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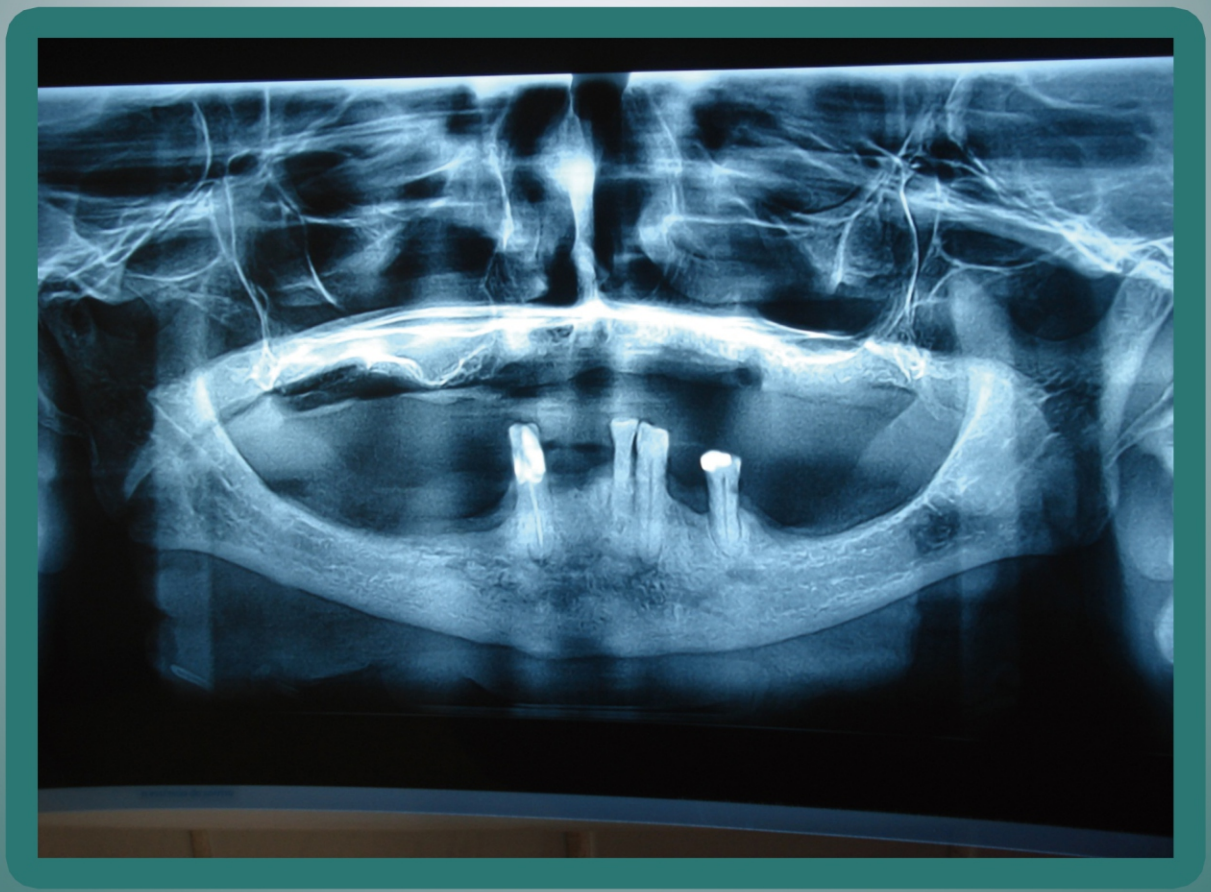

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Clinical Safety and Efficacy of Platelet-Rich Plasma in Wound Healing

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Abstract

Background: Platelet-rich plasma has been extensively used in several clinical settings. However, there still a lack of conclusive evidence concerning the benefits of platelet-rich plasma in the field of wound healing. We aimed to evaluate the safety and the efficacy of autologous platelet-rich plasma in acute wound healing. **Methods:** This prospective study enrolled forty adult patients of both sexes and aged between 18 - 50 years. All patients in need for split-thickness skin graft were included in our study. The donor sites were randomly divided into two equal halves: the platelet-rich plasma side, which was injected with recently activated platelet-rich plasma; and the control side, in which the conventional method of dressing was used. Measurement of the platelet count and transforming growth factor-B1 concentration in each platelet-rich plasma preparation and the whole blood was done for all patients. Clinical monitoring of the donor sites was done every 7 days for 3 weeks, regarding pain perception, epithelialization surface area and possible side effects of the platelet-rich plasma. Histopathological monitoring was done on the 7th postoperative day. **Results:** The platelet count was increased about 3.5 folds and transforming growth factor-B1 was increased 2.4 folds in the platelet-rich plasma compared to the patients' blood. The platelet-rich plasma side had significantly lower pain scores at day 7 (4.8 ± 0.18 vs 5.9 ± 0.07) and day 14 (1.4 ± 0.11 vs 1.9 ± 0.09) postoperative ($p = 0.002$ and $p = 0.004$, respectively) and had significantly higher rate of epithelialization at day 7 (9.8 ± 0.35 cm^2 vs 7.5 ± 0.32 cm^2) and day 14 (38.4 ± 0.36 cm^2 vs 36.9 ± 0.42 cm^2) postoperative ($p < 0.001$ and $p = 0.039$, respectively), while at day 21 postoperative, there was no significant difference between both sides. There was no significant difference between both sides regarding the incidence of complications. The platelet-rich plasma side showed intact epithelium, differentiation of the cells in stratum spongiosum and stratum granulosum, neovascularization and earlier collagen deposition. **Conclusion:** The platelet-rich plasma is safe and effective adjuvant in the management of acute wounds. However, we recommend for larger clinical trials for standardized method for PRP preparation and better understanding of the efficacy of this blood product.

Keywords

Platelet-Rich Plasma (PRP), Wound Healing, Acute Wounds

1. Introduction

Wound healing is a dynamic and complex process controlled by interacting signals that regulate a myriad of cellular and molecular events. Therefore, no single agent can efficiently mediate all aspects of the wound healing process [1]. Platelets not only assist in clot formation, but also are a rich source of a host of growth factors and cytokines essential to wound healing [2]. Platelets activation by proteins as thrombin causes the α-granules to fuse with the platelet cell membrane releasing these growth factors, such as transforming growth factor-b (TGF-b), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and insulin-like growth factor (IGF) [3]. These growth factors are crucial in attraction of mesenchymal cells into the wound, enhancing their proliferation and promoting extracellular matrix deposition during the healing process [4].

When the natural healing process becomes interrupted by either wound factors (*i.e.* infection) or patient factors (*i.e.* comorbidities), the standard wound care is not enough to improve the healing outcome and advanced therapeutic modalities are always required, such as negative pressure therapy, hyperbaric oxygen therapy, low level laser therapy, growth factors and platelet-rich plasma (PRP) [5] [6]. Platelet-rich plasma is a blood derivative that contains a higher concentration of platelets, about 3 to 5 times the normal value [7]. PRP also contains a variable number of white blood cells and red blood cells according to the preparation method [8].

PRP mechanism of action is still questionable; however, it may act by enhancing the natural healing process, as the molecules contained within the PRP preparation act as adjuvant in the inflammatory and proliferative phases [9]. Although PRP applications are now widely used in many medical fields, including orthopedics, maxillofacial surgery, cardiothoracic surgery, plastic surgery, trauma surgery and wound healing, their efficacy in human subjects is still debated [10]. We aimed in this study to evaluate the safety and the efficacy of autologous platelet-rich plasma (PRP) as an aid in the healing process of acute wounds; the donor site of the split-thickness skin graft (STSG) was used as a model of acute wounds.

2. Materials and Methods

This prospective study enrolled forty adult patients, of both sexes (28 males and 12 females), aged between 18 - 50 years (mean—28.6 years), who were admitted to the Plastic Surgery Department, Tanta University Hospitals between August 2013 and August 2015. All patients had post-traumatic raw areas and were in need for STSG obtained from the thigh were included in our study. Patients with chronic diseases such as hepatic insufficiency and diabetes, those on steroids or immunosuppressive therapy, or

those with blood and collagen diseases as well as smokers were excluded from the study. All materials and procedures were approved by the Ethics Committee of the University. Informed consent was obtained, after detailed description of the procedure, from all patients.

2.1. Preparation of Platelet-Rich Plasma (PRP)

Before the surgical phase, 50 ml of the autologous venous blood was withdrawn from every patient and collected in a sterile tube containing 5 ml of citrate phosphate dextrose (CPD) as anticoagulant. The blood sample was centrifuged at room temperature for 5 min at 2500 r.p.m in the centrifuge machine (eppendorf centrifuge 5804). After the 1st centrifugation, the blood was separated in red blood cells and plasma. The red cells were removed, and the remaining plasma was centrifuged at 3500 r.p.m for 5 min. After the 2nd centrifugation, the centrifuge was separated into platelet-rich plasma (PRP) at the bottom layer; constituting 10% of the withdrawn blood volume and platelet-poor plasma (PPP) at the upper layer. Measurement of the platelet count and the transforming growth factor-B1 concentration using the DRG TGF-B1 ELISA kit in each PRP preparation and the whole blood were done for all patients.

2.2. Surgical Procedure

All surgical procedures were done under general anaesthesia. A STSG was harvested from the thigh using the Humby's Knife. The donor sites were randomly divided into two equal halfs: the PRP side, which was injected with recently activated PRP by mixing with 2% calcium chloride at a ratio 7:1; and the control side, in which the conventional method of dressing was used. Vaselinized gauze and secondary absorbant layer dressing were used to cover the donor sites in all patients. The time needed from preparation till injection of the activated PRP was recorded for all patients.

