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Review Article

The Efficacy of low-intensity pulsed ultrasound therapy on maxillofacial bone healing- A review

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Abstract: Current management of fracture healing does not involve ultrasound therapy. We describe a systematic review of randomized controlled clinical trials of low intensity pulsed ultrasound therapy for bone healing and its clinical efficacy in maxillofacial surgeries. We searched 3 electronic databases (MEDLINE, EMBASE, Cochrane Database of Randomised Clinical Trials) and selected studies done in the area of ultrasound therapy and fracture healing and evaluated separately. Therapeutic effects of ultrasound therapy have been studied in the past few decades and various clinical studies have been published, showing its beneficial results on bone healing and its mechanism of action. Ultrasound treatment is an innovative, noninvasive modality to enhance bone healing, with minimal side effects. It may be considered as an adjunct treatment of choice, in management of fractures, reconstructive surgeries and healing of bony pathologies. Further clinical trials are advised, to access its mechanism of action and application in surgeries of maxillofacial region.

Keywords: bone healing, low-intensity pulsed ultrasound, maxillofacial surgery, therapeutic ultrasound

INTRODUCTION

Bone is a dynamic tissue and its healing is affected by various biomechanical, bio chemical, cellular, hormonal and pathologic factors. Delayed healing or non union, results in functional impairment. In order to overcome this problem and to stimulate bone healing, several therapeutic modalities have been proposed in the literature. These include local and systemic drug delivery, electromagnetic fields, extracorporeal shock, low-intensity lasers and ultrasound therapy [1]. Ultrasound has been used in treating soft tissue disorders and its effects on bone healing are well established in numerous studies published over the past decade. In this article, we discuss the mechanism of ultrasound therapy and its potential to enhance maxillofacial bone healing.

MATERIALS AND METHODS

The review was based on 3 electronic databases (MEDLINE, EMBASE, Cochrane Database of Randomised Clinical Trials) for trials of ultrasonography and fracture healing, published from 1939 to December 2014. In addition, selected journals were searched by hand for relevant articles, in the area of ultrasound therapy and fracture healing. Trials selected for review met the following criteria: random allocation of treatments, inclusion of skeletally mature patients of either sex with 1 or more fractures, administration of low-intensity pulsed ultrasound treatments to at least 1 of the treatment groups; and assessment of time to fracture healing, determined radiographically on follow up visits.

Historical perspective

The foundation of ultrasound was laid in 1880, by Jacques and Pierre Curie, when they discovered that some crystals produce acoustic waves, if alternating current is applied to them at their resonance frequency [2] (piezoelectric effect). Pohlman in 1939 [3], first used ultrasound in treatment of back pain, neuralgia and myalgia. Dussik in 1942 [4], used ultrasound beams to locate brain tumors and cerebral ventricles. Initially, it was believed that ultrasound caused damage to the bones, but in 1950 Maintz [5], first published its stimulatory effects on bone healing in rabbits, by exposing radius osteotomies to 0.5, 1, 1.5 and 2.5 W/cm^2 , but also concluded, atrophy of bone, when exposed to higher intensities. In order to reduce the thermal damage Shiro [6] advocated, use of lower doses and applied, pulsed ultrasound which showed increased osteoblastic and chondroblastic activity, at an intensity of 0.2 W/cm^2 . Halsscheidt [7], treated two cases of osteoradionecrosis, in which ultrasound treatment, caused fresh granulation tissue formation over non healing bone. Xavier and Duarte [8] reported, complete healing in 27 non-union cases by applying low intensity pulsed ultrasound at 30mW/cm^2, for 20 minutes. The first randomized double-blind controlled study of LIPU, was on tibia fractures in humans, published by Heckman *et al*. [9], they reported accelerated fracture healing rate by 38%. Kristiansen *et al*. [10] reported accelerated healing of dorsal radius fractures with LIPU treatment. Tsai *et al*. [11] showed greater mineral apposition in rabbit fibula fractures, treated with 1.5-MHz compared with 3- MHz ultrasound, at an intensity of 500 m W/cm^2. Azuma *et al*. [12] implied that LIPU treatment accelerates all phases of fracture healing. Currently LIPU devices are cleared for local application, by US Food and Drug Administration in 1994, for treatment of fresh, closed fractures, planned for closed reduction [13].

Insight into the Mechanism of Ultrasound on Bone Healing

New bone forms by endochondral ossification (transformation of cartilage to bone), intramembranous ossification (calicification around an organic matrix) or by appositional ossification (growth of new bone over existing one) [14]. Healing of fractures occurs through three stages, first the inflammatory stage, the repair stage and lastly the remodeling stage [15]. In the first stage, hematoma develops and fibroblasts infiltrate in the fractured site, forming granulation tissue, migration of mesenchymal cells occurs and vascular tissues grow within the fractured segments. Repair stage comprises of formation of collagen matrix and angiogenesis, leading to development of callus and providing stability to the fractured bone.

In the remodeling stage [16] bone healing is completed by combination of bone resorption and formation. Ultrasound therapy enhances bone healing by cellular responses through a combination of physical, piezoelectric and biological effects.

