The Effect of Postoperative Dexamethasone on Wound Healing After Rigid Fixation of Facial Fracture

"Randomized Clinical Trial"

A thesis

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Introduction

Introduction

Edema is a pattern of swelling. Simply, when any part of the body becomes swollen because fluids accumulate in its tissues, this is called edema. Edema could be formed by inflammation, postsurgical, water retention, as symptom of various diseases (congestive heart failure, kidney disease, liver disease, low proteins level in blood and some lung conditions), lymphatic obstruction, deep venous thrombosis, allergy or as side effect of some medications. Inflammation and edema post any surgical maneuver is inevitable including reduction and fixation of maxillofacial fractures.[1-7]

To control such swelling, edema and pain, anti-inflammatory drugs are used. The most common anti-inflammatory drugs are either non-steroidal anti-inflammatory drugs, proteolytic enzymes (trypsin and chymotrypsin) or corticosteroids.[8-11]

Approximately half of the surgeons use perioperative glucocorticoids to control postoperative edema according to questionnaire to North American members of the American Society of Maxillofacial Surgeons. Although glucocorticoids control postoperative edema, pain, nausea and vomiting, this drug has several adverse effects.[12]

These adverse effects include growth retardation in children, immunosuppression, hypertension, inhibition of wound repair, osteoporosis, and metabolic disturbances. So prolonged use of glucocorticoids is usually avoided unless there is no alternative.

The exposure of the fracture site resulted in surgical wound which undergo the normal sequence of primary wound healing and as previously mentioned , one of the adverse effects of the glucocorticoids is impaired wound healing.[10]

Several studies [12-19] done to evaluate the effect of glucocorticoids on wound healing. Some of these studies[12, 14-20] compared the use of glucocorticoids postoperatively versus not to use with different patterns of fractures, others[13] compared long term versus short term use of these drugs. Some studies also compared effects of different doses.

Unfortunately, the results of these studies are different and there is still debate whether the perioperative use of glucocorticoids contribute in impairment of wound healing or not and further research is topic worthy.

Review of Literature

Review of literature

Maxillofacial area is considered the most important area of the human body. It extends from the base of the skull to the hyoid bone where very important organs are included in this area. At social life level, face is very important as it is first personal identity in personal relationships and any damage to this region provides some sort of imbalance and mental health problem. The bones of facial skeleton vary in strength from one to another with the zygomatico-maxillary complex being the weakest bone and the frontal bone is the strongest.[21-28]

The incidence of facial fracture is different from one country to another. The degree of civilization and amount of traffic influence the trauma to this part of the body. Motor vehicle accidents, cars, crashes and fights etc, are the most common causes of facial fractures. The incidence of maxillofacial trauma in Jordon in 1998[28] was reported as 74.4%. Another study[28] in United Arab Emirates in 2007 reported that the prevalence of mandibular fracture is 70% among facial fractures. In Japan[28], road accidents 52% is the most common cause of maxillofacial injuries and the most common site is mandibular fracture 56.9%. So the incidence of maxillofacial trauma is ranged from 46.1%to74.4%.[25]

Facial fractures that cause esthetic and/or functional disturbances need to be corrected surgically. The fracture site is exposed, after which the fractured fragments are adjusted to the correct position and fixed with plates and screws. The exposure of the fracture site resulted in surgical wound which undergoes the normal sequence of primary wound healing.

Wound healing is a complex process involving multiple elements of cells, cytokines, growth factors and matrix elements. It is divided into three phases: inflammatory, proliferative and remodeling phases. These three phases are preceded by hemostasis which considered preparation for wound healing. A defect in any phase will result in disturbed wound healing which in turn affect underlying repairing fracture.[29]

Starting with hemostasis, the immediate response to injury is vasoconstriction which is induced by the release of thromboxane and prostaglandin. The injury resulted in exposure of the collagen of the blood vessels to which platelets adhere. The platelets in turn release the content of their granules and continue the coagulation cascade. In addition to controlling hemorrhage, the resulting fibrin-platelet matrix, concentrates growth factors and serves as a scaffold for wound healing.[30-32]