2.3. Postoperative Care and Monitoring

All patients were discharged on the 2nd postoperative day and recalled again once weekly for one month and once monthly for 3 months. Clinical monitoring of the donor sites was done every 7 days for 3 weeks, regarding pain perception, epithelialization surface area and possible side effects of the PRP (reaction to PRP-infection-hypertrophic scar-hyperpigmentation). The pain was measured using the visual analogue scale (0 - 10). Histopathological monitoring was done on the 7th postoperative day. Under local anaesthesia (0.5% xylocaine), a 3-mm punch biopsy was taken from the PRP and the control sides then fixed with 10% paraformaldehyde. The paraffin fixed specimens were stained using the H&E stain. Thereafter, examination of the specimen was done regarding keratin formation, epidermal thickening, infiltration of the dermis with inflammatory cells, neovascularization and collagen deposition.

The data collected for statistical analysis were expressed as means and standard error of the means (SEM). Student's t-test and Chi-square test were used for comparative analysis. Statistical significance was defined as p value of <0.05.

3. Results

Over a two-year period, forty patients subjected to STSG and PRP application to one half of the donor site. As shown in Table 1, there were significant increase in the mean concentrations of the platelets and TGF-B1 in the PRP compared to the patients' blood ($p < 0.001$), with the platelets being about 3.5-fold higher, and TGF-B1 about 2.4-fold higher, than in the serum. The time needed from preparation till injection of the activated PRP ranged from 45 to 82 min (mean—68.3 min).

Table 2 shows that, there was no significant difference between the PRP side and the control side in the pain scores at day 0 and day 21 postoperative, but the PRP side had significantly lower pain scores at days 7 and 14 postoperative ($p = 0.002$ and $p = 0.004$ respectively). Furthermore, there was improvement in the wound healing in the PRP side as evident by the significant increase in the epithelialization surface area in the PRP side at days 7 and 14 postoperative ($p < 0.001$ and $p = 0.039$ respectively), while at day 21 postoperative there was no significant difference between both sides. One patient had infection and another developed hypertrophic scar at both sides, while two patients had hyperpigmentation and hypertrophic scar at the PRP side only. There was no significant difference between both sides regarding the incidence of complications.

As regards histopathological monitoring, the PRP side (Figure 1) showed differentiation of the epidermal keratinocytes with intact epithelium, differentiation of the cells in stratum spongiosum and stratum granulosum, neovascularization and beginning of collagen deposition, while the control side (Figure 2) showed minimal epithelial covering with extensive areas of ulceration, edema below the epidermis with extensive perivascular inflammatory infiltrate with acute inflammatory cells mainly neutrophils, undifferentiated keratinocytes in stratum spongiosum and stratum granulosum and minimal collagen deposition.

Table 1. Laboratory data (mean ± SEM).

Variable	Patient's blood	PRP	*p* value
Platelets count (cell/mm^3)	210.250 ± 9.38	742.450 ± 36.68	<0.001
TGF-B1 concentration (ng/dl)	670.0 ± 27.94	1650.0 ± 65.52	<0.001

Table 2. Outcome clinical data.

Variable	PRP side (n = 40)	Control side (n = 40)	*p* value
Pain scores[a]			
Day 0	7.9 ± 0.17	8.2 ± 0.19	NS
Day 7	4.8 ± 0.18	5.9 ± 0.07	0.002
Day 14	1.4 ± 0.11	1.9 ± 0.09	0.004
Day 21	0.6 ± 0.13	0.8 ± 0.11	NS
Epithelialization surface area (cm^2)[b]			
Day 7	9.8 ± 0.35	7.5 ± 0.32	<0.001
Day 14	38.4 ± 0.36	36.9 ± 0.42	0.039
Day 21	86.3 ± 0.66	85.8 ± 0.68	NS
Complications (n. %)	4 (10%)	2 (5%)	NS

[a,b]Mean ± SEM.

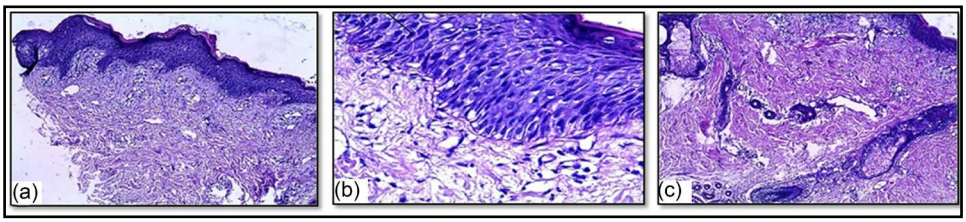

Figure 1. Light micrograph of PRP side at day 7 using H&E stain. (a) Regenerated intact epithelium with differentiated epidermal keratinocyes (×100); (b) Differentiated polyhydral cells in stratum spongiosum and cells in stratum granulosum (×400); (c) Collagen deposition with minimal infiltration of inflammatory cells (×200).

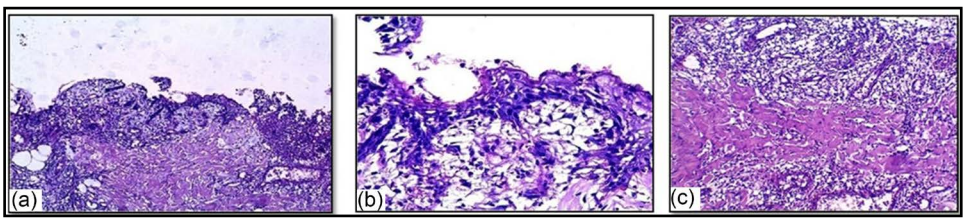

Figure 2. Light micrograph of control side at day 7 using H&E stain. (a) Minimal and partial epithelial covering with extensive areas of ulceration (×100); (b) Thin epidermal covering in high power field (×400); (c) Extensive perivascular inflammatory infiltrate and minimal collagen deposition (×200).

4. Discussion

Platelet-rich plasma (PRP) has been largely used in several clinical settings. Moreover, it is considered to promote tissue regeneration due to presence of growth factors and essential cytokines. Nevertheless, many studies fail to deliver conclusive evidence concerning the benefits of PRP in the field of wound healing. This study was undertaken to evaluate the safety and the efficacy of autologus platelet-rich plasma (PRP) in acute wound healing.

In our study, we chose the donor sites of STSGs as model of acute wounds. Similarly, Danielsen *et al.* [11] tested the effect of PRP on the epithelialization of the donor sites of STSGs. In other studies, Hom *et al.* [12] and Kazakos *et al.* [3] evaluated the effect of PRP on full thickness skin punch wounds and acute traumatic wounds as open fracture tibia respectively.

Sommeling *et al.* [13] in their systematic review of 15 randomised controlled trials and 25 case control studies found that there is no standard technique of PRP preparation. In this study, we adapted the double spin technique and observed that the platelet count was increased about 3.5 folds and TGF-B1 was increased 2.4 folds. In a similar study, Marukawa *et al.* [14] used the double spin technique for PRP preparation and noticed that the platelet count was increased about 3 times and the platelet released growth factors increased about 2 - 3 times. Conversely, Pietrzak *et al.* [15] suggested that a four to five fold increase in the baseline of platelet count is needed but they show no clear evidence that lower or higher concentration may decrease or increase the positive effect of PRP.

We found that the mean time needed from preparation till injection of the activated PRP was 68.3 min. Unlike us, Kazakos *et al.* [3] reported a relatively shorter time (mean—52 min), which could be attributed to the single centrifugation protocol adapted by them. This series witnessed improvement in the wound healing in the PRP side as evident by the significant increase in the epithelialization surface area in the PRP side at days 7 and 14 postoperative ($p < 0.001$ and $p = 0.039$ respectively). Similar to our study and findings, Kakudo *et al.* [16] studied the effect of PRP on the donor site of STSG and noticed macroscopic epithelialization on the 5th day of PRP application. In another study, Spyridakis *et al.* [17] noted that complete wound closure was statistically faster in the PRP treated wounds. Contrary to our results, Danielsen *et al.* [11] observed no significant difference in the macroscopic epithelialization between PRP and control groups in their study.

In our series, the pain scores, while not differing at day 0 and 21 postoperative, significantly decreased by day 7 and 14 postoperative in the PRP side compared to the control side ($p = 0.002$ and $p = 0.004$ respectively). In similar studies, Englert *et al.* [18] found that postoperative pain was significantly reduced for the PRP treated wounds and Khalifi *et al.* [19] observed that intravenous narcotic use was statistically lower in the PRP treated subjects. In another study, Kazakos *et al.* [3] noticed that there was no pain difference between both groups at the end of the 1st week, while there was lower pain scores in the PRP treated group at the end of the 2nd week.

This study demonstrated that the PRP side exhibits intact epithelium with thicker epidermis, differentiated epidermal keratinocytes, neovascularization and beginning of collagen deposition. These data are in accordance with that of Hom *et al.* [12], who reported thicker epidermis at the 7th day of PRP application to acute wounds and Marx *et al.* [20], who noticed thicker epithelium and newly formed blood vessels in the PRP side. In experimental study, Carter *et al.* [21] tested the effect of PRP gel on equine wounds and observed that PRP gel induced accelerated epithelial differentiation and early collagen deposition.

We observed that there was no significant difference between both sides regarding the incidence of complications which is consistent with Wang-Saegusa *et al.* [22] who studied the effect of PRP injection into the knee joint of over 800 patients and noticed no adverse effects, and is also consistent with Mazzucco *et al.* [23] who used PRP gel to treat heal wounds and reported no serious adverse events. Moreover, Powell *et al.* [24] demonstrated that wound treatment with PRP gel can reduce the incidence of ecchymosis and the formation of edema. In our point of view, the small sample size and the single injection time are the main limitations of our study.

