The Influence of Oral Administration of Simvastatin on Delayed Non-Union Facial Fractures-Clinical Study

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Abstract: In this study ten patients with delayed facial fractures presented to our clinic, three of them were in the Research institute of ophthalmology clinic, dental and maxillofacial unit and the other seven were in AL Haram hospital clinic, maxillofacial unit. The patients were in a range of age 25-45 years old, two females and eight males (table.1). All of the patients had non-union fibrous healing and most of them had facial scars at different sites of the face. Others had a chief complaint of pain or numbness of different areas of the face. All of them underwent physical, clinical and radiographic investigations using computed tomograph. Reduction of bone fragments using bone holder was done. The infraorbital nerve was evaluated and decompressed when necessary. Following alignment of the fractures, fixation was maintained by a titanium miniplate and in some cases microplates and screws, after adaptation of the plates to the area. Postoperative care included antibiotics (Clindamycin 300mg.) for a total of 7 days, ice compresses intermittently for 24h., Voltaren 75mg. I.M. every12 h.. Simvastatin (zocor 20 mg. tab.) daily dose was prescribed only to five patients for 3 months (group1) while the other five patients received only the ordinary postoperative prescription (group 2). The aim of this study is to evaluate the effect of oral administration of simvastatin drug on accelerating delayed non –union fractured bone healing. Results: Follow up of the cases revealed slight edema, swelling and hematoma in the first2 weeks; however, it was less in simvastatin group patients, while no infection was noticed in all the patients. Clinical examination of the patients revealed good stability of the bones immediately postoperative. Three months postoperative CT. and/ or three dimensional (3D) facial bone CT scans for all patients revealed that the displaced bone was reduced to its normal anatomy. . It was noticed that patients on the regimen of simvastatin (zocor tablets) (group1) had ameliorated recovery without any complications than in (group2), as the inflammatory reaction was more severe in this group. Bone healing seemed to be accelerated as seen in the CT. radiograph in (group1). At 6-month follow- up, all patients complained of no particular discomfort in everyday life activities and were satisfied with their external appearance. Conclusion:-From this study it could concluded that oral administration of simvastatin 20mg.tablets (zocor) could be prescribed as a regimen postoperatively for all patients with fractures specially in delayed cases for acceleration of bone and soft tissue healing and enhancement of postoperative inflammatory reactions.
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1. Introduction

Maxillofacial trauma has recently increased due to increases in social activities and advances in diagnostic methods [(1)]. The evaluation and treatment of maxillofacial trauma tends to be delayed when it is associated with injuries to other parts of the body. If treatment is delayed due to concurrent systemic diseases, permanent facial deformities may be unavoidable because surgical manipulation is frequently difficult or even impossible. Considering that maxillofacial injuries occur mostly in younger subjects [(2)], the problem of aesthetic outcome is especially serious.

Still today, there is no classification of non-unions in maxillofacial traumatology. There is a broad spectrum of definitions that simultaneously describe the pathological conditions and functional implications determined by the anatomical location of the fractures and the time factor.

Weber, in 1973, introduced the term "pseudo-arthrosis" to describe an altered process of bone healing characterised by the presence of fibrous tissue interposed between the fracture segments, that was lined with cartilaginous tissue and joined by a capsule; Spiessl, in 1988, used the term "non-union" to define any alteration of the bone healing process after a time period of more than 6 months from the initial traumatic event; Rosen, in 1990, proposed a new classification of the modes of altered bone healing in fractures, distinguishing 5 categories: delayed consolidation, non-union, non-union vascular, non union avascular, pseudoarthrosis. There is also the term "poor bone positioning", This term describes the incorrect anatomical position of the

bone fragments despite perfectly normal healing according to Gruss. [3]

A substantial part of the maxillofacial surgery practice deals with maxillofacial bone healing. In the past decades, low-intensity ultrasound treatment has been shown to reduce the healing time of fresh fractures of the extremities up to 38%, and to heal delayed and non-unions up to 90% and 83%, respectively. Based on the assumption that the process of bone healing in the bones of the extremities and maxillofacial skeleton is essentially the same, the potential of ultrasound to stimulate maxillofacial bone healing was investigated. Although limited evidence is available to support the susceptibility of maxillofacial bone to the ultrasound signal, ultrasound may be of value in the treatment of delayed unions, in callus maturation after distraction, and in the treatment of osteoradionecrosis [4].

