Reactive oxygen species (ROS) play an important role in pathophysiology of obstructive uropathy[9]. They may have an important role in the tubulointerstitial inflammation associated with obstructive nephropathy [10], due to the tubular injury caused by mechanical disturbance, which leads to a proinflammatory state and tubulointerstitial fibrosis[11]. After release of the obstruction, ROS12 causes overexpression of fibrogenic cytokines and chemoattractants[11]. It was reported that reduction of endogenous antioxidants (such as catalase) during obstructive uropathy aggravates renal apoptosis, while the administration of exogenous antioxidants attenuates tubular apoptosis[13,14]. Also, chronic UO increases the renal expression of tumor necrosis factor [alpha] (TNF-alpha), FAS ligand, and caspase activity[15]. In a recently study from our lab, we found that ferulic acid (FA), powerful antioxidant, enhanced the recovery of renal functions when given after relief of obstruction[16]. This was done increasing the activity of Bcl

2 (proapoptotic protein) and decreasing the activity of caspase 316.

Angiotensin II, a potent vasoconstrictor, mediates its biological action through its interaction with one of two receptors: angiotensin II type 1 (AT_1) and AT_2[17]. AT_1 receptors are more abundant and appear to be more biologically significant than AT_2 receptors in mammalian kidneys[18,19]. In prolonged UUO, a significant rise is noted in both AT_1 receptor expression and renal angiotensin II content[20]. Angiotensin II and AT_1 receptors have been linked to many of the pathophysiologic processes involved in renal obstruction, including alterations in renal hemodynamics, fibrosis, and apoptosis[21,22]. Angiotensin II up-regulates the expression of several profibrotic cytokines and transcription factors, including TGF-β1, TNF-α, and NF-κB [23,24]. Moreover, the blockade of AT_1 receptor inhibition has been correlated with a reduction in collagen expression, macrophage recruitment, and renal tubulointerstitial fibrosis[24]. Also, in a recent study by our lab, we reported that losartan (AT_1 receptor blocker) enhanced the recovery of renal functions in a canine model of chronic partial ureteral obstruction [25].

On the basis of the observations that reactive oxygen species and AngII are imperative in initiating and promoting renal damage, apoptosis, and fibrosis even after relief of obstruction, we hypothesized that a combined therapy with exogenous antioxidant and AngII blockade may have additive or synergistic effects on recovery of renal functions after release of obstruction by simultaneously blocking the pathogenic actions of ROS and Ang II. In this study, we aimed to study the impact of a combination of losartan and ferulic acid on the recovery of renal functions after relief of UO in a solitary kidney, and its effect on apoptosis, fibrosis, and oxidative stress markers after UO relief.

Materials and Methods

Experimental animals and design :

Thirty two male mongrel dogs aged 2-3 years, weighing 18-25 kg were involved in this study. The dogs were randomly divided into 3

groups: i) Sham group: 8 dogs; right nephrectomy + left sham surgery + no medications, ii) Control group: 12 dogs; right nephrectomy + left partial ureteral obstruction (PUO) + no medications, and iii) Study (FA and Losartan) group: 12 dogs; right nephrectomy + PUO + FA. The dogs were housed in individual boxes under habitual conditions in a temperature controlled room (24^{o}C). They received a balanced diet plus free access to water. Experiments were performed according to the Guide for the Care and Use of Laboratory Animals. All protocols were approved by our local committee of Animal Care and Use Committee. Our institution approved the study and animal care standards were adhered to Institute for Laboratory Animal Research, National Research Council, Washington, DC: National Academy Press, no. 85-23, revised 1996.

Experimental model

Dogs were anaesthetized by thiopental sodium (10mg/kg) with endotracheal intubation and mechanical ventilation. Right nephrectomy was carried out. The model of unilateral left PUO was performed as described by Shokeir, [26]. The study and control groups were subjected to 4 weeks of left PUO. Then, were reopened and subjected to Lich-Grigoir ureterovesical re-implantation. All dogs of the control and study groups were sacrificed by the end of the 8th week after relief of obstruction.

Sham operated animals

The abdomen was entered with a midline incision and right nephrectomy was done. The bladder was opened, a 6 F ureteric catheter was inserted into the left ureteric orifice for 2 hours for collection of urine samples and a blood sample was taken from the left renal vein. The catheter was then removed and the bladder and wound were closed without induction of left PUO. Dogs of the sham group were subjected to sham surgery at basal condition, 4 and 8 weeks and sacrificed thereafter.

Ferulic acid and losartan treatment

Dogs of the study group were given FA (purchased from Sigma, USA) in the drinking water (or

milk or bone soup) at a dose 70 mg/Kg per day with the onset of relief of 4 -week obstruction and continued until sacrifice. Also, Losartan was given at a dose of 2 mg/kg once daily in drinking water (after overnight fasting of dogs) throughout the duration of the study.

Renal functions :

Blood and urine samples were collected from the corresponding kidney during surgery just before induction of obstruction, during relief of obstruction (at 4 weeks of obstruction) and at sacrifice of the dogs at the end of the 8th week after relief of obstruction. Two urine samples were collected, each for 2 hours from the corresponding ureter and blood samples obtained from the corresponding renal vein. Blood samples and the mean of two readings of urine samples were used for calculation of the creatinine clearance (CrCl) from the following equation[27]:

$$\text{CrCl (ml/min)} = \frac{\text{Urine creatinine (mg/dl)} \times \text{urine volume (ml/24hr)}}{\text{Serum creatinine (mg/dl)} \times 1440 \text{ (minutes)}}$$

Doppler ultrasonography and resistive index

Doppler ultrasonography (DUS) with measurement of renal resistive index (RI) of the corresponding kidney were carried out at basal condition before induction of obstruction, just before relief of obstruction (at 4th week of obstruction) and at 4 and 8 weeks after relief of obstruction.

Renograms :

Radioisotope renography with calculation of the split function of the corresponding kidney was performed. Renogram was carried out at basal condition before induction of obstruction, just before relief of obstruction (at 4th week of obstruction) and at 4 and 8 weeks after relief of obstruction as previously described[28].

Morphometric evaluation of renal interstitial fibrosis

Kidney tissues for the histological study were fixed in 10% formalin (pH 7.4) and embedded in paraffin. Sections (3 µm thick) were prepared, and stained with Hx & E and Masson's trichrome to evaluate the fibrosis of cortical interstitium. The sections were

observed on a Olymbus BX51 light microscopy. Pictures were obtained by a PC-driven digital camera (Olymbus E-620). The computer software (Cell* Olymbus Soft Imaging Solution GmbH) allowed the performance of morphometric analysis. Interstitial volume index was determined as described before[29] by superposing a grid containing 100 (10x10) sampling points on pictures of 10 non-overlapping fields (x 200) of Masson's trichrome stained sectons. The number of points overlaying interstitial space were counted and expressed as percentage of all points. Large arteries and glomeruli are excluded from the quantification.

Immunohistochemistry for assessment of apoptotic index, antiapoptotic activity and proliferative index

For immunohistochemistry, 3 µm thick sections were prepared on coated slides and deparaffinised. All sections were incubated for 30min with 0.3% hydrogen peroxide in methanol and microwave heated in 10mM citrate buffer, pH 6.0, for 10-20 min. Subsequently, an indirect immunoperoxidase technique was applied, using monoclonal antibodies for: Anti-caspase 3 (Abcam Cat.# ab79123) cytoplasmic staining with human tonsils as positive control. Anti-Bcl2 (Abcam Cat.# ab59348) cytoplasmic staining with human colon carcinoma tissue as positive control. Anti-K67 (Abcam Cat.# ab86373) nuclear staining with human lymph node as positive control. Indirect immunoperoxidase was performed using ImmunoPure Ultra-Sensitive ABC Peroxidase (Thermo Scientific Cat. # 32052) with (DAB) as chromogen.

Apoptotic index and antiapoptotic activity were assessed with a standard point counting method for the percentage of labelled tubular cells in each of the examined ten non-overlapping randomly selected X 400 fields of each slide. Labelling indices were expressed as the average scores of the[10] fields[30]. The proliferation index was defined as the percentage of the counted immunoreactive nuclei per at least 1000 tubular cells[31].

Estimation of oxidative and antioxidative parameters.

Kidney tissue was perfused with a PBS (phosphate buffered saline) solution, pH 7.4 containing 0.16 mg / ml heparin to remove any red blood cells and clots. Then, kidney was weighed, minced, homogenized in 5 - 10 ml cold buffer (i.e. 50 mM potassium phosphate, pH 7.5. 1 mM EDTA). Homogenates were centrifuged at 10000 x g for 15 minutes at 4°C and the supernatant was kept at -80°C till used for analysis of lipid peroxides malondialdehyde, MDA), superoxide dismutase (SOD), and reduced glutathione (GSH). MDA, SOD, and GSH were measured by using colorimetric kit (Bio-Diagnostics, Dokki, Giza, Egypt) according to manufacturer's instructions.

Statistical analysis :

The data of dogs of the three groups were compared at different time points of assessment. Statistical analyses were carried out with the 2-tail student's t and ANOVA tests. A p value <0.05 was considered as significant.

Results

Changes in the serum creatinine :

The mean values of serum creatinine were comparable among dogs of the sham, control and combination groups at the basal conditions. The sham operated group showed stable serum creatinine level during the whole duration of the study (Fig. 1). By the end of the 4^{th} week of obstruction, the mean values of serum creatinine of both the combination and control groups were significantly higher than the sham group ($P < 0.01$) (Fig. 1). There was no significant difference in the mean value of serum creatinine of the combination group (4.1 ± 0.8 mg/ dl) and the control group (3.5 ± 0.62 mg/ dl) at the end of the 4th week of obstruction (Fig. 1). The mean serum creatinine of the combination group (1.2 ± 0.3 mg/ dl) was significantly lower than that of the control group (2.1 ± 0.19 mg/ dl) by the end of the 8th week after relief of obstruction, ($P<0.01$) (Fig. 1). At 4 weeks of obstruction; there was no significant difference in the percentage decrease of serum creati-

nine in both combination and control groups. The ability of the kidney to regain its function at 8 weeks after relief of obstruction was significantly better in the combination group compared with the control one. Combination of losartan and Ferulic acid enhanced regain of the serum creatinine at 8-weeks after relief of obstruction by extra 30% in comparison to the control group (Table 1).

Changes in the Creatinine clearance

The mean values of creatinine clearance of the left kidney were comparable among dogs of the three groups at the basal conditions. The sham operated group showed stable creatinine clearance level of the left kidney during the whole duration of the study (Fig. 2). By the end of the 4th week of obstruction, the mean values of creatinine clearance of both the combination and control groups were significantly lower than the sham group. There was no significant difference in the mean value of creatinine clearance of the combination group (22.8 ± 2.6 ml/ min) and control group (25.6 ± 2.8 ml/ min) at the end of the 4th week of obstruction (P = 0.39) (Fig. 2). The mean creatinine clearance of the combination group (34.8 ± 3.5ml/ min) was significantly higher than that of the control group (31.5 ± 4.5 ml/ min) by the end of the 8th week after relief of obstruction, (P< 0.01) (Fig. 2). At 4 weeks of obstruction; there was no significant difference in the percentage decrease of creatinine clearance in both combination and control groups. The ability of the kidney to regain its function at 8 weeks after relief of obstruction was significantly better in the combination group compared with the control one. Combination of losartan and Ferulic acid enhanced regain of creatinine clearance at 8-weeks after relief of obstruction by extra 30% of the basal value in comparison to the control group (Table 1).

Changes in the renographic clearance :

The mean values of split renographic clearance of the left kidney were comparable among dogs of the three groups at the basal conditions. The sham operated group showed stable split renographic clearance level of the left kidney during the whole duration

of the study (Fig. 3). By the end of the 4th week of obstruction, the mean values of renographic clearance of both the combination and control groups were significantly lower than the sham group. There was no significant difference in the mean value of renographic clearance of the combination group (21.93 ± 3.6 ml/min) and the control group (23.8 ± 2.4ml/min) at the end of the 4th week of obstruction (P = 0.67) (Fig. 3). Significant higher values of the split renographic clearance in combination group compared with the control one was observed at 4 and 8 weeks after relief of obstruction (Fig. 3). The mean split renographic clearance in combination group (36.4 ± 1.7 ml/min) is significantly higher than the control group (28.2 ± 4.2 ml/min) at 8 weeks after relief of obstruction (P<0.01). At 4 weeks of obstruction; there was no significant difference in the percentage decrease of renographic clearance in both combination and control groups. The ability of the kidney to regain its function at 8 weeks after relief of obstruction was significantly better in the combination group compared with the control one. Combination of losartan and Ferulic acid enhanced regain of split renographic clearance at 8-weeks after relief of obstruction by extra 47 % of the basal value in comparison to the control group (Table 1).

Renal resistive index (RI)

There was no significant difference in the mean RI of the left kidney of the sham (0.45 ± 0.04); control (0.47 ± 0.03) and combination group (0.49 ± 0.06) groups at basal condition. The mean RI of the sham operated group remained stable during the whole study duration (Fig.4). After 4 weeks of obstruction, there was a significant rise in mean renal RI from a basal value of 0.47 ± 0.03 to 0.71 ± 0.02 in the control group and from a basal value of 0.48±0.04 to 0.7±0.05 in the combination group; (P values < 0.001 & < 0.001, respectively). By the end of the 4th week of obstruction, there was no significant difference in the mean RI of the combination group (0.7 ± 0.05) and the control one (0.71 ± 0.02). Marked drop of the RI to near basal values was observed at 4 weeks after relief of obstruction in both the control (0.48±0.02) and

the combination (0.47 ± 0.05) groups. Follow-up of RI at 8 weeks after relief of obstruction showed almost stable values similar to those of 4 weeks after relief of obstruction in both the control and combination groups (Fig. 4).

Morphometric evaluation of renal interstitial fibrosis

Compared with the sham-operated animals, the harvested kidneys of the control group exhibited a marked interstitial fibrosis mostly in perivascular and intertubular areas, indicated by a positive blue color in Masson's trichrome-stained sections. In contrast, harvested kidneys from animals treated with FA and losartan had significantly less sclerotic damage. The mean percentage of fibrosis in the animals treated with FA and losartan was significantly lower than the control group ($p < 0.05$) (table 2). A combination of FA and losartan reduced interstitial fibrosis by 49.23% in comparison with control. Figure 5-a represents one of the sham group, figure 5-b represents the control group, while figure 5-c represents one of the animals treated with FA and losartan.

Assessment of apoptotic indices, antiapoptotic activity and proliferation indices:

There was significantly lower tubular apoptosis, higher expression of Bcl2, and higher expression of Ki 67 in the kidneys harvested from animals treated with FA and losartan compared with the control one (table 2). A combination of FA and losartan reduced apoptosis by 58.86%, increased expression of Bcl2 by 191.64%, and increased expression of Ki 67 by 98.01% compared with control group (table 2). Figures 6-a & b, 7-a & b, and 8-a & b are examples of the tubular apoptosis indices, Bcl2, and Ki67 expression in the control and combination groups, respectively.

Assay of oxidants and antioxidants :

There was significantly lower MDA, higher GSH, and higher SOD levels in the combination group compared with the control one ($p<0.05$). A combination of losartan and FA reduced MDA by 57.27%, increased levels of GSH by 85.06%, and increased levels of SOD by 70.65% compared with the control group respectively (table 3).

Table (1): Percentage regain of renal function 8 weeks after relief of obstruction in the Combination and control groups

	Control group	Combination group	P value
Serum creatinine (mean ± SD, mg/dl)			
4 W obstruction	3.5±0.62	4.1±0.8	0.1
8W after relief of obstruction	2.1± 0.19	1.2 ± 0.3	< 0.01
Creatinine improvement	1.4	2.9	<0.01
% improvement from basal value	40	70	< 0.01
Creatinine Clearance (mean ± SD, ml/min)			
4 W obstruction	25.6±2.8	22.8±2.6	0.39
8W after relief of obstruction	31.5±4.5	34.8±3.5	< 0.01
Cr Cl improvement	5.9	12	< 0.01
% improvement from basal value	23	53	< 0.01
Renographic Clearance (mean ± SD, ml/min)			
4 W obstruction	23.8±2.4	21.9 ±3.6	0.67
8W after relief of obstruction	28.2±4.2	36.3±1.7	< 0.01
Cr Cl improvement	4.4	14.4	<0.01
% improvement from basal value	18	65	< 0.01

Table (2): Score of interstitial fibrosis (%), Ki 67 expression, Bcl2 expression, and apoptosis (caspase 3) expression in different groups at the end of study

Group	% Interstitial fibrosis	Apoptosis (caspase +ve cells)	Antiapoptotic Bcl2	Ki 67
Sham group	1.17 ± 0 .98	2.67 ± 0.81	13.83 ± 4.44	0.67 ± 0.81
Control group	26.0 ± 6.0[a]	12.76 ± 2.31[a]	6.46 ± 2.87[a]	5.54 ± 1.51[a]
Combined group	13.20 ± 3.39[ab]	5.25 ± 1.6[ab]	18.84 ± 3.45[ab]	10.97 ± 1.30[ab]
% change of the mean in combined group compared with control group	- 49.23	-58.86	+ 191.64	+ 98.01

All data are expressed as Mean ± SD. One way ANOVA test with posthoc Scheffe's test. a= significant with sham, and b= significant with control.

Table (3): Markers of oxidative stress (MDA) and antioxidants (GSH and SOD) in different groups at the end of study

Group	MDA mmol/gm tissue	GSH mg/gm tissue	SOD % inhibition
Sham group	1.56 ± 0 .46	177.02 ± 7.808	89.91 ± 4.82
Control group	11.61 ± 3.94[a]	111.24 ± 4.78[ab]	41.80 ± 7.18[a]
Combined group	4.96 ± 1.87[ab]	205.87 ± 47.29[bc]	71.33 ± 12.60[ab]
% change of the mean in combined group compared with control group	- 57.27	+ 85.06	+ 70.65

MDA= malondialdehyde, GSH= reduced glutathione, SOD (superoxide dismutase).All data are expressed as M±SD. One way ANOVA test with posthoc Scheffe's test. a= significant with sham, b= significant with control.

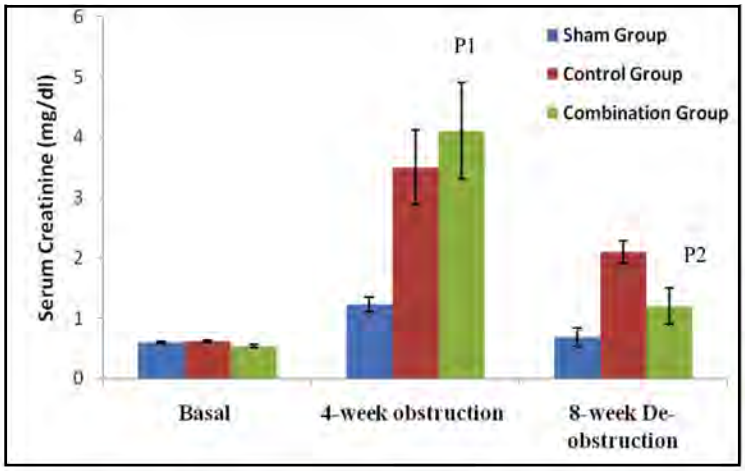

Fig. (1): Changes in the mean serum creatinine of the left kidney after 4 weeks of obstruction and 8 weeks after relief of obstruction in the study and combination groups and in the sham group at basal condition, 4 and 8 weeks of sham surgery (W=Week; Obst= obstruction; De-obst. = de-obstruction; P_1 = combination and control versus sham; P_2 = combination versus control).

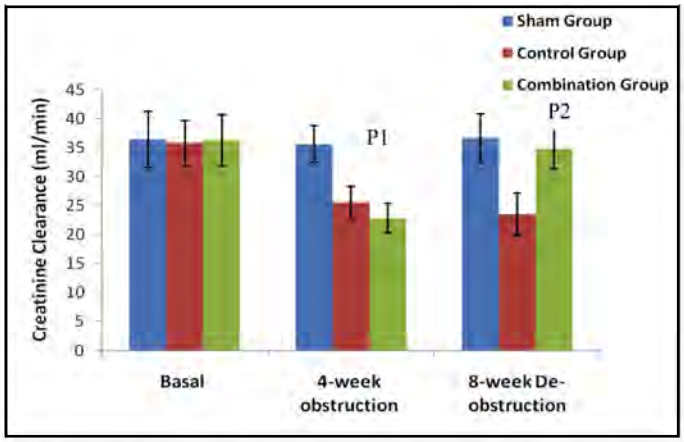

Fig. (2): Changes in the mean creatinine clearance of the left kidney after 4 weeks of obstruction and 8 weeks after relief of obstruction in the combination and control groups and in the sham group at basal condition, 4 and 8 weeks of sham surgery (W=Week; Obst. = obstruction; De-obst. =de-obstruction; P_1 = combination versus control versus sham; P_2 = combination versus control).

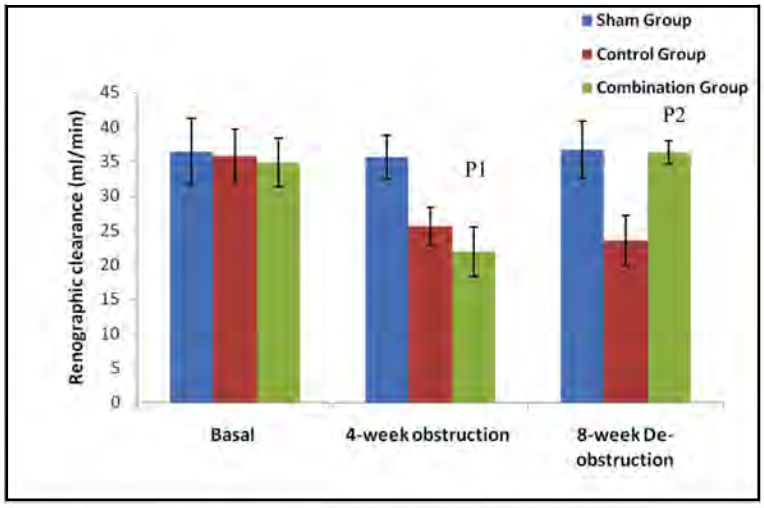

Fig. (3): Changes in the split renographic clearance of the left kidney after 4 weeks of obstruction and 4 and 8 weeks after relief of obstruction in the combination and control groups and in the sham group at basal condition, 4 and 8 weeks of sham surgery (W=Week; Obst. = obstruction; De-obst. =de-obstruction; P_1 = combination versus control versus sham; P_2 = combination versus control).

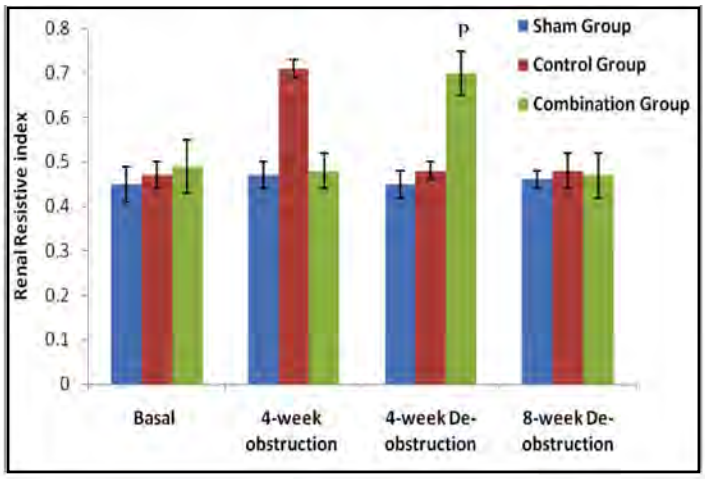

Fig. (4): Changes in the renal RI of the left kidney after 4 weeks of obstruction and 4 and 8 weeks after relief of obstruction in the combination and control groups and in the sham group at basal condition, 4 and 8 weeks of sham surgery (W=Week; Obst. = obstruction; De-obst. =de-obstruction; P = combination and control versus sham).

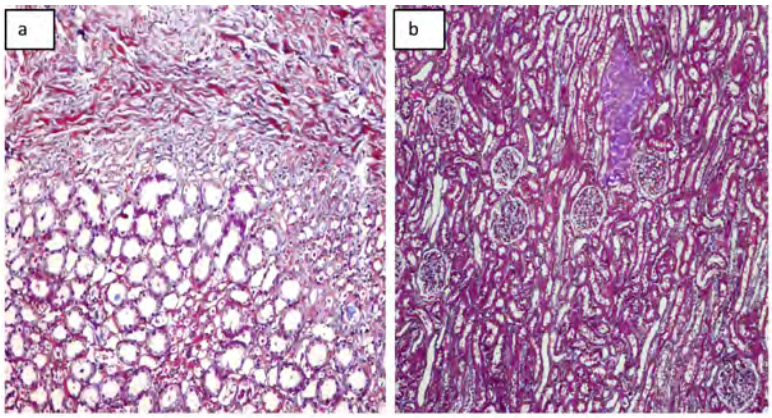

Fig. (5): The cross section of the harvested kidney from animals of different groups showed minimal interstitial fibrosis mostly in perivascular and intertubular areas, indicated by a positive blue color in Masson's trichrome-stained sections. Interstitial fibrosis is 45% in the control group (a), and 11% in the combination group (Masson trichrome stain X 100)

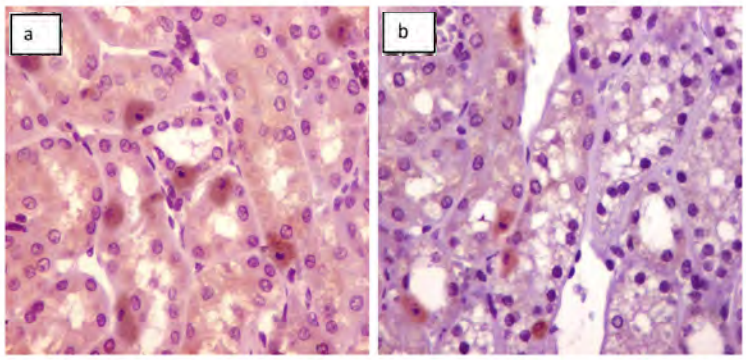

Fig. (6): The cross section of the harvested kidney from control and combination group-treated animals. Immunostaining of caspase 3 labeling index is 10% in the control group (a), and 5% in the combination group (Immunoperoxidase DAP X 400)

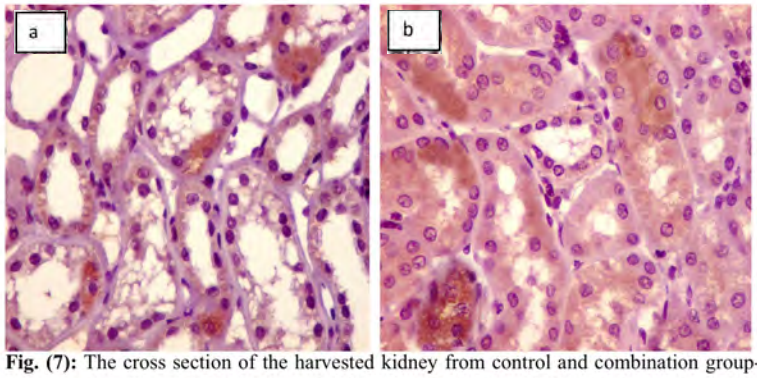

Fig. (7): The cross section of the harvested kidney from control and combination group-treated animals. Immunostaining of Bcl2 labeling index is 4% in the control group (a), and 24% in the combination group (Immunoperoxidase DAP X 400)

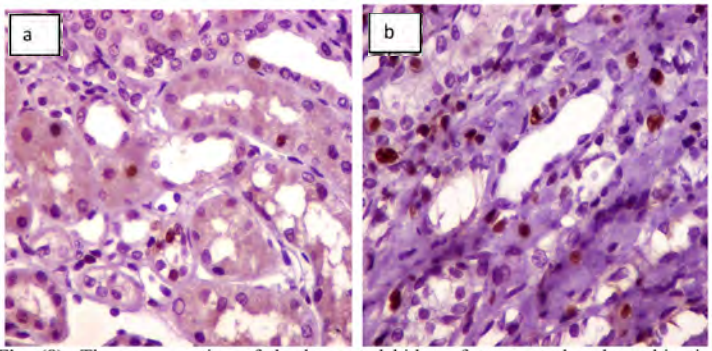

Fig. (8): The cross section of the harvested kidney from control and combination group-treated animals. Immunostaining of Ki 67 labeling index is 7% in the control group (a), and 14% in the combination group (Immunoperoxidase DAP X 400)

Discussion

Many factors may play an active role in the progression of renal damage in obstructive uropathy after relief of obstruction. In this regard, it is not surprising to find out that targeting hyperactive RAS alone as in current clinical therapy may only have limited efficacy in preventing the progressive loss of renal function in UO. In, the present study we examined the hypothesis that a combined therapy by simultaneously targeting multiple pathogenic pathways may be more effective in preventing the progression of chronic renal fibrosis and damage in UO in solitary kidney. In the present study, we found that a combination of losartan and ferulic acid enhanced regain of the serum creatinine, creatinine clearance, and renographic clearance at 8-weeks after relief of obstruction by extra 30%, 30%, and 47% respectively in comparison to the control group. These findings indicate this combination enhanced the recovery of renal function after relief of UO. In a recent study from our lab we found that FA alone enhanced regain of serum creatinine, creatinine clearance, and renographic clearance by extra 22%, 26%, and 33.7% respectively. Also, Soliman et al[25] found that losartan enhanced regain of creatinine clearance, and renographic clearance by extra 26%, and 26%, respectively. These findings indicate that this combination do not provide more protection than each drug alone in enhancing the recovery of renal functions after relief of UO in solitary kidney.

Both oxidative stress and hyperactive renin angiotensin system are involved in pathogenesis of renal damage caused by UO. Also, many studies reported that they are involved in progression of renal damage after relief of obstruction[2,16]. The renal damage involves tubular cell apoptosis and necrosis[5], interstitial inflammatory infiltration[6], and progressive fibrosis with deposition of extracellular matrix[7,8]. So, the next step of our study was to investigate the impact of the combination on renal fibrosis induced by UO. In the present study, we found that a combination of losartan and ferulic acid improved renal fibrosis by 49.23%. This is more than FA alone because FA

alone improved renal fibrosis by 34.81%[16]. These findings suggest that addition of AT1 receptor blocker to FA might stop or slow the process of fibrosis. In agreement with our results, Young et al.,[12] examined a combination of AT1 receptor blocker, losartan, and hepatocyte growth factor (HGF) in protection against renal damage caused by UO. They found that AT1 blocker synergistically inhibits renal smooth muscle actin (SMA) expression (marker of renal fibrosis) and myofibroblast activation and attenuates renal interstitial fibrosis in obstructive nephropathy in mice.

In a previous study by our group, we reported that tubular cell apoptosis (as indicated by significant elevation of caspase3 and significant lowering of antiapoptotic protein Bcl-2) was still evident after 8 weeks after UO release. Moreover, tubular cell proliferation (as indicated by significant elevation of ki67) was significantly increased in obstructed kidney when compared to sham group16. In the present study we found that a combination of losartan and FA significantly reduced apoptosis by 58.86%, increased expression of Bcl2 by 191.64%, and increased expression of Ki 67 by 98.01% compared with control group. This effect is better than FA alone as reported by our previous study[16].

As mentioned in the background, oxidative stress plays an important role in pathogenesis of tubulo-interstitial inflammation during obstructive nephropathy[32], and after relief of obstruction[12]. Manucha et al.[33] and Sugiyama et al.,[34] demonstrated an increase in the concentration of reactive oxygen species (ROS) in obstructed kidney, together with decreased activities of the major protective antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px). The downregulation of antioxidant enzymes CAT, GSH-Px, and SOD from tubular cells from the obstructed kidney increases the vulnerability of the kidney to oxidative damage[35]. The results of our study are in consistence with the findings of the previous studies. In the present study, a combination of losartan and FA reduced MDA

by 57.27%, increased levels of GSH by 85.06%, and increased levels of SOD by 70.65% compared with the control group respectively. When we compare these findings with the results of our previous study[16], we can say that addition of losartan to FA don't offer more protective effect on oxidative stress in UO than FA alone. These findings suggest that this combination might slow the progress of fibrosis by a mechanism other than inhibition of oxidative stress. This may include inhibition of the release of transforming growth factor β (TGF-β). Both losartan and FA might act synergistically to inhibit the expression of TGF-β. However, in our study this was not measured, so this point is one of the limitations of our study and it will considered on a next studies.

In conclusion, a combination of FA and losartan did not enhance the recovery of renal functions in UO of a solitary kidney model of dogs. However, this combination slows the progress of fibrosis and apoptosis of renal tubular cells. Further studies are recommended to understand the underlying mechanisms of this combination in inhibition of renal fibrosis.

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COMBINED EFFECT OF ANGIOTENSIN RECEPTOR BLOCKER, AND ANTIOXIDANTS ON RECOVERABILITY OF RENAL FUNCTIONS AFTER RELIEF OF PARTIAL URETERAL OBSTRUCTION OF SOLITARY KIDNEY

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PSYCHIATRIC ADVERSE EFFECTS DURING COMBINATION THERAPY OF PEGYLATED INTERFERON PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C PATIENTS : A PROSPECTIVE LONGITUDINAL STUDY

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Abstract

Background : *Quality of life is an area of increasing interest in hepatology. Health related quality of life (HQL) issues have been examined in patients with chronic HCV infection, recurrent infection, and those undergoing treatment.* ***Objective:*** *the present study is designed to explore the relation between psychiatric comorbidity and its effect on quality of life (QOL) of those patients.* ***Methods :*** *485 patients who fulfilled the inclusion and exclusion criteria were assessed using psychological [social class scale, mini international neuropsychiatric interview (MINI), and hepatitis quality of life questionnaire (HQOLQ)].* ***Results:*** *Quality of life subscales median scores were lower in those showing psychiatric disorders than those who don't at baseline assessment and throughout treatment. The mostly affected domains were Mental Health scale, Vitality scale and social functioning. As for the subscales concerned with HCV, the low scores were for Positive well being and Hepatitis specific health distress. Mental component summary scores were lower than physical component summary.* ***Conclusions:*** *the combination therapy of pegylated interferon plus ribavirin affects quality of life in HCV patients. Presence of psychiatric comorbidity makes the condition worse.*

Keywords: *Hepatitis C; Genotype 4; Psychiatry; Quality of Life, Egypt.*

Introduction

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus belonging to the Flaviviridae family. It is a major cause of liver disease worldwide, to the degree that the World Health Organization (WHO) declared that HCV is a global health problem and about 3% of the population worldwide is infected with HCV[1]. In Egypt the situation is quite worse as it has a high prevalence of HCV specially HCV-4 (which is responsible for nearly 90% of infections). According to the Egyptian Demographic and Health Survey (EDHS) the prevalence of HCV in Egyptians is; 15 % in the age group 15 - 59 years old and 39.4 % in the age group 55-59 years old, while the prevalence in males is 17.4 % and 12.2 % in females[2,3].

Several studies have shown that patients with chronic hepatitis C have a reduced quality of life[4]. Reduction in quality of life is not associated with how the infection is acquired or with the severity of the liver disease[5,6]. The impact of IFN-α treatment is less clear. Hunt et al[7] prospectively followed patients with hepatitis C who were treated with IFN-α and found that the health status of these patients was similar to that of the general U.S. population and did not change during IFN-α therapy. In contrast, Bonkovsky et al.[6], in a much larger study, showed that successful therapy with IFN-α improves quality of life and that the degree of improvement is related to sustained virological or biochemical response to treatment. However, the patients were not blinded to their state of infection. Further study is needed to establish whether eradication of hepatitis C improves quality of life.

Interferon therapy may exacerbate health-related quality of life (HRQL) deficits associated with hepatitis C virus (HCV) early in the course of therapy. Treatment with polyethylene glycol-modified interferon (peginterferon) alfa-2a provides improved sustained response over interferon alfa-2a, but its effect on health-related quality of life (HRQOL) is unknown. The purpose of this study was to evaluate the effect of chronic hepatitis C infection on patients' perceptions of HRQOL and to evaluate

how treatment with interferon affects HRQOL.

Patients and Methods

Patients: 485 patients with chronic HCV were recruited from the outpatient clinic of the Association of Hepatic Patients Care in Mansoura. The patients who came to the clinic on Saturdays and Mondays (days of visit to the clinic) from June 2009 till May 2011 to start their investigations to begin the combination therapy of pegylated interferon plus ribavirin were chosen. The study protocol was approved by the Research Ethics Committee of Mansoura Faculty of Medicine, Mansoura University. All individuals provided written informed consent prior to their participation.

Inclusion Criteria: Patients were eligible to participate if they were; males or female ≥18 years of age, with serologic evidence of chronic HCV infection by anti-HCV antibody test, and liver biopsy findings consistent with the diagnosis of chronic HCV infection with or without compensated cirrhosis.

Exclusion Criteria: Patients were excluded if they were women with ongoing pregnancy or breast feeding; on therapy with any systemic anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation); ≤ 6 months prior to the first dose of interferon; on any investigational drug ≤ 6 weeks prior to the first dose of interferon; presence of co-infection with active hepatitis A; hepatitis B and / or human immunodeficiency virus (HIV); history or other evidence of a medical condition associated with chronic liver disease other than HCV (e.g. hemochromatosis; autoimmune hepatitis; metabolic liver disease; toxin exposures); signs or symptoms of hepatocellular carcinoma; history or other evidence of bleeding from esophageal varices or other conditions consistent with decompensated liver disease; inability or unwillingness to provide informed consent.

Methods: For each patient the following was done:

1. Clinical examination.
2. Semi-structured psychiatric interview:

- The patients were interviewed concerning demographic characteristics (name, age, sex, occupation, marital status and education). Social class will be assessed by using the social class scale [8].

3. Psychometric assessment:

- Mini international neuropsychiatric interview (MINI) to detect presence of any psychiatric disorders.
- Hepatitis quality of life questionnaire (HQOLQ) for assessment of quality of life.

Statistical Analysis:

The statistical analysis of data was done by using excel program and SPSS (SPSS, Inc, Chicago, IL, program statistical package for social science version 16). To test the normality of data distribution K-S (Kolmogorov-Smirnov) test was done. The description of the data was done in the form of mean (+/-) SD for quantitative data. While frequency and proportion were used for qualitative data.

Results

Table (1): shows the sociodemographic data of the studied group (those who did not show psychiatric disorders are called (free) Vs those who show psychiatric disorders (cases). In the current study males were found to be more (68.7%) than females (31.3%) and there was a highly statistically significant difference between both groups as females were more in the cases (55.7%). Regarding age, there was no statistically significant difference between groups (where in both groups those above 40 years old constitute about 50%) so as to marital status. As for education there was a statistically significant difference in education between both groups. There was a high rate of illiterates in our sample (32.4%) as well as secondary school education (36.5%). The percentage of persons in the cases group is more in the lower educational levels. As for social class there was a predominance of class IV in both groups while the other classes particularly I was higher among cases. The sample contained more rural patients in both groups. Housewives, manual workers, farmers, skilled workers constituted about 81% of both groups.

Table 2 showed highly statisti-

cally significant difference between those who showed psychiatric disorders (cases) and those who did not (free) regarding Physical functioning (PF) at baseline assessment and after 3 months of treatment and a statistically significant difference after 6 and 9 months of treatment where no significant difference was detected at the end of treatment (P=0.137). Physical functioning tended to be lower in cases group than in free group from the beginning till the end.

As for Role physical functioning, there was a highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline assessment and after 3, 6 and 9 months of treatment and a statistically significant difference after 12 months of treatment. Role Physical functioning tended to be more limited in cases group than in free group from the beginning till the end.

For general health scale, there was a highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline assessment and after 3, 6 and 9 months of treatment and no statistically significant difference after 12 months of treatment. General health (GH) perception tended to be lower in both group but more in the cases group.

Table 3 showed that there was a highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) regarding Vitality Scale (VT) at baseline assessment and after 3, 6 and 9 months of treatment and no statistically significant difference at the end of treatment. Vitality tended to be lower in cases group than in free group from the beginning till the end.

For the Social functioning, there was a highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline assessment and after 3 and 9 months of treatment and a statistically significant difference after 12 months of treatment. No statistically significant difference was found at 6 months. Social functioning tended to be

better in the free group than in the cases group from the beginning till the end.

For Role Emotional, there was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline assessment and throughout treatment till the end of treatment. Role Emotional (RE) tended to be better in the free group than in the cases group.

For mental health scale (MH), here was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline assessment and throughout treatment till the end of treatment. Better Mental health (MH) was found in the free group than in the cases group.

Table 4 showed a highly statistically significant difference between between those who showed psychiatric disorders (cases) and those who did not (free) regarding Physical Component Summary (PCS) at baseline, 3 and 12 months of treatment. There was no statistically significant difference at 6 (P= 0.695) and 9 (P= 0.504) months of follow up.

For the Mental Component Summary (MCS), there was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline and throughout treatment

Table 5 showed a highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) regarding Health Distress (HD) at baseline and throughout treatment. Health distress was less in the free group than in the cases group.

For Positive Well-being (PWB), there was there was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline and at 3 months. There was a statistically significant difference at 9 months. No statistical significant difference was found between both groups at 6 and 12 months of treatment. The mean of scores in both groups tended to be low but much lower in the cases group.

For Hepatitis Specific Limitation (HLIM), there was there was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at baseline, 3, 9 and 12 months. There was a statistically significant difference at 6 months. Limitations related to hepatitis were observed to be more in the cases group.

For Hepatitis Specific Health Distress (HHD), there was there was highly statistically significant difference between those who showed psychiatric disorders (cases) and those who did not (free) at 6, 9, and 12 months of treatment. There was a statistically significant difference at 3 months. Distress related to hepatitis was observed to be more in the cases group.

Table 1: The Sociodemographic Data of the Studied Group (either with or without psychiatric disorders) (n = 485).

Sociodemographic data		Free N (%)	Cases N (%)	Total N (%)	P
Sex	**Male**	298 (73.4%)	35 (44.3 %)	333 (68.7%)	**0.000****
	Female	108 (26.6%)	44 (55.7%)	152 (31.3%)	
Age	**< 25**	42 (10.3%)	9 (11.4 %)	51(10.5 %)	**0.860**
	25-40	162 (39.9%)	29 (36.7 %)	191 (39.4 %)	
	> 40	202 (49.8 %)	41(51.9 %)	243(50.1 %)	
Marital status	**Single**	38(9.4%)	7(8.9%)	45(9.3%)	**0.339**
	Married	354 (87.2%)	66(83.5%)	420(86.6%)	
	Divorced	3(0.7 %)	2(2.5%)	5(1.0 %)	
	Widow	11(2.7%)	4(5.1%)	15(3.1 %)	
Education	**Illiterate**	***128(31.5%)***	***29(36.7%)***	***157(32.4%)***	**0.013***
	Can read & write	***49(12.1%)***	***3(3.8%)***	***52(10.7%)***	
	Primary	***11(2.7%)***	***7(8.9%)***	***18(3.7%)***	
	Preparatory	***19(4.7%)***	***6(7.6%)***	***25(5.2%)***	
	Secondary	***154(37.9%)***	***23(29.1%)***	***177(36.5%)***	
	College	***45(11.1%)***	***11(13.9%)***	***56(11.5%)***	
Occupation	**House Wife**	***96(23.6%)***	***34(43.0%)***	***130(26.8%)***	**0.051**
	Manual worker	***65(16.0%)***	***11(13.9%)***	***76(15.7%)***	
	Farmer	***60(14.8%)***	***5(6.3%)***	***65(13.4%)***	
	Skilled worker	***108(26.6%)***	***14(17.7%)***	***122(25.2%)***	
	Driver	***30(7.4%)***	***4(5.1%)***	***34(7.0%)***	
	Student	***1(.2%)***	***0(.0%)***	***1(.2%)***	
	Clerk	***10(2.5%)***	***2(2.5%)***	***12(2.5%)***	
	Professional	***23(5.7%)***	***5(6.3%)***	***28(5.8%)***	
	Unemployed	***12(3.0%)***	***4(5.1%)***	***16(3.3%)***	
	Retired	***1(.2%)***	***0(.0%)***	***1(.2%)***	
Social class	**I**	***5(1.2%)***	***4(5.1%)***	***9(1.9%)***	**0.042***
	II	***9(2.2%)***	***4(5.1%)***	***13(2.7%)***	
	III	***14(3.4%)***	***4(5.1%)***	***18(3.7%)***	
	IV	***378(93.1%)***	***67(84.8%)***	***445(91.8%)***	
Residence	**Urban**	56(***13.8%***)	17(***21.5%***)	73(***15.1%***)	**0.079**
	Rural	350(***86.2%***)	62(***78.5%***)	412(***84.9%***)	

*P is significant if ≤ 0.05
** P is highly significant if ≤ 0.01.

Table 2: Physical functioning scale (PF), Role physical scale (RP), Bodily pain scale (BP) and General Health scale (GH) differences between free and cases at baseline and throughout the duration of treatment.

		Physical functioninig (PF)		Role Physical functioninig(RP)		Bodily Pain (BP)		General Health Scale (GH)	
		Free	Cases	Free	Cases	Free	Cases	Free	Cases
Baseline	N	406	79	406	79	406	79	406	79
	Mean	93.0624	77.8481	81.0837	54.9367	85.8621	76.0759	65.5000	48.2911
	SD	14.35998	27.23826	34.80894	45.23084	13.46677	22.44182	15.85891	21.57702
	P	.000		.000		.000		.000	
3 months	N	96	52	96	52	96	52	96	52
	Mean	64.4097	51.2821	52.2917	19.2308	78.7500	59.4231	45.0521	31.6538
	SD	17.31822	18.36369	35.34727	29.62816	20.98872	28.92949	14.52212	15.13324
	P	.000		.000		.000		.000	
6 months	N	70	57	70	57	70	57	70	57
	Mean	59.7619	52.7290	42.2857	25.6140	74.5714	66.4912	38.4000	32.4211
	SD	12.74029	18.45925	27.77609	31.11141	22.04644	27.74187	10.25529	18.17175
	P	.013		.002		.070		.021	
9 months	N	79	41	79	41	79	41	79	41
	Mean	60.9705	51.7615	55.9494	22.9268	77.3418	63.6585	38.3418	29.3171
	SD	13.98046	16.45416	34.10087	31.79968	20.55068	26.43446	11.37686	16.01942
	P	.002		.000		.002		.001	
12 months	N	102	16	102	16	102	16	102	16
	Mean	63.8344	57.6389	71.99	39.56	79.2157	58.7500	41.0294	35.5625
	SD	13.09899	25.96888	18.8	24.7	18.96773	23.90955	11.64530	26.25254
	P	.137		.012		.000		.160	

* The P is significant at the 0.05 level.
** The P is highly significant at the 0.01 level

Table 3: Vitality scale (VT), Social functioning scale (SF), Role Emotional scale (RE) and Mental health scale (MH) differences between free and cases at baseline and throughout the duration of treatment.

		Vitality Scale (VT)		Social Functioning Scale (SF)		Role Emotional Scale (RE)		Mental Health Scale (MH)	
		Free	Cases	Free	Cases	Free	Cases	Free	Cases
Baseline	N	406	79	406	79	406	79	406	79
	Mean	63.7069	47.1519	68.9501	48.1804	89.3473	45.8861	60.7488	40.1013
	SD	13.67580	18.26941	16.67414	28.07870	26.96830	44.83416	14.66501	13.70719
	P	.000		.000		.000		.000	
3 months	N	96	52	96	52	96	52	96	52
	Mean	40.3125	28.7500	63.0859	33.8942	93.7500	27.4038	52.1667	33.3077
	SD	10.73147	12.71386	19.95221	25.01060	19.86799	37.78798	8.10285	12.81473
	P	.000		.000		.000		.000	
6 months	N	70	57	70	57	70	57	70	57
	Mean	37.0000	27.9825	53.0357	44.2982	88.2143	25.4386	50.1143	35.1579
	SD	8.73938	14.75574	23.23339	27.35250	26.48538	35.19437	8.71371	14.39716
	P	.000		.054		.000		.000	
9 months	N	79	41	79	41	79	41	79	41
	Mean	40.9494	28.0488	54.6677	37.9573	92.0886	12.8049	55.0380	33.3659
	SD	11.09620	12.88788	19.95258	26.04797	22.83732	30.16722	9.35269	12.38095
	P	.000		.000		.000		.000	
12 months	N	102	16	102	16	102	16	102	16
	Mean	43.9000	1.3625	56.1275	43.3594	95.3431	39.0625	60.1176	40.0000
	SD	14.150	11.24	18.63580	32.87197	16.77250	49.13311	10.15454	18.18424
	P	.000		.026		.000		.000	

* The P is significant at the 0.05 level.
** The P is highly significant at the 0.01 level

Table 4 : Physical component summary (PCS) and Mental component summary scale (MCS) differences between free and cases at baseline and throughout the duration of treatment.

		Physical Component Summary (PCS)		Mental Component Summary (MCS)	
		Free	Cases	Free	Cases
Baseline	N	406	79	406	79
	Mean	53.9001	47.5415	44.5675	31.9455
	SD	7.28626	12.06443	7.16480	9.91960
	P	.000		.000	
3 months	N	96	52	96	52
	Mean	46.4884	40.3274	43.8705	28.6815
	SD	6.97671	7.42795	4.47666	9.16565
	P	.000		.000	
6 months	N	70	57	70	57
	Mean	39.4743	39.9861	42.0582	29.4092
	SD	6.51486	8.17663	5.97868	9.04188
	P	.695		.000	
9 months	N	79	41	79	41
	Mean	40.6856	39.7383	43.8391	26.8480
	SD	7.30048	7.44548	5.19848	8.50981
	P	.504		.000	
12 months	N	102	16	102	16
	Mean	35.3632	38.8760	43.0278	30.1233
	SD	3.54580	4.99723	4.70864	12.29434
	P	.001		.000	

* The P is significant at the 0.05 level.
** The P is highly significant at the 0.01 level

Table 5: Health distress (HD), Positive well-being (PWB), Hepatitis specific limitation (HLIM) and Hepatitis specific health distress (HHD) differences between free and cases at baseline and throughout the duration of treatment

		Health Distress (HD)		Positive Well-being (PWB)		Hepatitis Specific Limitation (HLIM)		Hepatitis Specific Health Distress (HHD)	
		Free	Cases	Free	Cases	Free	Cases	Free	Cases
Baseline	N	406	79	406	79	406	79	406	79
	Mean	92.3892	68.9241	29.0887	10.3165	95.4844	84.3882	55.77	42.7
	SD	17.81472	31.44665	14.11704	16.80090	13.97129	27.38116	29.7	27
	P	.000		.000		.000		.000	
3 months	N	96	52	96	52	96	52	96	52
	Mean	80.2083	50.3846	16.6146	2.9808	83.6111	64.6154	57.1875	47.1154
	SD	22.71003	20.38469	12.19350	8.81507	18.80442	25.37865	26.87997	22.01484
	P	.000		.000		.000		.022	
6 months	N	70	57	70	57	70	57	70	57
	Mean	72.0714	52.8947	8.2857	4.9123	75.0476	66.4327	61.2143	47.3684
	SD	21.87734	21.19104	11.02979	14.28321	18.84544	23.73681	24.58991	19.57370
	P	.000		.136		.024		.001	
9 months	N	79	41	79	41	79	41	79	41
	Mean	75.8861	47.8049	10.5063	4.3902	77.4684	60.8130	80.8228	69.2683
	SD	21.11870	16.04871	10.96600	14.49979	19.28357	21.14475	22.03480	22.51558
	P	.000		.011		.000		.008	
12 months	N	102	16	102	16	102	16	102	16
	Mean	83.3824	63.7500	18.0392	12.5000	83.2026	62.9167	79.1667	59.3750
	SD	19.91519	24.46085	8.67901	22.94922	19.44738	27.43005	20.08747	31.08456
	P	.001		.077		.000		.001	

* The P is significant at the 0.05 level.
** The P is highly significant at the 0.01 level

Discussion

Hepatitis C virus (HCV), a member of the Flaviviridae family of RNA viruses. At least 6 major HCV genotypes are identified[2]. Egypt has the highest prevalence of HCV worldwide (15%)[3] and the highest prevalence of HCV-4, which is responsible for almost 90% of infections[9]. It is common in persons with significant medical illnesses to have comorbid psychological symptoms and for their quality of life to be affected[10,11].

The current standard and only effective treatment for chronic hepatitis C (CHC) is pegylated (PEG) interferon alfa in combination with ribavirin[12,13]. Under optimal treatment conditions it is possible to achieve a sustained virological response (SVR) in 60% to 80% of cases. Achieving such a good SVR depends importantly on management of the drugs' side effects[14].

In the current study, all Quality of life subscales median scores were lower in those showing psychiatric disorders than those who don't at baseline assessment and throughout treatment. These observations are consistent with other studies demonstrating a strong link between emotional status and health-related quality of life[15,16]. The mostly affected domains were Mental Health scale, Vitality scale and social functioning. As for the subscales concerned with HCV, the low scores were for Positive well being and Hepatitis specific health distress. Mental component summary scores were lower than physical component summary. A systematic review of 15 studies comparing HRQoL in HCV-infected patients vs healthy controls showed that HCV infection most profoundly impaired vitality, general health, physical function and social function. Of these, vitality was considered the most important scale to patients [17].

Several studies have shown that patients with chronic hepatitis C have a reduced quality of life[4]. Reduction in quality of life is not associated with how the infection is acquired or with the severity of the liver disease [5,6]. The impact of IFN-α treatment is less clear. Hunt et al.[7] prospectively followed patients with hepatitis C who were treated with IFN-α and

found that the health status of these patients was similar to that of the general U.S. population and did not change during IFN-α therapy. In contrast, 6 in a much larger study, showed that successful therapy with IFN-α improves quality of life and that the degree of improvement is related to sustained virological or biochemical response to treatment. However, the patients were not blinded to their state of infection.

Fontana et al [18] found that Baseline physical health and mental health summary scores of the entire group were significantly lower than those of healthy comparison subjects in the population. During the first 24 weeks of treatment, the mean physical and mental health summary scores of the 15 patients with psychiatric problems were lower than those of the 11 patients without neuropsychiatric problems ($p<0.0001$). However, more striking differences were noted in the role emotional and mental health subscale scores over time in the two patient groups ($p<0.0001$).

McHutchison et al. [19] reported that health related quality of life Mean scores declined during treatment. Scales most affected were role-physical, vitality, social functioning and role-emotional, which showed decrements at the 12 week on-treatment assessment. An analysis of subgroups showed that for two scales (physical functioning and role-physical), combination therapy patients showed a transient but slightly deeper decline during treatment, in both the 24 and 48 week arms. At follow-up week 24 all scores had returned to pretreatment levels.

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PSYCHIATRIC ADVERSE EFFECTS DURING COMBINATION THERAPY OF PEGYLATED INTERFERON PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C PATIENTS : A PROSPECTIVE LONGITUDINAL STUDY

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POPLITEAL SCIATIC NERVE BLOCK FOR ANKLE AND FOOT SURGERY, A COMPARITIVE STUDY BETWEEN THE MODIFIED INTERTENDINOUS AND THE LATERAL APPROACHES

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Abstract

Aim: *The aim of this study is to compare a single injection modified intertendinous with the lateral approach to popliteal sciatic nerve(SN) block by using the peripheral nerve stimulator for patients undergoing ankle and foot surgery for intraoperative anesthesia and postoperative analgesia.*

Patients& methods: *This is a randomized interventional prospective study, where patients were randomly allocated into two equal groups, 60 patients in each group; group A(the modified intertendinous approach) and group B(the lateral approach).Each group was subdivided into three equal subgroups (I,II,III) according to the medications they received: subgroup I received plain bupivacaine + 1ml saline 0.9%, subgroup II received plain bupivacaine + 1ml of clonidine (100 μg) and subgroup III received plain bupivacaine + 1ml of hyaluronidase (1500 IU).*

The initial stimulation of tibial nerve and common peroneal nerve, the time required to perform the block, the number of attempts till successful nerve localization and their complicatios and sensory block assessement (onset, peak, duration and postoperative analgesia "VAS") and the motor block assessement (onset, peak and duration) were recorded.

Results: *The technique in group A is easier with a higher success rate than that in group B but the quality of block for both groups is the same. In subgroups AII and BII the duration of*

sensory block, postoperative analgesia and motor block is more than in other subgroups (p <0.05). In subgroups AIII and BIII the onset of sensory and motor block is faster than in other subgroups (p <0.05).

Conclusion: *Although the lateral approach has the advantage that it can be done while the patient lying supine; the modified intertendinous approach proved to be easier. The addition of 100 µg clonidine to bupivacaine 0.5% prolonges the duration of sensory block, postoperative analgesia and motor block duration during popliteal sciatic nerve blockade. The addition of hyaluronidase (1500 IU) to bupivacaine 0.5% speeds the onset of sensory and motor block but it has no effect on the peak, duration of anaesthesia and post operative analgesia.*

Introduction

The sciatic nerve supplies motor innervation to the entire lower leg via the posterior tibial nerve, superficial and deep peroneal nerves, and the sural nerve. The sural nerve is sensory only. These major branches of the sciatic nerve also supply sensory innervation to the lower leg, except for the medial inner strip, which is supplied by the saphenous nerve (a branch of the femoral nerve)[1],[2]. Blockade of the SN at this level provides an appropriate anesthesia / analgesia with a duration that exceeds, in many cases, 18 hours. Additionally, this blockade has the advantage, over more proximal blockades, of preserving the flexion of the knee and allowing early ambulation with crutches[3].

The modified intertendinous approach to the SN in the popliteal fossa requires placement of the patient in the prone position which may be contraindicated in pregnant women or impossible in trauma patients. McLeod et al 1995[4] described another technique of blocking the SN in the popliteal fossa using a lateral approach with the patient lying supine. A subcutaneous block of the saphenous nerve as described by Scott was later added for additional pain control[5]. Popliteal blockade with bupivacaine, can reduce postoperative pain for 14-20h after major foot and ankle surgery with minimal side effects. Moreover the choice of additives to local anaesthetic influence the onset and, particularily,the duration of the blockade[6]. Clonidine is an al-

pha-2 adrenergic agonist which produces analgesia through central and peripheral mechanisms it is associated with specific side effects specially bradycardia and hypotension. It enhances both sensory and motor blockade from epidural or peripheral nerve injection of local anaesthetics, it blocks conduction of C and A gamma fibres, increases and intensifies conduction block of LA[7]. A major component of connective tissue is hyaluronic acid, which is reversibly depolymerized by hyaluronidase, initially called "skin spreading factor".

Patients and Methods

This study was conducted on 120 patients of both sexes, ASA I-III presented for elective surgery of the foot or ankle in The Benha University Hospital. Their ages was ≥ 18 years and their weight ranged from 60 to 85 Kg.Approval of ethical committee.

Exclusion criteria included patients refusing local anesthetic technique, patients with coagulopathy, patients with known sensitivity to the investigated drugs,dementia,patients with peripheral neuropathy, pregnancy and infection at the site of puncture.

All patients were visited before surgery and were given a full explanation; informed consent was obtained and patients were instructed to the use of the visual analogue scale (VAS) of pain.All patients were subjected to careful history taking, clinical examination and laboratory investigations. After 8 hours of fasting premedication was given in the form of 0.1 mg/kg diazepam orally 1 hour before starting the block. On the patient's arrival to the operating room a 20G intravenous cannula was inserted in the forearm before starting the block, perioperative fluid requirements were calculated and administered throughout the procedure, full non invasive monitoring commenced [Baseline level of consciousness, Pulse oximter, Vital signs (Respiratory rate, Blood pressure and Heart rate) and ECG and oxygen 2- 4 liters/ min was administered through a nasal pronge. Patients were randomly allocated into two equal groups A and B according to the technique of block.

Popliteal sciatic block was performed using the peripheral nerve stimulation method. PLEX-GON nerve stimulator was used together with 50mm & 100mm LOCO-PLEX® insulated needles for modified intertendinous approach and lateral approach respectively. it was set at a frequency of 2 Hz, pulse width 100 μs, and current intensity 1.5 mA to locate the nerve branches then reduction of the stimulating current to ≤0.5mA was done to confirm close proximity to the nerves.

Group A:

In this group, the modified intertendinous popliteal block using a peripheral nerve stimulator was performed on 60 patients presenting for surgery of the foot or ankle. With the patient lying prone with the leg on the side to be blocked is supported to permit unrestricted movement of the foot. The modified intertendinous approach site was determined by palpating the groove between the biceps femoris and semitendinosus muscle until the point of overlap. The point of needle insertion was identified in the intermuscular groove perpendicular to the skin just distal to muscle overlap[8].

The skin was cleaned with an antiseptic solution (Povidon iodine) and then anesthetized with 4-5 ml lidocaine 2%. The stimulating needle (a 22G-50mm insulated) was connected to the negative lead of the nerve stimulator, whereas the positive lead was connected to the lateral calf via an ECG electrode.

The needle was inserted perpendiculary to a depth of 2-5cm until motor response was elicited with the nerve stimulator. If the nerve was not localized on the first needle insertion, the needle was slowly withdrawn to the skin and reinserted through the same skin puncture at an angle 5º then 10º lateral to the initial insertion plane(first attempt). Failure to stimulate the sciatic nerve, resulted in removal of the needle and repetition of the same maneuvers through a new puncture site 5mm lateral to the initial insertion site (second attempt). The needle position will be considered acceptable if an evoked motor response of plantar flexion, inversion, eversion or a dorsiflexion of the ipsilateral

foot is elicited at ≤0.5 mA. then the local anesthetic was injected, the proximity of the insulated needle to the nerve was confirmed when an injection of 1 or 2 ml of local anesthetic results in an immediate cessation of the elicited motor response.

Patients of this group were further subdivided into three subgroups according to the used drugs number of each=20:

Subgroup AI :

Patients of this subgroup received 0.4 ml /kg (24-34ml) of 0.5% bupivacain plus 1ml saline.

Subgroup AII:

Patients of this subgroup received 0.4 ml /kg (24-34ml) of 0.5% bupivacain plus 1ml Clonidine (100 µg).

Subgroup AIII:

Patients of this subgroup received 0.4 ml/kg (24-34ml) of 0.5% bupivacain plus 1ml hyaluronidase (1500 IU).

Group B:

In this group, the lateral approach using a peripheral nerve stimulator was performed on 60 patients presenting for surgery of the foot or ankle. While the patient is placed in the supine position, with the leg extended at the knee joint, a 10-pound sandbag or a bump will be placed beneath the calf and the leg internally rotated by an assistant. The point of needle insertion was identified as a point in the groove between vastus lateralis and biceps femoris,which lies 7cm cephalad to the lateral femoral epicondyle.

After preparation as for group A using a 22G-100mm insulated short-bevel needle, it is inserted through the identified site at a horizontal plane and the needle was advanced until the shaft of the femur bone was intentionally contacted. After the femur was contacted, the needle was then withdrawn to the skin and redirected posteriorly at a 30^{o} angle to the horizontal plane. The biceps femoris muscle fibers will be stimulated and contract until the needle passes completely through. Advancing the needle further will then stimulate the CP branch of the SN and cause eversion and dorsiflexion of the foot. Continue

to advance the needle until the more medial TN stimulates the flexor muscles to the toes If, after stimulating the CP branch, the flexor muscles are not reacting, the needle needs to be withdrawn to the skin and reinserted through the same skin puncture, first 5-10^{o} anterior and then 5-10^{o} posterior relative to the initial insertion plane (30^{o}). if this redirection (first attempt) did not result in nerve localization, the same technique is repeated through new skin punctures. The needle position will be considered acceptable if an evoked motor response of plantar flexion, inversion, eversion or a dorsiflexion of the ipsilateral foot is elicited at ≤0.5 mA, then the local anesthetic was injected.

Patients of this group were further subdivided into three subgroups according to the used drugs.

Subgroup B I:

Patients of this subgroup received 0.4 ml /kg (24-34ml)of 0.5% bupivacain plus 1ml saline.

Subgroup B II:

Patients of this subgroup received 0.4 ml/kg (24-34ml) of 0.5% bupivacain plus 1ml Clonidine (100 μg).

Subgroup B III:

Patients of this subgroup received 0.4 ml/kg (24-34ml) of 0.5% bupivacain plus 1ml hyaluronidase (1500 I.U).

In both groups, the saphenous nerve was then blocked by subcutaneous infilteration at the anteromedial side of the upper part of the leg with 3-5ml of 2% lidocain solution.

Difficulty in obtaining a proper motor response to a stimulus <0.5mA 2Hz and the initial response to electrical stimulation of the tibial and common peroneal nerves was recorded along with the time needed to perform the block.

Sensory block was assessed by the pin-prick test using 27G needle in the skin areas along the distribution of the superficial and deep peroneal nerves, and medial plantar, lateral plantar, and calcaneal branches of the tibial nerve. the patient was given a degree

from a 3-point scale rating (2= no block, 1= hypoesthesia, 0= anesthesia).

Motor assessments included plantar flexion and dorsiflexion of the foot at the ankle, and toes movement. Onset of motor blockade ,time to peak motor blockade and the duration of motor blockade were recorded. the patient was given a degree from a 3-point scale rating (2= no block, 1= paresis, 0= paralysis).

Time from injection to onset of sensory blockade (loss of sensation of sharpness) and time from injection to peak sensory effect (loss of touch sensation) were recorded. Duration of anesthesia was taken from establishment of peak sensory effect until first return of pinprick sensation in any skin dermatome supplied by the TN and CPN.

A successful complete block was defined as pinprick sensory anesthesia and motor paralysis affecting both divisions of the sciatic nerve i.e. the peroneal nerve (the superficial and deep peroneal nerves) (dorsum of the foot) and the tibial nerve(medial plantar, lateral plantar, and calcaneal branches), sole of the foot, within 30min and absence of pain on surgical instrumentation. Anesthetic failure was managed with general anesthesia as appropriate. Intraoperative sedation was provided by an intermittent bolus of 1mg midazolam and 50µg fentanyl.

A failed block was the one where there was no elicited motor response or where the sensory blockade involved only a single or none of the following nerves: the superficial and deep peroneal nerves, and medial plantar, lateral plantar, and calcaneal branches of the tibial nerve.

After completion of the block procedure, all patients were monitored for signs of local anesthetic toxicity for 30 minutes after block placement(dizziness, visual and auditory disturbances, tinnitus, tremors, muscular twitching, convulsions and metalic taste).

The complications of the used drugs as hypotention and bradycardia for clonidine and hypersen-

sitivity or anaphylaxis for hyalurinidase was also recorded. Patients were also observed for other complications as bruising, bleeding at the injection site, arterial puncture (hematoma) and peripheral nerve injury (parasthesia).

Postoperative analgesia was assessed using the visual analog scale (VAS). Duration of postoperative analgesia was recorded as the time elapsed from the first return of pinprick sensation in any skin dermatome supplied by the blocked nerves up to the patient's first request for analgesia for pain in the vicinity of the operation. Rescue analgesia in the form of paracetamol 500mg tablets up to 8 tablets/24 hr orally or mepridine 0.5mg/kg IM will be available on patient request or if VAS ≥4.

Results

There was no statistically significant difference (P>0.05) between the 6 subgroups as regard age, weight, sex and type of surgery table (1) and table (2).

During the performance of the blocks success rate was 95% and 90% in the groups A & B respectively. motor response to electrical stimulation ≤ 0.5 mA 2Hz was elicited after first attempt (Easy) in 58.3% & 16.7% of cases in the groups A & B respectively (P<0.001). Motor response to electrical stimulation ≤ 0.5 mA 2Hz was elicited after second attempt (Intermediate) in 18.3% & 30.0%of cases in the groups A & B respectively (P<0.001). Motor response to electrical stimulation ≤ 0.5 mA 2Hz was elicited after third attempt (Difficult) in 18.3% & 43.3% of cases in the groups A & B respectively (P<0.001). Motor response to electrical stimulation ≤ 0.5 mA 2Hz elicited hardly in 5.0% & 10.0% of cases in the groups A & B respectively. In group (A) 3 cases required general anesthesia while in group (B) 6 cases required general anesthesia i.e. failed block, fig (1).

In this study, motor response to electrical stimulation to tibial nerve (inversion and planter flextion of the foot) occurred in 76.7% and 28.3% for the groups A & B respectively (P<0.001). Motor response to electrical stimulation to common peroneal nerve (eversion and dorsiflexion of the

foot) occurred in 23.3% and 71.7% for the groups A & B respectively (P<0.001), fig (1).

Mean time to perform the block (start of skin disinfection – end of injection) was 8.3 ± 1.4 and 10.9 ± 1.3 min for group A and B respectively (P<0.001) fig. (2)

In subgroup AI, the onset time of sensory nerve blockade was 14.84±0.800 min. Peak sensory effect was 26.84±0.8 min. Duration of anesthesia was 4.711±0.7 hr. Postoperative analgesia was 6.92±0.629 hr., fig (3)-(4). The onset time of motor nerve blockade was 11.89 ± 0.922 min. Peak motor effect was 23.45± 1.189 min. Duration of motor block was 4.18 ± 0.803 hr., fig (5)-(6).

In subgroup BI, the onset time of sensory nerve blockade was 15.39 ± 0.979 min. Peak sensory effect was 26.44 ± 1.626 min. Duration of anesthesia was 4.694± 0.6216 hr. Postoperative analgesia was 6.83±0.728 hr., fig (3)-(4). The onset time of motor nerve blockade was 12.33±0.891 min. Peak motor effect was 23.00±0.922 min. Duration of motor block was 4.97 ±0.469 hr , fig (5)-(6).

In subgroup AII, the onset time of sensory nerve blockade was 14.87 ± 0.549 min. Peak sensory effect was 26.66±0.8 min. the, Duration of anesthesia was 6.289±0.6 hr, Postoperative analgesia was 8.47±0.889 hr, fig (3)-(4). The onset time of motor nerve blockade was 11.05 ± 0.643 min. Peak motor effect was 23.79 ± 0.805 min. Duration of motor block was 6.82 ± 0.582 hr, fig (5)-(6) .

In subgroup BII, the onset time of sensory nerve blockade was 14.94 ± 0.682 min. Peak sensory effect was 25.56 ± 0.837 min. Duration of anesthesia was 6.839± 0.7823 hr. Postoperative analgesia was 8.1 ± 0.912 hr. fig (3)-(4). The onset time of motor nerve blockade was 12.18 ± 0.752 min. Peak motor effect was 24.36 ± 0.837 min. Duration of motor block was 6.12 ± 0.712hr fig (5)-(6). These results show that there is enhancement of sensory and motor blockade by clonidine added to bupivacain during popliteal sciatic nerve blockade as regards

duration of sensory block, postoperative analgesia and duration of motor blockade and there was no complications from its use.

In subgroup AIII, the onset time of sensory nerve blockade was 12.13±0.704 min. Peak sensory effect was 26.76±1.032min. the, Duration of anesthesia was 4.537 ± 0.6946 hr, Postoperative analgesia was 6.93± 0.513hr., fig (3-(4). The onset time of motor nerve blockade was 9.53±0.230min. Peak motor effect was 23.58±0.902min. Duration of motor block was 4.74±0.632 hr, fig 5)-(6).

In subgroup BIII, the onset time of sensory nerve blockade was 12.67 ± 0.618min. Peak sensory effect was 26.33 ± 1.455 min. Duration of anesthesia was 4.411±0.5830 hr. Postoperative analgesia was 6.81±0.730 hr, fig (3)-(4). The onset time of motor nerve blockade was 10.61 ± 0.631min. Peak motor effect was 24.61 ± 0.979min. Duration of motor block was 4.69 ± 0.572 hr, fig (5)-(6). These results show that adding hyaluronidase to bupivacain during popliteal sciatic nerve blockade speeds the onset of sensory and motor blockade but it had no effect on the peak, duration of anaesthesia and post operative analgesia and there was no complications from its use.

There was no statistically significant difference (P > 0.05) between six subgroups AI, AII, AIII, BI, BII and BIII as regards the postoperative analgesic characteristics (VAS and analgesic supplements) (4h), (6h) and (8h) postoperatively. There was statistically significant difference (P < 0.05) between the 6 subgroups (10h) and (12h) postoperatively. The mean VAS (10h) was 4.40±1.56, 3.8±0.89, 4.41±1.46, 4.43±0.84, 3.9±.04 and 4.48±0.78 for subgroups AI, AII, AIII, BI, BII and BIII respectively. The mean VAS (12h) was 5.4±1.56, 4.57±0.89, 5.41±1.46, 5.43±1.84, 4.47±0.04 and 5.48±0.78 for subgroups AI, AII, AIII, BI, BII and BIII respectively fig (7).

Complications during performance of procedures are summarized in (Table 8). hematoma was observed in 8.3% and 6.7% of group A and B respectively. There

was no statistically significant difference between the 2 groups (P > 0.05). Accidental puncture of popliteal vesseles was observed in 3.3% and 1.7% of group A and B respectively. There was no statistically significant difference between the 2 groups (P > 0.05). Tinnitus and anxiety (occurred 5 min after the injection of local anesthetic , lasted for only 5 min and resolved spontaneously without any intervention it may be a sign of CNS toxicity of bupivacain) was observed in 5% and 3.3% of group A and B respectively.

Table (1) : Comparison between A& B groups in type of surgery.

		Gr. A		Gr. B		Total		X^2	P
		No.		No.		No.			
Type of surgery	ankle	44	73.3	44	73.3	88	73.3	2.7	>0.05
	L.tibia	4	6.7	8	13.3	12	10.0		
	calcaneus	4	6.7	4	6.7	8	6.7		
	halux	8	13.3	4	6.7	12	10.0		
	Total	60	100.0	60	100.0	120	100.0		

Table (2) : Comparison of age, weight and sex in the six subgroups.

		Age (years)	Weight (kg)	Sex			
				Male		Female	
Group	Subgroup	Mean ± SD	Mean ± SD	No	%	No	
Group A	AI	38.90±11.951	76.25±7.333	11	55%	9	45%
	AII	42.30±13.207	77.65±7.555	12	60%	8	40%
	AIII	37.05±12.314	71.40±8.242	11	55%	9	45%
Group B	BI	38.00±11.448	76.20±5.709	9	45%	11	55%
	BII	35.55±10.986	73.70±9.314	11	55%	9	45%
	BIII	37.55±10.495	75.90±7.887	8	40%	12	60%
Significance test		ANOVA(F)=0.8 P>0.05	ANOVA(F)=1.7 P>0.05	$X^2 = 2.3$ p>0.05			

(P<0.001)

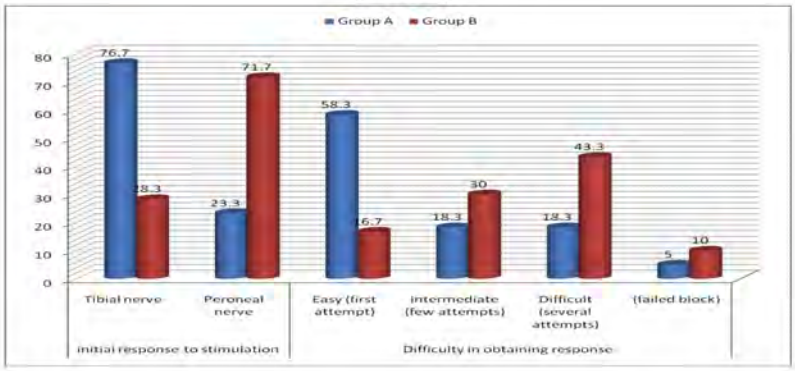


Fig. (1) : Difficulty and initial response to electrical stimulation.

(P<0.001)

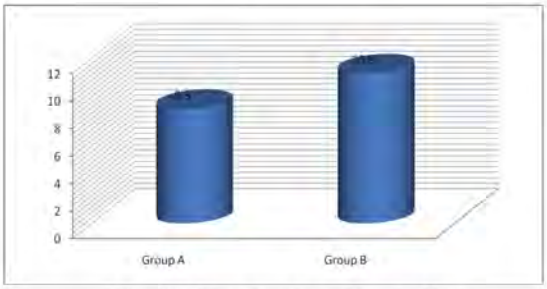
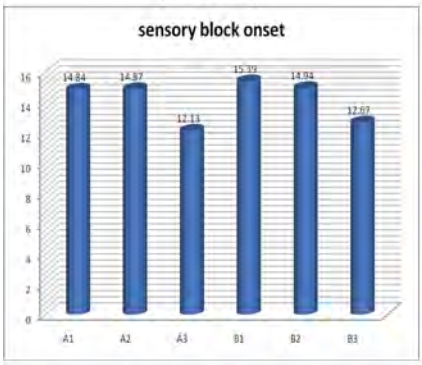


Fig. (2) : Mean time to perform the block

(P < 0.05)



(P > 0.05)

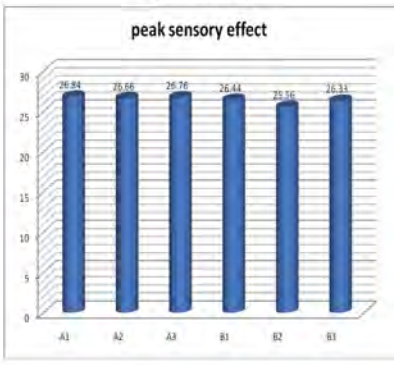


Fig. (3) Comparison of sensory block onset time and peak sensory effect between six subgroups.

(P < 0.05) (P < 0.05)

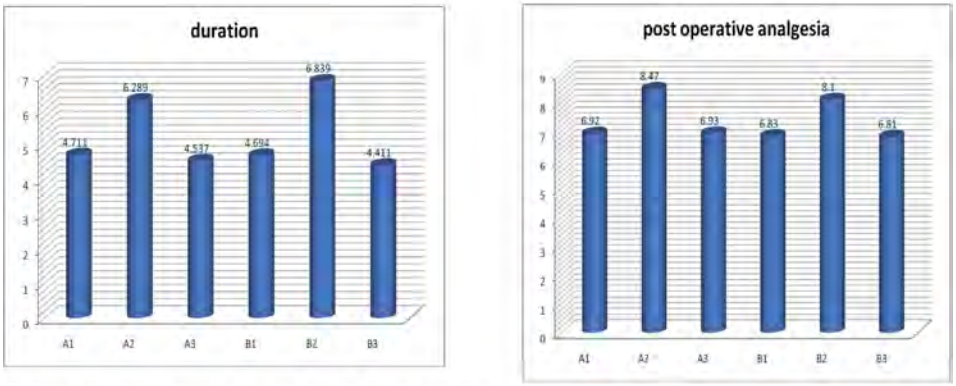


Figure (4) Comparison of sensory block duration and postoperative analgesia between six subgroups.

(P < 0.05) (P > 0.05)

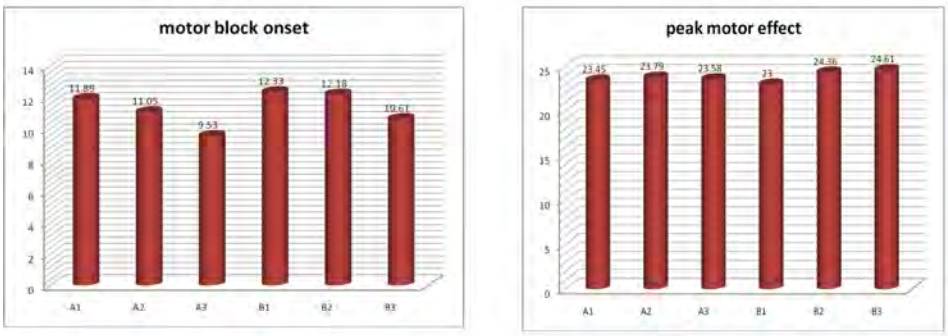


Figure (5) Comparison of motor block onset and peak motor effect between six subgroups.

($P < 0.05$)

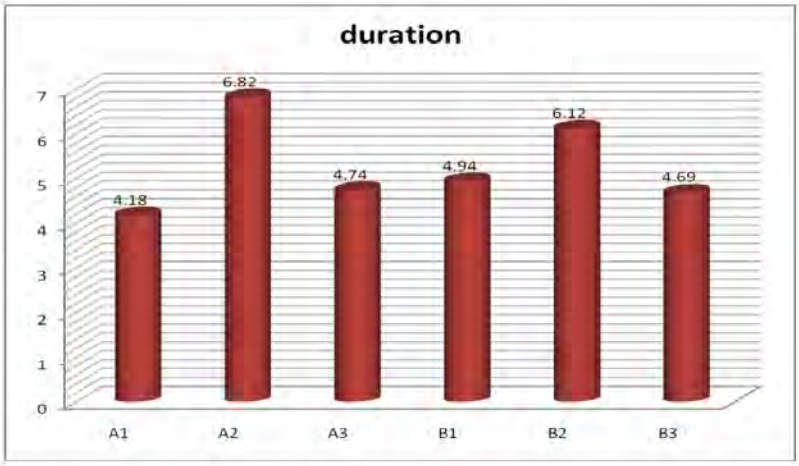


Fig. (6) : Comparison of motor block duration between six subgroups.

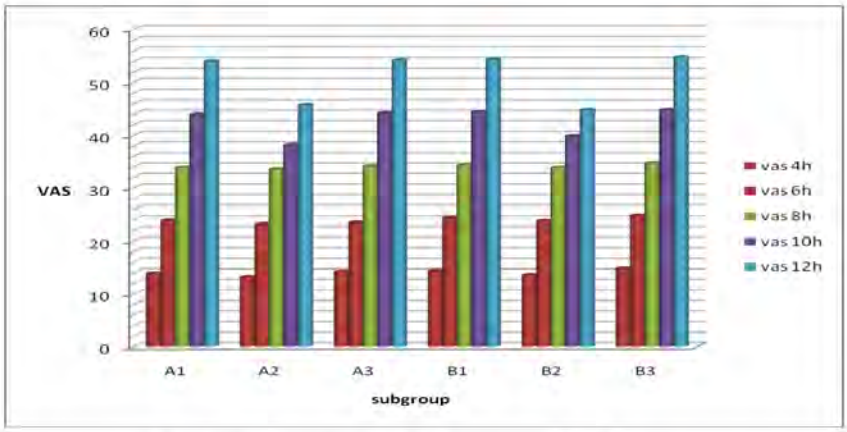


Fig. (7) : Comparison of postoperative VAS.

Discussion

In this current study, the block performance time is significantly longer (P<0.001) in the lateral approach than in the modified intertendinous approach and this was probably because of the fact that the 100 mm, needle used tended to bend on insertion between the tendons of biceps femoris and vastus lateralis muscles in the lateral approach which does not happen in the modified intertendinos approach.

In the study performed by Zetloui P et al, 1988[9], a shorter performance time for lateral approach was also obtained (4.10+1.26 min). This could be attributed to the fact that they performed the block using a shorter needle (50 mm insulated) which has less tendency to bend during progression leading to a more consistent needle path or may be due to racial difference.

In the present study, the lateral approach required more attempts to perform the block than the modified intertendinous approach, this may be due to the more simple technique of the modified intertendinous approach that is only relies upon manual identification of the intermuscular plane separating the biceps femoris and semitendinosus / semimembranosus muscles or may be due to the lack of experience with the lateral approach.

Borgeat et al, 2006[10] in their clinical study of the continuous popliteal nerve block in a 1001-case survey, and all patients received the modified posterior approach, they stated that, for 97% of the patients, one puncture attempt was sufficient to obtain inversion or plantar flexion. A second puncture site (more lateral) was necessary in 3%. Borgeat et al, 2004[11] in their Clinical evaluation of the modified posterior anatomical approach for performing the popliteal block in Five-hundred patients undergoing surgery of ankle or foot were prospectively included also showed in their results that The first attempt was successful in 97.5% of the patients, as we noticed this very high percentages may be due to the more experience they had in performing this technique.

Regarding the initial response to electrical stimulation, the results of the present study showed significant difference between the two approaches .

These results agrees with the results of Palaniappan et al, 2006 [12] in their study as in posterior (classic) approach group, the tibial nerve got stimulated in 69% resulting in plantar flexion and inversion. In the lateral approach group, the peroneal nerve got stimulated in 72% of the patients resulting in dorsiflexion and eversion. This difference was statistically significant.

Regarding success rate (90%) of group B showed complete sensory and motor block and only (10%) had paraesthesia and paresis, while in group A (95%) showed complete sensory and motor block and only (5%) had paraesthesia and paresis this may be due to the more difficult lateral technique.

Borgeat et al, 2004[11] in their Clinical evaluation of the modified posterior anatomical approach for performing the popliteal block also showed in their results complete sensory and motor block in 94% of the patients had the block and they stated that this technique has a high success rate thus the location of the needle insertion point is assessed without any measurement, thus avoiding inaccuracies caused by repeated skin-distance measurements so this goes definitely with our study in the modified intertendinous approach.

