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The effect of low-intensity pulsed ultrasound on callus maturation in tibial distraction osteogenesis

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Abstract Callus distraction is currently the most popular method of bone lengthening. Prolonged treatment time is one of its major problems. In this study, we investigated the effect of low-intensity pulsed ultrasound on tibial distraction osteogenesis. We managed 20 patients with tibial defects ranging from 5 cm to 8 cm with distraction osteogenesis using the Ilizarov external fixator. After the completion of distraction, ten patients received daily 20 min of low-intensity pulsed ultrasound stimulation (30 mW/cm^2) onto the bone lengthening site (group A) while rigid fixation was maintained in the remaining patients (group B). All patients were followed with weekly radiographs to determine the formation of an external cortex and an intramedullary canal, at which time the fixator was removed. The mean healing index in group A was 30 (27–36) days/cm while it was 48 (42–75) days/cm in group B. In group B, one patient failed to consolidate the regenerated bone. Low-intensity pulsed ultrasound stimulation is highly effective in achieving maturation of bone and reducing time of distraction osteogenesis.

Résumé La distraction du cal est la méthode d'allongement de l'os la plus populaire actuellement. La longueur du traitement est un de ses problèmes majeurs. Nous avons étudié l'effet des ultrasons pulsés de basse intensité sur l'ostéogénèse dans la distraction tibiale. Nous avons traité 20 malades présentant un défaut tibial de 5 à 8 centimètres avec ostéogénèse de distraction utilisant un fixateur externe d'Ilizarov. Après l'achèvement de la distraction 10 malades ont reçu quotidiennement une stimulation par ultrasons (30 mW/cm^2) sur l'emplacement de l'allongement osseux pendant 20 minutes (groupe A), pendant que la fixation rigide était maintenue pour le restant des malades (groupe

B). Tous les malades ont été suivis avec des radiographies hebdomadaires pour déterminer la formation d'un cortex périphérique et d'un canal intramédullaire au moment où le fixateur a été enlevé. L'index de consolidation moyen dans le groupe A était 30 (27–36) jours/cm pendant qu'il était 48 (42–75) jours/cm dans le groupe B. Dans le groupe B un malade n'a pas consolidé l'os régénéré. La stimulation par ultrasons pulsés de basse intensité est très efficace pour favoriser la maturation osseuse et réduire le temps d'ostéogénèse dans la distraction.

Introduction

Elimination of a long tubular bone defect has long been, and continues to be, one of the most difficult problems in orthopaedic surgery. Free-bone graft was once the benchmark in the management of skeletal defects. However, a high failure rate has been reported with this method [7]. In 1956, Ilizarov developed the technique of distraction osteogenesis where he used the stimulus of pure distraction applied to a special corticotomy site within an individual bone to induce new bone formation at the distraction gap. At first distraction osteogenesis was used for limb lengthening, but nowadays, it is used in the treatment of bone defects. Thus, limb length is maintained after elimination of the defect [9].

The rate-limiting step of distraction osteogenesis is the consolidation phase. Regenerate bone takes two or three times as long as the distraction period to mature, and attempts to remove the external fixator prematurely result in malunion or fracture [4, 18].

The use of biophysical modalities to accelerate the process of bone formation has recently earned renewed interest among clinicians. One example of such an approach is low-intensity pulsed ultrasound (LIPUS), a non-invasive form of mechanical energy transmitted transcutaneously as high-frequency acoustical pressure waves in biological organisms [13]. Significant evidence exists, at the basic science level, that LIPUS can modulate aggrecan gene expression [11], increase calcium incorporation in both

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cartilage and bone cell cultures [14], modulate transforming growth factor-B (TGF-B) synthesis in osteoblastic cells [14], and accelerate soft callus formation and enchondral ossification of the callus at the fracture site in animal models [2]. Clinical studies have shown that LIPUS is capable of accelerating the healing of fresh fractures [3, 8] and it is also effective in treatment of delayed union and non-union [5].

If ultrasound stimulation could accelerate the rate of callus formation and maturation of regenerate bone in distraction osteogenesis, the external fixator could be removed earlier, the treatment period could be shortened, complications would decrease and patients could return to daily activities more quickly. This study was designed to examine whether the use of LIPUS accelerates bone maturation during the consolidation phase of tibial distraction osteogenesis.

Materials and methods

The study included 20 male patients with tibial bone defects who were admitted to Mansoura University Hospital and managed by distraction osteogenesis. Their ages ranged from 18 to 45 years with a mean age of 35 years. The right tibia was affected in eight patients and the left in 12. Defects were located in the upper third of the tibia in two cases, in the middle third in five and in the lower third in 13. The aetiology of bone loss was trauma in 18 cases and congenital anterolateral bowing of the tibia in two. The mean time from injury to the Ilizarov procedure was 13.2 (1–18) months. Distraction osteogenesis was done as a primary management in four cases (two with open fractures and two with congenital anterolateral bowing of the tibia) while the remaining patients were treated later after development of non-union. The mean length of the defects after debridement was 6.1 cm (range 5–8 cm). Monofocal osteotomy was performed to allow a bone segment to be transported to fill the defect produced. Following a delay of 7 days, distraction of 0.25 mm four times daily was performed using the external fixator device. Distraction was continued until the defect was eliminated. From the day after cessation of distraction, the patients were divided randomly into two groups. Group A (ten patients) underwent 20 min/day of stimulation by LIPUS. An ultrasound transducer (SAFHA; Exogen Inc., Piscataway, NJ, USA) was applied over the lateral aspect of the distraction site using ultrasonic coupling gel. The ultrasound signal was composed of a burst width of 200 μ s containing 1.5 MHz sine waves with a repetition rate of 1 kHz and intensity of 30 mW/cm² [17]. Rigid fixation was maintained with the inactive device in the remaining ten patients (group B).