The first phase is inflammation which extend from 3 to 5 days in which Prostaglandins, histamine, serotonin, kinins, and bacterial products cause vasodilatation and capillary permeability, which result in edema. Fibronectin, interleukin-1, tumor necrosis factor, platelet-derived growth factor and other factors attract granulocytes to the wound.[33, 34] After short time of injury, neutrophils appear in the wound and phagocytize debris and bacteria. Neutrophils secrete proteases which digest debris and injured tissues, whereas oxygen-dependent killing mechanisms are used to control bacterial contamination. Local monocytes migrate into the wound and become macrophages during the first 2 days. This microphages not only have phagocytic activity but also produce a wide array of growth factors. In some experiments, it was revealed that wound healing process can proceed without neutrophils but cannot with absence of macrophages. Despite the importance of inflammatory phase in controlling contamination and inducing proliferative phase, prolonged inflammation can cause tissue damage.[35, 36]

The second phase is proliferative phase which extend from 4 to 14 day. Re-epithelialization, angiogenesis and formation of collagen and fibrous matrix occur during this phase. Re-epithelialization starts with the migration of epithelial cells from edges of the wound. Complete re-epithelialization occurred in which epithelial migration and proliferation continue until the wound is covered and an intact epithelial barrier is reestablished. A moist environment helps promote more rapid epithelialization, So washing a surgical incision the day after surgery does increase the incidence of wound healing complications. Because of low oxygen tension and production of lactate, angiogenic factors are released from these poorly perfused tissues and formation of new capillaries starts. Penetration of these new vessels through tissues is facilitated by matrix metalloproteinases. Through 2-3 days, fibroblasts migrate to the wound and start secreting matrix which is primarily

composed of fibrin and fibronectin with supplementation by proteoglycans, glycosaminoglycans and protiens from fibroblasts. Fibroblasts also start secreting immature disorganized collagen type 3 with some of this fibroblasts is stimulated to differentiate into myofibroblast which is responsible for wound contraction. [37-45]

The third phase is remodeling phase which extend from the 8th day to as much as 1 year. During this phase, the fibroblasts continue to form collagen. Collagen synthesis lasts 4 to 5 weeks but turnover may last for 1 year. Gradually, the weak collagen type 3 is replaced with stronger collagen type 1 and fibrils become more organized. The wound strength slowly increases being only 3 % of pre-injury strength after 1 week, 30% after 3 weeks and 80 % after 3 months.[46-50]

Post trauma, the injury itself and surgical intervention cause inflammation. Inflammation is normal body reflex in response to either infection, binding of antigen to antibody, injury or mechanical irritation. These triggers cause synthesis and release of what is called inflammatory mediators. These inflammatory mediators make acute effects on vasculature including localized vasodilatation, increased vascular permeability, plasma proteins extravasation and leukocytes migration in the area of damage to produce classic signs of inflammation and what is called postsurgical edema is formed.[10, 51, 52]

Edema is a pattern of swelling. Simply, when any part of body become swollen because fluids accumulate in its tissues, this is called edema. Edema could be caused by inflammation, postsurgical, water retention, as symptom of various diseases (congestive heart failure, kidney disease, liver disease, low proteins level in blood and some lung conditions), lymphatic obstruction, deep venous thrombosis, allergy or as side effect of some medication. Accumulation of fluids may be intracellular which called intracellular edema or in interstitial tissue which called interstitial edema. Edema formed by trauma or surgery is of the interstitial type.[4, 6, 7]

Edema has a detrimental effect on function the surrounding tissues. As the fluids accumulate in the interstitial tissues, it increases the area of diffusion for oxygen and nutrients of the surrounding cell. By the same mechanism, edema affects the diffusion of harmful byproducts from these cells. On the

other hand, some tissues cannot expand because of the nature of their anatomy such as in bone. Edema in such tissues can compromise their blood supply by increasing the hydrostatic pressure around vasculature. Although limited inflammation is beneficial, excessive or persistent inflammation can cause tissue damage or even death such as in allergic and autoimmune conditions. In addition edema also has serious consequences such as airway obstruction, chemosis with possible transient loss of vision, pain .[2, 3, 5, 51, 53, 54)]

To control such swelling, edema and pain , anti-inflammatory drugs are used. The most common anti-inflammatory drugs are either non-steroidal anti-inflammatory drugs, proteolytic enzymes (trypsin and chymotrypsin) or corticosteroids.[8-11)]