Michael et al,2010[13] hypothesized that blocking the tibial and common peroneal nerves individually in the popliteal fossa using the lateral approach using ultrasound distal to sciatic bifurcation would decrease time to complete block. A mixture of 28 mL 1.5% mepivacaine with 100 µg clonidine was used. Ultrasound was used to guide needle adjustments to achieve circumferential spread. Patients had significantly faster time to complete block than that in our study (19.2 vs 25.56 min), this may explained by the accurate visualization and identification of both divisions of the sciatic nerve using U/S guided technique or may be due to the use of mepiv-

acaine which has a faster onset than bupivacaine.

Geffen et al,2009[14] done Randomized controlled clinical study of ultrasound guided versus nerve stimulation guided distal sciatic nerve block at the popliteal fossa on 40 adult patients undergoing foot or ankle surgery receiving only a popliteal fossa sciatic nerve block. The block success rate was 100% in the US-guided group and 75% in the NS-guided group. Of the NS-guided group, the nerve could not be located in 2 patients and the block was not performed. Success rate in the patients who did receive a block was 83%. The median local anesthetic volume used was 17 vs 37 mL in the US-guided and NS-guided groups respectively. Block performance time, onset and duration were similar between the two groups. Significantly fewer needle insertion attempts were required in the US-guided group. This very high success rate is also higher than that of our study as U/S guided nerve block provides a real visualization of the nerve to be blocked and local anesthetic spread can be observed in real time during injection rather than by blind stimulation.

The addition of clonidine (100 µg) in our study to bupivacain (subgroup AII and BII) resulted in increased duration of anaesthesia and post operative analgesia but it had no effect on the onset and peak of anaesthesia and there was no complications from its use. Jacques et al 2008[15] in their study support our results, they stated that Clonidine significantly prolongs the analgesic duration after popliteal fossa nerve blockade with bupivacaine. Patients received a popliteal fossa block (nerve stimulator technique, via the posterior approach) using 30 mL 0.375% bupivacaine, with epinephrine. Patients were randomized to receive no clonidine, 100 µg clonidine IM, or 100 µg clonidine with bupivacaine for the popliteal block. Patients also received a combined spinal epidural anesthetic, a saphenous nerve block, and postoperative IV patient controlled analgesia.Duration of analgesia was statistically longer in the block clonidine group (18 ± 6 h for clonidine with bupivacaine vs 14 ± 7 h for IM clonidine and

15 ± 7 h for control, P = 0.016 for control vs clonidine with bupivacaine). Pain scores, analgesic use, and side effects attributable to pain management were similar among groups.

Also Colin, et al 2007[16] support our study they stated that Clonidine improves duration of analgesia and anesthesia when used as an adjunct to intermediate-acting local anesthetics for some peripheral nerve blocks. Side-effects appear to be limited at doses up to 150 μg. Based on qualitative analysis, clonidine appeared to prolong analgesia when added to intermediate-acting local anesthetics for axillary and peribulbar blocks.

On the other hand Dareen, et al 2004[17] do not recommend the addition of clonidine to a femoral-sciatic nerve block when given to facilitate postoperative analgesia in patients undergoing ACL reconstruction. Patients are assigned randomly to receive a femoral-sciatic nerve block using 30 ml 0.5% bupivacaine (control group) or 30 ml 0.5%bupivacaine and 1 μg /kg clonidine (expremental group), No significant differences were noted between groups for pain intensity scores, duration of sensory analgesia, postoperative analgesic requirements or overall patient satisfaction. Both groups reported minimal amounts of postoperative pain and high analgesic satisfaction scores. This may be due the fact that the sciatic nerve is thicker and deeper in its origin than it is in the popliteal fossa, or may be due to the use of lower doses of clonidine than we used.

The addition of hyaluronidase (1500 IU) in our study to bupivacain 0.5% (subgroup AIII and BIII) resulted in speeds the onset of anaesthesia only but it had no effect on the peak, duration of anaesthesia and post operative analgesia. There are many controversies about the use of hyaluronidase in peripheral nerve blocks and regional anaesthesia. Keeler et al 1992[18] studied the effect of adding hyaluronidase to bupivacaine during axillary brachial plexus block (BPB) in a double-blind design. Patients received BPB using bupivacaine 2 mg kg^{-1} with adrenaline 1 in 200000,

either with or without hyaluronidase (3000 IU), in a volume of 0.5 ml per 2.54 cm of the patient's height. The use of hyaluronidase did not increase the speed of onset of anaesthesia or reduce the incidence of inadequate nerve block. Hyaluronidase produced a significant reduction in the duration of anaesthesia.

Tempestini 2008[19] performed third molar surgeries in 20 healthy patients. Inferior alveolar nerve block was induced using 2.8 mL 2% mepivacaine with epinephrine. Hyaluronidase (75 IU) or a placebo was injected 40 minutes after the beginning of pulpar anesthesia (randomized and double-blind trial). In both tissues, the duration of anesthetic effect with hyaluronidase was longer ($P<0.01$) than with the placebo. Hyaluronidase increases the duration of mepivacaine in inferior alveolar nerve blocks.

As regard Complications during performance of procedures, hematoma was observed in 8.3% and 6.7% of group A and B respectively. There was no statistically significant difference between the 2 groups, Accidental puncture of popliteal vesseles was observed in 3.3% and 1.7% of group A and B respectively. There was no statistically significant difference between the 2 groups. Tinnitus and anxiety (occurred 5 min after the injection of local anesthetic, lasted for only 5 min and resolved spontaneously without any intervention it may be a sign of CNS toxicity of bupivacain) was observed in 5% and 3.3% of group A and B respectively.

Borgeat et al, 2006[10] in their Clinical study, all patients received the modified posterior approach, they found that acute complications were observed in (1.7%), (0.5%) reported transient paresthesias during nerve localization, which resolved immediately after needle repositioning, (0.8%) noted painful sensations during application of local anesthetic, which resolved after slight withdrawal of the catheter. In (0.4%), blood was aspirated through the needle. In these patients, the needle was withdrawn, the puncture point compressed until bleeding stopped, and the block was successfully performed. No central

nervous system or cardiac toxicity occurred.

Compere et al 2005[20] reported a case of thigh abscess as a complication of continuous popliteal sciatic nerve block . Five days after surgery, the catheter was removed. Fifteen days after, the patient complained of pain in the thigh with fever. Ultrasonography revealed a thigh mass and the abscess was treated by surgery.

Conclusion

In conclusion, the sciatic nerve block in the popliteal fossa by a single injection using either the modified intertendinous approach or the lateral approach by aid of the peripheral nerve stimulator and that have been proven to be useful, simple, safe and reliable. But the use of U/S guided nerve block seemed to be more useful as it provides a higher success rate.

Using additive (clonidine and hyaluronidase) with local anesthetic prolonges the duration of sensory and motor block (clonidine) and speeds the onset of sensory and motor block (hyaluronidase) .

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POPLITEAL SCIATIC NERVE BLOCK FOR ANKLE AND FOOT SURGERY, A COMPARITIVE STUDY BETWEEN THE MODIFIED INTERTENDINOUS AND THE LATERAL APPROACHES

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MANSOURA EXPERIENCE IN PARTIAL ULNAR NERVE TRANSFER TO RESTORE ELBOW FLEXION IN UPPER TRUNK TRAUMATIC BRACHIAL PLEXUS INJURY

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Abstract

Purpose: *Restoration of elbow flexion following upper trunk brachial plexus injury is a critical priority. Partial ulnar nerve transfer to musculocutaneous branch of biceps muscle is an innovating reconstructive procedure. We evaluate our results of this procedure in upper limb surgery unit in orthopedic department in Mansoura University Hospital.*

Method: *Retrospective review was performed on 10 consecutive patients who had direct nerve transfer of a motor fascicle of ulnar nerve to the musculocutaneous branch of biceps muscle. Outcome assessment included recovery of elbow flexion.*

Results: *Clinical evidence of reinnervation was noted at (3.9± 0.99) months ranging from 2 to 5 months after surgery. Mean follow up period was 2.2 years ranging from 2 to 3 years. 9 patients had biceps power graded at least as M4.*

Conclusion: *Transfer of ulnar nerve fascicles to restore elbow flexion is a reliable technique.*

Introduction

Nerve transfers (neurotization) involve the repair of a distal denervated nerve element using a proximal foreign nerve as the donor of neurons and their axons, which will reinnervate the distal targets. The concept is to sacrifice the function of a (lesser valued) donor muscle to revive function in

the recipient nerve and muscle that will undergo reinnervation [1].

The first report of neurotization in an attempt to restore injured plexus function was published by Tuttle[2] in 1913. A review of the historical precedents as well as the anatomical basis and rationale for nerve transfers in brachial plexus surgery was most clearly presented 20 years ago by Narakas[3]. Since then, nerve transfers have become increasingly popular and used for the repair of BPIs, Specially in cases in which the proximal motor source of the denervated element is absent due to avulsion from the spinal cord[4].

Susan Mackinnon[5] reported the following indications for nerve transfer in brachial plexus injuries:

1. Brachial plexus injuries in which only very proximal or no nerve is available for grafting.
2. High proximal injuries that require a long distance for regeneration.
3. Avoidance of scarred areas in critical locations with potential for injury to critical structures.
4. Major limb trauma with segmental loss of nerve tissue.
5. As an alternative to nerve grafting when time from injury to reconstruction is prolonged.
6. Partial nerve injuries with a defined functional loss;
7. Spinal cord root avulsion injuries.
8. Nerve injuries in which the level of injury is uncertain, such as with idiopathic neuritides or radiation trauma and nerve injuries with multiple levels of injury.

Rationale And Principles Of Neurotization

The suitability of one nerve as a donor in nerve transfer procedures is determined predominantly by its anatomic proximity to the brachial plexus elements, the extent of brachial plexus damage, the patient's functional impairment after donor nerve sacrifice, and the number of nerve fibers. Although the functional relationship between the donor and recipient nerves is advantageous, central plasticity may be efficient in

producing useful functional recovery even if there is a great functional difference, such as in intercostal nerves transfer. The technically ideal nerve transfer allows direct nerve anastomosis between the donor and recipient nerves. The relative efficiency of neurotization in humans is explained by the fact that the neurotizer is severed with minimal trauma with a very sharp instrument, far from the neuron. It is connected within minutes to the recipient nerve; thus, the time during which its stump is in a pathologic state is minimal. This may favor the production of healthy vigorous sprouts[6].

Nerve regeneration following nerve transfer relies on well-known phenomena that govern nerve repair. Certain principles must be respected in order to achieve success[5-7]:

- An adequate neurosynthesis between the donor and recipient nerves should be ensured so that the healthy proximal stump supplies a maximal number of axon sprouts to the distal stump. The latter is undergoing wallerian degeneration.
- Immobilization of the repair site is carried out until nerve fibers have crossed from one stump into the other (2-3 weeks).
- Whenever possible, motor fascicles are connected to motor fascicles.
- Conjectural concerns are the reciprocal proportion of numbers and types of nerve fibers versus mass and numbers of muscle fibers in donors compared with those of recipients. These factors probably influence power, speed, and endurance in reinnervated muscles. The musculocutaneous nerve contains approximately 3000 motor fibers, of which 60% are efferent and 40% afferent. Ideally it should be reinnervated by the same number of nerve fibers.
- An anastomosis should be performed as close to the recipient muscle as feasible. Greater distances for axonal regeneration decrease the likelihood that an axon will remain on its intended course. Neurotization of cords and trunks has met with poor results because there are too many opportunities for the regenerating axon to travel along the wrong pathway.

• Anastomosis should be performed as soon after the injury as possible. Atrophic changes are evident in denervated muscles soon after the injury, and by 2 years the muscle cells become fragmented and disintegrated. Controversy exists as to how long after the initial injury surgery can be performed. Some authors reported a 25% failure rate in neurotization cases done 4 to 6 months after the injury and 60% failure rate in those performed 7 to 9 months.

In cases of upper-trunk palsy involving loss of shoulder function and the flexion of the elbow, the C5 and C6 roots are often found avulsed from the spinal card and this precludes nerve grafting. In such cases, conventional surgery involved palliative procedures[8] such as a Stiendler flexoplasty combined with arthrodesis of the shoulder or nerve transfers to suprascapular and musculocutaneous nerves[1].

The transfer of some fascicles from the intact ulnar nerve to the nerve to the biceps is a technique supported by several hypotheses[9]:

1. The reinnervation of the biceps gives better results than palliative treatment.
2. The closest normal nerve to the biceps is the ulnar nerve. This close proximity allows a direct repair that results in rapid reinnervation of the biceps.
3. The nerve of the biceps is very small and needs only a thin fascicle for reinnervation. The selection of a suitable fascicle for transfer is facilitated by electrical stimulation of the nerve during surgery.

Patients and Methods

We present our experience in Mansoura University Hospital, in orthopedic department with 10 consecutive cases of traumatic brachial plexus injury treated by this set of nerve transfer, involving partial transfer of ulnar nerve to biceps motor branch.

This is a retrospective study of 10 consecutive cases of traumatic brachial plexus injury with lost active elbow flexion with good hand function who presented to us within 10 months of injury

during period of 2006 and 2010.

- The average age of patients was (21.3) years. It varies from 5 to 49 years.
- They were all males.
- In 9 cases the mode of injury was road traffic accident while one patient was a victim of traction injury by a cart.
- All the patients were right handed. Left side was affected in 9 cases, while right side was affected in only one case.
- The average denervation time was (4.4) months, it varies from 1 to 10 months.
- The average follow up period was (2.2) years, it varies from 2 to 3 years.
- A careful meticulous detailed history was taken from all patients or their relatives, including handeness, side of injury, mechanism of injury and denervation time.
- Motor power examination of muscles of upper limb was assessed and recorded in brachial plexus sheet (fig. 1[10]).
- Sensory examination in all dermatomes was done and perception of pain and touch.
- In all patients biceps and bachioradialis was graded as M0 according to Medical Research Council Scoring.
- In 8 cases, supra and infra clavicular exploration was performed. While direct neurotization was performed in 2 cases due to relatively prolonged denervation time.

Technique

We use the original technique, 1st described by Oberlin[9].

All the patients received anaesthesia without muscle relaxation and maintained on opiod or isoflurane.

The origin of the branch of the musculocutaneous nerve to the biceps muscle is marked on the skin over the anterior aspect of the arm, four centimeters distal to the humeral insertion of the pectoralis major tendon. The skin is incised longitudinally over 8–10 cm, straddling this point. The fascia covering the biceps is incised, and the muscle is retracted laterally. The musculocutaneous nerve is approached between the biceps and the coracobrachialis muscles. The nerve to the biceps is identi-

fied. Twelve centimeters is the mean distance from the acromion to the origin of the nerve to the biceps . The ulnar nerve is approached at the same level. Its identification is formally assessed by means of electrical stimulation. Further dissection is performed under microscopic magnification.

The branch(s) destined to the biceps are identified. Usually, the vascular pedicle. to the biceps has a more transverse orientation and does not interfere with the dissection of the nerve.

The branch(s) to the biceps muscle is (are) split proximally from the musculocutaneous nerve for approximately 2 cm and transected. The distal part is then rotated medially toward the previously dissected ulnar nerve.

The epineurium of the ulnar nerve is incised. One (or two) fascicle(s) with an adequate size is (are) selected. They are subjected to low intensity electrical stimulation. It is possible to distinguish precisely between sensory and motor fascicles. Usually, one is able to locate fascicles with a response in the extrinsic flexors and those corresponding to the intrinsic muscles of the hand. In these cases, the fascicles innervating the flexor carpi ulnaris are selected for transfer. This fascicle is often located anteriorly and medially within the ulnar nerve. The chosen fascicle is separated from the rest of the ulnar nerve over 2 cm and divided distally (Fig. 2). The fascicle is turned laterally and sutured to the nerve to the biceps, with 10.0 nylon without any tension at the repair site. The nerve repair is performed in front of the brachial vascular bundle.

Outcome assessment

Strength of muscle was graded using MRC scoring and range of movements was recorded with Goniometry. The range of elbow flexion was measured as the angle formed between the long axis of the arm and the forearm. Elbow function were graded using the scale proposed by Waikakul et al [11]with minimal modification as shown in table (1).

To detect any consequence of sectioning of ulnar nerve fascicles, preoperative and postoperative grasping and key pinch strength

were compared and ulnar side of hand sensibility was assessed.

Physiotherapy protocol

Stretching exercises are started at three weeks and electrical stimulation is started after 6 weeks[12].

Results

- 9 of ten patients have biceps power graded as at least M4 while only in one patient it was M2.
- The average time required for clinical reinnervation of biceps (flicker of movement) was (3.9±.99) months.
- The details of patients and final grading of their elbow flexion are shown in table (2).

Table (1): Grading of elbow function (Waikakul et al [11] modified):

Grade Functional status	
Excellent	Ability to lift 2 Kg weight from 0 to 90 degrees of elbow flexion more than 30 times successively.
Good	Ability to lift 2 Kg weight from 0 to 90 degrees of elbow flexion, but less than 30 repetitions successively.
Fair	Motor power more than M3 power but unable to lift a 2 Kg weight.
Poor	Motor power less than M3.

Table (2): patients' details and elbow flexion grading

No	Age	Side	Mechanism of injury	Denervation time	Associated injury	Follow up	Biceps grading
1	9 y	Left	Road traffic accident	7 m		3 y	M4+
2	5 y	Left	Pulled by a cart	2 m	Supracondylar Fracture humerus	3 y	M4+
3	49 y	Right	Road traffic accident	5 m		2 y	M4+
4	31 y	Left	Road traffic accident	10 m		2 y	M4+
5	22 y	Left	Road traffic accident	6 m	Internal haemorrhage	2 y	M4
6	7 y	Left	Road traffic accident	2 m		2 y	M4+
7	23 y	Left	Road traffic accident	4 m		2 y	M4
8	21 y	Left	Road traffic accident	1 m	Fracture clavicle	2 y	M2
9	25 y	Left	Road traffic accident	3 m		2 y	M4+
10	21 y	right	Road traffic accident	4 m		2 y	M4+

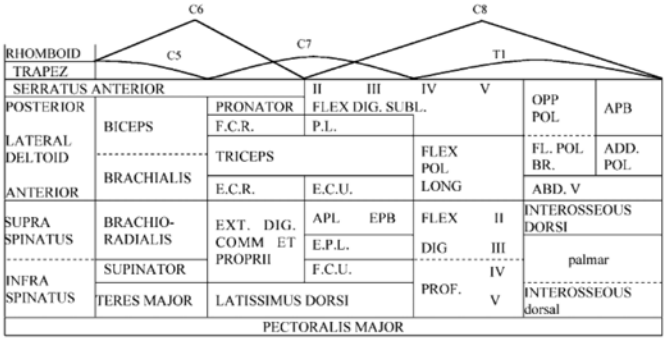
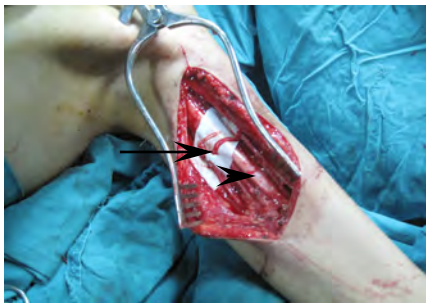
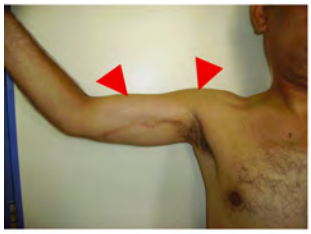
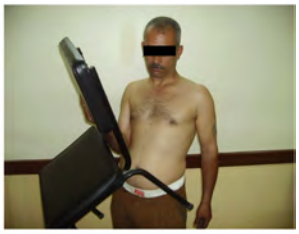


Fig 1 : Brachial plexus chart [10]

Fig 2 : Motor fascicles of the ulnar nerve(arrow) are separated from the rest of the nerve over 2-3 cm distance and turned laterally towards the biceps motor branch (head arrow)







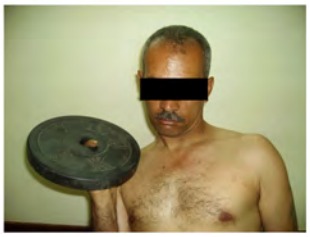


Fig 3: Clinical photo of case number 3 showing excellent results of elbow flexion. The patient could easily do more than 30 repetitions of elbow flexion with 2 kg weight.

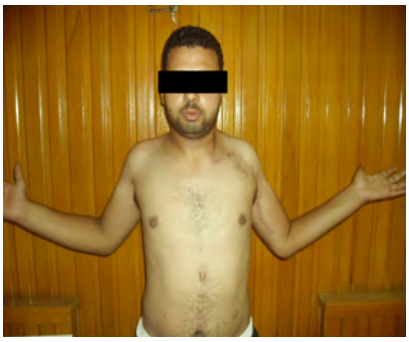


Fig 4: clinical photo of case number 5 showing results of elbow flexion .

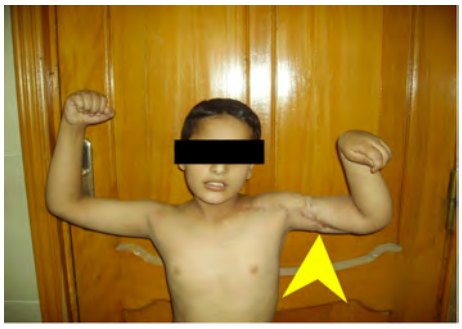


Fig 5: clinical photo of case number 6 showing results of elbow flexion.

Discussion

In 1994 Oberlin and coworkers introduced a new technique for restoration of elbow flexion [13]. They transferred about 10% of the fascicles of ulnar nerve to the motor branch of the biceps. Presence of interfascicular connection prevents any deficit in the ulnar nerve distribution following this procedure[13]. Bertelli and Ghizoni[14], Loy et al. [15], Leechavengvongs et al. [16], Sungpet et al. [17], Kakinoki et al. [18] and Venkatramani et al. [19] have used this method in 10, 18, 15, 36, 8 and 15 cases respectively with consistent good results. In our series, good and excellent results were seen in 90% without any objective or subjective sequlae of the hand which is in accordance with the published studies.

Several aspects accounted for the success of the proposed surgery[20]:

1. The use of motor nerve transfers to recipient motor nerves, which avoided exteroceptive sensory and motor mismatching.

2. Nerve transfer performed close to the target muscle. This allows faster recovery and distal inspection of the recipient nerves, excluding double lesions and probably favoring the contact of healthy donor and recipient nerves.

3. The use of synergistic nerve transfer. Digital and wrist flexion is synergic to elbow flexion. Moreover, hand function (i.e., digital flexion) has a large cortical representation. These aspects favor patient postoperative re-education and voluntary control of the transfer. Conversely, when "clumsy" nerves such as the intercostals and phrenic nerves are used, voluntary control may be acquired only after several years[21]; moreover, despite the acquisition of active control, respiration will permanently influence muscular target contraction[22].

4. Non use of nerve grafts. The use of nerve grafts in nerve transfer negatively affects the outcome[13].

5. Nerve coaptation performed without any tension, allowing limb motion without rupture. Intraoperative checking of the nerve coaptation after the patient's limb motion should be performed routinely.

Success rate of intercostals to musculocutaneous reported in literature is 33–87% [23]. The success rate depends on the level of the intercostal nerve transaction, the number of nerves anatomosed, and use of nerve graft. El-Gammal & Fathi [23] reported good results in 89.5% probably because three nerves were used and they were directly coapted to the musculocutaneous nerve. Phrenic to musculocutaneous has a reported success rate of about 75% but involuntary movements with respiration and cough persist for about two years. Samardzic et al. [24] reported 65% recovery rate with spinal accessory to musculocutaneous nerve transfer and Waikakul et al. [11] reported good recovery in 83% of their cases. But since this, transfer necessitates use of nerve graft the reinnervation takes long time. In Waikakul's [11] series the electromyographic evidence of reinnervation was first seen at an average of 11.5 months.

The greatest advantage of oberlin procedure is early recovery as nerve coaptation is done close to the target muscle without any interposing graft. In our cases, the site of coaptation was about 2 cm

from the biceps muscle[20].

Merrel et al.[25] in systematic review and meta-analysis of the results of neurotization and nerve graft in cases of traumatic brachial plexus palsies, concluded that results of restoration of elbow function improved with nerve transfer rather than autogenous graft. They recommended direct nerve transfer without exploration in patients with upper trunk brachial plexus injury without clinical or electromyographic evidence of recovery within 3-6 months after injury.

Conclusion

Use of ulnar nerve fascicles to restore elbow flexion is reliable technique provided that the denervation time does not exceed 10 months and the ulnar nerve function is not downgraded.

Competing interests

The authors declare that they have no competing interests.

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BENHA MEDICAL JOURNAL

MANSOURA EXPERIENCE IN PARTIAL ULNAR NERVE TRANSFER TO RESTORE ELBOW FLEXION IN UPPER TRUNK TRAUMATIC BRACHIAL PLEXUS INJURY

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PREDICTIVE VALUE OF TISSUE DOPPLER ECHOCARDIOGRAPHY IN DIFFERENTIATING PRIMARY DILATED CARDIOMYOPATHY FROM ISCHEMIC CARDIOMYOPATHY

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Abstract

Background: *Differentiating ischemic from non-ischemic etiology of left ventricular dysfunction has important clinical and therapeutic implications. The gold standard method for such differentiation is the coronary angiography. Many non-invasive techniques were studied for this purpose; however, the results were always controversial.*

Aim of the work: *To identify the accuracy of pulsed wave tissue Doppler imaging (PW-TDI), especially tricuspid annular velocities, as a non-invasive diagnostic tool in differentiation between primary and ischemic dilated cardiomyopathy.*

Patients and Methods: *According to the results of coronary angiography, we studied 40 patients with ischemic cardiomyopathy (ICM group) and 40 patients with primary dilated cardiomyopathy (DCM group) and 20 healthy volunteers as a control group. All patients were subjected to thorough history taking, clinical examination, 12-lead surface electrocardiogram and most importantly echo-Doppler study.*

Results: *In ischemic group there were statistically significant lower peak mitral annular systolic (Sa) and early diastolic (Ea) velocities in all studied portions of mitral annulus as well as their averaged values compared with DCM patients, with no significant difference between both groups regarding peak late diastolic (Aa) velocity. Also, there were significantly higher peak tricuspid annular systolic and late diastolic velocities with lower early diastolic velocity in ischemic group. The ratios of*

early to late diastolic annular velocities of both mitral and tricuspid valves were significantly lower in ischemic patients. Another two important parameters for diagnosing ischemic etiology in the present study were a) lateral tricuspid annular Sa velocity with a cut point of ≥ 8.5 cm/sec. which has 88% sensitivity and 93% specificity and b) the tricuspid to average mitral Sa ratio with a cut point of ≥ 1.2 which has 100% sensitivity and 95% specificity.

Conclusion: *RV dysfunction is more pronounced in patients with DCM than in patients with ICM. PW-TDI (especially of the tricuspid annulus) can be used as an easy, widely available and reproducible non-invasive technique for diagnosing ischemic etiology of heart failure.*

Key Words: *Primary dilated cardiomyopathy; Ischemic cardiomyopathy; Tissue Doppler echocardiography.*

Introduction

Chronic heart failure (CHF) has emerged as the most prevalent cause of mortality, morbidity and hospitalization in industrialized countries over the past years.[1]

Differentiation between the two main causes of CHF (ischemic and primary cardiomyopathy) is a very important issue. Patients with ischemic cardiomyopathy tend to have a poorer prognosis because of the residual ischemia, and their prognosis usually changes dramatically when revascularization done, either surgically or interventionally.[2]

The traditional non-invasive methods for such differentiation are the presence of chest pain, ECG ischemic changes or resting segmental wall motion abnormalities (SWMA) in patients with ischemic cardiomyopathy.[3] However; this is not a fixed role. Chest pain, ECG ischemic changes and SWMA may be present in up to two thirds of patients with non-ischemic cardiomyopathy, whereas patients with ischemic cardiomyopathy might have uniform hypokinesis.[4] Several non-invasive techniques (i.e. echocardiography, dobutamine echocardiography, thallium-scintigraphy, positron emission tomography, magnetic resonance) have been proposed to establish

the etiology of left ventricular dysfunction, but the results are controversial and the optimal strategy remains unsettled.[5] Tissue Doppler imaging (TDI) is an easy, widely used, non-invasive, objective promising tool for differentiating ischemic from non-ischemic etiologies of cardiomyopathy.[6] It does not only quantify left ventricular function, but moreover, it is a promising objective tool in the detection of RV dysfunction which is claimed to be a powerful predictor of mortality in patients with CHF.[7] Accordingly, the present study aimed to identify the accuracy of tissue Doppler study (especially tricuspid annular velocities) as a non-invasive diagnostic tool in differentiating primary from ischemic cardiomyopathy.

Patients and Methods

The study is a case control analytic randomized study that was conducted during the period from January 2010 to September 2011 in Cardiology Department, Faculty of Medicine; Mansoura University; Egypt.

This study included 3 groups; group I which consists of 20 healthy subjects without any history of cardiac symptoms or risk factors and normal bed-side investigations (ECG and echo-Doppler). They were 14 males and 6 females with a mean age of 32.25 ± 7 years. Their parameters were taken as reference values.

Regarding patients, there were 80 patients with evidence of heart failure (EF < 40%, LVEDD > 57 mm and ESD > 40 mm) which were furtherly divided according to the results of coronary angiography into group II (ischemic cardiomyopathy; ICM group) which consists of 40 patients with significant epicardial coronary lesions (at least 70% narrowing in one or more of the major epicardial coronaries or 50% narrowing in the left main trunk)[5] and group III (idiopathic dilated cardiomyopathy; DCM group) which consists of 40 patients with normal coronary angiogram.[8]

Exclusion criteria included patients with recent onset heart failure within 2 weeks, MI within 3 month, unstable angina within 1 month, valvular heart disease, congenital heart disease, atrial fib-

rillation and left bundle branch block (LBBB).

All patients were subjected to thorough history taking, clinical examination, routine laboratory tests, chest X-ray, ECG, echo-Doppler study, pulsed-wave tissue Doppler imaging (PW-TDI) and coronary angiography.

1) Transthoracic conventional echo-Doppler study:

We used General Electric System Vivid-3 machine having tissue Doppler imaging capability with (2.5-5) MHZ probe at Mansoura Specialized Medical Hospital. The echocardiogram was performed with the patient breathing quietly and lying in the left lateral position. Simultaneously recorded ECG renders the cardiac cycle phase reference. All standard views were obtained according to the recommendation of American society of Echocardiography.[9] The following measures were obtained guided by parasternal long axis view; end-diastolic and end-systolic diameters of the LV, RV end-diastolic dimension. Left ventricular ejection fraction was obtained by using Simpson's biplane method in 2-dimensional echocardiography.

Assessment of resting segmental wall motion abnormalities (SWMA) was recorded according to the American society of Echocardiography criteria which divided LV into 16 segments.

To obtain tricuspid annular plane systolic excursion (TAPSE), the apical four-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Off-line, the brightness was adjusted to maximize the contrast between the M-mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the total displacement of the tricuspid annulus (in millimeters) from end-diastole to end-systole, with values representing the average TAPSE of three to five beats.[10]

Mitral and tricuspid regurgitations were assessed quantitatively by color Doppler according to surface area of regurgitant jet as follows; mild regurge (grade I) if jet area < 4 cm^2, moderate regurge

(grade II) if jet are = 4-8 cm^2, moderately severe regurge (grade III) if jet area > 8 cm2 and severe regurge (grade IV) if jet area > 8 cm^2 and associated with retrograde flow through pulmonary veins in case of MR and through inferior vena cava (IVC) in case of TR. [11]

Pulmonary artery flow was recorded from parasternal short axis view by placing the sample volume between the leaflet tips in the center of the flow stream and the mean pulmonary artery pressure was calculated according to the following equation;

PAMP= 80-1/2 acceleration time[12]

2) Pulsed wave-tissue Doppler imaging (PW-TDI):

We obtained best quality of PW-TDI by minimizing the gain, bypassing the filter, and decreasing the velocity scale to a range between - 20 and + 20 cm /s with a sample gate of 2-4 mm and a sweep of 100-150 mm/s, the sample volume was placed at the angles of the mitral valve annulus with a special care to obtain an ultrasound beam parallel to the direction of the mitral annular motion in the following views; a) apical 4 chamber view to obtain septal and lateral angles, b) apical 2-chamber view to obtain anterior and inferior angles. On studying tricuspid annulus, the sample volume was placed on its angle at the lateral free wall of RV in the apical 4-chamber view.

To avoid beat-to-beat variations TDI measures were averaged over three consecutive cardiac cycles. For each annular site, we measured peak TDI velocities in cm/s as the following; systolic velocity (Sa), early diastolic filling velocity (Ea) and late diastolic filling velocity (Aa).[13]

3) Coronary angiography:

Coronary angiography was done utilizing the retrograde percutaneous transfemoral technique (Judkin's technique). The study was carried out with Siemens imaging system and was stored using a DICOM digital system. Multiple angulated views of each coronary artery were obtained. Coronary stenosis was evaluated qualitatively by an experienced observer, unaware of our study. A coronary stenosis was considered significant when the vessel diame-

ter was narrowed by ≥ 50% of left main trunk or by ≥ 70% of major epicardial coronary vessels.[5]

4) Statistical analysis:

The SPSS statistical program version 15 (SPSS Inc., Chicago, IL) was used for statistical study. Continuous variables were given as mean ± SD, and categorical variables were given as percentages. A value of $P < 0.05$ was considered statistically significant. A receiver operating characteristic curve (ROC) was constructed to establish the sensitivity and specificity of cut-off values for TDI parameters.

Results

Table 1 represents the difference between both groups regarding clinical and demographic criteria that showed statistically significant younger age, higher heart rate, lower blood pressure and more evident manifestations of HF (dyspnea, congested neck veins, lower limbs oedema and cardiomegaly) in idiopathic DCM compared with ischemic group. There was no significant difference regarding sex distribution.

Figure 1 represents the difference between both groups regarding the therapeutic history. Showing more use of anti-ischemic drugs (nitrates, beta blockers, aspirin, colopidogrel and statins) in ischemic group while anti-failure drugs (diuretics and digoxin) were more prescribed in the idiopathic group.

Table 2 represents the difference in echo-Doppler parameters between both groups. Showing that there were statistically significant higher chamber dimensions in idiopathic DCM group whereas there was no significant difference in EF and FS. Ischemic group showed significantly higher pulmonary artery mean pressure (PAMP) and tricuspid annular plane systolic excursion (TAPSE) compared with idiopathic group. Tricuspid regurge (TR) was significantly more severe among patients with idiopathic DCM whereas there was no significant difference between both groups regarding mitral regurge (MR).

Table 3 represents PW-TDI parameters in both groups showing significantly lower peak mitral

annular systolic (Sa) and early diastolic (Ea) velocities from septal, anterior, inferior and lateral portions of the mitral annulus in ischemic patients compared with idiopathic DCM patients as well as their averaged values. There was no statistically significant difference between both groups regarding peak mitral annular late diastolic (Aa) velocity from all recorded portions of the mitral annulus as well as their averaged value. Regarding tricuspid annular velocities there were statistically significant higher peak systolic and late diastolic velocities whereas lower early diastolic velocity in ischemic patients compared with DCM patients. The ratios of early to late diastolic annular velocities of both mitral and tricuspid valves were significantly lower in ischemic patients.

Based on the ROC analysis (Fig. 3), lateral tricuspid annular Sa velocity with cut point of ≥ 8.5 can be used as a distinguishing parameter for ischemic cardiomyopathy with 88 % sensitivity and 93 % specificity (Fig. 3a). The tricuspid to average mitral Sa ratio can be used as another differentiating parameter with a cut point of ≥ 1.2 which has 100% sensitivity and 95% specificity for diagnosing ischemic etiology of dilated cardiomyopathy (Fig. 3b).

Table 1: Clinical and demographic criteria

	Control	ICM group	DCM group	P value ICM Vs DCM
Age	32.25 ± 7	51.2 ± 8.2	44.6 ± 9.6	0.002 **
Male	14 (70%)	30 (75%)	32 (82%)	0.592
Female	6 (30%)	10 (25%)	8 (20%)	
HR	75.4 ± 7.91	74.38 ± 8.6	80 ± 10.99	0.013 *
SBP	115 ± 8.89	114.75 ± 9.3	102.25 ± 9.9	0.000 **
DBP	74.75 ± 5.96	77.88 ± 7.4	70.25 ± 7.1	0.000 **
NYHA I		3 (7.5%)	2 (5%)	0.034 *
NYHA II		29 (72.5%)	19 (47.5%)	
NYHA III		8 (20%)	19 (47.5%)	
Congested neck veins		23 (57.5%)	35 (87.5%)	0.003 **
Lower limb oedema		17 (42.5%)	26 (65%)	0.044 *
Cardiomegaly		18 (45%)	32 (80%)	0.001 **
Chest Pain		19 (47.5%)	17 (42.5%)	0.653

* = Significant (P value < 0.05), ** = Highly significant (P value < 0.01).

Table 2: Echo-Doppler parameters

	Control	ICM	DCM	P Value ICM Vs DCM
LVEDD (mm)	48.4 ± 3.24	63.3 ± 4.1	75.0 ± 7.4	0.000 **
LVESD (mm)	29.2 ± 3.09	51.3 ± 3.4	61.8 ± 5.9	0.000 **
EF %	69.25 ± 4.73	34.9 ± 2.9	34.2 ± 3.6	0.375
FS %	39.7 ± 4.41	18.6 ± 2.9	18.0 ± 2.5	0.266
RV (mm)	16.05 ± 1.73	23.0 ± 4.0	31.3 ± 3.33	0.000 **
LVEDD/RV	3.02 ± 0.18	2.8 ± 0.5	2.4 ± 0.29	0.000 **
TAPSE (mm)	22.75 ± 3.23	15.9 ± 2.2	10.2 ± 1.2	0.000 **
PAMP	38 ± 7.2	38 ± 7.2	30.3 ± 4.5	0.000 **
Mitral Regurge Grade I		13 (32.5%)	6 (15%)	0.125
Mitral Regurge Grade II		17 (42.5%)	25 (62.5%)	
Mitral Regurge Grade III		10 (25%)	9 (22.5%)	
Tricuspid Regurge Grade I		17 (42.5%)	5 (12.5%)	0.004 **
Tricuspid Regurge Grade II		19 (47.5%)	23 (57.5%)	
Tricuspid Regurge Grade III		4 (10%)	12 (30%)	

Table 3: Tissue Doppler parameters of mitral and tricuspid annulus

	Control	ICM	DCM	P Value ICM Vs DCM
M Septal S	10.45 ± 1.54	6.2 ± 0.9	6.8 ± 1.2	0.017*
M Septal E	12.75 ± 1.45	8.5 ± 1.6	9.8 ± 1.8	0.001**
M Septal A	10.25 ± 1.45	9.2 ± 1.9	8.8 ± 1.7	0.261
M Lateral S	10.7 ± 1.69	6.3 ± 0.8	7 ± 0.96	0.001**
M Lateral E	13 ± 2.15	8.2 ± 1.8	9.3 ± 2	0.011*
M Lateral A	10.35 ± 1.46	9.2 ± 1.9	8.6 ± 1.1	0.09
M Inferior S	9.95 ± 1.43	5.9 ± 0. 97	6.5 ± 1.28	0.02*
M Inferior E	12.55 ± 1.23	9 ± 1.5	10.2 ± 1.6	0.002**
M Inferior A	10.05 ± 1.32	9.4 ± 1.87	8.9 ± 1.6	0.2
M Anterior S	10.5 ± 1.32	6.3 ± 0.88	6.7 ± 0.85	0.022*
M Anterior E	13 ± 1.75	8.7 ± 1.5	9.6 ± 1.9	0.004**
M Anterior A	10 ± 1.34	9.5 ± 2.08	8.8 ± 1.2	0.103
M Average S	10.42 ± 1.24	6.2 ± 0.67	6.7 ± 0.93	0.002**
M Average E	12.86 ± 0.96	8.6 ± 1.5	9.8 ± 1.68	0.001**
M Average A	10.19 ± 1.04	9.3 ± 1.8	8.8 ± 1.1	0.106
M Average E/A	1.29 ± 0.17	0.95 ± 0.2	1.1 ± 0.16	0.000**
Tricuspid S	15.4 ± 1.1	11.1 ± 2.2	7.1 ± 1.1	0.000**
Tricuspid E	15.55 ± 1.54	11.1 ± 1.7	12.6 ± 2.96	0.005**
Tricuspid A	11.7 ± 2.2	12.2 ± 2.7	10.3 ± 2.5	0.001**
Tricuspid E/A	1.36 ± 0.22	0.95 ± 0.24	1.3 ± 0.2	0.000**

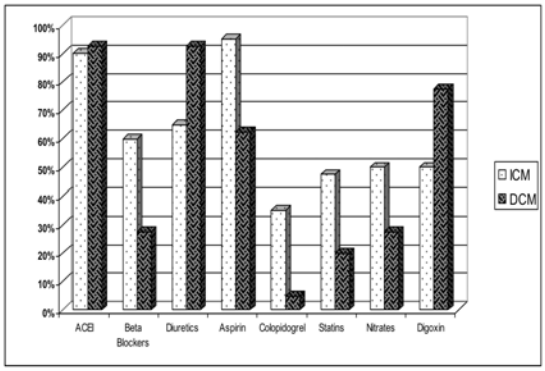
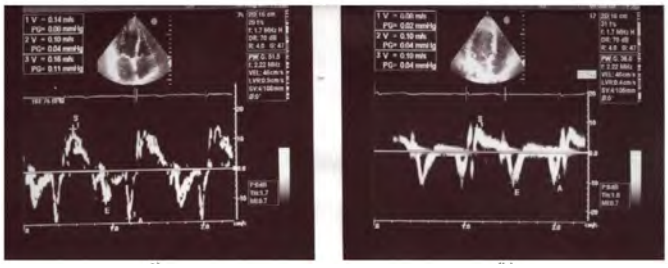
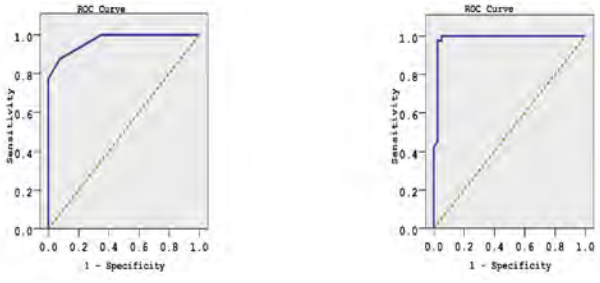


Figure 1: represents the difference between both groups regarding the therapeutic history. Showing more use of anti-ischemic drugs (nitrates, beta blockers, aspirin, colopidogrel and statins) in ischemic group while anti-failure drugs (diuretics and digoxin) were more prescribed in the idiopathic group.



(A) **(B)**

Figure 2: PW-TDI of lateral tricuspid annulus in a patient with ischemic cardiomyopathy (Fig.2a) and another with idiopathic dilated cardiomyopathy (Fig.2b) with reduced tricuspid systolic velocity in the patient with idiopathic dilated cardiomyopathy.



(A) **(B)**

Figure 3: Receiver-operating characteristic curves (ROC) for prediction of ischemic etiology in patients with dilated cardiomyopathy. a) Tricuspid Sa velocity, b) Tricuspid to average mitral Sa ratio.

Discussion

The present study aimed to identify the accuracy of tissue Doppler study (especially tricuspid annular velocities) as a non invasive diagnostic tool in differentiation between primary and ischemic cardiomyopathy. In our study it was found that patients with ICM were significantly older than those with DCM. This is in agreement with previous reports[14] which explained this finding by the fact that acute coronary syndromes are more prevalent in older patients unlike myocarditis which is more prevalent in younger age population. Risk factors for ischemic heart disease (IHD) were found to be more common in ischemic group but without statistically significant difference (P value > 0.05).

Anti-ischemic drugs (nitrates, beta blockers, aspirin, colopidogrel and statins) were more used in ICM patients whereas, antifailure therapy (diuretics and digoxin) were more prescribed in DCM group. There was no statistically significant difference between both patient groups regarding the use of ACEI. These results are logic because therapy was prescribed to ischemic patients based on their angiographic evidence of CAD, while DCM patients had more clinical and radiological manifestations of heart failure (dyspnea, tachycardia, hypotension, congested neck veins, lower limb oedema and cardiomegally). These results are in agreement with those of previous series.[15]

Regarding the history of anginal attacks and ischemic changes in ECG, the present study revealed no statistically significant difference in-between the two patient groups. These results are supported by Plewka et al[5] who found that many patients with idiopathic dilated cardiomyopathy report episodes of angina and have electrocardiographic signs suggesting previous myocardial infarction when there is extensive left ventricular fibrosis even without discreet myocardial scar. On the other hand, these results are discordant to that of Pirwitz et al.[16] who stated that the presence of any diagnostic Q wave had a positive predictive value of 92%, sensitivity of 57%, and specificity of 80% for identifying severe CAD.

Ventricular dimensions were higher in DCM patients compared with ICM group. These results are in accordance to a previous report that explained these findings by the more diffuse nature of myocarditis in idiopathic DCM group contradictory to the localized scar in the territory of occluded vessel in case of ICM group[17].

There was no statistically significant difference in prevalence of SWMA in the two groups. This result was in agreement with Diaz et al.[4] who reported that large areas of scarring may also develop after myocarditis and mild to moderate regional dyssynergy is common in primary DCM. Whereas, global left ventricular dysfunction occurs in patients with diffuse coronary artery disease. Another supporting opinion was that of Vigna et al[18] who do not agree that SWMA alone is a reliable method for differentiation. On contrary, Medina et al[19] reported that the presence of SWMA by 2D echocardiography had 83% sensitivity, 57% specificity, and a 77% predictive accuracy in detecting CAD in patients with DCM and thus in distinguishing ischemic from idiopathic DCM.

Regarding atrioventricular (A-V) incompetence, there was more severe tricuspid regurge (TR) in DCM group in comparison to ICM, while there was no significant difference between both groups in the degree of mitral regurgitation (MR). These findings can be explained by larger dimensions of RV in DCM patients leading to more dilatation of tricuspid ring with more resultant functional TR, whereas the resultant rise in the degree of functional MR because of larger dimensions of LV in DCM group is nullified by occurrence of ischemic MR in ICM patients and this result coincides with the report of weiland et al[20] who demonstrated that a large percentage of patients with severe LV systolic dysfunction have clinically relevant MR whatever the cause of left ventricular failure.

We found that DCM group has a significantly lower pulmonary artery mean pressure (PAMP) compared to ischemic patients, which can be explained by larger dimensions of RV with more resultant TR and right sided heart failure (RSHF) that act as a decongestant

factor for pulmonary bed. This result was in accordance to Parcharidou et al.[21]

As regards PW-TDI of the mitral annulus, our study revealed that all segments which had been studied with tissue-Doppler showed significantly smaller S-wave in ICM than in DCM patients. Similar results were found by other auothers.[22,23] This result can be explained by the fact that ischemia is more affecting subendocardial layer which consists mainly of longitudinal fibers leading to weaker long axis motion of the heart with resultant smaller S-wave in ischemic patients.[24] The greater sensitivity of changes in long-axis function over wall motion score index (WMSI) might have several explanations. The mitral ring gives rise to a strong echo, even when image quality is suboptimal, so that systolic amplitude and signals are simple to quantify even in patients with LBBB, thereby providing objective and reproducible measurements.[25] In contrast, WMSI analysis remains semi-quantitative and dependent on operator experience.[3]

Also, it was found that early diastolic annular velocity is lower in ischemic group. This can be explained by the observation of Shan et al.,[26] who stated that; in patients with ischemic left ventricular dysfunction systolic and early diastolic velocities are strongly dependent on both the percent of interstitial fibrosis and the myocardial beta-adrenergic receptor density, which is abnormal in heart failure, whereas Schwarz et al.,[27] observed an increase in fiber diameter in patients with idiopathic cardiomyopathy. An increase in fibrosis and reduction in myofibrilar mass was not observed except when the ejection fraction is markedly declined.

Unlike the left ventricle, which shortens relatively in a symmetrical manner through the transverse and longitudinal planes, muscle fiber orientation of the right ventricle dictates that contraction occurs predominantly along the longitudinal plane.[28] As a result, systolic displacement of the tricuspid annulus toward the RV apex (longitudinal plane), referred to as tricuspid annular plane systolic excursion (TAPSE),

closely correlates with RV ejection fraction.[29] Importantly, TAPSE does not require geometric assumptions or RV endocardial definition, and thus has been found to be highly reproducible and practical[30]. Our study revealed that tricuspid annular systolic motion (TAPSE) and velocity (S-wave by PW-TDI) were significantly higher in ICM patients indicating that RV systolic function is preserved in ischemic group unlike the idiopathic one. This finding coincides with previous reports that reached the same result despite the different methods of measurement of RV ejection fraction (multigated radionuclide angiography[31], thermodilution technique[32] or cardiac catheterization[33]).

Diastolic dysfunction of both ventricles (as evidenced by reversed Ea/Aa ratio at both mitral and tricuspid annuli) was significantly more prevalent in ischemic patients. This result could be explained by the fact that diastolic dysfunction precedes systolic one in ischemic cascade. A similar result was found in a previous series.[21]

In DCM group, we found a statistically significant positive correlation between RV dysfunction (represented by low tricuspid annular motion and velocity) and LV dysfunction (represented by low EF). On the other side such correlation was absent in ischemic patients confirming the observation of previous reports that primary cardiomyopathy is a biventricular disease.[33] In addition, this result coincides with WHO definition of idiopathic dilated cardiomyopathy.[8] In agreement with this definition; another confirming result of our study is the presence of a significant positive correlation between LV and RV dimensions with lower LV/RV ratio in idiopathic group and absence of such correlation with higher LV/RV ratio in the ischemic one.

It is known that RV function is strongly afterload dependent so that an increase in pulmonary pressure translates into a decrease in RV systolic function.[34] A negative correlation between pulmonary artery pressure and RV ejection fraction has been observed in different series.[35] In our

series, a non significant negative correlation between pulmonary artery pressures and RV ejection fraction was found in DCM patients, whereas the same two variables showed a significant negative correlation in ischemic group. Thus, among determinants of RV dysfunction, the relative role of pulmonary hypertension is less relevant in DCM compared with CAD for the same entity of LV dysfunction. On the basis of all these observations, we can conclude that RV systolic dysfunction in CAD represents a marker for advanced disease, in which a significant role is played by an elevation of pulmonary pressures. On the other hand, RV dysfunction may be found in earlier stages of idiopathic DCM as a consequence of the diffuse nature of the disease. In this instance, RV dysfunction seems to be related more to the entity of concomitant LV dysfunction than to pulmonary hypertension.

Finally, we can say that absence of RV dysfunction (as evidenced by preserved tricuspid annular velocity) is the major characteristic sign for ICM in the present study with a cut point of 8.5 cm/s (or more) which has 88 % sensitivity and 93 % specificity. Another important measure is the ratio of tricuspid annular systolic velocity divided by averaged mitral annular systolic velocity with a cut point of 1.2 (> or = 1.2) which has 100% sensitivity and 95% specificity for diagnosing ischemic etiology of dilated cardiomyopathy.

Study limitations:

A limitation of velocity measurements by TDI is that these data may be affected by cardiac rotation or whole heart motion. Our study evaluated RV longitudinal systolic function in apical 4-chamber view only, evaluation of other views might be beneficial inspite of its technical difficulties.

Conclusion

Tissue Doppler echocardiography is a quantitative, reproducible and non-invasive diagnostic tool that could be complementary to clinical and standard echocardiographic findings in differentiating ischemic from primary dilated cardiomyopathy.

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PREDICTIVE VALUE OF TISSUE DOPPLER ECHOCARDIOGRAPHY IN DIFFERENTIATING PRIMARY DILATED CARDIOMYOPATHY FROM ISCHEMIC CARDIOMYOPATHY

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POSTOPERATIVE COGNITIVE DYSFUNCTION IN DIABETIC VERSUS NON DIABETIC PATIENTS: EFFECTS OF PERIOPERATIVE BLOOD GLUCOSE CONTROL REGIMENS

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Abstract

Introduction: *Increasingly, postoperative cognitive dysfunction (POCD) is recognized as a complication after non cardiac surgery in the elderly. Diabetes is considered an independent risk factor for POCD.*

Aim of the work (Objective): *This prospective, randomized study was designed to investigate the early and late post operative cognitive dysfunction (POCD) in patients with type 2 diabetes after major abdominal surgery with general anesthesia as a primary outcome. The possible effect of targeting intra operative blood glucose either more than 100 mg/dl or more than 150 mg/dl on POCD was the second outcome.*

Patients & Methods: *105 patients were enrolled for the study. 35 patients were allocated for non diabetic group. 70 patients were allocated for diabetic group. Diabetic patients were randomly assigned to continuous insulin infusion either (target glucose 100-150 mg/dl) or (target glucose 150-200 mg/dl). Patients undergoing different abdominal surgical procedures expected to be > 2 hours. Mini mental state examination (MMSE) test was administered 3 times: the day before surgery, postoperatively at 5- 7 day, and again 3 months later. The test was considered positive if change is more than 2S.D from basal.*

Results: *The rate of early POCD development was 31.4% in the non diabetic group and 50% in diabetic patients. On the other hand, the rate of late POCD development was 13.6% in the non diabetic group,*

36.9% in diabetic patients. Both MMSE1week scores and MMSE3month scores were insignificant when evaluated in the two diabetic groups.

Conclusion: *From the study we can conclude that, advancing age, duration of diabetes, postoperative pain and low education level were associated with early POCD while, advancing age and early POCD were risk factors for late POCD. No beneficial effect of the both intraoperative blood glucose control regimens among diabetic patients concerning performance in the (MMSE) test, while, duration of diabetes was the main determent of POCD occurrence.*

Key Words: *postoperative cognitive dysfunction (POCD); diabetes mellitus; perioperative blood glucose control.*

Introduction

The early study of Bedford (1955) on a retrospective observational report for old patients who underwent surgery and anesthesia, minor degrees of dementia were common in this group of patients and 7% experienced extreme dementia. This was the first published data about this issue [(1)].

The majority of researches on POCD had focused on cardiac surgery, but similar cognitive changes were reported with off pump cardiac surgery[(2)]. The study of POCD associated with non cardiac surgery is still in its infancy and the field is relatively new. The etiology of POCD and delirium is still not understood, but most of studies in this field agreed that a variety of medications can precipitate acute cognitive decline. Pre-existing patient factors as well as intra operative and post operative changes can be also involved e.g. age of patients, prior cognitive impairment, type of surgery, duration of anesthesia, and peri-operative hypoxemia and hypotension[(3)]. Postoperative pain and methods to manage associated with cognitive decline, so proper management of postoperative pain has particular interest to minimize its incidence[(4)].

Among patient related and preexisting factors, diabetes has been claimed for possible decline in cognition. Abnormalities in cognitive functions mediated by frontal lobe (executive functions), includ-

ing a number of complex behaviors such as problem solving, planning, organization, reasoning, and attention, are noted in patients with diabetes[5]. Diabetes is associated with rapid fluctuation of blood sugar and as the brain is dependent on continuous flow of glucose as it is the principle source of energy, changes of blood glucose concentration can rapidly affect cerebral function. Evidence is accumulating that diabetic patients are at high risk of developing cognitive impairment. This is probably a consequence of interaction between metabolic derangement associated with diabetes and functional changes of CNS as apart of normal aging process[6].

Sommerfield AJ and colleagues[7], reported that acute hyperglycemia impair cognitive performance in people with type II diabetes mellitus, so diabetic patients if exposed to stress of anesthesia and surgery might have different patterns of postoperative cognitive impairment. No previous trial investigates this issue before. In this study a prospective clinical trial was carried out to compare the POCD in diabetic and non diabetic group of patients following non cardiac surgery.

The association between acute hyperglycemia and impaired cognitive function[7], raised a second question, can control of blood glucose through continuous insulin infusion in perioperative period provide a protection against the expected decline in cerebral functions and minimizing the POCD in this group of patients or not?

Patients and Methods

After institutional approval, informed consents were obtained by all participants in this prospective trial.

- The first group (non diabetic group): ASA I & II surgical patients.
- The second group: type 2 diabetic patients.

Patients included in this group were divided randomly using computer generated, random lists according to blood glucose control regimen during the operation time into two subgroups.

1- Group $BG_{>100}$: the target blood glucose concentration was 100-150 mg/dl. If blood glucose

levels exceeded 150 mg/dl, a continuous insulin infusion was initiated. Adjustments to the insulin infusion were determined by both the current blood glucose concentrations and insulin infusion rates (8).

2-Group $BG_{>150}$: the target blood glucose concentration was 150-200 mg/dl. If blood glucose levels exceeded 180 mg/dl, a continuous insulin infusion was initiated. Adjustments to the insulin infusion rate [9].

During the intraoperative period, the infusion of dextrose was maintained at the rate 5 g/h for the both groups.

Inclusion criteria:

Adult patients of both sexes ranging in age from 50 to 70 yr were exposed to different abdominal surgical procedures expected to be > 2 hours and the duration of diabetes was not less than 4 years for the diabetic groups were included in the study.

Exclusion criteria:

Patients were excluded if they had a history of cerebrovascular disease with residual deficit, uncontrolled hypertension, alcoholism, psychiatric illness, cardiac disease defined as ejection fraction less than 50%, renal disease (defined as creatinine > 2 mg/dL), liver cirrhosis and liver dysfunction (defined by a serum total bilirubin concentration >2.0 mg/dL), less than six years of education, or certain types of surgery e.g. cardiac, carotid artery, thyroid or cranial surgery. Additional exclusion criteria included a score of 23 or less on the mini-mental state examination (MMSE) before surgery.

Preoperative management:

All patients were clinically examined and routine laboratory investigations for inclusion criteria were done before surgery.

Diabetic patients were preoperativelly controlled and the level of fasting blood sugar before the operation was below 150 mg/dl. Oral hypoglycemics and normal subcutaneous insulin were stopped 1-2 days before operation.

Anesthetic management:

Standard monitoring included

three-lead ECG, pulse oximetry, noninvasive arterial pressure measurements, and the measurement of end-tidal carbon dioxide, and anesthetic gas concentrations.

Analgesia was carried out either with preemptive single epidural injection of bupivacaine and fentanyl or intraoperative increments of intra venous fentanyl 20 ug every 30-40 min.

All patients received intravenous midazolam 0.03 mg kg^{-1}, fentanyl 1ug kg^{-1}, thiopentone sodium 5-6 mg kg^{-1}, and rocronium 0.6 mg kg^{-1} then 0.1 mg kg^{-1} when needed. Maintenance of anesthesia was carried out with Isoflurane with air and O_2 mixture Fio2 0.35. Residual neuromuscular block was antagonized with 0.04mg kg^{-1} neostigmine and 0.02mg kg^{-1} atropine at the end of operation.

Intra-operative data:

Blood glucose concentration was measured immediately after the induction of anesthesia and was repeated every 30 min. Hemodynamic data (heart rate and mean arterial blood pressure), were measured immediately before the induction of anesthesia and were recorded every 15 min.

Pos-operative data

1- Hemodynamics (heart rate and mean arterial blood pressure), and blood glucose level were recorded every 30 min for two hours in PACU.

2- Axillary body temperature.

3- Pain was estimated by using a 100-mm visual analog scale (VAS) (with 0 mm representing no pain and 100 mm representing the worst imaginable pain).

Cognitive test:

Mini mental state examination (MMSE) test (10), was administered 3 times: the day before surgery, postoperatively at 5- 7 day, and again 3 months later.

Statistical Analysis:

Power analysis was performed by G power program version 3.0.4.The sample size was based on estimated enrollment over 30 months period for diabetic patients exposed to 2 different blood glucose levels during major abdominal surgery and postoperative

cognitive dysfunction was studied as a primary outcome variant. A post. hoc power analysis showed that the study had 78% power to get effect size convention 0.3 at an α-error of 0.05.

The description of the data was done in form of mean ± SD, Frequency (proportion) and median (IQR). Kolmogorov Smirnov (K-S) test was used to test the normal distribution of data. One way ANOVA test was applied to compare demographic, preoperative and immediate postoperative investigations in the three studied groups. Kruskals- Wallis test was used for analysis of mini mental state examination (MMSE) scores followed by Mann- Whitney U-test for intergroup significant difference. Wilcoxon Rank Sum Test was used for intragroup difference. Chi- square test was applied for categorical data.

Factors found to be statistically significant from univariate analysis were fitted in a multivariable logistic regression model in a forward stepwise selection manner for analysis of independent risk factors of postoperative cognitive dysfunction in diabetic patients. Estimate of adjusted odds ratios (ORS), 95% confidence interval (CIS) and results of likelihood tests for significance were compared.

The statistical analysis of data done by using SPSS program (statistical package for social science Inc, Chicago, IL version 16). Statistical significance was considered at $p < 0.05$.

Results

This study was conducted on 105 adult patients of either sex, with an age ranging from 50 to 70 years, were exposed to different abdominal surgical procedures expected to be > 2 hours and the duration of diabetes was not less than four years for the diabetic patients. Patients of the three groups showed no significant differences concerning age, sex, BMI, levels of education, history of hypertension or smoking. Also patients of the two diabetic groups were comparable concerning duration of diabetes and their associated therapy (table 1).

Tables 2 and 3 show periopera-

tive investigations that include blood hemoglobin, hematocrit, serum sodium and serum potassium, serum creatinine, serum albumin and liver enzymes. There was no significant difference between the studied three groups whether in the preoperative or in the immediate post operative period.

As regard to the table 4, seven patients of $BG_{>100}$ group showed (1-2) episodes of blood glucose less than 65 mg/dl. However, only two patients in that group showed one and two events of blood glucose more than 200mg/dl. On the other hand, in $BG_{>150}$ group no patients showed blood glucose less than 65mg/dl and 9 patients showed episodes of blood glucose more than 200mg/dl. The hypotension was comparable in the studied groups.

Basal mini mental state examination (MMSE) score was significantly lower in the two diabetic groups when compared with the non diabetic group. The early MMSE1 week scores were significantly lower than basal in the three studied groups. However, late MMSE3 month scores after 3 months postoperatively were lower than basal MMSE scores but not reach statistically significant in the three studied groups. Both MMSE1 week scores and MMSE3 month scores were insignificant when evaluated in the two diabetic groups (table 5).

The rate of early POCD development was 31.4% in the non diabetic group and 50% in diabetic patients. On the other hand, the rate of late POCD development was 13.6% in the non diabetic group, 36.9% in diabetic patients distributed as 30% in the $BG_{>100}$ group and 43.4% in the $BG_{>150}$ group (table 6).

Table (7) shows univariate analysis of possible associated risk factors. Neither hypoglycemic, hyperglycemic nor hypotension episodes has significant risk factors for early (POCD). However, age >60 years, duration of diabetes >10 years, education level ≤ 12 years, anesthesia time >3 hours, post operative pain (VAS ≥ 30) are significant risk factors for early (POCD). These risky factors were fitted in the multivaria-

ble logistic regression model (table 8). Patients with age > 60 years had 2.6 time higher risk for early POCD development if compared with patients aged <60 years (CI 95% 1.047-6.004). Also patients with longer duration of diabetes had 2.3 times higher risk for early POCD development in comparison with duration of diabetes < 10 years (CI 95% 1.237-5.9). Additionally, patients who developed postoperative pain had higher risk for early POCD development (CI 95% 1.193-7.187). However, low education level reveals a strong association for early POCD development (CI 95% 1.193-7.187).

In univariate analysis of late POCD, neither hypoglycemic, hyperglycemic nor hypotension episodes has significant risk factors for POCD. However, age > 60 years, duration of diabetes > 10 years, education level ≤ 12 years and early POCD are significant risk factors for late (POCD) (table 7). These significant risk factors were entered in a multivariable logistic regression model (table 9). Patients aged > 60 years continue to have higher risk for POCD if compared with patients aged < 60 years (CI 95% 1.071-32.381). Also patients who developed early POCD had approximating 49 times higher rate for late POCD development (CI 95% 4.558-53.043).

Table 1. Patients Characteristics

	Non diabetic (n=35)	BG>100 (n=35)	BG>150 (n=35)	P value
Male sex (no, %)	22 (62.9%)	21 (60%)	17 (48.6%)	0.4
Age (years)	58.9±5.8	57.5±5.1	59.6±4.6	0.6
BMI (kg/m^2)	32.3±3.3	31.22±3.1	30.45±2.7	0.06
Education level (no, %) ≤ 12 yr > 12 yr	 24 (25.7%) 11 (31.4%)	 31(34.3%) 4 (11.4%)	 28(31.4%) 7 (20%)	0.1
DM Duration (years)		9.05±4	9.8±4.6	0.4
DM treatment (no, %) Oral Insulin		 22(62.9%) 13(37.1%)	 25 (71.4%) 10 (28.5%)	0.4
HTN (no, %)	19 (54.3%)	14(40.0%)	20 (57.1%)	0.3
Smokers (no, %)	9 (25.7%)	11(31.4%)	12 (34.2%)	0.7

Values are in no, (%) and mean ± SD, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension.

Table 2. Preoperative investigations; blood hemoglobin (Bl. Hb), Hematocrit (Hct), serum sodium ($S.Na^+$) and serum potassium ($S.K^+$) , serum Creatinine, serum albumin and liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST).

	Non diabetic (n=35)	**BG>100** *(n=35)*	**BG>150** *(n=35)*	*P*
Bl. Hb (gm/dl)	12.1±1.7	11.7±1.3	12.4±1.6	0.3
Hct (%)	39.1±5.1	36.7±4.7	37.6±4.5	0.1
S.Na+(meq/L)	137.9±3.2	136.7±3.4	137.7±4.0	0.3
S.K+(meq/L)	3.9±0.5	4.1±0.4	3.9±0.4	0.1
S.Creatinine (mg/dl)	1.0±0.3	1.1±0.3	1.1±0.4	0.6
S. albumin (gm/dl)	3.8±0.5	3.8±0.5	3.8±0.4	0.9
ALT (IU/ml)	23.6±16.1	27.8±14.1	24.8±13.7	0.5
AST (IU/ml)	24.3±15.7	29.8±21.3	24.1±13.8	0.3

Values are in means± SD

Table 3. Immediate postoperative investigations; blood hemoglobin (Bl.Hb), Hematocrit (Hct), serum sodium ($S.Na^+$) and serum potassium ($S.K^+$).

	Non diabetic (n=35)	**BG>100** *(n=35)*	**BG>150** *(n=35)*	*P*
Bl. Hb (gm/dl)	10.1±1.9	11.1±1.8	10.9±1.5	0.4
Hct (%)	35.5±5.7	32.5±5.6	33.6±7.6	0.1
S.Na+(meq/L)	135.2±3.4	133.7±3.8	135.6±3.4	0.06
S.K+(meq/L)	3.7±0.4	3.6±0.7	3.4±0.4	0.5

Values are in means± SD

Table 4. Perioperative events

	Non diabetic (n=35)	BG>100 *(n=35)*	BG>150 *(n=35)*	*P*
Intraoperative fluid transfusion Crystalloids (ml) Colloid (ml) RBCs (250ml/unit)	 3114.3±569.9 611.1±114 642.8±173	 3085.7±521.3 583.5±94 750±96	 3600.1±627.7 571.4±103 666.6±111	 0.9 0.76 0.43
Anesthesia time≥ 3 hours (no, %) Intraoperative UOP (ml)	 17(48.5 %) 635.7±249.8	 21(60%) 770.1±177.9	 19 (54.2 %) 687.6±205.8	 0.3
Postoperative body temperature(°C)	36.1±0.5	35.2±0.6	36.25±0.5	0.1
65 mg/dl ≤Perioperative BG (no, %) Events no. median(range)	-	7 (20%) 1(0-2)	0 0	0.005
Perioperative BG≥200mg/dl (no, %) Events no. median(range)	-	2 (5.7%) 1(0-2)	9 (25.7%) 1(0-3)	0.001
Perioperative MAP<60 mmHg (no, %) Events no. median(range)	3 (8.5%) 1 (0-2)	5 (14.3%) 1 (0-2)	4 (11.4%) 1(0-3)	0.9
Intra-operative analgesia Iv Fentanyl (no, %) Epidural (bupivacaine +fentanyl) (no, %) Post- operative Iv meperdine	 21(60%) 14 (40%) 9 (25.7%)	 6 (17%) 29 (82.8%) 11(31.4%)	 9 (25.7%) 26 (74.2%) 9 (25.7%)	 0.001 0.8

Values are in no., (%) and mean and SD.
UOP. urine output, MAP. Mean arterial blood pressure.

Table 5. Preoperative and postoperative mini mental state examination (MMSE) scores in the studied groups.

	Non diabetic	**BG>100**	**BG>150**
Patients no. $MMSE_{Basal}$	35 30 (29-30)	35 28* (26- 30)	35 27* (26- 28)
Patients no. $MMSE_{1week}$	35 28# (27- 29)	35 26# (23- 28)	35 24# (22- 26)
Patients no. $MMSE_{3\ month}$	22 30 (27- 30)	23 27 (24- 28)	23 26 (22- 27)

Values are in median and (interquartile range)
* Significant with non diabetic, # significant with basal.

Table 6. Rate of early and late postoperative cognitive dysfunction (POCD) in the studied groups.

	Non diabetic	BG>100	BG>150
Early POCD	11/35 (31.4)	16/35 (45.70%)	19/35 (54.30%)
Late POCD *	3/22 (13.6%)	7/23 (30.4%)	10 /23 (34.4%)

Values are no. (%),
* dropped cases: 13(non diabetic), 12 (BG 100), 12 (BG 150).

Table 7. Univariate analysis of risk factors of early (1 week) and late (3 month) postoperative cognitive dysfunction.

	1 week(n= 105)			3 month (n=68)		
Risk factor	Cognitive dysfunction (n= 46)	No Cognitive dysfunction (n= 59)	P value	Cognitive dysfunction (n= 20)	No Cognitive dysfunction (n= 48)	P value
Age > 60 yr	24 (52.2%)	8 (13.6%)	0.001	13 (65%)	12 (25%)	0.002
Male sex	30 (65.2%)	30 (50.8%)	0.1	14 (65.2%)	29 (60.4%)	4.5
BMI > 35(kg/ m²)	7 (15.2%)	8 (13.5%)	0.4	3 (15%)	6 (12.5%)	0.78
Diabetes duration ≥10 yr	24 (68.6%)	4 (11.4%)	0.01	12 (70.6%)	7 (24.1%)	0.002
Treatment :-						
Oral hypoglycemic	21 (45.6%)	26 (44.6%)	0.5	10 (60%)	19 (40%)	1.07
Insulin	14 (30.4%)	9 (15.2%)	0.4	7 (25%)	10 (20.8%)	0.6
12 yr≤Education level	43 (93.5%)	40(67.7%)	0.001	20 (100%)	35 (72.9%)	0.009
Hypertension	27 (58.7%)	26 (44.1%)	0.1	9 (45%)	15 (31.2%)	0.32
Smoking	17 (37%)	14 (23.7%)	0.1	6 (30%)	16 (33.3%)	0.78
Pain : VAS ≥ 30	31 (67.4%)	27 (45.8%)	0.03	15 (75%)	26 (54.2%)	0.11
anesthesia time > 3 hours	35 (78.3%)	22 (37.3%)	0.001	12 (60%)	24 (50%)	0.45
65 mg/dl≤BG	3 (6.5%)	4 (6.7%)	0.9	1 (5%)	4 (8.3%)	0.95
BG≥ 200 mg/dl	6 (13%)	5 (8.4%)	0.8	3 (15%)	6 (12.5%)	0.58
MAP < 60 mmHg	5 (10.8%)	7 (11.8%)	0.6	2 (10%)	15 (31.2%)	0.61
$POCD_{1\ week}$				19 (95%)	17 (35.4%)	0.001

Values are in no. (%)

Table 8. Multivariate logistic regression analysis of risk factors of early (one week) postoperative cognitive dysfunction.

Variable	B*	Exp(B)#	95% CI	P value
Age < 60 yr Age > 60 yr	1.012	2.6	1.047-6.004	0.05
Duration of diabetes < 10 yr Duration of diabetes > 10 yr	1.874	2.3	1.237-5.9	0.03
Pain : VAS <30 Pain : VAS ≥30	1.074	2.9	1.193-7.187	0.01
Education >level 12 yr level 12 yr≤Education	1.917	6.8	1.420-32.45	0.01

*: regression coefficient, #: relative risk, CI: confidences interval

Table 9. Multivariate logistic regression analysis of risk factors of late (3 months) postoperative cognitive dysfunction.

Variable	B*	Exp(B)#	95% CI	P value
Age < 60 yr Age > 60 yr	1.728	5.6	1.071-32.793	.042
No $POCD_{1week}$ $POCD_{1week}$	3.897	49.2	4.558-53.043	0.001

*: regression coefficient, #: relative risk, CI: confidences interval

Discussion

The current results indicate that advancing age, duration of diabetes, postoperative pain and low education level were associated with early POCD while, advancing age and early POCD were risk factors for late POCD. Also this study showed that, the rate of early POCD development was 31.4% in the non diabetic group and 50% in diabetic patients distributed as 45.70% in the $BG_{>100}$ group and 54.30% in the $BG_{>150}$ group. On the other hand, the rate of late POCD development was 13.6% in the non diabetic group, 36.9% in diabetic patients distributed as 30% in the $BG_{>100}$ group and 43.4% in the $BG_{>150}$ group.

In this study, basal MMSE score was significantly lower in the two diabetic groups when

compared with the non diabetic group. This finding is in accordance with previous study which studied 60 diabetic patients, amongst whom, 30 had a well-controlled diabetes status and the other 30 had not. These patients were compared to 60 non-diabetic controls whose age, sex and educational class matched with the individuals of the first group and concluded that, subjects with diabetes had lower MMSE score than those without diabetes [11]. While there were no significant differences between postoperative MMSE scores (MMSE1week and MMSE 3 month) in the two diabetic groups indicating that there was no beneficial effect of the two glucose control regimens concerning MMSE score. This may explained by the main determent of cognitive performance among diabetic patients is the long duration of the disease as shown in (table 7).

The present study demonstrated that, the rate of cognitive dysfunction was 31.4% at 1 week and 13.6% at 3 months after surgery in non diabetic patients. The results are nearly similar to the International Study of Postoperative Cognitive Dysfunction (ISPOCD1) which evaluated cognitive decline in 1,218 elderly patients, aged 60 yr or older, who had undergone major noncardiac surgery, and found that cognitive dysfunction was present in 26% of older patients 1 week after surgery and in 10% 3 months after surgery [12]. Dijkstra et al., [13] investigated the severity and character of postoperative cognitive dysfunction after major non cardiac surgery in patients older than 65yr at one week after surgery 27% of patients develop POCD and 8% of patients develop POCD three months after surgery which nearly similar to our results. In another study, 336 elderly patients (median age 69 years, range 60-86) was studied after major surgery under general anesthesia. Cognitive dysfunction was found in 80 out of 322 patients tested one week after surgery by the rate of 24.8%. At the 2nd postoperative test 3 months after the operation, cognitive dysfunction was found in 33 out of 326 tested patients by the rate of 10.3% which nearly similar to our result [14]. While the prevalence of cognitive dysfunction was 50% at

1 week and 36.9% at 3 months after surgery in diabetic patients. This finding is nearly similar to previous results documented that that rate of early POCD is 50% and rate of late POCD 23.3% in diabetic patients [15].

Our results show, advanced age has been identified as a risk factor for both early and late POCD development. This result runs parallel to Monk et al., [16] who studied one thousand sixty-four patients aged 18 yr or older completed neuropsychological tests before surgery, at hospital discharge, and 3 months after surgery. Patients were categorized as young (18-39 yr), middle-aged (40-59 yr), or elderly (60 yr or older) and concluded that the elderly patients had a higher incidence of POCD than the middle-aged patients. Also, similar results were reported by Bitsch et al.,[17] who studied one hundred hip fracture patients. Patients were tested upon admission and on the second, fourth and seventh post-operative days with the mini mental state examination (MMSE) score. Thirty-two per cent of patients developed a significant post-operative cognitive decline, and were documented that one of the main pre-operative predisposing factors was primarily found to be advanced age. Elderly patients may have preexisting conditions or limited cognitive reserve to cope with the physiologic challenges of anesthesia and surgery [18]. The aged human brain differs from the younger adult brain in several respects, including size, distribution and type of neurotransmitters, metabolic function, and capacity for plasticity, suggesting that it might be more susceptible to anesthetic mediated changes [19].

In our study, the duration of diabetes was a stronger determinant for early POCD development. This result in agreement with Roberts RO et al., [20] who were compared 329 subjects having mild cognitive impairment with 1640 subjects free of mild cognitive impairment and dementia. And founded that, cognitive impairment was associated with DM duration of 10 years or longer. Long duration of DM may be associated with greater cerebral macrovascular disease, clinical cerebral infarctions, and subclinical infarctions that may

impair cognitive functions [21].

In this study, patients with low education level had greater risk for early POCD development when compared to that high education level. Our study confirms the findings of ISPOCD1, which found that advancing age and lower educational levels are risk factors for the development of cognitive decline after noncardiac surgery [12]. One proposed theory for this relationship involves the concept of cerebral cognitive reserve; however, it is not clear how a greater number of years of education translates to a cognitive reserve. Education presumably increases the synaptic density in the neocortex by recruiting neurons, increasing neuronal communication, and minimizing the signs of cognitive and functional impairment. Thus the educational level serves as a marker of cognitive reserve [18].

In our study, postoperative pain carries risk for early POCD development. Our results are in agreement with those reported with Mann c et al., [22]. who conducted a study of comparison of intravenous or epidural patient controlled analgesia in the elderly after major abdominal surgery and concluded that, the epidural route using local anesthetics and an opioid provides better pain relief and improves mental status. Another study, demonstrated that the incidence of POCD at 1week was significantly lower in elderly patients undergoing minor surgery than major surgery and one of several factors may be important to explain differences in rates of POCD between major and minor surgery is postoperative pain [23].

In this study, hypotensive episodes during surgery have no influence on POCD development as MAP < 60 mmHge did not show any significant risk for early POCD development. This result in accordance with Williams-Russo et al., [24]. who evaluated the impact of intraoperative hypotension on POCD by studying a group of hypertensive patients undergoing major orthopaedic surgery. MAP was maintained at either 45-55 or 55-70mmHg, which was substantially lower than the patients' normal level, but no significant difference in the occurrence of POCD

was found. The first international study of postoperative cognitive dysfunction (ISPOCD1) revealed that perioperative hypotension (mean arterial pressure < 60% of basal for >30 minutes) was not significant risk factor for the development of POCD [12].

Additionally, Hypoglycemia BG ≥60 mg/dl carries no risk for POCD in our study. The usually short duration of hypoglycemia and the capability of the brain to use alternative substrates during hypoglycemia might explain this finding. This finding concluded by a study was investigated the effect of infusing lactate (a potential non-glucose fuel for brain metabolism) on protective, symptomatic neurohumoral responses and on brain function during hypoglycemic episodes. Lactate was associated with a significant lowering of the glucose level at which brain function deteriorated, suggesting that brain function was protected during the hypoglycemia [25].

Our data illustrate the duration of anesthesia more 3 hours was not found a significant risk for POCD. In contrast to the ISPOCD1 study, duration of anesthesia was a significant risk for POCD at 7 days. In that study the incidence of POCD at 1 week was 18% when the duration was less than 2 h and 27% when the duration was longer [12]. This difference may be attributable to the higher median age 68 (61-79) and longer duration of anesthesia which more than 241min in 33% of patients than in our study. Also Smith et al., (26) studied the mental function after general anaesthesia for transurethral procedures founded that duration of anesthesia (mean 30.9 min) was not a contributing risk factor for mental dysfunction after transurethral procedures in elderly patients and the risk of POCD probably increases when surgery lasts longer than 1 h. This may be explained by the difference of the surgical procedures of that study which may be play a role of cognition performance. Also this result is in contrast to previous study that investigated cognitive dysfunction 1-2 years after non-cardiac surgery in 336 the elderly patients after major surgery under general anesthesia that documented that 18% of patients whom duration of anesthe-

sia less than 120 min were not developed POCD at one week postoperative in contrast to 33% patients whom duration of anesthesia more than 240 min were developed POCD at one week postoperative [14]. This is may be attributed to the higher median age of patients of that study 69 years, range 60-86 y than in the current study and the duration of anesthesia at which POCD is more prominent was more than 4 hours

We found a significant correlation between early POCD (7 days postoperative) and late cognitive dysfunction (3 months later) and this result supported by a previous study documented that the patients with early POCD were at significantly greater risk for long-term cognitive dysfunction [14]. Surprising there is only one patient had late POCD without developing early POCD and this finding may be attributed to, some patients may be able to compensate for a period of time and then relapse into the group fulfilling the criteria for cognitive dysfunction [14].

From the study we can conclude that, advancing age, duration of diabetes, postoperative pain and low education level were associated with early POCD while, advancing age and early POCD were risk factors for late POCD. No beneficial effect of the both intraoperative blood glucose control regimens among diabetic patients concerning performance in the (MMSE) test, while, duration of diabetes was the main determent of POCD occurrence.

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POSTOPERATIVE COGNITIVE DYSFUNCTION IN DIABETIC VERSUS NON DIABETIC PATIENTS: EFFECTS OF PERIOPERATIVE BLOOD GLUCOSE CONTROL REGIMENS

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BCL10 PROTEIN EXPRESSION IN MALT LYMPHOMA

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Abstract

Mmucosa - associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell lymphoma. Chromosomal translocations t (1; 14) (p22; q32) resulting in BCL10 rearrangements have been identified in MALT lymphomas. The aim of this study is to evaluate diagnostic role of BCL-10 protein expression in MALT Lymphoma. Twenty six cases of extranodal MALT lymphoma of different organs (17 gastric, 4 salivary gland, 3 small intestine, one in thyroid and one in nasopharyngeal area) were collected from pathology laboratory of Gastroenterology Surgery Center and pathology department, Mansoura University during the period 2007 to 2011. All cases were reviewed and diagnosed as extranodal marginal zone lymphomas according to the recent criteria of the WHO. Additional 17 cases of lymphoid hyperplasia were included in the study. Immunohistochemical staining was performed. The following antibodies were used: CD20, CD3, Ig M and BCL10. MALT lymphoma cases showed lymphoepithelial lesion in 100% of cases, reactive follicles in 61.5%, colonized follicles in 34.6% and subepithelial sheeting of plasma cells in 19.2% of cases. In comparison, eleven of reactive cases showed lymphoepithelial lesion and seven of them were located in the nasopharengx. The remaining three nasopharengeal reactive lesions showed transmigrating lymphocyte. None of the reactive lesions showed colonized follicles or subepithelial sheeting of plasma cells. Centrocyte like cells predominated in 76.9% of MALT lymphoma cases, monocytoid cells in 35.2%, plasmacytoid cells in 11.5% of cases. Comparatively, the

reactive cases showed predominant lymphoplasma cellular infiltrate. All cases of MALT lymphoma were CD20 positive, CD3 negative. About 96% of MALT cases were IgM positive and about 85% of cases were BCL10 positive. The reactive cases were positive for CD20 and CD3 and negative for IgM except for only scattered positive plasma cells. A weak expression of the BCL10 protein was restricted to the cytoplasm of germinal centre cells and marginal zone cells. On the other hand, nuclear staining was not seen in the reactive cases. In conclusion, most MALT lymphoma express either strong nuclear or strong nuclear and cytoplasmic BCL10 protein. In contrast, benign lymphoproliferative disorders express no nuclear BCL10 staining. So, BCL10 may carry some diagnostic implications in assessment of MALT lymphoma.

Introduction

MALT lymphoma is a low-grade B-cell lymphoma, firstly, described by Isaacson and Wright [(1)]. MALT lymphoma represents the third most frequent subtype of Non Hodgekin lymphoma (NHL) B cell type (after diffuse large B-cell lymphoma and follicular lymphoma). It comprises about 7% of all newly diagnosed NHL [(2)].

Two types of MALT can be identified in disparate organs: native type consists of lymphoid tissue physiologically present in Peyer patches and tonsil, whereas acquired MALT develops in sites of inflammation in response to either infectious conditions, such as Helicobacter pylori gastritis, or autoimmune processes, such as Hashimoto thyroiditis. MALT lymphoma commonly involves the sites of acquired MALT and rarely in sites of native MALT [(3)].

Several genetic aberrations have been identified in MALT lymphomas, some of which appear to be specific for, or at least closely related to, this subtype of marginal zone (MZ) lymphoma. Chromosomal translocations t(1;14) (p22;q32), t(14;18) (q32; q21), t (11;18) (q21;q21) and t(3;14) (p13;q32) occur with variable frequencies in MALT lymphomas, resulting in BCL10, MALT1, API2-MALT1 and forkhead box protein P1 (FOXP1) rearrangements, respectively[(4)]. In contrast, both

mantle cell and follicular lymphomas generally don't show Bcl10 expression suggesting that deregulation of Bcl10 expression is unlikely to be involved in the development of these tumors [5, 6].