5. Conclusion

We can conclude that the platelet-rich plasma is safe and effective adjuvant in the management of acute wounds. However, we recommend for larger clinical trials for standardized method for PRP preparation and better understanding of the efficacy and the safety of this blood product.

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Blunt Abdominal Trauma Leading to Pancreatic Injury in Childhood. Delay in Diagnosis Leads to Poor Outcomes—A Case Presentation

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Abstract

This case report illustrates the difficulty in diagnosing paediatric patients with life threatening pancreatic injuries. A high index of suspicion is essential as late diagnosis significantly affects outcomes. A 9-year-old child presented with epigastric pain following an accident on his pushbike. The patient was examined in paediatric accident and emergency (A/E) and was discharged. He returned twice more to A/E and on the third visit, 5 days after the initial incident, a CT scan was performed. This showed a classical injury to the body of the pancreas with a collection in the lesser sac. The patient was transferred to the regional hepato-pancreato-biliary unit (HPB unit) and underwent surgery. Pancreatic injuries can be difficult to detect clinically and patients may be well on initial presentation with normal observations and routine bloods. Early CT scanning confirms the diagnosis and results in early specialist referral and better outcomes.

Keywords

Paediatric Trauma, Blunt Abdominal Injury, Pancreatic Injury

1. Introduction

Blunt abdominal injury in paediatric patients is the primary mechanism for pancreatic injury. These injuries can lead to serious morbidity. The pancreas is a retroperitoneal structure and can be injured in blunt trauma to the epigastrium. These patients may initially present with minimal clinical signs. It has also been documented that complaints from paediatric patients are commonly unspecific; thus, the diagnosis is often delayed and therefore so is the treatment resulting in poorer outcomes. A high level of

suspicion is essential for early diagnosis and improved outcomes. Imaging is essential as all other tests are non-specific. At initial presentation abdominal examination may be unremarkable due to the retroperitoneal nature of the pancreas. Routine blood tests at presentation including amylase may be normal in major pancreatic trauma. A FAST scan in A/E may be useful but as demonstrated in this case was misleading. CT scan remains the gold standard for imaging the pancreas and other abdominal viscera. This paper highlights the importance of having a high index of suspicion for pancreatic injury in blunt abdominal trauma to the abdomen.

2. Case Presentation

A 9-year-old boy presented to paediatric A/E with abdominal pain. He was brought by his mother who gave a six-hour history of the child falling over the handlebar of his pushbike. He was complaining of abdominal pain and had vomited four times. He was assessed and found to have tenderness and bruising to the epigastric area. His vital signs were normal and he was discharged without a diagnosis or investigations.

Following discharge he continued to have abdominal pain and felt nauseated. As his symptoms failed to settle on day 3 his mother brought him to the A/E again. He continued to suffer with upper abdominal pain and gave a history of one vomit with no blood. According to his mother he was refusing to eat or drink. General examination was unremarkable, but he remained tender in the upper abdomen. On this occasion plain chest and abdominal films were performed and appeared normal. Respiratory rate was 26, pulse 97, Blood pressure was 119/79 and temperature was 37.1˚C with oxygen saturation of 100% on air. Urinalysis was negative for blood. No blood were undertaken and he was discharged on Ibuprofen with a diagnosis of soft tissue injury.

He re-presented 48 hours later having been referred by his General Practitioner who was concerned about this child's severe epigastric pain and a history of vomiting on ten occasions since his initial injury. In A/E he appeared unwell, dehydrated and in pain. He had only passed urine once in the last 24 hours. On examination his pulse was 98/minute, temperature was 37.8˚C, saturation remained 100% on air. He was tender in the epigastrium. He was referred to the on call general surgeons who arranged for blood tests and an urgent CT scan of the abdomen and pelvis. His Haemoglobin was 116 g/L, WBC 79, C Reactive Protein (CRP) 95 mg/L, Liver function tests were normal, however his serum Amylase was 1049 U/L. The CT scan demonstrated a classical injury to the body of the pancreas with a collection in the lesser sac (**Figure 1**). The patient was resuscitated and referred to the regional paediatric hepato-pancreato-biliary unit (HPB unit). There he underwent laparoscopic surgery, debridement and drain placement. He also required endoscopic stenting of the pancreatic duct. He had a slow post-operative recovery and was discharged 12 weeks later. Although he has made a good recovery he continues to be troubled by mild non-specific upper abdominal pain.

3. Discussion

Blunt trauma to the upper abdomen is a frequent cause of presentation to the

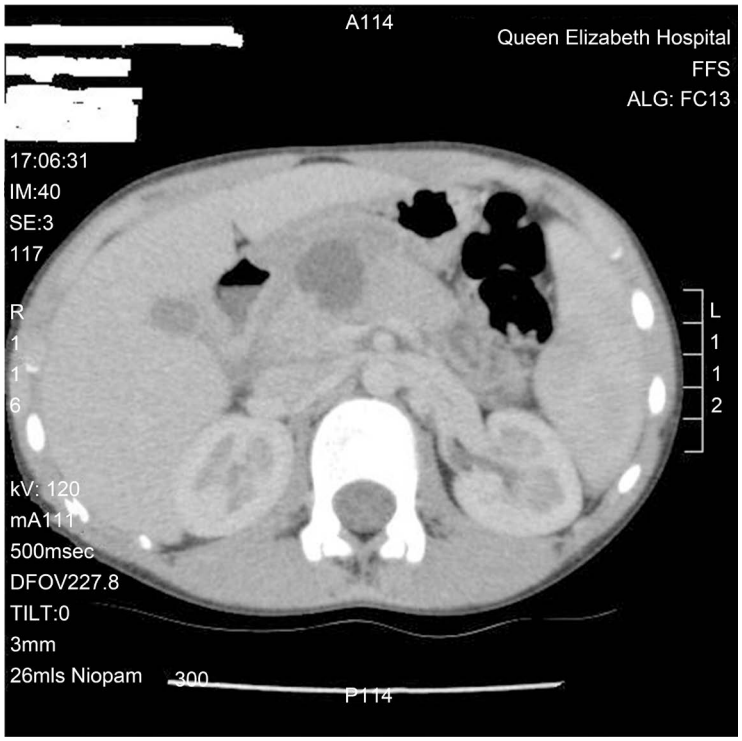

Figure 1. CT scan showing a classical injury to the body of the pancreas with a collection in the lesser sac.

emergency department. In children the abdomen is the second most common site of injury [1].

In blunt abdominal trauma, the visceral organs are commonly injured where the spleen and liver are the two most frequently damaged [2]. However injuries to the pancreas are important as they can be missed on initial examination which leads to significant morbidity [2].

Blunt trauma to the upper abdomen compresses the body of the pancreas against the spine resulting in injury [3]. Bicycle handlebar injuries are a classic cause of pancreatic injuries [4].

Presentation as in this case may be delayed because the pancreas is a retroperitoneal structure and following an injury the collection is contained in the retro-peritoneum and/or lesser sac. As a result the clinical presentation can be misleading as the patient may not have many clinical signs on initial examination [5].

We report this interesting case of a child with a pancreatic injury and want to raise awareness of the presentation and lack of clinical signs on initial presentation and examination. Ultrasound scanning may be diagnostic however during the initial presentation the ultrasound may be normal. Imaging modalities such as CT scans are essential for diagnosis [6] [7] [8] and blood tests including CRP, serum Amylase and WBC may help in the diagnosis; studies have shown that serum amylase and lipase are not reliable or cost effective as screening tools but may support clinical suspicions in the diagnosis of paediatric pancreatic trauma [9]. MRI scanning may be an alternative to CT [10], but

is more difficult to organise out of hours and less well tolerated in the paediatric age group.

A high index of suspicion is essential as delay in diagnosis increases morbidity. Early diagnosis ensures these life-threatening injuries are appropriately treated in a timely fashion. Initial imaging may be negative and repeat scanning is recommended if clinically appropriate. All such injuries should be referred to the regional HPB unit.

4. Conclusions

Blunt abdominal trauma is a common cause for paediatric admissions to A/E.

The pancreas is a retroperitoneal structure; therefore, clinical signs may be absent on initial presentation. Early investigations including FAST scans and routine blood tests may be normal. A high index of suspicion is essential. CT scan is the investigation of choice. Early diagnosis improves outcomes. All doctors dealing with paediatric emergencies should understand the mechanism of injury to the pancreas and other retroperitoneal organs. Early referral to regional HPB centres is essential to improve outcomes in paediatric pancreatic injuries. Delay in diagnosis has a significant risk of increased morbidity and mortality.

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Ocular Manifestations in Thyroid Eye Disorder: A Cross-Sectional Study from Nepal

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Abstract

Background: Thyroid eye disease represents an organ-specific autoimmune process that is usually associated with thyroid disease. Graves' disease is the most common thyroid abnormality associated with thyroid eye disease. **Aim:** This study was conducted for the profile of ocular manifestation in Thyroid Eye Disease (TED). **Methodology:** A cross-sectional study of 117 cases of thyroid dysfunction was carried out at BP Koirala Institute of Health System, out of which 84 (71.79%) cases had ocular manifestation. They were evaluated and analyzed in detail and the characteristics documented included patient's demography, ocular and systemic history and as well as ocular examination and some of the systemic and laboratory findings. **Results:** In this study, mean age of presentation of TED was 39.7 years. 59 patients were female and 25 were male. The maximum patients of both sexes were in the fourth decade of their lives. The common lid signs were lid retraction and lid lag. Proptosis was seen in 33.3% of cases out of which 68% had bilateral proptosis. Corneal ulcer was seen in 7.1% and optic neuropathy in 1.2% of cases. In 27.3% of cases there was elevation of IOP. Dry eye was seen in 61.9% of cases and POAG seen in 8.3% of cases. In the study population 75% were hyperthyroiditic, 16.7% were hypothyroiditic and 8.3% were in euthyroid state. **Conclusion:** Female was more commonly affected. The maximum number of patients of both sexes was in the fourth decade of their lives. Hyperthyroidism patient had greater chance of ocular manifestation.

