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The Efficacy of Zinc Supplementation for Accelerate Bone Healing and Reduce Edema, Trismus and Pain as Post-Operative Sequelae in Maxillofacial Surgery: A Literature Review

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ABSTRACT

Maxillofacial surgery involves an operation to correct a disease, injury or defect of face, jaw or mouth. Recently some strategies have been developed for minimizing postoperative discomfort after maxillofacial surgery, including the use of pharmacological therapy and alternative medicine. However, patients still suffer some pain, swelling, and limitation in mouth mobility and other symptoms after surgery. Reducing malaise and postoperative complications is a critical issue for Plastic Reconstructive doctors. Zinc is a group II b metal that is involved in diverse physiological processes such as growth, immune system modulation and tissue repair, significant reduction in the use of analgesics for oral pain, acts as anti- inflammatory agent can promote wound healing, increases the number of osteoblasts by stimulating protein synthesis in the osteoblastic cells and has many impacts on the bone healing process.

KEYWORDS: Zinc, Maxillofacial Surgery, Postoperative Sequelae, Bone Heali

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INTRODUCTION

Maxillofacial surgery is an operation performed by a highly trained plastic surgeon. A variety of maxillofacial procedures can treat diseases, fix injuries or correct defects in face, jaw or mouth.[1] As with any operation, maxillofacial surgery has post-operative sequelae. Recently some strategies have been developed for minimizing postoperative discomfort after maxillofacial surgery, including the use of pharmacological therapy and alternative medicine. However, patients still suffer some pain, swelling, and limitation in mouth mobility and other symptoms after surgery.[2-3]

Wound healing is an intricately coordinated series of processes that involve cellular and subcellular responses to tissue injury, leading to the release of cytokines and growth factors, cell activation, and resultant tissue regeneration. A solid understanding of the repair process is essential for optimizing patients' perioperative healing and is the basis for minimizing iatrogenic injury. It is especially important for surgeons treating maxillofacial injuries to possess a thorough knowledge of the wound-healing process, because nowhere else in the body are the effects of poor healing more noticeable and potentially disfiguring. To optimize the restoration of function and esthetic harmony after facial trauma, the surgeon must also be cognizant of patient-specific comorbidities and understand how health status influences the healing process.[4]

Zinc is a group IIb metal that is involved in diverse physiological processes such as growth, immune system modulation and tissue repair, acts as anti- inflammatory agent can promote wound healing, increases the number of osteoblasts by stimulating protein synthesis in the osteoblastic cells and has many impacts on the bone healing process. A recent oncologic study, zinc showed a significant reduction in the use of analgesics for oral pain. The advantages of this treatment are simplicity of execution, good tolerance of patients, absence of side effects or adverse reactions and high medical-social efficiency. [5,8]

After Surgery, Pain results from damaged tissues, which irritates the nerves. Destruction of tissue during surgery leads to edema and swelling of the face as part of the normal reactive edema. Moderate swelling is a protective reaction to trauma; however, excessive swelling has damaging

consequences and even leads to infection. The mechanism explaining the limited mouth opening is that cutting soft tissue during surgery irritates the temporal tendon and the muscle in nasal alar, causing a reflex spasm.[6,13]

There a study to evaluated a significant difference in Pain at 6h, 24h, 48h & 72 hour between Zinc and Control. In the zinc group, the reduction in Pain is likely due to reduced localized inflammatory response as a result of decreased production of reactive oxygen species and subsequent reduction in COX-2 expression and PGE-2 production. This likely explains the significant difference in the incidence of Pain between the groups. The present study showed that oral zinc lozenge administered 30 min before surgery reduced the incidence of pain, swelling, and trismus till 72h after surgery. Although the use of zinc sulphate did not decrease the incidence of Pain in patients, it decreased the intensity of pain.[13]

EFFECT OF ZINC ON FACIAL BONE FRACTURE HEALING

Maxillofacial fracture is a serious injury in the head region which is frequently found in the emergency room. These injuries can affect both skeletal and soft tissue structures of the facial region and often times, based on the etiology and mechanism of injury, occur in association with other systemic injuries thereby requiring multidisciplinary approach for their management.[1,2]