MALT lymphoma may be difficult to diagnose as there are common histological features with mucosa-associated lymphoid tissue, namely, prominent reactive-appearing lymphoid follicles, plasma cells, and transmigrating epithelial lymphocytes[7]. It is this category that benefits the most by using immunophenotyping. The aim of this study is to evaluate diagnostic role of BCL-10 protein expression in MALT Lymphoma.

Patients and Methods

This study was performed on 26 cases of extranodal MALT lymphoma of different organs. The cases were collected from pathology laboratory of Gastroenterology Surgery Center and pathology department, Mansoura University during the period 2007 to 2011. All cases were reviewed and diagnosed as extranodal marginal zone lymphomas according to the recent criteria of the WHO [8]. Additional 17 cases of reactive lymphoproliferative disorders were included in the study.

Immunohistochemical staining:

Immunohistochemical staining was performed using the avidin-biotin-peroxidase complex detection technique with DAB as chromogen. The following antibodies were used: CD20 (Monoclonal mouse, antihuman, code M0755, ready to use, DAKO Cytomation), CD3 (Monoclonal mouse, antihuman,code M7254, 1:50, DAKO Denemark), IgM (polyclonal rabbit, antihuman, code A0425, 1:250 DAKO Cytomation), BCL10 (Monoclonal mouse, antihuman, code M7260, 1:300, DAKO Cytomation). In brief, 4 mm paraffin sections were dewaxed in xylene and rehydrated in decreasing concentrations of ethanol. Slides were placed in citrate buffer ph 6.0 and heated using a microwave oven for 5 min to perform epitope retrieval. Incubation with the antibodies was carried out for 45 minutes. All incubation steps were followed by a wash in three changes of phosphate-buffered saline (pH 7.6).

Interpretation of immunohistochemical staining:

The results were interpreted in light of the appropriate staining of all positive and negative controls, compared with H & E slides. A brown precipitate at sites of specific cellular antigen localization indicates a positive reaction. The tissue reaction to specific stain considered negative when less than 10% of the tissue appeared stained. BCL10 appears as cytoplasmic and or nuclear brownish staining. It considered positive if the lymphoid infiltrate shows diffuse cytoplasmic and/or nuclear staining[6].

Results

Among the 26 cases of MALT lymphoma, 14 were females and 12 were males. The age ranged from 24 to 70 years with mean age 46 years. Seventeen cases (65.3%) were located in the stomach, 4 (15.4%) in salivary gland, 3 (11.6%) in small intestine, one case (3.8%) in thyroid gland and one (3.8%) in nasopharyngeal region. The reactive lymphoproliferative lesions were 17 cases with age ranging from 25 to 68 years with mean age 45.5 years. Ten cases (58.8%) were located in the nasopharyngeal region, 3 (17.7%) in the salivary gland, 2 (11.9%) in the stomach, one case (5.8%) in the small intestine and one case (5.8%). of cases in the thyroid gland (table1). Both two groups of cases didn't differ in the presenting clinical symptoms.

Microscopic features:

As showen in table (1), MALT lymphoma cases showed lymphoepithelial lesion in 100% of cases in which atypical lymphocytes infiltrate the epithelium with degenerative changes. Reactive follicles were seen in 61.5% of cases, colonized follicles in 34.6%, subepithelial sheeting of plasma cells in 19.2% of cases. In comparison, eleven of reactive cases (64.7%) showed lymphoepithelial lesion and seven of them were located in the nasopharengx. The remaining three nasopharengeal reactive lesions showed transmigrating lymphocyte. None of the reactive lesions showed colonized follicles or subepithelial sheeting of plasma cells.

The neoplastic cells presented a serial small cell lineage of centro-

cyte-like cell, monocyte-like B cell, plasmacytoid cell, with scattered centroblast like cells. In all MALT cases, the above cells were in a mixed distribution, but usually one type of cells was predominant. Centrocyte like cells predominated in 76.9% of cases, monocytoid cells predominated in 35.2%, plasmacytoid cells predominated in 11.5% of cases. Comparatively, the reactive cases showed predominant lymphoplasma cellular infiltrate.

Immunohistochemical results:

All cases of MALT lymphoma were CD20 positive (figure 1) and CD3 negative. Twenty four cases (96.2%) were IgM positive (figure 2). Twenty -two cases (84.6%) were BCL10 positive. BCL10 was expressed in two patterns (nuclear and cytoplasmic in 19 cases (figure 3, 4), exclusively nuclear in 2 cases, and strong cytoplasmic in one case. The reactive cases showed positive CD20 and CD3, negative IgM with only scattered positive plasma cells. A weak expression of the BCL10 protein, restricted to the cytoplasm of germinal centre cells and marginal zone cells. In none of the reactive lesions analyzed, nuclear staining was observed (Table 1).

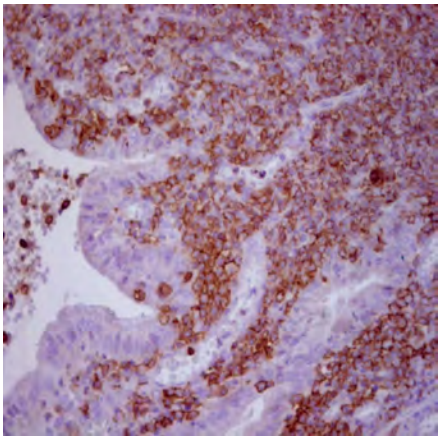

Fig. (1): Diffuse positive membranous staining for CD20. Lymphoepithelial cells formed by neoplastic B lymphocyte in gastric MALT lymphoma was seen (DAB x 200).

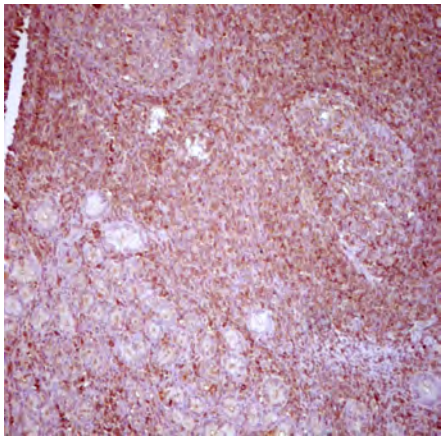

Fig. (2): Diffuse staining for IgM in gastric MALT lymphoma (DAB x 100).

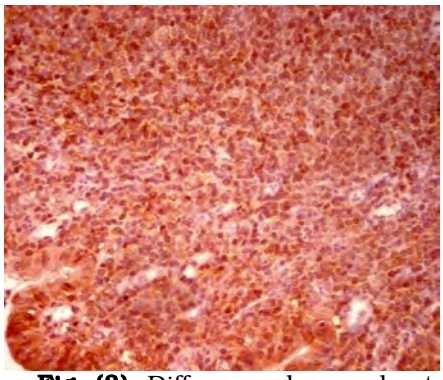

Fig. (3): Diffuse nuclear and cytoplasmic positive staining for BCL10in gastric MALT lymphoma (DABX 200).

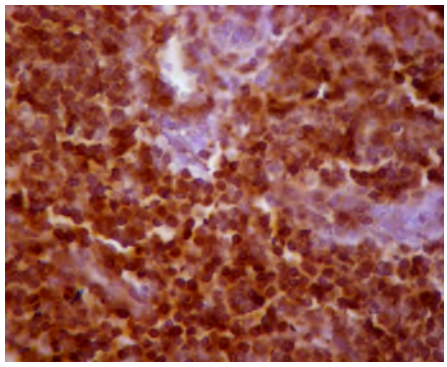

Fig. (4): Diffuse nuclear and cytoplasmic staining for BCL10 in salivary gland MALT lymphoma (DABX 400).

Table (1): Histopathological and immunohistochemical features of MALT lymphoma and reactive lesions

The histopathological and immunohistochemical features	MALT lymphoma 26 cases		Reactive lesions 17 cases	
	No	%	No	%
Site				
-Stomach	17	65.4%	2	11.9%
-Salivary	4	15.4%	3	17.7%
-Small intestine	3	11.6%	1	5.8%
-Thyroid	1	3.8%	1	5.8%
-Nasopharynx	1	3.8%	10	58.8%
Lymphoepithelial lesion	26	100%	11	64.7%
Reactive follicles	16	61.5%	15	88.2%
Colonized follicles	9	34.6%	0	0%
Subepithelial plasma cells	5	19.2%	0	0%
CD 20 and CD3				
- CD20 positive with or without scattered positive CD3	26	100%	0	0%
- Mixed both	0	0%	17	100%
Ig M				
-Diffuse positive	24	96.2%	0	0%
-Negative	2	3.8%	17	100%*
BCL-10 expression				
-Diffuse cytoplasmic and or nuclear staining	22	84.6%	0	0%
-Weak cytoplasmic staining	4	15.4%	17	100%

* only scattered positive plasma cells

Discussion

In this study, the stomach was the commonest site for MALT lymphoma while salivary gland was the prevalent extragastric site. These results are in agreement with the results of the study performed by Mokhtar and Khaled[9]. Different results recorded by Wohrer et al.[3] as 39% of their MALT lymphoma cases were gastric and 61% was extragastric. This is could be explained by high prevalence of H Pylori organism in Egypt[9]. In this study, only one case of MALT lymphoma was located in the nasopharyngeal area. Also, Menaarguez et al.,[10] reported only one case and Sagaert et al.,[6] reported four cases.

In this study, lymphoepithelial lesions were demonstrated in all MALT lymphoma cases and colonized follicle in about one third of cases. These results are in agreement with Issacson et al., [11] who reported that both lymphoepithelial lesion and follicular colonization are characteristic features for diagnosis of MALT lymphoma, but they could only be seen in some of the cases. Also, these results are in agreement with Cheng et al.,[12]. In this study, about half of the cases of nasopharyngeal reactive lymphoproliferative lesion showed lymphoepithelial lesion. Boyaka et al.,[13] reported that lymphocytes may infiltrate overlying epithelium but this does not indicate lymphoma at this site.

In the studied cases, centrocyte like cells predominated in about 80% of MALT cases and monocytoid B cells in about one third of cases. These results are in agreement with results obtained by Cheng et al.,[12] and Malikhova et al.,[14]. Lymphoplasmacytic differentiation was detected in 11.5% cases of our MALT lymphoma cases. Wohrer et al.,[3] and Malikhova et al.,[14] demonstrated somewhat higher percentage of plasmacytic differentiation in their series. This could be explained by higher percentage of extragastric MALT lymphoma cases in their series as plasmacytic differentiation is more common with extragastric MALT lymphoma[15]. The MALT lymphoma exhibiting plasmacytic differentiation explained by the capacity of post germinal center marginal zone cells (MZC) for diffe-

rentiation into plasma cells during the course of Bcell development. When plasmacytic differentiation is extensive, it can be confused with plasmacytoma [16].

In this study, CD20 and CD3 highlighted the proportion of B and T lymphocytes in the infiltrate and all MALT lymphoma cases showed extensive diffuse positive staining for CD20 with negative or scattered positive CD3 T cells. These results cope with almost of the previous studies[9,17]. The scattered positive CD3 cells in MALT lymphoma cases could be explained by the fact that B cells need to be in contact with the intratumoral T cells to receive costimulatory signals (CD40-CD40L) favor continuous proliferation[18,19].

In the present study, 96.2% of MALT cases expressed IgM. The remaining MALT lymphoma and reactive cases were completely negative apart from scattered positive plasma cells. These results are in agreement with Bacon et al,[16] who mentioned that MALT lymphoma express IgM mostly, IgA or IgG to lesser extent. The IgM negative cases could be probably explained by possible expression of other types of immunoglobulin like IgA or IgG [11,20].

In the present study, BCL10 exhibited two pattern of expression strong nuclear, strong nuclear and cytoplasmic in MALT lymphoma cases. Weak cytoplasmic staining were recorded in reactive cases. These results are of much higher incidence as compared to the data published by Sagaert et al.,[6] who documented that 66% of MALT lymphomas were positive. They described five patterns of BCL10 expression: an exclusive nuclear BCL10 expression, a combined nuclear and cytoplasmic BCL10 positivity, a perinuclear BCL10 expression, a strong diffuse cytoplasmic BCL10 expression, and a weak diffuse cytoplasmic BCL10 expression. They reported that the latter staining pattern did not differ in any way from the BCL10 expression in germinal centre cells and marginal zone cells in control tissues and was therefore not considered to be abnormal. Thus, presence of aberrant bcl-10 expression found by immunohistochemistry is helpful

in the diagnosis of MALT lymphomas and this finding might be an indication of an underlying genetic anomaly either involving the BCL10 or MALT1 gene. Ye et al.,[5] reported that t (1; 14)-positive MALT lymphoma cells have a strong BCL10 expression both in the cytoplasm and in the nucleus while normal marginal zone B cells present BCL10 cytoplasmic expression. Liu et al., [21] reported that more than half of MALT lymphomas without the t(1;14) also show moderate cytoplasmic and nuclear expression and the t (11;18) API2/MLT chimeric transcript might determine the abnormal subcellular localisation of BCL10. All t (11;18)-positive MALT lymphomas showed nuclear BCL10 expression, whereas only 23% without t (11;18) have detectable BCL10 in nuclei. Moreover, many studies stated that BCL10 has prognostic value in gastric MALT lymphoma as it is closely associated with advanced-stage diseases [5,7].

In conclusion, most MALT lymphoma expresses either strong nuclear or strong nuclear and cytoplasmic BCL10 protein. In contrast, reactive lymphoproliferative disorders express weak cytoplasmic with no nuclear BCL10 staining. So, BCL10 may carry some diagnostic implications in assessment of MALT lymphoma.

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Fig. (1): Diffuse positive membranous staining for CD20. Lymphoepithelial cells formed by neoplastic B lymphocyte in gastric MALT lymphoma was seen (DAB x 200).

Fig. (2): Diffuse staining for IgM in gastric MALT lymphoma (DAB x 100).

Fig. (3): Diffuse nuclear and cytoplasmic positive staining for BCL10in gastric MALT lymphoma (DABX 200).

Fig. (4): Diffuse nuclear and cytoplasmic staining for BCL10 in salivary gland MALT lymphoma (DABX 400).

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BCL10 PROTEIN EXPRESSION IN MALT LYMPHOMA

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ROLE OF GAMMA KNIFE IN MANAGEMENT OF SKULL BASE TUMORS

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Abstract

Background: *Skull base tumors arise from the cranial base or reach it, either from an intracranial or extra cranial origin. A diverse group, these tumors present unique management challenges because of their relative rarity, typically deep location, close proximity to critical neurovascular structures, and extension beyond classically taught anatomic and specialty boundaries. To decrease the morbidity associated with surgical resection of small sized tumors, gamma knife radiosurgery (GKS) was performed as an alternative in 50 patients with different types of skull base tumors to evaluate its safety and efficacy.*

Methods: *A review of 50 residual or unresectable skull base tumors treated with GKS between 2007 and 2011.*

Results: *The tumor volume decreased in 32 patients and stable in size in 14 patients with reduced central contrast enhancement indicating marked tumor necrosis and local tumor control, the rest 4 patients showed enlargement of the tumor size. all 18 pituitary adenoma patients (100% of pituitary adenoma) were had hormonal response (HR) after six months of gamma knife treatment and 16 patients with pituitary adenoma (88.88% of pituitary adenoma patients) were had hormonal normalization (HN) within 16 to 24 months after gamma knife treatment*

Conclusion: *The long term outcome following GKRS for many of skull base tumors treatment favourably compares with the results obtained by microsurgery, conventional radiotherapy.The apparently bet-*

ter results of GKRS in the treatment for skull base tumors should provide the impetus for even more aggressive application of this approach as a primary management of skull base tumors.

Introduction

Skull base tumors may originate from the neurovascular structures of the base of the brain and the basal meninges (e.g., meningioma, pituitary adenoma, schwannoma, paraganglioma), the cranial base itself (e.g., chordoma, chondrosarcoma), or the subcranial structures of the head and neck (e.g., paranasal sinus carcinomas). A unified classification system does not exist for the plethora of pathologies, some quite rare, that may affect this area of the brain (Table 1).

Tumor location is also the prime determinant of the surgical approach that is selected. Whereas location is the most important consideration for surgical planning, the tumor's biologic behavior dictates the need for, and order of, the various available therapies needed to optimize patient outcome. Some tumors, such as meningiomas and schwannomas, may require complete surgical excision only to optimize patient outcome. Pathologies such as paranasal sinus carcinomas may, however, require induction chemotherapy, surgical excision, and radiation therapy (RT) to achieve local control and possibly cure. In general, the outcome of surgery for basal tumors depends on the type, size, and location of the neoplasm, patient's age and general medical status, and extent of preoperative neurologic disability [1].

Stereotactic radiosurgery differs from open surgery insofar as stereotactic radiosurgery has no immediate cytoreductive role. Instead, the goal of radiosurgery is to change the biology of tumor cells so as to inhibit their proliferative potential. A successful outcome of radiosurgical treatment is therefore arrest of tumor growth, not disappearance of the tumor. Radiosurgery is therefore inappropriate for patients who are symptomatic from mass effect of tumors. Regardless of mass effect, however, another limiting aspect of radiosurgery is tumor size: Be-

cause external beam techniques can achieve only a limited degree of conformity, radiosurgical treatment of larger tumors may expose normal tissue to an unacceptably high level of radiation. Large tumors may require surgical debulking (ie, to reduce tumor volume) so that single-fraction radiosurgical treatment can be used [2].

Radiosurgery has been used extensively for treating benign tumors of the central nervous system. The most extensively developed data for radiosurgical treatments have pertained to treatment of acoustic neuroma (vestibular schwannoma) and meningioma of the skull base. The clear margins and discrete imaging characteristics of these tumors make them ideal candidates for radiosurgical treatment [2].

Radiosurgical treatment eliminates risks of blood loss, infection, anesthesia complications, and other perioperative risks. In addition, radiosurgery is administered on an outpatient basis, thereby eliminating the need for hospitalization, specialized care in the intensive care unit (ICU), and rehabilitation. For these reasons, radiosurgery is a compelling treatment alternative for many patients. For patients who are medically fragile or who cannot accept the potential complications of surgery (eg, risks inherent in blood transfusion), radiosurgery may be the only feasible treatment alternative [2].

In 1949, Leksell described a system, which concentrated radiation therapy on intracranial targets within the brain [3].

He conceived image guided, multiple, cross-firing, tightly collimated and small radiation portals "focusing" a high single radiotherapy dose on an intracranial target. His first clinical work was aimed at destroying intracerebral pathways in functional disorders and he coined the name stereotactic "radiosurgery" - a nickname which has endured. The early work was hampered by inadequate equipment, as only a 200 KV X-ray apparatus was available [3].

The concept was next furthered in 1968, again in Sweden .Gamma Knife; Electa Instruments AB, Lin-

ko¨ ping, Sweden is 201 fixed cobalt-60 sources, each a thin rod of 1 mm diameter, the long axis of which is oriented along a radius of a hemisphere – the helmet, into which the patient's head, within a stereotactic frame, fits. The centre point (or isocentre) of this hemisphere is the point at which them stereotactic co-ordinates of the mapped intracranial target are positioned [4].

Materials and Methods

Objective:

This thesis aims to present the response of skull base tumous treated with Gamma knife and evaluation the efficacy of gamma knife by clinical picture improvement and follow up with MRI imaging's to asses the role of gamma knife as a useful modality for treatment of primary, residual, recurrent skull base tumours or tumours in medically fragile patient can not stand the risk of open surgery.

Methods:

Fifty patients with skull base tumors with tumor size less than 3.5 cm in diameter are included in this study. These cases were brought to clinical attention in international medical center (IMC) in Cairo, during a period starting from January 2007 up to June 2011. This study contained 9 different types of pathological groups: chordoma, craniopharyngioma, gloms jugular tumor, nasopharyngeal carcinoma, acoustic neuroma, skull base meningioma and three pathological types of fuctional secretory pituitary adenoma which are prolactinoma, GH secreting adenoma and ACTH secreting adenoma. 4 patients harboring chordoma (8% of all patients), 2 patients harboring craniopharyngioma (4% of all patients), 4 patients harboring glomus jugular tumor (8% of all patients), 7 patients harboring skull base meningioma(14% of all patients), 14 patients harboring acoustic neroma (28% of all patients), 8 patients harboring GH secreting adenoma (16% of all patients), 6 patients harboring prolactin secreting adenoma (12% of all patients), 4patients harboring ACTH secreting adenoma (4% of all patients), so there were 18 patients of pituitary adenoma (36% of all patients), and one patient harboring nasophayngeal carcino-

ma (2% of all patients) (figure 1). All patients had serial MRI brain imaging at 6,12,24,36,48 months after gamma knife and follow up period ranged from 8 to 54 months (mean 31.9).

Radiosurgery technique:

The Elekta Leksell gamma knife was used for the treatment. Target localization was achieved using MRI performed with T1 axial and coronal-weighted sequence at 2 mm slice thickness with and without contrast, T1- fat saturation sequence and also T2 axial sequence was used to eliminate tumor edema. Treatment planning was performed with Elekta Leksell Gamma Plan. Treatment peripheral dose ranged between 10-30 Gy (mean 16.76) usually at 35% to 50% (mean 41.6%) isodose curve. The maximum dose to the adjacent brain stem area ranged between 10-12 Gy.

Results

Seventeen patients were treated surgically for there skull base tumors prior to gamma knife treatment, the rest of patients underwent gamma knife surgery as primary treatment. The age of the patients ranged between 13years and 69 years with mean and stander deviation is 42.6 ± 13.9. Twenty six patients were males (52% of all patients) and twenty four were females (48% of all patients).

All of the tumors that underwent GKS , the tumor diameter ranged between .5-3.5 cm. The tumor peripheral dose ranged between 10-30 Gy(mean 16.76) (table 2) usually at 35% to 50% (mean 41.6%) isodose curve (Table 3).

The follow up period ranged from 8 to 54 months (mean 31.9). All patients had serial MRI brain imaging at 6,12,24,36,48 months after gamma knife.

The tumor volume decreased in 32 patients and stable in size in 14 patients with reduced central contrast enhancement indicating marked tumor necrosis and local tumor control, the rest 4 patients showed enlargement of the tumor size (table 4, Figure 2).

In pituitary adenoma cases we

compared hormonal profiles pre and post gamma knife treatment to identify the hormonal control (HC) which either :

- Hormonal response (HR): decline the hormone to more than 50% of previous level before gamma knife treatment.
- Hormonal normalization (HN): reach the normal hormonal level after gamma knife treatment.

We found that, all 18 pituitary adenoma patients (100% of pituitary adenoma) were had hormonal response (HR) after six months of gamma knife treatment and 16 patients with pituitary adenoma (88.88% of pituitary adenoma patients) were had hormonal normalization (HN) within 16 to 24 months after gamma knife treatment (table 5).

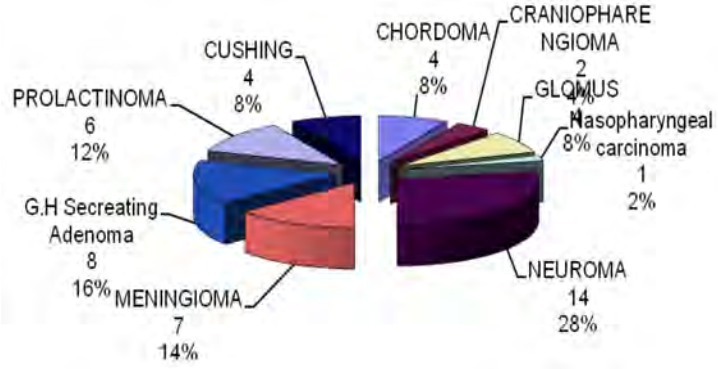


Figure (1) Pathological distribution of all lesions.

Table 1. Tumors of the Skull Base.

Site of Tumor Origin	Tumor Pathology
Basal neurovascular structures and meninges	Meningioma Schwannoma Pituitary adenoma Craniopharyngioma Paraganglioma Hemangiopericytoma
Cranial base	Chordoma Chondrosarcoma Osteosarcoma Plasmacytoma Metastasis
Subcranial with upward extension	Sinonasal carcinomas Olfactory neuroblastoma Juvenile angiofibroma Nasopharyngeal carcinoma Adenoid cystic carcinoma Primary sarcomas

Table. (2) peripheral dose (Gy) for tumors treatment with Gk

GRAY	N	Mean	Std. Deviation	Minimum	Maximum
CHORDOMA	4	13.8	1.5	12.00	15.00
CRANIOPHARYNGIOMA	2	10.0	0.0	10.00	10.00
GLOMUS	4	15.0	0.0	15.00	15.00
Nasopharyngeal carcinoma	1	13.0	0.0.	13.00	13.00
NEUROMA	14	12.6	1.3	12.00	15.00
MENINGIOMA	7	14.6	1.1	12.00	15.00
G.H Secreting Adenoma	8	23.9	1.6	22.00	25.00
PROLACTINOMA	6	20.7	1.6	18.00	22.00
CUSHING	4	24.0	4.0	22.00	30.00
Total	50	16.8	5.0	10.00	30.00

Table. (3) isodose curve for tumors tumors treatment with Gk

ISODOSE CURVE	N	Mean%	Std. Deviation	Minimum %	Maximum %
CHORDOMA	4	38.8	7.5	35.00	50.00
CRANIOPHARYNGIOMA	2	50.0	0.0	50.00	50.00
GLOMUS	4	35.0	0.0	35.00	35.00
Nasopharyngeal carcinoma	1	40.0	0.0.	40.00	40.00
NEUROMA	14	46.8	6.4	35.00	50.00
MENINGIOMA	7	37.1	5.7	35.00	50.00
G.H Secreting Adenoma	8	38.8	5.8	35.00	50.00
PROLACTINOMA	6	39.2	5.8	35.00	50.00
CUSHING	4	46.3	7.5	35.00	50.00
Total	50	41.6	7.2	35.00	50.00

Table (4) outcome after Gk knife treatment as regard tumor volume

	Local tumor control				Progression in tumor size		Total	
	Stable size of tumor		Shrinkage in tumor size					
	Count	%	Count	%	Count	%	Count	%
CHORDOMA	0	0%	0	0%	4	100.0 %	4	100.0 %
CRANIOPHARENGIOMA	0	0%	2	100%	0	0%	2	100.0 %
GLOMUS	0	0%	4	100%	0	0%	4	100.0 %
Nasopharyngeal carcinoma	1	100.0 %	0	0%	0	0%	1	100.0 %
NEUROMA	4	28.57 %	10	71.43%	0	0%	14	100.0 %
MENINGIOMA	3	42.9%.	4	57.1%	0	0%	7	100.0 %
GH-ADENOMA	2	25%	6	75%	0	0%	8	100.0 %
PROLACTINOMA	4	66.67 %	2	33.33%	0	0%	6	100.0 %
ACTH ADENOMA	0	0%	4	100%	0	0%	4	100.0 %
Total	14	28.0%	32	64%	4	8%	50	100.0 %

Table. (5) pituitary hormones response after Gk knife treatment

Tumor type	Hormonal control (HC)			
	Hormonal response (HR)		Hormonal Normalization(HN)	
	Count	%	Count	%
GH-ADENOMA	8	44.44%	8	44.44%
PROLACTINOMA	6	33.33%	4	22.22%
ACTH ADENOMA	4	22.22%	4	22.22%
Total	18	100%	16	88.88%

Table 6 Summary of GKRS based series for meningioma treatmen

Author	No. of patients	Follow up, range (median)	volume (cm3),range (median)	Marginal dose (Gy),range (median)	Tumour control rate (%)	Comp (%)
Kondziolka	50	6 to 34 (N/A)	N/A	10 to 25(16.7)	96	6
Duma	34	6 to 54 (26)	0.5 to 20.4 (5.17)	10 to 20 (16)	100	20
Ganz	20	12 to 27(N/A)	N/A	5.1 to 28.5 (N/A)	80	0
Nikolato	50	4 to 31 (14)	0.6 to 20 (8.6)	10 to 28 (18)	98	6
Liscak	53	2 to 60 (19)	0.9 to 31.4 (7.8)	10 to 14 (12)	100	13
Iwai	24	6 to 36 (17.1)	0.1 to 28.6 (11)	8 to 15 (10.6)	100	4
Morita	88	12 to 83 (35)	N/A (10)	12 to 20 (16)	98	14.8
Nakaya	11	21 to 57 (35.7)	1.6 to 28.9 (7.1)	9.9 to 10 (10)	100	9
Kondziolka	99	60 to 120 (N/A)	0.24 to 24 (4.7)	9 to 25 (16)	93	13
Aichholzer	46	36 to 76 (48)	N/A	9 to 25 (15.9)	97.5	4.3
Pendl	164	25 to 97 (55)	0.5 to 89.9 (8.3)	7 to 25 (12)	98	1.8
Kobayashi	54	60 to 108 (84)	N/A	N/A (14.5)	89	5.5
Eustacchio	121	60 to 117 (82)	0.5 to 89.9 (6.8)	7 to 25 (13)	98.3	3.3
W Kreil et al	200	60 to 144 (95)	0.38 to 89.9 (6.5)	7 to 25 (12)	97.5	2.5
Current study	7	11 to 48(27.1)	N/A	12-15(14.6)	100	0

Table 7 Clinical results of published large series of acoustic neuromas treated with gamma knife

Centre [ref]	Number of patients	Follow up (months)	Tumour volume (cm3)	Tumour control	Peripheral dose(Gy)	Persisting facial paresis	Persisting trigeminal symptoms	Hearing preservation
Charlottesville	153	51	2.7	94%	13.2 Gy	1%	1%	40%
Graz	192	62		98%	12–14Gy	1%	1.5%	62%
Pittsburgh	190	30	2.7	97%	13 Gy	1%	2.5%	71%
Tokyo	138	37	1.8	91%	15.4 Gy	6.5%	25%	58%
Rowe J el al, 2002	238	35	3.7	92-97%	14.6 Gy	1%	1.5%	75%
Current study	14	37.4	Na	100%	12.6Gy	0	0	85.71%

Figure (2 A) Gk treatment protocol for a case with glomus tumor

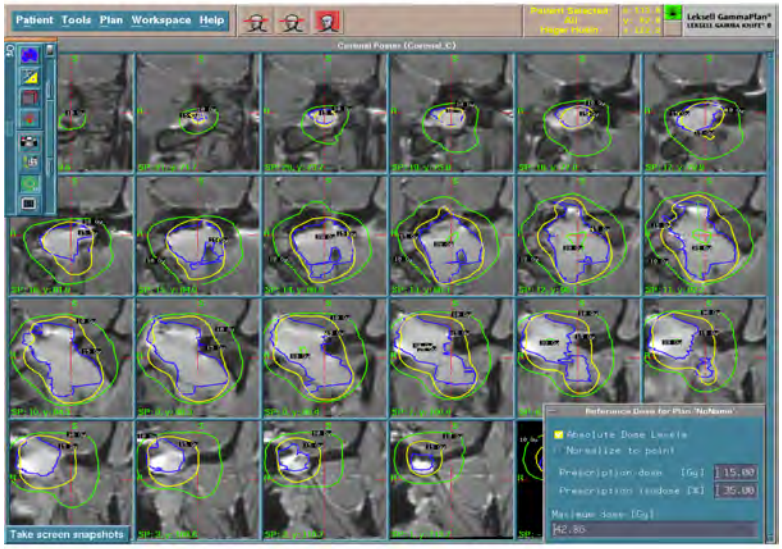
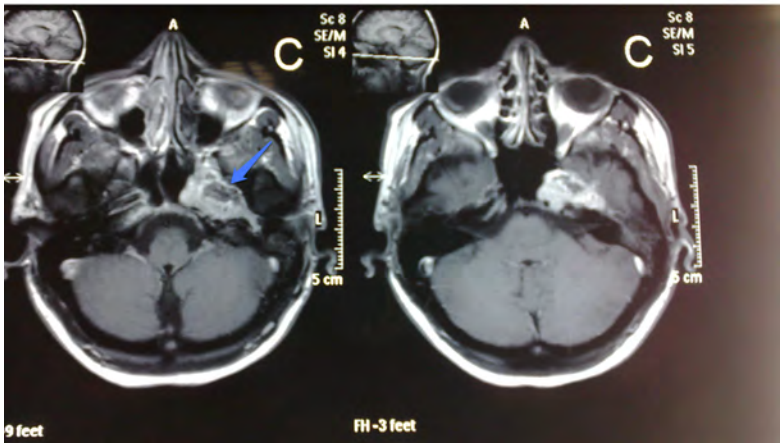


Figure (2 B) Follow up MRI of the treated glomus jugulare tumor



Discussion

As regard skull base meningioma , within the past few years, GKRS has begun to play an increasingly important role as a non-invasive alternative therapeutic modality for patients with skull base meningiomas. Excellent results were related in the early to interim gamma knife series (table 6) [5,6,7,8,9,10,11,12,13].

As regard Glomus jagulare tumors which is radioresistant, radiation has been found to be helpful in controlling tumor growth by inducing fibrosis around the supplying vessels [14,15,16].

In a study by Pollock (2004) GKS was used as the primary management in 19 patients and for recurrent glomus jugulare tumors for 23 patients. Of these, 12 tumors (31%) decreased in size, 26 (67%) remained unchanged, and one (2%) grew. The patient whose tumor grew underwent repeated GKS. Progression-free survival after GKS was 100% at 3 and 7 years, and 75% at 10 years. Six patients (15%) experienced new deficits (hearing loss alone in three, facial numbness and hearing loss in one, vocal cord paralysis and hearing loss in one, and temporary imbalance and/or vertigo in one). In 26 patients in whom hearing could be tested before GKS, hearing preservation was achieved in 86% and 81% at 1 and 4 years post treatment, respectively [17].

In our study , GKS was used as the primary management in 3 patients and for recurrent glomus jugulare tumors for one patient. All our patients showed shrinkage in their tumor size with local tumor control and this closely similar to Pollock [17] study.

As regard acoustic neuroma, the results reported here are a tumor control rate of 100%, shrinkage in 71.43% combined with a 85.71% hearing preservation rate, and a risk of persisting trigeminal neuropathies of 0%. It is possible that careful patient selection was the cause of these results.

These results are broadly close to those reported by other radiosurgery groups (table 7), although there are differences both in complication rates and tumour

control rates [18,19,20,21,22].

As regard the treatment of pituitary adenomas, radiotherapy is classically indicated in cases of incomplete resection or recurrent tumors, functioning tumors uncontrolled by medical therapy and patients inoperable or who refuse surgery. The objectives of radiotherapy are the control of tumor growth and/or the normalization of hormonal secretion, the maintenance of pituitary function and preservation of neurological function, especially visual acuity.

In a recent review, Prasad reported a control rate of tumor growth 67-100% with conventional radiotherapy [23].

Brada et al., reported tumor progression-free survival at 10 and 20 years of 94% and 89%, respectively [24].

The various retrospective series with RS published to date have shown the same results as conventional radiotherapy.

Sheehan et al.[25] in an extensive review of 1283 patients showed a mean tumor control rate of 96%. Considering only the series with mean or median follow-up of 4 years or more, the control ranged from 83 to 100%. Importantly, in all cases, control was defined as the persistence or reduction of tumor volume, as in our study.

The reduction in tumor volume, as observed in 12 cases in our series (66.67%), with 100% tumor control which is closely similar for that which reported by others.

In our study, we found hormone normalization in 100% of patients with Cushing's disease, 100% of acromegalic patients and 75% of patients with prolactinoma.

When we compare our results with recent retrospective series of patients treated with the RS and criteria for radiological control and hormonal defined and similar, we observe similar results.

Petrovich et al.[26] reported a median time to normalization of hormonal 22, 18 and 24 months for patients with tumors that pro-

duce ACTH, GH and PRL, respectively. In our series, we observed a median time to hormonal normalization of 24, 18 and 24 months respectively.

Choi et al.[27] reported a mean time to hormonal normalization of 21 months (2.8-59.1 months) and actuarial incidence of hormonal normalization at 1 and 3 years of 16.1% and 37.6%.

More recently, Niranjan et al. (28) reported that the overall survival rate following GKS was 97.5% at 5 years, and the 3- and 5-year local tumor control rate (for solid portion of tumor control) were both 91.6% based on their long-term follow-up (mean 62.2 months) of 46 patients. The goals set by them were pathological confirmation, surgical decompression of optic chiasm, neural and endocrine preservation, and long-term tumor control.

In our current study, the local tumor control rate were 100%. Our results are closely similar to Niranjan et al. [28], but we are different to Hasegawa et al. [29] demonstrated a 5- and 10-year PFS of 62 and 52%, respectively, in their 100-patient cohort.

The reasonable explanation for the above discrepancies could be attributed to small number of patients in our series. As regard nasopharyngeal carcinoma, stereotactic radiotherapy has occasionally been employed for NPC recurrence; the majority of cases have used linear accelerator-based methods. In such a series of three patients, one remained disease-free 1 year after radiosurgery, one had neurological deterioration 6 months after treatment, and one had recurrence 6 months after radiosurgery [30].

Gamma Knife radiosurgery has previously been used in a small number of patients with NPC both at recurrence and as a primary treatment. Treatment was found to be effective for a short period of time but reported follow-up periods are brief [31].

The 2-year follow-up of O'DONNELL et al.[32] first patient treated withGamma Knife has been event free. No clinical evidence of recurrence has manifest and, reassur-

ingly, a recent PET scan has not shown any FDG uptake in the nasopharynx, or indeed elsewhere, to suggest recurrent disease. In the second case presented, treatment also appears successful, albeit with shorter follow-up.

In our study, we are similar to O'DONNELL et al.[32] results as our single patient with NPC were event free in 4 year follow up.

In our current study. We treated skull base chordoma with failure of tumor control in all four patients, two tumors were stable in their size just for 18 months and then there were progressed in their size, the other two patients showed progression in their tumors in their first year of treatment without sign of central tumor necrosis which is different to Liu et al [33] who showed tumor control rate 64.2 % and 21.4% after 3 and 5 years, respectively on their 32 patients of skull base chordoma treated with gamma knife radiosurgery.

This difference in results may related to our few cases in our current study, but in Liu AL et al. we found that their were declined in the tumor control rate with long follow up time (21.4% at 5 years) which correlated with radio resistant nature of skull base chordoma.

On the other hands all skull base chordoma patient complained from symptoms due to tumor mass effect which were not prospected to respond to gamma knife radiosurgery as the aim of this type of treatment was the local tumor control, So we advise to surgical intervention rather than gamma knife radiosurgey for this type of skull base tumors.

Conclusion

The long term outcome following GKRS for many of skull base tumors treatment favourably compares with the results obtained by microsurgery, conventional radiotherapy.The apparently better results of GKRS in the treatment for skull base tumors should provide the impetus for even more aggressive application of this approach as a primary management of skull base tumors.

With regard to the possibility of

an additional radiosurgical approach to residual tumours and the excellent results, following combined microsurgical- radiosurgical treatment, the objective of surgical treatment of skull base tumors should be preservation of function and of as much normal tissue as possible, rather than radical resection. Patients harbouring recurrences of skull base tumors should receive GKRS rather than undergo repeated open resection.

In patients with advanced age, significant concomitant medical problems, high risk tumour location or patients who are not willing to undergo an open microsurgical procedure, we would recommend performing GKRS as a safe and effective alternative primary treatment modality, with close and frequent clinical and neuroradiological follow up.

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ROLE OF GAMMA KNIFE IN MANAGEMENT OF SKULL BASE TUMORS

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IMMEDIATE MATERNAL AND NEONATAL MORBIDITY ASSOCIATED WITH VACUUM EXTRACTOR DELIVERY, AT UNIVERSITY TEACHING HOSPITAL EXPERIENCE

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Abstract

Objectives: *to compare the immediate maternal and neonatal morbidity associated with ventouse delivery at full cervical dilation in a teaching hospital in the western region of Saudi Arabia with those reported in the literature.*

Material and Methods: *A retrospective case study of 436 women, who had term, singleton, cephalic pregnancies requiring operative delivery at full cervical dilatation for 6 year period. . Maternal morbidities' including the presence of genital tract tears and lacerations, extended episiotomy post partum hemorrhage, the need for blood transfusion and emergency cesarean section were studied. Neonatal outcome evaluations were Apgar scores, neonatal intensive care unit admissions, cephalohematomas, instrument marks and bruising, intracranial hemorrhage and bone fractures.*

Results: *During the study period 436 women had vacuum assisted vaginal delivery at King Abdul-Aziz university hospital. The success rate for vaginal delivery was 91.1%, the majority of patients were primgravidas 64.7%.The most frequent indication was fetal distress. Seventy five percent of cases had episiotomy, 12.4% had perineal tears, 5.5% were third and fourth degree tears .The neonatal outcome showed that 19 % of all newborns hat at least one complication, the commonest complication was cephalohematoma that occurred in 14.4% of the neoborns, 8.9% of the neonates were admitted to Special care baby unit or neonatal intensive care unit.*

Conclusions: *The rate of Soft tissue injuries associate with vacuum extraction is comparable with the literature. There is higher failure rate for the procedure. The commonest reported maternal complication is perineal tears and the most frequent neonatal complication is cephalohematoma.*

Key words: *Ventouse, Instrumental delivery, cephalohematoma, maternal and neonatal rabidity.*

Introduction

In the middle of the nineteenth century a Swedish obstetrician, Malmström T (1957), introduced a stainless steel metal cup for vacuum assisted delivery to the clinical practice. Suction tubing attached to the dome of the cup and a traction chain passed through the tubing subsequently added to form the currently available vacuum extractor systems Miksovsky, P, et al (2001), Vacca, A (2004).

In the developed countries 4.5 percent of the vaginal deliveries are achieved by instrumental deliveries including vacuum extractor (ventouse) and obstetric forceps, however the number of vaginal deliveries conducted by vacuum extractor has been increasing in the last few decades and is now four times the rate of obstetric forceps with 0.8% with forceps assisted and 3.7% vacuum assisted deliveries [15].

By 1992, in the United States the number of vacuum assisted deliveries surpassed the number of forceps deliveries, and by 2000, approximately two-thirds of operative vaginal deliveries were by vacuum [8]. Generally the vacuum devises are safer than obstetric forceps for the mother, easier to apply, place less force on the fetal head, require less anesthesia and results in less maternal soft tissue injury compared to forceps. The maternal and fetal outcome depends on many confounding variables including parity, experience of the operator, the type, size and position of the cup. It also includes the head position and station during the application as well as the appropriate patient's selection. Complications of the vacuum may affect the mother and the neonate. This retrospective chart re-

view study was designed to test the immediate maternal and neonatal outcomes in teaching tertiary care center.

Patients and Methods

This is a retrospective chart review study of all cases of ventouse delivery at King Abdul-Aziz university hospital in Jeddah Kingdome of Saudi Arabia which is the largest teaching hospital in the western part of Saudi Arabia during the period between January 2000 till the end of December 2005 .All women who delivered a singleton fetus in vertex presentation at full cervical dilation were included. Women who delivered by elective cesarean section, or had multiple pregnancies were excluded. Medical records of those women were retrieved and data of the outcome were collected in SPSS spread sheet.

Maternal demographic data included age, nationality, parity; gestational age and booking status are reported.

Risk factors associated with pregnancy including medical complications of pregnancy, oligohydramnios, premature rupture of membranes, intrauterine fetal demise, infertility, previous cesarean section were examined.

Data regarding the onset of labor, the use of oxytocin and the indication for instrumental delivery were also collected. The course of delivery including fetal head position and the presence of caput or moulding.

Maternal morbidity including extended episiotomy vaginal lacerations, perineal 1^{st} 2^{nd}, 3^{rd} and 4^{th} degree tears, paraurethral tears and lacerations, urethral hematoma, cervical tears, postpartum hemorrhage , blood transfusion, disseminated intravascular coagulopathy and failure of the procedure ending by cesarean delivery were reported.

Neonatal outcomes evaluated were Apgar scores, birth weight, shoulder dystocia neonatal intensive care unit admissions, special care baby unit SCBU admission, birth asphyxia, respiratory distress syndrome (RDS), cephalohematomas, instrument marks and bruising, intracranial hemorrhage,

brachial plexus injury, skull fractures, long bones fractures, neonatal seizures.

All maternal and neonatal data were collected and statistical analysis was done using SPSS version 16.

Results

During the study period between January 2000 till December 2005, 24643 women gave birth in King Abdul-Aziz University hospital, Jeddah, Kingdome of Saudi Arabia. Four thousands and sixty six (4066) women delivered by elective cesarean section, 344 had breech delivery and 403 women had multiple pregnancies these women were excluded from any further analysis as they do not fulfill the inclusion criteria's.

The total number of instrumental deliveries was 455with a rate of 1.9%, 436 were ventouse and only 19 women had low forceps deliveries indicating that for each 22 venouse delivery there is one forceps delivery, the rate of cesarean section during the study period was 16.5%.

Forceps deliveries were excluded from any further analysis and the four hundred and thirty six ventouse deliveries were statistically analyzed.

The maternal age among the vacuum delivery group, range between 16 and 49 years with a mean of 26 years +2SD.

The majority of the women (62%) were Saudi, the non Saudi represented (38%). Out of the 436 women who had ventouse delivery (358, 82%) were booked and (34, 18%) unbooked, the gestational age range from 37 to 42 weeks with a mean gestational age at delivery of 38 weeks.

Two hundred and eighty two (282, 64.7%) women were primigravidas and one hundred fifty four (35.3%) were multiparous women.

Exploring the risk factors for the women who delivered by ventouse revealed that 37 women (8.5%) had a previous cesarean and planned to have vaginal birth after cesarean section (VBAC), ten women 2.3% had

gestational diabetes mellitus, 9 women 2.1% had a history of infertility, 9 women 2.1% were known to have cardiac disease and (8, 1.8%) women presented with premature rupture of the membranes.

Regarding the onset of labor 370 (84.9%) cases had spontaneous onset, out of those 333 (90%) had successful ventouse vaginal delivery, 37 (1%) failed of which 9 had forceps delivery and 28 delivered by cesarean section.

Sixty six women (15.3%) were induced for obstetrical indications. 44 women (10.1%) had prostein induction, 2 (0.5%) women induced with propess and 20 (4.6%) women induced by artificial rupture of membranes and oxytocin.

One hundred thirty nine women (31.9%) needed augmentation during labor. Of those women 122 (87.8%) had successful vaginal vacuum delivery and 17 (12.2%) failed ventouse and ended by cesarean section.

The indications for instrumental deliveries were as follow 261 (59.8%) fetal distress,82 (18.8%) poor maternal effort,78 (17.9%) prolonged second stage and 15 women (3.4%) to shorten the second stage of labor because of medical condition.

The success rate in fetal distress 246 cases (94%), in prolonged second stage 60(77%), poor maternal effort 71(86.6) and shortening second stage 15(100%) Tab 1.

The overall success rate for women who had ventouse delivery was (90.1%). Sixteen women (3.7%) had forceps after failed ventous with successful vaginal delivery and 38, 8.7% women had emergency cesarean section.

Fetal head position was reported in 157 patients only, 99 were occipito- anterior, 32 were occipito- posterior 26 occipito- transverse.Vaginal assisted vacuum delivery was more successful if the head position was occipito anterior 87%, followed by occipito-transverse 34% and the least successful was occipito-transverse 23%.

Maternal outcome showed 328 (75.2%) women had episiotomy. Seventy eight women had soft tissue injury during the assisted delivery with a prevalence of (17.9%). Fifty four women (12.4%) had perineal tears as follow, 19 had first degree tear, 12 second degree, 22 third degree and one patient had fourth degree tear.14 women (3.2%) had lateral vaginal tear, 2 cases paraurethral tear, one case of extended episiotomy and one case of urethral hematoma.5 women (1.4%) had cervical tear needed repair under anesthesia. One patient with previous cesarean had rupture uterus which was repaired under general anesthesia.

Twenty eight women (6.4%) had post partum hemorrhage, three patients needed blood transfusion and one developed DIC. One woman was admitted to the intensive care unit after severe postpartum hemorrhage. 40 women (9.2%) had intact perineum Tab 3.

Nine women had shoulder dystocia with favorable outcome except for one case who had clavicular fracture.

The neonatal outcome showed sixty three cases (14.4%) of cephalohematoma, fifteen cases (3.4%) of scalp lacerations, five cases (1.1%) of birth asphyxia, two cases of Erbs palsy, 2 developed RDS, one clavicular fracture, one case of meningitis, one subdural hematoma, one neonate developed neonatal seizures., one cut wound on the scalp and One neonate had multiple bruises on the body. 24 (5.5%) babies were admitted to the special care baby unit SCBU and 15 (3.4%) were admitted to the NICU. Two babies were still born due to causes that are not related to the instrumental delivery.

Table 1: the success rate of vacuum assisted delivery according to the indications

Indication	Number of cases	Number of successful cases	Success rate
Shortening second stage	15	15	100%
Poor maternal effort	82	71	86.6%
Fetal distress	261	246	94%
Prolonged second stage	78	60	77%
Overall vacuum deliveries	436	392	90.1%

Table 2: the success rate of vacuum assisted delivery according to the fetal head position

Fetal head position	Number of cases	Number of successful cases	Success rate
Occipito-anterior	99	86	87%
Occipito-posterior	32	11	34%
Occipito-transverse	26	6	23%

Table 3: Maternal complications associated with vacuum assisted vaginal deliveries.

Maternal complications	Number of cases	Percentage
First degree tear	19	4.4%
Second degree tear	12	2.75%
Third degree tear	22	5%
Fourth degree tear	1	0.23%
lateral vaginal wall tear	14	3.2%
Paraurethral tear	2	0.46%
Extended episiotomy	1	0.23%
Urethral hematoma	1	0.23%
Cervical tear	5	1.1%
Rupture uterus	1	0.23%
Post partum hemorrhage	28	6.4%
Blood transfusion	3	0.69
DIC	1	0.23%
ICU admission	1	0.23%

Table 4: Neonatal complications associated with vacuum assisted vaginal deliveries.

Neonatal complications	Number of cases	Percentage
Cephalohematoma	63	14.5%
Scalp lacerations	15	3.4%
Birth asphyxia	5	1.1%
Erbs palsy	2	0.46%
RDS	2	0.46%
Clavicle fracture	1	0.23%
Meningitis	1	0.23%
Subdural hematoma	1	0.23%
Neonatal seizures	1	0.23%
Cut wound on the scalp	1	0.23%
Multiple bruises on the body	1	0.23%
Admission to NICU	15	3.4%
Admission to SCBU	24	5.5%+
Still birth	2	0.46%

Discussion

Assisted vaginal birth is commonly used to expedite birth for the benefit of either mother or baby or both. It is sometimes associated with significant complications for the mother and her baby. The choice of instrument may be influenced by clinical circumstances, operator experience and choice and availability of specific instruments.

The increasing risks of failed delivery with the chosen instrument from forceps to metal cup and the risks for the maternal and neonatal trauma need to be considered when choosing an instrument[19]. A recent review by[13] in an obstetrical unit in the united Kingdome over ten years period, showed increasing preference for the ventouse over forceps ratio from 0.2:1 in favor of forceps to 1.9:1 in favor of ventouse over the decade ($p = 0.002$). In the current study the use of vacuum extractor for assisted vaginal delivery surpasses forceps significantly, over the study period only 19 women delivered using forceps with ventouse to forceps ratio of 22:1, these findings are alarming and indicating that residents in training are not gaining enough skills to perform forceps assisted vaginal deliveries this issue should be addressed and appropriate steps should be taken to ensure that

residents are getting enough training In assisted vaginal deliveries particularly forceps deliveries.

In the same study by Loudon an increasing failures of operative vaginal delivery, especially using the ventouse and reduced attempts at instrumentation was observed [13].

In concurrence with the Loudon report, our study showed that the rate of instrumental delivery was noticeably lower than what was reported in the developed countries being only 1.9 % compared to 4.5 in the united state [14], this is probably because of reduced attempts of assisted vaginal delivery.

In a study from developing country by Nkwabong et al(2011) to assess the prevalence, indications, neonatal wellbeing and maternal complications of instrumental deliveries, of 3623 vaginal deliveries, 84 (2.3%) instrumental deliveries were conducted these figures are similar to our figures of 1.9% instrumental deliveries. They reported a low rate of maternal complications including vaginal and perineal tears.[18] The neonatal outcome was based on Apgar score only and concluded that Instrumental delivery should be encouraged. The limitation of their study was the small number of patients and the limited neonatal outcomes they reported.

In the current study only vacuum assisted deliveries were studied with a total of 436 women and the neonatal outcome was examined in detail.

Regarding the early neonatal outcome assessment, Benedetto et al (2007) studied women with antenatally normal singleton pregnancies at term, who underwent instrumental vaginal delivery (no. 201), spontaneous delivery (no. 402), planned caesarean section without labor (no. 402) and caesarean section in labor (no. 402) and they concluded that, in healthy women with antenatally normal singleton pregnancies at term, instrumental deliveries are associated with the highest rate of short-term maternal and neonatal complications the findings are similar to what we have observed in our study.

• Vacuum assisted delivery should be indicated for specific obstetrical indications including prolonged second stage of labor, non reassuring fetal cadiotocography and maternal cardiac or neurological disease [10] .

In the current study the main indication for vacuum assisted delivery was fetal distress (59.8%), followed by poor maternal effort(18.8%), prolonged second stage(17.9%) and shortening of the second stage (23,15) which showed no major difference than what was reported in the literature[10].

Routine episiotomy is not necessary for an assisted vaginal birth and may increase the risk of significant perineal trauma [12]. In a series of 1000 consecutive omnicup-ventouse assisted deliveries, the incidence of third and fourth degree tears with versus without an episiotomy was 15.8 and 5.8 percent, respectively [3]. In the current study the incidence of episiotomy was 75.2% and the incidence of the third and fourth degree perineal tears was 5.5%, the high incidence of 3rd and 4th degree tears can be explained by the liberal use of episiotomy in vacuum assisted vaginal deliveries. The relationship between episiotomy and preaneal tears is beyond the scope of this study.

In recent years, the success rate for operative vaginal deliveries has been quite high (99 percent) [6]. This likely reflects appropriate choice of candidates for this intervention. In the current study the success rate was 91.1% which is lower than what was reported from the developed countries, this is probably related to patient selection and the differences in the social cultures.

Some experts have recommended abandoning the procedure after three pulls. A cohort study found that 82 percent of completed operative deliveries occurred with one to three pulls, and that pulling more than three times was associated with neonatal trauma in 45 percent of such deliveries [17]. In the current study the number of pulls were max of three with a success rate of 90.1% and a neonatal injury of 19%.

In a meta-analysis from the Cochrane data base by Johanson R, Menon V (2000) included, ten trials the use of the vacuum extractor for assisted vaginal delivery when compared to forceps delivery was associated with significantly less maternal trauma (odds ratio 0.41, 95% confidence interval 0.33 to 0.50) and with less general and regional anesthesia. There were more deliveries with vacuum extraction (odds ratio 1.69, 95% confidence interval 1.31 to 2.19). Fewer caesarean sections were carried out in the vacuum extractor group. However the vacuum extractor was associated with an increase in neonatal cephalhaematomata and retinal hemorrhages. Serious neonatal injury was uncommon with either instrument. The authors concluded that Using of vacuum extractor rather than forceps for assisted delivery appears to reduce maternal complications.

Neonates delivered by vacuum extraction had more neonatal cephalohematoma (OR 2.38) and retinal hemorrhages (OR 1.99) than those delivered by forceps [10]. These problems generally are not associated with long-term complications.

In a randomized controlled trial by Dell et al (1985) at least one maternal adverse outcome was reported with a prevalence of 22 % in metallic cup vacuum extractor.

The prevalence of maternal soft tissue injuries in the current study was 17.7% which concurs with the reported figures in Dells trail.

In a retrospective study by Angioli et al (2000) of 50,210 vaginal deliveries they reported a rate of third and fourth degree lacerations for spontaneous, vacuum extraction, and forceps delivery were approximately 2, 10, and 20 percent, respectively. The rate of third and fourth degree in our study was 5.3% which lower than what was reported in Angioli study which is reporting a high rate of tears in all the three groups that were studied.

The incidence of postpartum hemorrhage report in our study is 6.2% with no difference than the incidence among normal sponta-

neous vaginal deliveries reported in the literature.

The incidence of serious neonatal complications with vacuum extraction is approximately 5 percent [20]. Torsion and traction of the vacuum cup can cause fetal scalp abrasions and lacerations, separation of the scalp from underlying structures leading to cephalohematoma, subgaleal hematoma occurs in 26 to 45 per 1000 vacuum deliveries (ACOG Practice Bulletin 2000), intracranial hemorrhage, hyperbilirubinemia, and retinal hemorrhage are also recognized complications of vacuum assisted deliveries [22].

Towner D et al (1999) reported in a large study, the incidence of subdural or cerebral hemorrhage in infants delivered by vacuum alone was approximately 10 per 10,000 births.

In the current study the reported neonatal complications related to ventous delivery including cephalohematoma, scalp injury Erbs palsy clavicular fracture, subdural hematoma, neonatal seizures cut wound and multiple bruises were reported in 83 neonates with a rate of 19% the higher figure may be due to the inclusion of minor complications unlike other studies which include only major serious complications.

Cephalohematoma, in particular, is more common after vacuum-assisted extraction than forceps delivery (approximately 15 versus 2 percent) [8, 10].

In general, the incidence of retinal hemorrhage is higher for vacuum-assisted than for spontaneous vaginal or cesarean deliveries 75, 33, and 7 percent, respectively [9]. These hemorrhages typically resolve without sequelae within four weeks of birth, no cases of retinal hemorrhage observed in or study this is one of the limitation of the current study as minor self limited conditions are rarely reported.

Cephalohematoma was the commonest neonatal complications occurred in 63 newborns, (14.5%), followed by scalp lacerations and clavicular fracture subsequently.

Other reported complications which may or may not be related to the delivery itself including SCBU admission 5.5%, NICU admission 3.4% and birth asphyxia 1.2%. The cause of these complications may be due to the risk factors with those cases that had led to the assisted deliveries. Shoulder dystocia was reported to occurs in higher frequency with vacuum assisted delivery [5]. In the current study 9 cases of shoulder dystocia with an incidence of 2.1%The early neonatal complications was reported in prospective study that follows 79 term infants after vacuum assisted delivery found all delivery related complaints were identified within the first 10 hours of life [21]. In the current study most of the neonatal complications were recognized in the first 24 hours of the neonatal life.

Conclusion

Vacuum extractor deliveries exceed forceps delivery with a rate of 22:1.The failure rate for the procedure was higher than what was reported in the literature. Complications rate of ventouse delivery in our study are comparable to what was reported in the literature. The commonest maternal complication was perineal tears and the commonest neonatal was cephalohematoma.

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IMMEDIATE MATERNAL AND NEONATAL MORBIDITY ASSOCIATED WITH VACUUM EXTRACTOR DELIVERY, AT UNIVERSITY TEACHING HOSPITAL EXPERIENCE

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EVALUATION OF N-ACETYL CYSTEINE (NAC) AS A POSSIBLE PROTECTIVE FACTOR IN THE PREVENTION OF RETINOPATHY OF PREMATURITY (ROP) : HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

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Abstract

Background: *Retinopathy of prematurity (ROP) is a vasoprolifrative disorder of the eye that primarily affects premature infants. It occurs when the normal pattern of progressive blood vessel growth within the retina is interrupted by premature birth.*

Aim of the work: *This work was carried out to study that hyperoxia potentiates retinal neovascularization and to study the possible protective role of N-acetyl cysteine (NAC) in preventing abnormal angiogenesis. Moreover, to evaluate the role of insulin-like growth factor-1 (IGF-1) in the treatment of ROP.*

Materials & Methods: *60 litters of rats were obtained and classified into 3 groups. Group I raised from birth in room air and served as control. Group II exposed to 60% oxygen continuously for 14 days then removed with their mothers to room air. Group III placed in the same condition as group II and received intraperitoneal (IP) injection of a single dose of NAC (150 mg/Kg) at the postnatal days 2,6,10. After 35 days, the two eyes from all groups were enucleated and stained with haematoxylin and eosin and immunohistochemical stain for localization of IGF-1. Frozen sections were stained for adenosine triphosphatase (ATPase) enzyme. Results: Signs of neovascularization began to appear in group II while in group III, the neovascularization was less marked.*

Conclusion: *High concentration of oxygen could induce retinopathy in newborn rats and NAC can be used in the treatment of ROP.*

Introduction

The blood vessels of the retina begin to develop 3 months after conception and complete their development at the time of normal birth. When a baby is born prematurely, normal blood vessel development may cease and abnormal growth may begin [1]. Retinopathy of prematurity (ROP) was reported to be a serious vasoproliferative disorder occurring in infants that are born prematurely and receive high levels of oxygen postnatally to compensate for their unstable pulmonary status [2]. IGF-1 is an important contributer to the physiological development of the retinal vasculature [3]. The absence of IGF-1 prevents normal retinal vascular growth despite the presence of VEGF [4]. IGF-I can act as a direct angiogenic factor on retinal endothelial cells or indirectly through increased VEGF gene expression [5]. Following hypoxic exposure, sever ROP has been associated with increase in serum IGF-1 level [3].

Materials & Methods

Timed pregnant albino rats (250-275 gm) were obtained from the animal house of Mansoura Faculty of Medicine. Immediately after birth a total of 60 litters of rats were obtained. The duration of the experiment was 35 days. The rats were classified into 3 groups:

Group I : It included 20 rats. They were raised from birth in room air, served as control and sacrificed after 35 days of birth.

Group II : It included 20 rats. They were placed with their mothers in an incubat (modified isolette) especially designed for this experiment and exposed to 60% oxygen continuously for 14 days then abruptly removed with their mothers to room air and sacrificed at P35 (21 days after stoppage of O_2).

Group III : It included 20 rats. They were placed in the same condition as group II. They received IP (intra peritoneal) injection of a single dose of NAC (150 mg/Kg) at the postnatal days 2,6,10 then abruptly removed with their mothers to room air and sacrificed at P35 (21 days after stoppage of O_2).

The two eyes from all groups

were enucleated and fixed in 10% neutral buffered formalin for 24 hours. Dehydration was carried out in ascending grades of ethanol. Xylol was used as a clearing agent. Impregnation and embedding was done in paraplast. Serial sections were cut at 4-5 micrometter (μm) in thickness and stained by:

- Haematoxylin and Eosin stain (6).
- Immunohistochemical stain for localization of IGF-1 by

Labeled Avidin-Biotin method (LAB) [8] using polyclonal rabbit anti-IGF-1.

Frozen sections were prepared for histochemical staining for adenosine triphosphatase (ATPase) enzymatic activity [7].

Results

Group I (Control group):

1-Hx& E:

Examination of paraffin sections of the retina of the control rats stained with Hx&E stain revealed that it consisted from outside to inside of nine layers. The first layer is the retinal pigment epithelium. The 2nd layer is the photoreceptor cells (rod and cone cells). It is formed of an outer lightly stained segment formed of parallel processes and an inner deeply stained segment. The third one is the outer nuclear layer (ONL) which was formed of densely stained packed nuclei containing the cell bodies of rod and cone cells. The outer plexiform layer (OPL) had a reticular appearance. The inner nuclear layer (INL) seemed to be thinner and its cells appeared larger and paler in comparison to those of the outer nuclear layer. The cells were variable in shape, size and density. The inner plexiform layer (IPL) was located between the inner nuclear layer and the ganglion cell layer of the retina. It had a reticular appearance. This layer was thicker than the outer plexiform layer. The ganglion cell layer (GCL) was formed of slightly irregular interrupted row of rounded variable sized cells. These cells were larger and widely separated from each other than those of the other nuclear layers. The nerve fiber layer was composed of axons of ganglion cells. The inner limiting membrane (ILM) was the last layer which separated the retina

from the vitreous cavity.

There was normal pattern of vascularity, consisted of blood vessels confined to the inner retina which comprised the inner limiting membrane (ILM), ganglion cell layer (GCL), inner plexiform layer (IPL) and inner nuclear layer (INL). No blood vessels were seen to extend beyond the internal limiting membrane (Fig. 1).

2- ATPase:

Examination of frozen sections of the control retina stained with ATPase stain revealed that there was a moderate to strong ATPase activity in the endothelium of the intra-retinal blood vessels. A strong ATPase activity was seen in the inner segment of photoreceptor cells while a moderate activity was seen in the outer and inner plexiform layers. The outer segment of photoreceptor cells, outer nuclear layer, inner nuclear layer and ganglion cell layer displayed background levels of activity (Fig. 2).

3- Immunohistochemical staining:

Immunohistochemical staining of the control retina with IGF-1 revealed weak IGF-I expression in the neurons of the ganglion cell layer, the inner and outer plexiform layers and the photoreceptor layer of the retina (Fig. 3).

Group II:-

1- H x & E:-

Signs of neovascularization began to appear. Patent vascular loops were developed towards the vitreous (Fig. 4A). Superficial newly growing blood vessels were also developed (Fig. 4B). The superficial newly growing blood vessels were seen to be connected with the deep intra-retinal ones (Fig. 4C). There was canalization of most of the blood vessels (Fig. 4D).

2- ATPase:

A strong positive ATPase activity was observed in the endothelial lining of the patent vascular loops which extended toward the vitreous (Fig. 5A&B). Moreover, a strong positive ATPase activity was observed in the endothelium of both the superficial and deep blood vessels which were connected to each other (Fig. 5C).

3- Immunohistochemical staining:

IGF-I expression was increased in neurons of the ganglion cell layer, the inner and outer plexiforms, the photoreceptor layers of the retina and in the cytoplasm of the endothelial cells of the superficial and deep blood vessels (Fig. 6).

Group III :-

1- H x & E:-

The pattern of vascularization was similar to that of the control rats (Fig. 7).

2- ATPase:

There was a moderate to strong ATPase activity in the endothelium of the intra-retinal blood vessels (Fig. 8). These findings were similar to that of the control rats.

3- Immunohistochemical staining:

IGF-I expression in neurons of the ganglion cell layer, the inner and outer plexiforms and the photoreceptor layers of the retina was similar to that of the age-matched room air-raised rats (Fig. 9).

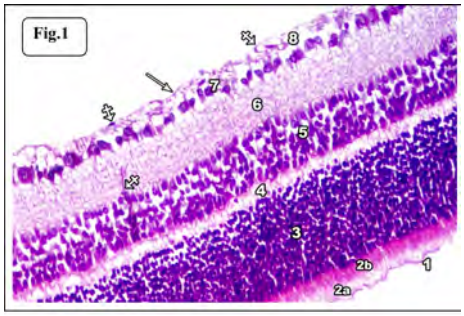


Fig. (1): A photomicrograph of a paraffin section in the retina of control rats showing the retinal pigment epithelium (1), outer (2a) and inner segments (2b) of photoreceptor cells, the cells of outer nuclear layer (3), outer plexiform layer of reticular appearance (4), the cells of inner nuclear layer (5), thick inner plexiform layer of reticular appearance (6), ganglion cell layer (7), nerve fiber layer (8) and the internal limiting membrane (arrow). No blood vessels (crossed arrows) are seen to extend beyond the inner limiting membrane. (Hx & E x 400).

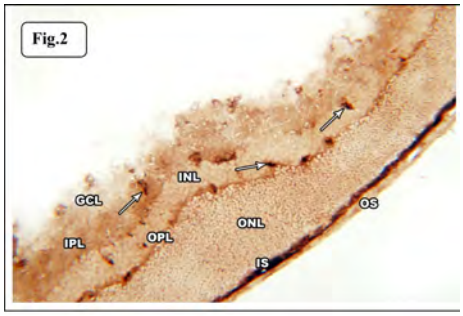


Fig. (2): A photomicrograph of a frozen section in the retina of control rats showing a moderate to strong ATPase activity in the endothelium of the intra-retinal small blood vessels (arrows). A strong ATPase activity is seen in the inner segments (IS) of photoreceptor cells and a moderate activity is seen in the outer plexiform layer (OPL) and inner plexiform layer (IPL). The outer segment (OS) of photoreceptor cells, the outer nuclear layer (ONL), inner nuclear layer (INL) and ganglion cell layer (GCL) display background levels of activity. (ATPase x 400).

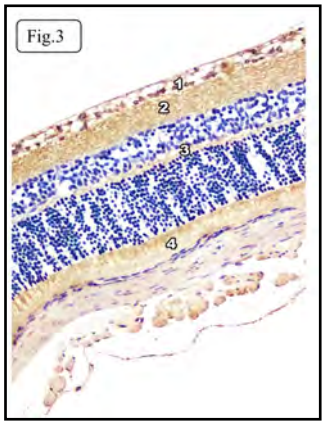


Fig. (3): A photomicrograph of a paraffin section in the retina of control rats showing weak IGF-I expression in neurons of the ganglion cell layer (1), the inner plexiform layer (2), the outer plexiform layer (3) and the photoreceptor layer of the retina (4) (IHC reaction of IGF-1 x 250) .

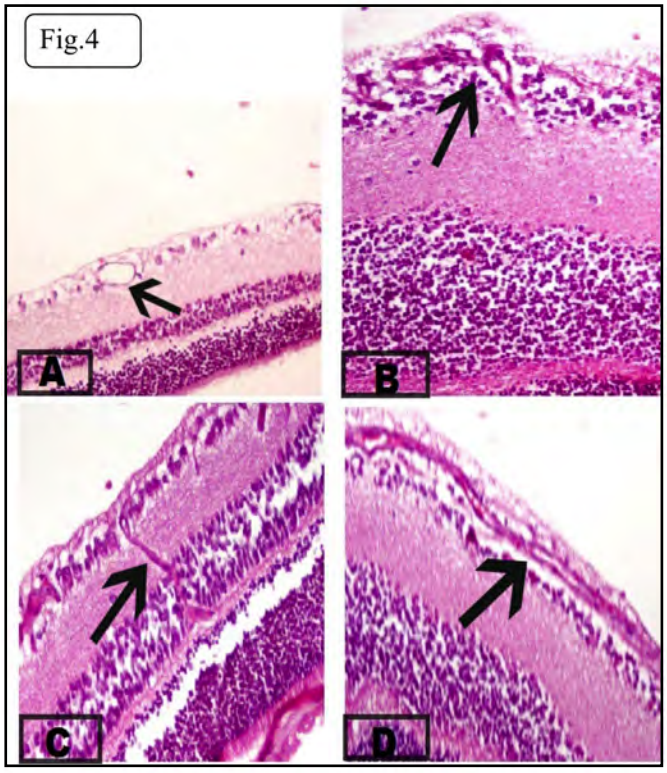


Fig. (4): A photomicrograph of a paraffin section in the retina of group II rats showing (A) a patent vascular loop (arrow) (B) superficial newly growing blood vessels (arrow) (C) the superficial newly growing blood vessels are connected with the deep intra-retinal ones (arrow) and (D) canalization of intra-retinal blood vessels (arrow). (Hx & E x 400) .

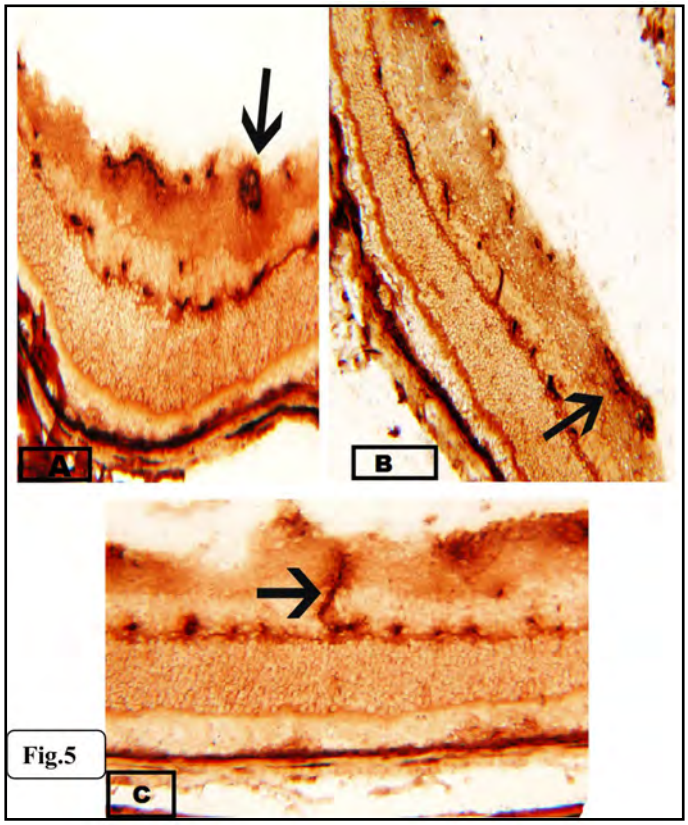
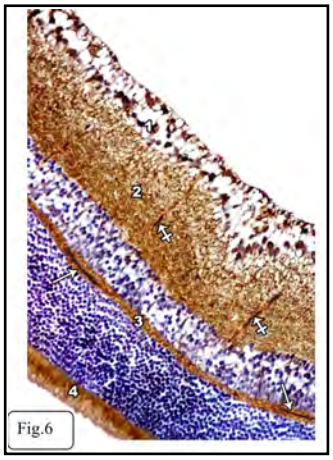


Fig. (5): A photomicrograph of a frozen section in the retina of group II rats showing a strong positive ATPase activity in (A and B) the patent vascular loop (arrow) which extends towards the vitreous and (C) the superficial newly growing blood vessels which connected with the deep intra-retinal ones (arrow) (ATPase x 250).

Fig. (6): A photomicrograph of a paraffin section in the retina of group II rat. It shows a strong positive IGF-I expression in neurons of the ganglion cell layer (1), the inner plexiform layer (2), the outer plexiform layer (3), the photoreceptor layer of the retina (4) and in the cytoplasm of the endothelial lining of the superficial (arrows) and deep (crossed arrows) blood vessels. (IHC reaction of IGF-1 x 400) .



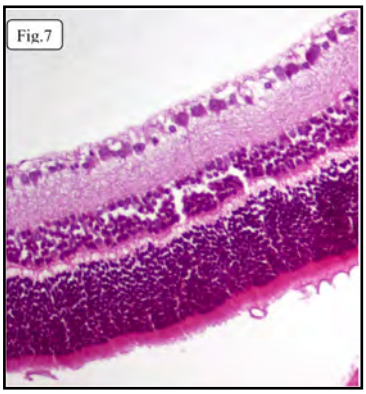


Fig. (7): A photomicrograph of a paraffin section in the retina of group III rats. The pattern of vascularization is similar to that of the control retina. (Hx & E x 400)

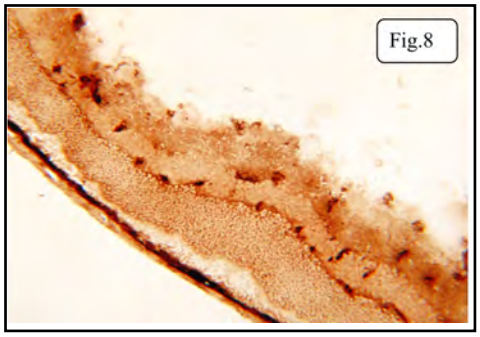


Fig. (8): A photomicrograph of a frozen section in the retina of group III rats. It shows the same pattern of vascularity and ATPase enzymatic activity as seen in the control retina. (ATPase x 250)

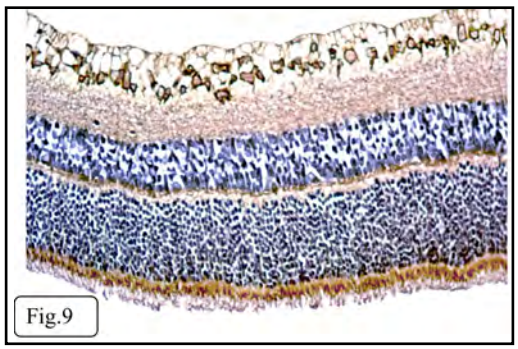


Fig. (9): A photomicrograph of a paraffin section in the retina of group III rats. It shows a weak IGF-I expression in neurons of the ganglion cell layer, the inner plexiform layer , the outer plexiform layer and the photoreceptor layer of the retina . (IHC reaction of IGF-1 x 400)

Discussion

Retinopathy of prematurity (ROP) was reported to be a serious vaso- proliferative disorder occurring principally but not exclusively in infants that are born prematurely and receive high levels of oxygen postnatally to compensate for their unstable pulmonary status [2]. Its incidence has been rising in recent years, probably because of the increased survival of very low-birth weight premature infants in modern neonatal intensive care units [9]. Exposure of premature infants to hyperoxia or relative hyperoxia of the non uterine environments is associated with this form of retinopathy. It usually regresses but can lead to irreversible vision loss if there is progression from retinal neovascularization to cicatrization and retinal detachment[10]. It is characterized by two stages; primary stage of retinal vasoconstriction in which vessels are obliterated in response to high levels of oxygen which prevents normal vascular growth towards the retinal periphery and a secondary stage of retinal neovascularisation on the return to a normoxic environment which is the result of an inadequate blood supply [2].

A disease model is required to study ROP. The eyes of animals such as mice, rats and cats, though born full term, are incompletely vascularized at birth and are similar to the retinal vascular development of premature infants. Exposure of these neonatal animals to hyperoxia leads to cessation of normal retinal blood vessels development, which mimics phase I of ROP. When animals return to room air, the non-perfused portions of the retina become hypoxic, similar to phase II of ROP. The ischemic portions of the retina produce angiogenic factors that result in neovascularization. This ROP model has been useful to delineate the growth factor changes in both phases of the disease [11]. Therefore, the aim of this work was to develop oxygen induced retinopathy in the newborn rat to study the hypothesis that hyperoxia potentiates pre-retinal neovascularization and to establish a more reliable animal model of ROP for studying the possible protective role of N-acetyl cysteine in preventing abnormal angiogenesis

and to evaluate the role of IGF-1 in the treatment of ROP.

In the current study, the retina of the control rats (group I) was found to consist of nine layers these findings were in agreement with [16]. On exposure to hyperoxia (group II), patent vascular loops and superficial newly growing blood vessels continuous with the deeper retinal vessels were developed. This might occur as a result of exposure of the retina to a relative hypoxia on return to room air. The relatively low O_2 tension might stimulate the delivery of some angiogenic factors in isolated retina. These factors initiate the second phase of oxygen induced retinopathy and resulted in vascular proliferation. Complete canalization of most of vessels was seen.

Growth of new vessels occurred when an individual with significant obliterated retinal vessels began to breathe room air[17&18]. The continuity of the superficial blood vessels with the deeper retinal vessels confirmed their origin to be from the retinal rather than vitreal or hyaloid vessels[19]. In rat[20] and mice models[11], mature luminized vessels containing red blood cells was demonstrated.

In the current work, the possible use of N- acetyl cysteine (NAC) in prevention and treatment of retinopathy of prematurity was studied. The use of NAC was based on its antioxidant[21], anti-angiogenic[22] and anti-inflammatory effects[23]. The oxidative compounds play a role in ROP. The retina is susceptible to oxidative damage due to its high metabolic rate and rapid rate of oxygen consumption. In addition, the premature infant has a reduced ability to scavenge reactive oxidative species (OH, H_2O_2 and O_2) increasing its vulnerability to oxidative stress [24]. NAC significantly reduced lipid peroxidation and retinal neovascularization[21]. A significant decrease in retinal neovascularization and immunoreactivity was observed in the treated groups (group III). Our results were postulated by[25],[26] and confirmed recently by [21].

From the results of our study, it could be concluded that, exposure to high concentration of oxy-

gen could induce retinopathy in newborn rats as in human. NAC can be used in the treatment of ROP. Moreover, IGF-1 is overexpressed during ROP and its role in facilitating the treatment is well manifested.

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EVALUATION OF N-ACETYL CYSTEINE (NAC) AS A POSSIBLE PROTECTIVE FACTOR IN THE PREVENTION OF RETINOPATHY OF PREMATURITY (ROP): HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

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MICRODEBRIDER OUTCOME VERSUS PARTIAL TURBINECTOMY : IN CHRONIC HYPERTROPHIED TURBINATE

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Abstract

Background: *Chronic hypertrophied inferior turbinate is a common cause of nasal airway obstruction. A variety of surgical procedures are performed in this aspect, but none of them is completely effective. Cauterization, partial or total turbinate resection, cryosurgery, radiofrequency and laser therapy are different techniques that could be utilized. However, these procedures carry the disadvantages of bleeding, crusting, synechiae formation, imprecise volume reduction and atrophic changes. The ideal turbinate surgery would effectively reduce the volume of sub-mucosal stromal tissue, while preserving the overlying respiratory epithelium. The primary goal of therapy is to maximize the nasal airway for as extended period as possible while minimizing complications. Endoscopic microdebrider-assisted turbinoplasty is effective in decreasing nasal resistance with preservation of the respiratory mucosa.* ***Objective:*** *To compare the subjective and objective outcome results of sub-mucosal reduction by microdebrider versus partial trimming of chronic hypertrophied turbinate.* ***Study design:*** *A prospective blind-randomized clinical trial.* ***Methods:*** *Forty-two adult patients of both sexes with bilateral chronic hypertrophied turbinate, who had not responded to systemic or local treatment were enrolled in this study. They were divided equally and randomly into two groups. Group A, underwent inferior turbinate reduction by microdebrider while group B, were exposed to conventional partial turbinectomy. Subjective and objective assessments of nasal patency were done, pre-and up to 9 months post- operatively.* ***Setting:*** *Benha Teaching Hospital.* ***Results:*** *There were objective and subjective improvements in nasal patency for up to 6 months post-operative in both groups, however; 9 months follow up showed better subjective improvement in group A 67.6% compared*

with 64.5% in group B (p=0.028). ***Conclusions:*** *Both microdebrider-assisted turbinate reduction and conventional partial inferior turbinectomy were effective as regard objective and subjective improvement of nasal patency within a limited period postoperatively, however microdebrider technique had a better and longer term subjective outcome.*

Introduction

Hypertrophied turbinate and nasal septum deviations are the main causes of chronic nasal obstruction.[1] Surgical interference can be performed for hypertrophied inferior turbinate in patient refractory to medical treatment. Moore et al[2] confirmed that patients suffering from chronic nasal obstruction and hypertrophied turbinate often benefit from turbinate reduction when other regimens fail. Partial inferior turbinectomy,[3] total inferior turbinectomy,[4] cryosurgery,[5] submucosal diathermy,[6] laser surgery,[7] radiofrequency volume reduction,[8] coblation,[9] and microdebrider-assisted turbinoplasty[10] are all performed indicating the lacking of consensus on a standard technique with debatable efficacy. The optimum turbinate surgery would effectively reduce the volume of sub-mucosal stromal tissue and preserve the overlying respiratory mucosa with minimal short and long term complications. Microdebrider achieves volume reduction with mucosal preservation, provides real time suction and precise tissue resection.[11] Partial inferior turbinectomy reduces not only nasal congestion, but also sneezing and rhino rhea in patients with allergic rhinitis.[12] Our aim was to compare the objective and subjective outcomes of inferior turbinate reduction using microdebrider versus conventional method.

Patients and Methods

Forty two consecutive adult patients of both sexes with bilateral nasal obstruction due to substantial mucosal hypertrophy of the inferior turbinate not responsive to systemic or local medical therapy for at least 3 months were enrolled in the study. They were submitted to full medical, ENT exam, nasal, nasopharyngeal endoscopic evaluations and computer tomography of the paranasal

sinuses. The exclusion criteria included: those who had undergone any kind of nasal; turbinate surgery, significant septum deviation, nasal valve collapse, nasal polypoidal diseases, recurrent sinusitis and those who were under antidepressant or hypertension medications. Patients were divided randomly and equally into two groups. Group A, age ranged (18-48 years) and mean (23.6 yr) composed of 15 men and 6 women who underwent inferior turbinate reduction by microdebrider. Group B, age ranged (19-53 years) and mean (27.3 yr) included 18 males and 3 females who were exposed to conventional partial turbinectomy. Method of randomization was carried out by putting the odd number of the patients into the 1st group and the even number into the 2nd one. Informed consent was obtained from each case and all surgical procedures were performed under general anesthesia by the same surgeon. The subjective assessment of the nasal patency, nasal discharge, postnasal drip, headache and smell changes was achieved by patient questionnaire preoperatively and after surgery by 1, 3, 6 and 9 months. It was graded on 0-3 scales: 0= worse result, 1= no change, 2= partial improvement, 3= significant improvement. Also, a 10 cm visual analog scale (VAS) as subjective measure was used to grade nasal obstruction preoperatively and after removal of the nasal pack at the times of assessment; a score of 0 represents no obstruction and a score of 10 indicates a complete nasal obstruction. The outcome was considered successful when the difference between preoperative and postoperative assessment without nasal decongestion by (VAS) is 50% or more,[13] The participant filled out VAS concerning nasal obstruction. In both groups, local infiltration with combined 2% Lidocain HCL and 1:100.1000 epinephrine into the inferior turbinate was done. In group A, Microdebrider (KARL STORZ, unidrive ECO- GmbH - Germany) set at a speed of 3500-2500 rpm, oscillating mode, was used in performing inferior turbinate reduction (turbinoplasty). An incision of 3-4mm is made medial to the muco-cutaneous junction of the head of the turbinate with a scalpel, then a sub-mucosal

pocket is dissected by tunneling with a sucker-dissector in an anterior to posterior and superior to inferior sweeping motion. Once a pocket has been developed, the shaver blade is introduced and its cutting edge is rotated laterally to face the bony turbinete and the sub-mucosal layer is shaved and sucked. We used a straight suction shaver blade 3 mm Ø, length 12cm (STORZ, Germany), with the tip moving in a circular motion to remove most of the stromal tissue inside the turbinate with preservation of the mucosal flap. Thinning of the inferior bonny part of the turbinate was carried out when necessary without resection using aggressive shaver. There were 5 cases of hypertrophied posterior turbinate tails (mulberry-tip) in group A, where a secondary entry point was made at the mid-portion of the inferior turbinate to gain better access to the posterior end. Partial inferior turbinectomy was performed in the 2nd group using angled scissors with monopole diathermy for hem stasis when necessary.[14] It allows de-bulking of the hypertrophied bony and soft vascular tissue after medialization of the turbinate. Both techniques were assisted using Hopkins telescope 30°, 4mm diameter. Postoperative saline nasal douching was advised. Gertner's method 15 for objective assessment of nasal patency was done pre- and 1, 3, 6, 9 months postoperatively.It is based on measuring the area of vapor condensed on a metal plate that was placed under the nostrils. The patient was instructed to breathe through the nose only with a closed mouth. By measuring the area of condensed vapor, we could measure the breathing function of the nose. In this study, we used a flat mirror instead of the metal plate.The volume of blood loss intra-operatively, was collected in the suction container and it was considered significant volume when it is ≥ 100 ml. Post-operative complications were recorded in both groups up to 9 months follow up. Chi-square and t-student test were used for statistical analysis.