Keywords

Thyroid Eye Disease, Ocular Manifestation, Nepal

1. Background

The thyroid gland is an endocrine gland in the body, and consists of two inter connected lobes. It is located at the front of the neck region, below the laryngeal promi-

nence. The thyroid gland secretes thyroid hormones, which influence the metabolic rate, protein synthesis, and have a wide range of other effects, including on development. The thyroid hormones T_3 and T_4 are synthesized from iodine and tyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis [1]. Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) secreted from the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus [2]. Any structural or functional deficit either in thyroid gland or in their stimulating hormone due to any reason (genetical, environmental etc.) causes thyroid disorder and thus causes its deleterious effect on the body [3]. A cross-sectional multicenter study done in urban population of eight cities in India reported the prevalence of hyperthyroidism to be 10.95% (n = 5376) [4]. In Nepal, a retrospective hospital based study done in central region reported the prevalence of thyroid dysfunction to be 29.00% [5].

Thyroid Eye Disease also known as Graves' orbitopathy is typically a self-limiting autoimmune process associated with dysthyroid states. The clinical presentation may vary from very mild disease to severe irreversible sight-threatening complications. It is the most common disease affecting the orbit. It is detectable in approximately 25% of unselected patients with Graves' disease if eyelid signs are excluded, and 40% if eyelid signs are included [6]. It generally presents during 4th and 5th decade of life while it can affect neonates and elderly.

Nepal is a developing country where around 18% people are of age group 40 - 60 [7], and females are more in numbers than males (male to female ratio: 0.96) [8]. Also there is high rate of smokers (25% - 73%) in Nepal [9]. Hence, Nepal is a country with high risk factors but no any study is attempted to know the burden of thyroid ophthalmopathy and the varieties of ocular manifestations due to thyroid disorder. This study is designed to find the rate of ocular manifestation in thyroid disorder in a hospital setting.

2. Methodology

A hospital based cross-sectional study was designed to evaluate the ocular manifestations in patients with thyroid disorder. A sample size was calculated assuming the prevalence of 8%, in 95% of confidence interval with permissible error of 5%. The total sample size calculated was 114. The required sample was collected randomly from outdoor patient department of BP Koirala lions centre for Ophthalmological Studies (BPKLCOS).

The thyroid disorder cases that had sign symptoms mimicking thyroid ophthalmopathy (proptosis, eyelid retraction) due to other causes were excluded. Each patient was informed about the study and only the patients were enrolled if he gave consent for the study. A detailed protocol for data collection was prepared and approved by Institute of Medicine Tribhuwan University Teaching Hospital Institution review board.

Mean was used as a measure of central tendency. Similarly, standard deviation and range were used as a measure of dispersion. Prevalence was calculated in percentage at

95% confidence interval. For risk factor, univariate as well as multivariate analysis were performed and odds ratio was calculated. The level of significance was set at 95%.

3. Data Collection Protocol

After having a verbal consent, a detailed history was taken including the chief visual complaint, history of present illness, medical history, personal and professional history. Visual acuity (unaided, with previous glass and with pinhole) was measured with self illuminated Snellen chart at 6 meter distance at room illumination. Subjective as well as objective refraction were performed for every case and the required glasses were prescribed.

Extra ocular movement and cover test were performed with the help of torch light in all the cardinal gazes and any restriction or over action was noted. Forced duction test was performed in cases with restricted extraocular motility to differentiate restrictive and paralytic. Detail examination of lid was done with the help of torchlight to see if there was any eyelid sign of thyroid ophthalmopathy. The signs that were looked for were Lid retraction (Dalrymple's sign), Lid lag, Enroth's sign (Edema esp. of the upper eyelid), thin tremors when closed eyelid (Rosenbach's sign) [10].

Detail proptosis evaluation was done on for pain, progression, amount and type of proptosis (axial or non axial and measured by Hertel's exophthalmometer), palpation, pulsation and retro pulsation and periorbital changes. Detail examination of conjunctiva, cornea and anterior segment was done with the help of torch light followed by Haag Streit 900 Slit lamp biomicroscopy to find out any abnormalities present. Presence of congestion at the site of insertion of extra ocular muscle, superior limbic keratoconjunctivitis, and any tear film abnormalities were noted. Pupillary light reflex both direct and consensual was noted using bright torch light. Fundus examination was done after pupillary dilatation using eye drop Tropicamide 1% with the help of direct and indirect ophthalmoscope and using + 90 lens in selected cases wherever necessary. IOP was taken with the help of Goldman applanaton tonometer attached to the slit lamp in primary and up gazes.

All patients were sent for thyroid function test if not done. CT scan was ordered in cases of proptosis and with any one of the signs of vision threatening condition (exposure keratopathy, squint or optic nerve involvement). Colour vision was performed in suspected cases of optic neuropathy. In cases of corneal ulcer corneal scraping and culture were done. B scan for orbit was performed in all cases of proptosis.

4. Results

A total of 117 cases, 80 female (68.4%) and 37 male (31.6%), of Thyroid dysfunction were included in this study. The mean age of presentation was 39.7 years that ranged from 17 - 65 years. The majority of the cases (64.1%, n = 75) in their 3rd and 4th decade. The gender distribution with age range is given in Table 1.

As shown in Table 2, Among 117 cases of thyroid dysfunction 71.7% (n – 84) of cases had some form of ocular manifestations (at least one sign of NOSPECS) and thus

Table 1. Table showing age range and gender distribution of the cases of thyroid.

	Sex of patient				Total	
Age	Male	%	Female	%	Number of cases	%
0 - 10 yrs	0	0	0	0	0	0
11 - 20 yrs	1	2.7	0	0	1	0.9
21 - 30 yrs	7	18.9	18	22.5	25	21.4
31 - 40 yrs	8	21.6	22	27.5	30	25.6
41 - 50 yrs	13	35.13	32	40	45	38.5
51 - 60 yrs	5	13.5	7	8.75	12	10.3
>60 yrs	3	8.1	1	1.25	4	3.4
Total	37	100	80	100	117	100

Table 2. Gender distribution with thyroid eye disease and without thyroid eye disease.

	Male	Female	
With TED	25	59	84
Without TED	12	21	33
	37	80	117

TED: Thyroid Eye Disease

had thyroid eye disease. Odds ratio was calculated for female for being risk of developing thyroid eye disease among thyroid disorder cases. The odds of female to be more affected by TED to male were 1.35.

Ocular manifestations were analyzed with age group in thyroid disorders patients. Out of 117 thyroid eye disease patients, 75 (64.1%) were in 4th and 5th decade as shown in the bar diagram of Figure 1. Out of 84 thyroid eye disease cases, 54 (64.28%) cases were thyroid eye disorder. The odds ratio of having thyroid eye disorder in 4th and 5th decade was 1.008.

As shown in Figure 2, among the cases with TED (n – 84), 97.6% (n – 82) of cases had FB sensation, 94% (n – 74) of cases had discomfort in the eyes, 73.8% (n – 62) of cases had swelling of eyelids, 54.8% (n – 46) of cases had watering, 50% (n – 42) of cases had redness of eye, 44% (n – 37) of cases had blurring of vision, 38.1% (n – 32) of cases had proptosis, 26.2% (n – 22) of cases had reading problem, and 4.8% (n – 4) of cases had diplopia in the study population with TED.

Among the cases of TED (n = 84), the most common presenting lid sign was lid retraction 67 (79.8%) followed by lid lag 64 (76.2%), infrequent blinking 43 (51.2%), poor convergence 42 (50%), Enroth's sign 28 (33.3%) as shown in Figure 3. Proptosis was seen in 28 cases (33.3%), in 19 (22.61%) cases, the proptosis was bilateral and in 9 (10.71%) cases it was unilateral. Bell's phenomenon was poor in 3 (3.6%) and there was restriction in EOM in 10 (11.9%) cases in the study population with TED. Conjunctival sign like chemosis, congestion over the insertion of the rectus muscle were seen in 25 cases (29.8%).

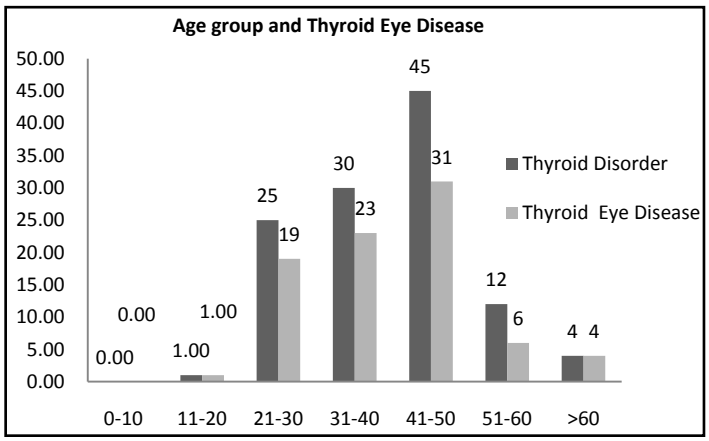

Figure 1. Bar diagram showing the thyroid eye disease distribution among age groups.

