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Low-intensity pulsed ultrasound for bone healing: An overview

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Summary Low-intensity ultrasound is a biophysical form of intervention in the fracture-repair process, which through several mechanisms accelerates healing of fresh fractures and enhances callus formation in delayed unions and nonunions. The goal of this review is to present the current knowledge obtained from basic science and animal studies, as well as existing evidence from clinical trials and case series with the different applications of ultrasound in the management of fractures, delayed unions, nonunions and distraction osteogenesis. Low-intensity pulsed ultrasound is currently applied transcutaneoulsy, although recent experimental studies have proven the efficacy of a trans-osseous application for both enhancement and monitoring of the bone healing process with modern smart implant technologies.

Introduction

Since the 1950s, researchers working on dry bone noted that bone subjected to stress, generated an electric potential from the concave to the convex side. This work on piezoelectric properties of bone was first published in the Japanese literature and initially was not widely appreciated in the West.[19] However, one of the fundamental concepts in orthopaedics is the understanding that the mechanical environment at the site of a fracture influences the pattern of fracture repair.[7,11,15,41,42,54,58,65]

The millions of fractures occurring annually as a result of human activity, mobility and from bone fragility, initiate a natural healing process of callus formation. The healing of a fractured bone involves the spatial and temporal coordinated action of several different cell types, proteins and the expression of hundreds of genes working towards restoring its structural integrity. In about 4—10%, impairment of the healing process may lead to delayed union or nonunion, requiring further surgical procedures.[17] In both cases pain, suffering and substantial morbidity become a major contributor to personal, societal and health care system expenses. The length of time to healing is also an important

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parameter with direct implications on the physical, emotional and monetary costs.[28]

In daily practice, the treating physician is challenged not only to manage the initial fracture using any of the least or noninvasive means available to enhance osteogenesis, but also to detect complications in the repair process early on that might necessitate prompt intervention. Currently, the assessment of fracture healing is performed by clinical and radiographic examination, both of which are dependent on the orthopaedic surgeon's expertise and clinical judgment.[3,12,25,62]

During the past 50 years, an intense effort has been made to enhance fracture healing using physical and biological methods. Physical methods include the use of mechanical stimulation,[23] electromagnetic fields[56] and low-intensity pulsed ultrasound. Low-intensity pulsed ultrasound (LIUS) is a form of mechanical energy that is transmitted through and into biological tissues as an acoustic pressure wave and has been widely used in medicine as a diagnostic and therapeutic tool.[69]

Basic science

In vitro studies using cell cultures and research on experimental fractures in animal models have demonstrated a stimulatory biologic effect of low-intensity ultrasonic energy on the intracellular activity, cytokine release and the bone healing process.[6,33] In animal models, ultrasound appears to alter the time course or the sequence of gene expression of several genes, notably aggrecan, which is a proteoglycan involved in enchondral osteogenesis.[24,64,67] Low-intensity ultrasound elevates intracellular calcium in cultured chondrocytes and stimulates endochondral bone formation in vitro.[39,49,64] It also has direct effects on cell physiology by increasing the incorporation of calcium ions in cartilage and bone cell cultures and by stimulating the expression of numerous genes involved in the healing process.[48,67] It alters potassium flux across the cell membrane in cultured thymocytes,[6] and it modulates adenyle cyclase activity and TGF-b synthesis in osteoblastic cell lines.[38,48] In addition to modulating gene expression, ultrasound may enhance angiogenesis and increase blood flow around the fracture.[45] Despite these well documented studies, the mechanism through which LIUS interacts with living tissue and stimulates bone healing remains unclear.

In addition to the above-mentioned molecular interactions, the acoustic pressure waves at the fracture site, facilitate fluid flow which, in turn, increases nutrient delivery and waste removal (acoustic streaming phenomenon), thus stimulating proliferation and differentiation of the fibroblasts, chondroblasts and osteoblasts.[24,48] In addition, the acoustic pressure waves produce micro-stress fields resulting in a mechanical response of the bone, analogous to the phenomena described by Wolf's law.[47] Small temperature fluctuations ($<1\,^{\circ}\mathrm{C}$) appear at the fracture site as a result of the conversion of ultrasound energy to heat. Some enzymes, such as collagenase, are exquisitely sensitive to these small temperature variations, thus, ultrasound may also facilitate some enzymatic processes.[63]

Trans-cutaneous application of ultrasound in the management of fresh fractures

The first clinical observation that ultrasound stimulates fracture healing was reported as early as 1953 by Corradi and Cozzolino.[10] They found that US enables earlier full weight bearing, thus decreases the time to healing. But it was only in the early 1980s when this observation attracted the attention of basic scientists and physicians. A good body of knowledge has now accumulated from in vitro and animal studies and from clinical trials and case series about the potential of LIUS to enhance fracture healing.