Results

We had missed 3 cases in the 1st group and 4 cases in the 2nd group after 6 months follow up. Also a further one patient in the 1st group did not follow up 9 months.

Post-operative outcome as

shown in table (1) revealed that there was a statistical significant objective improvement in group A up to 69.1% after 6 months follow up that declined to 66.9% after 9 months; compared with 81.7% objective improvement after 6 months which decreased to 74.5% at 9 months follow up in group B. The objective improvement showed significant results after the first month post-operatively and it reached its peak at the 6^{th} month in both groups. Subjective satisfaction of nasal patency was felt after the 1^{st} week in the 1^{st} group and after the 1st month in the 2nd group and reached up to 65.9% and 67.6% at 6 and 9 months post-operative with microdebrider technique, while it was 72.1% and 64.5% in comparable time with partial turbinectomy. Long term follow up 9 months showed that subjective improvement in group A was better than in group B ($p< 0.05$).

The mean volume of blood loss was 36.1±7.4 ml with microdebrider technique and 57.8±9.5 ml in partial turbinectomy (mean ± SD). There was statistically significant blood loss in partial turbinectomy 19% compared with 4.7% in microdebrider group ($p<0.05$). We had mucosal tear in 7 cases representing 33.3% of group A, but without mucosal loss. The mean duration of the nasal packing with shaver microdebrider was 24.2±6 hours, while it was 48.8±8 hours in partial turbinectomy and this was due to the sacrificing of nasal mucosa in the later technique. Most of the patients underwent microdebrider technique suffered from nasal obstruction within the 1^{st} week as a result of the reactionary tumescence of the turbinate mucosa. The incidence of post-operative infection in partial turbinectomy was double that occurred with microdebrider. Post-nasal drip was lesser in microdebrider procedure 28.5% compared with partial turbinectomy 57.1% that lasted up to 4 and 8 weeks respectively. There was high rate of nasal crusting with secretions 76.2% in partial turbinectomy group compared with 14.2% in microdebrider-assisted turbinoplasty. The incidence of synechiae formation was 9.5% in group A and 28.5% in group B; with no mucosal atrophic changes in both groups.

Table (1): Post-operative outcome of nasal obstruction.

Surgical procedure used	Outcome results	improvement after 6 months follow up	P value	improvement after 9 months follow up	P value
Microdebrider assisted turbinoplasty	Objective	69.1%	<0.05	66.9%	<0.05
	Subjective	65.9%	<0.05	67.6%	<0.05
Conventional Partial turbinectomy	Objective	81.7%	<0.05	74.5%	<0.05
	Subjective	72.1%	<0.05	64.5%	<0.05

Table (2): Intra & post-operative complications.

Complications	Microdebrider-assisted turbinoplasty	Conventional partial turbinectomy
Significant intra-operative bleeding	1 case=4.7%	4 cases=19%
Mean volume of blood loss	36.1 ± 7.4 ml	57.8 ± 9.5 ml
Mucosal tear	7 cases=33.3%	Not preserved
Mean duration of post-operative nasal packing	24.2±6 hours	48.8±8 hours
Postnasal drip	6 cases=28.5%	12 cases=57.1%
Infection	2 cases= 9.5%	4 cases=19%
Nasal secretions and crusting	3 cases=14.2%	16 cases=76.2%
Synechiae	2 cases= 9.5%	6 cases=28.5%
Clinical mucosal atrophic changes	No cases	No cases

Discussion

Partial inferior turbinectomy is widely used for treatment of hypertrophied inferior turbinate. It has the advantages of de-bulking both the mucosal and bony hypertrophy of the inferior turbinate. Microdebrider-assisted turbinoplasty is mucosa-preserving technique. It provides real time suction with precise tissue resection.[16] Elwany and Harrison[17] showed 75% success rate of improving the nasal patency with partial turbinectomy after one year. Youseph and Gabriel[18] had 81% improvement of nasal patency for one year follow up with partial turbinectomy in comparison with cryosurgery, while we had satisfactory outcome of 74.5% in partial turbinectomy group up to 9 months follow up. Endoscopic microdebrider-assisted inferior turbinoplsty decreases nasal resistance and improves quality of life in patients with perennial allergic rhinitis.[11] Microdebrider-assisted turbinate reduction is superior to laser-assisted one.[19] Liu et al[20] had a sustained nasal patency post reduction of the turbinate hypertrophy up to 3 years using microdebrider shaver. The submucous resection of the inferior turbinate with lateral displacement of the turbinate bone achieves a long-lasting improvement of the nasal passage with normalization of the mucociliary transport time and without post-operative bleeding. [21]Yu-Lin et al[22] had no active bleeding during or post-operative with microdebrider in managing hypertrophied turbinate in 80 patients, while we had an incidence of 4.7% significant intra - operative bleeding in group A and this might be attributed to non usage of hypotensive anesthesia in our cases. Dawes [23] recorded 9% intra-operative bleeding with partial turbinectomy, compared with 19% of significant bleeding in our partial turbinectomy group. The relatively large blood volume loss in this group was due to the inadvertent trauma to one of the branches of sphenopalatine artery. Friedman et al[24] in a group of 100 cases of chronic hypertrophied turbinate using microdebrider had 1.6% intra-operative bleeding, 55% mucosal tears and 5% postoperative synechiae, while our results showed the incidence of 4.7%, 33.3% and 9.5% respectively in group A. The

incidence of mucosal tears in the early patients of the 1st group with 3500 rpm speed was high, which was minimized after reduction the speed to 2500 rpm.

The objective improvements in partial turbinectomy (group B) were better than in microdebrider-assisted turbinoplasty (group A) at 6 and 9 months follow up and this may be due to the feasibility of soft tissue and bone removal in group B. Postoperative improvement of symptoms like nasal discharge, headache and smell changes were not as significant as the improvement of nasal patency, and this may be due to the concomitant pathological mucosal changes. The persistence of post-nasal drip in both groups, for up to 4 and 8 weeks respectively may be due to the des-improvement of the epithelial changes of chronic hypertrophied turbinate postoperatively.[25] The subjective improvement of nasal patency was 67.6% in the first group, compared with 64.5% in the second group 9 months follow up and this may be due to the preservation of both: turbinate function; acclimatization, humidification, cleaning and anatomy of the nasal valve area with microdebrider-assisted procedure. The internal nasal valve produces the most turbulent air-flow and its existence, gives the sensation of nasal patency.[26] It is formed by the lower edge of the upper lateral cartilages, the adjacent nasal septum and the anterior end of the inferior turbinate.[27] In partial turbinectomy, the turbinate head is not preserved and the subsequent post-operative soft tissue contraction may lead to nasal valve compromise with unsatisfactory subjective nasal patency. Rhinomanometry and acoustic rhinometry are major techniques used for measuring the nasal airway.[28] However, acoustic rhinometry causes distortation of the nasal valve area during testing and rhinomanomety has up to 50% day-to- day variation in results.[29] Ciprandi et al[30] concluded that the use of visual analog scale for assessing the nasal obstruction appears clinically relevant in that it allows, with good reliability to quantify this symptom in the absence of rhinomanometry. The assessment of nasal patency in this study was depended upon VAS and Gertner's methods.

Scheithauer[31] emphasized that radical resection of the turbinate may lead to severe functional disturbances developing a secondary atrophic rhinitis and the anterior turbinoplasty seems to fulfill the precautions of limited tissue reduction and mucosa preservation. Our results showed that the outcome improvement of nasal resistance might be consisted with patient's subjective interpretations of long term results and satisfaction and not to positive objective outcome. The perception of nasal obstruction at the level of the brain needs to be elucidated. Hol & Huizing[32] hypothesized that postoperative wider nasal cavity does not always mean that the nose functions better and the rhinosinus physiological mechanisms required about 2 years for restoration after inferior turbinate surgery. Thus, a longer follow up period might be needed in our study for proper assessment of the ultimate outcome.

Conclusion

Partial inferior turbinectomy may give a better objective improvement of nasal patency in chronic hypertrophied turbinate due to bulky removal of soft tissues and bone within a limited period; however, it carries more intra and post-operative complications. Microdebrider - assisted turbinoplasty has its advantages in preserving functional nasal mucosa, the internal nasal valve area and bone together with substantial volume reduction. We concluded that both microdebrider-assisted turbinoplasty and conventional partial turbinectomy are effective in improving nasal objective and subjective nasal patency within reasonable period, however, turbinoplasty has a longer subjective outcome term. Microdebrider technique keeps the morphological and physiological characteristics of the turbinate and can be repeated with less intra and post-operative morbidity.

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PEGYLATED INTERFERON / RIBAVIRIN-INDUCED THYROID DYSFUNCTION IN PATIENTS WITH CHRONIC HEPATITIS C

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Abstract

Background: *The therapeutic use of interferon- alfa in treatment of chronic HCV patients is complicated by many autoimmune disorders including production of autoimmune antibodies and exacerbation of pre-existing autoimmune diseases. As untreated HCV patients are at risk for developing dysthyroidism, the role of interferon alfa as a surrogate risk factor for developing thyroid dysfunction and a possible relation to treatment response need to be cleared.*

Aim of work: *To determine the prevalence of thyroid dysfunction among patients with chronic hepatitis C under pegylated interferon / ribavirin therapy and to detect risk factors predicting thyroid dysfunction and its relation to treatment response.*

Patients and Methods: *One hundred chronic HCV patients who received peg IFN-ribavirin therapy were included in this study during the period between January 2008 and June 2011 in the Tropical Mediicine Unit, Mansoura University Hospitals. The patients were selected according to the International Program Guideline Selection Criteria. Serum TSH, antithyroglobulin and antithyriod peroxidase antibodies were assayed by ELISA before and 6 months after therapy.*

Results: *The median values and frequency of positive antithyroid antibodies (antithyroglobulin and antipyroxidase) were significantly higher in patients after therapy ($p<0.001$). In addition, the median TSH value and frequency of thyroid hypofunction were significantly higher after*

therapy (p<0.001).

Thyroid hypofunction correlated significantly with age (p=0.03), female gender (p<0.001) and antithyroid antibodies (p<0.001) both before and after therapy.

Comparison of the frequency of clinical and laboratory variables between responders and non responders revealed only a significantly higher frequency of mild fibrosis grades and lower viral load in the responders (p=0.002 & p=0.045) without significant difference regarding other variables including hypothyroidism (p=0.1). Mild fibrosis and lower viral load levels were also the most significant predictor of response in regression analysis (p=0.012 & p=0.048) without significant difference regarding other variables including hypothyroidism (p=0.34), antiperoxidase or antithyroglobuline antibodies (p=0.53, p=0.5).

Conclusion: *Interferon alfa therapy can induce thyroid autoimmunity and exacerbate pre-existing thyroid autoimmunity. Presence of antithyriod antibodies before and during interferon therapy correlate with development of thyroid dysfunction mainly hypothyroidism but it can not predict response to therapy. Assessment of thyroid functions and antithyriod antibodies prior and during interferon alfa therapy may help predicting thyroid dysfunction and early management.*

Keywords: *HCV =Hepatitis C virus, SVR= sustained virological response, pegIFN -RBV= pegylated interferon-ribavirin, antithyriod antibodies, thyroid dysfunction.*

Introduction

Chronic infection with hepatitis C virus (HCV) represents a major cause of end-stage liver disease and liver cancer worldwide [1]. The therapeutic use of IFN alfa/ ribavirin is complicated by many autoimmune disorders including production of autoimmune antibodies and exacerbation of pre-existing autoimmune diseases such as systemic lupus, rheumatoid arthritis and autoimmune hepatitis. HCV infected patients also reported thyroid disorders like thyroid autoimmunity, hypothyroidism and papillary thyroid carcinoma[2,3]. Untreated HCV patients are at risk for developing dysthyriodism. Diagnosis of thyroid dysfunction may be delayed as the manifestation of hypothyroidism and interferon side effects are to some extent similar. So,

the role of interferon alfa as a surrogate risk factor for developing thyroid dysfunction need to be cleared. The aim of this study is to determine the prevalence of thyroid dysfunction among patients with chronic hepatitis c under pegylated interferon / ribavirin therapy, and to detect risk factors predicting thyroid dysfunction and its relation to treatment response.

Patients and Methods

A comparative cross sectional study was conducted on chronic HCV patients who received peg IFN-ribavirin therapy during the period between January 2008 and June 2011 in the Tropical Medicine Unit, Mansoura University Hospitals. The patients were selected according to following inclusion criteria: Age 18 -60 years, HCV RNA positive in serum, compensated liver disease and acceptable hematological and biochemical indices (hemoglobin ≥ 13 g/dL for men and 12 g/dL for women; platelet count (not less than) ≥ 90,000 mm, neutrophil count >1500 /mm3 and serum creatinine < 1.5 mg/dL. Exclusion criteria : Overt thyroid disease, positive for hepatitis B surface antigen (HBsAg, Axysm. Abbott) and human immunodeficiency virus infection, Major uncontrolled depressive illness, solid organ transplant (renal, heart, or lung), autoimmune hepatitis or other autoimmune condition known to be exacerbated by pegylated-interferon and ribavirin, pregnant or unwilling to comply with adequate contraception, severe chronic medical disease, and history of previous treatment with IFN-Ribavirin therapy. Informed consents were obtained from subjects included in the study. The study was approved by ethical committee of Mansoura Faculty of Medicine, Egypt.

Liver Histopathology:

All patients had liver biopsy showing chronic hepatitis performed within 12 month prior to starting therapy. Liver histology was graded and staged according to METAVIR fibrosis scaling system that classifies fibrosis into five stages (F0-F4) and activity into four grades (A0-A3) [4].

Blood samples were obtained from all subjects before and 6 months after initiation of therapy,

serum was isolated and preserved at -40 ¬C. HCV RNA quantification (Stratagene Mx3000P Real-Time PCR System with a detection limit of 15 IU/ml.) was done before, and at 12, 24, 48, 72 weeks of therapy.

Drug therapy and response to treatment:

Patients were given pegylated interferon alpha 2a in a fixed dose of 180 micrograms weekly by subcutaneous injection. All of them received ribavirin in an adjusted dose according to body weight; patients < 75 kg were given 1000/ day mg and those > 75 kg were given 1200 mg/day devided on two or three doses.

Drug safety was assessed by clinical evaluation and laboratory tests at week 1, 2, 4 and monthly thereafter during treatment.

At the end of the study, 52 of patients achieved SVR (defined as normalization of liver enzymes and negative HCV RNA PCR at the end of therapy and for 6 months after therapy), and 48 of patients who were non-responder (NR) (as they failed to attain a negative HCV RNA at week 24 from the start of treatment or a decline of HCV RNA of >2 log10 IU/mL at[12] week of treatment) were enrolled, patients with relapse were excluded. Serum thyroglobulin and antithyriod peroxidase antibodies were assayed by ELISA method supplied by calbiotech inc 10461 Austin Dr, springvally, CA 91978 from serum collected at baseline evaluation and after 6 month of therapy. Serum TSH was assayed at baseline evaluation and after 6,12,18 month of therapy. Thyriod dysfunction was defined as TSH level of either more than 4.0 (hypothyroidism or less than 0.3 (hyperthyroidism) mU/L irrespective of freeT3/T4 levels.

Statistical analysis:

Statistical analysis was done by SPSS version 18. Quantitative data were non parametric and Mann-Whitney test was used to compare between these variables. Qualitative data were compared by Chi-square test. The association of variables was tested by Spearman correlation while multiple regression analysis was used to test the predictive value of studied variables to

treatment outcome. Significance is considered when p value was <0.05.

Results

Clinical and demographic data of the studied patients are presented in table (1). During pegylated interferon –ribavirin therapy, hypothyroidism was developed in 9 (9%) of our cases while only one case developed hyperthyroidism (1%) and subjected to subtotal thyroidectomy. Interestingly this female patients complete the coarse of therapy and develop hypothyroidism latter. The median values and frequency of positive antithyroid antibodies were significantly higher in patients after therapy (P<0.001). In addition, the median TSH value with a wide range from 1.34 to 112 mIU/ml and frequency of thyroid hypofunction were significantly higher after therapy (p<0.0001, P=0.002 respectively) (table 2,3).

On univariate analysis of factors correlated with development of hypothyroidism during therapy, thyroid hypofunction was correlated significantly with younger age (p=0.03), female gender (p<0.001) and presence of antithyroid antibodies either before or after therapy (p<0.001) (table 4), but on logistic regression analysis, only young age (p=0.041), female gender (p=0.002) and presence of antiperoxidase antidodies before therapy (p<0.001) can predict development of hypothyriodism during interferon therapy with an overall predictivity (ie) accuracy of this model 90.3% (table 5).

Comparison of the frequency of clinical and laboratory variables between responders and non responders revealed only a significantly higher frequency of mild fibrosis grades (p=0.002) and lower viral load levels (p=0.045) in the responders without significant difference regarding other variables (table 6). In regression analysis low fibrosis stage, low viral load were the most significant predictor of response to therapy (p=0.012 and 0.048 respectively), with an overall predictivity (ie) accuracy of this model 77.5% while development of thyroid dysfunction was not one of the predictors of SVR (P=0.34) (table 7).

Table 1. Clinical and demographic data of patients.

Age (years)	
Mean ± SD	41.64 ± 5.76
Range	(28-55)
Gender	
♂	68
♀	32
Treatment Response	
Non	48
SVR	52
Serum ALT	
One fold	59
Two	12
Three	13
Four	16
Fibrosis Stage	
F1	29
F2 F3 F4	26 20 25
Viral load	
Low viremia (< 100.000 IU/ml)	14
Moderate (100.000 – 800.000IU/ml)	52
High (> 800.000 IU/ml)	34
Thyroid dysfunction after therapy	
Hypothyroidism	9
Hyperthyroidism	1

Table 2. Comparison of TSH and antithyroid antibodies levels in patients before and after therapy

Variable	Patients before therapy (n=100)	Patients after therapy (n=100)	Significance*
TSH (mIU/ml)			
Median	1.4	2.0	P<0.001
Range	0.9-2.17	1.34-112.0	
Antithyroglobulin Ab			
Median	8.5	38	P<0.001
Range	2.6-181.0	15-378	
Antiperioxidase Ab			
Median	16.7	35	P<0.001
Range	1.4-181.0	5-578	

* Wilcoxon rank Sum U test, p is significant if < 0.05

Table 3. Comparison of the frequency of thyroid dysfunction and qualitative antithyroid antibodies in patients before and after therapy

Variable	Patients before therapy (n=100)	Patients after therapy (n=100)	Significance*
Thyroid function			
Euthyroid	100	91	P=0.002
Hypothyroid	0	9	
Antithyroglobulin Ab			
Positive (>75mmol/dl)	1	8	P=0.01
Negative (<75mmol/dl)	99	92	
Antiperioxidase Ab			
Positive (>150mmol/dl)	6	16	P=0.02
Negative (<150mmol/dl)	94	84	

* Mc Nemar test, p is significant if < 0.05

Table 4 : Univariate analysis for prediction of hypothyroidism during ttt

variable	Significance	Correlation coefficient
Young age	0.03*	-0.21
Female Gender	<0.001*	0.7
High viral load	0.37	-0.1
High grade of Fibrosis	0.37	-0.1
Positive Antipx before(>150mmol/dl)	<0.001*	0.42
Positive Antipx after(>150mmol/dl)	<0.001*	-0.80
Positive Antithgb before(>75mmol/dl)	<0.001*	0.30
Positive Antithgb after(>75mmol/dl)	<0.001*	-0.68

Antithgb: Antithyroglobulin antibodies Antipx: antiperioxidase antibodies, p is significant if < 0.05

Table 5. logistic regression for prediction of hypothyroidism during ttt

variable	Adjusted odds ratio	95% CI	P
Age	1.5	(1.02-3.5)	0.041
Female sex	7.5	(3.5-18.5)	0.002
Positive antiperoxidase Abs before ttt	35.9	(20.9-99.12)	<0.001

OR: odd ratio, 95%CI: confidence interval, the overall predictivity (ie) accuracy of this model is 90.3%, p is significant if < 0.05

Table 6. Comparison of the frequency of clinical and laboratory variables between responders and non responders.

Variable	Non responder (n=48)	Responders (n=52)	OR (95% CI)	Significance*
Gender				
Male	13 (27%)	19 (36.5%)	0.79(.49-1.27)	X^2=1.02
Female	35 (73%)	33 (63.5%)	1.27(.79-204	P=0.30
Viral Load				
Low	5 (10.0%)	9 (17%)	reference	X^2=4.1
Moderate	22 (45.8%)	30 (58%)	1.18(0.55-2.56)	P=0.045
High	21 (44.2%)	13 (25%)	1.73(0.82-3.66)	
Fibrosis				
F1	9 (19%)	20 (38%)	Reference	X^2=21.3
F2	9 (19%)	17 (33%)	1.12(052-2.32)	P=0.002
F3	11 (22%)	9 (17%)	1.77(0.91-3.47)	
F4	19 (40%)	6 (12%)	2.45(1.36-4.4)	
Thyroid Function				
Euthyroid	46 (96%)	45 (87%)	referense	X^2=2.6
Hypothroid	2 (4%)	7 (13%)	0.44(0.13-1.52)	P=0.1
Antithyroglobulin before				
Positive	0	1 (1.9%)		X^2=0.93
Negative	48 (100%)	51 (98.1%)		P=0.3
Antithyroglobulin after				
Positive	2 (4%)	6 (11.5%)	0.50(0.15-1.69)	X^2=1.85
Negative	46 (96%)	46 (88.5%)	referense	P=0.17
Antiperioxidase before				
Positive	1 (2%)	5 (9.6%)	0.33(0.06-2.02)	X^2=2.51
Negative	47 (98%)	47 (90.4%)	Reference	P=0.11
Antiperioxidase after				
Positive	5 (10%)	11 (21%)	o.61(0.29-1.30)	X^2=2.1
Negative	43 (90%)	41(79%)	referense	P=0.14

*Chi-square test, OR: odd ratio, 95%CI: confidence interval, viral load : Low <100000, moderade (100.000 – 800.000IU/ml),moderate (100.000 – 800.000IU/ml), high 800.000IU/ml) p is significant if < 0.05

Table 7. Logistic regression analysis for prediction of response to treatment.

Variable	B coefficients	Adjusted odd ratio	95%CI	Significance
Viral load	0.169	1.56	(0.98-3.01)	0.048*
Fibrosis	0.288	2.05	(1.25-3.57)	0.012*
Hypothyriodism	0.108	0.95	(0.52-1.02)	0.34

OR: odd ratio, 95%CI: confidence interval, the overall predictivity (ie) accuracy of this model is 77.5% with Constant, 1.773, p is significant if < 0.05

Discussion

Thyroid dysfunction is the most common endocrinopathy associated with hepatitis C and interferon-based treatment. Thyroid dysfunctions includes hypothyroidism and to less extent hyperthyroidism with or without production of antithyroid antibodies[5]. In this study, antithyroid antibody (antithyroperoxidase and/or antithyroglobulin) before therapy were found in 7% of chronic HCV patients. This is very near to over all prevalence worldwide (10%) with a wide range of 2.9% in a study conducted by Baudin et al. in France to10.2% and 24% in another conducted by Carella et al. and Antonelli et al. in Italy[6,7,2]. The wide range in the prevalence is most probably due to the geographic difference, genetic background and difference in gender of studied population.

During pegylated interferon - ribavirin therapy, hypothyroidism was developed in 9% of our cases while only one case developed hyperthyroidism (1%). Eight patients (8%) developed antithyroglobulin antibody and 16% developed anti-peroxidase antibodies. The prevalence of dysthyroidism during interferon -ribavirin therapy ranged from 2.8% in the study of Betterle et al. to 16.2% in the study of Peoc'h et al.[8,9] with hypothyroidism representing most of cases in accordance with our results. In this study, development of hypothyroidism correlated significantly with age, female gender and presence of antithyroid antibodies either before or after therapy. In a study by Koh et al. they found that most of hypothyroidism patients developed antiperoxidase antibodies during therapy[10]. As serum levels of antithyriod antibodies usually increased with interferon therapy, presence of baseline antithyriod antibodies may be a reliable marker of risk to develop dysthyroidism as in this study. Many studies reported that up to 62.5% of patients with basal positive antithyroid antibodies (especially antithyroperoxidase) will develop hypothyroidism compared to patients negative for antithyroid antibody[11,12]. However, in some studies, hypothyroidism may developed during interferon therapy without presence of antithyroid antibodies but due

to direct toxic effect of interferon leads to destructive thyroiditis or non-autoimmune hypothyrioditis [12,13,14.15].

Interferon alpha induced hypothyroidism is generally benign with some cases resolved spontaneously after cessation of therapy and most cases in many studies reveal only partial reversal of thyroid dysfunction [7]. Patients with positive antithyroid antibodies present a better prognosis with up to 80% spontaneous resolution compared to 25% of patients negative for antithyroid antibodies[12,16,17]. In this study only three (about 33%) of patients who developed hypothyroidism get spontaneous recovery with decreasing the dose of replacement hormonal therapy and complete stoppage of therapy within one and half year.

The dual effect of pegylated interferon and ribavirin is a matter of controversy. In study using pegylated interferon and ribavirin, no aggravation of thyroid dysfunction has been reported [7]. This in contrast with previous study that found that the addition of ribavirin to pegylated interferon-alpha does not modify the thyroid autoantibody pattern but leads to fourfold increase the risk of developing hypothyroidism [18].

The use of interferon and ribavirin in treatment of chronic HCV infection is usually associated with autoimmune disorders. Interferon and ribavirin synergize to potently stimulate the immune system in order to eradicate the virus. Interferon -alpha seems to act through major histocompatibility complex class1 antigens to produce antithyroid antibodies and thyroid dysfunction [19].

The relation between development of thyroid dysfunction and response to therapy still unclear. In a study conducted by Tran et al., there was positive and significant association between thyroid disease and viral clearance. This was not supported by the meta-analysis,[5] On the other hand, many studies as well as this study detected no relation between thyroid dysfunction and sustained virological response [20,21].

Conclusion

Dysthyroidism is one of major side effects during interferon therapy. Presence of antithyriod antibodies before and during interferone therapy correlate with thyroid dysfunction mainly hypothyroidism. Assessment of TSH and anti-thyroid antibodies prior and during treatment is recommended, and patients should be informed about the risk of irreversibility of thyroid dysfunction.

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PEGYLATED INTERFERON / RIBAVIRIN-INDUCED THYROID DYSFUNCTION IN PATIENTS WITH CHRONIC HEPATITIS C

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THE EFFECT OF STIMULATION OF PROTEIN KINASE Cα ON EPIDERMAL WOUND HEALING IN MICE

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Abstract

Background: *Effective wound healing leads to restoration of tissue integrity and occurs through a highly organized multistage process involving various cell types. Protein kinase c alpha (PKCα) is thought to have a leading role in keratinocyte differentiation, epidermal tumor promotion and cutaneous inflammation.*

Aim of the work: *The present work is undertaken to explore the involvement of PKCα in the process of epidermal wound healing through the assessment of PKCα stimulation on progress of healing process.*

Material and Methods: *two paravertebral full thickness skin incisions were performed on the back of experimental mice. Tumor-promoting phorbol ester 4ß-12-O-Tetradecanoylphorbol-13-Acetate (TPA) which is stimulant for PKCα is topically applied on the skin wounds. Specimens were collected after 1st, 5th and 7th day. Histological sections were stained with hematoxylin and eosin and anti (PKCα) immunohistochemistry.*

Results: *the regeneration of injured epidermis was faster in TPA treated group than in unmanipulated wound group as indicted by the increase in the leading edge ratio in TPA treated group as compared with unmanipulated wound group. TPA also promotes formation of intercellular junctions at wound edge and in the newly formed epidermis. TPA treatment also induce epidermal hyperplasia at wound edge and in the neoepidermis as compared with unmanipulated wound group.*

Conclusion: *Stimulation of protein kinase c alpha promotes epidermal*

hyperplasia which may progress to tumour formation in intact epidermis but precise control of the dose of the stimulant may be helpful to promote healing in wound conditions.

Introduction

Healing of skin wounds is a complex programmed sequence of cellular and molecular processes that include inflammation, cell migration, angiogenesis, provisional matrix synthesis, collagen deposition, and re-epithelialization[1]. Epithelia of animal tissues are confluent cell sheets and remain so unless wounded or diseased. Desmosomes in vivo are calcium independent (hyperadhesive desmosomes). On wounding, when greater tissue liability is required to facilitate cell migration and wound repair, desmosomes spontaneously adopt a lower-affinity adhesive state. In doing so they appear to become Ca^{2+} dependent, their intercellular space narrows and they lose the highly organized structure of their adhesive material (2 and 3). Desmosomal adhesion may be rapidly modulated from calcium independent to calcium dependant in response to wounding and this modulation is signaled by protein kinase C alpha (PKCα) which is localized to calcium dependant desmosomes in epithelial cell sheets [4].

The PKC isoforms have been grouped into three subfamilies of enzymes: the conventional PKCs (α, β_1, β_2 and γ), the novel PKCs (δ, ε, ϕ and η), and the atypical PKCs (ξ, λ, and τ). Only 5 members of PKC family (α, δ, ε, η, ξ) are expressed in Keratinocytes [5].

TPA induces prolonged PKC association with the plasma membrane and sustained activation in which PKCα is translocated to the entire membrane in living cells [6]. Topical application of TPA induced epidermal hyperplasia consisting of four to six nucleated cell layers on day 2 in the wild-type mice[7]. Activation of PKC triggerd desmosome formation in low-calcium conditions, or in cells lacking desmosomes owing to mutation of adherens junction proteins[8].

Materials and Methods

• **Animals used:**-

Twenty eight male BALB/c mice aged 8-10 weeks were used

in this experiment. The experimental protocol and animal care were in compliance with the requirements of regulations of the Committee on animals experimentation of Mansoura Univeristy.

- **Drug used:-**

Tumor-promoting phorbol ester 4ß - 12 - O - Tetradecanoylphorbol - 13 - Acetate (TPA). It is applied in a dose of 10µg/200µL in Dimethyl sulfoxide (DMSO) per wound[7].

- **Experimental design:-**

A- Collection of unwounded skin specimens:

Four mice were used. The animals' back were shaved completely. Two unwounded skin specimens of 1 cm X 1 cm were excised from the shaved area after animal sacrificaion.

B- Wounding of mice skin:-

Twenty four mice were used. The wounding done on marks of 3 cm posterior to the animal's base of the skull, 1cm long, 2cm apart and 1cm lateral to the animal's dorsal midline. 2 Full thickness wounds were performed on these marks (cutting through the epidermis, dermis and panniculus carnosus muscle).

The animals were subdivided into two groups. It was decided to examine epidermal wounds at one, five and seven days after wounding, using four animals for each time points.

Group A (unmanipulatrd wounds -ve control):

Twelve mice used for studying epidermal wound healing, distribution and involvement of PKCα during this healing. Wounds are left unmanipulated.

Group B (TPA treated group):

Twelve mice were used. TPA was topically applied every 48 hours using micropipette to both (right and left) wounds starting immediately after wounding.

- **Microscopic examination:-**

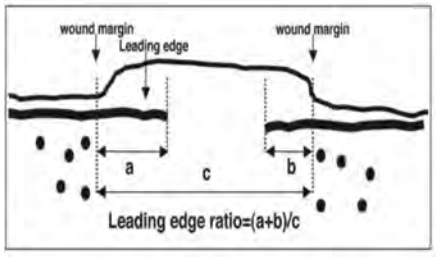
Paraffin sections were cut at 5 microns for Hematoxylin and Eosin stains and 4 microns for immunohistochemical stain for protein kinase c alpha.

- Morphometric study:-

1. Migration assay (non and early healed sections):-

To quantify the migration of

keratinocytes in wound healing, the length of the leading edge ratio in each wound was measured according to the following formula:- Leading edge ratio= (a+b) /c [9]



2. Epidermal thickness:-

The thickness of the epidermis at the border of the wound was evaluated. Ten measurements were performed per section (5 measurements on each side of the wound, from the margin to 1 mm at the intact side)[10].

Statistical study : The microscopic morphometric analysis of each specimen was recorded by digital camera at 4 x magnification. The data obtained were subjected to statistical analysis using independent samples t- test. The significance level considered was $P \leq 0.05$ [11].

Results

1. Haematoxylin & Eosin stained sections:-

•Unwounded skin specimens:

Examination of skin sections revealed normal parts of the skin which is divided into epidermis, dermis, stratum adiposum, panniculus carnosus and stratum fibrosum. The epidermal thickness was (0.011 ± 0.002 mm) (Fig.1)

- **First day after wounding:**

On the superficial part of the dermis, necrosis was observed. In addition, a demarcation line consisted of polymorph nuclear leukocytes was observed under the necrotic tissue on the surface of the incisions.

Morphometric measurement of the epidermis at margins of unmanipulated wound and TPA treated groups showed increase in thickness (0.022 ± 0.008 and 0.027 ± 0.015 mm respectively) as compared with unwounded skin sections (0.011 ± 0.002 mm). It was observed that epidermal thickness of TPA treated group was higher than unmanipulated wound (Table 1). The epidermis close to the wound margin was formed of 2-3

layers in unmanipulated wound group increasing to 3-5 layers in TPA treated group (Figs. 2 and 3).

Short Spur of proliferating keratinocytes start to migrate (leading edge) to cover raw surface beneath blood clot. The leading edge ratio in unmanipulated wound and TPA treated groups was (14.69 ± 7.71 and 29.46 ± 6.01% respectively) (Table 2). Leading edge ratio of TPA treated group was significantly higher than unmanipulated wound ($p < 0.05$).

•Fifth day after wounding:

There is increase in thickness of epidermis at the wound margins of unmanipulated wound and TPA treated groups (0.055 ± 0.016 and 0.062 ± 0.021 mm respectively) (Table 1). The epidermal thickness of TPA treated group was higher than unmanipulated wound. The epidermis at the wound margin was formed of 10-12 layers in unmanipulated wound group increasing to 12-14 layers in TPA treated group. (Figs. 4 and 5).

There is no evidence of complete re-epithelialisation in unmanipulated wound group. The leading edge ratio increased in this group to (74.72 ± 15.75%) (Table 2) while in TPA treated group, skin sections showed complete re-epithelialisation in all mice of the group. The newly formed epidermis was formed of 4 - 6 layers at the central part of neoepidermis.

•Seventh day after wounding:

There was reduction in thickness of epidermis at the wound edge of unmanipulated wound and TPA treated groups (0.043 ± 0.016 and 0.048 ± 0.020 mm respectively) (Table 1). The epidermis close to the wound margin was formed of 4 - 6 layers in unmanipulated wound increased to 6-8 in TPA treated group layers. There was also complete bridging of the incisions with newly synthesized epithelial cells in all skin sections (Figs. 6 and 7). The new epidermis is formed of 6-8 layers in unmanipulated wound increased to 8-10 layers in TPA treated group.

3-Immunohistochemistry of protein kinase c alpha:-

•Unwounded skin specimens:

Skin sections revealed positive

PKCα immunoreactivity in the form of cytoplasmic brown granules in epidermal cells mainly in basal layers (Fig. 8) however, some cells showed positive membranous intercellular immunoreactivity (Fig. 9).

•First day after wounding:

Skin sections of unmanipulated wound group showed positive weak membranous immunoreactivity at the wound edge in few numbers of basal cells in the form of faint streaks with stepladder appearance inbetween cells. The leading edge showed no immunoreactivity and cells are widely separated from each other (Fig. 10).

TPA treated group showed at the wound edge strong positive membranous PKCα immunoreactivity as compared with unmanipulated wound group. Some cells in the peripheral skin close to the wound edge exhibit very faint streaks with wide stepladder appearance (Fig. 11).

•Fifth day after wounding:

Skin sections of unmanipulated wound group showed positive membranous immunoreactivity expressed in the cells at wound edge with narrow spaces between them (Fig. 12). The leading edge showed positive membranous PKCα immunoreactivity with complete formation of intercellular junctions and cells become more closely packed together.

TPA treated group showed more localization of PKCα immunoreactivity to the membrane of basal cells at the wound edge and the cells are more closely packed together. There was positive membranous and cytoplasmic PKCα immunoreactivity in the cells of the basal and some suprabasal layers in the part of neoepidermis close to the peripheral skin while the reaction was weak in the basal cells in the central part of neoepidermis (Fig. 13).

•Seventh day after wounding:

Skin sections of unmanipulated wound group showed positive cytoplasmic and membranous PKCα immunoreactivity with complete formation of intercellular junction. The neoepidermis showed strong positive cytoplasmic and membranous immunoreactivity with complete formation of intercellular

junctions at both sides of neoepidermis close to the peripheral skin (Fig.14).

TPA treated group showed results similar to the 5th day with more organization of cell junctions in the form of strong positive membranous immunoreactivity in the basal and suprabasal layers of neoepidermis and complete formation of intercellular junction at the wound edge and in the neoepidermis (Fig.15).

Table (1): Thickness of the epidermis on the wound margins in skin mice (Microscopic) (n = 4 mice for each time point).

Time point	Animal groups	
	Group A (unmanipulated wound) thickness (mm)	**Group B (TPA treated group) thickness (mm)**
1st day	0.022 ± 0.008	0.027 ± 0.015
5th day	0.055 ± 0.016***	0.062 ± 0.021***
7th day	0.043 ± 0.016**	0.048 ± 0.020*

Table (2): leading edge ratio of migrating epithelial cells of wounded skin mice (Microscopic) (n = 4 mice for each time point).

Time point	Animal groups	
	Group A (unmanipulated wounds) (Ratio %)	**Group B (TPA treated group)** (Ratio %)
1st day	14.69 ± 7.71	29.46 ± 6.01^{b}
5th day	74.72 ± 15.75**	$100 \pm 0.00^{***,b}$
7th day	100 ± 0.00	100 ± 0.00

1) **The values** are the mean ± standard deviation.
2) P^{b}<0.05 was significant versus unmanipulated wounds
3) *P* *<0.05 was significant versus previous day
4) *P* **<0.01 was highly significant versus previous day
• *P* ***<0.001 was very highly significant versus previous day

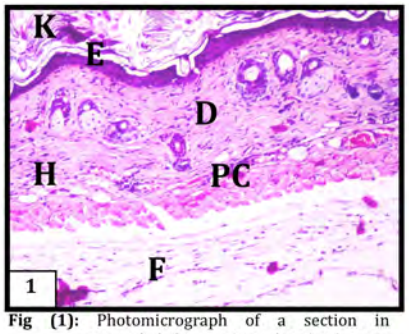


Fig (1): Photomicrograph of a section in unwounded skin sections showing keratin **(K),** epidermis **(E),** dermis **(D),** hypodermis **(H),** panniculus carnosus **(PC)** and stratum fibrosum **(F)** *(Hx&E stain x 40)*

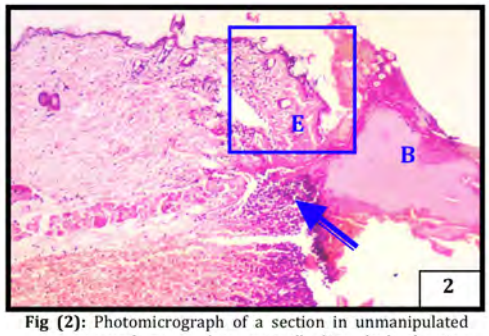


Fig (2): Photomicrograph of a section in unmanipulated wound group (-ve control) (1st day) showing necrotic tissue at wound edge **(E),** demarcation line **(arrow)** and dried blood clot **(B)** *(Hx&E stain x 40)*

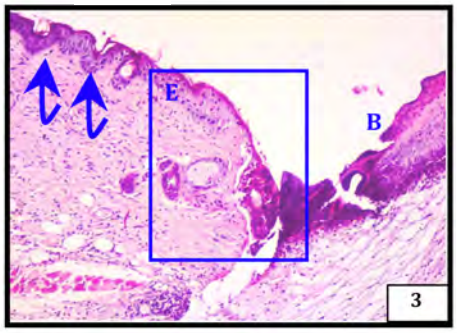


Fig (3): Photomicrograph of a section in TPA treated group (1st day after wounding) showing wound edge **(E)** , dried blood clot **(B)** and increased epidermal thickness at wound edge **(curved arrow)** *(Hx&E stain x 40)*

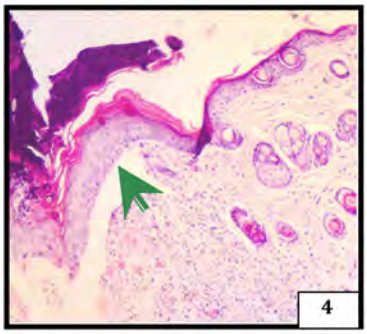


Fig (4): Photomicrograph of a section in unmanipulated wound group (5th day after wounding) showing thick leading edge **(short green arrow)** with no complete re-epitlelialisation *(Hx&E stain x 40)*

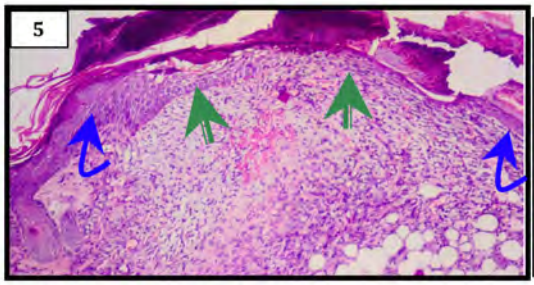


Fig (5): Photomicrograph of a section in TPA treated group (5th day after wounding) showing the two wound edges **(curved arrows)** and neoepidermis **(short green arrows)** *(Hx&E stain x 40)*

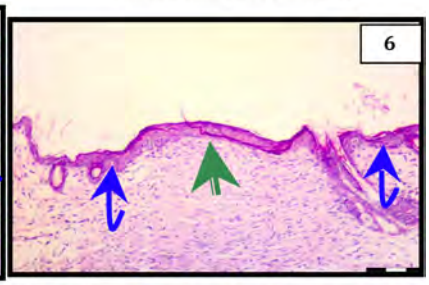


Fig (6): Photomicrograph of a section in unmanipulated wound group (7th day after wounding) showing the two wound edges **(curved arrows)** and neoepidermis **(short green arrows)** *(Hx&E stain x 40)*

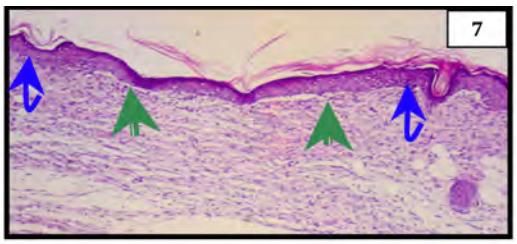


Fig (7): Photomicrograph of a section in TPA treated group (7th day after wounding) showing the two wound edges **(curved arrows)** and decrease in thickness of neoepidermis as compared with 5th day of the same group **(short green arrows)** *(Hx&E stain x 40)*

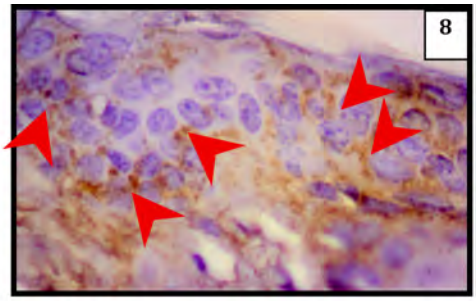


Fig (8): Photomicrograph of a section in unwounded skin sections showing cytoplasmic positive immunoreactivity in the form of diffuse brown granules **(arrow heads)** mainly in the basal layers *(immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*

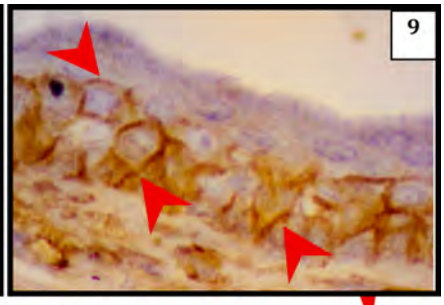
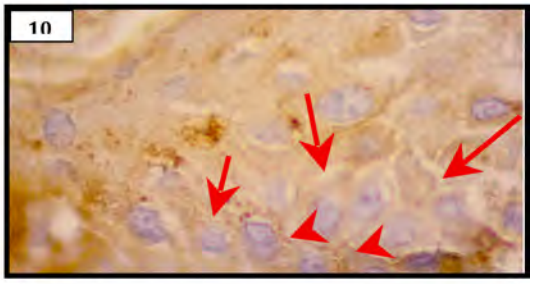


Fig (9): Photomicrograph of a section in unwounded skin sections showing membranous positive immunoreactivity expressed as brown dots drawing the cell membranes between epidermal cella **(arrow heads)** mainly in the basal layers *(immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*

Fig (10): Photomicrograph of a section in unmanipulated wound group (1st day after wounding) showing weak positive immnoreactivity localized to the cell membrane especially basal cells **(arrow heads)** and in the form of faint streaks with narrow stepladder appearance **(arrow)** between cells in intercellular junctions at wound edge *(immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*



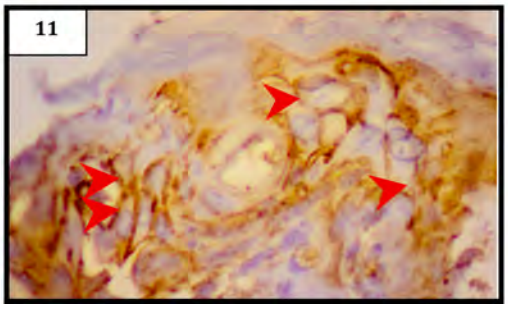


Fig (11): Photomicrograph of a section in TPA treated group (1st day after wounding) showing strong positive PKCα immunoreactivity in the membrane of the cells **(arrow heads)** in the hyperplastic epidermis close to the wound margin *(immunohistochemical technique for PKCα with haematoxylin counterstain, x400)*

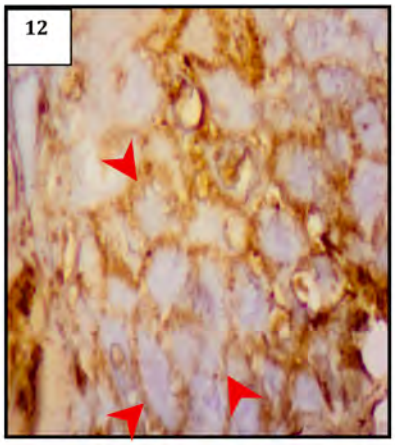


Fig (12): Photomicrograph of a section in unmanipulated wound group (5th day after wounding) showing positive membranous PKCα immunoreactivity with complete formation of intercellular junctions at wound edge **(arrow heads)** *(immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*

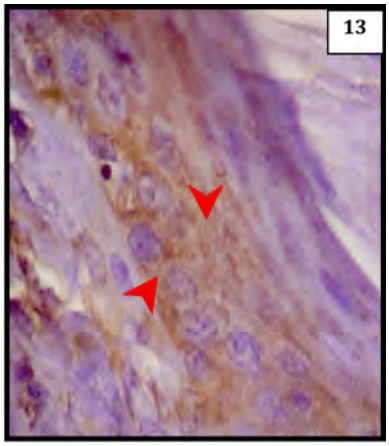


Fig (13): Photomicrograph of a section in TPA treated group (5th day after wounding) showing positive cytoplasmic PKCα immunoreactivity in the basal and suprabasal layers and cells become more closely packed together in neoepidermis close to wound edge **(arrow heads)** *(immunohistochemical technique for PKCα with haematoxylin counterstain, x400)*

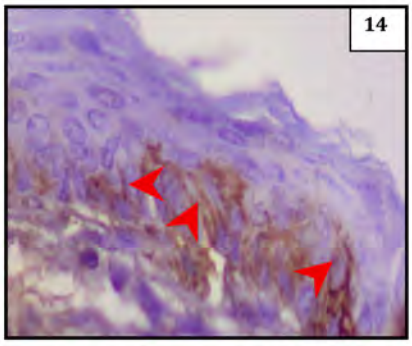


Fig (14): Photomicrograph of a section in unmanipulated wound group (7th day after wounding) showing positive membranous immunoreactivity drawing the membrane of the cells **(arrow heads)** in the intercellular junctions of the basal layers in neoepidermis *(immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*

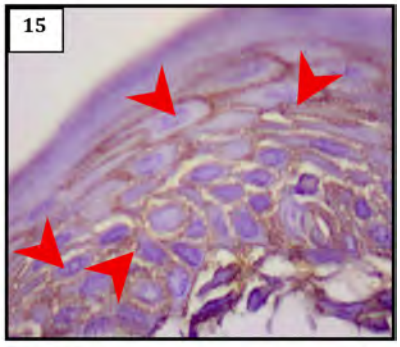


Fig (15): Photomicrograph of a section in TPA treated group (7th day after wounding) showing positive membranous immunoreactivity expressed as brown dots drawing completely the membrane of the cells **(arrow heads)** in new intercellular junctions in neoepidermis *(Immunohistochemical technique for PKCα with haematoxylin, counterstain, x400)*

Discussion

Cutaneous wound healing is a complex process requiring the collaborative interactions between distinct cell types that reside in different compartments of the skin. The basic steps include clotting, inflammation, re-epithelialisation, remodeling of the extracellular matrix, and contraction of the wound [1].

In the present study, histological assessment of skin sections in unmanipulated wound group showed time course increase of epidermal thickness on wound margin. Similar finding was reported by[12] in which by one day after surgery the epidermis was thickened at its cut edges because of the mitotic activity of basal cells. In the present work, on the other hand, skin sections in unmanipulated wound group showed decrease in epidermal thickness on the wound edges on the 7th day. This can be explained by the fact that the skin try to regain its homeostasis by differentiation of keratinocytes and excess cells undergo apoptosis to regain thin epidermis [13].

In the present study, skin sections in unmanipulated wound group revealed time course migration of keratinocytes to cover the wound gap till complete re-epithelialisation on 7th day. This finding is in agreement with the previous results of[14] who found that re-epithelialisation started on 6th day in about 20% of wound group. They also reported that the stage of 4 to 7 days post wounding is marked by scab formation and migration of the epidermal edges.

In the present study, skin sections in TPA treated group showed increase of epidermal thickness on wound margin more than unmanipulated wound. This was in agreement with[7] who noticed that single topical application of TPA at 10 µg induced the formation of a hyperplastic epidermis consisting of four to six nucleated cell layers of 42 ± 4.3 µm (mean ± SD) thickness on day 2 in the wild-type mice. In the present study, skin sections in TPA treated group revealed time course increase in leading edge ratio more than unmanipulated wound and re-epithelialisation started earlier on 5th day .

The timing of re-epithelialisation and sequence of hyperplasia of neoepidermis was more or less in agreement with [15] who reported that that by 3 days after TPA treatment, there is almost complete regeneration of the epidermis, and over the next several days there is a marked hyperplastic response in the epidermis.

PKCα had role in cell activities involved in wound healing as cell proliferation, migration, differentiation, secretion of chemical mediators and modulation of cell adhesion[4]. Immunohistochemistry stained sections of unwounded skin sections for PKCα showed positive cytoplasmic and membranous immunoreactivity mainly in basal layers. This was in agreement with[16] who reported that immunohistochemical and light microscopy of PKC within mouse skin revealed that basal epidermal cells displayed diffuse cytoplasmic staining by anti-PKCα antibody. They also investigated PKCα in intact mouse skin by immunogold electron microscopy techniques and reported that Gold beads were localized primarily over the cytoskeleton, including tonofilaments converging on tight junctions - desmosomes at the cell surface and at cell membranes.

Examination of wound edge of skin sections of unmanipulated wound group showed positive membranous immunoreactivity at the wound edge of basal cells in the form of faint streaks with step-ladder appearance inbetween cells in the 1st day. Whereas, the cells showed positive membranous immunoreactivity with narrow spaces between them close to the peripheral skin in the 5th day progressing to positive cytoplasmic and membranous PKCα immunoreactivity with complete formation of intercellular junction on the 7th day. This was in agreement with[4] who reported that the distribution of PKCα was found to change after wounding. They stated PKCα was found to be localized to the cell periphery. The cause of translocation to the cell membrane could be explained by colocalization of PKCα with the desmosomal plaque [2].

Immunohistochemical study of wound edge of skin sections of TPA treated group during the 1st

day showed strong positive PKCα immunoreactivity localized more to the cell membrane as compared with unmanipulated wound group. This was in agreement with[17] who reported that upon activation, PKC enzymes are translocated to the plasma membrane by RACK (receptor for activated C kinase) proteins to conduct various other signal transduction pathways. On the 5th day and 7th day, re-epithelialisation process was completed with strong immunoreactivity to the membrane of basal cells at the wound edge and the cells are more closely packed together with complete formation of intercellular junction.

Examination of progress of wound closure and its relation to protein kinase c alpha immunoreactivity in skin sections of unmanipulated wound revealed that the leading edge in the 1st day showed no immunoreactivity. In the 5th day, leading edge showed positive membranous immunoreactivity with complete formation of intercellular junctions in the basal layers in the part of leading edge close to the peripheral skin and its central part. In the 7th day, The neoepidermis showed strong positive cytoplasmic and membranous immunoreactivity of the basal and suprabasal with complete formation of intercellular junctions mainly at both sides of neoepidermis close to the peripheral skin.

This could be explained by that the basal cells are the first migrating cells so it begins to reform cell junctions while suprabasal cells migrate later so the spaces still wide between them. This was in agreement with[4] who reported that PKCα was found to be enriched at the leading edges of lamellipodia both at the edge of the sheet and submarginally. Krawczyk and Wilgram (1973)[18] also reported that the dissolution of desmosomes is a key step in wound healing. They found that restoration of desmosomes during reepithelialization occurs in several steps.

Skin sections of TPA treated groups revealed that the leading edge in the 1st day showed no immunoreactivity progressing to positive membranous and cytoplas-

mic PKCα immunoreactivity in the cells of the basal and some suprabasal layers in the part of neoepidermis close to the peripheral skin on the 5th day ending to include all parts of neoepidermis even the central part on the 7th day. This was in agreement with [8] who stated that activation of PKC alpha triggerd desmosome formation in low-calcium conditions as in case of wound edge in the present study, or in cells lacking desmosomes as in case of leading edge or neoepidermis in the present work owing to mutation of adherens junction proteins.

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BENHA MEDICAL JOURNAL

THE EFFECT OF STIMULATION OF PROTEIN KINASE Cα ON EPIDERMAL WOUND HEALING IN MICE

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BIOCHEMICAL ALTERATIONS IN ADIPONECTIN AND THE ACTIVITY OF MYELOPEROXYDASE IN ACUTE MYOCARDIAL INFARCTION INDIVIDUALS

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Abstract

The aim of the present study is to find a relationship between plasma Adiponectin level, Myeloperoxidase (MPO) activity, lipid profile and serum nitrite / nitrate and severity of Acute myocardial infarction (AMI) disease.

In order to achieve this aim 30- AMI patients ranged from 35 to over 70 years old and 10- clinically healthy subjects used as control.

The result of the present study showed a significant association between the occurrence of AMI and low Adiponectin level, high MPO activity, low Nitrite level, low Nitrate level, high total cholesterol level, high Triacyleglycerols (TG) level, high Low density lipoprotein-cholesterol (LDL-ch) level, low High density lipoprotein-cholesterol (HDL-ch) level, and high LDL/HDL-ch ratio. These parametrers may all be regarded as predictors or risk factors for AMI.

The findings of the present study suggest that hyperlipidemia and vascular inflammation, and oxidative stress are primary interacting mediators in the pathogenesis of AMI.

Introduction

Acute myocardial infarction (AMI) is a serious medical emergency syndrome resulting in most cases from complete thrombotic occlusion of infarct related coronary artery and in a substantial proportion of patients with suspected myocardial infraction, biochemical markers are needed for clinical decision making at the time of admission, because electrocardiographic (ECG) recordings may be inconclusive [1].

The role of adipose tissue as an endocrinal organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, which is an adipose tissue-specific protein accounts for 0.01% of the total plasma proteins concentration. Increasing attention has been paid to the vascular effects of adiponectin, where adiponectin was hypothesized to play a role in AMI [2].

Myeloperoxidase (MPO) is a member of heme peroxidase superfamily, abundant in neutrophils, monocytes, and macrophages. This enzyme plays a critical role as host defenses and inflammatory tissue injury. It also played a pathophysiologic role in AMI [3].

Nitric oxide (NO) is a signaling molecule involved in the regulation of many biological processes including activities in the cardiovascular, nervous, and immune systems. It also had a role in both acute and chronic inflammation. Moreover, NO was proposed to play a role in AMI atherogenesis [4].

The aim of the present study was to show the biochemical relationship between Adiponectin, Myeloperoxidase activity, Nitric oxide metabolites (nitrite / nitrate) and Lipid profile in acute Myocardial infarction patients.

Materials and Methods

This study conducted on 30 - patients who came in Emergency Center in Hospital Faculty of Medicine Alexandria University) were complaining of acute chest pain and (10- healthy individuals) as a control healthy group. After application of the Inclusion Criteria and the Exclusion criteria for Diagnosis of AMI patients according to (5): They classified into four groups according to ages: Group I: Control healthy individuals consists of 10-persons with ages ranged from 35-70 years.

And diseased groups : -

Group II: Consisted from 10 - AMI patients with age from 30 to 50 years.

Group III: Consisted from 10 - AMI patients with age from 51 to 70 years.

Group IV: Consisted from 10 -

AMI patients with age more than 70 years.

The diagnosis of AMI was finally established at coronary care unit (CCU) by a cardiologist guided by the world health organization (WHO) criteria.

Sampling

Ten ml blood were withdrawn from cardiac catheter during coronary angiography for every patient and control fasting healthy subjects after overnight fasting and collected. The blood samples divided into 2 portions the first one poured on 5% Ethylenediaminetetraacetic acid (EDTA). Plasma samples were collected after centrifugation and used freshly for determination of Adiponectin concentration [6], The resulting granulocyte/ erythrocyte pellets were further processed for separation of Neutrophils to assess myeloperoxidase activity[7&8].

The remained 5ml blood poured in tubes without anticoagulants allowed to clot then, and centrifuged for isolation of serum which used freshly for nitric oxide metabolites (Nitrate/ Nitrite)[9], Total cholesterol[10], Triacylglycerols (TG)[11]. HDL-ch and LDL-ch concentrations[12], and VLDL-ch [13].

Results

The presented data revealed that AMI is accompanied by significant decrease ($P<0.05$) in the mean values of plasma adiponectin level, serum nitrite, serum nitrate and serum HDL-cholesterol and a significant increase ($P<0.05$) in the activity of myeloperoxidase, serum total cholesterol, triacylglycerol, LDL-cholesterol and VLDL-cholesterol on comparison with the mean values recorded in the control healthy individual group.

Table (1): Mean values ± S.E. of *Plasma Adiponectin (ng/ml)*, *MPO activity (unit/mg protein)*, *Serum Nitrite (µmol/L) and Serum* Nitrate *(µmol/L)* in control healthy and AMI diseased individuals.

Group	***Plasma Adiponectin (ng/ml)***	***MPO activity (unit/mg protein)***	***Serum Nitrite (µmol/L)***	***Serum* Nitrate (µmol/L)**
Group I *(Healthy control)*	6408.80 ± 80.75	2.35 ± 0.71	6.70 ± 0.33	10.78 ± 1.11
Group II *(30-50 years)*	2730.90 ± 96.50*	5.99 ± 0.89*	4.25 ± 0.29	6.84 ± 0.97
Group III *(51-70 years)*	2580.53 ± 82.73*	9.13 ± 0.77**	3.38 ± 0.39*	6.01 ± 0.89*
Group IV *(More than 70 years)*	2004.80 ± 71.50**	14.57 ± 1.11**	2.17 ± 0.91**	4.75 ± 0.38*

X ± S.E. = Mean ± standard errors X = Means
No significant (Pp > 0.05) * Significant at (P < 0.05)
** High significant at (P < 0.01) *** Very high significant at (P < 0.001)

Table (2): Mean values ± S.E. of *Serum Total cholesterol (mg/dl), Triacylglycerols (mg/dl) ,HDL-cholesterol (mg/dl), LDL- cholesterol (mg/dl)* and *VLDL-cholesterol (mg/dl)*in control healthy and AMI diseased individuals.

Group	***Serum Total cholesterol (mg/dl)***	***Serum Triacylglycerols (mg/dl)***	***Serum HDL-cholesterol (mg/dl)***	***Serum LDL-cholesterol (mg/dl)***	***Serum VLDL-cholesterol (mg/dl)***
Group I *(Healthy control)*	138.60±3.40	97.25±2.11	49.81±2.13	70.10 ±3.15	19.45±0.42
Group II *(30-50 years)*	198.75±3.91	174.28±3.09*	32.40±2.11	130.61±4.11*	34.86±0.62*
Group III *(51-70 years)*	236.66±5.01*	200.81±3.27**	33.92±2.75	162.59±4.19**	40.03±0.66**
Group IV *(More than 70 years)*	265.35±5.90**	250.13±4.17**	24.16±2.25*	191.31±4.89***	50.13±0.84**

X ± S.E. = Mean ± standard errors X = Means - No significant (Pp > 0.05)
* Significant at (P < 0.05) ** High significant at (P < 0.01)
*** Very high significant at (P < 0.001)

Discussion

Millions of patients present in hospitals annually with chest pain, but only 10-15% has myocardial infarction which is the major killer in the western industrialized countries.. sensitive biochemical assays are essential for identification of novel markers associated with the extent or severity of AMI allowing better insight into the pathobiology of coronary atherosclerosis and may facilitate the development of preventive and therapeutic measures for that disease [14].

The present study showed that plasma adiponectin level was significantly lower in AMI patient groups (group II, III and IV compared to the control group which were in agreement with [15&16] who reported that the link between hypoadiponectinemia and AMI events which might be mediated by angiographically for quantified the disease severity.

The recorded low adiponectin concentration in AMI patients was could be attributed due to adiponectin gene mutations in AMI patients where, such mutations were associated with low adiponectin concentration as stated that by[17].

Moreover, the recorded decreased values of adiponectin in AMI may be related to accumulation of adiponectin in atherosclerotic vascular walls through its binding to collagens that are abundant in the vascular intimae. Such accumulation may suppress adiponectin elimination half-life from plasma. [18].

The present study showed a significant negative correlation between adiponectin level and age in AMI patients. This result could be due to a possible disturbed adipokines synthesis or secretion in old age individuals, an explanation that might support the concept of old age being a risk factor [19].

The present study showed a significant positive correlation between adiponectin and nitric oxide metabolites (nitrite/nitrate) levels which could be explained by the assumption that adiponectin increases NO production by promoting the activity of eNOS or by ameliorating the suppression of eNOS

activity by ox-LDL [20].

The MPO activities serve as a strong and independent predictor of endothelial dysfunction in human subjects, giving a mechanistic link between oxidation, inflammation and cardiovascular disease [21].

The present study showed a significant increase in MPO activity in AMI patient groups (group I, II and III) compared to the control subjects this might be related to it's secreted from activated leukocytes under inflammatory conditions which promotes numerous pathological events [22].

In this respect MPO has been shown to active metalloproteinases and to promote destabilization and rupture of atherosclerotic plaque surface, thus MPO could be related to the future risk of AMI events [21].

The present study showed a significant negative correlation between MPO activity and nitric oxide metabolites (nitrite/nitrate) levels due to it·s uptake by endothelial cells through transcytotic process, to accumulate within the sub-endothelial space, and to consume NO thus interfering with its atheroprotective effect [23].

The present study showed that serum levels of both nitric oxide metabolites (nitrite and nitrate) were significantly lower in AMI patient groups compared to the control group.

The degree of decrease in nitrite level was correlated with the increasing number of cardiovascular risk factors. and there was high level of NO metabolites in both acute and chronic inflammatory conditions including atherosclerosis [24].

Reduced NO bioavailability is the hallmark of endothelial dysfunction occurring early in cardiac diseases. It has potentially anti atherosclerotic as it inhibits platelet aggregation and adherence to endothelial cells, monocyte adherence to endothelial cells, expression of monocyte chemoattractant proteins, vascular smooth muscle proliferation, and in vivo intimae proliferative response to cardiac injury [25].

The detected decreased values of NO could be related to the hypercholesterolemia was found to be accompanied by increased super-oxide production which accounts for significant proportion of NO deficit [26].

Moreover, it was reported that dyslipidemia decreases basal activity and protein expression of cGMP-dependent protein kinase, and increases activity of cGMP-phosphodiesterase. The latter effect results in interference with NO signaling pathway as stated by [27].

Also the significantly decreased NO metabolites in AMI patients may be due to the hypertension followed AMI as stated by[28] Who reported that hypertensive patients showed oxidation of BH4 which results in loss of NOS demyelization and generation of significant amounts of super oxide besides reduction of endothelial NO production. Meanwhile L-arginine, a NO precursor, acutely improves endotheliul-dependent dilatation of brachial artery in hypertensive patients.

The present study showed a significant positive correlation between levels of NO metabolites and adiponectin and a significant negative correlation between levels of NO metabolites and MPO activity.

The low level of NO metabolites in the current study could be collectively due to Hypoadiponectinemia, which results in decreased production of NO and the increased MPO activity which results in increased NO scavenging, and MPO-derived oxidants (e.g. HOCL, chlorinated arginine) on NOS as proved by [25].

The recorded low level HDL-ch in AMI patients could be due to HDL has a protective effect against the inflammation followed AMI which has been attributed to its role in reverse cholesterol transport. This is beside the possible anti - inflammatory and antioxidant actions of HDL It can prevent LDL oxidation by hydrolyzing lipid peroxides, hydroperoxides and hydrogen peroxide and Paraxonase can also maintain the capacity of HDL to induce reverse cholesterol transport. [29]

In addition, HDL-associated enzyme, lecithin cholesterol acyl transferase (LCAT), can prevent the accumulation of oxidized lipids in LDL and increases lipoprotein oxidation and endothelial dysfunction [30].

The recorded high serum level of cholesterol might be due to induction of thrombosis through stimulating platelet adhesion and aggregation, enhancing the procoagulant activity of endothelium, reducing the fibrinolytic activity of endothelium, contributes to the formation of atherosclerotic plaques in arteries [31].

Moreover the hypertriacylelglyceridemia causes an independent risk factor for AMI, since high circulating levels of TG-rich lipoproteins can inhibit the efflux of cholesterol from macrophages to apo-A1, they also directly influence endothelial function through modulating NO and endothelin-1. and may thereby inhibit the arterial reverse cholesterol transport and promote the formation of atherosclerotic lesion [32].

The present study showed a significant correlation between lipid profile and Adiponectin and MPO. In addition, a significant correlation was found between lipid profile and NO metabolites as mentioned before [33].

In conclusion, AMI occurs accompanied by low levels of adiponectin, nitrite, nitrate, and HDL-ch, and high levels of MPO activity, total cholesterol, TG, LDL-ch ratio. These may all be regarded as risk factors and could be used as diagnostic tools for AMI.

The findings of the present study show the importance of NO as a predictor of AMI severity, a common mediator for the action of adiponectin and MPO, besides its possible interaction with dyslipidemia, hypertension. These findings point to the importance of NO in diagnosis and treatment of AMI.

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BIOCHEMICAL ALTERATIONS IN ADIPONECTIN AND THE ACTIVITY OF MYELOPEROXYDASE IN ACUTE MYOCARDIAL INFARCTION INDIVIDUALS

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PEDIATRIC ILIOINGUINAL/ILIOHYPOGASTRIC BLOCK (HIGH OR LOW APPROCHES)
"ANALGESIC & SURGICAL OUTCOME-SATISFACTION "

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Abstract

Background: *Ilioinguinal/iliohypogastric (IHNB) levobupivacaine produces effective analgesia after herniorrhaphy. This present study comparing two different block techeques aiming to detect the block effectiveness, the postoperative analgesic outcome, the surgon satisfation and surgical time prolongation in some cases of inguinal hernia repair have been observed in patients underwent IHNB block with accidental injection of the LA in the surgical field and to which extent this problem affect the surgical time, performance and results.*

Patients & Methods : *60 male pediatric patients admitted to pediatric surgery department IbnSina Hospital - ministry of health in Kuwait for Inguinal hernia repair, aged from 3- 8 years, body weight 25 Kg or less, subdivided into two groups each group 30 patient underwent a separate analgesic technique: just after completion of anesthesia induction & LMA insertion in Group I (high block group-pediatric high approach) 1cm above and 1 cm medial to the anterior superior iliac spine (ASIS) nerve block using 0.5 ml/kg of 0.5% levobupivacaine HCL plus 0.5ml epinephrine 1/200000. Group II (low block group-pediatric low approach) =1 cm below and 1 cm medial to the anterior superior iliac spine (ASIS) nerve block using 0.5 ml/kg of 0.5% levobupivacaine plus 0.5ml epinephrine 1/200000 .*

In both groups and just after the end of surgery& before LMA removal Intramuscular (IM) pethedine 1mg/Kg.

For both groups an increase in heart rate under General anesthesia indicates block less effectiveness or even failure.

Results : *(OPS) pain score: Group II showed significant increase in comparison to group I at 60, 90,120minutes. Heart rate (HR) values in the 1st 20 min after surgical incision showed significant increase*

in Group II in comparison to Group I at the 0 ,5,10 minutes. Duration of surgery showed Significant increase in pure operative time in Group II In comparison to Group I. Postoperative duration to discharge showed Significant increase in postoperative duration to home discharge in Group II In comparison to Group I. As regard the surgeon satisfaction about the field clarity showed that Group II revealed 20% surgeon non satisfaction compared to 0% in Group I .

Conclusion: *Ilioinguinal /iliohypogastric block at level above the ASIS just after anesthesia induction in pediatrics plus the IM pethedine injection just before recovery highblock group (group I) produces efficient intraoperative &postoperative analgesia less operative time, early home discharge postoperatively with high surgeon satisfaction.*

• ***Key words*** *Ilioinguinal, Iliohypogastric, pediatric, Approaches, Block.*

Introduction

Preemptive analgesia is crucial for pediatric patients subjected to surgery as that age of patients mostly can't explain their sufferings & pains except by crying and aggressive movement. Pain following hernia repair is moderate to severe and mostly opioids as a single analgesic is not enough to control such pain. (1) Simple opioid analgesic injection has the drawbacks of respiratory depression & postoperative nausea, vomiting, sedation and dizziness. Ilioinguinal / iliohypogastric block, when perfectly done, utilizing levobupivacaine [less cardiotoxic amide LA & pure S (-)- enantiomere of racemic bupivacaine] (15), alone produce to some extent effective pain control after herniorrhaphy[1].

Ilioinguinal nerve originates from the lowest thoracic&1st lumbar nerve roots then goes anteriorly near by the anterior superior iliac spine(ASIS) then branches to supply the tissues of the inguinal region and upper scrotum[2]. IHNB blocks is effective for Analgesia and / or anesthesia for any somatic procedure at the lower abdominal wall / inguinal region such as inguinal herniorrhaphy [3]. IHNB for herniorrhaphy helps in rapid oral intake after surgery, less need for Postoperative analgesia & shorter time to home readiness compared to spinal anesthesia.[4]

Anatomical Consideration : Union between lowest thoracic & 1st lumbar nerve roots gives rise to ilioinguinal nerve which comes out of the lateral edge of the psoas muscle; then pierces the anterior abdominal wall near the iliac crest &below the hypogastric nerve. then pierces the transversus abdominis and internal oblique muscles supplying them& send neural branches connection to the iliohypogastric nerve. The nerve then supplies sensory branches to innervate the symphysis pubis, the superior and medial walls of the femoral triangle, the penil root & anterior part of the scrotum in the male or the mons pubis and labia majora in the female.(4)

Patients & methods

After approval by the ethics committee of the regional Medical board and with parents written informed consent, 60 male pediatric patients (dmitted to pediatric surgery department in IbnSina pediatric surgery Hospital - Ministry of health in Kuwait) were included in this present study &why male only ? this is for the seek of the surgical importance of the presence of the spermatic cord near by the surgical field during dissection which requires clear undisturbed surgical field planes(surgeon opinion goal directed issue).

Full detailed medical history from the parents was taken .The selection of the patient as ASA physical status I or II, undergoing minor day case surgical procedures in supine position in specific (Inguinal hernia repair), admitted to pediatric surgery department, patients aged from 3- 8 years & body weight 25 Kg or less, subdivided into two groups each group underwent a separate(block-analgesic) technique :

Group I (high block group): IHNB block performed simultaneously by locating a point (pediatric high approach) (7) 1cm above and 1 cm medial to the anterior superior iliac spine (ASIS) nerve block using 0.5 ml/kg of 0.5% levobupivacaine HCL (Chirocaine 5mg/ml -0.5% -10 ml plastic vials each) plus 0.5ml epinephrine 1/ 200000(5) can be injected to produce surface analgesia just after completion of the general anesthesia induction IV line fixation & LMA insertion, then after the end of surgery & just before LMA re-

moval Intramuscular (IM) pethedine 1mg/Kg in the lateral aspect of the quadriceps femoris muscle.

Group II (low block group): IHNB block performed simultaneously by locating a point (pediatric low approach) (9) =1 cm below and 1 cm medial to the anterior superior iliac spine (ASIS) nerve block using 0.5 ml/kg of 0.5% levobupivacaine HCL (Chirocaine 5mg/ml -0.5% -10 ml plastic vials each) plus 0.5ml epinephrine 1/ 200000 (5)can be injected to produce surface analgesia just after completion of the general anesthesia induction, IV line fixation &LMA insertion, then after the end of surgery& just before LMA removal, (IM) pethedine 1mg/Kg in the lateral aspect of the quadriceps femoris muscle. The postoperative analgesic outcome of high and low techniques of IHNB block is the same[9] For both groups an increase in heart rate during the 1st 20 minutes after surgical incision under effective General anesthesia indicates less effective or even unsuccessful block.

Exclusion criteria : Obesity or bodyweight over 25 Kg ,age above 8 years, infection at the site of the block, temperature ≥ (38°C), respiratory tract infection, bronchial asthma ,and monoamine oxidase inhibitors treated patients as these drugs with pethdine such patients may suffer agitation, delirium, headache, convulsions.

Basic monitoring tools Non invasive blood pressure (NIBP), arterial O2 saturation oxymetry probe (SaO2), capniography, and ECG. There was no sedative or analgesic premedication. LMA Size No 1 for child from <5 Kg bodyweight ,No 1.5 for child from 5-10Kg bodyweight, size No 2 for child 10-20Kg ,and size no 2.5 for children from 20-25 Kg bodyweight .

For all cases preoperative fasting fixed time 6 hours, sevoflurane 8 % inhalational induction with N2O/O2 ratio 2/1 via mask T-piece bag rebreathing open system targeting deep inhalational anesthesia with a preserved respiratory drive, during that time Intravenous access was secured and IV fluid infusion connected and started (Dextrose 5% in Quarter

Normal saline). Muscle relaxants were avoided. After loss of eyelid reflex, LMA insertion (after back lubrication positioning performed according to the published LMA instruction manual, semi-inflated cuff with the back toward the hard palate and the anterior cuff facing the tongue upper surface then introduction deep till highest resistance then inflating & securing the LMA). Airway patency & lung aeration was confirmed by regular full capniogram waves and bilaterally chest breath sounds auscultation. The LMA was then taped to the chin and upper jaw. Spontaneous respiratory drive dependant ventilation was instituted using a semi closed circle-absorber anesthesia system. The patient's head was supported in central position using a circular head rest.

IHNB blocks technique: The skin site of block injection was sterilized using Alcohol 70%. The block was performed by experienced anesthetist performed at least 400 IHNB blocks, the technique of IHNB nerves block in pediatrics was performed simultaneously by locating a point differs according each group as follow:

Group I : (high block technique): 1cm above and 1cm medial ASIS[8].

Group II : (low block technique)1cm below and 1cm medial ASIS[9] wall penetration to 1.5 cm should prevent this complication of gut perforation, using 22 gaged needle that was inserted perpendicular then redirected laterally and medially in 45 degrees fan wise manner also up and down infiltration (fan technique), needle introduction through the 'tented' skin at the located point then after detecting the first 'fascial click following penetrating the (external oblique Aponeurosis and the internal oblique muscle fascia), The needle was advanced slowly with gentle pressure on the plunger of the syringe a sudden loss of resistance is felt, negative aspiration, 0.5 ml/kg of 0.5% levobupivacaine HCL [less cardio- toxic amide LA & pure S (-)- enantiomere of racemic bupivacaine][15] (Chirocaine 5mg/ml) plus 0.5ml epinephrine 1/200000 was injected during needle withdrawal, in addition SC infiltration of 1/3 of the total LA volume along a line from the pubic

tubercle till the ASIS improve the block quality by blocking the upcoming coetaneous branches of pudendal nerve [10].

The anesthesia was continued only via inhalational agents in the form of sevoflurane 3-4 % and N2O/O2 ratio 2/1 fixed for all cases with maintenance of the normal respiratory drive of the patients and any case lost the drive and needed mechanical ventilation to be pressure controlled mode with inspiratory pressure 12cmH2o in a rate of 20-25 breath /minute and to be manipulated guided by an End tidal Co2 of 30-35mmhg all over the operative time putting in mind an effective inhalational anesthetic level to avoid light anesthesia drawbacks like laryngiospasm, bronchospasm, desaturation, coughing and bucking.

After at least 5 minutes of N2O closure LMA removal out of patients was done under deep anesthesia (to avoid N2O induced diffusion hypoxia, then 5 Litres O2 100% mask utilizing chin lift jaw thrust maneuver ensuring patent ventilated airway till complete recovery (opening eyes ,moving limbs with a continuous effective ventilation & maintained respiratory drive). Then children after 6 hours were discharged home, pain free without any medical indication for ward admission. Oral acetaminophen suspension (25 mg/kg) for further analgesia to be given by their parents at home.

The following parameters & scores to be recorded in the following order :

Postoperative modified objective pain score "Diagrams" (OPS) (12) just after LMA removal=0 minutes, then at minute 30, 60, 90, 120, 150, 180 (see below) were monitored in the recovery room 30 min &then in the day case unite. OPS score was used to detect the effectiveness of postoperative analgesia using variables of objective behavioral (agitation, crying, posture, movement, and pain localization. Each criterion scores from 0 to 2 to give a total score from(0-10) are assessed. Additive postoperative analgesia to be given to children when their OPS reached 4 or more to be given rectal paraceta-

mol (25mg/kg) as supporting analgesic for all the study cases.

Duration of postoperative analgesia was defined as the time from LMA removal till the first administration of rescue analgesia.[10].

Pure operative time (from skin incision till skin closure) recorded.

Postoperative duration to discharge surgeon satisfaction (satisfied = 1 & unsatisfied = 2).

Statistical Analysis :

Data entry and analyses were performed using SPSS statistical package version 10 (SPSS, Inc., Chicago, IL, USA). The Chi-Square test ($\chi 2$) was used to test the association between raw and column variables of nominal data. Student t-test (unpaired) was conducted to compare the mean of continuous variables for the two groups at each point of time. The t-test was used in data proved to be normally distributed (Kolmogrove-Smirnov test), while Man-Whitney-U test was used for data away from normal distribution .The P value of <0.05 indicates significant results.

Results

AS regard; Demographic data shown in Table (1) values are in (Median &Range) showing no significant difference in between the two groups.

As regard; OPS PAIN SCORE shown in Table (2) AT 0, 30, 60, 90, 120, 150, 180 min postoperative values are in (mean ± Standard deviation) Group II shows significant increase in OPS pain scoring in comparison to group I at 60, 90, 120 minutes statistical results indicating less analgesia in group II in comparison to group I.

OPS score 4 is the upper limit in this present study beyond which additional analgesia should be given at postoperative minute 150 and 180 and this indicates the endpoint of the analgesia of both techniques.

AS regard; Heart rate (HR) shown in Table (3) taken as a predictor of block success in the 1st 20 min after surgical incision (Values are in Median & Range) table shows significant increase in HR in Group II in comparison to Group I at 0, 5,10 minutes statis-

tical result after skin incision a strong predictor of insufficient block analgesia in the low block technique (group II) in comparison to high block technique (group1).

As regard; Duration of surgery & postoperative duration to discharge shown in Table (4) values are in (mean + / - SD) showed Significant increase in pure operative time in Group II In comparison to Group I. Also table (4) showed Significant increase in postoperative duration to home discharge in Group II In comparison to Group I .

As regard; The surgeon satisfaction about the field clarity in such a simple easy surgery Table (5) Showed 20% surgeon no satisfaction in group II compared to 0% in Group I .

(Diagram 1) Modified OPS Score (12)

Crying	No	=0
	Distractible	=1
	Screaming	=2
Agitation	Asleep-calm	=0
	Mild can be comforted	=1
	Hysterical not comforted	=2
Movement	No	=0
	Restless in bed	=1
	Wide movement	=2
Position	Normal	=0
	Flexed	=1
	Hold injury site	=2
Verbal- Pain localization	Asleep	=0
	Cant localize	=1
	Can localize	=2

Table (1) : *Demographic data* Values are in (Median & Range) .

Demographic data (Median &Range)	Group 1	Group 11
Age (months)	58(40-83)	62(42-88)
Weight (Kgs)	15(6-21)	15 (7-23)

Table shows no significant difference in between the two groups.

Table (2): *OPS PAIN SCORE* Values are in mean ±Standard deviation (mean+/-SD).

Group Minutes / Time	Group 1 Pain ops score Mean ±std	Group 11 Pain ops score Mean ±std	T test (p value)
0 min	0±0	0±0	-
30 min	0±0	0±0	-
60 min	1.856±(0.548)	2.247±(0.651) *	0.012
90 min	1.981±(0.414)	2.403±(0.507) *	0.001
120 min	2.691±(0.43)	3.792±(0.548) *	0.000
150 min	4.182±(0.651)	4.346±(0.73)	0.407
180 min	4.993±(0.776)	4.054±(0.679)	0.418

* = Group II shows significant increase in OPS pain scoring in comparison to group I (Mann-Whitney test)). OPS score ≥ 4 is the higher limit Beyond which additional analgesia should be given as at postoperative minute 150 and 180 and this indicates the endpoint of the analgesia of both techniques.

Table (3): Heart rate (HR) (Values are in Median & Range).

HR / Time min	Group 1	Group 11
0 min	91(77-99)	105(81-117)*
5 min	91(78-99)	103(81-119)*
10 min	92.5(78-115)	105.5(86-120)*
15 min	97(79-123)	106.5(86-122)
20 min	99(88-125)	108.5(86-122)

* = Significant increase in HR in group Group II in comparison to Group I.

Table (4) : *Duration of surgery & postoperative duration to discharge* Values are in (mean+/-SD).

Group / Duration(minutes)	Group 1	Group 11
Duration of surgery	27 (5)	35 (13)*
Time to discharge	159 (44)	194 (63)♣

Table showes :
*= Significant increase in pure operative time in Group II In comparison to Group I.
♣= Significant increase in postoperative duration to home discharge in Group II In comparison to Group I.

Table (5): Surgeon satisfaction was recorded/patient.

Surgeon satisfaction	Group 1 (number of patients)	Group 11 (number of patients)
Satisfied	30	24
Not satisfied	0	6♠

♠= Group II revealed **20% surgeon** non satisfaction compared to Group 1.