Statin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is the first-line drug for hyperlipidemia, and it has been recognized to be a safe and low-priced drug [5–7]. As a result of its worldwide long time usage statin has multiple functions including antiinflammation, bone formation by improving the osteoblast function via the BMP-2 pathway and suppresses osteoclast function; resulting in enhanced bone formation . [8, 9]

Statins can also induce angiogenesis, and improve the vascular endothelial cell function. For this reason statins could be used either alone or in combination with other bone substitute material(BSMs) for enhancement of its properties and acceleration of bone formation. [10, 11]

Statins include naturally occurring lovastatin, chemically modified simvastatin and pravastatin, and the synthetically derived atorvastatin, fluvastatin, and cerivastatin. Simvastatin has shown to be among the most potent in stimulating bone growth.[12,13,14]

Some authors have associated the use of statins, hypolipidemic drugs, and new bone formation to evaluate the effect of locally administered simvastatin on bone healing. It was concluded that locally administered simvastatin was detrimental to the repair of defects in the calvaria of rats.[15]

Suppression of residual ridge resorption after tooth extraction is a hot spot in dental research. Recently, simvastatin was reported to influence bone turnover by stimulating bone formation. The effect of simvastatin application on residual ridge resorption following tooth extraction was investigated. The findings indicate that local application of simvastatin would effectively preserve the residual alveolar bone by promoting bone formation in extraction socket.[16]

In other study simvastatin was administered either subcutaneously or directly to the fracture area, with the goal of stimulating fracture repair at acceptable doses. It was concluded that dramatic positive effect on biomechanical parameters of fracture healing by simvastatin treatment directly applied to the fracture area was obtained. [17]

HMG-CoA reductase inhibitors, statins, are widely prescribed to lower cholesterol. High doses of orally administered simvastatin have previously been shown to improve fracture healing in a mouse femur fracture model. [18]

The aim of this study is to evaluate the effect of oral administration of simvastatin drug on accelerating delayed non –union fractured bone healing.

2. Patients and Method:

In this study ten patients with delayed facial fractures presented to our clinic, three of them were in the Research institute of ophthalmology clinic, dental and maxillofacial unit and the other seven were in AL Haram hospital clinic, maxillofacial unit. The patients were in a range of age 25-45 years old, two females and eight males (table.1). All of the patients had non-union fibrous healing and most of them had facial scars at different sites of the face (Fig.1). Others had a chief complaint of pain or numbness of different areas of the face. All of them underwent physical, clinical and radiographic investigations using computed tomography (CT) (Fig.2, 3, 4, 5). The importance of the eye evaluation was stressed when indicated. Pre-and postoperative ophthalmic examination included assessment of visual acuity, papillary reaction ,and extraocular mobility. The degree of enophthalmos was assessed by direct observation from beneath the chin. The patients were prepared for general anesthesia. . In one case polyethylene sheet implant was needed to correct a missed bone segment of inferior orbital rim, the sheet was soaked in hot saline (autoclaved) for 10 min., to which a first generation cephalosporin had been added .The implant was molded and adapted to a template of the anatomy of the area, then fixed and secured to the site using microscrews.Irrigation and debridment of the wounds were done before closure using 4/0 Vicryl suture. For all patients with subciliary incision, a 4/0 silk suture was placed in the lower lid and taped to the forehead (Frost suture) for 48h. .This helps to redrape the lower lid and improves lymphatic drainage (19). All patients received the steroid methylpredisolone sodium 125 mg I.V.during the procedure.

Postoperative care included antibiotics (Clindamycin 300mg.) for a total of 7 days, ice compresses intermittently for 24h., Voltaren 75mg. I.M. every12 h.. Simvastatin (zocor 20 mg. tab.) daily dose was prescribed only to five patients for 3 months (group1) while the other five patients

received only the ordinary postoperative prescription (group 2).