In several studies LIUS was applied in various fracture models in animals. In an effort to determine the optimum signal parameters, Duarte[13] using radiographs and histological studies, demonstrated that ultrasound signals successfully accelerated cortical bridging after fibular osteotomy in rabbits by 28% compared with that in controls. Ultrasound increases soft callus formation and results in the earlier onset of endochondral ossification, suggesting that the most prominent effect is on the chondrocyte population. These findings correlate well to the results of the in vitro studies on chondrocyte cell cultures.[61,64] In a placebo-controlled study of bilateral mid-shaft fibular osteotomies in rabbits, Pilla et al.[43] found that low-intensity pulsed ultrasound applied for 20 min/day significantly accelerated the recovery of torsional strength and stiffness. Since then, several experimental studies have demonstrated the capability of LIUS to accelerate and augment the fracture healing process in various models.[13,60,67]

In October 1994, LIUS received approval from the Food and Drug Administration (FDA) for the treatment of fresh fractures. The clinical application of LIUS in the management of fractures has been evaluated in placebo-controlled clinical studies on closed or grade-I open tibial fractures,[29] in dorsally angulated fractures of the distal aspect of the radius,[31] and on open and high energy tibial fractures.[32]

Heckman et al.[29] performed a multicenter placebo control clinical trial on 67 closed or grade-I open tibial fractures to evaluate the effect of ultrasound on fracture healing. Ultrasound treatment led to a significant (24%) reduction in the time to clinical healing, as well as to a 38% decrease in the time to overall (clinical and radiographic) healing, compared with the control group. In another randomised controlled trial conducted in patients with tibial fractures fixed with intramedullary nailing, no beneficial effect of LIUS was detected.[18] Although the LIUS intervention was the same in the two studies (20 min/day), in the Heckman et al.[29] study it was compared with cast immobilisation while in the Emami et al.[18] study it was compared with treatment with an intramedullary rod which allows for early weight-bearing. It is possible that the mechanical stress imposed by early weight-bearing overshadows any advantage of LIUS. On the other hand, it is also conceivable that the metal of the rod might attenuate the effect of the ultrasound, although experimental findings in animals do not support this explanation.[51] In addition, the Emami et al.[18] study had only a small number of smokers in contrast to the previous study, and a possible interaction between smoking and response to LIUS has been suggested.[9] In an other randomised controlled clinical trial performed on 61 dorsally angulated fractures of the distal radius, the effect of ultrasound was in fact tested on trabecular bone lying just beneath the skin.[56] The time to union was 38% shorter for the fractures that were treated with ultrasound. This evidence is considered sufficient to cautiously support the efficacy of LIUS in the treatment of closed distal radius fractures in this unique patient population.

To date, only one study has been conducted in scaphoid fractures.[36] This study was not placebo-controlled, so both patients and treatment providers were aware of their treatment. Assessment of healing status was made by three radiologists blind to treatment intervention. While the study results suggest accelerated healing, it is not possible to conclude greater efficacy than cast immobilisation on the basis of this unblinded study alone.

The studies reviewed in this assessment investigated different fracture sites with inherently different healing characteristics. The quality of the evidence available to support the use of trans-cutaneous LIUS in the treatment of fresh fractures varies considerably, although remains significant for fractured bones lying under the skin.

Trans-osseous application of the LIUS for the enhancement of callus formation

In all the above-mentioned clinical studies, LIUS was applied with the use of a module where the head of the transducer is attached to the skin and focuses on the fracture site. However, the surrounding soft tissue envelope of some long bones (i.e. femur, humerus) results in high attenuation of the propagating ultrasonic waves due to absorption which is proportional to the thickness of this envelope, as well as to beam scattering phenomena.[22,24] Recently our research group, reported on the first trans-osseous application of ultrasound on a sheep tibial osteotomy model and demonstrated a 23% acceleration in the time to radiographic healing and a significant increase in the bone mineral density, strength and stiffness for the LIUS-treated sheep tibiae on the 75th post-operative day.[26] These findings were confirmed by another study employing the same animal model with the ultrasound transducers placed directly on the periosteum adjacent to the osteotomy.[44] The treated bones demonstrated significantly stiffer and stronger callus with higher bone mineral density compared to the untreated tibiae.