Discussion

The Ilioinguinal/iliohypogastric block supposed to provides postoperative analgesia after inguinal incisions[11], for example orchidopexy or herniotomy but don't cover peritoneal sac traction so block alone is not enough for complete postoperative analgesia (that's why the addition of IM).

Drawbacks my happen with this block for example transient femoral nerve block in a ratio of 8.8% of the cases, even with correct technique, rapid local anesthetic absorption Leeds to high plasma levels which occurs especially in young children), Perforation of abdominal wall also colonic injury may happen. Ilioinguinal/ iliohypogastric nerves are only 1-2 mm away from the peritoneal cavity, so intraperitoneal injections can occur[13], but injection inside the hernial sac and near by the cord with distortion of the anatomical planes of surgical dissection may add difficulty to the surgical procedure (surgeon satisfaction) and utilizing more surgical time leading to longer anesthesia exposure, also we can imagine many problems of the surgical postoperative complication (hematoma, infection and swelling) and longer time to home discharge.

AS regard duration of surgery & postoperative duration to home discharge values are in (mean+/- SD) shows Significant increase in pure operative time & postoperative duration to home discharge in Group11 (low block technique) In comparison to Group I (high block technique) this prolongation in intraoperative time and postoperative time to home discharge was claimed to be attributed to the accidental injection of Local anesthetic solution in the surgical planes of dissection and near by the spermatic cord & vessels in the low block technique (group II) ,this could happen during the medial direction during fan injection of the block &this reflects the statistically significant increase in Surgeon non satisfaction in low block technique (Group II) compared to the high block technique (Group I) due to the added surgical difficulty due to distortion of the surgical planes of dissection and the postoperative burden of complication that could be expect-

ed (the own words of the surgeon complaint).

In line with this result Marion et al[14] reported that successful ilioinguinal/iliohypogastric block is only 62% of the cases due to LA Accurate placement utilizing technique depending on standard anatomical landmark is around this figer (62%) of the injected LA and The remaining 38% of the LA were injected in the tissue nearby so blind technique usually carry high incidence of partially imperfect injection which also may distort the surgical plans adding more difficulty to the surgical procedure. Clarifying this issue on the other hand ultrasound-guided techniques have achieved 100% success, even with less doses in children.[14]

As regard OPS PAIN SCORE (Table 2) shows postoperative significant increase in OPS pain scoring in group II in comparison to group I at 60,90,120 minute reading, OPS score ≥ 4 is the higher limit beyond which additional analgesia should be given as at postoperative minute 150 and 180 and this indicates the end-point of the analgesia of both techniques utilizing levobupivacaine prolonged intense intraoperative & postoperative analgesia could be attributed to the use of epinephrine 1/200000 as documented by Doyletal [6] which produce local vasoconstriction with slow release of the LA prolonging duration of LA action that could be intensified in this present study by the additive analgesia from the IM injected of pethedine just before LMA removal in both groups & also prolonged the postoperative analgesia up to 2 hours and may be more.

In accordance to our result Mark et al[15] documented that levobupivacaine injection in ilioinguinal/iliohypogastric block in pediatrics for day case surgery (herniorrhaphy), produced longer time till the 1st needed dose of additive analgesic administration, also decreased the need for additive analgesics needed and also less CHEOPS pain scores 15, 25, 30, and 60 minutes after surgery.

In line with this, Joel et al[16] stated that levobupivacaine in pediatrics has the advantages of being potentially less toxic, long-

acting, alternative to bupivacaine.

As regard the analgesic effectiveness of the blockade in both groups intraoperative HR (Table 3) was recorded as an effective predictor of block success during the 1st 20 min after surgical incision (IM pethedine was given after that time just before recovery) for that issue to clarify the real pure blockade analgesic success.

Intraoperative HR during the 1st 20 minutes after surgical incision showed significant increase in the HR statistical values in group II (low block technique)more than in group I (high block technique) at the minutes 0,5,10 indicating better analgesic outcome in(group I) this could be attributed to the anatomical consideration as documented long time back by two efficient studies by Yaster et al [2] & Dalens B[8] who recommended that both ilioinguinal & iliohypogastric nerves can be attacked simultaneously & more successfully by one injection point 1cm medial then 1cm above not below the ASIS (the high block technique) applicated in group I in this present study.

Conclusion

Ilioinguinal / iliohypogastric block at level above the ASIS just after anesthesia induction in pediatrics plus the IM pethedine injection just before recovery highblock group (group I) produces efficient intraoperative & postoperative analgesia less operative time, early home discharge postoperatively with high surgeon satisfaction.

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PEDIATRIC ILIOINGUINAL / ILIOHYPOGASTRIC BLOCK (HIGH OR LOW APPROCHES) "ANALGESIC & SURGICAL OUTCOME-SATISFACTION "

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LOCKED COMPRESSION PLATE FOR COMPLEX HUMERAL FRACTURES

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Abstract

Twenty two patients with humeral fractures had been treated by locking compression plate (LCP). There were 18 males and 4 females. Most of the fractures were closed injuries (86.4%). There were three open fractures (13.6%). one type I and two formed type II according to the Gustilo system. Four (18.2%) fractures were associated with multiple trauma. The average age was 43.3 years. The indications for LCP were cominnuted, segmental or intraarticular fractures, in addition to pathological and non-united fractures. The surgical technique had respected the biological principles. Autogenous bone graft had been used for all pathological and nonunited fractures. All fractures achieved complete union with excellent functional result. The aim of this study was to assess the outcome of LCP for treatment of complex humeral fractures.

Conclusion: *The use of locked plate is an effective tool for fixation of complex humeral fractures with indirect reduction. It is proved to have a high success rate of union. Good results using LCP require understanding the fixation principles of locked plate system.*

Introduction

Fracture of the humeral shaft accounts for 1% to 3% of all fractures and approximately 20% of all fractures involving the bone[1]. Most of humeral fractures are usually treated non-operatively. Surgical treatment of humeral fractures should be considered for unaccepted closed reduction, segmental fractures, polytraumatized patients, pathological fractures, bilateral humeral fractures, progressive or new onset of radial

nerve palsy after beginning of non-operative treatment, open fractures, ipsilateral upper extremity fracture, delayed union and non union[6].

Various implants have been used for fixation of humeral fractures such as conventional plate and intramedullary nails. Each of the method has its own advantages and complications. Recently, locked compression plate is a new type for extramedullary system for treatment of difficult fractures. LCP was introduced to permits the use of standard screws and locking head screws. The development of locked plating in the 1990s marked a turning point in fixation technology by providing fracture stability by using fixed angle screws with a plate [8,10].

Materials and Methods

Twenty two patients with complex humeral fractures were treated by LCP from 2005 to 2009 at Alzhraa University Hospital and El-Helal Hospital. Age of patients ranged from 20 to 65 with an average of 43.3 years. There were 18 males and 4 females. Nineteen fractures (86.4%) were closed and three (13.6%) were open fractures. Two out of three open fractures were grade II and the remaining one was grade I according to Gustilo system[4]. Four (18.2%) fractures were associated with multiple trauma. 15 patients had fresh fractures, 2 had pathological fractures and 5 had nonunion after failure of previous treatment either conservative in 4 patients and implant failure with radial nerve palsy in one. All fractures were comminuted, segmental and intaarticular. Most of fractures were caused by high energy trauma. Seventeen were caused by road traffic accident (RTA) and five by fall on the ground. Biological fixation was the treatment of choice for all fresh fractures, also periosteum stripping was minimized and the plate was placed over the periosteum. Only the fracture side was exposed for freshen the edges, removal of soft tissues interposition and shingling. Autogenous bone graft was used for nonunited and pathological fractures. The side of fractures was right in 16 patients and left in 6 patients. The background data for the series is shown in (Table 1).

Results

The average follow up was 12.7 months (range 6-24). All wounds healed without complications. There were no infection, neuro-vascular complications and nonunion. All fresh fractures united with an average of 9.1 weeks (range 8-11), while the average union time for pathological and nonunited fractures was 13.6 weeks (range 12-16). The overall average union time for all types of fractures was 10.6 weeks (range 8-16). Twenty one patients had no pain, in addition to normal shoulder and elbow functions. One patient had shoulder abduction less than 100 degrees as the patient did not follow in out patient clinic, after removal of sutures for 4 months postoperatively. Pain relief and normal shoulder function had regained at latest follow up by intensive course of physiotherapy. Complete recovery of redial nerve palsy was obtained in patient with implant failure 3 months postoperatively.

Table1: Patients description.

Case	Age	Sex	Side	FOP (months)	Trauma	Union time (weeks)
1	24	M	RT	6	RTA	9
2	65	F	RT	12	RTA	11
3	50	M	LT	12	Fall	10
4	54	M	RT	9	RTA	10
5	57	M	RT	9	RTA	8
6	33	M	RT	6	RTA	8
7	26	M	LT	10	RTA	10
8	53	F	RT	12	Fall	8
9	26	M	LT	8	RTA	9
10	60	M	RT	6	Fall	8
11	49	F	RT	9	RTA	10
12	28	M	RT	9	RTA	8
13	62	F	LT	12	RTA	8
14	37	M	RT	14	RTA	9
15	49	M	RT	12	RTA	10
16	20	M	RT	12	Fall	12
17	22	M	LT	20	Fall	16
18	43	M	RT	9	RTA	14
19	33	M	LT	24	RTA	12
20	44	M	RT	24	RTA	14
21	65	M	RT	20	RTA	16
22	53	M	RT	24	RTA	13

RTA= road traffic accident **M** = male **F** = female

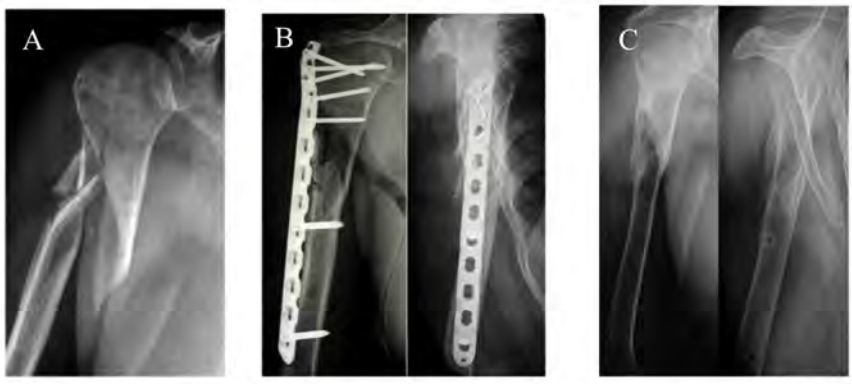

Fig. 1. Case NO. 2: Sixty five years old woman sustained comminuted fracture of the right humerus. Fixation of the fracture after closed indirect reduction with narrow locked DCP.
a- Preoperative X-ray.
b- Post operative X-ray
c- Follow up X-ray showing complete union after implant removal.

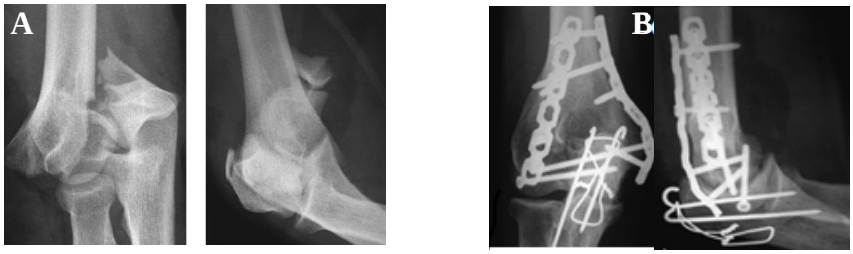

Fig. (2): Case No. 8: Fifty three years old woman sustained supracondylar fracture humerus with intraaricular extension. Fixation of the fracture after open reduction by two locked reconstruction plates was done on the second day.
A- Pre- operative X-ray.
B- Two months post-operative X-ray shows radiological union at the fracture site.

Fig. (3): Case No. 19. Male patient 33 years old, presented by nonunited fracture left humerus with redial nerve palsy.
A- After exposure, redial nerve was overstretched by plate and adherent to scar tissues.
B- After neurolysis and application of LCP.
C- Preoperative X-ray.
D- Follow up X-ray showing complete union. The patient had complete recovery of redial nerve palsy.

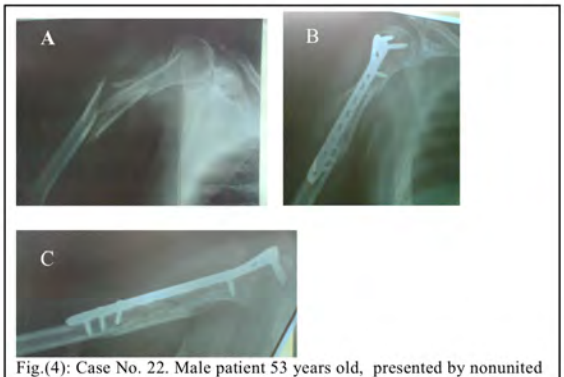

Fig.(4): Case No. 22. Male patient 53 years old, presented by nonunited fracture after failure of conservative treatment by U-shaped slab.
A- Preoperative X-ray.
B- 2 months post operative.
C- Follow up X-ray showing complete union.

Disscusion

The original principles of fracture fixation included direct fracture exposure, precise reduction, and rigid internal fixation through compression in an effort to achieve an anatomic fracture union[2,3]. This conventional fracture management technique often required a significant surgical exposure, altering the biologic environment at and around the fracture site through soft tissue stripping and devascularization [3,5].

These techniques require compression of the plate to the bone and rely on friction at the bone-plate interface. With increasing axial loading cycles, the screws can begin to toggle, which decreases the friction force and leads to plate loosening. If this occurs prematurely, fracture instability will occur, leading to implant failure, delayed fracture union, nonunion, and infection. Thus, the more difficult it is to achieve and maintain tight screw fixation (as for example, in metaphyseal and osteoporotic bone), the more difficult it is to maintain stability [8].

A refined understanding of bone biology and the roles tissue vascularity and gap strain play in fracture healing, contributed to the development of the concept of bridging plate osteosynthesis and the use of locked plate technology[2,5].

Early fixed-angle plate systems evolved out of the goal to reduce plate contact with the periosteum, while providing fracture stability [9].

The LCP system with its various types of screws (compression and locked) offers a very wide range of possible applications.

Numerous studies have reported the successful use of LCPs in a variety of clinical situations such as metaphyseal fractures, intraarticular fractures, fractures in osteoporotic bones as well as difficult non-unions [10,11].

The present study led to documentation of the results of the applications of the LCP system to a hetero-geneous patient population and across a mixed spectrum of indications. All fresh fractures

united in this series without the need for any supplemental procedure. The overall average union time was 10.6 weeks (range 8-16). The average union time for fresh fractures (15 patients) was 9.1 weeks and 13.6 weeks for pathological and nonunited fractures.

In this study, all patients got 100% radiological union, this is seems to be better than results published by Sommer et al [10]. They recorded 86% fracture healing without complications but their study had included different sites of long bone fractures. They reported that the complications and lower rate of healing which occurred predominantly in early phase. These were due to intraoperative technical errors due to ignorance of the ideal fixation principle. Walia et al[11] achieved 100% fracture healing in their study of 50 cases of long bone fractures treated with LCP.

I agree with previous studies that LCP gave excellent results for treatment of nonunited fractures. In this series 5 patients out of twenty two formed nonunited fractures had complete union. Wenzle et al[12] did a comparative retrospective study between two groups of patients with delayed or non-union of the humeral diaphysis. They reported a hardware failure in group A treated by 4.5-mm low-contact dynamic compression plate due to osteoporosis which required reosteosynthesis. Whereas, 100% union rate achieved in group B treated by LCP. Although; the patients of group B were older, had longer-lasting non-unions, more previous operations and more severe initial injuries.

Ring et al[7] found that Locking compression plates provide stable fixation of poor quality bone in patients with delayed union or nonunion of the humerus. Successful union and restoration of function are achieved in most patients.

In this study, as mentioned before all patients got 100% radiological union, had no pain and obtained normal and elbow functions at final follow up. This may attributed to early movement and rehablitation as LCP provide good fixation even in osteoporotic bones. The locking implant provid-

ed good anchorage. With locked fixation, a good purchase is achieved between the threaded plate and threaded screw head. The screws virtually act as pegs resisting axial rotation, translation and bending in porotic bone.

Conclusion: The use of locked plate is an effective tool for fixation of complex humeral fractures with indirect reduction. It is proved to have a high success rate of union. Good results using LCP require understanding the fixation principles of locked plate system.

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PHENYTOIN : IS IT GENOTOXIC IN ISOLATED CULTURED HUMAN LYMPHOCYTES WITHOUT METABOLIC ACTIVATION?

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Abstract

There is a debate around the phenytoin (PHT)-induced genotoxic effect observed in many conflicting reports. To test the genetic effect of PHT in comparison to the well known genotoxin Doxorubicin (DOX), an in vitro model of isolated cultured human lymphocytes was designed. After the end of culture period, the effects of PHT and DOX on the lymphocytes were investigated by levels of chromosomal aberrations (CAs); mitotic index (MI); reduced glutathione (GSH); malondialdehyde (MDA); and 8-hydroxydeoxyguanosine (8-OH-dG). DOX caused significant increase in the levels of structural CAs, MDA and 8-OH-dG together with significant decrease in the levels of MI and GSH when compared to non treated group. However, PHT caused only dose dependant increase in the MI and no significant changes were observed in the other parameters. The genotoxic effect of DOX may be due to oxidative stress as shown by increased MDA and 8-OH-dG together with decreased GSH. PHT was claimed to cause genotoxic effect by metabolic intermediates. However, by reviewing the distribution and activity of the enzymes responsible for PHT metabolism, we found that PHT is rarely metabolized in isolated cultured human lymphocytes. Hence, the present study is the first to record that PHT without metabolic activation in isolated human lymphocytes from non epileptic donors cause dose dependant direct toxic effect rather than genotoxic effect.

Introduction

Genotoxins are compounds causing chemical or physical alterations in DNA structure leading to inaccurate replication of that region of the genome [1]. Approxi-

mately 30% of all marketed drugs, exhibit genotoxic effect when tested by the standard genetic toxicology tests[2]. Doxorubicin (DOX) is used in the treatment of several types of human malignancies. However, it has a wide variety of toxic effects, including cardiotoxicity, cytotoxicity and the induction of chromosomal aberrations[3]. DOX was selected in this study as it is an effective clastogenic that do not require enzymatic activation[4]. Phenytoin (PHT), the well known antiepileptic drug has been suspected for teratogenic and mutagenic effects during pregnancy[5]. However, there is a big debate around its genotoxic effect observed in many conflicting reports[6.7.8.9]. The aim of this study is to investigate the debate around the genotoxic effect of phenytoin in comparison to DOX in an in-vitro model using isolated cultured human lymphocytes.

Materials and Methods

1. Human blood samples: 10 ml fresh venous blood samples were taken from 30 adult donors after consent. All donors were of either sexes between the ages of 20-45 years, apparently healthy, non-smoking, non-alcoholic and they did not take any medications recently. The donors were obtained from the blood-banking center of Mansoura university hospital, Mansoura faculty of medicine, Egypt. All blood samples were taken on heparin to prevent clotting.

2. Chemicals: all chemicals and reagents used in this study except DOX were of the highest analytical grade from Sigma-Aldrich (St. Louis, MO, USA). Phenytoin was purchased as sodium salt ≥ 99%, 25 g soluble in water. Doxorubicin was purchased as a 10 mg vial ready for infusion (Adriamycin® - Pharmacia), with a concentration of 2 mg/ml.

3. Isolation and culture of human lymphocytes: lymphocytes were isolated from whole blood samples and cultured as described by Durante et al. [10] with minor modification. All blood samples were collected in an isolation tube for blood cells. The sample was centrifuged at 1600 g (2900 rpm) for 20 min, and the layer of mononuclear cells and platelets was collected by a pipette and

transferred to 10 ml centrifuge tube. PRMI 1640 medium was added up to 10 ml. and the sample was centrifuged at 390 g (1500 rpm) for 10 min. After the removal of the supernatant, the cell pellet was re-suspended in 10 ml RPMI 1640 medium at a density of 1.0 X 106 cells/ml. Isolated lymphocytes from each blood sample were cultured in 10 ml RPMI 1640 culture medium for a total period of 72 hrs at 370 c in the dark in a 5 % CO_2 humidified atmosphere [11].

4. Plan of the study and grouping of isolated lymphocytes: Isolated lymphocytes from each blood samples were divided randomly into 5 groups, each of 6 samples: the 1st group was none treated; the 2nd treated with DOX 0.15 ug/ml [12]; the 3rd treated with PHT 60 ug/ml[13]; the 4th treated with PHT 90 ug/ml[13] and the 5th treated with PHT 120 ug/ml that was tried for the first time by this study. The potential genotoxic drugs were added twice, at 24 hr and 48 hr from the start of culture period and after stimulation of mitotic division with phytohaemagglutinin that was added at the start of culture period to induce mitosis within 24 hr according to standard protocol of Poddar et al.[14]. The genoprotective drugs were added as a prophylactic therapy 2 hr prior to addition of the genotoxic drug.

5. Evaluation of the drug effects: to investigate the chromosomal effect induced by DOX and PHT, cells were harvested at the end of the culture period (72 hrs) for screening CAs following the standard protocol[15] in order to avoid heterogenecity of cycle stage of the treated cells and to score only the first division mitotic cells. Colcemid 0.1 ml. was added to stop mitosis and prevent spindle formation and was left 1.5 hours. The isolated lymphocytes after recovery of from the incubator were investigated for chromosomal aberrations (CAs), mitotic index (MI), 8-hydroxy-2'-deoxyguanosine (8-OH-dG), reduced glutathione (GSH) and malondialdehyde (MDA).

Assay of chromosomal aberrations (Karyotype) in isolated lymphocytes using Gimsa stain: It was done according to the pro-

tocol of Poddar et al.[14]. Cells were stained using 10% Giemsa for 12 minutes immersed in distilled water for washing and air-dried. Analysis of cytogenetic data was performed using light microscopy. Slides were scored blind and individual aberrations were recorded. Fifty metaphases were examined for each sample in the different groups (300 metaphase for each group), searching for any chromosomal anomalies either structurally or numerically.

Determination of mitotic index (MI) as a measure of cytotoxicity: The mitotic index (MI) was used as indicators of adequate cell proliferation. Its inhibition could be considered as cellular death, or delay in the cell proliferation kinetics[16]. The mitotic index evaluates the cytotoxicity of chemical agents[17]. MI, is easily assessed when CAs are performed. The number of lymphocytes in metaphase was counted in 2000 lymphocytes per sample to determine the mitotic index[18].

Measurement of intracellular reduced glutathione (GSH): Intracellular reduced GSH in the isolated lymphocytes was extracted according to the method described by Anderson[19], and then reduced GSH was measured according to the method described by Beulter et al.[20] employing colorimetric method using spectrophotometer determination method (JENWAY 6405, spectrophotometer).

Measurement of malondialdehyde level (MDA): Lipid peroxidation products (MDA) were released from isolated lymphocytes by sonication according to the method described by Stacey and Klaassen[21]. Then MDA was measured by thiobarbituric acid (TBA) test according to the method described by Draper and Hadley[22], employing colorimetric method using spectrophotometer determination method (JENWAY 6405, spectrophotometer).

Measurement of 8-hydroxy-2-deoxy Guanosine (8-OH-dG): The 8-OH-dG was assayed using Cayman 8-hydroxy-2-deoxy Guanosine enzyme-linked immunosorbent assay (elisa = EIA) Kit (Cayman Chemical's ACE™, USA). Cayman's 8-OH-dG EIA is a com-

petitive assay that can be used for the quantification of 8-OH-dG in urine, cell culture, plasma, and other sample matrices. This assay is based on the competition between 8-OH-dG and a 8-OH-dG-acetylcholinesterase (AChE) conjugate (8-OH-dG Tracer) for a limited amount of 8-OH-dG Monoclonal Antibody [23.24].

Statistical Analysis : All statistical calculations of the data were performed with SPSS® version 15.0. Multiple comparisons of the data for each biochemical parameter were performed using one-way analysis of variance (ANOVA) followed by post-Hoc test for comparing the different groups with each other. P-value of ≤ 0.05 was considered significant.

Results

The assessment of the types of chromosomal aberrations (CAs) in the isolated cultured human lymphocytes in all groups of this study caused only structural CAs and no numerical CAs were found.

1. In vitro effects of Doxorubicin (DOX): DOX 0.15 µg/ml caused significant increase in the structural CAs when compared to control normal group (Table 1, Fig 1). DOX caused also cytotoxicity and decrease in lymphocyte proliferation indicated by significant decrease in the MI when compared to control normal group (table 1). In addition, there was significant increase in the MDA level, 8-OH-dG level and significant decrease in the GSH level when compared to control group (Table 1).

2. In vitro effects of Phenytoin (PHT) 60, 90 µg/ml : There was dose dependant increase in the structural CAs (Table 1, Fig 1). However, these dose dependant changes in the CAs were not significant when compared to each other and to the non-treated control group (Table 1). There was also dose dependant cytotoxicity and decrease in lymphocyte proliferation indicated by significant decrease in the MI when compared to each other and to the control normal group (table 1). In addition, there was no significant change in the MDA, GSH, or 8-OH-dG levels when compared to each other and to the non-treated normal group (Table 1).

3. In vitro effects of Phenytoin 120 µg/ml : PHT 120 µg/ml induced cytotoxic effect resulting in death and shrinkage of most of cells with marked reduction in the number of analyzable clear metaphases in which chromosomes are not clear to be counted or differentiated from each other (Fig. 1). There was significant decrease in the MI when compared to control normal group (table 1). The levels of CAs, MDA, GSH, and 8-OH-dG could not be assessed in the cell culture.

4. Comparisons between in vitro effects of DOX 0.15 µg/ml and PHT 60, 90 and 120 µg/ml: The toxic effects of DOX treated group on CAs, MDA, GSH (Table 1), and 8-OH-dG were more evident and more significant when compared to PHT 60, 90 µg/ml treated groups (Table 1, Fig. 1). However, the toxic effects of DOX treated group on MI was non-significant when compared to PHT 60 µg/ml and less significant when compared to the effects of PHT 90 µg/ml and PHT 120 µg/ml treated groups (table 1).

Table 1. *In vitro* effects of Doxorubicin (DOX) 0.15 $_{\mu g/ml}$, Phenytoin (PHT) 60, 90 and 120 $_{\mu g/ml}$ on structural chromosomal aberrations (CAs), mitotic index (MI), malondialdehyde (MDA), glutathione (GSH) and 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in isolated human lymphocytes after 72 hours of incubation (*one way ANOVA, mean ± SD, P ≤ 0.05 indicates significance*).

Groups[a]	Total CAs / 300 metaphase[b] (Mean ± SD[c])	MI[d] (mean ± SD)	MDA (mean ± SD) (nm/10^6 cell)	GSH (mean ± SD) (nm/10^6 cell)	8-OH-dG (mean ± SD) (pg/10^6 cell)
Control	8.83 ± 1.47	10.45 ±1.63	1.96 ± 0.29	12.93 ± 1.21	42.63 ± 8.23
DOX	165.83± 23.51 Ж	3.60 ±0.38 Ж	9.94 ± 1.081 Ж	2.57 ± 0.97 Ж	170.27 ± 4.53 Ж
PHT 60 µg/ml	14.00 ± 1.55 Ω	4.00 ±0.62 Ж	3.18 ± 0.55 Ω	12.28 ± 1.61 Ω	39.05 ± 12.08 Ω
PHT 90 µg/ml	17.17 ± 3.43 Ω	2.10 ±0.53 Ж Ω Ψ	3.08 ± 0.49 Ω	11.31 ± 0.87 Ω	46.01 ± 7.80 Ω
PHT 120 µg/ml	CAs could not be assessed	0.510 ±0.14 Ж Ω Ψ Ø	Could not be assessed		

[a] Each group consists of 6 samples, [b] 50 metaphases were examined for each sample = 300 metaphase for each group, [c] SD = standard deviation, [d] *MI was obtained for each sample by counting metaphases in 2000 cells.* **Ж** = significant difference when compared with control normal group, **Ω** = significant difference when compared with DOX group, **Ψ** = significant when compared with PHT 60 $_{\mu g}$ml, and Ø = significant when compared with PHT 90 $_{\mu g}$ml.

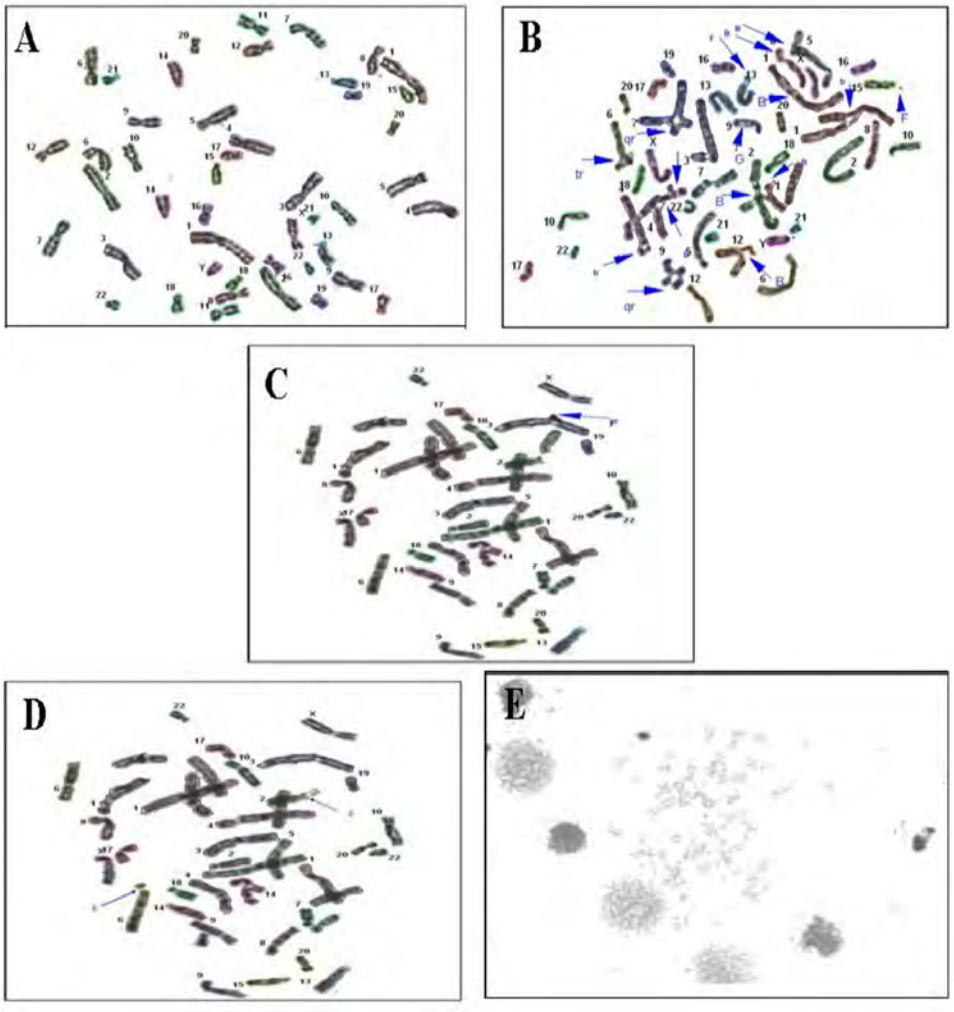

Fig. 1: A microphotograph with Gimsa stain X 1000 of (A) normal metaphase and karyotyping, (B) Doxorubicin treated group showing multiple different structural chromosomal aberrations, (C) Phenytoin treated group 60 µg/ml shoeing little CAs, (D) Phenytoin treated group 90 ug / ml showing little CAs, (E) Phenytoin 120 µg/ml treated group showing shrinked dead cells with arrested mitosis and few number of metaphases in which chromosomes are not clear to be counted or differentiated.

Discussion

1. In vitro effects of Doxorubicin (DOX) on the isolated cultured human lymphocytes.

DOX caused genotoxic effect with increased oxidative stress as shown by increased levels of CAs, MDA, and 8-OH-dG, together with decreased MI and GSH levels. The clastogenic effect of DOX reported by this study was also described by Dhawan et al.[25], and Ramos et al.[26], they described the genotoxic effect of DOX with increased micronuclei in cultured human lymphocytes. Gülkaç et al.[27] described the DOX-induced chromosomal aberrations in bone marrow cells of rats. Fragiorge et al.[4] described the direct genotoxicity of DOX in somatic cells of Drosophila melanogaster. In addition, many researchers found that acceleration of intracellular formation of reactive oxygen species (ROS) may be one of the major causes of doxorubicin-induced DNA damage and cell death[28.4.29]. Two different routes of free radical formation by DOX have been described. The first implicates a non-enzymatic reaction of DOX with iron to form a stable complex, which reacts with oxygen, forming superoxide anions, hydrogen peroxide, and hydroxyl radicals. The second implicates the formation of highly reactive semiquinone intermediates through redox modifications [27].

DOX is prone to redox modifications due to the relative reactivity of its functional group quinone[29]. Redox cycling is characterized by enzymatic reduction of the quinone molecule to a highly reactive semiquinone upon the addition of one electron, or to hydroquinone by the addition of two-electrons[30]. The subsequent non-enzymatic oxidation of the semiquinone or hydroquinone radical by molecular oxygen promotes the formation of ROS such as superoxide anion, hydroxyl radicals, and hydrogen peroxide[31]. The various forms of ROS formed during DOX redox cycling may oxidize proteins, lipids and nucleic acids and potentially cause DNA strand breaks and lipid peroxidation, leading to cell death[29]. In addition, different mechanisms of genotoxic effects of DOX have been proposed, including DNA intercalation, inhibition of topoisomerase II, and induction of apoptosis[26].

There is a large body of evidence to show that the dominant cellular target of doxorubicin is DNA, DOX intercalates DNA between base pairs [27] resulting in DNA adducts and protein-associated single and double strand DNA breaks [32].

2. In vitro effects of phenytoin (PHT) on the isolated cultured human lymphocytes.

Apart from significantly deteriorated cell proliferation (MI), PHT 60, 90 µg/ml did not show any statistically significant genotoxic effect as shown by non significant changes in the CAs, MDA, GSH, or 8-OH-dG when compared to control normal group. Additionally, when a larger dose of PHT (120 µg/ml) was administered to isolated lymphocytes, marked deterioration in MI and cytotoxic effects were observed, which shown by death of most of cells with marked reduction in analyzable metaphases. The levels of MDA, GSH, and 8-OH-dG could not be assessed for this high dose (120 µg/ml), which may be due to rapid cell death caused by the acidic pH of PHT [33] and inability to extract these measured compounds from the cell proteins.

To the best of our knowledge, this study was the first to record that PHT without metabolic activation is not genotoxic in isolated human lymphocytes collected from non epileptic donors. However, many studies reported that PHT is not genotoxic in cultured human lymphocytes isolated from epileptic patients pretreated with PHT. Witczak et al.[34] assessed the potential genotoxic effect of PHT therapy in pregnancy on DNA of umbilical cord blood lymphocytes using Micronucleus (MN) assay. They did not show any significant differences between the MN rates of PHT-treated patients and controls, indicating a lack of genotoxicity of the PHT. Schaumann et al.[35], tested the potential genotoxic effect of PHT using sister chromatid exchange (SCE) assay in isolated cultured lymphocytes from adult epileptic patients treated with PHT. He did not show any significant differences between the SCE rates of PHT-treated patients and controls, indicating a lack of mutagenicity of the PHT. In addition, the negative tests for PHT genotoxicity were observed in

germ cells of male Drosophila melunogaster [36], many strains of Salmonella typhimurium (37), and cultured Chinese hamster ovary cells [38].

On the other hand, the positive tests for PHT genotoxicity were observed in Chinese hamster ovary cell [39], rodents [40], and some isolated human cells (13.41). This strong debate around the ability of phenytoin to induce genotoxic effects observed in many conflicting reports [6.7.8.9]. Most of the positive genotoxic studies of PHT claimed that this toxic effect resulted from the action of some PHT metabolic intermediates, mainly the para hydroxyphenyl phenyl hydantion (p-HPPH)[5]. These metabolic intermediates induce production of ROS leading to exhaustion of the cellular antioxidant systems[42] with subsequent oxidation of DNA, proteins, and lipids[43]. This toxic effect will lead to oxidative DNA base modification with DNA strand breaks, lipid peroxidation and decreased GSH-mediated cytoprotection [41].

There are three main metabolic pathways for the metabolism of PHT. The first include the bioactivation of about 80% of PHT to reactive epoxides (arene oxide) which is hydroxylated to form the main metabolite para hydroxyphenyl phenyl hydantion (p-HPPH)[44]. This process is catalyzed primarily by the cytochrome P450 (CYP 450) system mainly the CYP2C9 and to much lesser by CYP2C18 and CYP2C19[41]. The second pathway includes the bioactivation of PHT to reactive free radical intermediates through the hydroperoxidase component of Prostaglandin endoperoxide synthetase pathway responsible for conversion of arachidonic acid to prostaglandins[45]. The last metabolic pathway included the bioactivation of PHT to reactive free radical intermediates through the myeloperoxidase enzyme commonly present in leukocytes[46]. However, by reviewing the distribution and activity of the enzymes responsible for PHT metabolism, we found that PHT is rarely metabolized in isolated cultured human lymphocytes. This is because the CYP 450s are abundant in the liver[47] and quite low in leukocytes[48]; thus, they are not considered to be the main pathway

for drug metabolism in isolated lymphocytes. In addition, the CP450s present in lymphocytes are mainly CYP1A1, CYP1B1, CYP 2E1 and CYP3A4, while those included in PHT metabolism are CYP2C9 and to much lesser by CYP2C18 and CYP2C19[41]. The prostaglandin endoperoxide synthetase was found in relatively high concentrations in lymphocytes[49]. However, this enzyme can not metabolize PHT without metabolic activation through addition of high amounts of arachidonic acid[50]. The last enzyme myeloperoxidase was found to be distributed unequally between leucocytes where it is excess in nutrophils and very little in lymphocytes [51].

The absence of PHT metabolism in isolated cultured human lymphocytes may support and explain the negative genotoxic effects of PHT in this study and in the previously mentioned studies that used cultured cells to investigate the genetic effect of PHT. These results suggest that PHT it self is not genotoxic and its toxicity could be achieved only after metabolic activation to reactive metabolic intermediates. This idea was supported by studies that reported PHT genotoxic effect after metabolic activation in the presence of an exogenous metabolic activation system (S9) in bacteria[52] and Chinese hamster ovary cells [53].

The dose dependant effect on lymphocyte proliferation and cell death caused by PHT (60, 90, 120 µg/ml) shown by MI was in accordance with the study of Bittigau et al.[54], they revealed that phenytoin, cause apoptotic neurodegeneration and neuronal death in the developing rat brain. Moreover, Kawamura et al.[55] reported the induction of apoptosis by large dose PHT in human tumor cells, when used to increase the cytotoxicity of the anticancer vinblastin. Additionally, Ponnala et al.[13], recorded partial cell death in isolated human lymphpocytes but at smaller doses (60 µg/ml). This large concentration is very dangerous for the human where the fatal cases typically involve phenytoin concentrations of more than 400-500 µM/L (120-125 µg/ml)[33].

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REPRINT

BENHA MEDICAL JOURNAL

PHENYTOIN : IS IT GENOTOXIC IN ISOLATED CULTURED HUMAN LYMPHOCYTES WITHOUT METABOLIC ACTIVATION?

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THE ROLE OF TISSUE DOPPLER IMAGING DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN DIFFERENTIATING ISCHEMIC FROM NON-ISCHEMIC CASES OF DILATED CARDIOMYOPATHY

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Abstract

Background: *Dobutamine stress echocardiography (DSE) has several potential advantages over currently used non-invasive techniques. It is inexpensive and provides an alternative in the patients who cannot perform leg or arm exercise. The equipment used is highly portable and thus studies can be performed in coronary care units.*

Objectives: *To study the role of tissue Doppler imaging during dobutamine stress echocardiography for differentiating ischemic from non-ischemic cardiomyopathy.*

Patients and methods: *forty six patients were included in this study, and diagnosed as dilated cardiomyopathy by resting conventional echocardiography. The patients were divided into two groups: group 1 (18 patients) with normal coronary angiography, and group ll(28 patients) with coronary artery disease. All patients were subjected to full history taking, clinical examination, resting surface electrocardiograms, echocardiography, low and peak dose DSE associated with tissue Doppler with detection of mitral annulus systolic and diastolic velocities in six sectors of LV myocardium (anterior, inferior, anterior septum, posterior septum, posterior and lateral walls).*

Results: *In group I, there was no change in the mean value of systolic velocities of all six sectors at baseline was (6.5±1.6 cm/s) and at low dose was (6.9±2.3 cm/s) p value > 0.05, while in group II there was significant improvement in the mean value of systolic velocities of six*

sectors at low dose (11.3±3.1 cm/s) compared to that in the baseline resting stat (7.0±1.6 cm/s) followed by gradual decrease in the systolic velocity to peak dose (9.1±2.6 cm/s) (Biphasic response) p value < 0.01. The E'/A' ratio of diastolic function estimated by TDI at base line and during DSE, there was insignificant changes in both groups. The sensitivity of tissue Doppler with DSE for detection of coronary artery disease in patients with dilated cardiomyopathy was 85.7%, and specificity was 77.8%.

***Conclusion**: Tissue Doppler with DSE is non invasive simple method with high sensitivity and specificity for detection of coronary artery disease in patients with dilated cardiomyopathy.*

Introduction

Dobutamine stress echocardiography (DSE) has several potential advantages over currently used non-invasive techniques. It is inexpensive and provides an alternative in the patients who cannot perform leg or arm exercise. The equipment used is highly portable and thus studies can be performed in coronary care units. (1).

High quality images from DSE may be obtained more easly than those with exercise stress echocardiography because the absence of patient motion and respiratory interference, and the level of stress achieved can be controlled and the heart rate achieved can be suppressed by B-Blockers (2).

Aim of the work

To study the role of tissue Doppler imaging during dobutamine stress echocardiography for differentiation of ischemic from non-ischemic cases of dilated cardiomyopathy.

Patients and methods

This study was carried out in the cardiology department of both Benha faculty of medicine and Ain Shams faculty of medicine during the period from August 2008 to June 2010.

Inclusion criteria:

Patients who had documented echocardiographic diagnosis of dilated cardiomyopathy: dilated LV with generalized hypokinesis, posteriorly displaced mitral valve, estimated LV end diastolic diameter

> 60mm and percentage ejection fraction < 45%) [3].

All patients underwent left sided cardiac catheterization via femoral artery puncture using Seldenger's technique with left and right coronary angiography in multiple projections and angulations. According to the results of the diagnostic coronary angiography, patients were divided into two groups:

Group I : patients with dilated cardiomyopathy and normal coronary arteries (18 patients).

Group II: patients with dilated cardiomyopathy and significant narrowing of one or more coronary arteries. Significant narrowing was defined as > 70% reduction in the absolute lumen diameter of a major epicardial artery or major branch vessel. [4] This group included 28 patients.

Exclusion criteria:

1- Evidence of previous myocardial infarction.

2- Significant arrhythmias.

3- Valvular or pericardial disease.

4- Uncontrolled hypertension or diabetes mellitus.

5- History of chronic obstructive airway disease.

6- Poor echocardiographic window.

7- Echocardiographic evidence of left ventricular hypertrophy.

8- Decompensated heart failure.

9-Patients who didn't complete the test due to early development of complications.

Methods: All patients were subjected to:

1) Careful history taking.

2) Thorough clinical examination.

3) Resting electro-cardiogram: 12 leads surface resting electrocardiogram.

4) Echocardiographic study:

Trans-thoracic echocardiographic examination using Vivid 5 machine and probe 3S frequency 1.5 – 3.6 MHz GE Probe was done for all subjects enrolled in the study.

M-mode, two dimensional as well as color and pulsed Doppler flow examination were done in su-

pine and left lateral position. According to the American Society of Echocardiography guide lines the following measurements were obtained:

1) Left atrial diameter.

2) End diastolic and end systolic LV cavity dimensions and volumes. Left ventricular Ejection fraction (EF) was then calculated according to the equation: EF %=(LV diastolic volume–LV systolic volume)/LV diastolic volume.[5]

Using apical 4-chamber view, pulsed wave Doppler sample was put at the tips of mitral valve leaflets to record the mitral flow velocities, E and A waves. The ratio of E/A was then calculated.

Dobutamine stress Echocardiography:

Adequate arrangement of the testing equipment, with availability of appropriate emergency equipment, dobutamine stress echocardiography was performed to all patients in the fasting state; nitrates were stopped 24 hours before the test while beta blockers and calcium channel blockers were stopped 48 hours before the test. Intravenous infusion of dobutamine started by rate 5 ug / kg / min. for 5 minutes increased gradually 5 ug /kg /min. every 3 minutes up to maximum dose 40 ug / kg /min.

In patients not achieving 85% of their maximum heart rate without symptoms or signs of myocardial ischemia, atropine was administered intravenously; starting dose was 0.25 mg up to maximum of 2.0mg within 8 minutes while continuing infusion of dobutamine. [6]. Throughout dobutamine infusion, continuous ECG monitoring was done and at each stage heart rate and blood pressure were measured ,left ventricular wall motion was evaluated with two dimensional echocardiography and mitral annular motion velocity patterns were recorded with pulsed TDI at rest and at a maximum dose of 40 ug / kg /m [7].

End points of the test:

- Significant chest pain.
- Extensive new wall motion abnormalities.
- Achievement of 85% of maximum predicted target heart rate.
- Additional ST segment depression or elevation about 2.0mm in at least two contiguous

leads compared to the rest.

- Hypotension: systolic blood pressure < 90mm Hg or reduction more than 40mmHg of pretest level or increased systolic pressure >200.

- Significant arrhythmia.

Dobutamine stress echocardiography (DSE) was considered positive for induced myocardial ischemia after detection of **biphasic response** that means at low dose of stress the contractile function improved and at higher doses the myocardial demand increased leading to ischemia and systolic function deterioration again.[8]

Pulsed wave tissue Doppler imaging study:

The echocardiography machine was switched to TDI mode thereby resulting in lowering of the velocity range to encode myocardial velocities.

The acoustic power and filter frequencies of the ultrasound scan system were set to the lowest values possible. Sample volumes were set at the mitral annulus. Mitral annular motion velocities were recorded on a strip chart.

Systolic mitral annular motion velocities at 6 mitral annular sites reflect the synergy at the sites corresponding to the ischemic regions in patients with myocardial ischemia, sample volumes were set on the endocardial side at the mitral annulus in regions corresponding to:

- Anterior mitral, posterior mitral, inferior, anterior, lateral, and posterior walls. The peak velocity of the systolic mitral annular motion (S) were determined, also the peak diastolic velocities (E', A') were determined from six consecutive beats and the mean was calculated for each parameter and expressed in centimeters per second. Recording and measurements were repeated at baseline, low dose (5ug /kg/min) and maximum dobutamine infusion rate.

Statistical analysis

Data were collected from all patients (group I and II), and expressed as the mean value, standard deviation and percentages.

Kruskal – Wallis test was used to compare different parameters between groups. When inter-group

differences were found, Mann-Whitney test was performed to determine which group was significantly different.

Categorical variables were analyzed with the Chi square test. Paired student's t-test was used to compare different parameters of DSE in studied groups.

A value of P < 0.05 was considered statistically significant. [9]

Results

Demographic data: Forty six patients were included in this study their mean age was (42.5 ±7.1 years) in group I versus (59.4 ± 6.9 years) in group II, 11 of them were males and 7 females in group I versus 17 males and 11 females in group II.

Seven patients (38.9%) were diabetic in group I versus 18 (64.3%) in group II, 5 patients were hypertensive (27.8%) in group I versus 15 (53.5%) in group II, 8 patients (44.4%) were smokers in group I versus15 (53.5%) in group II, 7 patients (38.9) had dyslipidemia in group I versus 17(60.7) in group II, and only 3 patients (16.7%)had positive family history in group I versus11(39.3%) in group II.

Conventional echocardiography response during dobutamine stress:

In group I EF was (35 ± 3.5) with low dose DSE and nearly the same with high dose DSE, and in group II EF was (45.2 ± 4.1) with low dose DSE, while it was (41.4 ± 4.6) in high dose DSE. Statistically significant difference was found between both groups (p value < 0.01). This means that in non-ischemic cardiomyopathy, dobutamine stress induces no recordable change in global systolic function from the low dose to peak dose (mono-phase response). On the other hand, in ischemic cardiomyopathy there was an initial improvement at low dose followed by impairment of systolic function (Biphasic response). Fig. (1).

- LV diastolic function (E/A ratio):

In group I E/A ratio was (1.12 ±0.31) during resting state, (1.1±0.27) at low dose DSE and became (1.05±0.26) at maximum dose DSE, and in group II E/A ra-

tio was (0.97±0.26) during resting state, (0.91±0.27) at low dose DSE and became (o.85 ± 0.46) at maximum dose DSE, with statistically significant difference between both groups (P value < 0.01). These result means that in non-ischemic cardiomyopathy, there is insignificant change in E/A ratio during dobutamine stress, while in ischemic group there is significant decrease in this ratio, most probably due to stress induced myocardial ischemia. Fig. (2).

Tissue Doppler parameters during dobutamine stress echocardiography:

**** Systolic velocities during DSE in group I:*** there is insignificant monophasic response in all six sectors. (P value >0.05) (Tab.2, Fig. 3).

- In anterior aspect S at baseline was (6.6 ±1.9) cm/s, at low dose dobutamine (6.8 ±2.1) cm/s while S at peak dose became (7.1 ±3.1) cm/s.

- In inferior aspect S at baseline was (6.4 ±1.7) cm/s, S at low dose (6.6 ±2.8) cm/s while S at peak dose became (7.2 ±2.3) cm/s.

- In posterior aspect S at baseline was (5.5 ±1.9) cm/s, S at low dose (5.9 ±2.5) cm/s while S at peak dose became(6.2 ±3.1) cm/s.

- In anterior septal aspect S at baseline was (5.9 ±1.7) cm/s, S at low dose dobutamine was (6.1 ±2.4) cm/s while S at peak dose became (6.4 ±2.8) cm/s.

- In posterior septal aspect S at baseline was (7.0 ±1.9) cm/s, S at low dose dobutamine was (8.2 ±2.1) cm/s while S at peak dose became (9.1 ±3.5) cm/s.

- In lateral aspect S at baseline was (7.7 ±1.4) cm/s, S at low dose dobutamine was (8.3 ±1.9) cm/s while S at peak dose became (8.6 ±2.1) cm/s.

**** Diastolic velocities E'/A' ratio during DSE in group I:*** The mean value of diastolic velocity (E'/A') in group I at baseline was (1.0 ±0.3) cm/s, at low dose dobutamine (1.0 ±0.2) cm/s, and became (0.9±0.3) cm/s at high dose. (P value > 0.05).

**** Systolic velocities of myo-***

cardial aspects during DSE in group II: there is biphasic response with significant changes in all six sectors. (P value < 0.01) (Tab.3, Fig.4) .

- In anterior aspect S at baseline was (7.4 ± 1.3) cm/s, S at low dose dobutamine was (14.6 ±4.7) cm/s, and became (9.1 ± 3.1) cm/s at high dose.

- In inferior aspect S at baseline was (7.4 ±1.9) cm/s, S at low dose dobutamine was (12.3±3.6) cm/s, and became at peak dose (10.7 ±2.8) cm/s.

- In posterior aspect S at baseline was (5.3 ± 1.1) cm/s, S at low dose dobutamine was (10.4 ±2.7) cm/s while became at peak dose (7.8 ±2.5) cm/s.

- In anterior septal aspect S at baseline was (5.6 ± 1.6) cm/s, at low dose dobutamine was (9.6 ±3.1) cm/s while S at peak dose of dobutamine was (7.2 ±2.7) cm/s.

- In posterior septal aspect S at baseline was (7.6 ± 1.2) cm/s, at low dose dobutamine was (11.9 ±3.8) cm/s while S at peak dose of dobutamine was (8.9 ±2.9) cm/s.

- In lateral aspect S at baseline was (8.7 ± 1.3) cm/s, at low dose dobutamine was (15.2 ±3.9) cm/s while S at peak dose of dobutamine was (10.4 ±2.3) cm/s.

**** Diastolic velocities E?/A? ratio in Group II:*** there is insignificant changes during DSE; the mean value at baseline was (0.93±0.3) cm/s, at low dose (97.0 ±0.2) cm/s while S at peak dose became (0.96±0.2) cm/s.(P value > 0.05).

Complications during dobutamine stress echocardiography:

- Patients excluded from the test due to development of complication included:

1- Two patients developed significant hypotension.

2- Three patients developed rapid atrial fibrillation.

3- One patient developed runs of ventricular tachycardia.

Specificity and sensitivity of Dobutamine Stress Echocardiography:

- The test was positive for stress induced myocardial ische-

mia in 28 patients, 23 of them was true positive while in 5 patients was false positive, also the test was negative in 18 patients, 13 of them was true negative while 5 patients was false negative

- The specificity of the test was 72.2% and the sensitivity was 82.1%.

Specificity and sensitivity of TDI with DSE according to systolic velocity:

- The test was positive for stress induced myocardial ischemia in 28 patients, 24 of them was true positive and only 4 patients were falsely negative, also the test was negative in 18 patients, 14 of them were true and only 4 were false.

- The specificity of the test was 77.8% and the sensitivity was 85.7%.

Table (1): comparison between studied groups in demographic data

variable	Group I(N=18)	Group II(N=28)	P value
Age (mean value)(years)	42.5 ± 7.1	59.4 ± 6.9	< 0.05
Male Female	11(61.1%) 7 (38.9%)	17(60.7%) 11(39.3%)	>0.05
Diabetics	7 (38.9%)	18 (64.3%)	0.032
Hypertensive	5 (27.8%)	15 (53.5%)	0.039
Dyslipidemia	7 (38.9%)	17 (60.7%)	0.042
Smokers	8 (44.4%)	15 (53.5%)	0.086
+ve Family history	3 (16.7%)	11 (39.3%)	0.023

Table (2):Tissue Doppler parameters during DSE in group I.

	Resting	Low dose	High dose	p.value
Anterior wall	6.6±1.9	6.8±2.1	7.1±3.1	0.22
Inferior wall	6.4±1.7	6.6±2.8	7.2±2.3	0.10
Posterior wall	5.5±1.9	5.9±2.5	6.2±3.1	0.19
Anterior septal	5.9±1.7	6.1±2.4	6.4±2.8	0.09
Posterior septal	7.0±1.9	8.2±2.1	9.1±3.5	0.12
Lateral wall	7.7±1.4	8.3±1.9	8.6±2.1	0.18
E´/A´ ratio	1.0±0.3	1.0±0.2	0.9±0.3	0.07

Table (3):Tissue Doppler parameters during DSE in group II.

	Resting	Low dose	High dose	p. value
Anterior wall	7.4±1.3	14.6±1.7	9.1±3.1	< 0.01
Inferior wall	7.4±1.9	12.3±3.6	10.7±2.8	< 0.01
Posterior wall	5.3±1.1	10.4±2.7	7.8±2.5	< 0.01
Anterior septal	5.6±1.6	9.6±3.1	7.2±2.7	< 0.01
Posterior septal	7.6±1.2	11.9±3.8	8.9±2.9	< 0.01
Lateral wall	8.7±1.3	15.2±3.9	10.4±2.3	< 0.01
Mean value E/A ratio	0.93±0.3	0.97±0.2	0.96±0.2	> 0.05

Table (4):Specificity and sensitivity of DSE.

DSE	All cases	True cases	False cases
+ve cases	28 patients	23 patients	5 patients
-ve cases	18 patients	13 patients	5 patients
Specificity	72.2%		
sensitivity	82.1%		

Table (5):Specificity and sensitivity of TDI with DSE:

DSE	All cases	True cases	False cases
+ve cases	28 patients	24 patients	4 patients
-ve cases	18 patients	14 patients	4 patients
Specificity	77.8%		
Sensitivity	85.7%		

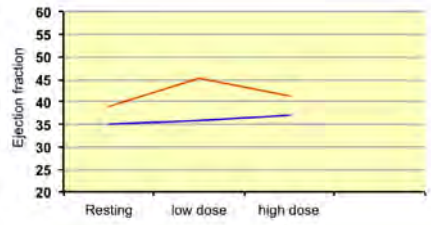

Figure (1): *variation of ejection fraction during DSE in both studied groups.*

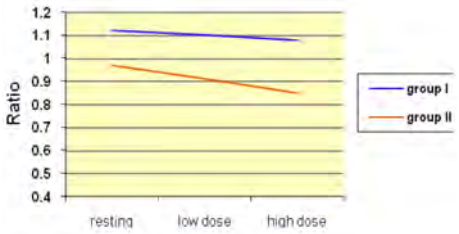

Figure (2): *variation of diastolic function during DSE in both studied groups.*

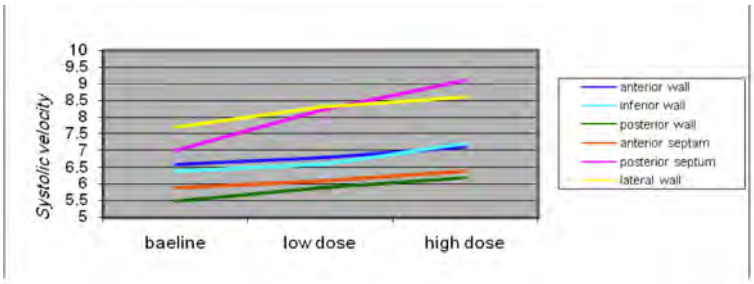

Figure (3): systolic velocities in all myocardial aspects during DSE in group I.

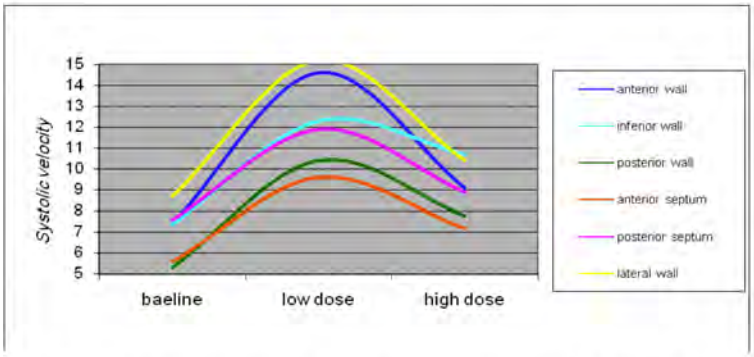

Figure (4): Systolic velocities in all myocardial aspects during DSE in group II.

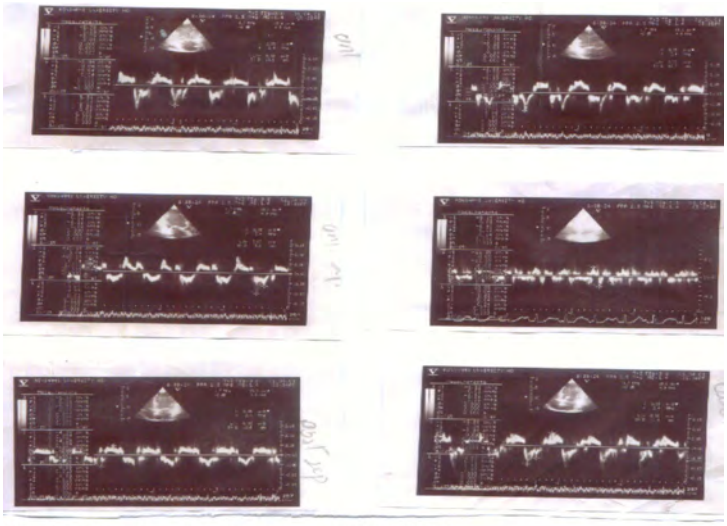

Fig. (5) Tissue Doppler parameters on patient No (1)

Discussion

Tissue Doppler imaging, obtained from the apical windows during dobutamine stress, offers a quantitative and highly sensitive mean for measuring systolic and diastolic alterations due to myocardial ischemia [10].

The present study aimed to compare the changes in myocardial velocities as reflected by measuring annular mitral velocities at rest and during dobutamine stress in ischemic and non-ischemic cardiomyopathy and thus define criteria for differentiating between them.

For this purpose, in the present study, forty-six patients with dilated cardiomyopathy had been evaluated by TDI at rest and during dobutamine stress echocardiography. All patients underwent coronary angiography within one week before the stress test. According to the results of coronary angiography, the patients were classified into two groups; group I who had normal coronary arteries and group II who had significant coronary artery disease.

In the present work, group II patients were significantly older than group I patients (mean age in years = 59.4 ± 6.9 versus 45 ± 7.1 years, $p<0.05$) (table 1)

In contrary, Vogel et al. (2003) reported that there is no significant difference in age in ischemic cardiomyopathic patients and idiopathic cardioyomyopathic patients (56±6.3ys versus 53±4ys). [11]

In present study, there is a significant increase in the prevalence of diabetes in group II (18) (64.3%) versus (7) patients (38.9%) in group I ($P < 0.05$). (Table 1)

These results are in agreement with those reported by Peter, et al. (2001) They found a higher prevalence of diabetes in patients with ischemic cardiomyopathy (22%) than those who had non-ischemic cardiomyopahty (5%). [12]

In the present study there is a higher prevalence of dyslipidamia in group II than in group I (60.7% versus 38.9%, $p< 0.05$). (Table 1)

This is in accord with Vogel et

al. (2003) who found a higher prevalence of hypercholesterolemia in patients with ischemic cardiomyopathy than in patients with non-ischemic cardiomyopathy (62% Vs 18%), p <0.05. (11)

In the present study, atropine was used to reach the target stress level in 10 cases (55.5%) of group I and in 12 (42.8%) cases of group II.

This finding is in agreement with that of Rambaldi et al. (1998) who found that 47% of group I needed addition of atropine compared to 45% of the group II. (13)

In the current study, the global systolic function as calculated by EF in both groups , there was nearly no changes in group ? while in group II there is initial increase then decrease in EF from low dose to peak dose (Biphasic response) (fig.1).

Pauliks et al. (2005) detect that there is an increase in global LV systolic function in low dose dobutamine stress echocardiography in ischemic cardiomypathy that decrease again with high doses dobutamine stress. (14)

As regard diastolic parameters during dobutamine stress in the present work, there is insignificant decrease in the E/A ratio in group I while there is significant decrease in that ratio in group II (Fig. 2)

This is in agreement with Alison et al. (2003), who found that marked deterioration of diastolic function in ischemic than in idiopathic cardiomyopathic patients during dobutamine stress echocardiography. This deterioration of diastolic function may be due to increase of myocardial rigidity during stress as a result of ischemia in group II. (5)

But this result not in agreement with, Hanekom et al. (2005), who reported that there is insignificant changes of diastolic function during dobutamine stress echocardiograthy in ischemic and idiopathic cardiomyopathy. (15)

In the present study the peak systolic velocities in tissue Doppler during DSE study in group I, at the six sectors show insignifi-

cant and monophasic response. (Fig.3, Table 2).

While there is significant increase in systolic velocity at low dose compared to that in the baseline resting state and followed by gradual decrease in the systolic velocity towards the peak dose in all six sectors (Biphasic response). (Fig.4, Table 3).

This is in accordance with Peteiro et al. (2001) who used pulsed tissue Doppler imaging during dobutamine - atropine stress testing to detect significant coronary lesions and they found that at rest peak systolic velocity in territories supplied by diseased artery was insignificantly less than that of non-ischemic cardiomyopathy but with low stress, the peak systolic velocity was significantly higher in ischemic cardiomyopathy. (16)

This is in agreement with the results of Elzaky et al., (2005), who found that systolic velocities as assessed by pulsed tissue Doppler imaging were significantly reduced in ischemic region when compared with the corresponding walls in healthy patients and high in ischemic patients when compared with myopathic patients. (17)

On the other hand Tsutsi et al. (1998) demonstrated that pulse-wave Doppler tissue imaging at rest could not differentiate between ischemic cardiomyopathy and non-ischemic cardiomyopathy segments depending on the peak systolic velocity. This difference may be related to different demographic data and involvement of multi-vessel disease in CAD group. (18)

Also the results of current study are in accordance with Alison et al., (2003) who used dobutamine tissue Doppler with measurement of mitral trans-annular systolic velocities, the study showed a reduction in systolic velocities in non-ischemic myopathic patients compared to CAD group. (5)

The diastolic parameters of tissue Doppler detected by E'/A' in the present work were evaluated during dobutamine stress, we found in group I, the E'/A' ratio at rest was 1.0±0.3, at low dose it

was 1.0±0.2 and at peak dose it was 0.9±0.3 (Table 2). This means that there is insignificant decrease in E'/A' ratio in this group with non-ischemic cardiomyopathy.

Similarly, in group II, the E'/A' ratio during the test were insignificant changes as in group I (Table 3).

So, there were no changes in diastolic parameters as estimated by TDI during dobutamine stress in both groups.

This may be explained by non-linear changes in diastolic myocardial velocities in response to ischemia; the ratio may increase with restrictive response or decreased with abnormal relaxation response. The different responses of diastolic function may be related to the amount of myocardial fibrosis and level of end-diastolic pressure which is depends on patient age and duration of disease.

Similar conclusions were obtained by Alison et al. (2003), who found that diastolic velocities as assessed by pulsed tissue Doppler imaging were insignificantly reduced in ischemic region when compared with the corresponding walls in idiopathic cardiomyopathic patients. (5)

Contradictory results were obtained by Elzaky et al., (2005) who found that diastolic velocities as assessed by pulsed tissue Doppler imaging were significantly reduced in ischemic region when compared with the corresponding walls in healthy patients and high in ischemic patients when compared with other myopathic patients. (17)

Hegazy et al., (2007) concluded that mitral trans-annular systolic and diastolic velocities were an indicator for predicting significant coronary stenosis, their study revealed that the impaired TDI derived variables; S, E', A' and E'/A' ratio, were an indicator for CAD. (19)

In the present study the sensitivity and specificity of TDI during DSE in prediction of coronary artery disease in myopathic patients were significantly higher than that of the conventional dobutamine stress echocardiography: it was in tissue Doppler 85.7% versus

82.1% in conventional echocardiography, specificity was 77.8% in TDI versus 72.2%.(Table 4).

This is in accordance to Alison et al. (2003) who found that, tissue Doppler imaging with dobutamine stress echocardiography identified 41 of 48 of myopathic patients with CAD and 22 of 25 without CAD with a sensitivity 85% and specificity 88%. [5]

The difference in values between the present study and other studies may be attributed to the differences in age, gender, and other risk factors like hypertension, diabetes mellitus, and dyslipedamia, also maybe due to different degrees of diameter stenosis, and various combinations of ischemic, hibernating, and infarcted myocardium.

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THE ROLE OF TISSUE DOPPLER IMAGING DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN DIFFERENTIATING ISCHEMIC FROM NON-ISCHEMIC CASES OF DILATED CARDIOMYOPATHY

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PREDICTORS OF SUCCESS OF MICROSURGICAL EPIDIDYMOVASOSTOMY FOR OBSTRUCTIVE AZOOSPERMIA

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Abstract

Objective: *To evaluate the outcome of seminal ductal Patency rate with different predictors after reconstructive surgery.*

Patients and Methods: *This study comprised 40 patients (mean age 31.5 years, range 21-41 years), 30 patients operated upon with various reconstructive surgery (mainly epididymovasostomy) for obstructive azoospermia and 10 patients were inoperable. All the patients followed for 1 year by semen analysis every 4 months. The patient's findings will be correlated with different factors that affect the surgical outcome.*

Results: *Of 30 azoospermic patients due to operable causes, sperms appeared in seminal fluid in 15 patients (50%) postoperatively. Irrespective to the type of surgery', factors affecting patency rate are studied and correlated with the patency rate.*

Conclusion: *Although all techniques performed by microsurgery the success rate was low. The most important predictive factor is the demonstration of sperms in the epididymal fluid.*

Key words: *infertility, epididymovasostomy, microsurgery. In- vitro fertilization, intracytoplasmic sperm injection.*

Abbreviations:

-ART: assisted reproductive techniques.

-ASA: antisperm antibodies

-OA: obstructive azoospermia *-IVF: invitro fertilization*

-ICSI: intracytoplasmic sperm injection

Introduction

Treatment of patients with seminal tract obstruction consists of microsurgical repair of obstruction or sperm retrival and in-vitro fertilization (IVF) with or without intracytoplasmic sperm injection [1], [2], [3].

Despite recent advances in assisted reproductive techniques (ARTS), microsurgical reanastemosis of the seminal tract remains the treatment of choice when possible as it results in high patency rate and equal or better pregnancy rates with natural intercourse than those achieved with assisted reproductive techniques [4], [5].

Vasoepididymostomy is among the most difficult microsurgical technique performed by urologists [6], [7]. The success rate of epididymovasostomy has improved markedly with the development of specific tubule end to end [8] and end to side [9] microsurgical anastomosis, these microsurgical approaches allow accurate approximation of the vasal mucosa to that of a single epididymal lobule [10].

Furthermore, the new technique of vasoepididymostomy using a triangulation with epididymal invagination gives a success rate 100%[11]. Recent reports have demonestrated that the outcome of microsurgical reconstruction in men with obstructive azoospermia is dependent on the etiology of obstruction. It is the best when the cause of obstruction is inflammation and the worse when the cause is idiopathic obstructive azoospermia.

Patients and Methods

This study was conducted on 40 patients proved by history, physical examination including testicular size and vasal palpation, and investigations including hormonal assay (FSH, LH and testosterone), seminal fructose test, seminal alpha glucosidase test. Seminal and serum antisperm antibodies, transrectal ultrasonography, and bilateral testicular biopsies.

By exploration and vasography at the time of reconstruction with repeated semen analysis the diagnosis of obstructive azoospermia was confirmed.

The mean age is 31.5 years ±11.5 (ranged from 21-42 years). The majority have primary infertility (95%) and secondary infertility in 5% with previous pregnancies irrespective to its outcome.

The duration of infertility ranges from 2 to 15 years with a mean of 6.5 years ±3.5 years. Past history of related surgical procedures was obtained in 5 patients (12.5%) which were removal of epididymal mass in 1 patient, hydrocelectomy in 3 patients and drainage of scrotal abscess in one patient. Pelvic operations were done to 8 patients (20%), inguinal herniorrhaphy in 3 patients, Pelvic uretero lithotomy in 3 patients, partial cystectomy in one patient and pelvic fixation of rectal prolapse in one patient. Past history of related medical disease was obtained in 27 patients. Ten Patients had history of epididymoorchitis (37%), 15 patients had history of bilharisiasis, 1 patient had history of pulmonary tuberculosis and one patient had history of chronic obstructive pulmonary disease with repeated respiratory tract infection (2.5%). The surgical techniques used for reconstruction of obstructive azoospermia are illustrated in table.

The Causes of inoperability in 10 patients (25%) were

1- Congenital Causes: 8 cases (80%).

a- Congenital bilateral absence of the vas deference 6 cases (60)%.

b- Mullerian duct cyst, 1 case detected during scrotal exploration and vasography. The cyst was present posterior to the bladder 4x4 cm in the midline compressing the distal part of the vas and ejaculatory duct.

c- Ectopic insertion of the vas deference in the left ejaculatory duct which is atretic in one case.

2- Acquired causes: 2 cases (20%)

a- Sever epididymal scarring from previous surgery for removal of epididymal mass (1 case).

b- Fixation of rectal prolapse with open pelvic fixation leading to pelvic adhesion and vasal obstruction in one case.

Results

Post-operative seminal analyses were done every four months for one year. Anatomical success is

defined as presence of sperms in the seminal fluid regardless its count which indicate patency.

Patency rate in our operable 30 patients was detected in 15 patients (50%), sperms appeared postoperatively after a latency period ranging from 4 months to l year with a mean of 7 months ±S.D and sperm count ranging from 100,000 to 4 millions/ml with a mean of 3 millions/ml. Many factors were analyzed and correlated with the patency rate including :

1. Seminal alpha-glucosidase activity.
2. Presence of antisperm antibodies.
3. Type of surgery done.
4. Laterality of surgery.
5. Causes of obstruction.
6. Level of anastomosis.
7. Presence of sperms proximal to obstruction (positive touch preparation test).

1-Patency rate according to seminal alpha-glucosidase activity: we found that when seminal alpha-glucosidase activity below 20 mu/ml the patency rate was higher than if it was above 20 mu/ml, 14 patients out of 26 (53.8%) versus 1 patient out of 4 (25%) with statistical significant difference.

2-Patency rate according to the presence of antisperm antibodies: we detected antisperm antibodies in 9 patients (30%) and negative in 21 patients (70%). Patency rate was 55.6% in the +ve group and 47.6% in the -ve group with no statistical significance.

3-Patency rate according to the type of operations: According to the four types of operations carried out for reconstruction of the seminal patency, we found that side to side epididymovasostomy had the highest patency rate, 12 out of 23 patients (52.2%).Four patients had crossed transeptal epidiymovasostomy due to unreconstructable vasal obstruction on one side and defective spermatogenesis on the contralateral side. Post-operative patency rate was detected in one case (25%).

End to end epididymovasostomy was carried out in one case and patency was detected after 4 months with sperm count

4,000,000/ml. However statistical significance could not be documented because it is only one case. Non anastomotic operations were carried out in two patients. The first for releasing external epididymal compression by fibrous band & the second was spermatocele excision. Patency rate occurred in one patient 50%.

4-Patency rate according to the laterality of surgery: Bilateral reconstructive epididymovasostomy, had higher patency rate 69.2% than unilaterally managed cases 35.3% which showed statistical significant difference.

5-Patency rate according to the cause of obstruction: the causes of seminal tract obstruction was either idiopathic in 12 patients, post-inflammatory in 16 patients or post surgical in 2 patients. The best results of patency rate was detected in the post inflammatory group with patency rate 62.5% in comparison with idiopathic obstruction and post-surgical obstruction, 33.3% and 50% respectively .

6-Patency rate according to the level of anastomosis: The anastomosis of the vas to the epididymis depends on the detection of positive touch preparation test at the epididymal site. If no sperms could be detected, higher level in the epididymis should be chosen. Therefore anastomosis was carried out to the caput epididymis in 12 cases and patency was detected in 3 cases 25%. In another 12 patients anastomosis was carried out to the corpus epididymis, seven cases were bilateral. Touch preparation test was positive in all and patency was detected in 8 cases (66.7%). When anastomosis was carried out to the cauda epididymis (3 cases), two cases were bilateral and patency was detected in 2 cases. The results show statistical significant difference with higher patency rate in cauda rather than corpus and the later rather than the caput.

7-Patency rate according to the presence of intraepididymal sperms: (Positive touch preparation test). Touch preparation test was positive in 17 patients (60.7%) and 11 patients were negative (39.3%). From the positive

group 10 patients had bilateral epidiymovasosyomy. Patency rate was detected in 13 patients (76.5%) with statistical significant difference higher than negative touch preparation group where patency was detected in one out of 11 patients (9.1%).

Type of operation	No. of patients	%
1-Side to Side epididymovasostomv	23	57.5%
2-Crossed Transeptal epididymovasoatomy	4	10%
3-Non anastomotic operation (relieving epididymal external Compression	2	5%
4-End to end vasovasostomy	1	2.5%
5-Inoperable	10	25%
Total	40	100%
X2		3.99
P		0.03

Discussion

Treatment of infertile patients with seminal tract obstruction may be either surgical reconstruction or sperm retrival and in vitro fertilization (IVF) with intracytoplasmic sperm injection ICSI [1]. It gives success rate 25-65% reported in different centers [12].

Furthermore, testicular sperm inspite of being with very poor motility, can achieve good motility & good capacity of fertilizing ova by IVF with ICSI after 1-2 hour of culture in a petridish at 37ºc after washing and centrifugation [13], However, Hibi et al,[14] and Pasqualotto et al,[15] stated that; despite the recent advances in assisted reproductive techniques (ART), surgical reanastomosis of the seminal tract in ductal obstruction remains the treatment of choice, when possible, as it results in high patency rate and equal or better pregnancy rates with natural intercourse than those achieved with assisted reproductive techniques. Vasoepididymostomy is indicated when testis biopsy reveals complete spermatogenesis and scrotal exploration reveals the absence of sperms in the vasal lumen with no vasal or ejaculatory duct obstruction. In conjunction to reconstructive surgery for obstructive azoospermia Hibi et al, confirmed the necessity of sperm retrival during surgery and cryo-preservation for ART if surgery failed [11]. Schlegel calculated the cost per live birth to be approximately 87.000$ for surgical sperm aspiration and intracytoplasmic injection, while epididymovasostomy is 31,099$ [16]. This is added to the female complications of ARTs due to pharmacological super ovulation, oocyte retrival and embryo transfer [17]. On the other hand the success rate of epididymovasostomy and vasovasostomy in patients with primary epididymal or vasal obstruction unrelated to vasectomy is unclear [18], Zhuo et al, reported that surgery of the inguinal hernia in infancy & childhood is the commonest cause of vasal injury and could not be corrected in adulthood[19], and, Smirkoli et al, concluded that the pregnancy rates obtained after surgery were not statistically different from those obtained by TESE-ICSI, but when considering multiple pregnancies, miscarriag-

es and side effects, the results obtained with surgery are better than those obtained after TESE-ICSI [20], and, Lee et al, stated that; recent analyses clearly indicate that specific treatments for male factor infertility such as microsurgical reconstruction for obstructive azoospermia and varicocelectomy for impaired testis function in properly selected patients, remain the safest and most cost-effective ways of managing infertile men [21]. Our present study aims to evaluate factors that may affect anatomical outcome (patency of the seminal tract).

We found that the patency rate after reconstructive surgery was 50% (15/30) and Goldstein stated that with the classic end to side or end to end method of epididymovasostomy, the patency rate is about 70% and 43% of men will impregnate their wives after a minimum follow up of 2 years [22]. In our study the correlation between patency rate and laterality revealed that it was higher if the cases underwent bilateral reconstructive surgery than unilateral 69.2% versus 35.3% .This was confirmed by Jarow et al, where patency rate in bilateral versus unilateral epididymovasostomv were 74% &52% respectively[23], and also our results were comparable to that of Schroeder-Priittzen et al, who stated that patency and pregnancy rates are usually higher with bilateral reconstruction and recommended aspiration and cryopreservation of the epididymial spermatozoa before performing microsurgery to be used for ICSI in cases of surgical failure[24], and our results were also compatible to that of Peng et al, who achieved patency rate 80.7% for bilateral cases and 27.6% for the unilateral cases [25].

Relative to the cause of obstruction we found that the patency rate in patients with idiopathic obstruction was 33.3% while in post-inflammatory it was 62.51% and 50% patency rate was obtained when the cause of obstruction was iatrogenic. This could be explained in our study by the character of each cause. In idiopathic obstruction the site is usually in the upper half of the epididymis 80% which showed lower patency rate and positive touch preparation test in only 30%. On

contrast, the site of obstruction in post-inflammatory obstruction is present in the lower half of the epididymis and the convoluted part of the vas which has higher positive touch preperation test and higher patency rate 81.3%. This finding were confirmed by Hendery et al, who found that each pathology affect a different site [26], and in a study of Smirkoli and his colleaques, they performed microsurgical side to side epididymovasostomy in 34 azoospermic men with obstructive azoospermia mostly due to inflammation and duct system patency was recovered in 21 (63.6%) men that is nearly comparable with our results [20].

Post inflammatory obstruction typically occur in the body & tail of the epididymis near its junction with the vas deference (caudal block) and epididymovasosiomy has given better results of patency 52% than caput block 12%, similar results were reported by Jarvi et al, [27], the patency rate in men with obstructive azoospermia secondary to infection was 100% followed by post-surgical obstruction (80%) and the least in idiopathic obstruction (66%). Nigam and Handry, reported similar results, when the obstruction is caudal block, epididymovasostomy gives 52% patency rate & 38% pregnancy while when it is capital (caput) patency rate drops to 12% & pregnancy to 3%. They explained their results by the finding of high incidence of ejaculatory duct and seminal vesicles abnormalities in men with idiopathic epididymal obstruction 33% which may affect the surgical outcome [28].

In this study, antisperm antibodies(ASA) were detected in 9 patients (30%) and not detected in 70%, patency rate was 55.6% in the positive group and 47.6% in the negative group with no statistical significance, Lee et al, stated that ASA is thought to be a consequence of the inflammatory process rather than cross reactivity to microorganisms[21]. However, Bolduc et al, found that; according to multivariate analysis, there was a significant association between the absence of ASA in the seminal fluid and the success of achieving pregnancy, and the presence of high titres of ASA in the semen decreased the probabil-

ity of achieving pregnancy after surgery [29] .

Regarding to the level of anastomosis and patency rate we found that the lower the level of the anastomosis, the higher will be the rate of patency; Caput, corpus & cauda were 25%, 42.8% and 66.7% respectively. This is confirmed by Jarow et al, who found that the patency rate is higher when epididymovasostomy done to the cauda 85% & less when done to the corpus 72% and least when done to the caput epididymis (54%) [23], and in agreement to results of Jarvi et al, who concluded that moving from the corpus to the caput epididymis involves a significant adverse effect upon patency and pregnancy outcome during surgical recommendation [27], also,our results were inagreement with that of Peng and his colleaques who found 100% patency rate with caudal anastomosis, with the least if it was done with the capout 38.5% [25].

The correlation between seminal alpha-glucosidase enzyme activity and patency rate was studied. We found that when the activity was lower than 20 mu/ml the patency rate was 50% , but when it exceeded 20 mu/ml the patency reduced to the half (25%). Cooper, et al, explained this findings on the basis that the higher the level of epididymal obstruction the higher the level of alpha-glucosidase activity and consequenlty the lower the rate of post-epididymovasostomy patency [30]. The last and the most important predictor for success of reconstructive surgery of obstructive azoospermia is the touch preparation test. Shevnkin et al, found that when no sperms could be detected in the proximal end of the seminal duct, the result was poor [31]. When touch preparation test is positive i.e sperm detection proximal to the site of obstruction, the patency rate will rise to 76.5%, while when the test is negative the patency rate will drop to 9.1% that is in agreement with the results of Peng et al,who achieved a patency rate of 87.2% with the epididymal fullness [25]. Thus the presence of sperms in the epididymis at the site of anastomosis is the most significant predictor factor in our study. Also it may be the only factor that all previous

studies document its importance. Fox in his study reported that when touch preparation test is -ve during reconstructive surgery of azoospermic men, the patency rate is nil & all patients still azoospemic [32]. Kim et al, also reported that intra- operative epididymal fluid quality correlates positively with patency but not with pregnancy [18]. Jarow et al, found a patency rate of 57% when the test is positive and 0% when it was negative. He suggested that when the test is negative the obstruction may be in the rete testis or the diagnosis of obstructive azoospermia is incorrect, and the patients have defect in spermatogenesis rather than obstruction. Furthermore he reported that this spermatogenic defect may be secondary to prolonged obstruction which promoting apoptosis [23]. Nieder-Berger and Ross found similar results and concluded that demonstration of sperms in the epididymal fluid is the only parameter that predict success [33].

Conclusion

Surgical treatment of obstructive azoospermia (epididymovasostomy and vasovasostomy). remains the cornerstone in the management of obstructive azoospermia, since it has lowered cost, less side effects and comparable results to in vitro fertilization (IVF) with intra cytoplasmic sperm injection (ICSI).

We prefer to offer ARTs to the cases which are inoperable or with history of repeated reconstructive surgical techniques. There are several factors that improved the anatomical success (patency). The most important predictor factor is positivity of touch preparation test. The negativity of this test markedly lowers the rate of success.

The site of obstruction and consequenty the level of anastomosis gives better results when it is in the lower half of the epididymis rather than the upper half. Also post-inflammatory obstruction shows better patency rate after surgery than idiopathic or iatrogenic obstruction. Bilateral surgery gives better results than if surgery carried out on one side.

Seminal alpha-glucosidase activity could be used as a diagnos-

tic test for bilateral obstructive azoospermia in proximal epididymal obstruction in which an overlap exists between obstructive and non obstructive azoospermia, lower level of seminal alpha-glucosidase enzymes activity shows higher patency rate as it reflects lower site of obstruction.

Antisperm antibody has no correlation with the patency rate. Semen banking is recommended whenever possible during surgery for unfavourable surgical outcome. Again if no sperms could be detected during surgery, testicular biopsy is recommended for revision of the diagnosis and biopsy banking for future assisted reproductive techniques .

