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 transcutaneously, 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. 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. 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. 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
parameter with direct implications on the physical, emotional and monetary costs. 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.

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, electromagnetic fields 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. 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. They found that US doubles the time to healing. But it was only in the early 1980s that 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 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. In a placebo-controlled study of bilateral mid-shaft fibular osteotomies in rabbits, Pilla et al. 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.

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, in dorsally angulated fractures of the distal aspect of the radius, and on open and high energy tibial fractures.

Heckman et al. 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. Although the LIUS intervention was the same in the two studies (20 min/day), in the Heckman et al. study it was compared with cast immobilisation while in the Emami et al. 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. In addition, the Emami et al. 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.

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. 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. 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. 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. 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. 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 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. Animal and clinical studies have demonstrated that the velocity of completely healed bones reaches at least 80% that of intact bones. 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 to moderate. 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. 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. As stated by Mandt and Gershuni, “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%. 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. 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/cm²). The same group in a retrospective study on 385 established nonunions reported an 85% healing rate. In more recent clinical trials, Mayr et al. reported a healing rate of 88% and 93% in a group of 29 patients with delayed unions and nonunions, respectively. Nolte et al. 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. 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. 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 treat-
ments. 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 compensa-
tion costs are increasing. Considering the inci-
dence of delayed unions and nonunions in tibia
fractures Heckman and Sarasohn-Kahn 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 applica-
tion 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 treat-
ment 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 endochon-
dral ossification normally is of minor importance.

The effects of low-intensity pulsed ultrasound on
maturation of the distracted callus have been inves-
tigated in several animal studies, with controversial
results. In a rabbit study, Shimazaki et al. found that
bone mineral density, hard callus area,
and mechanical test scores were greater in distrac-
tion callus treated with low-intensity pulsed ultra-
sound than in the control group. In a study of rats,
Ebroker et al. found that radiographically 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. 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. nor Tis et al. found a difference
in bone mineral density or mechanical strength of
distraction callus between ultrasound-treated
bones and controls, although Eberson et al. observed a trend toward greater mechanical
strength in ultrasound-treated bones. Uglow
et al. found no substantial difference in bone
mineral content, crosssectional area, or strength
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-inten-
sity ultrasound were applied transcutaneously after
the distraction was complete and only throughout
the maturation phase. Histologic analysis of the
cortical defect zone showed approximately 32%
more bone in the group stimulated by ultrasound.
Although it presented seven times more intramem-
branous bone formation compared to endochondral
in the control group, which is in accordance with
results of another study, there was a three times
higher rate of endochondral ossification in the speci-
mens treated with ultrasound. Biomechanical tests
showed significantly higher axial compression stiff-
ness (1.4—2.7 times the control values) and signifi-
cantly 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 investiga-
tion on rabbits showed that low-intensity pulsed
ultrasound stimulates bone formation most effec-
tively during the distraction phase.

In a randomised study (block randomisation) in
humans with internal controls, the low-intensity
pulsed ultrasound applied only during the consoli-
dation phase (after distraction had ceased) on hemi-
callotasis after high tibial ostetomy, significantly
enhanced the mineralisation of the callus. 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.

References