Fig. 1: Preoperative picture showing scars on the nasal bridge and right upper eye lid with telecanthus. case.(Case No. 1)

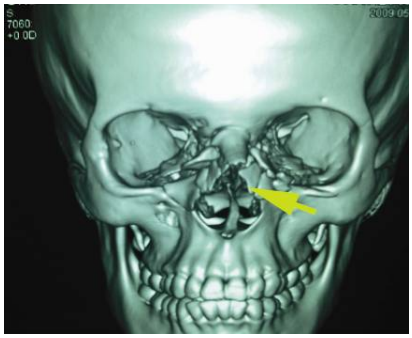

Fig. 2: Photograph showing reconstructed 3D from CT of the same

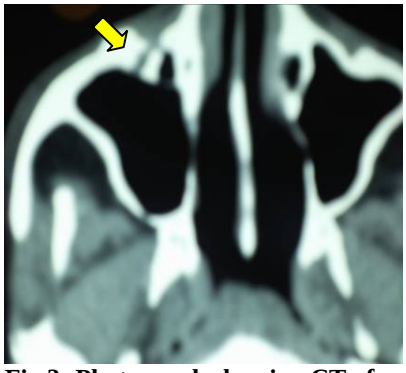

Fig.3: Photograph showing CT of another case with fractured inferior orbital rim impinging on the infraorbital foramen. (Case No.2)

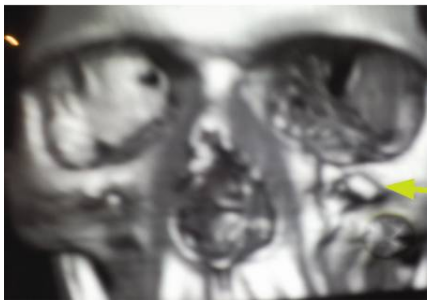

Fig.4: Photograph showing reconstructed 3D from CT of the same case.

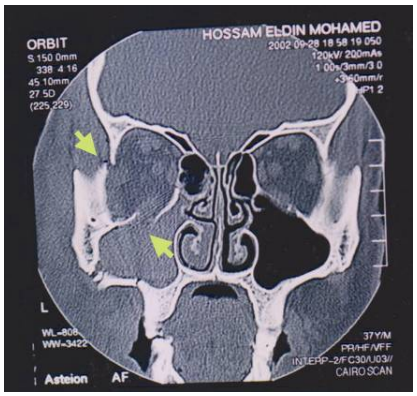

Fig.5: Photograph showing coronal cut CT of case 3 fracture of the lateral and inferior orbital rim.

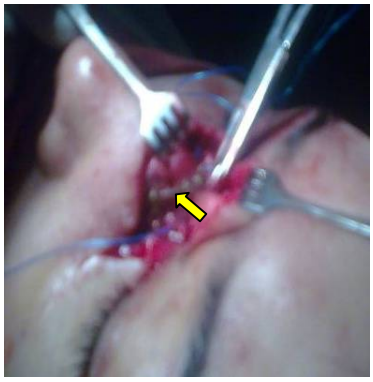

Fig. 6: Picture showing plating of the nasal bridge and bone. (Case No. 1)

Table (1): List of cases:

Case no.	Age	Sex	Delay	Site of fracture	Chief complaint
1	٢٧	female	3/ m.	Nasal bridge and nasal bone with telecanthus	Esthetics
٢	٣٥	male	٤/ m.	Inferior orbital rim pressing on the inferior orbital foramen. R	Pain at the area of the cheek with numbness of the upper lip
٣	٣٧	male	٢ / m.	Inferior and lateral orbital rim. L	Esthetics
٤	٤٠	female	٨/ m.	Inferior orbital rim with deformity of the lateral corner of the eye. R	Esthetics
٥	٢٥	male	٢ /m.	Anterior maxillary wall and lateral nasal bone. L	Esthetics
٦	٤٢	male	٨ /m.	Inferior orbital rim medial side with diplopia and lateral motility restriction of the eye	Diplopia
٧	٣٠	male	٤/ m.	Inferior orbital rim with lateral nasal bone. L	Numbness at the area of the cheek and esthetics
٨	٣٥	male	٣/ m.	Anterior maxillary wall and lateral nasal bone. R	Esthetics
9	30	male	4/m	Inferior and lateral orbital rim with diplopia due to motility restriction of the upper gaze	Esthetics and Diplopia
10	45	male	3/m	Anterior maxillary wall and lateral nasal bone. L	Esthetics