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PREDICTORS OF SUCCESS OF MICROSURGICAL EPIDIDYMOVASOSTOMY FOR OBSTRUCTIVE AZOOSPERMIA

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DIAGNOSTIC VALUES OF CRP, IL-6 AND ICAM-1 AS MARKERS OF BACTERIAL INFECTION IN THE NEONATES

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Abstract

Background: *Neonatal sepsis is the most common cause of neonatal morbidity and mortality, particularly in developing countries. The aim of the present study was to assess the value of these markers for the early diagnosis of bacterial Infection in the neonates.* ***Methods:*** *CRP, IL-6 and ICAM-1 were measured in blood samples collected from 60 neonates admitted to neonatal ICU in Demiatta hospital, Al-Azhar University from March 2011 to August 2011. The diagnostic efficacies of these markers were evaluated calculating the sensitivity, specificity, and likelihood ratio of positive and negative results.* ***Results:*** *hematological markers (WBCs and platelets), CRP, and immunological markers (IL-6 and ICAM-1) were significantly different in patient versus control, infected versus non infected and bacterial culture positive versus bacterial negative neonates.* ***Conclusion:*** *increased CRP, IL6 and sICAM-1 levels can be detected as early as neonatal sepsis developed.*

Keywords: *Intercellular adhesion molecule-1, interleukin 6 and C-reactive protein, Sepsis.*

Introduction

Neonatal sepsis remains a serious and potentially life-threatening disease with a mortality rate ranging from 1.5-40% [(1)]. Early onset (within first week of life) neonatal sepsis is generally acquired from pathogens of maternal genital tract, whereas late onset sepsis (after first week till 28 days of life) has its environmental origin either in home or in hospital [(2)].

The blood culture is a gold standard test for confirming diagnosis of neonatal sepsis, however, its results are not available for 48

hours after starting the culture, and if blood cultures are drawn after administration of antibiotics, growth of microorganisms can be suppressed [3]. Thus, it is extremely important to make an early and accurate identification of neonatal sepsis and its pathogenic factors for prompt antimicrobial therapy and better outcomes.

C-reactive protein (CRP) is widely used as a marker of acute inflammation and one of the more studied sepsis biomarkers. CRP is thought to assist in complement binding to foreign and damaged cells [4]. As a classical acute phase reactant, however, CRP elevation alone has insufficient specificity for diagnosis of neonatal infection [5].

The interleukins have been logical targets of sepsis biomarker investigations related to their role in inflammation and sepsis. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that is produced in response to infection and other conditions of inflammation [6].

ICAM-1 (Intercellular Adhesion Molecule 1) also known as CD54 is a protein that in humans is encoded by the ICAM-1gene [7]. ICAM-1 participates in the adhesion of leukocytes to the endothelium and may be crucial in regulating leukocyte activation at a very early inflammatory response [8]. Expression of adhesion molecules is regulated by cytokine activation, and it has been shown that several membrane-bound adhesion molecules can be detected in the circulation in a soluble form. Soluble ICAM-1 (sICAM-1) is normally present in the serum of healthy adults, and recent studies examined the role of sICAM-1 in neonatal infections, but with controversial results [9].

Patients and Methods

This study included sixty neonates with clinical signs and symptoms suggestive of neonatal infection with temperature instability, tachycardia or bradycardia, poor perfusion, shock, apnea, cyanosis, intercostal retractions, tachypnea, hypotonia, lethargy, seizures, abdominal distension, gastrointestinal bleeding or petechiae. They were attending the neonatal ICU in Demiatta Hospi-

tal, Al-Azhar University and twenty neonates apparently normal as a control group.

Preterm neonate, infant of diabetic mother, neonates with jaundice or intracranial hemorrhage, babies, who had received antibiotics prior to admission or had major surgical intervention, suspected chromosomal disorder or major congenital anomalies were excluded from the study.

All neonates underwent the following:

1- Detailed history with stress on maternal risk factors for infection.
2- Complete blood count with differential leucocytic count.
3- Urine examination to exclude urinary tract infection (UTI) and culture was done for specimens with WBCs >10/mm3 in a 10 mL centrifuged sample.
4- Blood culture was done by ensuring standard antiseptic measures.
5- Lumber puncture done in 11 neonates in the presence of a positive blood culture or if the clinical picture is consistent with septicemia.
6- Umbilical and throat swabs were taken from suspected cases of oompholitis and pneumonia.
7- CRP was determined using Reactivos GPL CRP-TURBILATEX kit.
8- IL-6 estimated by ELISA technique using commercial assay kit (Human IL-6, ELISA kit, Germany).
9- ICAM-1 estimated by ELISA technique (Human ICAM-1, ELISA kit,Germany).

Peripheral blood samples prior to the administration of antibiotics were taken, 1.5-3 ml added to vial of blood culture while remaining part used for CBC, while serum used for ICAM-1, IL-6 and CRP was then separated and stored at -30°C until later analysis. Venous blood samples were also taken at the time of routine vein puncture from a number of infants undergoing intensive care with no acute signs of deterioration, as controls.

Statistical Analysis

Data were expressed as mean ± SD. Comparisons between two

groups were analyzed by Mann-Whitney test. To determine a diagnostic cutoff value for CRP, IL6 and ICAM-1 in newborns, a ROC curve was constructed for each sampling point. The optimal cutoff value for study measurements were selected on the graph with sensitivity, specificity, PPV, NPV and AUC. All data were analyzed using IBM SPSS ver. 18.0 (Medcalc® version 10.0.2.0) (IBM, New York, USA). A P value <0.05 was considered to be statistically significant.

Results

1. Characteristics of study population

According to their clinical and/or laboratory findings, 60 neonates were assigned into two groups, infection group (41 neonates) and non-infection group (19 neonates).

• The infection group (group 1) (n=41) consisted of neonates who further sub-grouped into positive bacterial blood, urine or umbilical culture plus clinical signs of infection (n=25) or negative bacterial culture but the presence of three or more clinical signs of infection and abnormal laboratory signs consistent with infection or chest radiographs suggestive of pneumonia with (abnormal hematologic values and/or elevated CRP) (n=16).

• The non-infection group (group 2) comprised 19 neonates. These group characterized by there initially clinical symptoms suggestive of sepsis but there was no hematological, microbiological or radiological evidence of infection, their clinical deterioration was transient and no clinical improvement after administration of antibiotics.

• 21/60 (35.0%) were suspected of infection in first week of life (early onset infection) and 39/60 (65.0%) of infection after first week and less than 28 days (late onset infection).

• 11/25 (44.0%) of positive bacterial culture were in early onset of sepsis while all negative bacterial culture 16 (100.0%) were in late onset.

• Twenty healthy neonates whose blood had been taken for

other routine examinations were selected as a control group (group 3).

2. CRP, IL-6, ICAM-1 and hematologic profiles

WBCs, CRP, IL-6, and ICAM-1 were significantly elevated in patient group (as compared with control neonates with p value < 0.0001. While platelets were significantly decreased in patient group with p value = 0.0001 (table, 1).

Also WBCs, CRP, IL-6, and ICAM-1 were significantly elevated in infected neonates as compared with non-infected neonates with p value < 0.01, while platelets were significantly decreased in infected neonates with p value < 0.0001 (table, 2).

When neonates sub-grouped according to onset of infection into early and late onset, there were no statistically significant differences between them as regard to CRP, IL-6, ICAM-1, WBCs and platelets with p value > 0.05 (table, 3).

When neonates sub-grouped according to results of bacterial culture, there were statistically significant differences between group with positive and group with negative bacterial culture as regard to CRP, IL-6, ICAM-1, and platelets with p value < 0.001, neonates with positive bacterial culture have elevated levels as regard to CRP, IL6 and ICAM-1 with lower levels of platelets (table 4).

3. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CRP, IL-6 and ICAM-1 (table, 5):

For diagnosis of infection, CRP, IL-6 and ICAM-1 had a sensitivity of 70.73%, 60.98% and 73.17%, a specificity of 73.68%, 73.68% and 68.42%, a PPV of 85.3%, 83.3% and 83.3% and an NPV of 53.8%, 46.7% and 54.2%, respectively, with a cutoff value of 25 mg/L for CRP, 46 for IL6 and 398 for ICAM-1.

For onset of infection, CRP, IL-6 and ICAM-1 had a sensitivity of 38.10%, 66.67% and 52.38%, a specificity of 76.92 %, 43.59% and 64.10%, a PPV of 47.1 %, 38.9% and 44.0% and an NPV of 69.8 %,

70.8% and 71.4%, respectively, with a cutoff value of 20 mg/L for CRP, 52 for IL6 and 456 for ICAM -1.

For culture-positive sepsis, CRP, IL-6 and ICAM-1 had a sensitivity of 72%, 64% and 88%, a specificity of 93.75%, 100% and 100%, a PPV of 94.7%, 100% and 100% and an NPV of 68.2%, 64.0% and 84.2%, respectively, with a cutoff value of 29 mg/L for CRP, 55 for IL-6 and 456 for ICAM-1.

4. ROC-curve of CRP, IL-6 and ICAM-1

The ROC curves of CRP, IL-6 and ICAM-1 for the sepsis are taken using the control group as reference (table 5).

For the detection of sepsis, CRP had an area under curve (AUC, 0.768) in the ROC analysis, IL-6 had an AUC of 0.711, whereas ICAM-1 had AUC, of 0.757 with ($P<0.01$) (Figure, 1).

For onset of sepsis, CRP had an AUC of 0.558, IL-6 had an AUC of 0.479, whereas ICAM-1 had AUC, of 0.503 with ($P>0.05$) (Figure, 2).

For culture-positive sepsis, CRP had an AUC of 0.891, IL-6 had an AUC of 0.882, whereas ICAM had an AUC of 0.966 in the ROC analysis ($P<0.001$) (Figure, 3).

Isolated Microorganisms:

Microorganisms identified by different sample cultured on different media and identification of organism was done by different biochemical reactions in the culture positive infection subgroup (n= 25) included: Coagulase-negative staphylococci were detected in 7 cases, E. coli in 5 cases, Group B Streptococcus in 4 cases, Staphylococcus aureus in 3 cases, Enterococci in 3 cases, Haemophilus influenzae in 2 cases, Streptococcus Viridans in 1 case (table; 6).

Table (1): Study measurements of patient and control groups

	Patient group No: 60		Control group No:20		P
	Mean ± SD	(Min-Max)	Mean ± SD	(Min-Max)	
WBCs x(1000 /cumm)	37.67±12.53	16.0-72.0	12.26±2.99	6.8-18.2	P < 0.0001
Platelets X(1000xcumm)	275.08±181.12	47.0-645.0	470.60±93.34	328.0-692.0	P = 0.0001
CRP (mg/L)	35.14±23.50	13.2-103.8	3.55±1.49	1.2-5.8	P < 0.0001
IL-6 (pg/ml)	54.06±21.16	18.9-98.1	22.2±3.04	12.4-25.4	P < 0.0001
ICAM-1 (ng/ml)	485.18±182.80	235.0-924.0	199.50±37.40	136.0-264.0	P < 0.0001

Table (2): Study measurements in infected and non infected groups

	infected group No: 41		non-infected group No:19		P
	Mean ± SD	(Min-Max)	Mean ± SD	(Min-Max)	
Onset	Early : late (11:30)		Early : late (10:9)		
WBCs x(1000/cu mm)	43.05±11.28	26.0-72.0	26.05±4.87	16.0-39.0	P < 0.0001
Platelets x(1000/cumm)	197.31±138.59	47.0-645.0	442.89±146.10	169.0-641.0	P < 0.0001
CRP	41.13±26.18	13.2-103.80	22.23±5.42	13.2-33.5	P = 0.0009
IL-6	59.03±22.97	18.9-98.1	43.31±10.82	25.9-72.1	P = 0.0089
ICAM-1	534.90±191.10	258.0-924.0	377.89±102.92	235.0-638.0	P = 0.0015

Table (3): Study measurements in early and late onset neonatal sepsis

	Early Onset No: 21		Late Onset No:39		P
	Mean ±SD	(Min-Max)	Mean ± SD	(Min-Max)	
B culture	±/- (11/10)		±/- (14/25)		
WBCs	34.67±12.26	20.0-63.0	39.28±12.54	16.0-72.0	P = 0.0868
Platelets	301.28±193.50	47.0-641.0	260.97±175.05	65.0-645.0	P = 0.2780
CRP	32.29±21.71	13.2-91.2	36.68±24.55	13.2-103.8	P = 0.4616
IL-6	55.47±21.99	25.9-98.1	53.3±20.96	18.9-96.8	P = 0.7862
ICAM-1	480.04±176.47	235.0-877.0	487.94±188.34	258.0-924.0	P = 0.9691

Table (4): Study measurements positive and negative bacterial culture

	Positive bacterial culture No: 25		Negative bacterial culture No:16		P
	Mean ± SD	(Min-Max)	Mean ± SD	(Min-Max)	
Onset	early/late (11/14)		early/late (0/16)		
WBCs	46.08±12.99	26.0-72.0	38.31±5.47	29.0-48.0	P = 0.0632
Platelets	146.96±89.42	47.0-478.0	276.0±166.11	138.0-645.0	P = 0.0008
CRP	52.62±27.69	19.8-103.8	23.18±6.10	13.2-38.6	P < 0.0001
IL-6	70.64±21.44	39.8-98.1	40.9±9.84	18.9-55.2	P < 0.0001
ICAM-1	642.12±167.82	389.0-924.0	367.37±56.87	258.0-456.0	P < 0.0001

Table (5): Cutoff, AUC, sensitivity, specificity and prediction of measurement for diagnosis, onset of infection and positive bacterial culture

CRITERION		CUTOFF LEVEL	AUC	SENSITIVITY	SPECIFICITY	±PV	-PV	P VALUE
Diagnosis	WBCs	29	0.945	90.24	94.74	97.4	81.8	0.0001
	Platelets	198	0.889	78.05	94.74	97.0	66.7	0.0001
	CRP	25	0.768	70.73	73.68	85.3	53.8	0.0001
	IL-6	46	0.711	60.98	73.68	83.3	46.7	0.0018
	ICAM-1	398	0.757	73.17	68.42	83.3	54.2	0.0001
Onset	CRP	20	0.558	38.10	76.92	47.1	69.8	0.4527
	IL-6	52	0.479	66.67	43.59	38.9	70.8	0.7869
	ICAM-1	456	0.503	52.38	64.10	44.0	71.4	0.9691
Positive bacterial culture	CRP	29	0.891	72.0	93.75	94.7	68.2	0.0001
	IL-6	55	0.882	64.0	100.0	100.0	64.0	0.0001
	ICAM-1	456	0.966	88.0	100.0	100.0	84.2	0.0001

Table (6): Study measurements according the pathogen in positive bacterial culture

	No	Early : Late	WBCs M±SD (min-max)	Platelets M±SD (min-max)	CRP M±SD (min-max)	IL-6 M±SD (min-max)	ICAM-1 M±SD (min-max)
Coagulase -ve staph	7	5 : 2	36.0±9.69 (27-54)	191.57±113.07 (81-478)	28.95±4.31 (52.2-38)	53.8±13.3 (39.8-72.6)	515.28±107.58 (389-659)
E coli	5	5 : 0	41.24±13.52 (26-62)	192.0±78.43 (82-291)	48.52±27.34 (19.8-91.2)	75.6±23.1 (50.1-96.3)	624.4±145.28 (478-832)
Group B strept	4	1 : 3	63.25±6.34 (57-72)	74.25±22.94 (47-99)	73.25±17.46 (50.2-89.5)	90.8±10.1 (76.1-98.1)	863.5±47.04 (821-924)
Staph aureus	3	0 : 3	53.33±6.42 (46-58)	114.66±17.38 (95-128)	75.96±26.43 (51.2-103.8)	75.9±28.5 (42.9-92.4)	731.33±191.91 (511-862)
Enterococci	3	0 : 3	42.0±6.08 (38-49)	147.33±37.87 (105-178)	28.30±3.55 (26.2-32.4)	54.4±11.6 (41.2-63.2)	490.66±54.30 (428-524)
Enterococci	3	0 : 3	42.0±6.08 (38-49)	147.33±37.87 (105-178)	28.30±3.55 (26.2-32.4)	54.4±11.6 (41.2-63.2)	490.66±54.30 (428-524)
H influenzae	2	0 : 2	48.5±10.60 (41-56)	93.5±6.36 (89-98)	85.50±4.80 (82.1-88.9)	92.7±4.8 (89.3-96.2)	763.0±49.49 (728-798)
St viridans	1	0 : 1	58.0	103.0	93.5	71.2	678.0
No pathogens	35	10 : 25	31.65±8.01 (16-48)	366.6±174.89 (138-645)	22.66±5.68 (13.2-38.6)	42.2±10.3 (18.9-72.1)	373.08±84.04 (235-638)

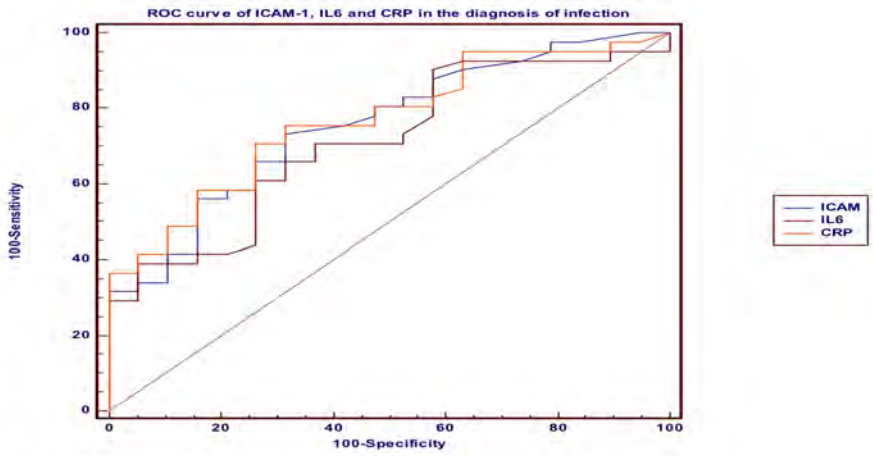

Figure (1): ROC curve of CRP, IL6 and ICAM-1 in diagnosis of infection

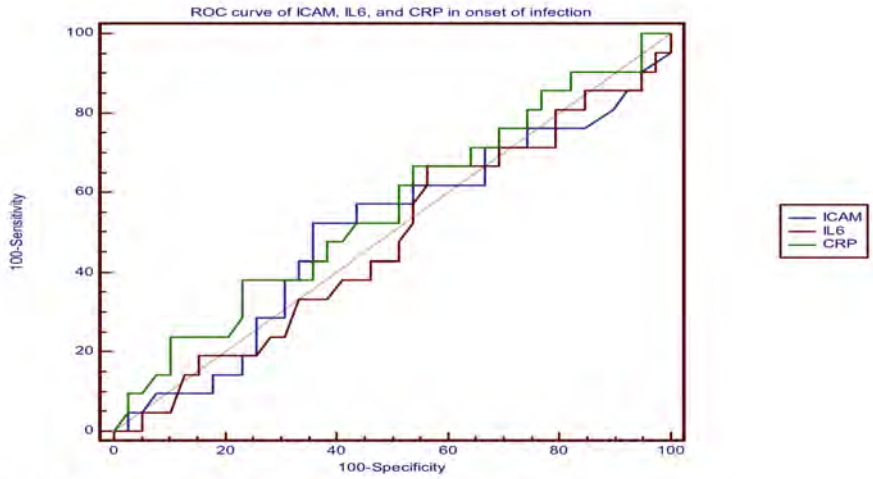

Figure (2): ROC curve of CRP, IL6 and ICAM-1 at onset of infection

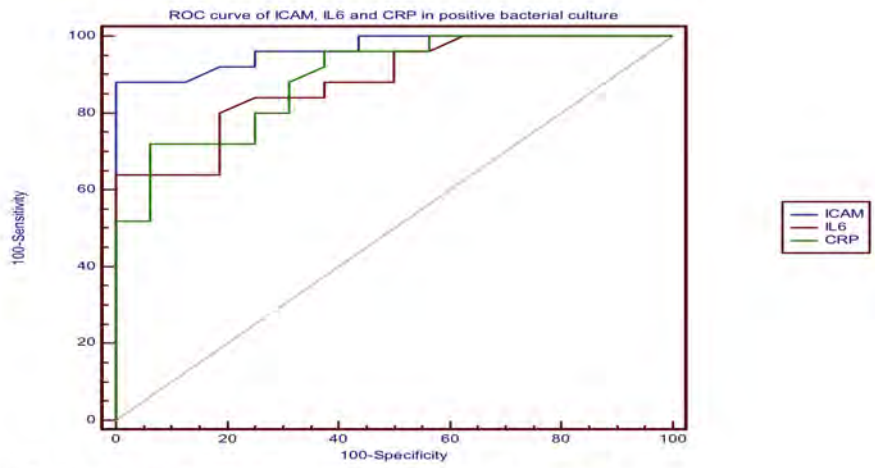

Figure (3): ROC curve of CRP, IL6 and ICAM-1 in positive bacterial culture.

Discussion

Over recent years there has been great interest in the potential diagnostic value of a range of haematological, and immunological surrogate markers of infection[5].

As regard to hematologic markers, WBCs and platelet counts were significantly differed among the studied groups. However, it has already been recognized that hematologic indices alone cannot be confidently used as decision criteria for the identification of sepsis or for guiding antibiotic treatment[10]. When WBC and platelet matched with diagnosis of infection, they had a sensitivity of 90.24% for WBCs, 78.05% for platelets, a specificity of 94.74% for WBCs, 94.74% for platelets, a PPV of 97.4% for WBCs, 97.0% for platelets and an NPV of 81.8% for WBCs, 66.7% for platelets, with a cutoff value of 29x1000/mm3 for WBCs, and 198x1000/mm3 for platelets. WBCs had an AUC of 0.945, whereas platelets had an AUC of 0.889 (P<0.001) (table, 5). These results were in agree with a Da Silva et al.,[10] study that showing variable sensitivity and specificity ranging from 17 to 90% for WBC and platelets.

Upon CRP recognition and binding to a phospholipid expressed on the membranes of many bacteria and damaged host

cell walls, the acute phase inflammatory response is initiated[11]. Accordingly increased levels of CRP are observed early in response to severe bacterial infection [12]. Plasma CRP levels were found to be statistically significantly higher in patients with septic syndrome symptoms, and CRP serum concentration correlated with severity of a patient's clinical state[13]. In fatal cases high plasma CRP concentration was recorded during hospitalization, whereas in cases of recovery, rapid decline of CRP was noted[14]. In our study, CRP was found to be increased in patient (35.14±23.50 mg/L) than control (3.55±1.49 mg/L) groups. Therefore, plasma CRP concentration in patients with bacterial sepsis may be helpful in evaluation of severity of clinical state and monitoring of the disease course as well as therapy efficacy.

In our study CRP has 25.3 mg/L, 68.3%, 70.73%, and 73.68% for cut-off, correlating prevalence, sensitivity and specificity respectively. These results were matched with many studies: Isaacman and Burke[15] found 44 mg/L, 11%, 62%, and 81%; Pulliam et al., [16] found 70 mg/L, 18%, 79%, and 90%; Lacour et al.,[17] found 40 mg/L, 23%, 89, and 75; Galetto-Lacour et al., [18] found 40 mg/L, 29%, 79%, and 79%; Berger et al.,[19] found 20 mg/L, 25%, 83%, and 67%; Andreola et al., [20] found >40 mg/L, 67%, 71%, and 81% for cut-off, correlating prevalence, sensitivity and specificity respectively.

In agreement with our results, numerous studies have demonstrated CRP levels to be elevated in sepsis[21,22]. but the data supporting its use as a diagnostic biomarker are less convincing[23,24]. The marker performs better than standard clinical parameters, such as white blood cell count and temperature, in predicting infection[25]. Alone and combined with five variables in a clinical prediction score, CRP had reasonable diagnostic accuracy. It has been suggested that CRP may be used to follow response to antibiotic therapy[25,26] but CRP performs poorly in discriminating septic from nonseptic shock[24], so that the CRP diagnostic accuracy varies widely within an unacceptable

range of sensitivity[27,28,29,30,31]. This may be related to the arbitrary choice of optimal cutoff points[32,33,34] as well as the insensitive analytic methods with various limits of quantification used in the past to detect the CRP pattern in the earliest course of neonatal infection.

Measurement of cytokine levels has also been investigated as a means to increase the diagnostic yield for neonatal sepsis. Our results show distinctly different patterns of expression of IL6 among different groups, IL6 show (54.06±21.16 versus 22.2±3.04 with p value < 0.01) for patients and controls respectively, 59.03± 22.97 versus 43.31±10.82 with p value < 0.01 for infected and non infected neonates respectively, 70.64±21.44 versus 40.9±9.84 with p value < 0.01 for bacterial positive and negative groups respectively, but similar in early (55.47±21.99) and late (53.3± 20.96) onset sepsis with p value >0.05. Like our results many studies have confirmed the utility of interleukin-6 as an early marker of neonatal sepsis [35,36,37,4,38].

Concentrations of ICAM-1 are very high in neonates with sepsis regardless of their gestational age. Even though only 25 out of 41 (60.9%) neonates with infection had positive blood culture, it is well known that a negative blood culture does not exclude sepsis. On the contrary, while the CRP levels, which are the most reliable marker in use, were nearly normal at the day of sampling, the ICAM and IL6 values were elevated in all infected neonates of the study, possibly indicative of a higher sensitivity to infection of this marker. The high number of negative blood cultures in cases of clinically diagnosed sepsis in combination with delayed elevation of CRP levels in neonates with infection further emphasizes the necessity for a more reliable index for early diagnosis. ICAM-1 and IL-6 measurement is not simpler than CRP detection, but does, however, require a minimum amount of serum, equipment available to most hospital laboratories, gives results within the day, and could probably be incorporated in routine infection laboratory tests.

The cutoff values for interleu-

kin-6 to diagnose sepsis in other studies have ranged from 18 to 31 pg/mL[35,36,4,39]. In our infected neonates, IL-6 cutoff value was 46 pg /mL.

Sensitivity of IL6 for diagnosing sepsis was 60.9%, specificity was 73.6%. When compared to CRP, IL-6 was found to be less sensitive in early diagnosis of sepsis as a single biomarker. In another study looking at children with sepsis and septic shock, IL-6 was compared to procalcitonin (PCT) and IL-6 levels were markedly higher at zero and twelve hours in the septic shock group and septic group. Magudumana et al.[4] also looked at sepsis in neonates and found that a combination of IL-6 and CRP gave the best prediction of infection and that IL-6 alone at the first sign of early infection can decrease the amount of unnecessary antibiotics in the neonatal intensive care unit.

When comparing use of IL-6 and CRP as biomarkers in sepsis includes cost, sensitivity and specificity, the cost of the assay seems to offset the benefit neonates would receive in terms of shortened hospital stay and increased availability of high risk intensive care beds[6]. IL-6 has a physiologic rise in the neonate peaking on day one of life. As regard to sensitivity, IL-6 has a sensitivity of 60.98% lower than CRP (70.73%) and as regard to specificity, IL6 has equal specificity to CRP (73.68%) and higher than specificity of ICAM (68.42%) (table, 5) indicating a wide range in clinical applicability.

ICAM was detected in all neonates enrolled in this study. This confirms the suggestion of Austgulen et al.[40] that constitutive shedding of at least this adhesion molecule is an established component of the immune system.

The present study show distinctly different patterns of expression of ICAM-1 among different groups, ICAM-1 show (485.18± 182.80 versus 199.50±37.40 with p value < 0.01) for patients and controls respectively, 534.90± 191.10 versus 377.89±102.92 with p value < 0.01 for infected and non infected neonates respectively, 642.12±167.82 versus 367.37±56.87 with p value < 0.01

for bacterial positive and negative groups respectively, but similar in early (480.04±176.47) and late (487.94±188.34) onset sepsis with p value >0.05.

This combination of infection with increased levels of ICAM-1 was in accordance with Kuster and Degitz,[41] who showed that sICAM-1 levels increased in a group of neonates with infection and with Giannaki et al.,[42] who showed that in infection-free full-term neonates there is an increased release of both ICAM-1 and soluble vascular cell adhesion molecule-1, although no infected neonates were included in this latter study. On the contrary, Austgulen et al.[40] did not find any differences in ICAM-1, vascular cell adhesion molecule-1 as well as E-selectin concentrations between the infected and non infected neonates. The discrepancy among these studies may be due to differences in the classification of the newborn infected infants and the postnatal age of neonates at sampling.

Based on the previous evidences showing that pediatric BACTEC system found 97% positive within 48 hours from starting of the blood culture, and microorganisms grown beyond 48 hours from starting of the blood cultures should mostly be caused by contamination[43], and in most circumstances, if blood culture results are not reported as positive by 48 hours, then empiric administration of antibiotics may be discontinued [35,44].

The most common organism detected in the current study was coagulase-negative Staphylococcus followed by E. coli, then Group B Streptococcus, Staphylococcus aureus, Enterococci, Haemophilus influenzae, and lastly Streptococcus viridans. These results were similar to many studies [35,45,46,47,48,49].

In conclusion, increased CRP, IL6 and sICAM-1 levels can be detected as early as neonatal sepsis developed as a response of the immune system to inflammatory stimuli.

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DIAGNOSTIC VALUES OF CRP, IL-6 AND ICAM-1 AS MARKERS OF BACTERIAL INFECTION IN THE NEONATES

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TRIPLE ATTACK IN MANAGEMENT OF DDH IN CHILDREN AFTER WALKING AGE UP TO FIVE YEARS

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Abstract

Developmental dysplasia of the hip (DDH) is the result of a disruption in the normal relationship between the acetabulum and femoral head. Without a normal, stable relationship, neither the acetabulum nor femur will develop normally. The etiology of DDH is multifactorial involving both genetic, hormonal and intra- uterine factors. Cases of developmental dislocation of the hip occur after walking age because of late or missed diagnosis and failed conservative or operative treatment. Up to now there is no consensus on the treatment of DDH after walking age. The purpose of this study was to evaluate the results of operative treatment in DDH after walking age in our patient population and to describe the treatment strategies and operative techniques used.

Introduction

Developmental dysplasia of the hip (DDH) is the preferred term to describe the condition in which the femoral head has an abnormal relationship to the acetabulum. DDH includes frank dislocation, (subluxation), instability where in the femoral head comes in and out of the socket, and an array of radiographic abnormalities that reflect inadequate formation of the acetabulum. Because many of these findings may not be present at birth, the term developmental more accurately reflects the biologic features than does the term congenital[1].

The term developmental dysplasia of the hip is necessarily general and encompasses many facts of the condition. This term realistically indicates a dynamic

disorder, potentially capable of getting better or worse and occurring prenatal or postnatal [2].

The incidence of DDH is still about 1/1000 of all live births; this incidence is higher with breach than cephalic presentation (10/1), more common in females than males 2/1, more common in European than African population, and more on left than right side [3].

Early diagnosis and treatment of developmental dysplasia of the hip is important for normal development [4].

Despite the widespread use of screening programs and the development of methods for treating newborns with congenital dislocation of the hip, children are still seen later in childhood with dysplastic hips [5].

Non-operative treatment is usually used in the management of developmental dysplasia of the hip in children younger than 1 year old [4,6].

By 18 months of age, the conservative treatment is difficult because of contracture of the extra-articular soft tissues, joint capsule, acetabular dysplasia and increased femoral anteversion. More force is required to reduce the dislocated femoral head into the acetabulum. Consequently, incomplete reduction, a high rate of complications, and unsatisfactory results can be expected [7,8].

The aim of this work is to assess the outcome of open reduction and triple attack in management of DDH in children after walking age up to five years.

Patients and Methods

In this study, 36 hips in 30 patients of DDH have bean treated surgically (September 2004 to February 2007) in Al-Azhar Damietta University Hospital.

All cases of neuromuscular disorder were excluded from this research.

The age at time of surgery ranged from 18-60 months with a mean average of 28.83 ± 8.89 months 25 patients were girls with

an incidence 83.3% and 5 patients were boys with an incidence of 16.7% with Male to Female ratio is 1: 5.

6 cases out of 30 cases (20.0%) were bilaterally affected while 24 cases were unilateral (80%), 2 on right side (8.3%) and 22 on left side (91.6%).

Obstetric history, 18 patients were normal delivery with cephalic presentation with an incidence 60% and 12 patients were delivered by caesarian section with an incidence of 40%.

No similar conditions were reported in the other members of the family.

A detailed pre-operative sheet was always completed for every patient, general examination, local examination and radiological examination. In all patients we did a routine plain x-ray pelvis (Neutral A-P view & Frog lateral view) showing both hip joints in neutral rotation.

Central edge angle (CE), acetabular index (AI), as well as neck shaft angle had been measured in every case.

CT with 3D formatting scans has been performed in some patients postoperatively for follow up as the plain x- ray cannot define the head was dislocated or reduced.

The patients have been divided into two groups according preoperative acetabular index and the stability of the reduced hip in extension intraoperatively. The first group with hip was stable in extension. In this group Salter, pelvic osteotomy is not indicated. Varus derotation femoral osteotomy was indicated whenever there was hip instability due to excessive femoral anteversion and valgus deformity. In cases where pulling the femoral head downward was difficult even after proper soft tissue release (including adductor tenotomy) femoral shortening was performed in association with other procedures .The second group was unstable reduced hip in extension. In such group Salter pelvic osteotomy was indicated. The indication of varus derotation femoral osteotomy was

the same as in the first group. Accordingly, open reduction alone was performed in 4 hips. Open reduction, pelvic osteotomy with varus derotation femoral osteotomy and shortening was performed in 32 hips. Adductor tenotomy was performed in 32 hips. Approach, the anterolateral Smith Peterson approach has been used in all cases. The advantage of this approach is that it include wide exposure of the capsule especially the superolateral and inferomedial parts. All obstructing elements are dealt with under direct vision, capsulorrhaphy can be done easily and Salter pelvic osteotomy was performed through the same approach. In cases that needed femoral osteotomy a separate lateral approach was used.

We evaluate the results in this study postoperatively according to McKay's modification method (clinical evaluation)[9] which emphases the presence of pain, limping, Trendelenberg sign, combined range of motion and radiological evaluation[10].

We collect preoperative data of the patients in (Tab.1).

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 10. For quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using the students (t) test. For qualitative data the number and percent distribution was calculated. Chi (X^2) square was used as a test of significance. Significance was adopted at $P < 0.05$ for interpretation of results of tests of significance.

Results

We used a scoring system that depends on both clinical and radiological criteria (Mc.kay1974 and thomas 1989) [9,10].

Relation between outcome and age, excellent and good results were observed in the younger age groups. In the age group from 18 - 36 months, there were 5 cases out of 7 (71.4%) excellent while 18 cases out of 20 cases (90.0%) were good in the same age group.

Trendelenberg sign (T sign),

was positive in all cases in preoperative period.

Postoperative T sign: On the left side (28 hips), 7 hips were positive (25%) and 21 hips were negative (75%) while on right side (8 hips), 2 hips were positive (25%) and 6 hips were negative (75%). Totally, 9 hips were negative (25%) and 27 hips were positive (75%).

Comparison between pre and postoperative AI, there was statistically significant decrease in postoperative AI in comparison to its preoperative levels on right, left and total values. (Tab.3 Fig.2).

Comparison between pre and postoperative neck shaft angle (NSA), there was statistically highly significant decrease in postoperative neck shaft angle in comparison to its preoperative levels on right, left and total values.

Relation between outcome and technique, excellent results were observed in 6 hips out of 32 hips (18.8%) in comparison to 1 out of 4 cases (25%) in open reduction while good results were observed in 19 cases (59.4%) in triple attack in comparison to 1 case (25%) in open reduction.

Relation between outcome and postoperative AI, it was noted that excellent outcome was associated with improvement of the acetabular index postoperatively.

Regarding postoperative AVN, it was positive in 5 hips out of 36 (13.9%) and negative in 31 hips (86.1%).

Final results, seven hips were excellent 19.4%, 20 were good (55.6%), four were fair (11.1%) and five were poor (13.9%). This means that our excellent and good results were 75%.

Table (1) : preoperative data of the patients.

	Preoperative data of the patients												Operative Technique
No		side	Age (m)	Sex	Delivery	AVN		T sign		AI		CE		
						L	R	L	R	L	R	L	R	
1	bilateral	right+left	24	female	normal	+ve	+ve	+ve	+ve	36	33	-ve	-ve	Triple attack
2	Bilateral	right+left	18	Male	normal	+ve	+ve	+ve	+ve	34	32	-ve	-ve	Open reduction
3	unilateral	left	60	female	normal	+ve		+ve		31		-ve		Triple attack
4	Bilateral	right+left	18	female	normal	+ve	+ve	+ve	+ve	32	30	-ve	-ve	Open reduction
5	unilateral	Right	23	male	normal	+ve		+ve		34		-ve		Triple attack
6	unilateral	left	28	female	normal	+ve		+ve		35		-ve		Triple attack
7	unilateral	left	29	male	normal	+ve		+ve		32		-ve		Triple attack
8	unilateral	right	38	female	cesarean		+ve		+ve		36		-ve	Triple attack
9	unilateral	left	18	female	cesarean	+ve		+ve		38		-ve		Open reduction
10	unilateral	left	37	female	normal	+ve		+ve		34		-ve		Triple attack
11	unilateral	left	25	female	cesarean	+ve		+ve		37		-ve		Triple attack
12	Bilateral	right+left	18	female	normal	+ve	+ve	+ve	+ve	40	35	-ve	-ve	Triple attack
13	unilateral	left	40	female	cesarean	+ve		+ve		34		-ve		Triple attack
14	unilateral	right	26	female	normal		+ve		+ve		32		-ve	Triple attack
15	unilateral	left	37	female	normal	+ve		+ve		34		-ve		Triple attack
16	unilateral	left	34	female	cesarean	+ve		+ve		35		-ve		Triple attack
17	Bilateral	right+left	18	female	normal	+ve	+ve	+ve	+ve	36	32	-ve	-ve	Triple attack
18	unilateral	Right	30	female	cesarean	+ve		+ve		34		-ve		Triple attack
19	unilateral	left	28	female	normal	+ve		+ve		32		-ve		Triple attack
20	unilateral	left	33	female	normal	+ve		+ve		35		-ve		Triple attack
21	unilateral	left	18	Male	cesarean	+ve		+ve		36		-ve		Open reduction
22	unilateral	left	35	female	normal	+ve		+ve		34		-ve		Triple attack
23	unilateral	left	25	female	normal	+ve		+ve		36		-ve		Triple attack
24	unilateral	left	23	Male	cesarean	+ve		+ve		35		-ve		Triple attack
25	unilateral	left	31	female	normal	+ve		+ve		34		-ve		Triple attack
26	Bilateral	right+left	30	female	cesarean	+ve	+ve	+ve	+ve	32	30	-ve	-ve	Triple attack
27	unilateral	left	26	female	cesarean	+ve		+ve		38		-ve		Triple attack
28	unilateral	left	32	female	cesarean	+ve		+ve		40		-ve		Triple attack
29	unilateral	left	28	female	normal	+ve		+ve		42		-ve		Triple attack
30	unilateral	left	35	female	cesarean	+ve		+ve		42		-ve		Triple attack

Table 2 : Postoperative Scoring System.

	POINTS	
T-sign (Trendelenberg sign)	2	Negative
	1	Positive
C.ROM (Combined range of motion)	4	C. ROM > 300°
	3	200o <C. ROM < 300°
	2	150o <C. ROM < 200°
	1	C. ROM <150°
CE-angle (Center edge angle)	4	Good coverage, CE angle >20°
	3	Minimal uncoverage CE angle 15-20°
	2	Uncoverage CE angle 10- 15°
	1	Uncoverage CE angle < 10°
AI (Acetabular index)	4	Acetabular index < 10°
	3	Acetabular index 10 – 20°
	2	Acetabular index 20 – 30°
	1	Acetabular index > 30°
AVN (Avascular necrosis)	2	Negative
	1	Positive
Excellent	14-16	
Good	10-13	
Fair	7-9	
Poor	≤ 6	

Table 3 : Comparison between pre and postoperative AI.

	Left		Right		Total	
	Pre	Post	Pre	Post	Pre	Post
Mean	35.35	18.78	32.75	17.75	34.77	18.55
S. D	2.87	7.18	2.65	11.24	2.99	8.07
T	11.92		3.37		11.86	
P	<0.001**		0.012*		<0.001**	

Table 4 : Relation between outcome and postoperative AI.

	Mean	S. D	Minimum	Maximum
Excellent	9.28	2.92	6.00	15.00
Good	19.50	5.52	12.00	37.00
Fair	23.50	1.91	22.00	26.00
Poor	23.80	14.04	8.00	36.00
Total	18.55	8.07	6.00	37.00

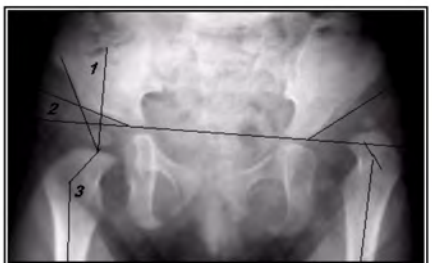

Fig. (1) : Pre-op radiological measurements.

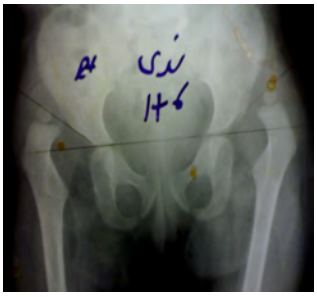

Fig. (4) : Female patient, 1.5 y. pre-op x ray bilateral DDH.

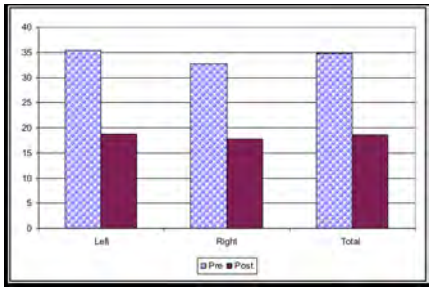

Fig. 2 : Comparison between pre and postoperative AI.

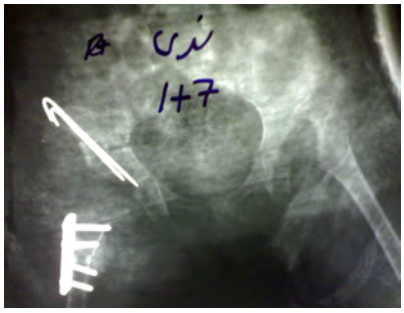

Fig. (5) : post op- follow up x ray.

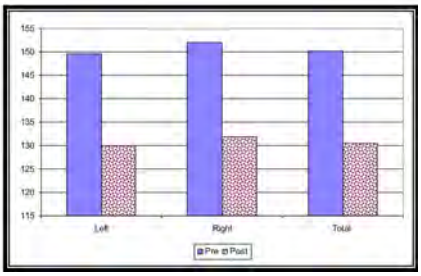

Fig. 3 : Comparison between pre and postoperative neck shaft angle (NSA).

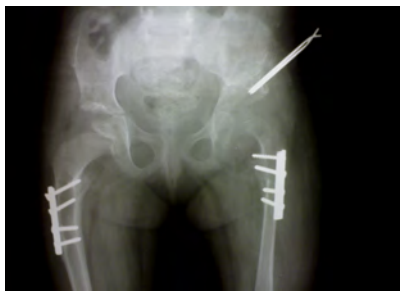

Fig. (6) : post op x ray for both hips.

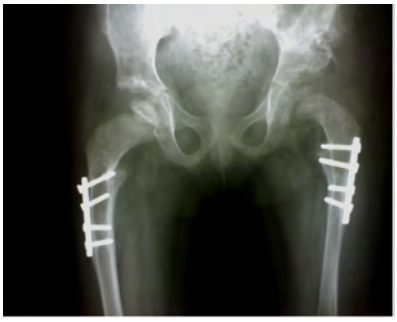

Fig. (7) : 6 months post op follow up x ray.

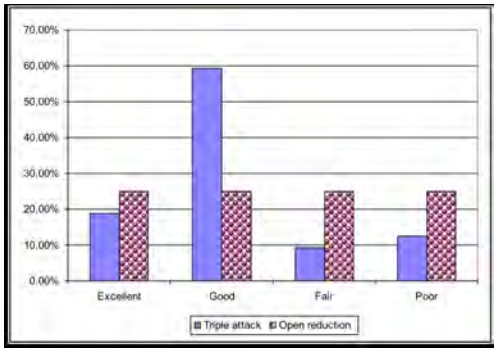

Fig. 8 : Relation between outcome and technique

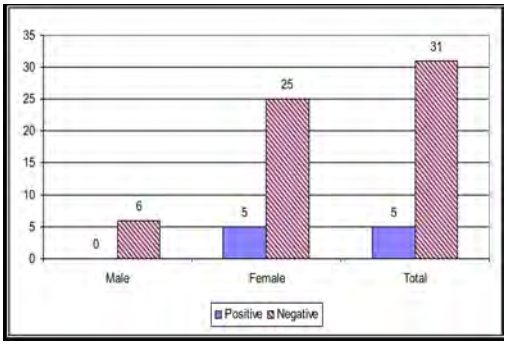

Fig. 9 : Postoperative AVN in studied cases.

Discussion

The patients in this work were missed cases of DDH that is, cases diagnosed after the age of 1.5 years up to 5 years when they are walking or after. Thus, they lost the chance for conservative treatment.

The reported incidence of male to female ratio in our study is 1: 5. Brougham et al., 1990 reported that girls were more commonly affected with an incidence of 75% (that is a three fold higher than boys)[11]. Chen et al., 1994 and Huang et al., 1997 reported similar cases [12,13].

Carter et al., 1964 had a theory that there is a probable sex determined quality in female ligaments which may explain higher DDH frequency in girls [14].

Also, Vadivelu et al., 2004 reported that 74% females, and Bohm et al., 1992 reported 83.7% female incidence in a study on 73 patients of DDH that is equal to that found in the present study[15,16].

In the present study the left side involvement was more common (66.7%). This is may be due to the fact that the common intrauterine position has the left hip adducted against maternal sacrum.

Harris et al., (1992) and Huang et al (1997) reported that left side affection was more common with an incidence of 75% while the right side was less commonly affected with an incidence of 15% and bilateral affection was of an incidence of 10%[17,13].

The increased number of bilateral cases in the present series (20%) may be attributed to the low number included in this study in comparison to other studies. On the other hand, Bohm et al., (1992) reported 18.7% bilateral cases and unilateral cases were 81.26% [16].

The average acetabular index (AI): was ranged preoperatively from 30 to 42 in all studied cases. The mean postoperative AI was18.55 and S.D was 8.07 with statistically significant decrease in postoperative acetabular index

in comparison to its preoperative levels.

In the present study, regarding type of operative intervention, triple attack was done in 32 hips out of 36 hips (88.88%) while open reduction was done in 4 cases (12.12%).

Rayan et al., 1998 also prefer one stage procedure consisting of open reduction, femoral shortening and Salter pelvic osteotomy for previously untreated case who are 3 -10 years old can result in remodeling of the acetabulum and a functional hip [18].

Also this study like to the study of Forlin et al., 2006. He prefers Triple attack after walking age [19].

In a series of 250 children who underwent open reduction and Salter osteotomies, Salter and Dubois (1974) reported that 65 percent had excellent results, 28 percent had good outcomes, and only 7 percent had fair or poor results [20].

Galpin et al., 1989 reviewed the primary operative treatment in 33 hips with no previous treatment or traction, they concluded that children who are 2 years or older with DDH safely treated by triple attack. The incidence of AVN was 10% after follow up of 2 - 6 years [21].

Regarding outcome in studied cases, it was excellent in 7 hips out of 36 hips (19.4%); good in 20 hips (55.6%); fair in 4 hips (11.1%) and poor in 5 hips (13.9%) with statistically non significant difference between males and females.

Excellent results were observed in 6 hips out of 32 hips (18.8%) in comparison to 1 out of 4 cases (25%) in open reduction while good results were observed in 19 cases (59.4%) in triple attack in comparison to 1 case (25%) in open reduction.

So, Triple attack is better for treatment of DDH patients after the walking age due to less incidence of AVN (in our study three cases developed AVN), no prolonged period of casting, early joint mobility postoperatively

and no joint stiffness,

Gulman et al., 1994 described their results after open reduction and Salter pelvic osteotomy performed in 52 hips. Clinical and radiological results were evaluated according to the patient age at time of treatment. They concluded that Salter provide good femoral head coverage even with developing AVN (63.3%)[22].

Rayan et al., 1998 reviewed the results of operative treatment of DDH in 25 hips with no previous lines of treatment (preliminary traction in 6 hips). They suggested that one stage procedure consisting of open reduction, femoral shortening and Salter pelvic osteotomy (if necessary) for previously untreated DDH in children who are 3 to 10 years old can result in remodeling of the acetabulum and a functional hip[18].

Zadeh et al., 2000 reported the clinical and radiological outcome in 95 hips with DDH treated by open reduction through an anterior approach in which a test of stability was used to asses the need for a concomitant osteotomy. They concluded that the test of stability is useful and reliable mean of assessing the need for a pelvic or femoral osteotomy at the same time as open reduction for DDH. This is what we had followed in our work and we do agree with them in that the intraoperative test of stability is a useful technique in the decision making with improved final results [23].

Forlin et al., 2006 reviewed 32 children who had 44 hips treated with open reduction and Salter osteotomy. Twenty-six hips had preliminary skeletal traction and 18 hips had a concomitant femoral shortening. There were 23 good, 12 fair, and 9 poor results. Ten hips had avascular necrosis (31%) and four had redislocation (12.5%)[21].

In another study from the same institution, the authors reviewed 24 hips of 20 patients treated after the age of 4 years (range, 4 to 12 years). The mean length of follow up was 5 years. Seventy percent of the hips had an excellent or good result.

Avascular necrosis was seen in

six hips (30%). Results were related to age at the time of operation; worse outcomes were found in patients older than seven years at the time of the operation. Femoral shortening is usually necessary in children of this age group especially age of more than 3 years, when at the time of the reduction, there is tension or difficulty in lowering the femoral head[11].

The combined use of open reduction and Salter's innominate osteotomy for developmental dysplasia of the hip under the same anaesthesia is controversial. While some authors reported acceptable results, it has been suggested that this combination may increase the rate of complications, in particular of avascular necrosis of the femoral head. The redirection of the acetabulum to provide increased anterior cover may lead to secondary posterior dislocation or subluxation [4].

Other authors reported that simultaneous open reduction and Salter's innominate osteotomy without preliminary traction resulted in a lower rate of avascular necrosis than in those who received prolonged closed treatment. They believe that the surgical release of soft tissues, removal of the internal and external obstructing factors and casting in a slightly abducted, flexed and neutrally rotated position are effective in reducing pressure on the femoral head and hence avascular necrosis[6]. Also, femoral shortening has been recommended to avoid the complication of avascular necrosis, it allows the tight structures that cross the level of the osteotomy to function as if they were lengthened and does so more effectively than a soft tissue release[13].

In our study regarding postoperative AVN, it was positive in 5 hips out of 36 hips (13.9%) and negative in 31 hips (86.1%) with statistically non significant difference between males and females.

The low AVN percentage in our study may be due to age range in our study 18-60 months, and may be due to short term follow up 15 -36 months. The cause of AVN in this study may be due to femoral shortening was not more enough

or excessive dissection during open reduction.

Lin et al., 2000 operate 89 children ageing 12 - 18 months by open reduction with result of AVN 25 % after follow up ranged from 61 - 98 months and he investigated the correlating factors of intraoperative instability as a guide to the additional Salter Osteotomy and to evaluate the radiological results. They concluded that the Salter Osteotomy does not heart the hip with regard to acetabular remodeling for children between 12 and 18 months but make the hip more stable [24].

Follow up period was ranged from 10 to 39 month with a mean of 23.86±6.45 months and there was statistically non significant increase in follow up period in males in comparison to females, this may be due to in this study there were four males only.

Summary

Our scheme of management of 36 hips of DDH in 30 patients between the age of 18 months and 5 years was open reduction in all cases due to the late presentation beyond 18 months concentric reduction could not be achieved by the closed methods. Open reduction only was done in 4 hips.

Open reduction, femoral osteotomy and shortening and Salter innominate osteotomy was done in 32 hips.The anterolateral approach is a satisfactory one. The important soft tissue obstacles of reduction should be visualized and managed properly. They include the iliopsoas tendon, inverted labrum, ligamentum teres, and transverse acetabular ligament.

Femoral shortening should be performed whenever reduction is difficult or impossible during the operation. After concentric reduction is achieved the femoral head is fixed in a varus position. At the same time Salter Osteotomy had been done and a hip spica cast is applied for 8-12 weeks according to tale radiological healing.

36 hips were the material of this study; 32 hips of them were treated by open reduction, Salter osteotomy with varus derotation osteotomy and femoral shortening. 6 patients were excellent (18.8%),

19 patients were good (59.4%), 3 patients were fair (9.4%) and 4 patients were poor (12.5%). On the other hand 4 patients had been treated by open reduction and the final results: One hip was excellent (25%), one hip was good (25%), one hip was fair (25%) and one hip was poor (25%).

So, Triple attack is advantageous in the treatment of DDH in this age group (beyond age of 18 months) due to the low incidence of AVN, no more casting, early joint mobility postoperatively, no joint stiffness and low incidence of recurrence and the good final results and minimal complications. We are waiting for long term results.

Conclusion

Although our study presents the results after a mid-term follow up the radiological results favor our clinical experience that a single stage combined procedure consisting of open reduction, pelvic osteotomy as well as a corrective osteotomy within the proximal femur with subsequent shortening should be recommended.

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TRIPLE ATTACK IN MANAGEMENT OF DDH IN CHILDREN AFTER WALKING AGE UP TO FIVE YEARS

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TIMING OF SURGERY IN ELDERLY PATIENTS WITH HIP FRACTURES

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Abstract

Hip fractures are associated with a high rate of complication, mortality and profound temporary and sometimes permanent impairment of quality of life. The effect of preoperative timing on complication, mortality and other patient-important outcomes across various age groups remains controversial and warrants a large randomized controlled trial to offer clear insights into the effects associated with early versus delayed surgery among hip fracture patients. We prospectively studied sixty elderly patients who had a fracture of the hip, to determine the effect of an operative delay on postoperative complication. We concluded that patients with hip fracture optimally should have the operation within two days after admission to the hospital.

Introduction

Surgical repair is the key element in the management of hip fracture. Before surgery, most patients are confined to bed. In theory, delay in surgery and mobilization could affect functional and other outcomes by increasing bed rest-associated complications, including thrombo embolism, urinary tract infections , atelectasis, and pressure ulcers. On the other hand, precipitous surgery and failing to stabilize medical problems could increase the risk of perioperative complications.

It is not only the mortality rate following surgery that is important. The quality of life of elderly patients who survive surgery and are expected to return, more or less, to normal daily activity is also a critical issue. The impor-

tance of the economic aspects of this controversy also cannot be overemphasized [1].

In the elderly patient with significant co morbidities, it is important to reverse easily correctible medical conditions before surgery, but surgery should be performed as soon as reasonably possible. Surgery should be performed when optimal medical support is available, preferably during normal surgical hours, because surgery performed in less optimal conditions is associated with increased risk of malreduction and other technical errors[2].

Delaying surgery will prolong the pain and discomfort involved with the injury and may also increase the length of hospital stay and may possibly reduce the chance of successful rehabilitation and the patient returning home. This study aimed to develop a consensus from the literature for the optimum timing of surgery for an acute hip fracture.

Patients and Method

Study duration :

We reviewed the records of 60 patients who had been managed with internal fixation or hip replacement for hip fracture between January 2009 to December 2010.

We investigated the relation ship of time-to-surgery with frequency of post-operative complications in elderly patients (age≥ 60) with isolated proximal femoral fracture (femoral neck fracture or pertrochanteric femoral fracture).

Polytrauma patients, patients with pathological fractures, a previous fracture or operation on the ipsilateral hip and initial conservative management were excluded. Also we excluded patients younger than 60 or patients who had other fractures rather than hip fracture.

Also documented were the times of the fracture event, of hospital admission, and of the start of the surgical intervention. Start of surgery within 48 hours after the fracture event was considered early surgery (short time-to-surgery), start of surgery from 48 to one week after the fracture event was

classified as intermediate and more than one week considered delayed surgery.

Counting from the time of the fracture event, were compared for patient characteristics, operative procedures, and post-operative complications.

Data collection :

Time Interval between Admission and Operation of Hip fracture in older patients Data Form

Name: Age:

Medical No.: Sex:

Chronic Medical Illness:

Diabetes mellitus (DM) Hypertension (HPT) Ischemic heart disease (IHD)

Others:

Mechanism of Injury:

Diagnosis: Hip fracture (Intracapsular fracture / Extra-capsular fracture)

Date and time of admission:

Procedure planned:

Dynamic hip screw (DHS). Hemiarthroplasty.

Others.

Reasons for delayed surgery:

Date and time of operation:

Type of anaesthesia either spinal anaesthesia or general anaesthesia.

blood loss, operative time, and complications.

Postoperative care:

Ward ICU

Complications:

Duration of hospital stay:

Outcome of the patient:

Results

Number of patients: 60

Table (1) : Age range.

Age range	61-70	71-80	81-90	> 90
Number of patients	26	19	10	5

Table (2) : Sex distribution.

Sex	Female	Mal
Number of patients	38	22

Table (3) : Associated medical condition (co-morbidities).

Co-morbidity	Diabetes mellitus	Hyper tension	Ischemic heart disease
Number of patients	20	38	28

Table (4) : Type of hip fractures.

Type of hip fractures	Extra capsular	Intra capsular
Number of patients	42	18

Table (5) : Surgical procedures .

Type of procedures	Osteosynthesis	Hip replacement
Number of patients	45	15

Table (6) : Type of anaesthesia.

Type of anesthesia	General	Spinal
Number of patients	25	35

Table (7) : Time Interval between admission and operative intervention.

Time interval	Less than 48 hours	Less than one week	More than one week
Number of patients	18	32	10
complication	4	20	26

Table (8): Reasons for delayed surgery.

Reasons for delayed surgery	No available ICU bed	Cardiac evaluation	Others
Number of patients	28	16	16

Table (9): Hospital stay.

Duration of stay	Less than one week	Less than two weeks	More than two weeks
Number of patients	20	24	16

Discussion

Hip fractures are a common and serious injury in older people and considered the 2nd leading cause of hospitalization for elderly people. On account of the advancing life expectancy, it is estimated that the numbers of these fractures will be doubled by the year 2040 [3].

Hip fractures are uncommon in young patients with normal bone. The average age of the patients with femoral neck fractures is 3 years younger than those with trochanteric fractures, both occurring most commonly in the eighth decade [4]. Studies suggest that femoral neck fractures should be considered fractures through pathologic bone secondary to either osteomalacia or osteoporosis[5]. Intertrchanteric fractures account for 50% of all fractures of the proximal femur. The ratio of women to men ranges from 2:1 to 8:1, likely because of postmenopausal metabolic changes in bone.

In our study hip fractures occurred in elderly population (average 66 years).

The majority of the patients (63.4% patients) were female and 70% were trochanteric fractures. This might be attributed to the fact that osteoporosis is common in this age group Approximately 1 in 1000 people each year in industrialized counties suffers a proximal fracture of the femur [6]. The mortality rate after six months is reported to range between 12 % and 41%. Davis et al reported a mortality rate of 24% and Sikorski and Senior [7] and Lucke, Philipe and Krause[8] 13% and 18% respectively after three months. Proximal femoral fractures lead to significantly reduced life expectancy and, for about 50% of patients, to an often dramatic deterioration in health and social conditions. For many, such fractures lead to loss of independence. Patients who already required some assistance prior to breaking their hip may become entirely dependent on nursing care after the fracture.

Management of hip fractures is based on individual patient factors, such as pre-injured ambulatory status, age, co morbidities, and on fracture factors, including fracture type and the degree of

displacement. Treatment options include nonsurgical management, percutaneous fixation, closed or open reduction and internal fixation (ORIF), and arthroplasty (hemiarthroplasty or total hip arthroplasty). Despite the variety of treatment options available, the question remains when and what is the best treatment of hip fractures in elderly patients (1).

The goals of treatment of hip fractures are to achieve anatomic reduction and to provide stability to the fracture fragments in order to maintain the reduction and allow complete fracture healing. In general, these goals are best achieved in the operating room with fracture reduction performed under fluoroscopic guidance and fracture stabilization with rigid internal fixation or prosthetic replacement.

Improvement in surgical techniques and more aggressive treatment have resulted in improved outcomes in the treatment of hip fractures.

The question of the optimum timing of surgery has been addressed in several studies and remains controversial. Surgery for a hip fracture should be within 24 hours of injury because earlier surgery is associated with better function outcome and lower rates of perioperative complications and mortality. Proponents of early treatment argue that this approach minimize the length of time a patient is confined to bed rest, thereby reducing the risk for associated complications, such as pressure sores, deep vein thrombosis chest and urinary tract infections. Those favouring delaying surgery beyond the guideline recommendations believe that this approach is required to medically optimize patients and therefore decrease the risk for perioperative complications[9].

The timing of surgery is controversial and relates both to different approaches to this issue in the medical community, and to the lack of adequate resources to operate on every fit patient in the shortest possible time. Orosz and co-workers[10] presented data on the causes of delay in surgical repair of hip fractures in four hospitals in the New York City

metropolitan area. The main cause in their series was a delay in medical clearance in 52% of those operated on later than 24 hours after hospital arrival. However, in 29% the delay was caused by the unavailability of an operating room or a surgeon. The arguments presented by each side of the controversy in this issue are clear and persuasive. This being the case, how can we solve the problem and draw conclusions that will assist anesthetic doctors and orthopedic surgeons in their routine clinical work.

The recommendation that fit patients should undergo surgery as quickly as possible. A long series of studies has demonstrated many advantages of an early surgical approach, i.e., within the first 24 hours of hospital admission. These advantages include improved 1 year survival[11], reduced hospital stay [12,13,14], and improved activities of daily living. On the other hand, patients with significant co morbidity and an evident need for preoperative assessment and preparation, Moran et al. [15] reported that mortality was not increased when surgery was delayed up to 96 hours.

Sikorski and Senior(7) and Dolk(16) believed hat early surgery would bring better surgery. and was consistently associated with decreased length of stay and less pain and probably with reduced major complications. They reported that clinical reasons (waiting for test results or for medical stabilization) were infrequent reasons for delayed surgery in patients operated on less than 48 hours. Instead, system problems (timely consultation or availability of the surgeon or operating room) accounted for the majority of cases of delay. Thus, it is feasible to improve surgical timing which could in turn translate to improved efficiency and reductions in severe pain.

Fractures of the femoral neck treated late present unique problems in management.

According to Massie(17) when surgery is performed within 12 hours of injury, there is a 25% incidence of aseptic necrosis. The incidence rises to 30% with a delay of 13 to 24 hours, to 40% be-

tween 24 hours and 48 hours, and to 100% after 1 week. This direct relationship between the time from injury to internal fixation and complication of aseptic necrosis and nonunion has also been reported by Brown and Abrami[18] and Soto-Hall and colleagues[19]. This factor is important for patients who will be operated for osteosynthesis.

Significantly higher mortality rates were reported by Todd et al[20] in patients operated on after 48 hours. They found extensive medical investigation to be of no benefit.

Parker and Pryor [21] recommended surgical treatment within 48 hours of admission. The incidence of age-related post-operative complications was significantly higher in those patients who underwent surgery on or after the third day compared with those who underwent surgery on the first or second days.

The theoretical advantage of allowing a delay from admission to surgery for a hip fracture is that it will allow some time for physiological stabilization after the injury. This is may be particularly relevant after an extra capsular fracture, in which a more extensive blood loss from the fracture site occurs. Other potential advantages of delaying surgery are that it allows more time for assessment of the patients and for correction of dehydration and fluid replacement. Many hip fracture patients are found to be hypovolaemic at the time of surgery. This may even be reflected in an increase in mortality.

Hoeing et al[6] described a shorter hospital stay in patients who underwent early surgery but no difference in complication.

Possible adverse effects of delaying surgery are there may be an increase in the incidence of the complications of recumbency. Namely pressure sources, thromboembolic complications, urinary infection and pneumonia.

The occurrence of pressure sore is a result of the damage of prolonged skin constantly under shear pressure due to prolonged

immobilization. Therefore, the earlier the patient is mobilized, the lesser the chance of getting pressure sore. Several authors have investigated whether the incidence of pressure sores would be increased with a delay of hip fracture surgery. Published reports generally supported the above theory [22, 23-14].

Lefaivre et al[22] showed that when the surgery was delayed for more than 24 h, it was significantly related to increase in pressure sore . Grimes et al[23] showed that the risk of decubitus ulcer increased as the surgery was delayed for more than 96 h. Al-Ani et al.[14] further proved that the incidence of pressure sore was not only related to delay in surgery, but the odds ratio increased progressively as the delay increased from 24 to 36 to 48 h .

We could not identify any study showing that the development of pressure ulcer is not related to prolonged pre-operative waiting time.In our study there was incidence of bed sores in the group of patients who has been operated after two days.

Length of stay is another important reason why many trials were conducted to investigate the impact of timing of surgery is that it has significant financial implication on the health care system[24,25]. One of the important indicators of the resources needed is the number of days in hospital or length of stay. Most of the evidence nowadays tends to agree that shortening the pre-operative waiting time would shorten the hospital stay in post-operative as well as the total period. Length of stay in our hospital in the present study were 30% more than one week and 26.7% more than two weeks.

Anaesthesia :

The goal of the anaesthetic technique selected is to eliminate pain, allow for appropriate intra-operative positioning and achieve muscle relaxation to effect the reduction.

Selection of anesthesia for surgical candidates is complex and multifactorial and must account for factors such as age, co morbid conditions, and patient preference.

In our study spinal anaesthesia were performed in most of our patients (58.3%). Spinal anesthesia patients generally did better than general anesthesia patients on several different measures. Use of spinal anesthesia decreased intraoperative and postoperative blood loss, and transfusion requirement. It has less post surgical confusion. It has lower incidence of deep venous thrombosis. These findings have significant implications for maximization of cost-effectiveness of the surgery as well as for quality of patient care and safety. But spinal anaesthesia may fail and converted to general anaesthesia.

General anaesthesia was found to be significant contributor to the risk of DVT, compared with regional anaesthesia. On the other hand it has shorter time which is an advantage for elderly patients with significant co morbidity. This finding is consistent with other similar studies[26]. We conclude that spinal anesthesia is superior to general anesthesia for hip surgery, especially in older patients or patients with significant co morbidities that may preclude use of endotracheal general anesthesia.

Summary and Conclusion

Of the total 60 patients with hip fractures, 18 patients (30%) were operated within 48 hours.

32 patients (53.3 %) were operated within one week. Still majority of patients 42(70%) patients were operated after 48 hours. In our study the main cause for delay the surgery were no available ICU bed, cardiac problems, uncontrolled DM and other geriatric diseases.

Although our sample size is small, still our results are comparable with international standards. Our data suggest that early stabilization may be associated with a lower complication rate.

The results of this review indicate that delaying surgery may increase morbidity, particularly the incidence of pressure sores and will increase hospital stay. Delaying surgery will inevitably prolong the distress involved from this injury. Therefore patients admitted

to hospital with a hip fracture, in which there are no specific conditions that van be improved prior to surgery, should have their operation as soon as possible after admission to hospital. Short delay prior to surgery may be justified to address medical problems.

Need of ICU bed and hospital stay remained a major concern.

We recommend that elderly patients with osteoporotic hip fractures should be operated on as soon as the body meets the basic anaesthetic requirements (within 48 hrs), during standard daytime, working hours including weekends if their medical condition allows. Surgical fixation should not be delayed more than 48 hours from admission unless there are clear reversible medical conditions.

This retrospective study confirms the trend towards more morbidity and a longer length of hospital stay if surgery for hip fracture patients was delayed beyond two calendar day from admission.

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EFFECT OF MALARIA ON PREGNANCY OUTCOME IN HAJJAH GOVERNATE IN YEMEN

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Abstract

Background: *Maternal or fetal malaria infection during pregnancy adversely affects development and survival of fetus through low birth weight, maternal anemia, and possibly abortion and stillbirth. These malaria induced medical problems constitute major clinical, public health and research challenges. Malaria during pregnancy is a major health problem in Yemen, where pregnant women are more susceptible to malaria than their non pregnant counterparts, the important aspect is that it is preventable cause of low birth weight deliveries worldwide.* ***Objective:*** *aim was to study the complications and outcome of malaria during pregnancy. In Hajjah governate in Yemen. Methods: This case control study was conducted at Saudi hospital in Hajjah governate in Yemen in period from Jan 2011 to end of the same year. Patients included in this study were 100 pregnant women, 50 were diagnosed with malaria as study group, and 50 were normal pregnancy as control group. Admitted at Saudi hospital in Hajjah . different kinds of variables were recorded on data sheet. These included demographic variables, miscellaneous variables and severity related variables. We compared between both group in age parity, week of pregnancy, mode of delivery, Apgar score, baby weight, parasite species, laboratory values, lines of treatment, length of hospital stay, pregnancy and malaria related complications, maternal and fetal morbidity and mortality).Results: in study group, Only 15 (30%) were primigravida, and 35 (70%) were multigravida while 13(26%) were primigravida, and 37 (74%) were multigravida in control group. In study group, most of patiets, 28 (56%) presented in second trimester, while 8 (16%) presented in 1st trimester of pregnancy, and 14 (28%) patients presented in 3rd*

trimesters. regarding pregnancy outcome, 5(10%) had spontaneous abortion, 10(20%) patients had pre-term labor,16(32%) developed puerperal pyrexia, 5(10%) babies of infected mothers died in neonatal period and Mean weight of babies in study group was 2.5 ± 0.6kg and 3.1± 0.4 kg in control group babies (P<0.05).10(20%) babies were delivered with preterm labor, all were< 2.5 kg in weight, 2 patients had IUFD. and congenital malformations were reported in two babies. Conclusion: Maternal malaria adversely affects the pregnancy outcome. It increases the risk of spontaneous abortion, stillbirths, premature delivery and low birth weight. P. falciparum sp, and p.vivax sp, is identified as common cause of malaria during pregnancy in Yemen. Malaria is more common in multigravida and in second trimester of pregnancy. It is significantly associated with decreased maternal hemoglobin and low birth weight of newborn.

Introduction

Malaria is a parasitic disease affecting red blood cells that is transmitted by female mosquitoes of the anopheles genus. Of the four parasitic protozoa causing malaria, plasmodium falciparum, p.vivax, p.malariae, p.ovale, p.falciparum is the most common and the most dangerous, causing between 700,000 and 2, 7 million deaths annually, most of which are in children and pregnant mothers.[1] Malaria and pregnancy usually affect the course of each other adversely. The physiological changes of pregnancy and pathological changes due to malaria have a deleterious effect on the course of each other. In endemic areas, clinical episodes of malaria are more frequent and more severe during pregnancy and mortality rate is higher among them as compared to non-pregnant.[2] Various studies have shown that pregnant women in endemic areas are highly susceptible to malaria and both the frequency and the severity of the disease is higher in pregnant than non-pregnant women.[3.4] This higher susceptibility has been hypothesized to be due to transient depression of cell mediated immunity which improves with delivery of neonate and decreases with number of subsequent pregnancies[5]. Pregnant ladies with Plasmodium falciparum are prone to get high levels of parasitaemia, hypoglycemia, acute pulmonary ede-

ma, fetal distress, premature labor, spontaneous abortions and still births. Also,[6] Malaria in pregnancy is significantly associated with higher mortality and morbidity including, cerebral malaria, maternal anemia, intrauterine growth retardation,, and stillbirth.[7.8] In addition; drugs used for treatment of malaria can also contribute significantly to complications associated with this disease. maternal mortality associated with p.falciparum malaria is highest in area of low and unstable transmission or in epidemic, where in area of higher transmission, the main complication of p. falciparum malaria during pregnancy are maternal anemia and low birth weight. This effect is most severe in primigravida, but in area of low transmission, women of higher gravidity are also affected.[9] It is well established that anemia the most common consequence of P. falciparum malaria infection and it is generally accepted that in malaria-endemic areas, P. falciparum is a major Contributor to anemia in pregnancy. It has been suggested that the ABO system has evolved under appositive selection pressure in both humans and other primates.[10] malaria during pregnancy is a major health problem in Yemen, where pregnant women are more susceptible to malaria than their non pregnant counterparts.[11] anemia is regarded as a major risk factor for an unfavorable outcome of pregnancy. It has been reported as a predictor of preterm labor, LBW, maternal and perinatal mortalities.[12-16] approximately 60%of Yemen population live in area endemic with malaria, and p.falciparum account for more than 90%of malaria cases.17while there is much literature concerned with the epidemiology of malaria and anemia during pregnancy in other setting.[18-19] few published data are available on the topics of Yemen.[20]

Patients and Methods

This case control study was conducted at Saudi hospital in hajjah governate in Yemen in period from Jan 2011 to end of the same year. Saudi hospital in Hajjah, serve much population in Yemen, especially in Hajjah and the surrounding subgovernates.. Malaria transmission in this area is perennial but usually at peak

towards the end of the rainy season. This area is characterized by unstable malaria transmission, and p.falciparum, p.vivax are the main species in this area, with a peak of infection following the rainy season. In this population, malaria affects all age group and most parasitimic episode is symptomatic. The most two group at risk of malaria complication are children and pregnant women.

Patients included in this study were 100 pregnant women, 50 were diagnosed with malaria as study group, and 50 were normal pregnancy as control group. Patients were admitted at Saudi hospital in Hajjah governate in Yemen in period from Jan 2011 to end of the same year. Controls were randomly selected from pregnant patients without malaria who were admitted for routine ANC and delivery at Saudi hospital in Hajjah governate in Yemen in the period of the study. Before being admitted to the clinical study, the patients consent to participate, after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. Information on the participants' age, parity, duration of pregnancy, occupation, etc., was recorded.

Personal, present, obstetric and past histories were obtained .Information also was obtained from the delivery room for labor outcome including; baby's weight, sex, Apgar score, and mode of delivery. About 5 ml of the maternal peripheral blood was obtained from each participant by venepuncture technique into sterile EDTA container for laboratory analysis. Malaria was confirmed by microscopic examination of Giemsa-stained thin films of blood smears after screening by malaria kites.

Three different kinds of variables were recorded on data sheet. These included 1-demographic variables, 2- severity related variables (parasite species, laboratory values, length of hospital stay, pregnancy and malaria related complications, maternal and fetal morbidity and mortality).

3-miscellaneous variables (parity, week of pregnancy, mode of delivery, Apgar score, baby

weight), The WHO definition of anemia in pregnancy (anemia was defined as hemoglobin< 11 g / dL), low birth weight as weight < 2500 g, the birth weight was determined in kilogram (kg) using an electronic weighing machine immediately after childbirth. Preterm labor was delivery before completing 37 weeks of pregnancy, and abortion (miscarriage) as complete expulsion of product of conception before completing 28 weeks of gestation. Selection of treatment regimen was based on individual physician's assessment and choice. Pregnant patients admitted with malaria were taken as cases and pregnant patients without malaria were taken as control. Data was recorded on standardized data sheet and analyzed; the descriptive analysis was done for demographic and clinical features. Results are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. Univariate analysis was performed by using the Independent Sample t-test corresponding to difference of means and Pearson Chi-square or Fisher's exact test corresponding to proportion whenever appropriate. P-value < 0.05 was considered as statistically significant and all p-values are two sided.

Results

A total of 50 pregnant patients were identified with malaria as study group and 50 pregnant women without malaria were taken as control group. Mean age of study group was 28.6 ± 4.4 (range 16-46) years and in control patient was 26.56± 4.3 (range 15- 43) years. In study group, (86%) 43 patients were illiterate, (78%) 39 lived in rural area those whose occupation was farming were significantly more infected with malaria parasite than individuals of other occupations. Women, who had no formal education, recorded the highest prevalence of malaria infection. Highest malaria infection was recorded among Women with blood group 'O' followed by those of blood group 'A' .

In study group 15 (30%) were primigravida, and 35 (70%) were multigravida, while 13 (26%) were primigravida, and 37 (74%) were multigravida in control group.

In study group, most of patiets, 28 (56%) presented in second trimester, while 8 (16%) presented in 1st trimester of pregnancy. And 14 (28%) patients presented in 3rd trimesters.

P. Falciparum was present in 30 (60%). Patients, While P. Vivax accounted for 20 (40%) patients. History of fever in45 (90%) patients, while nausea and vomiting in 23(46%) and myalgia in 12 (24%) patients. and abdominal pain in 38(76%) patients.

40(80%) patients had anemia. Mean hemoglobin was 9.6 ± 1.5g / dL (range 5.2 - 12.2 g / dL) in study group and 12.4 ± 0.7g / dL (range 11.4 - 14.8 g / dL) in control group (P-value <0.001). 7 (14%) patients had hemoglobin in the range of 5-8 g/dL. 40 (80%) patients had platelets < 150,000 / mm^3, among them 6 (12%) patients had platelets < 50,000 / mm^3. The mean length of hospital stay was 3.2 ± 0.8 days (range 1-6 days).

All patients were treated with Quinine, 10-15mg/kg body weight for 7 days. Two patients with cerebral malaria died during treatment.

All patients with falciparum malaria were treated with Quinine. 18 patients with vivax malaria were given quinine and two patients of whom received artemether. Drug regimen selection was based on individual physician's choice.

26 (54%) out of 50 patients of the study group had babies born in Saudi hospital in hajjah. Total number of babies in study group were lower because some pregnant patients who were admitted in our hospital for malaria, delivered their babies elsewhere and hence remained unaccounted in our records. Mean weight of babies in study group was 2.5 ± 0.6kg and 3.1± 0.4 kg in control babies (P<0.05).

Regarding pregnancy outcome, 5 (10%) had spontaneous abortion, 10 (20%) patients had preterm labor, 16 (32%) developed puerperal pyrexia, 5(10%) babies of infected mothers died in neonatal period and. 10 (20%) babies

were delivered with preterm labor, all were< 2.5 kg in weight, 2(4%) patients had IUFD. congenital malformations were reported in two babies. Two (4%) pregnant patient died in third trimester secondary to severe cerebral malaria and ARDS.

Table (1): Comparison between both group in demographic variables.

variables	Study group(n)	Control group(n)
Mean Age (years)	28.6 ± 4.4	26.56± 4.3
Primi	15	13
Multi	35	37
1st trimester	8	-
2nd trimester	28	-
3rd trimester	14	50

Table (2): Presentation of malaria with parity.

Parity	Plasmodium falciparum		Plasmodium vivax	
	Cases	Percentage	Cases	Percentage
Primigravida	12	24%	3	6%
Multigravida	18	36%	17	34%
total	30	60%	20	40%

Table (3): Presentation and complication in study group.

complication	no	%
fever	45	90
vomiting	23	46
myalgia	12	24
abdominal pain	38	56
preterm labour	10	20
abortion	5	10
congenital malformations	2	4
IUFD	2	4
cerebral malaria	4	8
Maternal death	2	4
puerperal pyrexia	16	32
Neonatal death	5	10
Severe anemia	7	14
No complication	8	16

Table (4): Comparison between two groups in mean HB, BW of newborn.

	study group	control group	p-value
Mean hemoglobin(g/dl)	9.6 ± 1.5	12.4± 0.7	<0.001
Mean weight of babies(kg)	2.5 ± 0.6	3.1± 0.4	<0.05

Discussion

Maternal or fetal malaria infection during pregnancy adversely affects development and survival of fetus through low birth weight, maternal anemia, and possibly abortion and stillbirth. These malaria induced medical problems constitute major clinical, public health and research challenges.[21] The important aspect is that it is preventable cause of low birth weight deliveries worldwide. In women from non-endemic areas or travelers to area, infection is associated with high risk of maternal and perinatal mortality. This infection can aggravate other infections, dual infection has additional detrimental effects on maternal and infant survival in an area where HIV and malaria coexist.[22]

Malaria poses a serious health problem to pregnant women. We have described important epidemiologic features and clinical characteristics of 50 patients who had malaria during pregnancy and compared some of the important complications with control 50 pregnant patients without malaria. Complications of malaria during pregnancy are more in primigravida than multigravida.[23] Local placental productions of chemokinesis increased in malaria which is an important trigger for monocyte accumulation in placenta,[24] these pigment containing placental monocytes are associated with anemia and low birth weight due to malaria and may be causative in their development.[25] Maternal malaria not only affects immediate infant health but can also result in high susceptibility of child to parasite during the first year of life.[26]

Complications of malaria are mostly seen in P. falciparum sp. The incidence of severity of infection and pregnancy related complications varies according to level of acquired immunity against infections and the parity.[27] although, Many studies have shown that primigravida are high risk group, as in areas of endemic transmission, the prevalence was high, ranging from 64% in primigravida to 30% in gravid.[5] In our study, the susceptibility to malaria infection was high in multigravida compared to primigravida. Patients but associated complica-

tions were statistically higher in primigravida. This is in agreement to various studies published from Indian subcontinent where complication rate was higher in primigravida compared to multigravida patients.4, 28, 29 but in contrast to Maqsood et al., 2007, In which the susceptibility to malaria infection was high in multigravida compared to primigravida patients but associated complications were not statistically significant in both groups.[30]

In our study anemia affect 80% of infected patients which is in agreement with Anisah et al., 2010 in a study done in Elhodaidah governate which concluded that anemia affect 76%of infected women regardless their age or parity. and malaria was not a risky factor for anemia, but it was a risk factor for LBW36. whever in other study, The risk of low birth weight is associated with extant of anaemia.[23] the prevalence of anemia was high in our study and in other36, whever this anemia should be investigated in the future with special interest in other risk factors such as pica, worm infestation, schistosomiasis and haemoglobinopathies.

In highly endemic areas the peak level of falciparum parasitemia occurs between 9 to 16 weeks of gestation and then decreases progressively until delivery.[4] In our study 56% of patients presented in second trimester of pregnancy, this is in agreement with previously reported higher incidence in second trimester of pregnancy.[4] but in contrast to Maqsood et al., 2007. In which 55.8% of patients presented in third trimester of pregnancy. 302 out of 50 patients died during hospitalization due to underlying severe cerebral malaria and ARDS. They presented in 28, 30^{th} week of IUFD, delivered vaginally after induction of labor. Both of them were with high parasitic load of falciparum, hemoglobin was< 6 gm / dl and platelet count<of 10,000 / mm^3 in both patients. The mortality rate in our patients was low and in agreement with Maqsood et al., 2007, in which there was only one case of maternal mortality among 43 patients infected with malaria. Whoever, the mortality rate in our patients was much lower than previously

reported figures from other countries.[4,29,31]

In Kocher et al. associated significant anemia (Hb. 5g%) was the prime cause of mortality in his cohort of patients. the prime cause of mortality in our study was ARDS secondary to severe cerebral malaria. In our patients malaria was significantly associated with hemoglobin decline of at least 2.6 gm compared to control group (P<0.001), but it was not associated with a higher mortality rate. The reason could be that in our group, the severity of anemia was much lower compared to the cohort in Kocher's study with higher mortality.[4]

Malarial infection also contributes to preterm labor. Maternal fever close to term is also associated with deaths of infant aged between1 and 3 months, whereas no risk factors could be identified for deaths that occurred later in infancy.[32] The clinico-epidemiological pattern of malaria infection in a cohort of prenatal women and infants was analyzed during malaria epidemic. They found that 88% infections were of Plasmodium falciparum, and its highest prevalence was recorded in second trimester (59%). Re-infection or treatment failure were found to be common, both in the infants and pregnant women.33In study conducted in Koraput district of Orissa, a tribal area endemic for malaria in India, there was significant different parasite incidence between primigravida and multigravida which clearly correlates with our study as well.4 It is clear that this infection contributes to major perinatal mortality by affecting both mother and fetus independently. Placental malaria is a significant cause of pregnancy related complications in the form of low birth weight babies, preterm deliveries, still birth and abortion.4 In our study, 10 pregnant patients had preterm live birth and all of those babies were less than 2500 gm in weight. Overall there was 400 gm decrease in birth weight of babies born to pregnant women with malaria compared to pregnant patient without malaria (P = 0.016). The biologic mechanism by which placental malaria infection leads to low birth weight is not fully established. P. falciparum infected

placenta shows thickening of basement membrane of placental trophoblast cells, potentially resulting in reduced nutrient transfer to the foetus.(34) Placental microinfarcts have been reported; transplacental passage of parasitized RBC to fetus does occur, and this may affect fetal nutrient use or stimulate preterm labour. (34) Limited data are available regarding spontaneous abortion as a complication of clinical malaria or associated anti-malarial drugs in therapeutic doses. In our study, 5 patients aborted. 4 patients were admitted with history of vaginal bleeding prior to treatment with quinine. The patients with abortion had some common features like, falciparum malaria with, hemoglobin < 10g/dL and platelet count of< 50,000 / mm^3. Various authors from other parts of the world have reported that malaria is not an important cause of spontaneous abortion in highly endemic areas.4, 28, 35 Although, our all 5 patients had severe malaria.

Conclusion

1- Maternal malaria adversely affects the pregnancy outcome. It increases the risk of spontaneous abortion, stillbirths, premature delivery and low birth weight.

2- Malaria is more common in multigravida and in second trimester of pregnancy. It is significantly associated with decreased maternal hemoglobin and low birth weight of newborn.

3- P. falciparum sp, and p.vivax sp, are identified as common cause of malaria during pregnancy in Yemen.