The present study demonstrated that serum zinc concentration was significantly lower in patients with bone fracture than normal range Zinc supplementation increased serum levels of zinc and alkaline phosphatase activity. It is supposed that an increase in serum zinc and alkaline phosphatase activity may be stimulated by fracture healing and can be defined as biochemical marker of fracture healing, as clinical studies have shown that the amount of skeletal alkaline phosphatase activity in serum can provide a useful index of the rate of bone formation. A study showed indicate that supplementation with zinc for 60 days had a stimulatory effect on callus formation under condition of fracture healing in humans. Zinc is an essential trace metal, has been demonstrated to stimulate protein synthesis due to activation of amino acyl-tRNA synthetase in osteoblastic cells and bone tissues.[7,8]

The oral administration of zinc caused a significant increase in bone components, calcium content, alkaline phosphatase activity, and protein content of rats with fracture healing. It has been suggested that zinc supplementation may be a useful tool as a stimulatory factor for fracture healing. The zinc also can promote osteoblast formation and reduces secretion of cytokines, which may inhibit osteoclast formation and activation.[8] Bone mineral density is appreciably increased by the administration of zinc in fracture healing in rats. The above-mentioned mechanisms are supposed that in the supplement group of this study the stimulatory effect of zinc on callus formation was in bone.[9,10] Given the necessity for zinc in skeletal development and growth, considerable research has been performed assessing the effects of zinc on osteoblast activity. A common finding was that zinc promotes osteoblast proliferation in established and primary osteoblast cell models and in animals.[7,10]

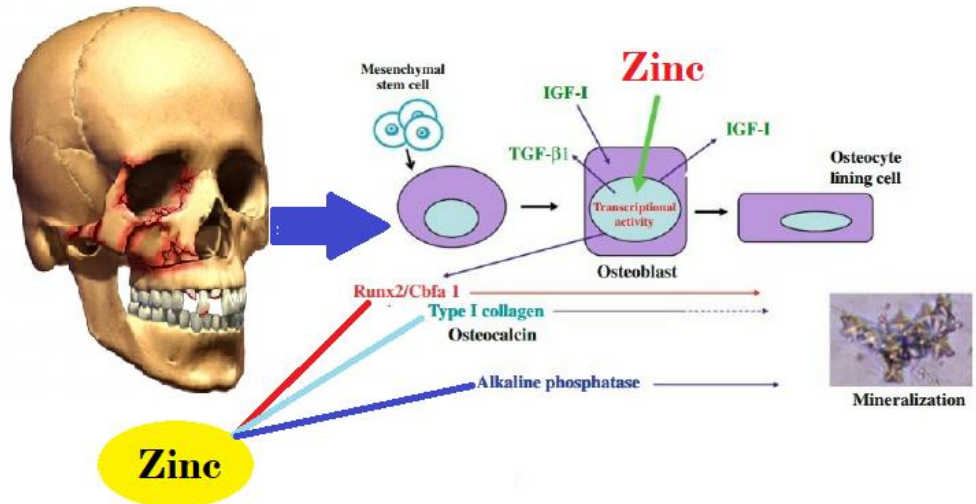

Figure 1. The mechanism of zinc action in stimulating osteoblastic bone formation and mineralization.

Several studies found that addition of zinc to tissue culture media or by growing cells on a substratum containing zinc increases Runx2 (Runt-related transcription factor 2) expression. Similarly, Runx2 expression was reduced in bones from rats fed a zinc-deficient diet. As Runx2 expression is essential for osteoblast differentiation, the results indicate that zinc can be osteo-inductive.[10] Effects of zinc treatment on matrix deposition and calcification by osteoblasts were more complex. Zinc also protects osteoblasts from apoptosis. When MC3T3-E1 cells were cultured in zinc-deficient or zinc-free media, apoptosis rates increased from 7% in normal media, to 75 and 90% respectively. Apoptosis was associated with increased cytoplasmic cytochrome C levels indicative of a mitochondrial activated apoptosis. The addition of zinc to culture media protected against H2O2-induced apoptosis by increasing ZnT7 (Slc30a7) expression

which lead to activation of extracellular-signal-regulated kinase (ERK) and protein kinase B (AKT). ZnT7 transports cytoplasmic zinc into the Golgi apparatus. In addition to the above effects, zinc has been noted to promote osteoblast cell spreading, attachment, and chemotaxis.[7]