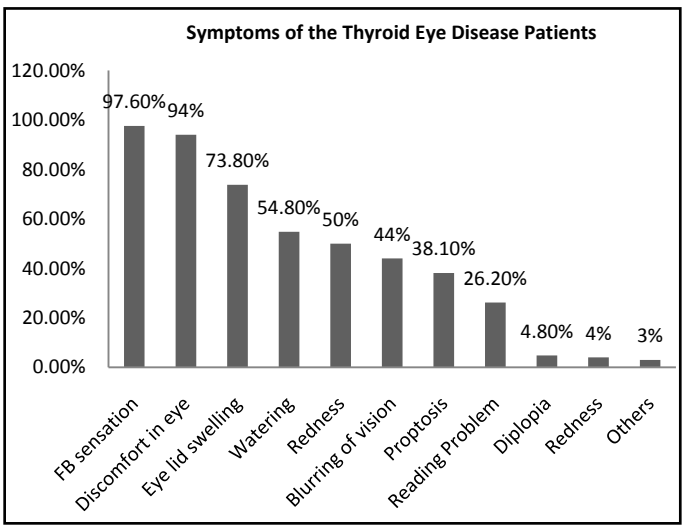

Figure 2. Bar diagram showing the presenting symptoms of Thyroid eye disease patients.

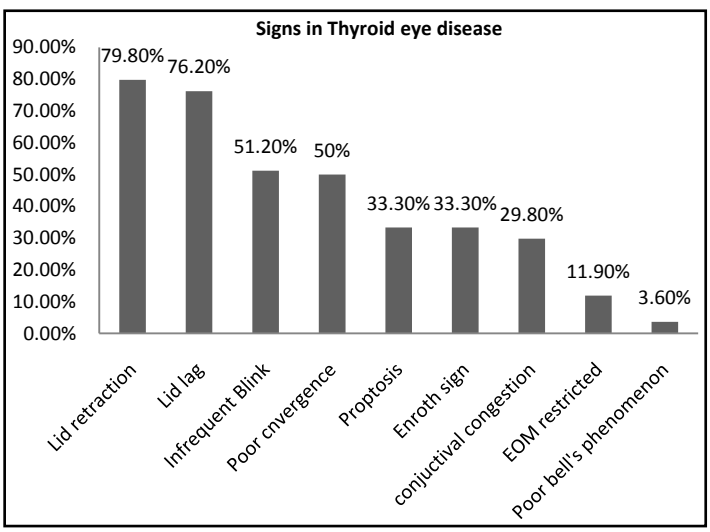

Figure 3. Bar diagram showing the signs of thyroid eye disease observed in patients.

21 (25%) cases had intraocular involvement in which 14 (16.66%) were superior limbic keratoconjunctivitis, 6 (7.14%) cases had corneal ulcer and 1 (1.19%) case was diagnosed as optic neuropathy. Out of 6 cases of corneal ulcer, 4 cases were bilateral and 2 cases were unilateral. Corneal scrapping was done in all the cases and culture positive was seen in 67% (n – 4) of cases. In all the culture positive cases *Staphylococal aureus* was isolated. Unilateral optic neuropathy seen in 1 case had severe degree of proptosis with bilateral corneal ulcer and visual acuity of no perception of light in that eye with optic neuropathy.

Intraocular pressure was measured in primary and up gaze and any pressure above 22 mm of hg at any of the gaze was recorded as high [11]. Out of 84 cases of thyroid eye disease, 21 (25%) had high IOP while 63 (75%) had normal IOP. All the cases with higher IOP were evaluated for glaucoma with cup-disc ratio evaluation and automated visual field and central corneal thickness evaluation. 7 cases (8.33%) were diagnosed as primary open angle glaucoma and 3 (3.57%) were put as suspect of glaucoma and rest were diagnosed as ocular hypertension.

Schirmer's test and tear break up time were evaluated for diagnosis of tear film disorder. The normal value for schirmer's test was set 10 and for tear break up time it was set 10 sec. [12]. 52 (61.9%) were diagnosed to have tear film disorder. 75% (n – 63) of cases were Hyperthyroiditic, 16.7% (n – 14) of cases were Hypothyroiditic and 8.3% (n-7) of case were having Euthyroid state.

A yes/No questionnaire on the knowledge of their being affected by thyroid eye disease was asked with all the patients. 34 (27.35%) patients were not aware of their thyroid status but presented in eye OPD for various eye problems. But on careful examination we suspected of thyroid eye disease and investigation was sent for it. They all turned out to have thyroid dysfunction and are now under treatment for it.

5. Discussion

Thyroid eye disease is a complex and poorly understood inflammatory disease that causes a wide variety of clinical problems. Clinical management is often frustrating for both the physician and the patient, because no immediate or dramatic cure exists. Each treatment modality has significant side effects and complications, and treatment decisions are rarely easy.

Thyroid disease, being autoimmune disorder mostly, effects mostly in 4^{th} and 5^{th} decade of life and commonly in females as cited by many previous studies [13] [14] [15]. The average age of presentation of the thyroid eye disease was 40 years in our study. This was similar to the result shown by Bartley GB et al of median age 43 years [16]. Another study by DeLisa Fair-weather *et al.* in their review quoted that Autoimmune diseases affects 8% of the population, 78% of whom are women. The exact reason for the high prevalence in women is unclear. But it is presumed that the effects of female gonadal hormones (prolactin and estrogen) and X chromosome inactivation on thyroid gland and immune system greatly contribute to the female predilection of thyroid disorder in female. The direct actions of estrogens on the thyroid tissue contribute

to the development of thyroid goitre, nodule and cancer in women [15]. From the literatures; it is evident that female predominant autoimmune diseases that manifest during the acute phase, such as Graves' disease and systemic lupus erythematosus, are diseases with a known antibody-mediated pathology. Autoimmune diseases with an increased incidence in females that appear clinically past age 50 are associated with a chronic, fibrotic Th2-mediated pathology. Th17 responses increase neutrophil inflammation and chronic fibrosis.

The prevalence of thyroid eye disease in thyroid disorder varies greatly as cited by different studies. It was reported as low as 17.3% by Kyung In Woo, *et al.* in Korea [17] and reported as high as 51.7% by Manji N *et al.* In contrast, our study reported the prevalence of any form of thyroid eye disorder in 71.7% (n – 84) cases that is much higher than the previous studies elsewhere. The higher prevalence of thyroid eye disease may be attributed to the definition of thyroid eye disease in our study. We have defined thyroid eye disease as presence of any one sign of thyroid eye disease (NOSPECS) while other studies have taken at least two signs [18]. In a study done in India by Mohsen Bahmani Kashkouli *et al.* [19], the prevalence was 35.6%.

Thyroid eye disease can occur in any form of thyroid dysfunction either hyper, hypo or euthyroid state. In our study, out of 84 thyroid eye disease patients, 63 (75%) were hyperthyroid, 14 (16.7%) were hypothyroid and 7 (8.3%) were euthyroid. A study reported by Bartley GB, Fatourechi V *et al.* at Mayo Clinic, Rochester USA has cited 90% of hyperthyroid, 6% euthyroid, 1% had primary hyperthyroidism and 3% had Hashimoto's thyroiditis [20]. Many explanations for the occurrence of thyroid ophthalmopathy in hyperthyroid, hypothyroid and euthyroid states are given in literature. One was that hyperthyroidism and hypothyroidism can occur concurrently in one patient, but the time of occurrence might be different, because of the possibility of spontaneous transition. There might be transformation in blocking antibodies into stimulating antibodies with time [21]. It was also hypothesized that different concentrations of blocking and stimulating antibodies attack the thyroid cell simultaneously, which might cause hypothyroidism or hyperthyroidism [22].

Ocular manifestation of thyroid disease includes eyelid retraction, periorbital edema, conjunctival injection and chemosis, proptosis, extraocular muscle restriction, exposure keratopathy, and optic nerve compromise. Sympathetic stimulation of the Müller muscle may be responsible for most of the medically reversible cases of eyelid retraction in patients with Graves disease [23]. Similarly, the perioebital edema, conjuctival injection, proptosis, extraocular muscle restriction all are attributed to the inflammation of intraorbital fat as well as extraocular muscle. The exposure keratopathy is due to severe proptosis and the compressive optic neuropathy is also due to severe proptosis [24].

Our study showed that eyelid retraction was present in 79.8% that was far less Bartley GB *et al.*'s [20] 90%. The difference might be due to ethnic variation or might be the severity of disease unequal in the study. Another study reported by Saks ND *et al.* reported the lid retraction in 98% of the patients [25]. Similarly, lid lag was present in 76.2% (n – 64) of cases in our study while it was reported 43.33% in Bartley GB *et al.*

study [20].

Exophthalmos is the most widely known sign of thyroid eye disease, occurs in 20% - 30% of patients with Graves' disease and up to 40% - 70% of patients with thyroid associated ophthalmolpathy. It is bilateral in 80% - 90% of cases [26]. In our study, Exophthalmos was present in only 33.3% (n – 28) of cases, restrictive extra ocular myopathy was seen in only in 11.95% (n – 10) of cases.

Other severe ocular manifestations of thyroid ophthalmopathy include diplopia, corneal ulcer due to exposure keratopathy and dysthyroid optic neuropathy. Diplopia was noted in 4.8% (n – 4). Corneal involvement was in the form of superior limbic kerato-conjunctivitis (16.7%) and corneal ulcer (7.1%). Decreased vision from optic neuropathy was present in only 1.2% of cases. Bartley *et al.* reported 17% of the patients presenting with diplopia, 10% of cases with corneal involvement and optic neuropathy in 5% to 9% [27]. The presence of this severe degree of eye involvement and blinding conditions in our set up may be due to late presentation and due to unawareness of their disease process at presentation. It may be also due to our centre being tertiary eye centre and we get majority of complicated and referred case.

Thyroid eye disease has been found to be usually associated with glaucoma. The possible cause of increased intraocular pressure and thus causing optic neuropathy might be increased episcleral pressure thus hindering the outflow and increasing intraocular pressure. The other mechanism if increased intraocular pressure might be compression of globe by inflamed and fibrosed inferior rectus muscle. In our study of the total no. of patients with thyroid eye disease 23 patients, which accounted for 27.38% cases had increased IOP. However only 7 cases (8.3%) had POAG and 3 cases were suspected for glaucoma. Cookerham and associates reviewed 500 patients with thyroid eye disease and found 120 (24%) had increased IOP. Of this 2% developed glaucomatous field defect over a follow up of 48 months [28].