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EFFECT OF MALARIA ON PREGNANCY OUTCOME IN HAJJAH GOVERNATE IN YEMEN

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COMPARISON BETWEEN TRANSPULMONARY VENOUS FLOW AND TISSUE DOPPLER OF DIASTOLIC FUNCTION IN HYPERTENSIVE PATIENTS

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Abstract

Background: *Systemic arterial hypertension has clearly been shown to be a major factor in the enhanced incidence of cardiac morbidity and mortality. Relaxation abnormalities are one of the earliest manifestations of cardiac dysfunction and frequently precede systolic dysfunction in hypertension. Severe diastolic dysfunction may cause pulmonary congestion even without any deterioration of systolic function. Thus assessment of left ventricular diastolic filling in individual patients is important from both the diagnostic and therapeutic points of view.*

Aim of the work: *to evaluate left ventricular diastolic function by pulmonary venous flow with pulse tissue Doppler in hypertensive patients.*

Patients and Methods: *Thirty hypertensive patients of both sexes were included in this study, and admitted at cardiology department of Benha University Hospital during the period from September 2010 to March 2011.The study also included ten apparently healthy volunteers as a control group with matched age and sex. All patients were evaluated by history taken, clinical examination. Conventional echocardiography was performed to all patients to assess LV functions, dimensions and hypertrophy.*

Pulmonary venous flow was done by Doppler to measure S, D wave and S/D ratio, also Doppler tissue imaging was performed on mitral annulus at apical four chamber view to measure E", A", and E"/A" ratio.

Results: *The maximal early diastolic flow velocity of conventional Echo. of the control group ranged from 45-116 cm/sec with a mean value 75.2±18.9 cm/sec, while that of patients group ranged from 48-76 cm/sec with a mean value 62.1±13.9 cm/sec. there was a significant decrease in mitral E wave in patients than that the control group (P<0.01).*

The mean of Em/Am Ratio of the patients group was 0.532±0.10 while that of controls groups was 1.426±0.4 There was significant decrease of E/A Ratio of patient group than in control group (P<0.01). The mean systolic forward flow maximal velocity of patients group was 60.1±9.75 while that of controls was 59.73±6.66, with insignificant difference (P>0.05), also the mean diastolic forward flow maximal velocity of pulmonary venous flow in patients group was 64.8±10.98 while that of controls was 39.09±11.55, with significant increase in D wave in cases than that controls (P<0.01).

The S/D ratio show a significant decrease in patients group than the control in cases it was0.93±0.11 while in control it was 1.43±0.05, the difference was significant (P<0.05).

The sensitivity of tissue Doppler for detection of diastolic function was 93.3% versus 70% in pulmonary venous flow, specificity was 90% in tissue Doppler while it was 60% in pulmonary venous flow.

Introduction

Systemic arterial hypertension has clearly been shown to be a major factor in the enhanced incidence of cardiac morbidity and mortality. Relaxation abnormalities are one of the earliest manifestations of cardiac dysfunction and frequently precede systolic dysfunction in hypertension [1].

Severe diastolic dysfunction may cause pulmonary congestion even without any deterioration of systolic function. Thus assessment of left ventricular diastolic filling in individual patients is important from both the diagnostic and therapeutic points of view [2].

Patients and Methods

Thirty hypertensive patients of both sexes were included in this study, and admitted at cardiology department of Benha University Hospital during the period from September 2010 to March 2011. The study also included ten apparently healthy volunteers as a control group with matched age and sex.

Echocardiography :

1- M mode and two dimensional evaluations of cardiac chambers in a standard manner from parasternal views assessing (Masyama et al., 2001).

A) Chamber size:

- Left atruim (normal 19-40 mm).
- Left ventricle End diastolic diameter (nor. 38-57 mm), End systolic diameter (nor. 33-40 mm).

B) Wall thickness:

- Inter ventricular septum (nor. 7-11 mm).
- Left ventricular posterior wall (nor. 7-11 mm).

C) Fractional shortening calculated as follows:

- Left ventricular and diastolic diameter ----left ventricular end systolic diameter.

D) Left ventricular mass:

*It was calculated by Hofmann et al., 1995; method in which: mass (in grams) = 1.04 X [(posterior wall thickness + septal thickness = left ventricular end-diastolic diameter) 3 - (left ventricular end diastolic diameter) 3]-13.6.[3].

N.B normal value=180-200 gram

2- Doppler echocardiographic recordings using a Doppler echocardiographic and a transducer array of 3 MH.z, Recordings were made at a paper speed 100 unit/sec:

A) Continuous wave Doppler to assess and exclude intracavitary pressure gradients.

B) Pulsed wave Doppler echocardiographic recordings using color flow mapping.

1-Mitral flow velocity pattern.

It was obtained in the apical four-chamber view with the sample volume carefully placed be-

tween the tips of the mitral valve leaflets and recordings maximal flow. The following parameters were recorded and measured.

- E wave maximal velocity (normal range 48 - 76 cm/sec).
- A wave maximal velocity (normal range 45 - 73 cm/sec).
- E/A ratio (normal range 1-1.4).

2- Pulmonary venous flow velocity pattern:

It was obtained in the apical four-chamber view. Left atrial filling from the pulmonary vein is characterized by red signal along inter atrial septum in the upper part of the left atrium in the color Doppler mode.

The orifice of the right pulmonary vein is imaged at the bottom of the flame like red signals and the pulsed Doppler sample volume was set just at the orifice of the right pulmonary vein and the waves were recorded.

The following parameters were measured:

- S wave maximal velocity (normal range 53-71 cm/sec).
- D wave maximal velocity (normal range 27-47 cm/sec).
- S/D ratio (normal range 1.1 – 1.8).

Tissue Doppler;

- Each left ventricular wall was divided into myocardial segments basal and mid wall. Apical segments were omitted because it is near the field of echo transducer. The Doppler velocity range of -20 to + 20 was selected and velocity was measured on line at speed of 55 mm/s.
- Pulse wave TDI of mitral annuals was obtained from the apical four chambers view for the measurement of :

  1- E' = early diastolic velocity (11.1-18.3 cm/sec.

  2- A' = late diastolic velocity (8.2-13.2 cm/sec).

  3- E' at, A' at = time to peak velocity

  4- E' DT, A' DT = deceleration time

  5- E' dur, A' dur = duration of velocity profile.

Evaluation of regional diastolic function by TDI in the basal and mid segment in different myocardial wall from two (anterior and

inferior wall) and four chambers view (septal and lateral wall) with measurement of:-

1- Peak velocity and rapid filling phase (Em wave)
2- Peak velocity during atrial contraction (Am wave)
3- Em/Am ratio

Results

A- Demographic data of all studied cases

This study included 30 hypertensive patients, 21 males (70%), and 9 females (30%). Their mean age was (55±9.5) years, also ten volunteers apparently normal as a control group 6 male (60%), And 4 females (40%), their mean age was 55±7.1. Table I.

B- Conventional Echocardiography:

The means inter-ventricular septum thickness of the patients group was 15.7±1.7 mm, while that of controls was 9. ±6.7, there was a significant group than that the control group (P<0.01).

The mean left ventricular end systolic diameter of patients group was 33.4±11.2 mm while that of controls was 28.3±6.2mm. There was a significant increase is LVESD in patients that that of control group (P<0.05).

The mean left ventricular end diastolic diameter was 65+9.8 while that of controls was 44.1±9.0 mm, there was a significant increase in LVEDD in patients than that the control group (P<0.05).

The mean ejection fraction of patients group was 50. ±02.9 while that of controls was 64.1±7.2, there was a significant decrease in EF in patients than that the control group (P<0.01).

Mitral flow velocity parameters:

1- Early diastolic flow maximal velocity (E)

The maximal early diastolic flow velocity of the control group ranged from 45-116 cm/sec with a mean value 72.2±18.9 cm/sec, while that of patients group ranged from 48-76 cm/sec with a mean value 62.1±13.9 cm/sec. there was a significant decrease in mitral E wave in patients than that the control group (P<0.01).

2- Atrial systolic flow maximal velocity (A):

The maximal atrial systolic flow velocity of the control group ranged from 45-73 cm/sec, mean value was 59.2±13.8 cm/sec, while that of patient group ranged from 40-92 cm/sec, with a mean value 75.1±18.9 cm/sec. There was a significant increase in mitral A wave in patients than that the control group (P<0.05).

C- Analysis of tissues Doppler

Doppler imagine of mitral annulus: (Table 2)

The mean E'm of patients group was 11.16± 3.08 while that of controls was 14.48±2.47, there was a significant decrease in E'm in cases than that in control group (P<0.05).

The mean A'm of patient group was 14.96±3.91 while of controls was 10.15±1.7, there was a significant increase in A'm in cases than that in control group (P<0.01).

The mean (Em'dur) of patients group was 0.08±0.05, while of controls was 0.12±0.04, there was a significant decrease in Em'dur in cases than that in control group (P<0.05).

The mean (Am'dur) of patients group was 0.13±0.05, while it was 0.07±0.02 in control group, with significant increase in Am'dur in cases than in control group (P<0.01).

The mean of Em/Am Ratio of the patients group was 0.53±0.10 while that of controls groups was 1.42±0.4 There was no significant decrease of E/A Ratio of patient group than in control group (P<0.01).

D- Pulmonary venous flow velocity Table(3) :

1- Systolic forward flow maximal velocity (S):

The mean systolic forward flow maximal velocity if patients group was 60.1±9.75 while that of controls was 59.73±6.66. The difference between patients and controls show no significant difference (P>0.05).

2- Diastolic forward flow maximal velocity (D) :

The mean diastolic forward flow maximal velocity of patients group

was 64.8±10.98 while that of controls was 39.09±11.55. There was a very high significant increase in D wave in cases than that controls (P<0.01).

The S/D ratio show a significant decrease in patients group than the control in cases it was0.93±0.11, while in control it was 1.43±0.05, the difference was significant (P<0.05).

Table (1): Echocardiography parameters.

variable	patients	control	p
IVS	15.7±1.7	9.6±0.8	<0.05
PW	12.2±1.7	8.9±0.7	<0.05
LVM	168±23	108±26	<0.01
LVEF	50±2.9	64.1±7.2	<0.01
E/A ratio	0.82±0.23	1.2±0.3	<0.05

Table (2): Tissue Doppler parameters.

variable	patients	control	p
E m	11.16±3	14.48±2.4	<0.05
A m	14.9±3.9	10.15±1.7	<0.05
Em dur	0.08±0.04	0.12±0.04	<0.05
Am dur	0.13±0.05	0.07±0.02	<0.01
E m / A m	0.53±0.1	1.42±0.1	<0.01

Table (3) : Pulmonary venous velocities.

variable	patients	control	p
S wave	60.1±9.4	59.7±6.6	>0.05
D wave	64.8±10	39.09±11.5	<0.01
S/D ratio	0.93±0.11	1.430±.05	<0.05

Table (4) : Sensitivity and specificity.

variable	Tissue Doppler	Pulmonary venous flow
True positive	28	21
True negative	9	6
False positive	1	4
False negative	2	9
Sensitivity	93.3%	70%
Specificity	90%	60%

Discussion

Systemic arterial hypertension has clearly been shown to be a major factor in the enhanced incidence of cardiac morbidity and mortality. Relaxation abnormalities are one of the earliest manifestations of cardiac dysfunction and frequently precede systolic dysfunction in hypertension [1].

Severe diastolic dysfunction may cause pulmonary congestion even without any deterioration of systolic function. Thus assessment of left ventricular diastolic filling in individual patients is im-

portant from both the diagnostic and therapeutic points of view [2].

The present work tries to characterize the pulmonary venous flow velocity pattern in hypertensive patients with and without left ventricular diastolic dysfunction and evaluate its usefulness in relation to the tissue Doppler imagining of the mitral annuls and the mitral flow velocity pattern for the assessment of left ventricular diastolic function.

In order to achieve this aim the present work was conducted on 30 hypertensive patients and compared with 10 healthy volunteer of matched age and sex.

Demographic data:

This study included 30 hypertensive patients 21 males (70%) and 9 females (30%) their mean age was (55±9.5) years also ten volunteer apparently normal as a control group 6 male (60%) and 4 females (40%) their mean age was (55±7.1. Also patient group had a mean systolic blood pressure 150 mmHg while 120 mmHg in control group with a p value <0.05. The mean diastolic blood pressure was 105 mmHg in patients group and 80 mmHg in control group with a p value<0.05.

Conventional echo:

Left ventricular echocardiographic parameters included the mean of IVS was 15.7 mm in patient group versus 9.6 mm in control group with a p value<0.05, and LVPW thickness was 12.2 mm in patients while in control group was 8.9 mm with (p value <0.05), also LV mass was 168 grams in patients versus 108 in control group (p value <0.01). The mitral flow velocity pattern was observed with "E" wave had a mean of 62.1 cm/sec in patient group and 75.2 cm/sec in control group with a p value <0.01,"A" wave mean value was 75.1 cm/sec while in patient group 59.2 with a p value <0.01 and E/A Ratio had a mean of 0.82 in patient group while 1.23 in control group with a P value < 0.05).

This result is in agreement with, Tisioufis et al (2005) who found that essential HTN is accompanied by LV diastolic dysfunction. He studied 106 patients (aged 51 years, 80 males) with es-

sential HTN, and 50 normotensives matched age, sex. LV diastolic function was estimated by echocardiography. Hypertensive compared with normotensive exhibited greater LV mass index than normotensive (155 versus 105 grams the P value <0.001), the mean of E wave was 65 cm/sec in patient group (Hypertensive) and 75.1 cm/sec in control group with a P value < 0.01, the mean of "A" wave was 7.2 cm in control group while in patient group it was 61.1 cm/sec with a P value < 0.01 and the mean of E/A ratio was 0.85 in patient group while 1.31 in control group the p value < 0.05.[5]

Arroja I et al (2001), who studied left ventricular diastolic function in 2 population of normotensive and hypertensive, they studied a group of 50 patients with the diagnosis of HTN (group H), which was compared with population of 50 normal subjects (group N) in each case pulsed Doppler mitral inflow was analyzed they found that the mean of E wave was 63 cm/sec in patient group and was 72.5 cm/sec in control group with a P value < 0.01, the mean of A wave was 74.1 cm/sec while in patient group was 60 cm/sec with a P value < 0.01 and the mean of E/A ratio was 0.80 in patient group while was 1.1 in control group. Sensitivity and specificity of mitral inflow was 70%, 53% respectively.[6]

Brush C et al (2000) studied 2 groups of subjects with ejection fraction > 45% 10 normal volunteer (50±10 y, HYP group). The mitral inflow profile (E, A, E/A) was measured by pulsed Doppler. The mean of E wave was 60 cm/sec in HYP group and it was 77 cm/sec. in control group with a P value < 0.01, A wave had a mean of 74 cm/sec while it was 58.6 cm/sec in HYP group with a P value <0.01 and E/A Ratio had a mean of .084 in patient group while it was 1.4 in control group with a P value <0.05, with sensitivity and specificity was 72% and 56% respectively.[7]

Ito T et al (2000) found that specificity and sensitivity of E/A Ratio was 80%, 61% respectively in (41 HTN patient), E/A ratio < 1 with a P value (0.01), so all these

studies agree with the present study.[8]

Kakavas A, et al 1999, studied 100 hypertensive patients of average 53±9 years, 50 normotensive subjects of average 53±9 years, and their performed conventional echo of mitral inflow. Their study showed that the mean of peal velocity of E wave decrease from 56 cm/sec in normotensives to 44 cm/sec in hypertensive patients with a P< 0.05. The peak velocity of A wave did not change.[9]

The present study does not agree with kakavas, A, et al (1999) who found that, the mean of A wave peak velocity didn't change in their study of 100 hypertensive patient of (average 53±9 years) they performing conventional echo of mitral inflow and their study shows no difference. This may be due to type of patient and severity of hypertension.

Pulmonary venous flow

The pulmonary venous flow velocity pattern in patients is as "S" wave in patient group, the mean value was 60.1 cm/sec while in the control group it was 59.73 cm/sec with a p value > 0.05 while "D" wave in patient group, mean was 64.8 cm/sec while in control group it was 39.09 cm/sec with a P value < 0.01 so the S/D ratio mean in patient group was 0.93 and in control group was 1.43 the P value < 0.05. Sensitivity and specificity of pulmonary venous flow was 70%, 60% respectively.

This study agreement with Arroja I et al (2001), who studied left ventricular diastolic function in 2 population of normotensive and hypertensive individuals, They had studied group of 50 patients with the diastolic of HTN (group H), which was compared with a population of 50 normal subjects (group N) in each case pulsed Doppler flow of the right upper pulmonary venous and diastolic inflow of the left ventricular cavity was done. Peak velocities of systolic, diastolic waves of pulmonary venous flow was found as "S" wave mean value was 61.1 cm/sec in (group H) while in (group N) it was 58.7 with a P value > 0.05, D wave had a mean of 41.1 cm/sec in (group N) it was 65.3 cm/sec in (group H) with a P value < 0.01.

The S/D ratio in patient group (group H) had a mean of 0.91 and in control group (group N) it was 1.4 with a value < 0.05. Sensitivity and specificity of pulmonary flow was 72%, 58% respectively.[6]

Tsioufis et al 2005 found that the essential HTN is accompanied by LV diastolic dysfunction. He studied 106 patients (aged 51 years. 80 males) with essential hypertension, and 50 normotensives with matched age and sex. Left ventricular diastolic function was estimated by pulmonary venous flow. Hypertensive compared with normotensives. The mean of "S" wave in patient group was 60.5 cm/sec and it was 59.3 cm/sec in control group with a P value <0.05, the mean of D wave was 42.1 cm/sec in control group and it was 66 cm /sec in patient group with a P value <0.05. The mean of S/D ratio in patient group was 0.94 and control group was 1.39 with a P value < 0.05, and sensitivity and specificity 45%, 35% respectively. This study doesn't agree with our study in the point of sensitivity and specificity because sensitivity and specificity in our study was 70% and 60% respectively. This is may be due to severity of hypertension and type of patients.[5]

Hofmann et al., 2001; have studied the relation between the pulmonary venous flow and atrial hypertension and left ventricular function in 84 patients (aged 55 years, 70 males) with essential HTN, and 40 normotensive, as control group with matched age and sex. They found that the mean of S wave in patient group was 62.1 cm/sec and 61.8 cm/sec in control group with a p value > 0.05, D wave had a mean of 0.90 and in control group it was 1.44 with a p value <0.05 sensitivity and specificity of pulmonary venous flow was 71.5%, 59% respectively.[4]

Masuyama et al., 2003; compared Transthoracic with Transesophageal Doppler echocardiographic measurement of pulmonary venous flow velocity pattern. They concluded that transthoracic measurement of pulmonary venous velocity pattern are feasible and accurate in hypertensive patient and may be used to assess left ventricular systolic function

through they study 150 hypertensive patient and 50 normotensive with matched age and sex. They found "S" wave is not significant with a P value <0.05 S/D ratio is significant with a P value < 0.05; pulmonary venous flow had specificity and sensitivity 72, 60.3 respectively in a meaner similar to our results.[3]

Tissue Doppler

Tissue Doppler of the mitral annulus revealed that true mean of (E'm wave) in patient group was 11.16 cm/sec and in control group was 14.48 cm/sec with a P value of <0.05, the mean of Em/Am ratio in patient group was 0.532 and in control group was 1.42 with a P value of <0.05, with sensitivity and specificity of Tissue Doppler imaging was 93.35%, 90% respectively.

This study agreement with Tsioufis, et al., 2005; they studied LV systolic function in 2 groups of population normotensives and hypertensive subject. They studied 160 patients (aged 53 years, 150 males) with essentials HTN, and 100 normotensive subjects as a control group with matched age and sex. LV diastolic function was estimated by pulsed tissue imagining (TDI) echocardiography, averaging diastolic mitral annular velocity measurements (E' wave, A' wave, E/A ratio) was calculated. The mean of E wave was 12.1 cm/sec in patients group and it was 15.5 cm/sec in control group with a p value < 0.05 while A wave id patients group had a mean of 16 cm/sec and it was 10.4 cm/sec in control group, with a P value <0.05. The E/A ratio of patients group had a mean of 0.553 and in control group was 1.43, with sensitivity and specificity if tissue Doppler was 95.2%, 92.4% respectively. [5]

Azvedo J et al., 2005, who compared 180 hypertensive patients (aged 54 years, 150 males) and 100 normotensive individuals with matched age and sec to estimate LV diastolic function by tissue Doppler imagining of mitral annulus. They found the mean of E wave in patients group was 11.41 cm/sec and in control group was 14.1 cm/sec with a P value of < 0.05 while A wave in patients group had a mean of 14.81 cm/sec and in control group was

10.21 cm/sec with a P value < , the mean of E/A ratio in patient group was 51.1 and in control group was 1.33 with a p value < 0.05 sensitivity and specificity and tissue Doppler imagining was 92.1, 91.3 respectively.[10]

Schmermud A et al, 2006 they found the diastolic mitral annulus velocity assessed by tissue Doppler echocardiography (TDE) was suggested to provide additional information about LV diastolic function affected by atrial hypertension, they studied 50 hypertensive group (patient group) (aged 50 years, 35 males) and 30 normotensive (control group) with matched age and sex. The mitral systolic, early, and late diastolic velocities of mitral annulus (E, A, E/A ratio) were assessed by pulsed Tissue Doppler Imagining (TDE). All studied individuals had invasive measurement of left ventricular end diastolic pressure during left heart catheter. The mean of E wave in patient group was 12.3 cm/sec and in control group was 14.7 cm/sec with a P value of < 0.05 while the mean of (A') in patient group was 15 cm/sec and it was 10.1 cm/sec in control group with a p value < 0.05, the mean of E/A ratio in patient was 53.3 and in control was 1.32 with a p value < 0.05, with sensitivity and specificity of tissue Doppler imagining 93.4, 92.1 respectively.[11]

Lraidogolitia et al., 2006, studied 20 patients with essentials hypertension of average age 54±10 years. They performed DTI of mitral annulus versus conventional eco pulsed Doppler and pulmonary venous flow. Their study showed that TDI show an abnormal relaxation on essential hypertensive patients than with pulmonary venous flow and mitral flow indices. They suggested that DTI in E/A ratio in the mitral annulus is more sensitive by 90% than pulmonary venous flow and transmitral Doppler and specificity = 80%. [12]

The present study agree with these results because the sensitivity of trans-mitral flow by pulsed Doppler was 66%, specificity of 50% and in pulmonary venous flow the sensitivity was 70% and specificity of 93% detecting LV relaxation abnormalities in hyper-

tensive patients group compared to normal .

In the present study there was a significant increase in both sensitivity and specificity on mitral annulus tissue Doppler than both pulmonary venous flow and mitral in-flow patterns, the pulmonary venous flow is more sensitive and specific than the mitral flow.

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COMPARISON BETWEEN TRANSPULMONARY VENOUS FLOW AND TISSUE DOPPLER OF DIASTOLIC FUNCTION IN HYPERTENSIVE PATIENTS

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SERUM TRACE ELEMENTS CONCENTRATIONS (CA – CU – ZN – CU/CA AND CU/ZN RATIO) IN RELATION TO DISEASE ACTIVITY SCORES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

48 patients with rheumatoid arthritis (RA) were selected from rheumatology and rehabilitation out patient clinic, Mansoura University hospital including 40 ♀ & 8 ♂ age ranged from 35-63 years, 12 healthy volunteers with matched age and sex served as control group. Assessment of over all disease activity in (RA) patients was performed using disease activity score and Eular Response criteria (DAS-28) including both clinical and laboratory markers.

Determination of serum Cu, Zn and Ca levels were done using Perkin-Elmer 2380 atomic absorption spectrophotometer. A significant decrease in both serum Ca and Zn levels and significant increase in serum Cu level (p=<0.04) was found among patients with (RA) compared with control group. A -ve correlation was found between disease activity scores (DAS) and both serum Ca and Zn Levels (p=<0.04) meanwhile a + ve correlation was observed between serum Cu level and disease activity (P=<0.04).

Both serum Cu/Ca and Cu/Zn Ratio are sensitive indicies of disease activity however serum Cu/Ca ratio is probably more sensitive.

Introduction and Aim of the work

Rheumatoid arthritis is a major public health problem. Among the many contributing agents that have been proposed to take part in the pathogenesis of this condition, nutritional status have also been investigated [1][2][3], The participation of micronutrients especially copper, zinc and calcium in the normal development and maintenance of skeleton is at least in part related to their catalytic functions in organic bone matrix synthesis or in the functioning of cells of bone or cartilage [4], Also Cu and Zn are components of the two major superoxide dismutase enzymes which have been shown to fight against the reactive intermediates that are linked to joint damage in arthritis[5,6]. The Aim of the present study was to investigate serum levels of micronutrients Ca, Cu, Zn, Cu/Ca and Cu/Zn ratio in relation to disease activity sores in patients with (RA).

Material and Methods

48 patients with (RA) selected from rheumatology and Rehabilitation out patient clinic Mansoua university hospital included 40 ♀ and 8 ♂ age ranged from 35-63 years (RA) patients receiving estrogen containing oral contraceptives (Known to increase serum copper values)[7] or wearing copper bracclets were excluded 12 healthy volunteers with matched age and sex served as control group.

Assessment of over all disease activity in (RA) patients was preformed using disease activity score and EULAR response criteria (DAS-28) including both clinical and laboratory markers Determination of serum Cu, Zn and Ca levels were done in both patients and volunteers using Perkin Elmer 2380 Atomic absorption spectrophotometer According to the method described by stockwell and corns[9].

Using (DAS-28) scores patients with (RA) were classified into, patients with mild and moderate disease activity 28 patients (24 ♀ and 4 ♂) and 20 patients with highly active disease (16 ♀ and 4 ♂).

Results

1) Significant increase in serum Cu level was found

among patient with (RA) compared with control group (P=<0.040 Table I.

2) Significant decreases in both serum Ca and Zn levels were found among patient with (RA) compared with control group. (P=<0.04) Table I.

3) Highly Significant increases in both serum Cu/Ca ratio (P=<0.001) and Cu/Zn Ratio (P=<0.002) were observed among patients with (RA) compared with control group. (Table I).

4) A+ ve correlation was found between serum Cu concentration and disease activity scores. Meanwhile a -ve correlation was found between both serum Ca and Zn concentrations and diseases activity scores (Table II, III, IV).

5) A highly significant increase in Both serum Cu/Ca ratio (P=<0.001) and Cu/Zin Ratio (P=<0.002) were observed among (RA) patients with High disease activity scores compared with those with Mild and moderate Disease activity (Table V).

Table I: Serum Ca, Cu, Zn, Cu/Ca & Cu/Zn Ratio in patients with (RA) Compared with control group.

Serum Micronutrient	*Patient with Rheumatoid Arthritis*	*Control group*	*P Value*
	M+SD	*M+SO*	
Ca mmol/L	*2.1 ± 0.01*	*2.4 ± 0.02*	*(<0.04)*
Cu/µmol/L	*25 ± 0.08*	*20 ± 1.2*	*(<0.04)*
Zn /µmol/L	*9 ± 0.04*	*12 ± 0.42*	*(<0.04)*
Cu/Ca Ratio	*11.9 + 0.01*	*8.10 + 0.01*	*(<0.001)*
Cu/Zn Ratio	*2.5 ± 0.02*	*1.8 ± 0.22*	*(<0.002)*

(Table II): Relation between serum Cu Concentration and disease activity scores.

(RA) Patients	*With high Disease activity scores*	*With Mild and moderate disease activity scores*	*P Value*
(DAS) M±SD	*5.6 ± 0. 3*	*4.6 ± 0.12*	*(<0.05)*
Serum Cu /μmol/L	*27 ± 0.1*	*24 ± 0.2*	*(<0.04)*

(Table III): Relation between serum Ca Concentration and disease activity scores.

(RA) Patients	*With high Disease activity scores*	*With Mild & moderate disease activity scores*	*P Value*
(DAS) M±SD	*5.6 ± 0. 3*	*4.6 ± 012*	*(<0.05)*
Serum Ca concentration m mol/L	*1.92 ± 0.01*	*2.2 ± 0.02*	*(<0.04*

(Table IV): Relation between serum Zn Concentration and disease activity in Patients with rheumatoid arthritis.

Rheumatoid arthritis patients	*With high Disease activity scores*	*With Mild and moderate disease activity scores*	*P Value*
(DAS) M±SD	*5.6 ± 0. 3*	*4.6 ± 0.12*	*(P=<0.05)*
Serum Zn /μmol/L	*8.6 ± 0.01*	*9.5 ± 0.02*	*(P=<0.05)*

Table (V): Relation between serum Cu/Ca Ratio, Cu/Zn Ratio and Disease activity in patients with rheumatoid arthritis.

Rheumatoid arthritis patients	*With high Disease activity scores*	*With Mild and moderate disease activity scores*	*P Value*
(DAS) M±SD	*5.6 ± 0. 3*	*4.6 ± 0.12*	*(<0.05)*
Cu/Ca Ratio	*13.8 ± 0.01*	*10.8 ± 0. 2*	*(<0.001)*
Cu/Zn Ratio	*3.6 ± 0.3*	*2.7 ± 0. 2*	*(<0.002)*

Discussion

Nutritional status is often impaired in patients with (RA)[10]. Disability and pain can interfere with consumption of food. Temporomandibular pain can impair mastication. Anti-iflammatory and anti-rheumatic medication commonly lead to nausea, dyspepsia and altered Taste In the present study significant lower level of serum Ca was found among patients with (RA) compared with control group Also a -ve correlation was observed between disease activity scores (DAS) and serum Ca level. Similar findings were previously reported by some authors [11] [12] and recently by afridi et al [13] low serum Ca in our patients with (RA) may result not only from malnutrition but also from high salt intake in our population which may exacerbate Ca deficiency at the proximal tubules were Na+ and Ca absorption are Linked [12]. Vitamine D is one important component of Ca metabolism it is possible that the intermediate metabolism of vitamine D may be abnormal in (RA) [14].

Significant increase in serum Cu level was found among our patients with (RA) compared with control group. Also a +ve correlation was observed between disease activity scores and serum Cu level similar findings were previously reported by some authors [1][15] and recently by Ala.[3] Copper is an essential trace element that may facilitate the activity of ceruloplasmin (acute phase reactive and serum cu carrier protein)

which is known to increase in response to inflammatory reactions with concomitant elevation in serum Cu level, copper also is known to activate copper-zinc superoxide dismutase which have antioxidant and anti-inflammatory properties that may prevent the onset of chronic joint disease [16].

Significant decrease in serum Zinc concentration was observed among our patients with (RA) compared with control group. Also a -ve correlation was found between disease activity scores and serum Zn levels, similar findings were previously reported by some authors [17] [18]. Zinc supplementation was reported to decrease peri-articular osteoporosis in (RA) patients[15]. Defects in skeletal development have been reported due to zinc deficiency and also due to acrodermatitis enteropathica an inherited disorder of zinc absorption [19]. Zinc plays important role in nucleic acid synthesis, Zinc has also been shown to be required by enzymes which have specific functions in bone metabolism. [20]

In the present study significant increase (P=<0.002) was observed in serum Cu/Zn Ratio with concomitant highly significant increase (P=<0.001) in serum Cu/Ca Ratio in our patient with high disease activity scores (DAS) compared with those with low and moderate disease activity scores indicating that both serum Cu/Ca Ratio and serum Cu/Zn Ratio are sensitive indicies of disease activity, however serum Cu/Ca Ratio is probably more sensitive.

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SERUM TRACE ELEMENTS CONCENTRATIONS (CA – CU – ZN – CU/CA AND CU/ZN RATIO) IN RELATION TO DISEASE ACTIVITY SCORES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SURGICAL TREATMENT OF POSTERIOR WALL FRACTURES OF THE ACETABELUM

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Abstract

Back ground : *Posterior wall fractures of the acetabulum are common. Hip with a posterior wall fracture fragment exceeding 40% are predicted to be unstable and theoretically must be treated with open reduction and internal fixation. The purpose of this study was to evaluate the clinical outcome in such patients.*

Patients and Methods : *Eighteen patients with posterior wall fracture of the acetabulum were treated operatively and fixed using interfragmental screws and reconstruction plates.*

Results : *Patients were followed up for a period from 10 - 30 months average 18 month, the clinical score was 13 patient excellent, 2 had good, 2 had fair and 1 had a poor result.*

Complications : *Superficial infection occurred in 2 cases and needed debridement, antibiotics and dressing. Only one with deep infection with no response to repeated debridement and ended with destruction of the hip joint.*

Conclusion : *Good results can be obtained in patients with posterior wall fracture of acetabulum after proper assessment preoperatively, proper incision and taking care of local nerves specially the sciatic nerve, also proper fixation and repair of soft tissue with meticulous adherence to postoperative rehabilitation program.*

Introduction

Posterior wall fractures of the acetabulum are common and comprise approximately up to 30% of all acetabular fractures[1]. Non operative treatment of these fractures is indicated only when joint congruity and hip stability are maintained after injury[2]. This situation occurs

when the remaining intact part of the acetabulum is large enough to maintain the femoral head in normal relationship with the acetabular roof. Historically the size of the posterior wall fragment as measured on a two dimensional C.T scan has been a commonly used predictor of the status of hip joint stability and the need for operative intervention.Hips with a posterior wall Fracture fragment exceeding 40% are predicated to be unstable and theoretically must be treated with open reduction and internal fixation[3,4].

Fractures involving < 20% of the posterior wall are predicted to be stable and theoretically can be treated non operatively.

Historically the indication for surgery was hip instability which was identified in several ways. Patients presenting with a hip dislocation were treated with emergent reduction of the dislocation. Patients exhibiting gross instability on physical examination after closed reduction, defined as joint instability occurring at ≤ 40° of hip flexion are treated operatively[5,6]. All other posterior wall fractures including those that were not associated with a known hip dislocation were considered potentially unstable. In these cases, dynamic fluoroscopic stress examination of the hip was performed with the patient under general anesthesia to identify fracture instability requiring surgical treatment[7].

Classified by Letorurnel (1) as one of the elementary fracture types, its simple appearance on plain radiographs belies its potential complexity. Rather than being one simple fracture fragment, the majority of posterior wall fractures are comminuted.

Investigators reporting on relatively small numbers of operatively treated fractures of posterior acetabular wall have found that the outcome is unsatisfactory in approximately 30% of case [8,9,10].

The cause of this relatively poor prognosis for posterior wall fractures as compared with the prognosis for other types of fractures remains obscure[11].

The purpose of this study was to evaluate the results of open reduction and internal fixation of posterior wall fractures of the acetabulum.

Exclusion criteria: patients with a delay in surgery of more than 3 weeks, those in whom the fracture was the result of a gunshot, those referred after previous surgical treatment and those operated on for removal of incarcerated fragments of bone or soft tissue but not requiring internal fixation, other exclusion criteria were skeletal immaturity, other injuries involving the affected hip joint or proximal part of ipsilateral femur.

Material and Methods

This study was done from July 2007 to June 2010 at Al-AZHAR University hospital New Damietta. Patients were either directly admitted through the emergency department of our hospital or referred from another hospital especially for treatment of the acetabular fracture after stabilization of their general medical condition. Patients presented with hip dislocation were treated with emergent reduction of the dislocation. Patients who had a fracture with gross instability on physical examination after closed reduction ..... were treated operatively. After a successful closed reduction as documented by plain radiography, the hip was further Evaluated by C.T scan and if this modality showed the fracture to involve >40% of the posterior wall the fracture was considered unstable. All other posterior wall fractures including those that were not associated with a known hip dislocation were considered potentially unstable.

The focus of the current study was on the outcome of acute treatment of unstable hip fractures caused by blunt trauma.

During this time period, eighteen patients with posterior wall acetabular fracture were evaluated. All patients met the inclusion criteria for the present study. Of the eighteen patients In the study five were female and thirteen were male table 1, and they ranged in age from seventeen to fifty-nine years (means thirty-one years) at the time of injury. Table 2 five of eighteen patients had

documented evidence of dislocation of the femoral head at the time of the initial injury table 3. six patients had a fracture of the left acetabulum and twelve had a fracture of the right table 4 .

Sixteen patients were injured in road accident and two were injured due to falling from height table 5 .In four patients, the injury was isolated to the acetabulum. The other fourteen patients sustained additional injuries, including eight patients with injuries to the spine, seven with injuries to other extremities, three with head injuries, four with injuries to the face, and two with abdominal trauma. Of the eighteen patients, fourteen had a fracture in the intermediate stability, size rang of 20% to 50% .

Table (1) : Sex distribution.

Sex	Number	%
Male	13	72
Female	5	28
Total	18	100

Table (2) : Age distribution.

Age in years	Number	%
15-30	8	44.4
30-45	6	33.3
45-60	4	22.3
Total	18	100

Table (3) : Side of injury.

Side affected	Number	%
Right side	12	66.6
Left side	6	33.3
Total	18	100

Table (4) : State of the hip at initial x-ray.

State of the hip	Number	%
Fracture +dislocation	5	28
Fracture without evident dislocation	13	72
Total	18	100

Table (5) : Cause of injury.

Cause of injury	Number	%
Road accident	16	89
Fall from height	2	11
Total	18	100

Surgical technique:-

- while under general or spinal anesthesia the patient is postioned prone on a radiolucent operating table with a bean bag used for support with the patient prone on the operating table, The sterile field consists of the buttock and the posterior and lateral aspects of the thigh.

I prefer the kocher- Langen beck posterior approvh for routine posterior wall fracture of the acetabulum.

To minimize the risk of iatrogenic sciatic nerve injury flexion of the ipsilateral knee is maintained throughout the operative procedure to place the nerve in a relaxed position.

In our cases the skin incision is centered over the greater trochanter, the proximal part of the incision is directed toward the posterior superior iliac spine, ending approximately 6 cm short of the osseous landmark. Distally, the incision extends approximately 15 cm along the midlateral aspect of the thigh. The skin incision is carried through the subcutaneous tissue and superficial fascia onto the fascia lata (The iliotibial tract) and the thin, deep fascia overlying the Glutus maximus muscle. The fascia lata is then divided in line with the skin incision, beginning at the distal aspect of the wound, continuing proximally toward the greater trochanter and ending at the first sighting of the Glutus maximus muscle fibers as they insert into the iliotibial tract. The next step is the splitting of the Glutus maximus muscle. Despite possessing a dual blood supply and thus having the potential for an intervascular plane of dissection, the Glutus maximus muscle has innervations from the inferior gluteal nerve consequently, there is no intervenous plane, and the nerve branches of the upper one - third of the muscle cross the interval of dissection slightly more than halfway between the level of the greater trochanter and the posterior superior iliac spine. Therefore, splitting of the muscle fibers should stop as soon as the first nerve branch to the upper part of the muscle is encountered. Partial release of the Glutus maximus insertion into the femur, which allows adequate posteromedial retraction of the large mass of the Glutus maximus muscle without undue stretch of inferior gluteal nerve. The sciatic nerve is located over the posterior surface of the Quadratus femoris muscle.

The piriformis and obuturator internous tendons (with the superior and inferior gmelli muscles on either side) are incised approximately 1.5 cm from their insertion points into the greater trochanter. It is important to preserve this distance from the insertion site in order to avoid injury to the blood supply of the femoral head. After reflection of these short external rotators and elevation of the Glutus medius and minimus muscle origins from the external surface of the ilium ,exposure of the pos-

terior acetabulum is essentially complete. A blunt Hohman retractor can be placed into the lesser sciatic notch in front of tendon of the obturator internus to protect the sciatic nerve and facilitate exposure the posterior column.

After completion of the surgical approach, the next step is to define all of the fracture fragments. Usually we find some free osteochondral fragments, in addition to multiple wall pieces still maintaining soft tissue attachments. The fragments are cleared of debris. The hip must then be sublaxated to allow inspection of the joint for removal of free fragments and to allow for joinr irrigation and debridement. The posterior wall fragments with their intact capsular attachments are then sequentially reduced and held with a pointed ball spike.

After this reduction is completed, the hip is inspected in all planes with C-arm fluoroscopy. The entire construct is the further supported with 3.5 mm reconstruction buttress plating. The plate should be placed as close to the acetabular rim as possible. In addition, each major posterior wall fragment should be held by at least one lag screw. These screws can be inserted before or after buttress- plate application. The hip is again inspected in all planes with C-arm to assess fracture reduction and hardware placement. The wound is then closed in layers over the suction drains. Before the patient is discharged from the hospital, three standard radiographs of the pelvis (anteroposterior, internal oblique, external oblique)and two dimensional C.T scan are made to assess fracture reduction. Non weight bearing with axillary crutches or a walker is maintained for six weeks. then toe - touch weight - bearing (10 - 15 kg) for another six weeks.

There is no range of motion restriction. Progression to full weight - bearing should be individualized on the basis of the appearance of the follow up radiographs. Physical therapy is continued until muscle strength and range of motion are regaines.

Results

At the final follow up examination, the functional outcome

was evaluated using the clinical grading system adopted by Letournal and Judet [1] and modified by Matta [9]. In this clinical garding system, pain, gait and the range of motion of the hip can each be assigned a maximum score of six points. The three individual scores are summed to drive the final clinical score, according to which the clinical results was classified as excellent (18 points), very good (17 points), good (15 - 16 points), fair (13 - 14 points), poor (<13 points).

The radiographs were graded according to the criteria described by Matta [9].

With this method a normal appearing hip joint is given excellent. A hip joint narrowing (≤1mm) with mild changes and minimal sclerosis is given good.

Intermediate changes with moderate sclerosis and joint narrowing (<50%) is given fair. Advanced changes are given poor.

The clinical outcome scores were collapsed from five to four correspondig categories (excellent, good, fair and poor) by elevating the clinical outcome grade of very good to excellent. Then, the clinical outcome score were divided into two categories, good to excellent and fair to poor.

The quality of fracture reduction as measured on the three standard plain radiographs of the pelvis was graded as anatomic in seventeen hips and as imperfect in one hip. Table (6).

Some residual defect (defined as a gap of >1 mm) was known to have been left in seven patients when osteochondral fragments were discarded during surgery. The clinical outcome was graded as excellent in thirteen patients, good in two patients and poor in one patient .In the three patients with poor and fair results, one with a deep infection, one with preexisting O. A. of the hip the progressed until THR was required, and one who had a delayed reduction of a hip dislocation and had the development of osteonecrosis requiring THR.

The final radiographic results were graded as excellent in four-

teen hips, good in one, fair in one and poor in two.

Heterotopic ossification was graded as class zero (absent) in thirteen patients.

Class I in three and class II in two patients.

Complications :-

- One deep wound infection.
- Two superficial infection.

The result after the deep infection was poor despite multiple aggressive debridements.

- No patient had evidence of penetration of the acetabular articular surface.
- No patient had evidence of heterotopic ossification.
- No iatrogenic nerve injuries.
- D.V.T occurred in one patient. This patient after medical treatment required the use of pressure stocking.

Factors that were found to contribute to fair and poor results were :

- Older age at the time of injury.
- Delayed in the time to reduction of the hip dislocation of more than twelve hours.
- Intra-articular comminution.
- Osteonecrosis.

Table (6) : Clinical and radiological results of follow up.

Parameter	Clinical score		%	Radiological results		%
	Excellent	13	83	Anatomic reduction with hip joint narrowing ≤ 1mm	17	94
	good	2				
	Fair	2	17	Imperfect reduction	1	6
	Poor	1				
	Total	18	100		18	100

Case 1: Male patient Twenty-four years old

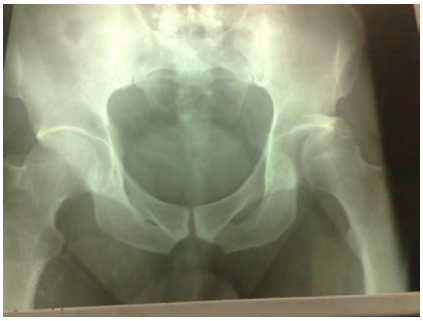

Fig. 1: Pre op. x-ray.

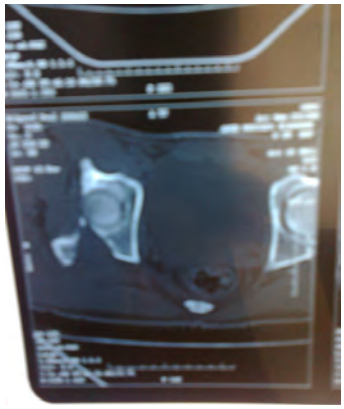

Fig. 2 : Pre op. CT showing posterior wall fracture with posterior wall fragment about 50%.

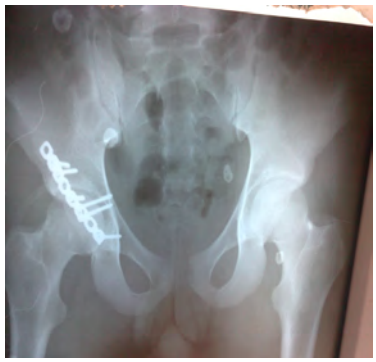

Fig. 3: Post op. x-ray.

Case 2 : Male patient Thirty-seven years old

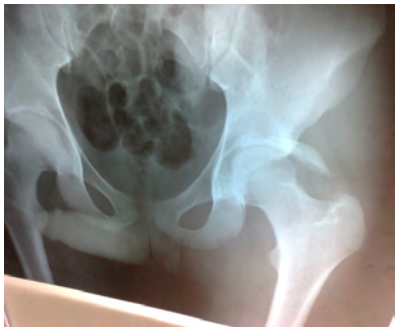

Fig. 4 : pre op. x-ray.

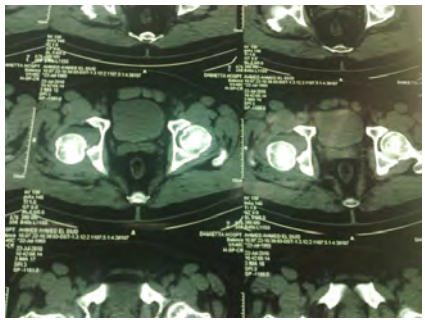

Fig. 5 : pre op. CT. showing posterior wall fracture of the acetabulum with posterior sublaxation of femoral head.

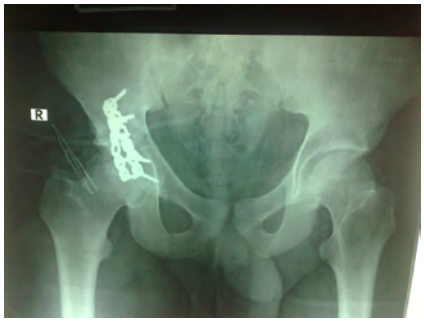

Fig. 6 : post op. x-ray.

Discussion

The complex nature of posterior wall fractures of the acetabular relative to their simple radiographic and the disparity between the accuracy of surgical fracture reduction (as determined, on plain post operative radiographs) and clinical outcome were well described[12].

The main indication for open reduction and internal fixation of a posterior fracture of the acetabulum is hip instability, which can be identified in several ways. Patients presenting with a hip dislocation should treated with emergent reduction. Patients exhibiting gross instability on physical examination after closed reduction,

defined as joint instability occurring at ≤ 40° of the hip flexion[6] are treated operatively. Letournel and Judet[1] Found that despite obtaining a perfect reduction in 94% of posterior wall fractures of acetabulum, only 82% had good to excellent clinical results.

They attributed this disparity to the occurrence of osteonecrosis and to the fact that reconstruction of the severely comminuted fractures was difficult to perform.

In Matta's series which included twenty- two posterior wall fractures, although the reduction of all fractures over anatomic only (68%) had a good to excellent clinical results, Matta[9] suggested that three may be imperfections in the articular surface.

Other investigators [13,14] reported up to 85% good to excellent clinical score, which paralleled the accuracy of the fracture reduction.

Our study was done to evaluate the results of the operatively treated posterior wall fractures of the acetabulum in an attempt to determine factors, other than the appearance on immediate postoperative plain radiographs, that may contribute to unsatisfactory clinical results. Our study showed some prognostic factors including delay of greater than twelve hours before the reduction of hip dislocation, age of more than fifty- five and the quality of fracture reduction. Sever intra-articular comminution was an additional prognostic risk factors.

Olson S A, et al [15] stated that marked alteration in the mechanics of load transmission across the hip joint occurs after a fracture of the posterior wall of the acetabulum.

Anatomic reconstruction of the acetabular articular surface remains the surgical goal. The satisfactory clinical results reported in our study support the opinion that it is the actual healing of the fracture in an anatomic position that ultimatel. Restore hip joint mechanics[16].

Conclusion

- The main indication for open reduction and internal fixation of

a posterior wall fracture of the acetabulum is hip instability.

- Dynamic fluoroscopic stress examination of the hip should be performed with the patient under general anesthesia to identify instability requiring surgical treatment.

- Accurate anatomic reduction of the fracture and rigid fixation is mandatory to obtain better results.

- Nerve injury is a serious complication of this procedure and should be avoided as possible.

- Hardware must be placed in close proximity to the joint surface in order to obtain stable fixation.

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SURGICAL TREATMENT OF POSTERIOR WALL FRACTURES OF THE ACETABELUM

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DEXMEDETOMIDINE, FENTANYLE AND KETAMINE PROVIDE DEEP SEDATION FOR DEBRIDEMENT AND DRESSING OF HAND SPACE INFECTION

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Abstract

Background: *Dexmedetomidin is a specific α2-receptor agonist, used to reduce anxiety and tension, and to promote relaxation and sedation with hemodynamic stability beside the postoperative analgesia. This controlled randomized study compared the effect of dexmedetomidine alone, and when combined with fentanyl or ketamine as sedative analgesic regimen for pain management during debridement and dressing of hand space infection.*

Method: *All patients received infusion of dexmedetomidine (0.5ug/kg) ten minutes before dressing. Then DS group (n=20) received isotonic saline intravenous. DF (n=20) group received fentanyl 1ug/kg intravenous. DK (n=20) group received ketamine 1mg/kg intravenous. Patients were monitored for mean blood pressure, peripheral arterial oxygen saturation, heart rate, end-tidal Co2 and end-tidal concentration of sevoflurane. Pain score (VAS), sedation score (from 0 to 5) and recovery time were recorded.*

Results: *Significant decrease in heart rate and blood pressure was noted 10 minutes after DEX infusion in the three groups. This significance was lost 10 minutes after ketamine injection in DK group. Patients of DK group scored a significant lower pain score and higher sedation score (1 and 2 h postoperative), beside a significant longer time for eye opening in comparison with other groups. DEX-Ketamine regimen recorded a higher degree of acceptance by both patient and the surgeon in comparison with other groups.*

Conclusion: *DEX- Ketamine regimen provided higher sedation and lower hemodynamic discrepancy during debridement and dressing of hand space in comparison with DEX- Fentanyl regimen.*

Key Words: *Hand infection, dexmedetomidine, sedation.*

Introduction

Hand injuries lead to high incidence of hand infections. The clinical signs of inflammation as pain, swelling, heat, limitation of function and redness are the most common presentation in all patients. More severe are infections of tendon sheath, joint, web space and deep palmer space [(1)].

Less common causes of hand pain include atypical mycobacterial infection, occult fractures, bone fragments, carpal ligament injuries and tendinitis. Also, the diabetic hand infection is less reported. Therefore, it is easily ignored and underestimated resulting in increased morbidity. Diabetic hand is rapid in progression, extensive with severe tissue destruction [(2)].

Treatment protocol of hand infections depends on the clinical picture, laboratory investigation, bacteriology and X-ray-examination; then surgical intervention including incision, irrigation, drainage, excision of necrosis and foreign bodies, early movement combined with ergotherapy and physiotherapy. Use of antibiotics is indicated in sepsis, lymphangitis, osteomyelitis. If pus is present in such cases there is no place for conservative treatment but operative treatment is Imperative [(3)].

Patients suffering from hand infection commonly experience high levels of pain and anxiety, particularly during dressing and debridement[(4)]. Pain experienced may be divided into a "background" pain and a "breakthrough" pain that associated with the painful procedures. While the background pain may be treated with opioids either intravenous or oral, breakthrough pain may be treated with a variety of interventions [(5)].

Sedation for surgical procedures can be achieved with a variety of intravenous medications, such as benzodiazepines, barbiturates, and propofol. That is because, these agents produce dose-related sedation as well as amnesia and anxiolysis[6].

Regarding analgesia, alternative methods may be beneficial to avoid the known side effects and complications of opioids, Local anaesthetic infusion either into the wound or as a local nerve block also used[7].

Dexmedetomidin is a specific α2-receptor agonist, used to reduce anxiety and tension, and to promote relaxation and sedation with hemodynamic stability [8]. Dexmedetomidine was used to induce postoperative analgesia and reduce the use of postoperative morphine [9].

Objective:

This is a controlled randomized study will be conducted to compare the effect of dexmedetomidine alone, and when combined with fentanyl or ketamine as sedative analgesic regimen for pain management during debridement and dressing of hand space infection.

Patients and Methods

The study was conducted at Mansoura University Principal Hospital.

60 ASA physical statuses I and II adult patients suffering from hand space infection who admitted for debridement and dressing; will be included in the study. After Individual informed written consent, Patients will be randomly divided into three groups via sealed envelope assignment.

General anaesthesia will be conducted by thiopental sodium 5mg/kg and vecuronium 0.1mg/kg, then the patient will be intubated and anesthesia will be maintained by sevoflurane 2% MAC (variable to maintain the hemodynamic within 20% of the basal values) and vecuronium to maintain muscle relaxation.

All patients will receive infusion of dexmedetomidine (0.5ug/kg) ten minutes before dressing. Then DS group (n=20) will receive

isotonic saline intravenous. DF (n=20) group will receive fentanyl 1ug/kg intravenous. DK (n=20) group will receive ketamine 1mg/kg intravenous. Patients will be monitored for mean blood pressure, peripheral arterial oxygen saturation, heart rate, end-tidal Co2 and end-tidal concentration of sevoflurane and recovery time will be recorded.

Patients will be instructed on the use of visual analogue scale (VAS) self rating method. All patients used a 10 cm VAS device to assess the level of pain (0= no pain; 10= worst possible pain). Sedation will be assessed on a five point scale(0= no sedation- patient wide awake and alert; 4= deep sleep- difficult to arouse). Pain and sedation were assessed by an assistant at 1, 2, 4, 6, 12 hours postoperatively.

All cases will be operated for drainage through generous incision of the skin associated with breaking of the subcutaneous fibrous septa for free drainage and excision of necrotic tissues. Wash with hydrogen peroxide 5% was indicated in some cases then baking of the wound was done.

At the end of the surgery and discontinuation of the inhalational anaesthesia, neuromusculare blockade will be reversed by atropine 0.02mg/kg and neostigmine 0.04mg/kg, tracheal extubation and transfer to the PACU. Postoperative observation and monitoring for nausea and vomiting. Patients' and surgeons' satisfaction also will be recorded.

The statistical analysis of data done by using excel program for figures and SPSS (SPSS, Inc, Chicago, IL). program Statistical Package for Social Science version 16.

The description of the data done in form of mean (+/-) SD for quantitative data .And Frequency & proportion for Qualitative data.

The analysis of the data was done to test statistical significant difference between groups.

For quantitative date student t-test was used to compare between two groups.

Chi square test was used for qualitative data.

N.B: P is significant if < or = 0.05 at confidence interval 95%.

Results

The characteristics of the 60 patients who completed the study are summarized in table (1). Demographic characteristics (age, weight, sex) were similar among the groups.

The heart rate was decreased significantly in the three groups 10 minutes after DEX infusion, this significant drop continues for another 10 minutes after saline injection in DS group and for 20 minutes after fentanyl injection in DF group. Heart rates in DF group was significantly decreased in comparison with DS group 10 minutes after fentanyl injection; whereas the DK group showed significantly increased heart rates in comparison with the other groups (DS, DF) for 20 minutes after ketamine injection (Table 2).

A significant drop in mean blood pressure was noted in all groups 10 minutes after DEX infusion (Table 3). This significance was lost 10 minutes after ketamine injection in DK group, but continued in DS group for 10 minutes after saline injection and for 20 minutes after fentanyl injection in DF group.

Patients in DK group showed a significant lower pain score (using the visual analogue scale) and a significant higher sedation score at 1 and 2 hours postoperative in comparison with the other groups (DS, DF). Similarly, DF group has a significant lower pain score (at 1h, 2h) and significant higher sedation score at 1 hour postoperative in comparison with DS group (Table 4 & 5). A significant longer time for eye opening was noted with DK group.

The surgeon's opinion was in agreement with opinion of patients. Nearly all patients of DK group (19 patients) were very satisfied and accepted to repeat the same technique if a similar surgery is needed in the future. One patient in DF group who exposed to nausea and vomiting, refuse the technique due to the bad experience.

Table (1): Demographic data. Values are (mean± SD).

	D (n=20)	DK (n=20)	DF (n=20)
Age	27.5±3.2	28±3.1	32.5±3.5
Weight	62.2±9.7	70.1±2.3	73.5±1.1
Sex	F: 8 M: 12	F: 14 M: 6	F: 11 M:9

Table (2): Heart rate in studied groups (bpm). Values are (mean± SD).

	DS (n=20)	DK (n=20)	DF (n=20)
Basal	97.3±7.57	99.2±5.9	97.2±9.9
After10 min DEX infusion	87.0±6.7•	88.3±8.9•	89.1±4.0•
10 min After S, K or F injection	89.6±5.7•	99.5±3.6†	83.9±2.9*•
After 20 min	94.0±2.9	98.6±6.4†	92.6±3.6•
After 30 min	94.7±3.5	96.3±2.5	94.5±4.5
After 40 min	94.5±3.1	96.2±6.2	94.2±3.6

*Sig drop in DF comp. with DS.
†sig increase in gp DK comp with DS and DF.
•sig decrease in comp with basal values.

Table (3): Perioperative mean blood pressure (mmHg). Values are (mean± SD).

	DS (n=20)	DK (n=20)	DF (n=20)
Basal	95.9±6.9	93.6±7.6	96.2±5.2
After10 min infusion	79.5±4.2*	78.6±5.8*	82.0±6.5*
10 min After S, K or F injection	88.0±8.3*	91.3±2.9	80.5±10.89†*
After 20 min	93.1±6.4	94.2±3.1	85.3±10.73†*
After 30 min	93.6±5.8	96.0±6.7	92.4±9.84
After 40 min	93.9±4.9	94.2±1.9	93.7±8.5

† sig drop in DF in comp. with DS and DK.
* sig drop in comp. with basal values.

Table (4): Pain score in the study groups. Values are (mean± SD).

VAS	DS (n=20)	DK (n=20)	DF (n=20)
1h	2.4±0.5*	1.4±0.5†	1.8±0.4
2h	2.0±0.5*	1.3±0.5†	1.7±0.4
4h	1.4±0.5	1.4±0.5	1.4±0.5
6h	1.0±0.0	0.9±0.4	1.0±0.0
12h	0.0±0.0	0.0±0.0	0.0±0.0

* sig increase in DS in comp. with DK, DF at 1h and 2h

† sig decrease in DK in comparison with DF at 1h and 2h.

Table (5): Sedation score in the study groups. Values are (mean± SD).

	DS (n=20)	DK (n=20)	DF (n=20)
1h	1.3±0.5	2.45±0.5*	1.8±0.4†
2h	0.8±0.4	1.8±0.4*	0.95±0.4
4h	0.0±0.0	0.55±0.5*	0.15±0.4
6h	0.0±0.0	0.0±0.0	0.0±0.0
12h	0.0±0.0	0.0±0.0	0.0±0.0

* sig elevation of DK in comp. with DS, DF at 1h , 2h and 4h

† sig elevation of DF in comp. with DS at 1h.

Table (6): Side effects in the study groups.

	DS (n=20)	DK (n=20)	DF (n=20)
N and V	---	---	2
Hypotention	---	---	1
Hypertention	---	---	---
Allergic rash	---	---	---
Hallucination	---	1	---

Table (7): Time of eye opening in the study groups.

Time of eye opening (min)	DS (n=20)	DK (n=20)	DF (n=20)
	7.4± 1.2	13.8± 3.5*	9.9± 2.96

*DK significantly higher than DS , DF (P= .000)

Table (8): Surgeon and patient satisfaction.

	DS (n=20)	DK (n=20)	DF (n=20)
Patient satisfaction	Very satisfy: 13 Satisf: 5 Not satisf: 2	Very satisfy: 19 Satisf: 1 Not satisf: 0	Very satisfy: 16 Satisf: 3 Not satisf: 1
Surgeon satisfaction.	Very satisfy: 15 Satisf: 5 Not satisf: 0	Very satisfy: 18 Satisf: 2 Not satisf: 0	Very satisfy: 17 Satisf: 3 Not satisf: 0

Patient satisfaction: P = 0.2

Surgeon satisfaction: P= 0.4

Discussion

Dexmedetomidine (DEX) is a highly selective and specific α2-adrenergic agonist which is characterized by rapid tissue distribution and short half life enabling it to induce controlled postoperative sedation and analgesia[10,11]. Moreover; DEX blunts the sympathetic mediated hyperdynamic response to surgical stress and tracheal intubation[12]. In comparison with midazolam; Koroglu et al 2005 concluded that, DEX produces more sedation but similar respiratory and hemodynamic effects [13]. In the same context, Arain et al 2004reported an advantage for DEX over midazolam as the former decreases the anesthetic and opioid requirements without increasing the respiratory depressant effect of opioids[14]. This randomized double blinded design study evaluates the added benefits and side effects resulting from the use of DEX in combination with either ketamine or fentanyl in comparison with the use of DEX alone in patients undergoing debridement and dressing of hand space infection which is a painful

procedure and may require an operating room environment.

DEX in a bolus dose of 1 μg/kg over ten minutes results in a biphasic hemodynamic response in the form of reflex bradycardia and a transient increase in blood pressure[15]. This increase in blood pressure starts one minute after bolus injection and is explained by the direct effects of α2- adrenoceptor stimulation of vascular smooth muscle. Then, this direct effect on vasculature is overcome by inhibition of sympathetic outflow[16]. However, Mauricio et al 2004 reported that the preoperative administration of 1 αg/kg in 10 minutes resulted in <20% reductions of HR and MAP in adults[17].

All patients in the three groups showed significant drop of heart rate and mean blood pressure ten minutes after DEX infusion. Twenty minutes after bolus fentanyl, the significant decreased heart rate and mean blood pressure continued, while this significance was lost twenty minutes after saline injection in DS group, this potentiation of opioid is in line with the opioid sparing effect of DEX. Patients in DK group lost the significant hemodynamic changes ten minutes after ketamine injection in comparison with basal value, while they gain significant elevation of heart rate and mean blood pressure in comparison with DF group. Push and pull between ketamine and DEX can be an explanation. DEX may prevent tachycardia and hypertension associated with ketamine. While ketamine may prevent bradycardia and hypotension which has been reported with DEX.

Because of the much higher selectivity of DEX for α2 adrenoceptor than other known agonist like clonidine, it can produce dose dependant analgesia at spinal and supra-spinal sites without respiratory depression[18 &19].

Ketamine is an agent that can be used in burn patients for achieving intra-operative and post-operative analgesia[20]. Humphries et al 1997 reported better analgesia and sedation with oral ketamine compared with other narcotics and sedatives during wound care procedures in children with burn[21]. Similarly, Ow-

ens et al 2006 concluded that ketamine is effective and safe for bedside procedures in burn patients with the advantage of preservation of airway patency and respiratory function[22]. This action of ketamine can be explained by the N-methyl-D- aspartate (NMDA) receptor antagonism, opioid receptor antagonism, and voltage-sensitive sodium channel interactions[5& 23].

In this study, the DK group has a significant lower pain score at 1 and 2 hours postoperative in comparison with other groups. At the same time, DF group showed a significant lower pain score in comparison with DS group at 1 and 2 hours, this potentiation of analgesic effect of fentanyl is in line with the well known DEX opioid sparing effect[10&11].

There are some reports in the literature about the use of DEX in combination with ketamine for procedural sedation. In this context, Koruk et al 2010 compared sedation using either regimen of DEX and ketamine or regimen of ketamine and midazolam during extracorporeal shock wave lithotripsy[24]. Both groups showed equally effective sedation with no significant changes in hemodynamic and respiratory parameters, but the time for eye opening, verbal response and cooperation were significantly decreased in DEX- ketamine group.

In agreement with the results of Koruk et al 2010, our study reported a significant high level of sedation in DK compared with other groups. Also, patients received DEX- fentanyl regimen showed a significant higher level of sedation in comparison with DS group at 1 hour. The time for eye opening in DK group was significantly longer than other two groups which may be due to longer sedative effect of ketamine compared with fentanyl which has shorter duration of action[25].

The DEX-ketamine regimen has the consent of nearly all patients of this group as well the surgeon. The reported nausea and vomiting in some cases of DEX-fentanyl group may be the cause of less acceptance in comparison with the former.

In conclusion, in patients undergoing debridement and dressing of hand space infection, although both regimens , viz., DEX-ketamine and DEX- fentanyl, provide effective sedoanalgesia without causing significant side effects, the former offered higher sedation and lower hemodynamic discrepancy.

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BENHA MEDICAL JOURNAL

DEXMEDETOMIDINE, FENTANYLE AND KETAMINE PROVIDE DEEP SEDATION FOR DEBRIDEMENT AND DRESSING OF HAND SPACE INFECTION

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BALLOON DISSECTION FOR EXTRAPLEURAL APPROACH IN (TRACHEO-ESOPHAGEAL FISTULA) TEF REPAIR

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Abstract

Purpose: *Esophageal atresia is a relatively common congenital malformation. The extrapleural approach is preferred to transpleural in thoracotomy because the anastomosis is outside the pleural cavity. This study describes an easy way for performing extrapleural dissection.*

Methods: *A novel technique for extrapleural dissection was performed for 16 patients with TEF/EA. It depends on using Foley's catheter in dissection. The balloon of the catheter is inflated gradually after introducing the catheter's tip between the pleura and the thoracic wall. By gradual increase of the size of the used catheter (10 F- 14 F) the pleura is dissected easily away from the chest wall.*

Results: *By comparing this technique with usual methods of pleural dissection, the operative time for this part of operation is reduced significantly, the incidence of pleural tear is diminished, moreover it is more easy than the traditional long tedious and careful dissection.*

Conclusion: *Balloon dissection makes extrapleural approach easier with less complications.*

Keywords: *Tracheo-esophageal fistula, Esophageal atresia and Extrapleural thoracotomy .*

Introduction

Esophageal atresia (EA) is a congenital anomaly in which there is a blind ending upper esophagus and the distal esophagus commonly connects to the trachea constituting a TEF [1]. It is a relatively common congenital malformation occurring in 1:3000-4500 live births [2-4]. The etiology of the anomaly is likely to be multifactorial. The familial/syndromic cases

represent less than 1% of the total whereas the overwhelming majority of cases are sporadic/ nonsyndromic [5].

Surgery for TEF/EA is urgent to prevent aspiration and respiratory complications. Surgery is usually performed on the first or second day of life after echocardiography and evaluation of comorbidities. The procedure involves fistula ligation and esophageal anastomosis [6]. The standard approach is a right posterolateral, muscle-sparing thoracotomy in the 4th intercostals space [2,7]. The extrapleural approach is preferred by most pediatric surgeons because possible substantial anastomotic leak will not be complicated by empyema but causes an esophagocutaneous fistula, which closes in 1-2 weeks. However, those who use transpleural route argue that the operative time is shorter and the risk of empyema after leak is minimal with the current antibiotics coverage [8].

Tedious dissection of the pleura is almost always needed for extrapleural approach of the esophagus and pleural tears during such dissection are not an unusual event. Consequently, a novel method is described in this study using the balloon of Foley's catheter to push the pleura away from the chest wall in easy manner and short time.

Patients and Methods

This study included 16 patients diagnosed as esophageal atresia with distal tracheoesopageal fistula (TEF/EA); managed at Pediatric Surgery unit and Neonatology unit in Mansoura University Children Hospital, Mansoura, Egypt.

The cases were included in the study randomly as regard age, sex, body weight and severity of associated anomalies. They were subjected to the usual screening for associated anomalies and were diagnosed by history of drooling and chocking with attempted feeding, failure to pass Ryle tube No. 8 F, and plain X-ray chest showing the kinked Ryle tube at the upper esophagus. Preoperative preparation included routine investigations, stabilization of respiratory condition, prophylactic antibiotics,

and preparation of 200 cc packed RBCs.

The standard posterolateral thoracotomy through the 4th intercostal space was used for the surgical approach. The intercostal muscles were divided and minimal dissection was performed cautiously by a wet piece of gauze to slightly separate the ribs and to create a space to introduce a catheter (Fig. 1). The tip of a Foley's catheter No. 10 F was introduced between the pleura and the ribcage. The balloon of the Foley's catheter was inflated by 10 cm saline (Fig. 2, 3). Then, the balloon was deflated and the catheter was removed and the procedure was repeated using Foley's No 12 F and 14 F inflated with 20 and 30 cm saline respectively until the pleura was separated from the rib cage and the azygus vein became visible (Fig. 4). The operation is completed as usual and a Nelaton catheter No 18 F was inserted in the chest outside the pleura as a drain at the end of the operation.

The time used for pleural dissection was calculated beginning after finishing division of intercostal muscles till the azygus vein became visible. Intraoperative pleural tears were reported; those that were 2 cm or less were considered as minor tears and others decided to be considered as major tears. The patients were followed postoperatively by regular chest examination and plain X-ray chest after 5 days looking for postoperative pleural complications.

Results

Sixteen patients (11 males and 5 females) with TEF/EA were included in the study. Three cases were operated at age of 2 days while one case was operated at age of 8 days. The rest of cases fall in between with the mean age at time of operation was 4 days. Other associated anomalies were reported in 7 cases (43.7%) with cardiac anomalies being the commonest as they were reported in 4 cases (25%).

The operative time for pleural dissection, using the balloon of Foley's catheters was calculated and the results were divided in 3 groups. Pleural dissection was accomplished within 2-4 minutes in 7 cases (43.75%); on the other

hand, more than 6 minutes were needed for such purpose in 2 cases (12.5%). The other 7 cases (43.75%) needed 4-6 minutes for dissection (Table 1). The shortest time needed for balloon dissection of the pleura was 2 minutes and 47 seconds (167 seconds) whereas the longest time was 6 minutes and 18 seconds (378 seconds) with the mean dissection time was 266.4 seconds.

A single minor pleural tear (2 cm or less) occurred during dissection in one case and was approximated by one Vicryl 5/0 suture. In another case, 3 separate minor tears occurred in the pleura and they were left to heal alone. Major pleural tears did not occur in any cases. The postoperative follow up revealed no pleural complications in the form of pleural effusion, empyema or pneumothorax in any case (Table 2). Anastomotic leak occurred in 3 cases (18.7%). They all develop esophagocutaneous fistula that were managed conservatively and closed in 7-10 days. These 3 cases didn't develop signs of sepsis and didn't need aggressive antibiotic regimens. Otherwise, the postoperative clinical course of all cases was uneventful.

Table 1: Operative time needed for pleural dissection.

Operative time	No. of patients	Percent
2-4 minutes	7	43.75%
4-6 minutes	7	43.75%
> 6 minutes	2	12.5%

Table 2: Intraoperative & Postoperative Complications.

Complications	No. of Patients	Percentage
Minor pleural tears	2	12.5%
Major pleural tears	0	0%
Anastmotic leak	3	18.7%
Postoperative pleural complications	0	0%

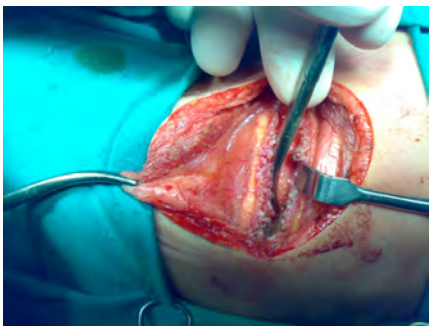

Fig. 1 : Minimal dissection of the pleura.

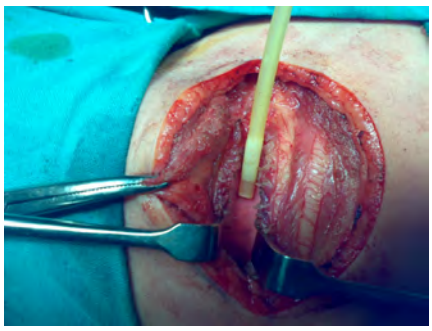

Fig. 3 : Pleura is separated from the ribs.

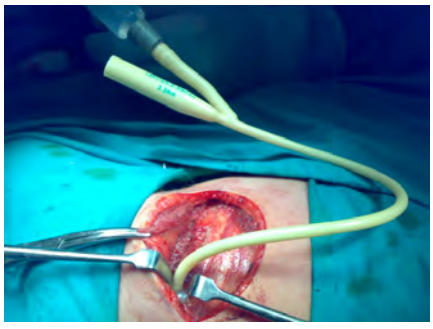

Fig. 2 : Filling of the balloon of Foley's catheter between the pleura and the ribcage.

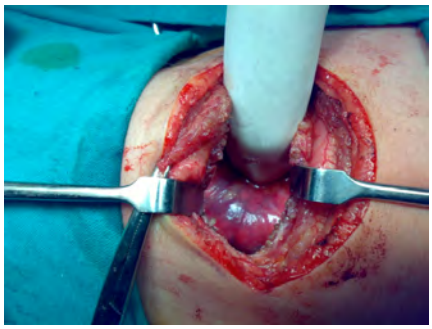

Fig. 4 : Intact pleura completely separated from chest wall

Discussion

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus. The survival of these patients improved markedly over the last two decades as a result of advances in neonatal intensive care, neonatal anesthesia, ventilatory and nutritional support, antibiotics, early surgical intervention, surgical materials and techniques[9]. Associated congenital anomalies occur in 40-60% of infants with oesophageal atresia [10,11,12]. Similarly, other major birth defects were reported in 43.7% of the cases included in this study. Cardiac anomalies detected in 25% of cases and were found to be the commonest association. This agrees with Chittmitrappap et al., 1989 [13] who reported 29% co-incidence of cardiac malformations.

The ideal time for primary repair is when the condition of the child is stable and the baby is fit for general anesthesia [14]. Hosie and Short, 2010 [1] suggested that the patient is stabilized and so the surgery can be planned usually within the first 48 hours. In the present study the mean age at time of operation was 4 days. This is mostly because of delayed referral of some cases from other centres.

Extrapleural approach is preferred nowadays by most pediatric surgeons; however it needs long time and tedious dissection [8]. In this study, such dissection was facilitated by using the balloon of Foley's catheter. The time needed for this task ranged from 2.5 to 6 minutes with the mean time being about 4.5 minutes. So, this way of dissection obviously overcomes the drawback of lengthy traditional extrapleural dissection and omits personal variation as well. Moreover, major pleural tears during dissection didn't occur in any case and only minor tears were reported in 2 cases only and didn't affect the postoperative outcome.

Anastmotic leaks occur in 14-21% of patients with EA [8,15-17]. Our 18.7% incidence of anastmotic leak falls within the same range. McKinnon and Kosloske, 1990[16] reported that the route of repair (transpleural or retropleural) didn't affect the incidence of anastomotic complica-

tions. Moreover, Bishop et al, 1985 [15]; who used the transpleural approach and reported 20% incidence of anastmotic leak, found that the leak related mortality falled from 88% during the period between 1951-1963 to 0% from 1974 to 1983. This is obviously related to the development of more effective antibiotics. However, with transpleural approach anastmotic leaks may be complicated by empyema or tension pneumothrax [8] which add to the morbidity of the patient and to the hospital cost using more aggressive antibiotic regimens. On the other hand, with extrapleural approach and a patent mediastinal drain, up to 95% of anastmotic leaks close spontaneously[18]. In the present study, all anastmotic leaks closed smoothly without additional morbidity and with the usual antiobiotics used in the postoperative care of such condition.

Conclusion

Balloon dissection is a valuable addition to management of esophageal atresia. It accomplishes pleural separation from the ribcage in short time and easy manner without incidence of significant pleural tears. Moreover, it improves the outcome of possible postoperative anastomotic leak without adding to the patient's morbidity or the hospital cost.

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BALLOON DISSECTION FOR EXTRAPLEURAL APPROACH IN (TRACHEO-ESOPHAGEAL FISTULA) TEF REPAIR

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COLORECTAL CARCINOMA BELOW 30 YEARS : A RETROSPECTIVE STUDY ON EGYPTIAN PATIENTS : 2000-2010

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Abstract

Background: *Colorectal cancer (CRC) is exceedingly rare in children and adolescents. Reports from small series indicate that poor prognostic factors are more common in children than in adults, resulting in worse outcome for the pediatric population. CRC is generally thought of as a disease of older persons; however a significant proportion of patients 30 years present with this disease. Many investigators have published single-institution series on CRC in the young, yet the data vary markedly. We performed a structured review of the current literature aiming to (1) Give an idea about increased incidence of CRC amongst young Egyptian adults. (2) Characterize CRC in the young population.*

Patients And Methods: *A retrospective study of 120 cases of CRC below the age of 30 years admitted to colorectal surgical unit in Mansoura University Hospital, Mansoura, Egypt during 2000-2010 was carried out.*

Results: *From January 2000 through December 2010, 120 children/adolescents (ages 4-30 years) were reported with a diagnosis of colorectal cancer. Rectal bleeding, change in bowel habit and abdominal pain were the commonest symptoms. The most common sites of involvement were the rectum (35%) and the transverse colon (28%). Adenocarcinoma was the most common histiotype however; children/adolescents had more unfavorable histiotype (i.e. mucinous adenocarcinoma [80%] and signet ring cell carcinoma [20%]). Poorly differentiated and undifferentiated tumors (grades III and IV, respectively) and distant stage were common in 70% of patients. 18 patients had a positive family history,*

while 12 others were diagnosed as index cases of familial adenomatous polyposis. Curative resection was attempted for 69 patients. 31 underwent palliative resections, 2 had an ileostomy and 18 patients have died.

Conclusion : *Patients younger than 30 years with colorectal cancer have a high-risk features and worse outcome than older patients. A high index of suspicion for CRC among young Egyptian adults is necessary. Age does not affect survival and early diagnosis, radical resection and adjuvant therapy still form the cornerstone in management of colorectal carcinoma in this age group.*

Keywords: *Young, colorectal carcinoma, risk factors, familial adenomatous polyposis.*

Introduction

Many studies have reported on colorectal cancers in those under the age of 40 years[1-4]. CRC has been thought to be less common amongst Africans compared with Caucasians. However, recent studies from Japan and Korea have shown high incidence rates (which has equaled or surpassed those in whites in the USA) with an increasing trend [5]. Most have documented similar clinical presentations and a greater incidence of mucinous and signet ring carcinomas as compared to older patients [1,3]. Disease characteristics in young adults are distinct from those in older patients in stage, grade, location of tumour and survival. The disease in the young is more aggressive, presents at a later stage and has poorer pathologic findings. In recent years, an increase in incidence of CRC among young adults has been noted worldwide [6-17]. Some have quoted a poorer prognosis while others have shown no significant difference in survival when thus compared [1,3,4]. Fewer studies have been reported recently about those under 30 years [18,19] in a single centre.

Patients and Methods

The study group comprised of 120 patients (62 M: 58 F) were operated on from January 2000 - December 2010 of CRC who attended the colorectal surgical unit in the department of surgery of

Mansoura University Hospital. A retrospective review of patients aged 30 years, operated for colorectal cancer at our department, was carried out. This involved searching for such patients in our department's operative database and reviewing the case notes of the patients. Standard workup included history and physical examination, rigid proctoscopy, complete colonoscopy with biopsy, transrectal ultrasound for rectal carcinoma, CT scan of abdomen, pelvis and chest (where indicated), chest X-ray, routine blood investigations and estimation of the serum carcinoembryonic antigen. The patients received standard therapy. Histopathological examination of the resected specimen was routinely carried out. The extent of tumor spread was assessed by AJCC classification based on histological examination of the resected specimen.

Follow up :

Survival status was evaluated by review of the medical database and telephone follow-up of all patients who had no regular outpatient department visits for more than 3 months at least. The median follow-up was 20 months (2-132 months); however eleven patients were lost to follow-up.

Results

We identified 120 patients below the age of 30 years with colorectal cancer who were diagnosed between January 2000 and December 2010. The majority of patients were between the ages of 15-25 years at diagnosis. Only 36 patients (30% of the cases) were aged <20 years (median age, 17.5 years) and were selected for the analysis of children / adolescents (among them, only 12 cases (10%) were aged <12 years). We compared the distribution of the main clinical characteristics of pediatric patients with those of adults. Unlike adults, who had nearly an equal distribution between males and females, a higher percentage of males (17%) were found in children / adolescents. The most common sites of involvement in children / adolescents were the rectum / anal canal and transverse colon, whereas the rectum/anal canal and ascending colon were the most common sites of disease in adults (Table 1).

18 patients had a family history of familial adenomatous polyposis (FAP), with carcinoma diagnosed in one of the polyps after examination of the proctocolectomy specimen. 12 other patients were diagnosed as index cases for FAP when colonoscopy showed a myriad of polyps within their colon. Their family members have since been invited for screening. One patient, with a strong family history of colonic and ovarian cancer, was diagnosed as an index case of Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and the other 120 patients were sporadic cases (Table 2).

The two most common clinical presentations of the patients in the study group were rectal bleeding (32.7%) and unexplained weight loss and anaemia (26.2%). Other major presentations included large gut obstruction (13.1%), altered bowel habits (12.4%) and abdominal lump (11.4%). Our patients presented at a mean of 4 months (0-60 months) from the onset of symptoms. Tumour characteristics of patients under 30 years in the study group showed predominance of poor differentiation of tumour (poor: 24%, moderate: 70%, well-differentiated : 6%) adenomatous adenocarcinoma (75%), mucinous adenocarcinoma (20%) and signet ring cell carcinoma [5%]. Left-sided CRC (defined as lesions distal to the splenic flexure) was found in 65% (rectal: 35%, left colon: 22%) of CRC patients. Of the patients with colon cancer, right - sided lesion (defined as lesions between caecum and splenic flexure) constituted 43% of the group (Table 3).

Curative resection was attempted for 69 patients. 31 had undergone palliative resections, 2 had required a defunctioning ileostomy for palliation of extensive pelvic disease and liver metastases. An abdominoperineal resection was performed in only 2 cases. Among those with curative resections, 8 had recurrences at a median of 12 months (8-22 months) postoperatively. All were Duke's C stage at first operation and most had undergone adjuvant chemotherapy. At median follow-up of 20 months, 18 patients had died of colorectal cancer. All patients with Duke's A and B tumours on follow-up were

alive with no evidence of disease. Six out of 14 patients with Duke's C cancers were alive with no evidence of disease on follow-up. The remaining 11 patients were lost to follow-up (Table 4,5).

Table 1: Patient Characteristics.

	Children/Adolescents (<20 years)		Adults (20-30years)	
	No.	**(%)**	**No.**	**(%)**
Sex				
Male	20	17	54	45
Female	16	13	30	25
Total	**36**	**30**	**84**	**70**
Site				
Ascending colon	4	3	6	5
Transverse colon	12	10	30	25
Descending colon	4	3	2	2
Sigmoid colon	6	5	14	12
Rectum/anus	10	8	32	27
Total	**36**	**30**	**84**	**70**

Table 2: Family history .

Variables	Number	(%)
FAP	18	15
Index cases of FAP	12	10
HNPCC	1	0.8
Sporadic	89	74.2
Total	**120**	**100**

Table 3: Tumour type, grading and staging.

Variables	Duke's A	Duke's B	Duke's C	Duke's D	Total (%)
Adenomatous	7	28	34	21	90 (75)
Mucinous	0	0	18	06	24 (20)
Signet ring	0	0	0	0	6 (5)
Total (%)	**7 (6)**	**28 (23)**	**53 (44)**	**32 (27)**	**120 (100)**
Well-differentiated	1	6	Nil	Nil	7 (6)
Moderately-differentiated	12	17	40	15	84 (70)
Poorly-differentiated	Nil	3	16	10	29 (24)
Total (%)	**13 (11)**	**26 (21)**	**56 (47)**	**25 (21)**	**120 (100)**

Table 4: Adjuvant chemotherapy and recurrence

	Duke's A		Duke's B		Duke's C		Total
	Chemo	No chemo	Chemo	No chemo	Chemo	No chemo	
Recurrence	0	0	0	0	7	1	8
No recurrence	22	2	12	40	5	1	82
Loss to follow-up	0	0	0	4	4	0	8
Total	22	2	12	44	16	2	98

Table 5: Survival according to stage.

	No evident disease	Alive with disease	Died of cancer	Lost to follow-up	Total
Duke's A	24	0	0	0	24
Duke's B	52	0	0	4	56
Duke's C	6	8	8	4	26
Duke's D	0	1	10	3	14
Total	**82**	**9**	**18**	**11**	**120**

Discussion

A recent study revealed that colorectal cancer incidence rates for both males and females increased in 27 of 51 countries worldwide between 1983 and 2002, and the most likely cause was postulated to be an increasingly "Western-style" diet consumed in those countries. The rise was seen primarily in developing countries including Eastern European countries, most parts of Asia, Africa and some countries in South America.