ROLE OF ZINC SUPPLEMENTATION FOR REDUCE PAIN AFTER MAXILLOFACIAL SURGERY

Maxillofacial surgery procedure such as Osteotomy has been known to induce changes in the maxillary and mandibular teeth, buccal mucosa, palatal mucosa, and facial skin sensation. Though skin sensation tends to recover over time, even after direct damage to the sensory nerves, it may not completely recover to the pre- surgical condition. Postoperative orofacial pain includes a number of clinical problems involving the masticatory muscles or TMJ, including muscle spasms in the head, neck, and jaw and pain in the teeth, face, or jaw due to the extensive bone and muscle manipulation during maxillofacial surgery.[3,12]

Zinc is abundant in the central nervous system and regulates pain, but the underlying mechanisms are unknown. *In vitro* studies have shown that extracellular zinc modulates a plethora of signaling membrane proteins, including NMDA receptors containing the NR2A subunit, which display exquisite zinc sensitivity. The NMDA receptors play an important role on the pain modulation process. Zinc slows down the NMDA receptor activities through inhibition of glycine receptor binding. The decrease of Zinc however will make glycine-NMDA receptor binding easier and increase NMDA receptors excitability. This will increase the calcium ion intake through ion channel related NMDA receptors, which will later activate nNOS and ends up with the increase of Nitric-Oxide (NO) in the cytosol. Nitric-Oxide as a gas will immediately spread to presynaptic neuron cells and stimulates glutamate production, which will increase the stimulus on NMDA receptor and causes hyperalgesia.[11]

THE MECHANISM OF ZINC AS AN ANTI-INFLAMMATORY IN REDUCING TRISMUS AND EDEMA AS A FORM OF SYMPTOMS AFTER SURGERY

After surgery in the oral and maxillofacial area, trismus and edema can occur often. These could appear cause of inflammation in wound healing process after surgery. During the inflammation phase, a number of important factors align for wound healing and appropriate immune response. Zinc is a required component of proliferating cells, including the cells of inflammation, neutrophils and macrophages.[5]

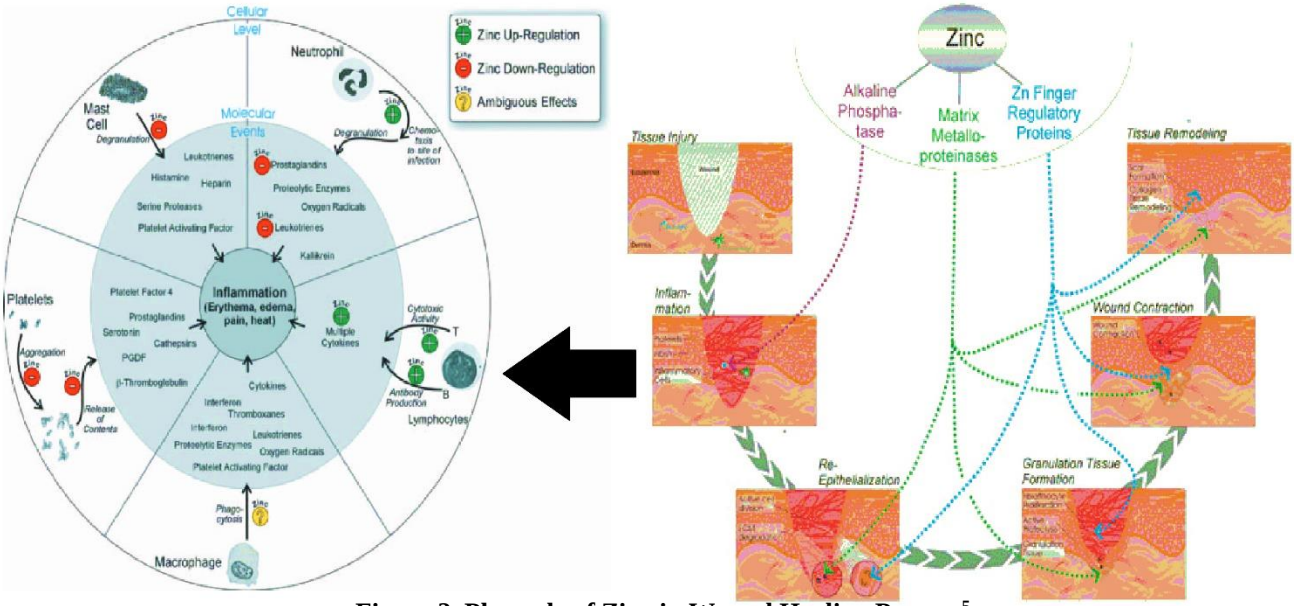

Figure 2. Play role of Zinc in Wound Healing Process[5]