Trans-osseous application of the LIUS for the monitoring of callus formation

In addition to the fracture-enhancement capabilities, ultrasonic methods have been employed as a monitoring tool of the healing process. The majority of the research groups used the so-called axial-transmission technique, in which a set of two or more transmitters and receivers (typical operating frequencies in the range from 0.2 to 2.5 MHz) are placed on the skin surface with a known distance in-between them. The ultrasound velocity, determined by the transit time of the first-arriving wave that propagates along the long axis of the bone, is used as an indicator of healing.[4,46] Animal[1,22] and clinical[2,21] studies have demonstrated that the velocity of completely healed bones reaches at least 80% that of intact bones.[1,21,22] However, the pattern with which velocity evolves as healing progress has not been quantified and no distinction has been made between partially healed bones and delayed unions. Moreover, the correlation between the velocity and the mechanical properties of the healing bone has been found to range from poor[22] to moderate.[1,2] Major disadvantages of the trans-cutaneous measurements are that the overlying soft tissues affect the repeatability and accuracy of the measurements and that the method is only applicable to subcutaneous skeletal sites, such as the tibia and the radius.

A system with trans-osseous application of the ultrasound was recently introduced for both the enhancement of healing in long bones and the monitoring of callus formation.[44] Among the several parameters evaluated, the propagation velocity of the ultrasound has been found the most sensitive in reflecting structural changes of the newly formed callus.

Low-intensity ultrasound in the treatment of nonunions

Although callus formation is the natural biologic response to fractures and leads to the restoration of skeletal integrity, union is not achieved or it is delayed in 5—10% of the 5.6 million fractures occurring annually in the United States.[17] As stated by Mandt and Gershuni[34] "nonunion is a state in which there is the failure of a fracture to heal within the expected time and where the fracture will not heal without intervention". Factors contributing to delayed union or nonunion include severe comminution of the bone, infection, extensive soft tissue damage, fracture location and inadequate fixation. Parameters, such as alcohol and tobacco overuse, diabetes and age may also contribute to the failure of union.

The "gold standard" for the management of the nonunion is surgical intervention aiming at the removal of the soft tissues interfering between the viable bone segments, stable fixation of the bone and biological augmentation of the repair process. The success rate is between 70—90%.[5,27] In order to enhance and stimulate healing in established nonunions, a number of biological and biophysical interventions have been developed. Biological interventions include the use of autogenous bone graft, artificial substitutes for bone graft, and purified or recombinant molecules with chondrogenic and osteogenic capacities (BMPs). Biophysical intervention includes noninvasive methods such as extracorporeal shock-wave therapy, electrical stimulation and low-intensity pulsed ultrasound (LIUS).

Experimental models for studying nonunion are difficult to establish. Takikawa et al.[53] in an experimental study using a rat nonunion model by muscle interposition in the fractured tibia of both limbs showed that 50% of the bones that were exposed to ultrasound treatment went on to healing in radiological assessment at 6 weeks, while all control tibias remained un-united. These results were also confirmed on three-dimensional micro-focused X-rays and in histological examination.

Xavier and Duarte in 1983 reported that 70% of 26 nonunions healed after brief exposure (20 min/day) to LIUS (30 mW/cm^2).[66] The same group in a retrospective study on 385 established nonunions reported an 85% healing rate.[14]

In more recent clinical trials, Mayr et al.[37] reported a healing rate of 88% and 93% in a group of 29 patients with delayed unions and nonunions, respectively. Nolte et al.[40] in a study of 29 nonunions at multiple sites with an average time 1.2 years after the fracture and an average of 1.4 failed surgical procedures, reported an 86% healing rate. Low-intensity pulsed ultrasound was the only treatment 52 weeks after other surgical procedures. The healing rate examined by the location of the nonunion was 100% for the tibia and 80% for the femur, radius, ulna and the scaphoid of the wrist. It is interesting to notice that approximately 75% of their patients demonstrated a compliance of greater than 75% with the treatment plan. Gebauer et al.[20] in a similar study evaluated the efficacy of low-intensity ultrasound in a group of patients with 67 long-lasting nonunions. The average time from the last operation was 24.2 months and the patients also had on average two failed surgical procedures. Eighty-six percent (57 of 67) of the nonunions healed at an average time of six months after the initiation of daily ultrasound application.

Rubin et al.[48] studied the prescription-use registry database as of June 2000 and found that delayed unions (151—255 days after the fracture) had a healing rate of 89% ($n = 1370$), and nonunions (more than 255 days after the injury) had a healing rate of 83% ($n = 1546$). The healing rate varied for the different locations of the nonunions of such as 69% for the humerus (102 of 148), 82% for the femur (213 of 259), 84% for the tibia (404 of 483), 86% for the scaphoid (101 of 118), 87% for the radius/ulna (60 of 69) and 89% for the metatarsals (81 of 91).

