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● *Review*

LOW-INTENSITY PULSED ULTRASOUND FOR THE TREATMENT OF BONE DELAYED UNION OR NONUNION: A REVIEW

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Abstract—The goal of this review is to present the most updated knowledge derived from basic science, animal studies and clinical trials, concerning biophysical stimulation of bone repair through low-intensity pulsed ultrasound (LIPUS), with particular reference to the management of delayed unions and nonunions. Low-intensity pulsed ultrasound LIPUS has been proved to significantly stimulate and accelerate fresh fracture healing in animal studies and in randomized controlled clinical trials. LIPUS also appears as an effective and safe home treatment of aseptic and septic delayed-unions and nonunions, with a healing rate ranging from 70% to 93% in different, nonrandomized, studies. Advantages of the use of this technology that may avoid the need for additional complex operations for the treatment of nonunions, include efficacy, safety, ease of use and favourable cost/benefit ratio. Outcomes depend on the site of nonunion, time elapsed from trauma, stability at the site of nonunion and host type. The detailed biophysical process by which low-intensity pulsed ultrasound LIPUS stimulates bone regeneration still remains unknown, even if various effects on bone cells *in vitro* and *in vivo* have been described. (E-mail: carlo.romano@grupposandonato.it) © 2009 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Low-intensity pulsed ultrasound, LIPUS, Fracture healing, Delayed unions, Nonunions, Callus formation.**

INTRODUCTION

Several millions of fractures occur annually worldwide, with nearly 6 million fractures reported in the United States alone (Einhorn 1995). The healing process of an injured bone requires proper reduction and fixation of the fracture site and the sequential activation of several different cell types and bioactive molecules.

Even with the most advanced treatment methods today available, approximately 5% to 10% of fractures do not heal. When the repair process is not sufficient to restore bony continuity within 3 mo from trauma or intervention, then a "delayed union" is said to occur; when bone healing does not take place after 9 mo, a "nonunion" occurs. Risk factors for delayed or nonunions include specific fracture site with poor blood supply, fracture comminution or bone gap, infection and/or extensive soft tissue damage, inadequate fracture fixation, and so on. Smoking, diabetes, alcohol abuse, old age and other systemic conditions are also important well known contributing factors to nonunions. Both delayed and nonunions lead to additional suffering and prolonged functional impairment to the patients and to increased costs for the health care systems (Heckman et al. 1997).

Nonunions may often require additional complex surgical procedures to heal (Einhorn 1995) and nonunions have also been defined as "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" (Mandt et al. 1987). In fact, open surgical debridement of the nonunion site and application of internal or external fixation, in most cases with bone grafting, is still considered by many authors as the "gold standard" of nonunion treatment. The success rate of the surgical treatment of nonunions is between 70% and 90%, depending on the bone location and surgical method (Boyd et al. 1961; Healy et al. 1990; Wu et al. 1996; Ackerman et al. 1988; Cooney et al. 1980; Marsh et al. 1997).

The possibility of stimulating bone healing through physical methods has been widely investigated in the last 50 y. In nonunion cases where surgery may not be required because there is acceptable stability, alignment

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and limb length discrepancy, several biophysical treatment methods have been proposed in recent years to achieve a heal rate similar to that of surgery: pulsed electromagnetic fields (Gossling et al. 1992; Hinsenkamp et al. 1985), electrical stimulation, induced by direct current and capacitive coupling (Brighton et al. 1981, 1985; Heppenstall 1983; Scott et al. 1994), extracorporeal shock-wave therapy, usually performed as middle- or high-energy shock-wave therapy (Diesch 1997; Rompe et al. 2001; Wang et al. 2001) and low-intensity pulsed ultrasound. While experimental and clinical studies with highly significant evidence levels did show a positive effect of low-intensity pulsed ultrasound on accelerating bone healing of fresh fractures (Corradi et al. 1953; Heckman et al. 1994; Kristiansen et al. 1997) and in distraction osteogenesis (Claes et al. 2005; Sakurakichi et al. 2004; Eberson et al. 2003; Shimazaki et al. 2000), in this review, we will particularly focus on the effectiveness and safety of low-intensity pulsed ultrasound as a conservative treatment option for delayed union and nonunions (Frankel et al. 2001; Mayr et al. 2000; Gebauer et al. 2005) that still remain the most challenging application field for biophysical methods of stimulation of bone repair.