Zinc is partially responsible for synthesis of protein, DNA, RNA and cell proliferation. Neutrophils, simply speaking, clear the wound of debris and signal the inflammatory cytokines, growth factors and enzymes. Macrophages clean the wound through phagocytosis, secrete growth hormones, recruit fibroblasts, create an initial framework for granulation and secrete nitric oxide, which has many functions, including vasodilation, thrombolysis, angiogenesis and cell regulation. Both neutrophils and macrophages are affected by low zinc levels that can cause disturbance in their functions. The result could be increased bacterial burden, wound debris, weakened immune response by the pro-inflammatory cytokines, reduced cell signaling, poor framework creation and slowed angiogenesis. Also occurring during the inflammation phase is free-radical action. Free radicals are effective in killing pathogens but also need to be kept in balance by antioxidants.[14]

Zinc is an essential part of antioxidant function as part of the zinc-copper superoxide dismutase; and a reduction of their action can prolong the inflammatory process in chronic wounds. A prolonged inflammation phase will predispose the patient to infection and delayed healing. The need for zinc is greatest during the inflammation phase. A person with a zinc level on the low end of the normal range could dip into a sub-therapeutic range during this time, resulting in a negative effect on wound healing.[5,15]

A study showed the proposed roles of zinc in MG53 mediated wound healing process. MG53 is an essential component of the cell membrane repair machinery, participating in the healing of dermal wounds. MG53 exists as intrinsic intracellular vesicles which could be secreted into blood circulation as a myokine to mediate wound healing. In response to dermal injury, MG53 could exert the following functions. (a) MG53-containing vesicles nucleate the cell membrane repair machinery and trafficking to damaged cell membrane to protect against acute membrane injury of keratinocytes and fibroblasts; (b) MG53 mediates cytoskeletal stress fibre remodelling to promote fibroblasts migration to the wound sites; and (c) MG53 regulates TGFβ signalling to modulate trans-differentiation of fibroblasts into myofibroblasts and suppresses deposition of ECM proteins during tissue remodelling stage of wound healing. Zinc is proposed to bind to MG53 on its two zinc-binding sites and modulates MG53-mediated wound healing process.[14,15]

DOSE OF ZINC FOR REDUCE POSTOPERATIVE SEQUELAE AND ACCELERATE BONE HEALING

Zinc is an essential trace metal, has been demonstrated to stimulate protein synthesis due to activation of amino acyl-tRNA synthetase in osteoblastic cells and bone tissues. The supplementation of zinc in an amount equal to 40-50 mg could have beneficial effects on bone health in terms of maintaining bone mineral density and faster healing in the event of fractures. Many clinicians recommend administering up to 50 mg of elemental zinc per day until epithelialization is well-established or until the wound is fully closed. Sadighi et al evaluated in their study with gave zinc 50 mg to 30 traumatic bone fracture for 60 days and they found result based bone radiographs significant change in callus formation after 60 days and fracture healing was faster in the patients had supplementation with zinc.[16]

A clinical study from Tanmay Sarkar et al, that preoperative administration of 40 mg dispersible zinc tablet effectively reduces the incidence and severity of postoperative sequelae in the immediate postoperative period.[17] It same with the result from Rajanna et all, zinc 40 mg administered 30 minutes preoperatively can reduce complications including pain, swelling, and limited mouth opening.[13]

CONCLUSION

As conclusion zinc can reduce complications after maxillofacial surgery, including pain, swelling, limited mouth opening, and also increases the number of osteoblasts by stimulating protein synthesis in the osteoblastic cells and has many impact on the bone healing process. Besides, Zinc can promote the recovery effect and improve the quality of life after surgery.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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