3. Results:

Follow up of the cases revealed slight edema, swelling and hematoma in the first2 weeks, however, it was less in simvastatin group patients, while no infection was noticed in all the patients .Pain and edema was controlled by analgesic and anti-inflammatory drugs. Clinical examination of the patients revealed good stability of the bones immediately postoperative. Three months postoperative CT. and/ or three dimensional (3D) facial bone CT scans for all patients revealed that the displaced bone was reduced to its normal anatomical location(Fig.7,8,9,10)..In case no.1 the patient was referred to ophthalmic plastic surgeon for correction of the old scares, dropping of the upper eye lid ,and reconstruction of artificial eye. In case no.3 also artificial eye was needed. In case no.2 the trigger zones of pain on the cheek disappeared immediately postoperative but the numbness of the upper lip lasted for 6months postoperative.

In case no. 4 in which polyethylene sheet was used some inflammatory reaction appeared in the eye, however, no implant extrusion occurred .In case no.6&9 diplopia was improved 2 weeks postoperative and the eye movement returned to its normal range immediately postoperative. It was noticed that patients on the regimen of simvastatin (zocor tablets) (group1) had uneventful recovery period without any complications than in (group2) as the inflammatory reaction was more severe in this group. Bone healing seemed to be accelerated as seen in the CT. radiograph in(group1). At 6-month follow- up, all patients complained of no particular discomfort in everyday life activities and were satisfied with their external appearance (fig.11,12).

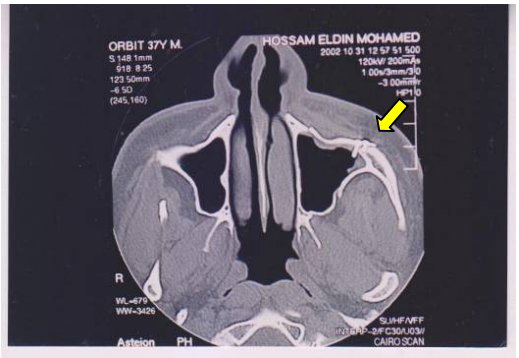

Fig.7.picture showing postoperative CT of case no.3

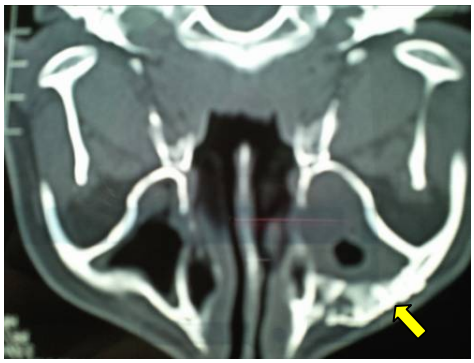

Fig.8.picture showing postoperative CT of case no 2. arrow showing the plate

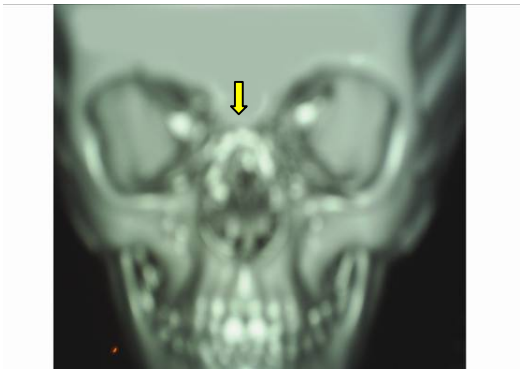

Fig. 9. Postoperative picture reconstructed 3D CT of case no. 1 showing miniplates fixed on the nasal bone &bridge