HISTORIC BACKGROUND

The first reports on the possibility to stimulate osteogenesis with ultrasound dates back to years 1949 to 1950 (Buchtala et al. 1950). In the same years, Maintz (1950) showed no histologic and radiographic changes after ultrasound treatment of rabbit radial fractures at 500 mW/cm^2, while reduced callus formation was observed at higher intensities (1000, 1500, 2500 mW/cm2). At the Gaetano Pini Orthopaedic Institute of Milan, Italy, Corradi and Cozzolino (1953) confirmed the acceleration of bone healing of fresh fractures compared with controls in rabbit radii, through ultrasound stimulation at 500 mW/cm^2 and excluded pathologic changes in the callus formation. They also reported similar results in humans, in a limited clinical series, pointing out the importance of maintaining the stability at the fracture site, the most relevant effect of ultrasound on periosteal new bone formation and proposing the stimulation through a hole in the cast. Accelerated bone healing was more recently confirmed in the studies on rabbit tibiae fractures made by Klug and coworkers (1986), while Chang et al. (2002) demonstrated a 36% increase in new bone formation and an 80% increase in torsional stiffness of limbs stimulated with 500 mW/cm^2 ultrasound compared with untreated limbs. Higher ultrasound intensities (5000 to 25,000 mW/cm2) have been reported to inhibit bone healing or induce necrosis and fibrous tissue formation in animal models (Bender et al. 1954; Herrick et al. 1956; Ardan et al. 1957). In these early studies, the ultrasound was continuous and the value of the intensity cited refers to the spatial average value.

At the beginning of the 1980s in Brazil, Duarte (1983) was the first to develop and clinically use biophysical treatment with low-intensity pulsed ultrasound system (LIPUS) to stimulate bone osteogenesis. The signal of LIPUS used by Duarte consisted of 200 ms burst of 1.5 MHz sine waves repeating at 1 kHz and delivering 30 mW/cm^2 spatial averaged and temporal averaged (SATA) intensity. In the following discussion, the term LIPUS will be used for applications of low-intensity pulsed ultrasound in which the conditions are similar to those used by Duarte (1983). Pilla et al. (1990) in a placebo controlled study of bilateral fibular osteotomies in rabbits showed that LIPUS applied for 20 min/d significantly accelerated the recovery of torsional strength and stiffness. Since then, several experimental studies have confirmed the capability of LIPUS to accelerate and increase the fracture healing process in various animal models (Wang et al. 1994; Yang et al. 1996). The use of LIPUS to accelerate bone healing in fresh fractures gradually extended to the rest of the world. In 1994, in the United States, a multicenter placebo-controlled clinical trial on closed or grade-I open tibial fractures (Heckman 1994) could demonstrate a significant (24%) reduction in the time to clinical healing, as well as a 38% decrease in the time to overall (clinical and radiographic) healing, compared with the control group. Rubin et al. (2001) reported that The Food and Drug Administration approved the use of low-intensity ultrasound for the accelerated healing of fresh fractures in October 1994 and for the treatment of established nonunions in February 2000. The clinical results were confirmed in other double-blind, randomized, placebo controlled clinical trials in wrist fractures (Kristiansen et al. 1997) and high energy tibial fractures (Leung et al. 2004).

LIPUS PARAMETERS AND TREATMENT MODALITIES

While ultrasound has been shown to improve radiographic fracture healing and increase bone density in rat femora at intensities as low as 11.8mW/cm^2, that lay in the range of those used in diagnostic setting (Heybeli et al. 2002), there is evidence that, in the range of low intensities (below 100 mW/cm^2), the response of osteoblasts to the application of ultrasound is directly related, *in vitro*, to the applied intensity (Harle et al. 2001).

The most commonly used signal frequency to stimulate osteogenesis is 1.5 MHz but higher values (3 MHz) were also proven to be effective in different animal models and at various intensities (Dyson et al. 1983; Tsai et al. 1992; Wang et al. 1994).