The results of the studies reviewed in this assessment appear to suggest that LIUS promotes healing in established nonunions. The use of ultrasound eliminated the need for additional operation, but the average time to healing remained substantial (approximately an additional five months). However, these case series studies do not have a parallel control group, nor are they blinded, thus raising the potential for bias. Considerable variation was present with respect to fracture site, initial fracture severity, initial fracture treatment and the number of subsequent surgical interventions. Interpretation of the findings of these studies is made more difficult due to the heterogeneous nature of the patients. Therefore, it is not possible to make a direct comparison with either no further treatment or with alternative treatments. To assess the comparative efficacy of the ultrasound in nonunions, it should rather compare LIUS with ORIF as first treatment upon confirmation of nonunion. Larger and maybe more homogenous series of patients might better delineate the indications and limitations of ultrasound. Data obtained from a registry for treatment of nonunions and from case series, should be interpreted in the context of expert opinion that fractures more than nine months old that have ceased healing are unlikely to heal without further treatment.

From the aspect of the health economics, it is recognised that the longer the delay to union the greater the total cost for the treatment of this fracture, because added secondary procedures such as intramedullary nailing or plates and screws and bone grafting are necessary and worker's compensation costs are increasing. Considering the incidence of delayed unions and nonunions in tibia fractures Heckman and Sarasohn-Kahn[28] recommend the use of low-intensity ultrasound as an adjunctive treatment. They estimated an overall cost savings of approximately US$ 13.000—15.000 per case.

In fact, on the basis of the studies which have been investigated and the existing level IV clinical evidence, it has been concluded that the application of low-intensity pulsed ultrasound as a sole treatment, is a harmless noninvasive adjunct, more applicable after failure of at least one prior surgical intervention for nonunion. The Food and Drug Administration approved the use of low-intensity pulsed ultrasound for the treatment of established nonunions, in USA, in February 2000.

The effect of ultrasound in distraction osteogenesis

Callus distraction is currently an established treatment for the management of defects larger than 3—4 cm in the long bones. However this technique carries the problem of the long time for healing and maturation of the newly formed bone and the burden to wear the external fixator for a very long time. The ossification process in distraction and maturation involves intramembranous bone as the dominant type of tissue formation while endochondral ossification normally is of minor importance.[30,68]

The effects of low-intensity pulsed ultrasound on maturation of the distracted callus have been investigated in several animal studies, with controversial results.[16,35,52,55] In a rabbit study, Shimazaki et al.[52] found that bone mineral density, hard callus area, and mechanical test scores were greater in distraction callus treated with low-intensity pulsed ultrasound than in the control group. In a study of rats, Eberson et al.[16] found that radiographicaly assessed healing occurred earlier in ultrasound treated bones than in control bones and that bone volume fraction and trabecular bone pattern, were higher in the ultrasound-treated bones. In a study of rabbits, Tis et al.[55] found a greater hard callus area and less fibrous tissue in bones treated with low-intensity pulsed ultrasound than in control bones. Neither Eberson et al.[16] nor Tis et al.[55] found a difference in bone mineral density or mechanical strength of distraction callus between ultrasound-treated bones and controls, although Eberson et al.[16] observed a trend toward greater mechanical strength in ultrasound-treated bones. Uglow et al.[59] found no substantial difference in bone mineral content, crosssectional area, or strength of distraction callus between ultrasound-treated bones and control bones of rabbits.

In a sheep metatarsal bone transfer model for the study of distraction osteogenesis, pulsed low-intensity ultrasound were applied transcutaneously after the distraction was complete and only throughout the maturation phase.[8] Histologic analysis of the cortical defect zone showed approximately 32% more bone in the group stimulated by ultrasound. Although it presented seven times more intramembranous bone formation compared to endochondral in the control group, which is in accordance with results of another study,[30] there was a three times higher rate of endochondral ossification in the specimens treated with ultrasound. Biomechanical tests showed significantly higher axial compression stiffness (1.4—2.7 times the control values) and significantly higher indentation stiffness of callus tissue in the healing zone of the treated bones. In all of the animal studies mentioned above, osteotomy and distraction were performed at the diaphysis, which consists of thick cortical bone. A recent investigation on rabbits showed that low-intensity pulsed ultrasound stimulates bone formation most effectively during the distraction phase.[50]

In a randomised study (block randomisation) in humans with internal controls, the low-intensity pulsed ultrasound applied only during the consolidation phase (after distraction had ceased) on hemicallotasis after high tibial ostetomy, significantly enhanced the mineralisation of the callus.[57] The bone mineral density in the metaphyseal segment adjacent to the distraction callus, in the previous study and also in animal studies collectively suggest that metaphyseal trabecular bone might be more susceptible than diaphyseal cortical bone to the mechanicalultrasonic stimuli.

Future clinical studies should address the question of whether additional low-intensity pulsed ultrasound treatment during the distraction phase can further shorten the period necessary for callus maturation. The distraction osteogenesis-specific mechanism that translates mechanical forces due to low-intensity pulsed ultrasound into bone formation need further clarification.

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