Colorectal cancer may be considered the second commonest cancer among Egypt males with an age-standardized rate of 37.5 and the females 29.4. Our study of 120 patients below the age of 30 years represents approximately 5% of the total number of patients with colorectal cancer operated at our hospital from 2000 to 2010.

Odone et al reported on 24 patients less than 20 years of age (13 black) who had an eight-month median survival from diagnosis. Twenty-one of the 24 had poorly differentiated mucin adenocarcinoma. The most common

presenting symptom was abdominal pain-observed in all 24 patients-followed in frequency by weight loss, nausea, vomiting, constipation, diarrhea, anemia, and anorexia. The most common symptom in the study patients was rectal bleeding followed closely by abdominal pain [24].

Pitluk and Poticha stated that abdominal pain, usually localized to the areas of the underlying tumor, was found almost twice as often as the other three important symptoms-rectal bleeding, change in bowel habits, and weight loss with anorexia. They reported an average interval of four to six months between the onset of symptoms and histopathologic diagnosis. However, 45 percent of the patients had delays in diagnosis greater than six months, and 32 percent, greater than one year. There was a 23 percent incidence of mucinous adenocarcinoma. The prognosis was dependent upon the stage of the disease, and that survival of patients with rectal disease was dismal [25].

Three patients in our study had presented with per rectal bleeding attributed to piles and had undergone haemorrhoidectomy. One patient had an on-table rigid sigmoidoscopy which showed a rectal tumour 7 cm from the anal verge. Another patient had persistent bleeding even 9 months after his haemorrhoidectomy and a colonoscopy later revealed a rectal tumour 8 cm from the anal verge. We therefore recommend that all patients undergoing haemorrhoidectomy should have an on-table sigmoidoscopy, if no prior colonoscopy has been performed. Many of our patients had multiple symptoms (3 or more) at presentation. An early colonoscopy may be offered at the time of initial consultation for such patients. Nevertheless, all patients with persistent symptoms have been offered either a colonoscopy, or a barium enema.

Petrek et al reported that 50 patients under 40 years of age (8.2 percent black) from a socioeconomically disadvantaged population had an increased five year survival (36 percent) compared with their older counterparts (24 percent over 40 years), and young women had significantly better

survival than young men. They noted that advanced stages, distribution of primary sites, precancerous conditions, and the higher incidence of extracellular mucin production in cancers from younger patients had no adverse effect on survival. This was not true of the patients reported here [26].

Family history of colorectal cancer was far more prevalent in younger patients[23]. This accounted for 26% (31 /120) of our patients, in comparison with 22% quoted in other studies [1]. Prompt surveillance in relatives of probands, especially early onset cases, may lead to earlier detection and better prognosis [27].

Seventy-one percent of patients presented at a late stage. Recent studies have quoted figures of between 59 and 78%[2,3]. However, the median survival of young patients was no different from older patients when compared by stage[3,5]. Mucinous adenocarcinomas accounted for 20% of all malignancies. This histological subtype has been described more commonly in young patients[4,13,18] and may be associated with a poorer prognosis [20]

Some studies have quoted 5-year survival of between 18 and 26% in those under 40 years[5,19]. Others have reported 54-56%[1,18]. In a study of those 30 years or younger, a 79% mortality was reported at median follow-up of 21.5 months[22]. This is in contrast to a mortality of 15% in our median follow-up of 20 months.

In this series rectal and rectosigmoid tumours made up 52% of all cancers in our series, while right-sided tumours accounted for only 43% of cases. Also, two factors correlated with the observed low survival rate: (1) histologic type of mucinous adenocarcinoma (24%) and (2) delay in diagnosis associated with an advanced stage of disease at operation. A high index of suspicion for colorectal cancer should be maintained in young patients with either rectal bleeding or abdominal pain. Only in this way can the poor survival rate be improved.

Conclusion

Rectal bleeding and pain are

more frequent in the young, although presenting symptoms are often similar to those in the older age group. Family history of colon cancer and a higher incidence of mucinous adenocarcinomas are more prevalent in the young. Age alone is not a poor prognostic marker; stage being the more accurate predictor of outcome. A higher index of suspicion coupled with early endoscopy for those with persistent symptoms, as well as radical resection of malignancies and use of adjuvant therapy may lead to more favourable outcomes [28].

The most important prognostic factor has been shown to be clinical staging, rather than age. Since the most common symptoms in colorectal cancer like rectal bleeding, abdominal pain, weight loss, and change in bowel habits including constipation and diarrhea are all nonspecific the clinicians should always be alert to the possibility of this cancer in younger adults. With early diagnosis, excellent survival rates can be achieved with current treatment options[29,30].

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THE RELATION BETWEEN HEMOGLOBIN LEVEL AND NUTRITIONAL STATUS OF PRESCHOOL CHILDREN IN TRIPOLI CITY

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Abstract

A cross sectional study involved nine day care centers in Tripoli, Libya. The study involved 932 preschool children attending those centers. Evaluation of nutritional status of those children was conducted. The examination included history, clinical, anthropometric and testing blood for hemoglobin, haematocrit value, and total RBCs count. The results showed that 3.4% of the anemic children were underweight. On the other hand 3.2% of the non anemic children were underweight. The difference was not statistically significant. 4.3% of anemic children had acute malnutrition as compared to 3.6% among non anemic children. The difference is statistically insignificant. Moreover 0.9% of anemic were stunted compared to 3.8% of non anemic children and there was no statistically significant difference between the groups.

Conclusions: *Nutritional anemia is not necessarily associated with total energy malnutrition. Iron deficiency anemia is caused by relative dietary deficiency in iron rather than total caloric deficiency.*

Introduction

Anemia is one of the major signs of disease and not a final diagnosis. It is never normal and its causes should always be investigated. It is also defined as a condition in which the hemoglobin (Hb) concentration in peripheral blood is lower than normal for age, sex and pregnancy state of the subjects.'

Anemia is possibly the most common manifestation of diseases

in the tropics. Prevalence and morbidity are greatest in preschool aged children and pregnant women. Anemia has multiple etiologies: it may be caused by nutritional deficiencies or congenital abnormalities, or it may be associated with a number of conditions, such as chronic kidney disease, cancer, parasitic diseases or human immunodeficiency virus (HIV)[2]. Anemia plays an important role in producing morbidity, especially in preschool age children who constitute an important section of the population. In this vulnerable age group the increased nutritional requirements due to accelerated growth rate coupled with inadequate dietary intake will lead to the development of anemia. This is particularly true where anemia is possibly the most common manifestation of diseases in the tropics[3].

Anemia is more prevalent during the first two years of life. Children need a relatively high iron intake because they are growing very rapidly. Added to this, the low iron intake of milk to meet infants requirement and also complementary foods are usually low in iron. With increasing age of children, their dietary intake is improving which in turn leads to decrease in the prevalence of anemia.[5'6'7]

The objective of this work is to examine the relation between hemoglobin levels and nutritional status of preschool children attending day care centers in Tripoli city Libya Arab Jamahiriya.

Materials and Methods

Study design :

A cross sectional study involved nine day care centers in Tripoli, Libya. The study involved 932 preschool children attending those centers. Evaluation of nutritional status of those children was conducted. The examination included history, clinical, anthropometric and testing blood for hemoglobin, heamatocrit value, and total RBCs count. Calculationand interpretation of anthropometric measurements:

The nutritional indices were calculated using Epi Info soft ware (version 9.0). Individual data on height for age, weight for height and weight for age were compared

with the standard of the National Center for Health Statistics (NCHS)[8] which is a standard reference population recommended for international use[9'10]. The data were expressed in terms of standard deviation scores (Z scores) which equal to:-

Individual value - median value of reference population divided by the standard deviation of reference population. The Z-score cut-off point recommended by the WHO (1986)[11] to classify low anthropocentric level is - 2SD units below the reference median for the three following indices:

1- Chronic malnutrition or stunting:

This refers to the children whose height for age is less than -2 standard deviation (SD) of the reference median. 2- Acute malnutrition or wasting:

This refers to the children whose weight for height is less than -2 SD of the reference median.

3- Under weight :

This refers to the children whose weight for age is less than -2 SD of the reference median.

In this study the child was considered anemic when the values of hemoglobin were below 11 gm/ 100ml according to the recommendation of the WHO (1968).[(12)].

Results

Table (1) shows the association between underweight and anemia among the studied sample. The results show that 3.4% of the anemic children were underweight. On the other hand 3.2% of the non anemic children were underweight. The difference was not statistically significant.

Table 2, shows the relation between acute malnutrition and anemia. 4.3% of anemic children had acute malnutrition as compared to 3.6% among non anemic children. The difference is statistically insignificant.

Table 3 shows the relation between anemia and chronic malnutrition. 0.9% of anemic were stunted compared to 3.8% of non anemic children and there was no statistically significant difference between the groups.

Table 1 : The relation between anemia and underweight among preschool children studied.

Nutritional status		Anemic (n=117)	Normal No (n=815)	Total (n=932)	Fisher exact p value
		No (%)	No (%)		
Weight / Age Z-score	<-2SD Underweight	4(3.4)	26(3.2)	30	0.547
	>-2SD Normal	113(96.6)	789(96.4)	902	

Table 2 : The relation between anemia and acute malnutrition in preschool children studied

Nutritional status		Anemic (n=117)	Normal No (n=815)	Total (n=932)	Fisher exact p value
		No (%)	No (%)		
Weight/Height Z-score	<-2SD Acute Malnutrition	5(4.3)	29(3.6)	34	0.4
	>-2SD normal	112(95.7)	789(96.4)	898	

Table 3: The relation between chronic malnutrition and anemia in preschool children studied.

Nutritional status		Anemic (n=117)	Normal No (n=815)	Total (n=932)	Fisher exact p value
		No (%)	No (%)		
Weight/Age Z-score	<-2SD Chronic malnutrition	1(0.9)	31(3.86)	32	0.07
	>-2SD normal	116(99.1)	784(96.2)	900	

Discussion

More than 2 billion people, mostly women and young children, are thought to be iron deficient[17].

Iron is found in all plant foods but is more plentiful and bioavailable in meat. Deficiency results from insufficient absorption of iron or excess loss. Absorption is tightly regulated in the intestines, depending on the iron status of the individual, the type of iron, and other nutritional factors. Once iron is absorbed, it is well conserved. Iron is depleted primarily through blood loss, including from parasitic infections such as schistosomiasis and hookworm.

Mainly found in hemoglobin, iron is essential for the binding and transport of oxygenT, as well as for the regulation of cell growth and differentiation[16]. Iron deficiency is the primary cause of anemia, although vitamin A deficiency, folate deficiency, malaria, and HIV also result in anemia. Iron deficiency anemia is most prevalent in South Asia and Sub-Saharan Africa, but it is not limited to developing countries.

In this work it was noticed that there was no association between anemia and energy malnutrition whether acute or chronic energy malnutrition. Iron deficiency anemia is due to consumption of diet deficient in iron rather than its deficiency in total calories. The iron deficiency anemia is the commonest anemia in infants and children as reported by Abbasy[13] in Egypt and Singla'[14]' in India.

Anemic children showed similar prevalence of acute and chronic malnutrition as non anemic children. This suggests that anemic children were fed an iron deficient diet but with enough total calories. Nutrition is defined not only by quantity of food but particularly by quality of food. Energy, measured by calorie consumption, and protein are referred to as macronutrients while vitamins and minerals also critical for normal healthy development constitute micronutrients. So dietary iron deficiency is greater than total dietary caloric deficiency. This is consistent with the findings of the survey conducted to evaluate

the nutritional status of preschool children at Gaza and West Bank 2002[18]. The prevalence of anemia much exceed the prevalence of acute and chronic malnutrition. The higher prevalence of anemic children than acute and chronic malnutrition also suggests that prevalence of anemia is a more sensitive measure that can be used to evaluate the nutritional status of children in the community as a whole.

Also presence of iron deficiency anemia in a child is an early indicator for the presence of dietary deficiency. Attention to child feeding should then be given to evaluate the quantity and quality of food given to the child for correction of the anemia and to correct other dietary deficiency to prevent development of other nutritional diseases in the child like total caloric and protein malnutrition diseases.

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THE RELATION BETWEEN HEMOGLOBIN LEVEL AND NUTRITIONAL STATUS OF PRESCHOOL CHILDREN IN TRIPOLI CITY

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EPIDEMIOLOGICAL FEATURES OF INTESTINAL AND ECTO-PARASITES IN PRESCHOOL CHILDREN IN TRIPOLI CITY

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Abstract

Objectives: *To estimate the prevalence of intestinal parasites & ectoparasites as pediculosis & scabies among a group of preschool children in nine day care centers in Tripoli city - Libyan Arab Jamahiriya .*

Introduction

Intestinal parasites account for large proportion of the morbidity and mortality among infants and young children; those who are under 5 years of age are the most affected group world wide[1-3]. Current estimates suggested that at least one-quarter of the worlds' population is chronically infected with intestinal parasites with high prevalence rates. Most of these infected people live in developing countries in tropical and subtropical areas [4] where people either accept the parasites as a fact of life or are completely unaware of themeis).

Methodology:

The study is a cross sectional study. It was carried out on the preschool children attending the nine day care centers in Tripoli city by multistage sampling method. The studied'Sample consisted of 1255 children (676 males and 579 females). Total stool samples collected from 1056 children (577 males and 479 females). Microscopic examination of the stool samples was examined by using Merthiiolate formaldehyde (MF) direct smear. MF preserved samples were concentrated using merthiolate iodine formaldehyde concentration technique. The total scotch

tape samples applied were 1204 (653 males and 551 females). Head louse infestation was diagnosed by direct inspection of the child's hair and scalp, particularly the nape of the neck and behind the ears by using a hand lens and a flash-light battery. All children are examined clinically, anthropometric measurement.

The questioner sheets were designed to cover a variety of items concerning personal socioeconomic data of the examined children which can be related to parasitic infections.

Pilot study :

Pilot study was done in selecting setting for following reasons:

1- To test the validity of the questioner.
2- To estimate the number of equipments and materials needed for the field work.

Statistical analysis :

Once the questioner sheets were filled out, the collected data were critically reviewed coded and computerized using Epi-Info 2000 program. After revision and verification of the data they were subjected to the statically program SPSS version 9.0 software for processing, tabulation and for statistical analysis, all test were tow sided and the cut: off P-value for statistical significant was 0.05.

The odds ratio (OR) together with its 95% confidence limits was used to estimate the risks of infections in relation to different factors.

Results

Out of 1056 children who submitted stool samples, 394 (37.3%) Were infected with intestinal parasites, including protozoa and helminthes other than E.vermicularis, G.lamblia was the commonest protozoa detected (19.5%), E.histolytica (9.3%), E.coli (7.8%). The helminthes parasites which were detected, H.nana (0.6%), A-lumbricoides (0.2%), and T.trichiura (0.2%). By using the scotch tab technique the prevalence infection of E.vermicularis was (30.3%), Pediculosis (6.5%) and scabies 0%.

Table 1: Distribution of the studied sample by parasitic infections.

Type of parasite	Number	%
Helminthes:		
Ascaris lumbricoides n=1056	2	0.2
Tricharis trichuira n=1056	2	0.2
Hymenolepis nana n=1056	6	0.6.
Entrobius vermicularis n=1204	365	30.3
Protozoa:		
Giardia lamblia n=1056	206	19.5
Enltamoeba histolytican=l056	98	9.3
Entameoba coli n=1056	80	7.8
Pediculosis	82	6.5

Number examined: 1255
Number of stool samples 1056 (No Stool available for 99 males and 100 females)
Number examined for scotch tape 1204 (23 mates and 28 females refused scotch tape)
Number examined for pediculosis 1255

Table (2): Association between parasitic infections among the studied sample and socio-economic levels.

Type of parasites		Socioeconomic level			Total
		Low	Middle	High ®	
		No. %	No. %	No. %	No. %
Intestinal parasites other than E.vermicularis	Examined	158	518	380	1056
	Positive	86-54.4	202 -38.9	106 -27.8	594 -37
OR 95%CI		3.09* 2.06-4.62	1.65* 1.23-2.22	1.00	
Enterobious vermicularis	Examined	178	601	425	1204
	Positive	79 -44.4	196- 32.6	90-21.2	365 -30.3
OR 95%CI		2.97* 2.00-4.40	1.80* 1.34-2.43	1.00	
Pediculosis	Examined	181	627	447	1255
	Positive	30-16.6	39-6.2	13-2.9	82-6.5
OR 95% Cl		6.63* 3.23-13.80	2.21* 1.13-4.42.	1.00	

® Reference categor * Significant (P<0.05)

Table (3): Association between parasitic infections among the studied sample and the levels of DCC.

Parasites	Level of DCC					
	Low		Middle		High®	
	No.	%	No	%	No.	%
Intestinal Parasites other than E.vermicularis:						
Examined (n=1056)	545		321		190	
Positive (n = 394)	243	44.6	98	30.5	53	27.8
Negative (n = 662)	302	55.4	223	69.5	137	72.2
OR	1.93*		0.50*		1	
95% CI	1.28-2.91		0.30-0.84		-	
Enterobius vermicidaris:						
Examined (n = 1204)	652		357		195	
Positive (n = 365)	246	37.7	79	22.1	40	20.5
Negative (n = 839)	406	62.3	278	77.9	155	79.5
OR	2.35*		1.10		1	
95% CI	1.58-3.51		0.70-1.73		-	
Pediculosis:						
Examined (n = 1255)	668		387		200	
Yes (n = 82)	71	10.6	6	1.6	5	2.5
No (n=1173)	597	89.4	381	98.4	195	97.5
OR	4.64*		0.61		1	
95% CI	1.86-14.92		0.15-2.58		-	

® Reference category * Significant (P<0.05)

Fig. 1 : Prevalence of parasitic infections among the studied sample by age group.

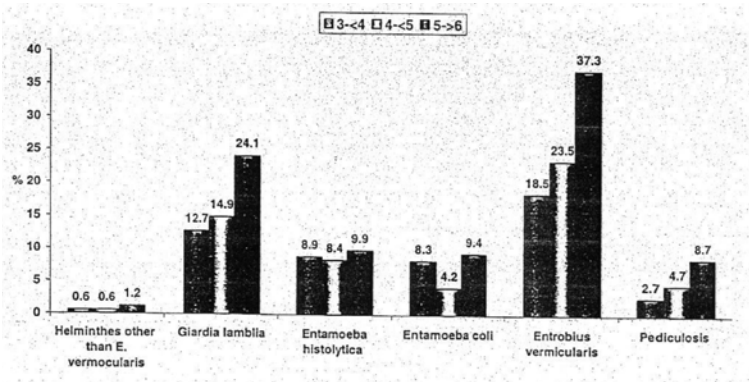

Fig. 1 : Shows age distribution of the sample, it can be noted that in all day care centers 53.4% were of the age group 5+ years in age group 4-<5 and 3-<4 years (32%, 14.6% respectively).

Fig. 1 : Prevalence of parasitic infections among the studied sample by sex.

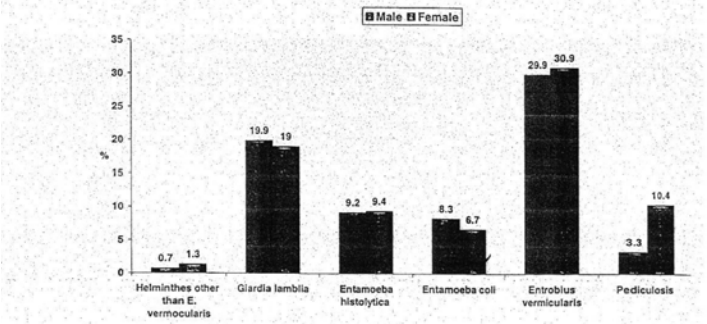

Fig. 2 : Shows that there is no statistical significant difference of intestinal parasitic infection between males & females.
For pediculosis infestation the total number of infested children was 82, 10.4 of them were femals & 3.3% were males the risk of developing pediculosis infestation was statistically significant.

Discussion

In the present study, the most common protozoan parasites was G.lamblia which was detected in 19.5% of the children. This is a considerable low rate as compared to the G.lamblia infection 33% reported in Cairo[6], 26% reported in Alexandria[7] and in rural area of Kafr El-Sheikh 23%[8]. Markedly lower percentages were reported in India 6.4%[9] and in Gaza Strip 2.2%[10] and in Saudi Arabian children 9%[11]. In the Sudanese towns the prevalence of Giardia was 56.8%[12].

As regards E.histolytica infection, the prevalence rate was 9.3%. This rate of infection was much lower than that recorded from a rural area of Kafr El-Sheikh 31.6%[8], and in Cairo 21%[6].

The present study showed that (30.3%) of the examined children were infected with E.vermicularis as indicated by the adhesive scotch tape and peri-anal swabs techniques. High prevalence rats of pin-worm infections were reported (68.8%) and (51.40%)[13] among visually handicapped and control children in Alexandria respectively, and 43.8%[14] among rural primary school children in Giza. Gilman et al. (1991)[15] reported that in Peruvian town 42% of the primary school children and approximately one fourth of both preschool arid secondary school

students were infected with pinworms.

On the other hand, the arthropod-ectoparasite or Pediculus humanus (head lice) in this study,- among 1255 children were examined the prevalence was 6.5%. In Egypt, in school children in Qualyob city (in the Nile Delta) the rate of head lice infestation was 16.04%[16].

Recommendations:

Urgent remedial steps are needed on a community basis to improve their control of parasitic infections.

- Medical and sanitary supervision are needed in every DCC to control the parasitic Infections and improve the health status of preschoole children who are the fastest through the following points.
- Health education programs should focus on the importance of personal hygienic practices.
- Improvement of sanitary conditions of DCC by proper refuse and sewage disposal and provision of safe water supply.
- Appropriate number of clean toilets and washing facilities should be provided in DCC.
- Health education of mothers by stressing the importance of hygiene using attractive posters in very simple language.

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TIVA VERSUS SEVOFLURANE EFFECT ON CEREBRAL BLOOD FLOW A TRANSCRANIAL DOPPLER STUDY

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Abstract

Transcranial Doppler ultrsongraphy is non invasive technique that measures cerebral blood flow velocity. Preliminary data on the effect of propofol on cerebral blood flow indicate that propofol causes decrease cerebral blood flow while there is some controversy concerning the effect of ketamine on cerebral circulation, conflicting results on the effect of sevoflurane on cerebral blood flow velocity.

Purpose: *this prospective, randomized controlled study was designed to evaluate the effect of propofol, ketamine, propofol-ketamine versus on middle cerebral artery blood flow velocity by using Transcranial Doppler ultrsongraphy.*

Methods: *one hundred twenty patients scheduled for orthopedic lower limb surgeries were randomly classified into four groups thirty patients each.*

Group I (p): *propofol was given as induction dose 2mg/kg and 6mg/kg/h as continuous infusion.*

Group II (k): *ketamine was given 2mg as induction dose then 2mg/kg/h as infusion till the end of surgery.*

Group III (pk): *propofol 1mg, ketamine 1mg/kg then continuous infusion of propofol 3mg/kg/h and ketamine 2mg/kg/h.*

Group IV (S): *anesthesia was induced with sevoflurane 8% then maintained with sevoflurane 2%.*

In all groups TCD ultrasonography measurements of the middle cerebral artery mean flow velocity before induction, immediately after induction and every 30 minutes till the end of surgery.

Results: *the middle cerebral artery main flow velocity (Vmca) was increased significantly ($p<0.05$) in group k and group s while decreased significantly ($p<0.01$) in group p. pulsatility index was significantly higher in group p than other three groups.*

Conclusion: *propofol decrease both cerebral blood flow velocity and systemic blood pressure while ketamine and sevoflurane increased both.*

Key words: *TCD- TIVA- Propofol-Ketamine-Sevoflurane- CBF.*

Introduction

Propofol is used increasingly for the induction and maintenance of anesthesia. Its use is characterized by rapid clearance and distribution, resulting in rapid emergence from anesthesia.[1] Studies using Xenon ^{133}(Xe) inhalation scintillography have demonstrated that propofol causes a significant decrease in cerebral blood flow and increases cerebral vascular resistance. [2]

Ketamine has gained attention as an analgesic for total intravenous anesthesia.[3] The combination of propofol and ketamine is recommended for total intravenous anesthesia because the opposing effects of the individual anesthetics result in intraoperative hemodynamic stability.[4] There is some controversy concerning the effects of ketamine on cerebral circulation, ketamine has been reported to increase cerebral blood flow and intracranial pressure.[5] However, other have reported that ketamine does not increase CBF velocity or ICP.[6]

Inhaled induction of general anesthesia has not been popular with patients or clinicians because of fear of excitement and respiratory symptoms related to the pungency and speed of available volatile anesthetics. However, sevoflurane has potential advantages (a relatively low blood gas solubility and a relative absence of pungency) that make the inhaled induction technique a feasible option.[7] Sevoflurane has been used to provide an inhaled induction by using a vital capacity breath, which is fast and has few side effects.[8, 9]

Inhalational anesthetics have been shown to produce a dose dependent increase in cerebral blood flow. The magnitude of this increase is dependent on the balance between the agents intrinsic vasodilatory action and the vasoconistriction secondary to flow metabolism coupling.[10]

Sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect less than that reported for halothane and isoflurane.[11]

Sevoflurane has became one of the most widely used inhalational agent in general anaesthesia due to its excellent physical, pharmacodynamic and pharma-cokinetic properties.[12] However, in neurosurgical anaesthesia there has been concern due to the known vasodilator effect of all inhalational agents. As cere-bral vasodilatation may result in increased cerebral blood flow and blood volume, the use of an inhala-tional agent may contribute to a secondary increase of the intracranial pressure in patients with space-occupying lesions.[11,13,14]

Conflicting results have been reported including that sevoflurane does not affect cerebral blood flow velocity[15] and global cerebral blood flow[16], increased global or regional cerebral blood flow[13,17,18], along with a decreased or unchanged cerebral metabolic rate for oxygen[17,19] and decreased cerebral blood flow[20,21,22] or cerebral blood flow velocity.[23,24] The vasodilator effect is dose dependent, and is more pronounced with incremental clinical doses. [11,25,26]

In the majority of the previous studies, different minimal alveolar concentrations of sevoflurane were used. However, only a few studies measured the effect of sevoflurane on cerebral circulation at a level of surgical anaesthesia as assessed by a depth of anaesthesia monitor.[23, 27] As the main goal of the routine anaesthesia practice is maintaining the level of appropriate depth of anaesthesia and analge-sia during surgical procedures, it seemed logical to assess the effect of anaesthesia on cerebral blood flow under such circumstances. Different methods have been used to assess the cerebrovascular effects among them

transcranial Doppler sonography (TCD), positron emission computed tomography and magnetic resonance angiography.[15]

Transcranial Doppler sonography is an emerging technique that uses a hand held directional, microprocessor-controlled, low-frequency (2MHz), pulsed Doppler transducer to measure the velocity and pulsatility of the blood flow within the arteries of the circle of Willis and vertebrobasilar system the procedure is noninvasive, non ionizing protable, safe for serial or prolonged studies and performed with relatively inexpensive equipment.

The diagnostic accuracy depends on the knowledge, skill and experience of the examiner, who must be familiar with anatomy and physiology of the intracranial vasculature. In most cases, the clearst understanding of transcranial Doppler data requires an integration with the results of other neuroradiologic studies and clinical and laboratory determinations. [28]

Transcranial Doppler (TCD) is a non invasive ultrasonic technique that measures local blood flow velocity and direction in the proximal portions of large intracranial arteries.[29]

The chief advantages of TCD are as follow: It can be performed at the bedside and repeated as needed or applied for continuous monitoring, it is frequently less expensive than other techniques, and dye contrast agents are not used. Its chief limitation is that it can demonstrate cerebral blood flow velocities only in certain segments of large intracranial vessels, although large-vessel intracranial arterial disease commonly occurs at these locations. In general, TCD is most useful when the clinical question pertains to those vessel segments. However, in some settings, TCD can detect indirect effects such as abnormal waveform characteristics suggestive of proximal hemodynamic or distal obstructive lesions. [30]

The aim of this study was to evaluate the effects of propofol alone, ketamine alone, propofol-ketamine versus sevoflurane on human middle cerebral artery

blood flow velocity by using transcranial Doppler ultrasonography during orthopedic surgeries.

Patients and Methods

This randomized prospective controlled study was carried out on 120 patients ASA physical status I and II of either sex aged between 20 and 40 years scheduled for orthopedic lower limb surgeries at Emergency hospital, Mansoura University from Jan 2007 - May 2009.

The protocol was approved by the scientific committee of the department and an informed consent was secured from every patients.

All patients were subjected to thorough medical history, clinical examination and routine laboratory investigation. Patients were randomly classified into four groups 30 patients each. Eighteen gauge IV cannula was inserted and 500 ml of lactated ringer's solution was infused.

Epidural block was done to all groups as follow:

While, the patient was in the sitting position a local infiltration of 2 ml 2% lidocaine subcutaneously was done, then 20 gauge catheter was inserted in the space between L4,5 using 18 gauge Touhy needle depending on loss of resistance to air technique then 15 ml of 0.75% concentration ropivacaine was injected.

Group I: (P: propofol induction and maintenance)

Anesthesia was induced with a sleep dose of propofol till loss of eyelid reflex (1.5 - 2 mg/kg) and tracheal intubation was facilitated with the use of vecronium bromide 0.04 mg/kg.

Anesthesia was maintained with continuous infusion of propofol 12 mg/kg/h for the first 15 minutes, and then 9 mg/kg/h for the next 25 minutes and 6 mg/kg/h till the end of the surgery.31

Group II: (K: Ketamine induction and maintenance)

Anesthesia was induced with a sleep dose of ketamine (1.5 - 2 mg/kg) and tracheal intubation was facilitated with the use of vecronium bromide 0.04 mg/kg.

Anesthesia was maintained

with continuous infusion of ketamine 2 mg/kg/h till the end of the surgery.

Group III: (PK: Propofol ketamine group).

Anesthesia was induced with a sleep dose of propofol (1 mg/kg) and ketamine (1 mg/kg) and tracheal intubation was facilitated with the use of vecronium bromide 0.04 mg/kg.

Anesthesia was maintained with continuous infusion of ketamine 2mg / kg / h throughout anaesthesia combined with a continuous infusion of propofol 6 mg/kg/h for the first 15 minutes and then 4 mg/kg/h for the next 25 minutes and 3 mg/kg/h to the end of the surgery.

Group IV: (S: Sevoflurane group)

Anesthesia was induced with sevoflurane 8% in oxygen (100%) at 9 litre/m until loss of eye lash reflex, tracheal intubation was facilitated with use of vecronium bromide 0.04 mg/kg.

Anesthesia was maintained with sevoflurane 2% in 100% oxygen at 5 liters/min.

In all groups:

Muscle relaxation was maintained by vecronium bromide 0.01 mg/kg, the lungs was ventilated with 100% O2 with tidal volume 5 - 7 ml/kg and a rate of 14 B/min to maintain end tidal CO2 between 30 - 35 mmHg.

At the end of surgery, residual neuromuscular block was reversed with 40 µ/kg neostigmine and 20 µm/kg atropine.

Fluid maintenance and replacement of blood loss:

In all groups:

Fluid was maintained at a rate of 3 ml/kg/h lactated ringer's throughout the time of the operation.

Blood loss of less than 0.75 liter was replaced by ringer's solution 3 ml/1 ml blood, more than 0.75 liter was replaced by whole blood.

Transcranial Doppler ultrasonography:

A 2-MHz pulsed Doppler ultrasound device (Multidop MDX4 TCD8; DWL Elektronische System GmbH, Sipplingen, Germany) (Fig. 1) was used for transcranial

measurements of CBFV in the right middle cerebral artery (MCA). Insonation of the MCA was initiated at a depth of 45mm. Confirmation of MCA identity was achieved by increasing insonation depth to visualization of the bi-directional flow pattern typical of the birfurcation of the internal carotid artery into the MCA and anterior cerebral artery. After individual adjustment of Doppler variables such as gain, sample volume and power of ultrasound, the probe was handheld to obtain an optimal flow velocity trace and then fixed in position for the measurement period 32 (Fig. 2).

Timing:

Basal before epidural block and induction.

Induction: immediately after injection of induction drugs.

Intubation: one minute after intubation.

Every 30 minutes until the end of the surgery.

Continuous monitoring of ECG (lead II), pulse oximetry, mean arterial blood pressure and end tidal CO2, Data were recorded at the same times of measurement of transcranial Doppler, parameters.

Cerebral blood flow velocity and MABP changes were calculated as percent changes of baseline values. [33]

Statistical Analysis

- The statistical analysis of data done using excel program and SPSS program (statistical Package for Social Science, version 10).
- The description of the data was done in form of mean ± SD for quantitative data, and frequency and proportion for qualitative data.
- N.B The distribution of data normality done by Kolmograve Smirnove test, all revealed to be parametric.
- The analysis of the data was done to test statistical significant difference between groups.
- For quantitative data (mean ± SD), One Way ANOVA test was used to compare between more than 2 groups. Student t-test was used to compare 2 groups. Post hoc test was used (least significant difference). Paired sample t-test was used to compare the 4 groups at different times.

- Chi-square test was used for qualitative data.
- P was significant if ≤ 0.05 at confidence interval 95%.

Results

This study included 120 orthopedic patients who were admitted at Emergency Hospital, Mansoura University.

The epidural block was successful in all patients and transcranial doppler measurements were completed in all patients. Ventilatory variables remained unchanged throughout the study period for each patient. End tidal PCO2 was kept within the planned range (between 30 and 35 mmHg) throughout the study period. The middle cerebral artery mean flow velocity (Vmca) was increased significantly (P < 0.05) in group K, and group S, while it decreased significantly (P < 0.01) in group P compared with their basal values. The middle cerebral artery mean flow velocity (Vmca) showed significant differences between group K, group PK and group S compared with group P, being lower in group P with the least value at recovery time (240min) (table 1).[1] Propofol significantly (P < 0.05) decreased Vmca after induction of anesthesia from 60.9 ± 11.5 to 51.5 ± 12.8 indicating a significant reduction by 16%. Then the Vmca was significantly elevated from 51.5 ± 12.8 to 55.6 ± 12.8 by 8% immediately after intubation. This decrease continued throughout the whole study period till it reached its maximum at recovery time, when it reached to 32 ± 5.3 indicating a significant reduction by (33%) (Table 1, 4).

During ketamine anesthesia Vmca was increased immediately after induction from 61.3 ± 15 to 71 ± 17.1 by 17% and significantly increased from 71 ± 17.1 to 79 ± 15.4 by 32% 1 min after intubation and continued throughout the study period (Table 1, 4).

During propofol / ketamine anesthesia Vmca was reduced immediately post induction from 75.1 ± 11.1 to 68.1 ± 11 by 9% then was increased one minute after intubation from 68.1 ± 11 to 84.1 ± 10.8 by 13% then Vmca returned to decrease significantly till the end of the operation (Table 1, 4).

Sevoflurane anesthesia caused a significant increase of Vmca from 58.3 ± 14.2 to 64.7 ± 14.8 by 12% immediately after induction. Then it was increased from 64.7 ± 14.8 to 73.3 ± 17.7 by 27% immediately after intubation. This elevation of Vmca was continued significantly throughout the study period till recovery time (Table 1, 4).

There was a significant ($P < 0.001$) elevation of Vmca post intubation values compared with post induction values in the four groups (Table 1, 4).

A statistically significant increase in PI was observed in group P: after induction of anesthesia, at 120 min and 180 min compared with basal values. In group K, PI did not show any significant change allover the study period apart from one reading at 60 min when it significantly ($P < 0.05$) decreased compared with basal value. In group PK, there was a significant increase in PI at post induction, 60 min, 120 min and 150 min compared with basal value. In group S, PI did not show any significant change allover the study period apart from one reading immediately after intubation when it significantly ($P < 0.05$) decreased compared with basal value (Table 2).

PI was significantly higher in propofol group than in the other three groups throughout the study period apart from few readings where the values were reversed but significantly (at 180 min, 210 min and 240 min) in group K, at 210 min in group PK and at 240 min in group S.

There was a significant ($P < 0.05$) reduction in PI between post induction and post intubation values in group P and PK. There was a strong significant ($P < 0.002$) negative correlation between Vmca and PI in all groups (Table 2).

MABP during propofol anesthesia decreased significantly ($P < 0.05$) from 84.9 ± 9.5 to 74.8 ± 9.5 by 12% after induction of anesthesia, but the MABP was rose after intubation from 74.8 ± 9.5 to 91.3 ± 16.9 by 7% then the MABP decreased significantly again till the end of the operation. The mean

arterial blood pressure (MABP) was significantly increased in group K from 85.2 ± 11.9 to 94.5 ± 14.3 by 11% after induction of anesthesia reaching its maximum increase 1 minute after intubation 94.5 ± 14.3 to 102.4 ± 13.9 by 21% then the increase continued till the end of study period. In group PK, MABP decreased post induction from 85.6 ± 10.7 to 77 ± 9.2 by 10% then the it rose post intubation from 77 ± 9.2 to 95.6 ± 10.3 by 12% then at 30 min it decreased and the decrease continued till recovery time. In group S the MABP significantly ($P < 0.05$) decreased immediately after induction from 87.8 ± 9.9 to 77.1 ± 10.5 by 12% then it rose after intubation from 77.1 ± 10.5 to 93.8 ± 14.4 by 7%, then at 30 min MABP decreased from 93.8 ± 14 to 84.2 ± 12.6, and this decrease continued till recovery time. There was a significant difference in MABP between post induction and post intubation values with ($P < 0.05$) in all groups. MABP was significantly ($P < 0.05$) higher in group K than in group P, PK and S throughout the study period (Table 3, 5).

Table (1): The middle cerebral artery mean flow velocity (Vmca) (cm/sec), data presented by mean ± SD (Fig 3).

	Group (P)	Group (K)	Group (PK)	Group (S)
Basal	60.9 ± 11.5	61.3 ± 15.0	75.1 ± 11.4	58.3 ± 14.2
Post induction	$51.5 \pm 12.8^{+\#}$	$71.0 \pm 17.1^{+*\#}$	$68.1 \pm 11.0^{+}‡^{\#}$	$64.7 \pm 14.8^{+}§^{\#}$
Post intubation	$55.6 \pm 12.8^{+\#}$	$79.0 \pm 15.4^{+*\#}$	$84.1 \pm 10.8^{+}‡^{\#}$	$73.3 \pm 17.7^{+}§^{\#}$
30	$47.9 \pm 15.0^{+}$	$72.3 \pm 16.5^{+}*$	$72.6 \pm 10.6^{+}‡$	$65.3 \pm 18.1^{+}§$
60	$49.4 \pm 11.8^{+}$	$70.1 \pm 15.5^{+}*$	$69.1 \pm 15.7^{+}‡$	$64.4 \pm 18.2^{+}§$
90	$47.6 \pm 12.0^{+}$	$66.8 \pm 18.5^{+}*$	$70.1 \pm 10.5^{+}‡$	$64.2 \pm 17.5^{+}§$
120	$47.1 \pm 12.1^{+}$	$68.5 \pm 15.4^{+}*$	$69.9 \pm 10.6^{+}‡$	$64.5 \pm 16.5^{+}§$
150	$47.3 \pm 11.4^{+}$	$67.3 \pm 16.8^{+}*$	$70.0 \pm 10.5^{+}‡$	$65.2 \pm 16.7^{+}§$
180	$47.0 \pm 13.5^{+}$	$67.9 \pm 13.0^{+}*$	$70 \pm 10.8^{+}‡$	$62.7 \pm 17.5^{+}§$
210	$33.0 \pm 4.2^{+}$	$74.2 \pm 13.5^{+}*$	$69.9 \pm 11.5^{+}‡$	$69.8 \pm 26.5^{+}§$
240	$32.0 \pm 5.3^{+}$	$83.0 \pm 13.1^{+}*$	$63.8 \pm 17.0^{+}‡$	$32.0 \pm 17.4^{+}§$

$^{+}$ There is a significance when compared with the basal values ($P < 0.05$).
* There is a significance between group P and group K ($P < 0.05$)
‡ There is a significance between group P and group PK ($P < 0.05$).
§ There is a significance between group P and group S ($P < 0.05$).
# There is a significance between post induction and post intubation values ($P < 0.05$).

Table (2): The middle cerebral artery pulsatility index (PI), data presented by mean ± SD.

	Group (P)	Group (K)	Group (PK)	Group (S)
Basal	1.19 ± 0.28	1.15 ± 0.26	1.11 ± 0.15	1.27 ± 0.39
Post induction	1.46 ± 0.41$^{+\#}$	1.17 ± 0.46*	1.16 ± 0.13^{+}‡$^{\#}$	1.18 ± 0.40§
Post intubation	1.26 ± 0.30$^{\#}$	1.23 ± 1.51*	1.09 ± 0.20‡$^{\#}$	1.09 ± 0.40^{+}§
30	1.32 ± 0.40	1.12 ± 0.25*	1.11 ± 0.14‡	1.20 ± 0.36§
60	1.32 ± 0.35	1.07 ± 0.25^{+}*	1.15 ± 0.12^{+}‡	1.18 ± 0.39§
90	1.37 ± 0.46	1.1 ± 0.27*	1.13 ± 0.14‡	1.17 ± 0.28§
120	1.34 ± 0.39^{+}	1.08 ± 0.24*	1.15 ± 0.11^{+}‡	1.19 ± 0.28§
150	1.34 ± 0.36	1.17 ± 0.33*	1.17 ± 0.11^{+}‡	1.11 ± 0.31§
180	1.37 ± 0.34^{+}	2.14 ± 4.39*	1.18 ± 0.11‡	1.19 ± 0.33§
210	1.03 ± 1.86	1.05 ± 0.36*	1.18 ± 0.11‡	0.83 ± 0.48§
240	1.27 ± 1.87	1.39 ± 0.40*	1.18 ± 0.15‡	1.5 ± 0.50§

$^{+}$ There is a significance when compared with the basal values ($P < 0.05$).
* There is a significance between group P and group K ($P < 0.05$)
‡ There is a significance between group P and group PK ($P < 0.05$).
§ There is a significance between group P and group S ($P < 0.05$).
# There is a significance between post induction and post intubation values ($P < 0.05$).

Table (3): The mean blood pressure (mmHg), data presented by mean ± SD (Fig 4).

	Group (P)	Group (K)	Group (PK)	Group (S)
Basal	84.9 ± 9.5	85.2 ± 11.9	85.6 ± 10.7	87.8 ± 9.9
Post induction	74.8 ± 9.5^{+}*$^{\#}$	94.5 ± 14.3$^{+\#}$	77.0 ± 9.2^{+}‡$^{\#}$	77.1 ± 10.5^{+}§$^{\#}$
Post intubation	91.3 ± 16.9^{+}*$^{\#}$	102.4 ± 13.9$^{+\#}$	95.6 ± 10.3^{+}‡$^{\#}$	93.8 ± 14.4^{+}§$^{\#}$
30	82.5 ± 13.2^{+}*	90.0 ± 13.1^{+}	82.4 ± 8.5^{+}‡	84.2 ± 12.6^{+}§
60	78.6 ± 12.6^{+}*	92.1 ± 13.1^{+}	80.6 ± 8.0^{+}‡	81.2 ± 12.1^{+}§
90	78.4 ± 14.1^{+}*	90.8 ± 12.0^{+}	80.0 ± 8.4^{+}‡	78.2 ± 12.2^{+}§
120	76.7 ± 12.9^{+}*	91.0 ± 12.8^{+}	79.4 ± 7.8^{+}‡	80.0 ± 13.3^{+}§
150	77.3 ± 11.8^{+}*	89.3 ± 13.6^{+}	78.6 ± 8.5^{+}‡	79.5 ± 11.3^{+}§
180	78.7 ± 13.1^{+}*	87.7 ± 14.0^{+}	76.5 ± 6.6^{+}‡	81.4 ± 10.3^{+}§
210	66.0 ± 14.0^{+}*	86.2 ± 12.3^{+}	76.2 ± 6.2^{+}‡	81.5 ± 12.4^{+}§
240	66.0 ± 14.2^{+}*	89.0 ± 11.1^{+}	74.7 ± 5.5^{+}‡	89.0 ± 11.3^{+}§

$^{+}$ There is a significance when compared with the basal values ($P < 0.05$).
* There is a significance between group P and group K ($P < 0.05$)
‡ There is a significance between group K and group PK ($P < 0.05$).
§ There is a significance between group K and group S ($P < 0.05$).
# There is a significance between post induction and post intubation values ($P < 0.05$).

Table (4): The percentage change in Vmca data presented by mean ± SD.

	Group (P)	Group (K)	Group (PK)	Group (S)
Induction	–15.6 ± 13.2$^{+\#}$	17 ± 7.7$^{+*\#}$	–9 ± 5.5$^{+}‡^{\#}$	12.2 ± 19.3$^{+}§^{\#}$
Intubation	–7.9 ± 18.3$^{+\#}$	31.8 ± 19.6$^{+*\#}$	12.7 ± 8$^{+}‡^{\#}$	27.4 ± 23.6$^{+}§^{\#}$
30	–16.8 ± 24.8^{+}	19.3 ± 15.9^{+*}	–3.1 ± 3.8$^{+}‡$	12.3 ± 17.9$^{+}§$
60	–17.9 ± 20.7^{+}	16 ± 14.7^{+*}	–8.5 ± 15.8$^{+}‡$	11.4 ± 24.1$^{+}§$
90	–22.9 ± 12.1^{+}	10.3 ± 24^{+*}	–6.5 ± 4.4$^{+}‡$	11.3 ± 20.8$^{+}§$
120	–23.4 ± 10.1^{+}	13.4 ± 15.5^{+*}	–6.9 ± 4$^{+}‡$	12.4 ± 21.1$^{+}§$
150	–22.3 ± 7.8^{+}	9.5 ± 12.9^{+*}	–7.3 ± 3.9$^{+}‡$	13.3 ± 20.8 $^{+}§$
180	–21.9 ± 9.8^{+}	10.9 ± 11.3^{+*}	–7.9 ± 4.3$^{+}‡$	10.9 ± 17.4$^{+}§$
210	–35.4 ± 2.9^{+}	14.3 ± 23^{+*}	–7.1 ± 4.9$^{+}‡$	20.7 ± 25.1$^{+}§$
240	–33.3 ± 3.4^{+}	3.7 ± 15^{+*}	–8.5 ± 5.1$^{+}‡$	6.7 ± 7.8$^{+}§$

$^{+}$ There is a significance when compared with the basal values ($P < 0.05$).
* There is a significance between group P and group K ($P < 0.05$)
‡ There is a significance between group P and group PK ($P < 0.05$).
§ There is a significance between group P and group S ($P < 0.05$).
# There is a significance between post induction and post intubation values ($P < 0.05$).

Table (5): The percentage change in MABP data presented by mean ± SD.

	Group (P)	Group (K)	Group (PK)	Group (S)
Induction	–11.8 ± 6.2$^{+*\#}$	11 ± 8.5$^{+\#}$	–9.8 ± 6.3$^{+}‡^{\#}$	–11.9 ± 8.8$^{+}§^{\#}$
Intubation	7.4 ± 16$^{+*\#}$	20.7 ± 9.5$^{+\#}$	12 ± 5$^{+}‡^{\#}$	7.1 ± 14.5$^{+}§^{\#}$
30	–2.6 ± 13.4^{+*}	11.9 ± 8.8^{+}	–3.1 ± 7.9$^{+}‡$	–3.6 ± 14.3$^{+}§$
60	–7.1 ± 12.9^{+*}	8.4 ± 7.8^{+}	–5.1 ± 9$^{+}‡$	–6.8 ± 14.9$^{+}§$
90	–7.2 ± 15.9^{+*}	7.1 ± 8.3^{+}	–5.9 ± 9.9$^{+}‡$	–10.5 ± 13.6$^{+}§$
120	–10.3 ± 9.5^{+*}	7.3 ± 9.3^{+}	–6.3 ± 11.3$^{+}‡$	–8.5 ± 14.2$^{+}§$
150	–9.3 ± 11.5^{+*}	5.7 ± 10^{+}	–7.5 ± 10.6$^{+}‡$	–9.1 ± 11.2$^{+}§$
180	–8.9 ± 12.2^{+*}	5.9 ± 9.7^{+}	–8.8 ± 6.6$^{+}‡$	–7.8 ± 9.9$^{+}§$
210	–34.7 ± 8.5^{+*}	7.9 ± 8.6^{+}	–7.8 ± 8.2$^{+}‡$	–7.5 ± 5.7$^{+}§$
240	–34.7 ± 7.6^{+*}	1.1 ± 5^{+}	–5.5 ± 7$^{+}‡$	–11 ± 2.3$^{+}§$

$^{+}$ There is a significance when compared with the basal values ($P < 0.05$).
* There is a significance between group P and group K ($P < 0.05$)
‡ There is a significance between group K and group PK ($P < 0.05$).
§ There is a significance between group K and group S ($P < 0.05$).
# There is a significance between post induction and post intubation values ($P < 0.05$).

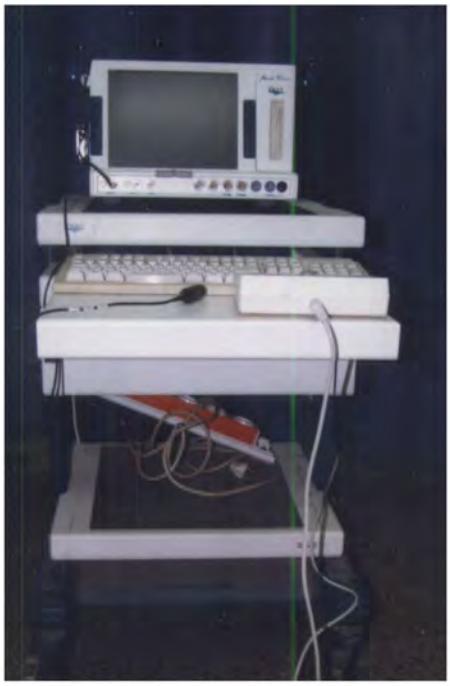

Fig (1): TCD multidop DWL used in (Mansoura University Emergency Hospital) Elektronische system GmbH, Sipplingen Germany.

Fig (2): Wheel Frame.

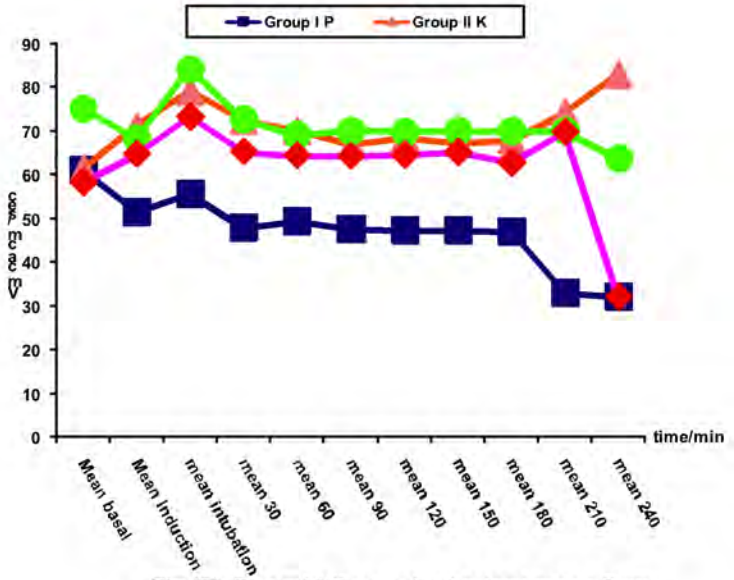

Fig (3): The middle cerebral artery mean flow velocity.

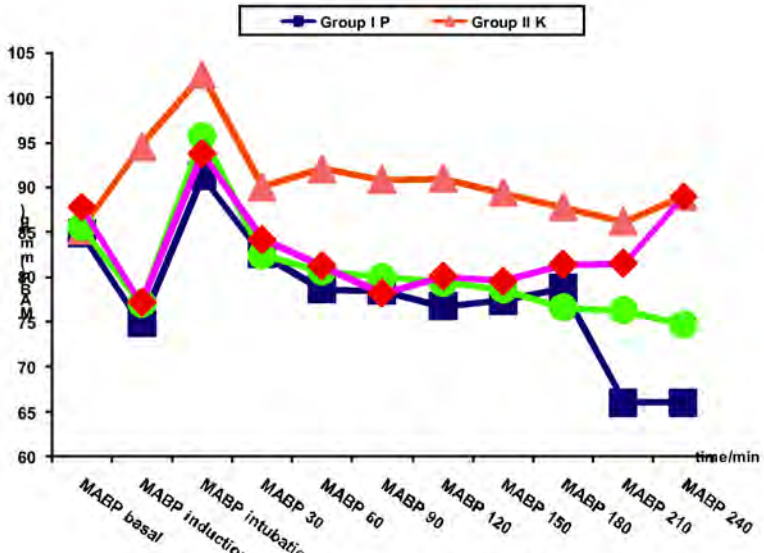

Fig (4): The mean arterial blood pressure.

Discussion

One of the challenges of neuroanesthesia is to maintain control of cerebral haemodynamics and hence intracranial pressure whilst facilitating a rapid emergence and recovery postoperatively.[34]

Cerebral autoregulation maintains cerebral blood flow (CBF) constant during changes in cerebral perfusion pressure (CPP) between 50 and 170 mmHg. Inhaled anesthetics impair both the ability to autoregulate (static autoregulation) and the rate of autoregulation (dynamic autoregulation) in a dose dependent manner.[5] Measurement of cerebral blood flow volume is required for identification and quantification of focal or generalized perfusion disturbances in the course of traumatic, infectious or neurodegenerative disorders [35] Total cerebral blood flow volume is defined as the blood flow through the right and left ICA and BA,[36] calculated the intravascular flow volume as the product of time averaged mean flow velocities and the cross-sectional area of the vessel.

Changes in CBF associated with different anesthetic techniques are of interest to neuroanaesthetists. Cerebral blood flow velocity (CBFV), as measured in the middle cerebral artery, is not a direct measurement of CBF [37] Changes in CBFV have been shown to correlate reliably with changes in CBF in presence of constant vessel diameter, which is preserved in conduction vessels of which the middle cerebral artery is an example. [38]

Transcranial Doppler sonography (TCD) is an exciting technology. TCD equipment is portable, inexpensive surprisingly useful in multiple situations, and well suited to address specific problems. Most importantly it provides real time information regarding the physiology of the itnracranial circulation. TCD provides information about the blood flow velocity and direction of flow in major intracranial arteries. The smallest TCD units are no longer than a bread box and are easily portable compared to other technologies used to study cerebrovascular anatomy and/or physiology, including MRI, CT, PET, SPECT and invasive angiography. TCD is very

inexpensive. TCD is used in a lab, the operating room or at the patients bedsides. [39]

Cerebral blood flow is one of the most important factors involved in the maintenance of brain metabolism CBF is known to be regulated by several different mechanisms (e.g. coupling, autoregulation). [40]

Transcranial Doppler sonography is now widely used as surrogate measure of cerebral blood flow. [41]

Interpatient variability in CBFV measurement can be due to variations in Doppler probe positioning, resulting in different angles of insonation (i.e. the angle at which the Doppler beam impacts on the artery).

Interpatient variability may result if the probe position changes during the course of the study. Thus in order to minimize these errors the Doppler probe should be fixed to the subject's head using an established wheel fram.[42]

The present research was primarily designed to study changes in cerebral blood flow during anesthesia with propofol, ketamine, propofol ketamine versus sevoflurane with the use of a transcranial Doppler ultrasonography.

The middle cerebral artery is a conductance rather than a resistance vessel. Changes in cerebral vascular resistance are caused by changes in arteriolar diameter, rather than by changes in the diameter of the arteries of the circle of Willis. [43]

In our study, the decrease in Vmca with propofol and propofol-ketamine immediately after induction of anesthesia is attributed to intrinsic vasoconstrictive properties on the cerebral vasculature.[14,38] In addition, propofol reduces CBF as a result of flow metabolism coupling [44] (table 4).

Several physiological factors are known to alter CBFV including PaCO2, surgical stimulation, body temperature, intrathoracic pressure and hypoxia. The end tidal CO2, ventilatory variables and FiO2 were kept constant throughout the study period and body

temperature and SPO2 remained unchanged. The epidural block was effective in all cases, eliminating cerebrovascular effects of surgical stimulation.[45,46] Because nitrous oxide increases cerebral blood flow velocity and CMRO2[47], we did not use it. Vecuronium bromide does not alter cerebral blood flow, hence do not affect cerebral autoregulation.[48] Anyhow, we did use it in all study groups.

We chose to use a propofol infusion regimen previously shown to produce steady plasma concentrations for up 90 minutes.[49] Cerebral perfusion pressure autoregulation and vasoreactivity to arterial carbon dioxide tension are maintained during propofol anesthesia.[10]

Propofol has been reported to decrease both cerebral metabolism and blood flow and increase cerebral vascular resistance in healthy adults even when MAP was kept constant with the use of phenylephrene infusion.[2] The intravenous anesthetic propofol has several properties that may be beneficial to patients with intracranial pathology.[40] Propofol reduces cerebral blood flow velocity, CBF and cerebral metabolic demand without affecting carbon dioxide reactivity and cerebral pressure autoregulation.[50] A number of studies have reported a significant reduction in CBFV occurring during propofol anesthesia.[38,51]

Our findings are consistent with[52]. They reported that propofol infusion results in 17% decrease in Vmca that outweighed the reduction (6%) in MABP. They used propofol 2.5 mg/kg as induction followed by infusion of [15,13], 11 mg/kg/h in 12 children aged one to 6 years requiring general anesthesia for urologic surgical received caudal epidural block. They stated that cerebral vasoconstrictive properties may be primarily responsible for this decrease in Vmca, also they demonstrated that propofol has the properties of an ideal neuroanesthetic agent.

[24]used propofol as induction and maintenance agent in 30 patients requiring general anesthesia for routine spinal surgery. They evaluated the effectiveness of

propofol 1.5 mg/kg induction and maintenance versus sevoflurane 7% MAC induction and maintenance and found that propofol reduced CBFV and systemic blood flow velocity and the reduction in CBFV was more pronounced than the reduction in systemic blood flow velocity, which might be due to lower cerebral metabolic demand.

[53]clearly demonstrated that propofol is the agent of choice during procedures that require intraoperative neurophysiologic monitoring of the spinal cord.

In our study Vmca was decreased after intubation with propofol anesthesia compared with the basal value (table 4). Laryngoscopy and tracheal intubation may cause significant cerebral and systemic hemodynamic responses, including tachycardia, hypertension and increased intracranial pressure. [54]

Controlling these responses on induction of anesthesia may be an important factor in improving outcome in neurosurgical patients.[55] The administration of propofol ablates the rise in ICP secondary to endotracheal intubation.[56] Propofol acutely reduces intraocular pressure secondary to endotracheal intubation.[57]

In the present study the maximum decrease in Vmca with propofol anesthesia occurred at recovery time (Table 4). This may be attributed to the fact propofol impairs its own clearance by decreasing hepatic blood flow.[58]

Our results showed that ketamine produced a significant change in Vmca in ketamine anesthetized patients with mechanically ventilated lung. Ketamine increased Vmca compared with awake state and throughout the study period.

[5]reported that ketamine induced increase in CBF velocity was not blocked by maintaining arterial pressure with esmolol and suggested that ketamine increases CBF velocity via a direct effect rather than a secondary effect caused by a change in arterial pressure. Another explanation for the ketamine-induced increase in CBF is that ketamine-induced

central nervous excitation stimulates cerebral metabolism.[59] reported that the ketamine-induced increase in CBF velocity was closely correlated to the increase in neuronal activation in healthy volunteers.

[60]concluded that S-ketamine increases cerebral blood flow while cerebral metabolic rate for oxygen (CMR O2) and glucose metabolic rate (GMR) does not change during ketamine anesthesia.

It was noticed that the addition of ketamine to propofol attenuated the decrease in Vmca and MABP caused by propofol alone and the attenuation was significant throughout the study period (Table 4). Our result was supported by [61] they stated that the excitatory properties of ketamine are blunted by propofol, and the sedative effects of the combination of ketamine and propofol were additive at hypotic and anesthesia end points.

This result is contradictory to some studies which showed that ketamine decreased electroencephalogram activity and decreased CBF in patients during propofol sedation or isoflurane / nitrous oxide anesthesia [6,62], on the other hand,[63] used propofol 2.5 mg/kg and ketamine 2 mg/kg IV induction and anesthesia was maintained with continuous infusion of propofol 6 mg/kg hr and ketamine, 2 mg/kg/hr in[38] patients scheduled for non neurologic elective surgery. They found ketamine did not produce any significant change in the middle cerebral artery mean flow velocity in propofol anesthetized patients with mechanically ventilated lungs, without neurologic complications, and attributed the inhibition of the increase in CBF during propofol-ketamine anesthesia to the possibility that propofol blocks ketamine induced increase in neuronal activity.

Comparison between inhalational and intravenous anaesthetic agents are difficult, owing to differences in pharmacokinetics, the difficulty in measuring intravenous drug concentrations in real time and the lack of equivalence for intravenous anaesthetics of minimum alveolar concentrations

(MAC) of inhalational anaesthetics.[64]

All volatile agents have been demonstrated to cause, cerebral vasodilatation which may be associated with inferior surgical conditions compared with propofol. In a recent study, the degree of cerebral swelling after opening the dura in adults cerebral tumors was found to be less in those patients receiving propofol compared with isoflurane or sevoflurane anesthesia. [14]

In the current study sevoflurane significantly elevated the middle cerebral artery mean flow velocity inspite of the reduction of the mean arterial pressure at 8 MAC induction and maintenance with 2 MAC sevoflurane. This increase in Vmca continued throughout the study period apart from the recovery time, at which the MAC of sevoflurane was reduced to 0.5%. Our results are comparable to the results of Mönkhoff et al. (2001), who used sevoflurane 1.5% as induction followed by 0.5% as maintenance in [23] children aged (0.4 - 9.7 yr) admitted for elective surgery, and found that sevoflurane significant decreased CBF.

Under normal circumstances, cerebral blood flow is coupled to the cerebral metabolic rate, with changes in metabolic rate matched closely by changes in CBF. This flow metabolism coupling has been shown to be altered but not abolished by volatile anesthetics such as halothane, isoflurane and desflurane. [65]

The net effect of an inhaled anesthetic on CBF depends on the cerebral metabolic rate before the drug is administered. When the cerebral metabolic rate is already depressed, the anesthetic increases CBF by vasodilatation, but should it be administered to patients who are in a “light plane of anesthesia” or awake, its cerebral metabolic depresent effect leads to decrease in CBF. Hence, although the major effect on CBF is vasoconstrictive secondary to flow metabolism coupling at lower concentrations, the direct vasodilatory effect predominates with increases in CBF and loss of cerebral autoregulation at high concentrations. [10]

Sevoflurane have less direct vasodilatory effect than either isoflurane or desflurane and sevoflurane (up to 1.5 MA) does not alter red blood cell velocity.[44] The cerebral vasculature remains capable of responding to changes in perfusion pressure during 1.5 MAC sevoflurane anesthesia when it is abolished during similar MAC concentrations of isoflurane and desflurane presumably because of cerebral vasodilatation. [5]

In another study the workers recorded that 1.5 MAC of either sevoflurane or isoflurane increased cerebral blood (17%, 25% respectively) and decreased cerebral metabolic rate of oxygen (26%, 38% respectively). [19]

Using PET (positron emission tomography) [26] demonstrated that cerebral blood flow during sevoflurane anaesthesia is dose dependent. The drug induces a decrease in cerebral blood flow in all regions of the brain of < 1 minimum alveolar concentration (MAC), whereas CBF gradually increases in the frontal cortex at 1-1.5 MAC.

On the other hand, [66] investigated the influence of sevoflurane on CBFV when used as the single anesthesia agent, compared with awake patient. In addition, they reported a reduction in CBF in the absence of nitrous oxide. Moreover, [44] reported reduced brain oxygen consumption without an effect on CBFV during inhalation of high concentration of sevoflurane during propofol anesthesia. Also, [24] found that sevoflurane reduced CBFV compared with awake state when anesthesia was induced with 7% sevoflurane and maintained with 1.5% versus propofol. At present the most widely accepted explanation for the different effects of sevoflurane on cerebral blood flow is that at low concentrations sevoflurane processes an indirect vasoactive action secondary to flow-metabolism coupling so that with the reduction in cerebral metabolism during anaesthesia CBF is also reduced. With higher concentrations the direct vasodilatory effects of sevoflurane are more important leading to increase in cerebral blood flow. [67]

The most important methodological limitation of TCD sonography is the fact that it is unable to

measure cerebral blood flow directly. Only changes in cerebral blood flow velocity as measured in the vessel is proportional to the change in CBF in the corresponding vascular territory. The prerequisite of the measurements is to accept that the blood flow changes during TCD measurement may only reflect changes in CBF when the diameter of the large vessels remains constant. [67]

For animal experiments inhalational agent exerts its dilative effect on both large and small cerebral vessels via ATP-sensitive potassium-channel activation. [25] Nitrous oxide increases cerebral metabolism and CBF in humans and animals. [68]

[69] reported that administration of 50% nitrous oxide with 1 MAC and 1.5 MAC sevoflurane increases Vmca (2.66%, 3.99% respectively). The mechanism by which nitrous oxide increase CBFV are secondary to its excitatory effects on cerebral metabolism. [70]

[47] used 1 MAC sevoflurane in 30% oxygen with intermittent positive pressure ventilation with either nitrous oxide or air and found that nitrous oxide increases cerebral blood flow velocity in healthy children anaesthetized with 1 MAC sevoflurane.

Our finding support the concept of 11 who stated that sevoflurane increased Vmca by 17% at 1.5 MAC and sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect. However, his effect is less than that reported for halothane, isoflurane and desflurane at equipotent anesthetic concentrations. They stated that these findings suggest that sevoflurane has a cerebral hemodynamic profile favoring its use in neuroanesthesia. This conclusion was based on their comparison of inhalational anesthetics (halothane, isoflurane and disflurane) but not with intravenous agents like propofol.

Our study showed that PI significantly increased in group P compared with groups K, PK and S. A statistically significant increase in PI was observed after induction of anesthesia in propofol group and there is a significant negative correlation between Vmca

and PI in all groups (Table 5). Our finding agreed with the results of [63] who reported that when the diameter of MCA is nearly constant, the reduction in Vmca associated with the an increase in PI during propofol or propofol-ketamine anesthesia is explainable as a decrease in CBF. [71] demonstrated that mean PI increased with advancing age, especially in subjects more than 40 years of age. In our study the age of groups between 20 to 40 years of age, which ablates the effect of advancing age on PI.

Moreover, other investigators reported that increased PI usually occurs because of increased cerebral peripheral resistance secondary to increased intracranial pressure or hypocapnia while decreased PI is typically displayed by vessels supplying an arteriovenous malformation due to decreased peripheral resistance or downstream to high grade stenosis. [72]

In another study the workers recorded that no changes in PI at 20 - 50 mmHg PCO2. This indicates that the resistance of the middle cerebral artery did not change and concluded that PI does not change significantly and CBFV correlates with CBF. They used 5 mg/kg thiopental for induction of anesthesia which was maintained with either sevoflurane 1.7% or 1.1% isoflurane with 67% nitrous oxide in oxygen with epidural block using 1% mepevacaine in 30 patients. [73]

The significant elevation in MABP in ketamine group compared with other groups and with basal values throughout the whole period of the study (with its maximum elevation immediately after intubation) (table 6) attributed to its stimulation to the cardiovascular system which is usually associated with increase in blood pressure, heart rate and cardiac output. Ketamine stimulates the circulatory system by attenuation of baroreceptor function through the effect on NMDA receptors in the nucleus tractus solitaries. [74] Ketamine also causes the sympathoneuronal release of norepinephrine. [75] Our finding support the concept of 60 who stated that ketamine infusion with serum concentration 30 ng/ml caused

elevation of MABP by 15.3% using positron emission tomography. There is weak positive correlation between the MABP and Vmca in our study. There are some explanations for the reported ketamine-induced increase in CBF. Ketamine is reported to increase CBF in part because of an increase in MABP and a direct effect on the brain. [76]

The significant reduction in MABP during propofol anesthesia in this study is due to direct myocardial depressant effects and vasodilatation. [77]

The maximum reduction in MABP that occuerd at recovery time is attributed to the cumulative effect of poropofol. This reduction in MABP outweighs the, decrease in Vmca. Propofol's cerebral vasoconstrictive properties may be primarily responsible for this decrease in CBFV.[52]

[76] was administrated norepinephrine and phenylephrine infusion in 40 patients scheduled for lumbar laminectomy anesthetized with isoflurane or propofol infusion, they found a significant increase in MABP and Vmca with norepinephrin and phenylephrine was observed during isoflurane anesthesia but not during propofol anesthesia.

[24] found a significant reduction in MABP during propofol anesthesia and the cerebral autoregulation is preserved, therefore, the reduction in MABP values during propofol anesthesia can't explain the observed reduction in CBFV values.

The MABP values during propofol-ketamine anesthesia administration were slightly and insignificantly lower than those during the awake state. However, it is unlikely that this slight decrease in MABP influenced the Vmca during the anesthesia. Propofol does not affect autoregulation of CBF in rats 40 or humans .[10] If autoregulation functions normally, CBF does not change when cerebral perfusion pressure increases or decreases within certain range. In the present study, MABP did not decrease to < 60 mmHg. Thus, the differences in MABP would not account for the low Vmca during anesthesia. Our

finding supports the results of [63] who proved that ketamine does not influence Vmca during propofol anesthesia.

The reduction in MABP in sevoflurane group throughout the study period is attributed to the decrease in systemic vascular resistance. [78]

Despite this decrease in MABP, a significant increase in Vmca observed in this group which suggests a direct cerebral vasodilatory effect which partially counteracts the decrease in CBF associated with the reduction in CMR (cerebral metabolic rate). This hypothesis is supported by the investigation by [44]

[79] found that the use of 1 MAC sevoflurane anesthesia caused a decrease in global CBF as a consequence of reduction in CMR. They used 1 MAC of sevoflurane as a maintenance anesthesia after induction with etomidate 0.3 mg/kg and nor-epinephrine was administered IV infusion 2 - 5 μg/min to keep the MABP constant compared with baseline values.

In the present study, the significant increase in HR in all groups immediately after intubation is attributed to that tracheal intubation may cause systemic hemodynamic responses, including tachycardia, and hypertension. [54]

HR was decreased but insignificantly with propofol anesthesia throughout the study period (Table 3). This decrease is attributed to the effect of propofol either on the baroreflex. [80] Propofol resets or inhibits the baroreflex, thus reducing the tachycardia response to hypotension. [81] It attenuates the HR response to atropine in a dose-dependent manner.[82]

The highly significant decrease at most of study period is attributed to the known depressant affect of propofol on cardiovascular system. [77]

The insignificant reduction in HR that occurred at 30min, 120min, 210min and 240min may be methodological in nature. The significant increase in HR during ketamine anesthesia: immediately after induction, postintubation

and at 30min is due to the cardiovascular stimulant effect of ketamine. The mechanism by which ketamine stimulates the circulatory system seems to be ketamine attenuates baroreceptor function through an effect on NMDA receptors in the nucleus tractus solitaries. [74] The insignificant decrease in HR starting at 60min and throughout the study period till recovery time is attributed to that a second dose of ketamine produces hemodynamic effects less than or even opposite those of the first dose [83]

[84] suggested that is also possible to lessen the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without benzodiazepine.

In the current study the addition of ketamine to propofol anesthesia increased HR immediately after induction and intubation, due to sympatho-adrenal reflex of intubation. The insignificant decrease in HR after that and throughout study period, may be attributed to the effect of propofol on baroreceptors. [85]

The significant increase in HR in sevoflurane group at post intubation time is due to sympathoadrenal effect of laryngescopy and intubation.[86]

Because of the use of 100% O2 in this study that there was no significant alteration in the oxygen saturation in all study patients. Also, the end tidal carbon dioxide was adjusted to be within the required physiological range. The influence of CO2 partial pressure and oxygen saturation (and oxygen tension) on vessel diameter and Vmca is well known. Therefore both variables were maintained constant throuughout the application of anesthesia

Conclusion

We found a decreased both cerebral blood flow velocity and systemic blood pressure at propofol anesthesia and an increase in systemic blood pressure, cerebral blood flow velocity at ketamine and sevoflurane anesthesia. These findings may have important implications in the neurosurgical setting.

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TIVA VERSUS SEVOFLURANE EFFECT ON CEREBRAL BLOOD FLOW A TRANSCRANIAL DOPPLER STUDY

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URINARY TRACT INFECTION IN INFANTS AND CHILDREN WITH DIARRHEA

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Abstract

The urinary tract is the most common site for serious bacterial infections in infants and young children. The epidemiology of UTI is confounded by the variability and non-specificity of signs and symptoms. Diarrhea may be the presenting symptom in younger children with UTI. ***Objective:*** *to estimate the incidence of UTI in infants and children with diarrhea and to identify the clinical correlates which may help to identify UTI cases.* ***Methods:*** *we studied 160 patients presented with diarrhea aged 4 weeks to 5 years, admitted to Benha children hospital, in the period from April to November 2011. Blood sample was taken for CBC, CRP, urea and creatinine. Urine samples were taken from all patients and examined by dipstick; in dipstick positive cases (either for leucocytes or nitrite), another sample for culture was taken.* ***Results:*** *one hundred sixty patients were included in the study. The incidence rate was 6.8%, 63.6% of them were females. The majority of the patients (45.5%) were between 2 to 5 years of age. E.coli was the most common isolated organism (90.9%). Fever, recurrent diarrhea and artificial feeding were significantly associated with UTI.*

Conclusion: *The results of our study shows that female, fever and history of recurrent diarrhea are significantly associated with UTI cases which presented by diarrhea.*

Introduction

Urinary tract infections (UTIs) in children are common and a major source of morbidity. The incidence of UTIs in childhood is not precisely known because it is not a reportable disease and in many cases, especially in infants, UTI

are probably under diagnosed[1]. Although UTI is infrequently associated with mortality, delay in the treatment of UTI can lead to vesico-ureteral reflux and renal scarring[2]. Recognition that UTI can cause renal parenchymal and functional loss has prompted recommendations for rapid diagnosis and evaluation of UTI with genitourinary imaging techniques and tests. In infants, UTI is a common cause of fever and may be the most common cause of renal parenchymal damage and loss[3].

Diarrheal disease is a fundamental threat to the health of children in the developing world. Second only to respiratory infection, diarrheal disease is a leading cause of death among the world's children, responsible for approximately two million deaths annually, under the age of 5[4]. Diarrhea may be the presenting symptom in younger children with UTI[5].

Objective :

The present study was undertaken to estimate the incidence of UTI in infants and children presenting with diarrhea and to identify the clinical correlates which may help to identify UTI cases.

Patients and Methods

One hundred and sixty patients enrolled within the study aged 1 month to 5years from pediatric department, Benha Children's Hospital, in the period from April to November 2011.

Inclusion criteria : Diarrhea less than 2 weeks is the presenting complaint and without use of antibiotics during the previous 48 hours.

1- Complete detailed history was obtained from all cases with special emphasis on:

- Frequency, consistency and volume of stool, the duration of diarrhea, and presence of mucus or blood in it.
- Child activity, frequency of urination, information about oral intake or thirst. Associated symptoms, such as fever preceding the onset of diarrhea, vomiting, abdominal pain (unexplained excessive crying in young infants).
- Any urinary symptoms like e.g.: interrupted stream seen by the mother, straining & crying with micturation.

2- Complete physical examination was performed, with particular attention to signs of dehydration.

3- Investigations :

All samples were taken after parent consent and before start any medications.

A- Blood sample for:

- Complete blood count, C-reactive protein
- Blood urea and serum creatinine.

B- Urine sample was taken from all patients. In infants, the application of collection bag after disinfection of the skin of the genitalia. In toilet trained children, the urine sample was midstream. The sample was tested immediately using urine dipstick. If the tested urine was positive for nitrite or leukocyte esterase, the patient was considered suspicious of UTI, and then urine culture was done.

C- The urine culture was withdrawn after disinfection of the genitalia; it was midstream in toilet trained and by catheterization in infants. Then the sample was sent immediately to the laboratory for culture. If the culture shows > 100,000 colony-forming units/mL of a single pathogen, the child was considered to have a UTI.

D- A stool sample was evaluated to determine number of pus cells, if >10/hpf, it was invasive diarrhea and if <10 it was non invasive diarrhea.

E- All patients who had UTI were subjected to ultrasound examination of the kidney, ureter and bladder, to exclude congenital anomalies.

Statistical methodology:

The collected data were tabulated and analyzed using the suitable statistical methods":

1- Test of proportion (Z test) which used to compare between 2 percentages.
2- Student t test which used to compare between 2 means and standard deviations of 2 groups.

3- Paired "t" test which used to compare between 2 means of the same group before and after treatment.

Results

The overall incidence of UTI in children presenting primarily with diarrhea was 6.8%. As regard the sex distribution of UTI cases, we found that 63.6% of our cases were females.

The distribution of our cases according to age was : (9.1%) in 1:5 months, (36.4%) in 6:11 months, (9.1%) in 12:23 months and (45.5%) in 2:5 years.

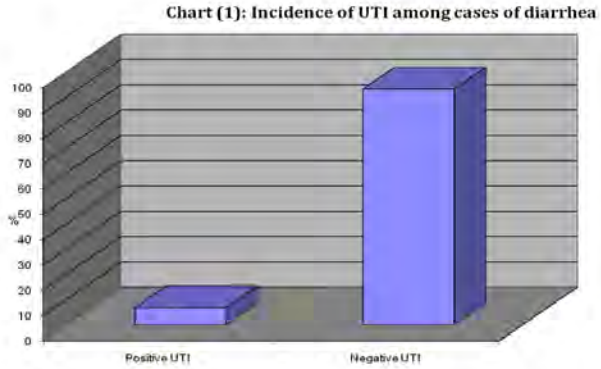
The incidence of UTI amongst those with malnutrition (weight less than 3rd percentile of the standard for age and sex) was 6.1% as compared to 7.5% among those with no malnutrition.

As regard the incidence of vomiting among UTI cases was 63.6% with no significant difference. In our study, the duration of diarrhea (≥7 days) among UTI cases was 81.8% as compared to 18.2% amongst those without UTI, which was statistically significant association. Fever among UTI cases was 100% as compared to 23.5% amongst those without UTI.

In our study, urinary symptoms like (interrupted stream seen by the mother, straining &crying with micturation) was present in 45.5% of UTI cases, which was statistically insignificant association. As regard history of recurrent diarrhea, it was present in 81.8% of UTI cases, which was statistically significant association fig. (1).

As regard the distribution of UTI cases according to degree of dehydration 54.5% no dehydration, 45.5% dehydrated which was statistically insignificant.

In our study, as regard type of feeding, among UTI cases 81.8% was artificially fed, which was statistically significant association with UTI cases. We found that E.coli was the most common isolated organism (90.9%) of cases, followed by klebseilla (9.1%) of cases.



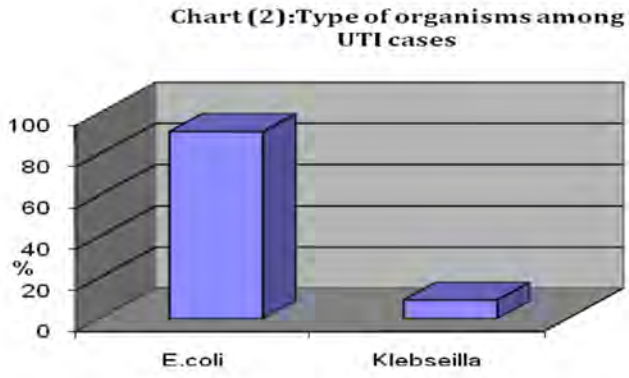


Figure (1): Clinical data of UTI cases.

variables	+ve UTI		P value
Sex	Males	36.4 %	> 0.05
	Females	63.6 %	
Fever	Present	100 %	--
	Absent	0.0 %	
Type of feeding	Breast	18.2 %	< 0.05
	Artificial	81.8 %	
Urinary symptoms	Present	45.5 %	> 0.05
	Absent	54.5 %	
H .of recurrent diarrhea	Present	81.8 %	< 0.05
	Absent	18.2 %	

Discussion

The urinary tract is a common site of infection in the pediatric population.Unlike the generally benign course of urinary tract infection (UTI) in the adult population, UTI in the pediatric population is well recognized as a cause of acute morbidity and chronic medical conditions, such as hypertension and renal insufficiency in adulthood. The true incidence of pediatric UTI is difficult to determine because there are varying presentations that range from an absence of specific urinary complaints to fulminate urosepsis[6].

Diarrhea is a common manifestation of UTI in this period. There have been a limited number of studies on the correlation between UTI and acute diarrhea and it is still not clear when to investigate for UTI in young children presenting with diarrhea[7].

Our study was undertaken to estimate the incidence of UTI in infants and children presenting with diarrhea and to identify the clinical correlates which may help to identify UTI cases.

The overall incidence of UTI in children presenting primarily with diarrhea was 6.8% in agreement with Thakar et al., 2000[7] 8 cases (8%) out of 100 children with diarrhea have UTI. Also 8 cases (6.7%) out of 120 children with diarrhea have UTI[8].

As regard the sex distribution of UTI cases, we found that 63.6% of our cases were female which is consistent with Shah et al., 2008[9] study where (65.3%) were females. Also agree with[8] 87.5% were females, Thakar et al., 2000.

As regard the age distribution of our cases, the majority of UTI cases were in the following age groups : (45.5%) were between 2:5 years and (36.4%) between 6:12 months. While in other reports (11.4%) in 12:24 months, (39.2%) in 3 : 6 years[2].

In other study (12.5%) in 0:6 months, (75%) 6:12 months and (12.5%) 12:24 months[7].

Shah et al., 2008[9] found that (20.2%) were 24 to 47 months old, and (32.7%) were greater than 4 years of age.

The incidence of UTI among those with malnutrition (weight less than 3rd percentile of the standard for age and sex) was 6.1% as compared to 7.5% amongst those with no malnutrition, in contrast to other investigators. UTI was found in 15.2% of malnourished patients and (1.8%) controls[10]. Also UTI was found in 17.2 % of severe malnutrition cases & 4.2% among cases without malnutrition[7].

As regard the incidence of vomiting among UTI cases was 63.6% with no significant difference.

In our study, the duration of diarrhea was (≥7 days) among UTI cases in 81.8% compared to 18.2% amongst those without UTI, which was statistically significant.

In this study, fever among UTI cases was 100% compared to 23.5% amongst those without UTI, in agreement with Bay and Anacleto (2010)[2] who found that fever was the most common presenting symptom, accounting for 63.6% of patients. Also Brein et al., 2011[11] said that fever was present in 69% of UTI cases, and[3] found that 67% of cases with UTI were feverish.

In our study, urinary symptoms (interrupted stream seen by the mother, straining & crying with micturation) were present in 45.5% of UTI cases, with statistically insignificant association, in agreement with[12] who found that urinary symptoms was present in 8.6% (insignificant).

As regard history of recurrent diarrhea, it was present in 81.8% of UTI cases, which was statistically significant, in agreement with[7]. Thakar et al., 2000 who found that 75% of UTI cases had history of recurrent diarrhea.

As regard the distribution of UTI cases according to degree of dehydration 54.5% had no dehydration and 45.5% dehydrated which was statistically insignificant association, in contrast to[7] : among UTI cases 75% were dehydrated.

In our study, as regard type of feeding among UTI cases 81.8% of the cases was artificially fed, with statistically significant

difference with breast fed ,in agreement with study that found that ongoing exclusive breast feeding has been shown to be associated with a significantly lower risk of UTI.[13]

Ladomenou 2010 found that prolonged exclusive breastfeeding was associated with fewer infectious episodes. In contrast to [15] The study that found no significant difference between the rates of positive urine cultures in exclusively breast fed and formula-fed infants.

We found that E.coli was the most common isolated organism from the cases, and secondly klebseilla (9.1%) of cases in agreement with [9] who found E. coli to be the cause of UTI in 82.7% of his patients, followed by Enterococcus spp, Staphylococcus spp, and then Proteus mirabilis/ Klebsiella / Streptococcus. Also agree with the study carried on 120 children with diarrhea, who found that E.coli in 87.5% of cases and 12.5% was pseudomonas[8].

Conclusion

In children presenting with diarrhea, it would be wise to screen febrile infants specially females with recurrent diarrhea for UTI.

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gram (s)	g	minute (s)	min
milligram (s)	mg	second (s)	S
microgram (s)	ug	centimeter (s)	cm
nanogram (s)	ng	cubic millimeter	cmm
micrometer	um	millilitre (s)	ml
millicurie(s)	mCi	milliequivalent	mEq
molar	mol/l	millimole	mmol

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