Physical Effects

As the ultrasound waves penetrate the tissues, it causes vibrations in cell membranes, intracellular and extracellular fluids, this results in movement of particles in the tissues [17, 18] causing micromassage effect and its mechanical stimulation. Acoustic vibrations have both thermal and non-thermal effects, but for bone healing lower intensities at 20 to 50m W/cm^2 is used, which generates increase in heat less than 1°C, thus resulting in no thermal damage. Non thermal effects of ultrasound are stable cavitation, microstreaming and acoustic streaming. Stable cavitation, is defined as the formation of gas bubbles due to ultrasound energy. These bubbles are of different shape and sizes and causes local movement called microstreaming in the body fluids [19]. Acoustic streaming is the eddying of fluid around gas bubbles [20], resulting in high velocity streams of fluid, through which intracellular and extracellular ions move and permeability of cell membranes are altered. These alterations, changes the electrophysiological properties of the cells and decreases their need for adenosine triphosphate consumption by sodium-potassium channels [21].

Piezoelectric Effects

It is the increase in electrical potential when pressure is applied on the bone [22], which induces bone remodeling. According to Wolff's law [23], bone remodels based on functional demands, but this active loading on the skeleton is lost after fractures. Ultrasound serves as a surrogate for regulatory signals, by generating piezoelectric effects and increasing the electrical potentials in the bone and helping in fracture healing [24].

Biological Effects

Application of LIPU stimulates aggrecan messenger RNA expression [25], proteoglycan synthesis by chondrocytes [26], and increase in prostaglandin E_2 synthesis by osteoblasts [27], also there is an increase in synthesis of platelet-derived growth factor [28]. Due to the physical effects, permeability of cell membrane is altered, which in turn causes changes in second messenger activity, leading to functional changes in gene expression and regulation of cartilage and bone specific genes [29, 30]. Studies have confirmed an increase in transforming growth factor β expression, increased outflow of potassium ions from intracellular spaces and increased deposition of calcium ions [3, 32]. Ultrasound therapy, increases angiogenesis related cytokines e.g interleukin 8, fibroblast growth factor and vascular endothelial growth factor [33], which promotes capillary formation at the fracture site and enhances bone healing.

Clinical Applications

Many research studies conducted on healing of long bones, have shown beneficial effects of ultrasound therapy, but its use in maxillofacial region have been limited and the results where controversial. One of the first study, was reported by Cavaliere [34], he applied ultrasound at high intensities (1-2W/cm^2) in 4 patients with mandibular fractures and showed increased callus formation and less pain. Harris [35] in 1992 applied ultrasound at 3MHz and 1W/cm^2 for 40 days to treat osteoradionecrosis of mandible and found accelerated growth in 10 of 21 patients. To achieve normal occlusion and function, is the main aim in treatment of maxillofacial fractures, even though rigid fixation is the common treatment modality in such cases, still there are few indications for closed reduction. Prolonged intermaxillary fixation causes feeding impairment, temporomandibular joint problems, compromised dental and periodontal status. In order to reduce the period of IMF, LIPU is advised. Mayr *et al.* in 2000 [36], concluded that ultrasound treatment had 88% success rate in cases of delayed or non unions. Apart from fracture management, ultrasound can influence bone healing, in reconstructive surgeries such as osteotomies [37], bone grafting and distraction osteogenesis [38]. In treatment planning of dental implants, usually 3 months waiting period is advised after surgical placement of implants, to allow complete osseointegration, it has been suggested that ultrasound stimulates bone ingrowth in such cases [39] and is used in resorbed or atrophic bones.

Complications and Side Effects

LIPU generates low intensity energy, which is equal to diagnostic doses. These pulsed signals have negligible thermal effects on tissues. Adverse reactions, reported in the literature are muscle spasms, mild erythema and mild swelling [32]. Ultrasound signals do not interfere with metal implants and its use in such areas are considered safe [40]. In areas with acute infections and tumours, its use is contraindicated, as it may cause progression of the disease. Patients on pacemakers should avoid ultrasound therapy, as it interferes with its function.

Future of Ultrasound Therapy

Osteoporosis is a major disease in developing countries, osseointegration around metal implants is impaired in these patients, and ultrasound signals have shown good results in such cases. As ultrasound therapy increases soft tissue wound healing [41], it is advised in open and comminuted fractures. Osteoradionecrosis, occurs due to hypoxia, hypocellularity and hypovascularity, after radiation doses, conventional treatment followed is surgical debridement, intravenous antibiotics and hyperbaric oxygen therapy. Ultrasound has been proved to increase vascularity and should be used as an adjunct therapy in reconstructive procedures post radiation.

CONCLUSION

Although ultrasound has been used since 1939, its use in fracture healing was established in the past few decades only. Ultrasound therapy has shown accelerated healing in delayed or non unions, callus consolidation after distraction and as a supportive measure in osteoradinecrosis. It is a noninvasive treatment modality with minimal complications or side effects. Still additional research is advised in this field to determine the beneficial potential and feasibility of ultrasound in maxillofacial region.

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