Other ocular pathology like dry eyes was seen in 61.9% (n – 52) in thyroid eye disease patients in our study. This may be due to the exposure or it may be due to the immunological process associated with thyroid eye disease. It is cited in literature that five factors potentially associated with corneal exposure-palpebral fissure width, exophthalmos, blink rate, lagophthalmos, and lid lag. All the factors were evaluated in 17 patients with Graves' disease in a study to determine which were associated with ocular surface damage. Multiple regression analysis revealed that increased palpebral fissure width and increased blink rate were both significant predictors of ocular surface damage [29].

6. Conclusion

Thyroid eye disease affects the majority of thyroid disease patients. The ocular manifestation ranges from mildest to the most severe form. Early diagnosis and intervention can be beneficial in saving sight and globe. Hence a proper referral system between ophthalmologists and physician is mandatory. Also, many thyroid disorders are first time diagnosed form ocular manifestations so a regular health check up including eye

check up is needed to pick the cases in early stage and referred among each other for better treatment outcome.

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Photodynamic Therapy for Medication-Related Osteonecrosis of the Jaws: A Case Report

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Abstract

Medication-related osteonecrosis of the jaws (MRONJ) is a relatively new disease. MARX reported first cases in 2003. MRONJ relates to oral and parenteral bisphosphonates as well as to the so-called target cancer therapies but the list of medications only grows. Although MRONJ is a relatively rare condition, it can be associated to significant morbidity with feeding limitations and intense pain. More severe cases can lead to potentially life-threatening infections. Every patient initiating bisphosphonate and/or target cancer therapy must visit a dentist before starting medication because preventive measures for MRONJ are much more effective compared to surgical management of the lesions. Surgical resolution can be especially difficult to obtain in the coexistence of certain complication factors like wider bone exposures, history of nitrogen containing bisphosphonates use (mainly zolendronate) and immunodeficiency. Recently, researchers have given attention to laser therapy associated to photosensitive agents as a possible option to management of some MRONJ lesions. Our case report demonstrates the use of photodynamic therapy in a denosumab related lesion in the mandible. It seems that denosumab related lesions are more amenable to treatment and total resolution because of the marked differences between its chemical and metabolic characteristics when compared to bisphosphonates.

Keywords

Laser, Phototherapy, Osteonecrosis, Jaws, Denosumab

1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is a relatively new disease;

MARX reported the first cases related to parenteral bisphosphonate in 2003 [1]. Later, a relation between MRONJ and oral bisphosphonates was established. More recently, medications like denosumab, used for the so-called target cancer therapies, received attention. Denosumab is a fully human monoclonal antibody that binds the cytokine RANKL (receptor activator of NFκB ligand), an essential factor initiating bone turnover. RANKL inhibition blocks osteoclast maturation, function and survival, thus reducing bone resorption [2].

Although considered a rare condition, MRONJ can be associated to significant morbidity. Lesions can begin in an insidious, asymptomatic fashion and then lead to intense pain in the affected bone (mostly the mandible, but maxilla can be affected too), bone exposure, draining pus, fistula formation, feeding limitations and pathological fracture [3] [4]. Carrying out surgical procedures to heal MRONJ lesions can be a very frustrating experience for the surgeon. This can be especially true in the coexistence of certain complication factors like wider bone exposures, history of nitrogen containing bisphosphonates using (mainly zolendronate) and immunodeficiency [1].

Recently, researchers have given attention to laser therapy associated to photosensitive agents as a possible option to management of some MRONJ lesions. Promising results have been reached by using Chimiolux 0.005%® (methylene blue; DMC) and posterior laser exposure.

2. Case Report

On February 2015, A.D.A, male, 83 years old, attended to FOUERJ complaining about "mild pain" in the lingual aspect of cortical bone near the lower right 3 during the last 4 months. History of denosumab use once a month until September 2014 for prevention of bone metastasis associated to prostate cancer was present. After removing upper and lower dentures, clinical examination revealed a painful area of exposed bone associated to pus drainage near the lower right 3 in association with a trauma of lower prosthesis in the region (**Figure 1**). Panoramic radiography showed an osteolytic lesion near the lower right 3 (**Figure 2**). The diagnostic of medication-related osteonecrosis of the jaws was clinically established. Initial management consisted in topical chlorhexidine 3 times a Day, after each brushing and penicillin intake Clavulin 875 mg (makes use of 1 tablet, 12 in 12 hours for 7 consecutive days). After almost 3 months patient related no pain and pus drainage disappeared. On July 2015, fifteen low level laser therapy (LLLT) were initiated. The laser therapy was used aiming at soft tissue repair (red laser), bone biostimulation (infrared laser), and nerve repair (infrared laser) for pain relief. The low-level laser therapy equipment used was XT Therapy, produced by DMC, emits red and infrared laser light to the anti-inflammatory, analgesic, bio stimulant and healing purposes. The infrared laser has a wavelength of 808 nm ± 10 nm the power output of the transmitter is 100 mW ± 20%. The red laser wavelength of 660 nm ± 10 nm the power output of the transmitter is 100 mW ± 20%. The equipment used is contraindicated in pregnant patients or who are breastfeeding, with episode of skin cancer in the irradiated region patients, glaucoma patients, patients with cataracts that are not under

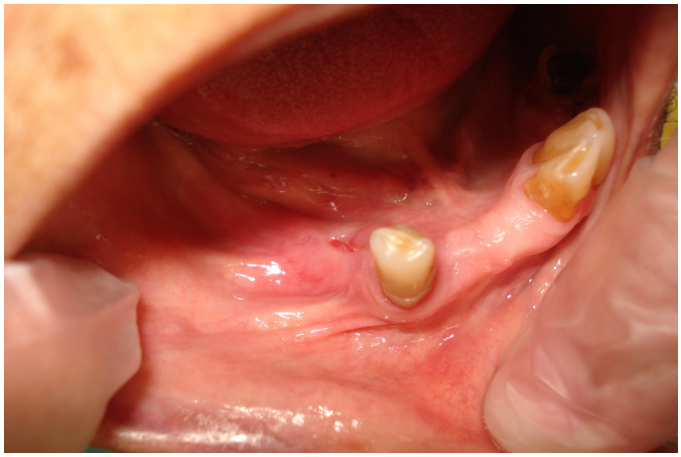

Figure 1. Clinical aspect with pus drainage near the lower right 3.

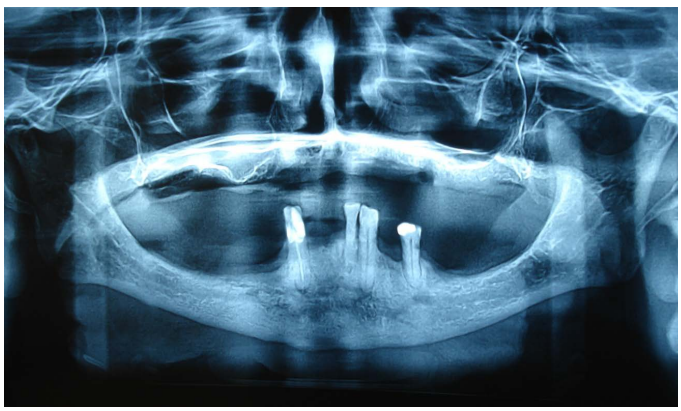

Figure 2. Panoramic radiography showing an osteolytic lesion near the lower right 3.

medical supervision. The low-power laser emits radiation without destructive potential and therapeutic effects on tissues. When used in combination with dyes has the potential to produce death of microorganisms in a process known as photodynamic therapy (PDT-Photodynamic therapy) [1]. At the first session was held photodynamic therapy (PDT) that used the Chimiolux 0.005% as photosensitizer. The Chimiolux was used at a concentration of 0.005% (Chimiolux 5) of methylene blue. In combination with red laser irradiation, the Chimiolux acts as photodynamic therapy (PDT) generating release of free radicals that provide bactericidal effect in contaminated areas. The application protocol followed the DMC laser manufacturer's recommendations: initially enters the solution from 0.005% methylene blue, then it is expected over 5 minutes (pre-irradiation time), then it proceeds to the red laser irradiation. The wavelength is 660 nm, a fluence of 320 J/cm^2 or power 9 J, a power of 100 mW, the application time of 90 seconds. Finally removes the photosensitizing agent with sterile saline irrigation. The laser's exposure was made weekly for a total of 15 treatment sessions. The irradiated area was 6 cm^2. The application protocol was given as follows: The infrared laser has a wavelength of 808 nm used in continuous mode and scan 2 mm distance to the mucosa to be irra-

diated, and the laser red has a wavelength of 808 nm irradiating at three points to one cm distance between them, or used the red ray with infrared radiating at three points with one cm distance between them. The power used with both the infrared laser as with laser red was 100 mW, varying only the fluence or power and the application time. The second session: 1 J red beam with infrared ray third, fourth and fifth session: 2 J with the red beam the sixth to tenth session: 2 J with the red beam and 4 J infrared ray Section 11:2 J red beam with the infrared ray. Thirteenth, fourth and fifth session: 2 J red beam with infrared ray and added 3 J with infrared ray in two oral extra points in the region of submentonianos lymph node in order to stimulate the defense of organism. In October 2015 panoramic examination showed kidnapping bony (**Figure 3**). There was good healing, without signs of infection and the presence of overlying mucosa under sequestration (**Figure 4**). Finally, on January 2016 spontaneous sequestration occurred with subsequent mucosal healing. Now, patient is clinically stable; free of signs and symptoms. The chlorhexidine gel is maintained and the management strategy was to conduct periodic follow-up radiographic evaluation.