Glucocorticoids are the most potent and widely used anti- inflammatory agents. However, The corticosteroids' adverse effects on wound healing is still under investigation. The anti-inflammatory effect of corticosteroids was first discovered by Hench and coworkers[(55)] in treatment of arthritis in 1949. This was described as medical miracle and this team was awarded the Nobel Prize in medicine the next year. Initial reports from Hench and coworker did not describe any concerns about adverse effects of corticosteroids on wound healing. Ragan et al[(43)] first reported the adverse effect of corticosteroids on wound healing in the same year that Hench et al described their ''medical miracle,''. This was found in 3 of 8 rheumatoid arthritis patients treated with 25 U/day of adrenocorticotropic hormone. These patients was noticed to develop a non healing biopsy site, a non healing episiotomy site and decubitus ulcer, and non healing abscess drainage sites. These led to more studies to evaluate this effect on wound healing.[18, 43, 55-70)]

Corticosteroids are derived from the endogenous hormone cortisol. They are lipophilic molecules that enter cells, bind and activate glucocorticoid receptors. Changing in the structure of cortisol result in corticosteroids having different distribution, different metabolic rate in liver and different affinity to glucocorticoid receptors. . Steroid molecule has a core of twenty carbon atoms bonded together to take the form of four fused rings: three cyclohexane rings and one cyclopentane ring.[71, 72)] (fig.1)

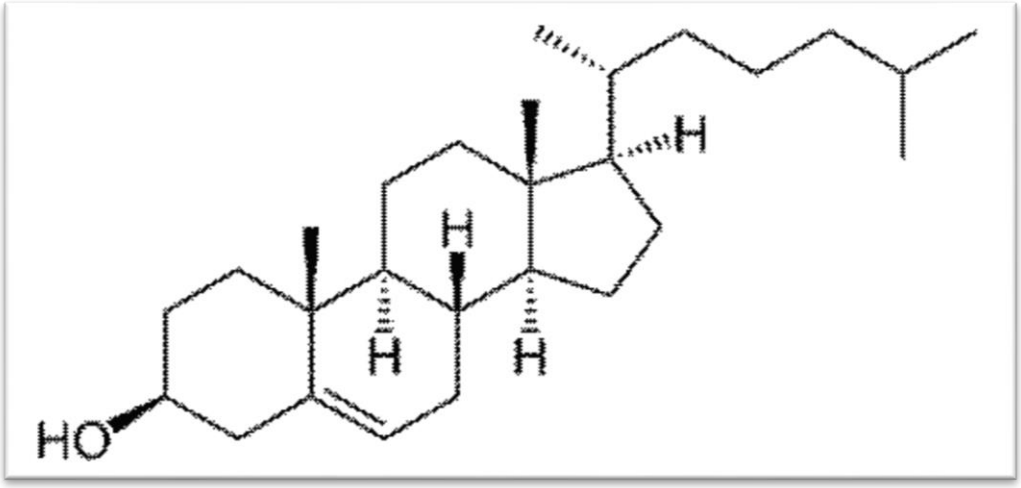

Figure 1: Structure of corticosteroids[71]

Steroids are used to reduce postoperative inflammation, pain, swelling nausea, vomiting and sensory impairment. Steroids are also used to suppress immune response in cases of organ transplant and autoimmune diseases, replacement therapy and to prevent airway obstruction after cleft palate repair. Multiple dermatologic problems are treated by steroids.[71, 72]

Under normal condition, the body produce 15 – 30 mg of hydrocortisone and it can reach 300 mg /day under stressful condition after stimulation of the adrenal gland with adrenocorticotropin hormone from hypothalamus.[71, 73] (fig.2)

Regarding the effect of the corticosteroids on edema, there is controversy in this point. Weber and Griffin in 1994 studied the effect of dexamethasone after bilateral sagittal split osteotomy on facial swelling. They found significant reduction in facial swelling as recorded by computer scanning 1 day postoperatively. On the other hand Gutierrez, Santiago Wuesthoff and Carolina tested the effect of long acting single dose of dexamethasone during perioperative time on edema and they found no reduction in edema in the post operative area.[71, 74]