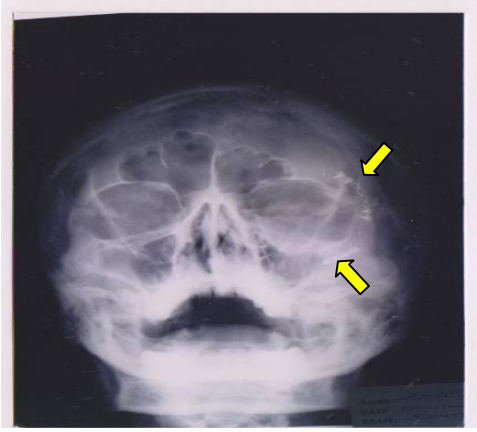

Fig.10. Postoperative picture showing sinus view of case no.3 with miniplates fixed to the lateral and inferior orbital rim

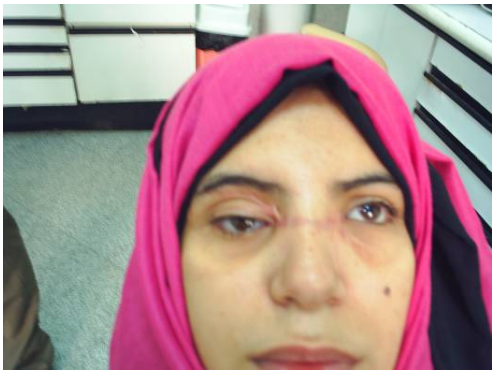

Fig.11.picture showing case (no.1) 3 months postoperatively

Fig.12.picture showing case (no.1) 6 months postoperatively

4. Discussion:

Traumas to the head and neck area can result from various causes including traffic accidents, violence, sports injuries and industrial accidents. It has been reported that associated injuries occur in approximately 30 percent of patients who sustain

facial trauma [20]. Maxillofacial injuries are often neglected in patients with serious clinical conditions such as intracranial injury and injury to the cervical spine. In cases that have neurosurgical conditions or underlying medical diseases, surgical manipulation may be difficult, and the success rate of the surgery may be lowered due to the delay in treatment. Some times fracture sites start to heal spontaneously 10 to 14 days after trauma without immediate management, healing of the fractures could be completed in a normal way after 2or 3months causing maluonion or fibrous tissues formation and multiple fracture lines may prevent normal healing to occur causing non-uonion and sever deformity of the face . It is generally accepted that fracture reduction is difficult or impossible in delayed maluonion cases even with the maximal force possible with an extractor. Such delayed cases may require surgical procedures such as loosening of the bony fragment by refracturing previous fracture sites with an osteotome [21] or plugging up the defect area using grafts [22].

In this study all patients had fibrous non-union fractures so reduction was not complicated, hwoever, some missed very small parts of the bone and other deeply displaced ones in some cases caused few changes of the normal anatomy. In(group1) simvastatin administration from the first day post operative makes the course of healing more easy and smooth due to its anti-inflammatory effect and angiogenic activity[10] ,in addition to its function of bone formation by improving the osteoblast function via the BMP-2pathway and suppressing osteoclast function; resulting in enhanced bone formation[8,9].In clinical studies the difference between (group1) with simvastatin oral administration and(group2) without simvastatin could not be obviously detected with accurate parameters as in the experimental studies ,however, the accelerated recovery and the improved clinical picture of the patients indicates that simvastatin 20mg.as daily dose tablets had an effective role in acceleration of recovery of patients with delayed fractures and bone healing in agreement with Skoglund B .and Aspenberg P., .who claimed that oral administration of simvastatin has previously been shown to improve fracture healing in a mouse femur fracture model. [18]

5. Conclusion:

From this study it could concluded that oral administration of simvastatin 20mg.tablets (zocor) could be prescribed as a regimen postoperatively for all patients with fractures specially in delayed cases for acceleration of bone and soft tissue healing and enhancement of postoperative inflammatory reactions.

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