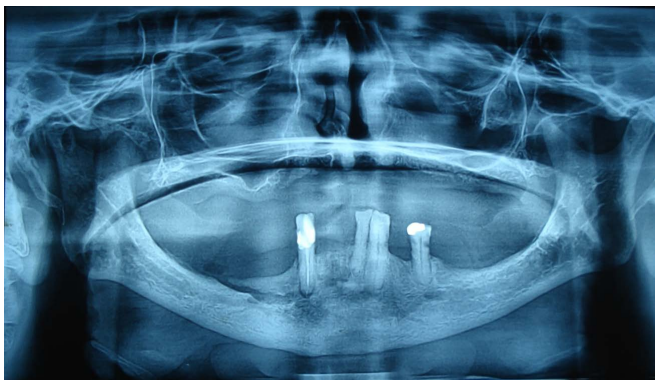

Figure 3. Panoramic radiography showing kidnapping bony near the lower right 3.

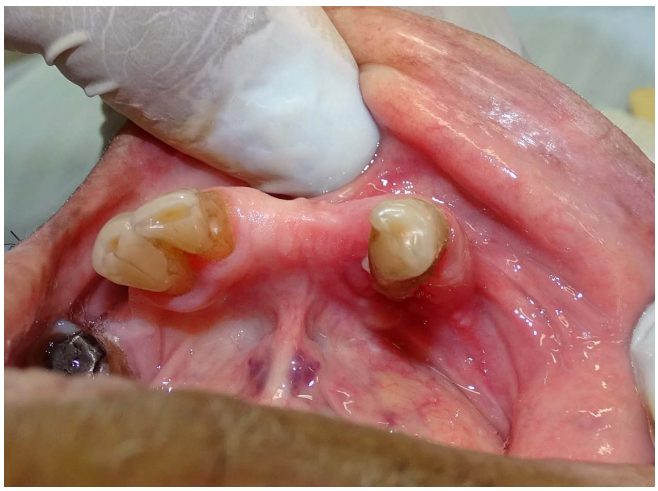

Figure 4. Clinical aspect showing good healing, without signs of infection and the presence of overlying mucosa under sequestration.

3. Discussion

Until now cases associated to bisphosphonates therapies are not only the most common ones, but also the most difficult to manage. SMEETS *et al.*, 2015 enfatized some important issues: the ten years bisphosphonates estimated half-life, the capacity of some of these drugs to lead to osteoclasts apoptosis, the alarming raising of prescriptions (including bisphosphonates indicated to osteopenia), the enhancement of drug-presentation leading to highly potent bisphosphonates, for example Aclasta®, Reclast® and the presence of bisphosphonates in uncountable day by day products. These factors are supposedly related to spread of cases worldwide [5].

Lesions related to denosumab seem to be more amenable to treatment and total resolution because of its chemical and metabolic characteristics (temporary inhibition of RANKL) [6]. It is important to differentiate MRONJ from other diseases like periodontal disease, necrotizing periodontal diseases, bone malignancies, osteomyelitis and herpes zoster virus related osteonecrosis. Obviously, applying different therapies to different causes of jaws osteonecrosis is mandatory [1]. We insist on recommending that every patient initiating bisphosphonate and/or target cancer therapy must visit a dentist before starting medication. Preventive measures for MRONJ are indispensable and much more effective compared to surgical management after developing of lesions.

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Early Surgery in Femoral Neck Fractures in Elderly: Does Preoperative ASA Score Matter?

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Abstract

Introduction: Early surgical treatment (within 48 hours) has been recommended for femoral neck fractures in order to avoid complications and reduce mortality rate, regardless of presence and severity of comorbidity and preoperative status (ASA score). However some studies evidenced that early surgery doesn't always have a beneficial effect on mortality and complications. Therefore further studies could be useful in order to better assess risk related factors of patients requiring surgical treatment for femoral neck fracture. The purpose of this study is to evaluate the effect of preoperative ASA score and timing of surgery on mortality, complications and clinical outcome. **Methods:** All 336 patients operated in our center from January 2013 to December 2014 were selected for this retrospective study. Patients were divided in three groups as follows: group 1 patients treated within 48 hours; group 2 patients treated between 48 to 96 hours; group 3 patients treated over 96 hours. The preoperative ASA score was recorded for each patient. Complication, clinical outcome and mortality at one-year follow-up were evaluated. At follow-up ambulation was graded as: confined to bed, assisted ambulation, and normal ambulation. Complications both local (infections, malunion, dislocation) and systemic (deep vein thrombosis, pulmonary embolism, lung infections, ischemic disorders of heart) were recorded as well as number of transfusions. Statistical analysis was performed with chi square test and P value < 0.05 was regarded significant. **Results:** 308 patients' data were fully available for this study. At one-year follow-up return to normal ambulation was higher for patients of group 1 as compared with group 2 and 3 and in group 2 as compared with group 3 ($P = 0.04$). There was no difference in mortality and return to ambulation between patients with ASA score 1 and 2 ($P = 0.06$); patients with ASA score ≥ 3 showed a statistically significant higher mortality ($P = 0.004$) and rate of complications (0.0008) regardless of timing of surgery. There was no statistically significance in blood transfusion among the three groups. **Discussion and Conclusion:** Clinical outcome, complications and mortality have been previously reported from

many authors and most studies agreed that early surgical treatment is recommended regardless of age and preoperative status of the patient. The present study suggests that early surgical treatment is actually able to reduce mortality and complications and to improve clinical outcome in patients with better preoperative conditions, while for patients with ASA score ≥ 3 treatment within 48 hours seems not to prevent mortality and complications and improve clinical outcome.

Keywords

Femur Fractures, ASA Score, Early Surgery, Elderly, Hip Surgery

1. Introduction

Each year there are 1.5 million femur neck fractures all over the world. They seem to be from 70,000 to 90,000 in Italy each year. Patients involved in these kinds of trauma are mostly elderly patients, with a lot of comorbidity, frailty, difficulties in recovering, and higher risk of surgical complications. For these patients mortality at one year is really high, nearby 12% - 27% despite improving in implant technology, surgical techniques, anesthesia, nursing care, and rehabilitation, and mortality during hospitalization seems to be 9% of the total [1] [2] [3]. About 20% of patients lose free ambulation capability after femur neck fracture and just 30% 40% of them gain complete recover.

Higher risk of fall in these patients is the reason of higher rate of femur neck fractures; this increased risk may be due to systemic causes such as loss of reflexes, higher risk of lypothymia, pressure changes, circulation alterations, and higher risk of ostheroporosis. All these comorbidities contribute to poor quality of life after femur neck fracture and to reduction of outcome quality. This pathology needs hospitalization and costs of treatment seem to be about 18,000 euros [4].

Last guidelines agree that time to treatment for these fractures is within 48 hours from trauma [5] in order to reduce bedridding. Time to surgery depends on patients' comorbidity and possibility to have operation room, surgical instruments and skilled staff. Other studies evidenced that early surgery has not always a beneficial effect on mortality and complications [3]. Therefore further studies could be useful in order to better assess risk related factors of patients requiring surgical treatment for femoral neck fracture.

There are not in literature studies that evaluate outcome after femur neck fractures in relation to early surgery and patients' ASA score.

Purpose of this study is to evaluate if ASA score influences perioperative mortality and ambulation after femur neck fracture early surgery.

2. Materials and Methods

All 336 patients operated in our center from January 2013 to December 2014 were selected for this retrospective study. Mean age of the patients was 83 years, (65 years to 99 years) there were 71 males (21%) and 265 females (79%). There were 101 lateral frac-

tures (30%) and 235 medial fractures (70%); 148 right fractures (44%) and 188 left fractures (56%). There were 77 arthroprothesis (23%), 44 hemiarthroplastis (13%), 20 screws (6%), 7 hip plates (2%) and 188 femur neck nails (56%). The mean length of stay was 11 days. Patients were divided in three groups as follows: group 1 patients treated within 48 hours, group 2 patients treated between 48 to 96 hours, group 3 patients treated over 96 hours. The preoperative ASA score was recorded for each patient. Complication, clinical outcome and mortality at one-year follow up were evaluated. At follow up ambulation was graded as: confined to bed, assisted ambulation, normal ambulation. Complications both local (infections, malunion, dislocation) and systemic (deep vein thrombosis, pulmonary embolism, lung infections, ischemic disorders of heart) were recorded as well as number of transfusions. Statistical analysis was performed with chi square test and P values < 0.05 was regarded significant. This study was approved by an ethic commette and each patient signed the consense. There were no missing patients at the follow up or incomplete datas.

3. Results

308 patients data were fully available for this study. Data are showed in Table 1.

Table 1. Results divided in three groups and ASA score.

		ASA 1	ASA 2	ASA 3
<48 H	Mortality	0%	5%	45%
	Bed confined	0%	5%	11%
	Assited ambulation	0%	25%	22%
	Normal ambulation	100%	13%	22%
	Complications	0%	70%	22.20%
48 H - 96 H	Mortality	25%	17%	50%
	Bed confined	0%	3%	4%
	Assited ambulation	25%	26%	23%
	Normal ambulation	50%	54%	23%
	Complications	25%	60%	29%
>48 H	Mortality	40%	32%	52.00%
	Bed confined	0%	7%	4%
	Assited ambulation	40%	22%	24%
	Normal ambulation	20%	39%	20%
	Complications	27%	50%	50%
	total			
	Mortality	41%	31%	*50%
	Bed confined	15%	18%	53%
	Assited ambulation	35%	30%	25%
	Normal ambulation	*45%	52%	22%
	Complications	5%	9%	*20%

*Statistical significance.