Radiographs were taken in two planes before and after surgery, then on a weekly basis during the distraction and consolidation period. The external fixator was removed when the distraction gap was sufficiently consolidated and corticalised on at least three of the four sides as seen on anteroposterior and lateral radiographs. The cortices had to be 2-mm thick and uninterrupted across the distraction gap. The regenerate bone needed to demonstrate uniform radio-

Table 1 Comparison of the healing index between patients treated with ultrasound (group A) and the controls (group B)

	Group	Number	Range	Mean $\pm$ standard deviation	<i>T</i>	<i>P</i>
Healing index (days/cm)	Group A	10	27–36	30 $\pm$ 2.96	5.302	<0.001
	Group B	9	42–75	48 $\pm$ 9.76		

graphic density halfway between the density of the adjacent normal bone's cortex and that of its marrow canal [7].

To assess and compare the rate of bone formation, the healing index was calculated for all patients. This was obtained by dividing the entire duration of external fixation by the length of distraction gap and expressed in days/centimetre [4]. Student's *t* test was used for data analysis.

Results

Union was achieved in all patients except one in group B who showed delayed consolidation of the regenerated bone. The mean healing index in group A was 30 days/cm. The mean healing index in group B was 48 days/cm (Table 1). The mean healing index in group A was significantly shorter than group B. Complications in group A included pin tract infection (eight patients) and delayed union in the docking site (one patient). In group B, complications were pin tract infection in nine patients, delayed union at the docking site in three and failure of regenerated bone to consolidate in one.

In one patient in group B, the quality of the regenerated bone did not improve despite 12 months in the fixator. This was a man aged 45, a heavy smoker with a distraction gap of 5 cm in length in the lower third of the right tibia. Therefore, LIPUS (30 mW/cm²) was applied daily for 20 min to the lengthening site in order to accelerate callus maturation. This was continued until pin removal. The quality of regenerated bone improved gradually, and it was possible to remove the external fixator 3 months after the application of ultrasound (Fig. 1).

Discussion

Managing a segmental skeletal defect is a challenge for any orthopaedic surgeon. Distraction osteogenesis developed by Ilizarov is now well established in the treatment of bone defects as it can eliminate bone defects, correct deformity, achieve union and re-establish limb length at the same time [1, 12]. However, the main disadvantage of the Ilizarov method is the prolonged treatment time. This imposes a psychological effect on the patient and family as several months are needed before the woven bone becomes corticalised sufficiently to allow for frame removal [18].

Fig. 1 A 45-five-year-old man with a 5-cm distraction in the lower third right tibia. **A** Radiographs 12 months after fixator application showed delayed maturation of the regenerated bone. **B, C** AP and lateral radiographs after ultrasound application six months after removal of the fixator.

The accelerating effect of LIPUS energy on fracture healing has been recognised through several animal experiments and clinical studies [13], although its effect on bone lengthening is still unclear. However, in distraction osteogenesis, bone formation is believed to take place by both enchondral and membranous ossification in a process similar to that occurring in fracture healing. Therefore, an accelerating effect on callus formation in distraction osteogenesis is also to be expected. In this study, the mean healing index of patients treated with ultrasound (group A) was significantly shorter than that of group B. This is consistent with the results of Sato et al. [15] who reported on a 22-year-old woman with short stature treated by the Ilizarov procedure.

Shimazaki et al. [16] investigated the effects of LIPUS on distraction osteogenesis in a rabbit tibia model in which two different distraction rates were used. Compared with the untreated limbs, those receiving ultrasound had significantly higher values for hard callus area, for bone mineral density and for mechanical strength. With fast distraction, immature bone regeneration was observed radiologically in the control group whereas bone maturation was achieved in the ultrasound group. Although these data were only preliminary, they indicated that even in difficult circumstances, ultrasound could still effectively influence the mineralisation process.

Mayr et al. [10], in an effort to study the potential for ultrasound to accelerate the maturation of regenerate callus, used LIPUS during the consolidation phase in a placebo-controlled segmental transport callus distraction model in the metatarsals of sheep. They found that ultrasound-treated limbs showed significant increase in bone mineral content on quantitative computed tomography. Also, the findings of Tis et al. [17] of increased callus size, decreased fibrous tissue and increased bone after LIPUS applied to rabbit tibiae are encouraging.

In addition Eberson et al. [6] found that healing of femurs treated by ultrasound in a rat model of distraction osteogenesis occurred before that of sham-treated bones. Bone volume and trabecular bone pattern factor were significantly higher in the ultrasound-treated animals. They suggested that LIPUS matures the regenerate tissue by altering the micro-architecture of newly formed bone.

LIPUS stimulation can have an accelerating effect on callus maturation during the consolidation phase in patients managed with tibial distraction osteogenesis and reduce the overall time to removal of the fixation device. However, additional research is needed to verify the use of LIPUS in such situations and to determine the optimal timing of application.

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