Mortality increases of 15% from group A to B and of 10% from group B to C. The amount of bedridden patients and with poor deambulation (wheelchair, medical walker) is constant among the three groups.

The amount of ambulanting patients (free ambulation, crutches) reduces by 10% from each group to the other. The difference is statistically significance for deambulation (P: 0.0398) even if for mortality is nearby significance (P: 0.0599). Analyzing groups divided by ASA, in the group with ASA 1 the percentage of bedridden patients doesn't vary; percentage of ambulating patients increases of 25% from group A to group B and another 20% from Group B to Group C. Ambulating patients reduce of 50% from Group A to Group B and of 30% from Group B to Group C. Days of hospital stay increase proportionally to time before surgery. These differences are not statistically significance.

Analyzing ASA 2 group the mortality patients increases of 10% from Group A to Group B and from Group B to Group C.

Bedridden and not ambulating patients number remains constant among the three groups. Ambulating patients number reduces of 10% from Group A to Group B and 15% from Group B to Group C.

Days of hospital stay increase proportionally to time to surgery. These differences are not statistically significance even if for mortality is nearby significance (P: 0.0599).

Analyzing ASA 3 group mortality increases of 5% from Group A to Group B, it doesn't vary from Group B to Group C.

Bedridden patients percentage decrease of 5% from Group A to Group B and it doesn't vary from Group B to Group C.

Ambulating patients number doesn't vary among the three groups.

Days of hospital stay increases according to time to surgery.

These differences have not statistically significance.

Analyzing groups only on ASA score, mortality percentage decreases of 5% from ASA 1 to ASA2 and increase of 30% from ASA 2 to ASA 3. The number of bedridden patients increases of 5% from ASA 1 to ASA 2 and ASA 3.

Chi square test shows significance for mortality (P: 0.0040) and ambulation (P: 0.0008).

Complications percentage in group A lesser than groups B and C, that have the same complications percentage one each other. This difference have not statistically significance.

In ASA 1 group complications number increases of 25% from Group A to Group B and of 15% from Group B to Group C.

These differences haven't statistically significance.

In ASA 2 group complications increase from Group A to Group B of 10% and of 10% from Group B to Group C. These differences haven't statistically significance.

In ASA 3 group complications number decreases of 10% from Group A to Group B and decreases of 15% from Group B to Group C.

These differences haven't statistically significance.

Analyzing complications only in ASA score groups they increase od 10% from ASA 1 to ASA 2 and 20% from ASA 2 to ASA 3.

These differences have statistically significance.

Group A presents lower percentage of transfusion, lesser than 10% then the other groups. These differences have not statistically significance.

ASA 1 group needs 20% less transfusion of the other groups. Chi Square test isn't significance.

Blood Transfusions number increases from Group A to Group B of 25%, it decreases of 10% from Group B to Group C. Chi square test is not significant.

In ASA 3 group percentage of blood transfusions is over 50%. Chi Square test is not significance.

ASA 2 and ASA3 patients present increase of 30% of blood transfusion then ASA 1 Group. Chi square is a bit over significance (P: 0.0733).

4. Discussion

In last years, some studies tried to find correlation between time to surgery and patients outcome, but findings are not univocal.

Some studies report improvement of complications and mortality at one year:

In the retrospective study of Moja *et al.* [1] 35 different articles were compared showing a reduction of mortality and pressure lesions in patients treated within 48 hours.

In a retrospective study of Khan' *et al.* [3] over three days of wait, there was an increase of mortality, morbidity and hospitalization. In this study seems that waiting for improving hydration causes an increase of pressure lesions, thrombo-embolisms and infections.

Uzoigwe *et al.* [2] presented a study comparing post-operative results of patients treated at 12-24-36-60-72 hours from hospitalization; results reported increasing of mortality during hospitalization and at 1 year in delayed surgery, and found an increase of pressure lesion risk proportional to patients ASA score.

Our study is in agreement with these works, reporting increase of mortality of 10% among groups A and B and of complications in ASA 1 and ASA 2 groups whit delayed surgery, but not for ASA 3 group where delayed surgery seems to reduce complications.

Other works found increase of mortality with delayed surgery but not a relation with complications:

Todd *et al.* [6] found a significance increase of mortality but not of morbidity in patients treated after 48h.

Dorotka *et al.* [7] compared surgery at 6-12-18-24-36 hours and recommended surgery within 36 hours after which there was an increase of mortality.

This work has same results for mortality that increases with delayed surgery and transfusions after surgery, but does not agree on complications.

Some authors found better results in early surgery only on complications but not on mortality.

Parker *et al.* [8] in their study found an increase of pressure lesions, pulmonary embolism, lung infections and hospitalization associated with increase of time before surgery. They also found a decrease of mortality in patients treated with arthroplasties and hemiarthroplasties; they attributed this difference on early mobilization of patients treated with prosthesis.

A German study of Smektala *et al.* [9], showed an increase of complications but not of mortality in patients treated after 36 hours. Complications observed were pressure lesions, urinary infections, thromboembolism, cardiovascular accidents, post-operative bleeding and implant complications.

Pillay *et al.* [10] showed a reduction of pulmonary infections in patients with delayed treatment but not of the mortality that seemed to be influenced only by preoperative conditions of the patients.

Our study showed an increasing of mortality with delayed surgery but only for patients ASA1 and ASA2.

Choi *et al.* [11] did not find significant differences of mortality and post-operative complications among groups treated within or after 3 days from hospitalization.

Our work does not agree with these conclusions but for post-operative transfusion.

Our results shows that death patients' percentage increases of 15% from Group A to Group B and other 10% from Group B to Group C. There seems not to be differences between bedridden patients, patients on wheelchair and patients with medical walker among three groups. There are differences in ambulating patients, with or without crutches: increase of 10% of mortality from each group to the other with increasing of time to surgery.

Looking at data significance, it was possible demonstrate by Chi Square test a significant difference for ambulation (P: 0.0398) and nearby significance for mortality (P: 0.0599). This may be due to small number of patients, however P value obtained is nearby significance and let suppose a potential correlation between these events analyzed.

In order to analyze the influence of clinical conditions on clinical outcome, data were organized on ASA score classification. The study of Yeho and Fazal analyzed the effect of ASA score on time to surgery and patients outcomes, were time to surgery was secondary to patients conditions and operating theater availability [12]. Our results agrees with the results of this study in therms of hospital stay and complications, but in our study is also evaluated the effect of early surgery on patients outcomes, even in patients with ASA 3 or more.

Analyzing data for patients ASA 1 mortality increases of 25% from Group A to Group B and other 20% from Group B to Group C; contemporary there is a massive reduction of ambulation capability with increasing of time to surgery.

Evaluating ASA 2 patients variations of mortality and ambulation ability has the same trend of ASA 1 patients, with 10% of difference among three groups.

ASA 3 patients have 8% increase of mortality between Group A and Group B.

Comparing ASA score without division in groups based on time to surgery, mortality

and ambulation show a decrease: of 10% of mortality from ASA 1 to ASA 2 and an increase of 30% from ASA 2 to ASA 3; ambulation does not change from ASA 1 to ASA 2 and decrease of 30% from ASA 2 to ASA 3.

These suggests a role of patients clinical status on final outcome, and a predominant influence of time to surgery on ASA 1 patients outcome; a middle influence in ASA 2 and a marginal effect on ASA3, where survivor is already affected by a strong presence of comorbidity.

Looking at postoperative complications, Group A showed a percentage lesser of 5% then Group B and C that has the same percentage of post-operative complications.

Evaluating data on ASA score:

In ASA 1 and ASA 2 patients with the increasing of time to surgery, there is an increasing of post-operative complications; 15% - 20% among ASA 1 Groups and 10% ASA 2.

In ASA 3 patients with the increasing of time to surgery complications reduces of 20% from Group A to Group C.

This suggests that also for post-operative complications, benefits of early surgery are more evident for ASA 1 and ASA2 patients, and that a short time to surgery for ASA 3 increases early complications.

Looking at complications on ASA score, removing Groups based on time to surgery, there is an increase of 10% from ASA 1 to ASA 2 and of 20% from ASA 2 to ASA 3. These differences are statistically significance at Chi Square Test.

These data show a strong influence of pre-operative clinical conditions of patients on post-operative early complications that matches with influence of early surgery.

Looking at blood transfusions: in Group A, blood transfusions are 10% less than other groups.

Evaluating patients on ASA classification we can see that in ASA 1, patients that need blood transfusion are 20% less than the total.

In ASA 2 group percentage increases from Group A to Group B of 25% and decreases of 10% from Group B to Group C.

In ASA 3 patients there is not influence of time to surgery, and transfusion need is just above 50%.

Comparing data only on ASA score, ASA 2 and ASA 3 patients show an increase of 30% of blood transfusion then ASA 1 patients, Chi Square is just above significance.

This suggests a higher influence of pre-operative clinical conditions of the patients on blood transfusion need, and a non-relevant influence of time to surgery.

5. Conclusions

Results of the study in patients with femur neck fractures show an increase of mortality and a worst ambulation capability associated with increasing of time to surgery in patients with ASA score 1 and 2. ASA score has shown to have influence on mortality and ambulation capability.

Early complications are shortened by early surgery in ASA 1 and ASA 2 groups, not

in ASA 3 where they increase. Even complications are influenced by pre-operative conditions, more than mortality and ambulation.

Blood transfusions are not influenced by early surgery, but seem to be influenced by ASA score; there is an increase of blood transfusions with increasing of ASA score.

The short number of patients and retrospectivity represent limit of this study, even if significant results suggest that with a higher number of patients results will be stronger.

This study suggests that early surgery is a good choice for patients with ASA score 1 and 2, but for patients with ASA 3 is better evaluate the option of delayed surgery.

Other studies will be useful to find a correct guideline to better treat these patients.

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