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No Effect of Low-Intensity Ultrasound on Healing Time of Intramedullary Fixed Tibial Fractures

[Original Articles]

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Exogen Inc. provided the ultrasound devices used in this study. The authors have received nothing else of value.
The legal/regulatory status of the device that is the subject of this manuscript is not applicable in our country.

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Abstract^

Objective: To determine whether stimulation with low-intensity ultrasound will reduce the radiologic healing time of fresh tibial shaft fractures fixed with a reamed and statically locked intramedullary rod.

Design: Prospective, randomized, double blinded, and placebo controlled.

Patients and Methods: Thirty-two adult patients were included, fifteen in the active ultrasound group and seventeen in the placebo group. They all used an ultrasound device twenty minutes daily for seventy-five days without knowing whether it was active or inactive. Standardized radiographs were taken

every third week until healing and at six and twelve months. All radiographs were assessed blinded and independently by a radiologist and an orthopaedic surgeon. The codes were not broken until all fractures had healed and all radiographs had been evaluated.

Results: The time until the first visible callus averaged 40 ± 3 days for the active group and 37 ± 3 days for the placebo (p = 0.44). The healing time, defined as radiologic bridging of three cortices, was on average 155 ± 22 days (median 113 days) for the active treatment group and 125 ± 11 days (median 112 days) for the placebo group (p = 0.76) as assessed by the radiologist and 128 ± 13 days for the active group and 114 ± 9 days for the placebo group (p = 0.40) as evaluated by the orthopaedic surgeon.

Conclusion: We conclude that low-intensity ultrasound treatment did not shorten healing time in fresh tibial fractures treated with a reamed and statically locked intramedullary nail. Our results are not in accordance with previous findings reporting reduced healing time in nonoperatively treated tibial shaft fractures when subjected to ultrasound.

During the last decades, several studies have been published describing the positive effect of low-intensity ultrasound on bone healing. In 1983, Duarte (4) reported on accelerated healing of fibular osteotomies and drilled holes in the femora in a rabbit model when assessed both radiographically and histologically. In subsequent animal studies and in vitro experiments, it has been shown that an ultrasound intensity of thirty milliwatts per square centimeter provides maximal acceleratory effect on bone healing (13). The exact mechanism by which low-intensity ultrasound stimulates the bone healing process is unknown, although one theory states that the ultrasound signal creates a micromechanical stress and strain at the cellular level (7). Effects have been reported, for instance, as an increased rate of endochondral ossification, stimulation of cartilage-related gene expression, and increased intracellular calcium in chondrocytes exposed to ultrasound (12,14-16).

In two recent clinical studies, the efficacy of low-intensity ultrasound has been tested in placebo-controlled and double-blinded trials in patients with either a tibial (7) or a distal radial (9) fracture treated with a cast. In both studies, it was shown that active ultrasound twenty minutes per day significantly reduced the healing time for both fracture types.

In tibial diaphyseal fractures, surgical treatment with fixation using an intramedullary nail has become a frequent alternative to treatment with a cast. In the clinical situation, it is unknown whether metal at the fracture site will interfere with the potential effect of low-intensity ultrasound. In an animal model, Wang et al. (15) reported increased strength and more advanced endochondral ossification in fractured rat femora fixed with a metal wire and exposed to ultrasound when compared with controls not subjected to ultrasound. In their animal study, the metal at the fracture did not seem to disturb the stimulating effect of ultrasound on bone healing.

In the present study, we investigated whether daily application of low-intensity ultrasound could shorten the healing time of fresh closed or Grade I open tibia fractures when fixed with a reamed and statically locked intramedullary nail.

PATIENTS AND METHODS^

The study was prospective, randomized, double blinded, and placebo controlled. Patients were recruited at our institution between May 1995 and January 1997. All patients from the age of sixteen years who were treated for a closed or Grade I open (6) primarily diaphyseal tibial fracture with closed reduction and a reamed and locked intramedullary nail (AO/ASIF Universal tibial nail, Stratec Medical AB, Stockholm, Sweden) were invited to participate in the study.

Patients were excluded if the radiographs showed severe comminution at the fracture site or open physes, if the fracture was a Gustilo-type Grade II or III open fracture, multiple fractures, or other injuries, alcoholism or drug abuse, neuropathy, arthritis, and malignant disease. Patients receiving steroids, anticoagulant therapy, nonsteroidal anti-inflammatory drugs, or bisphosphonate therapy were also excluded.

The study was approved by the local ethical committee, and patients were not included until they had given informed consent.

Thirty-three patients with as many tibial fractures were entered into the study. In one patient, it became obvious during the course of the study that he did not fulfill the inclusion/exclusion criteria. Thus, the patient was excluded from the study before breaking the codes. The remaining thirty-two patients (fifteen active and seventeen placebo) were all followed according to the protocol. The codes were not broken for any device until the radiographic reviews for all patients had been completed.

There were twenty-eight closed (twelve in the active and sixteen in the placebo group) and four open (three in the active and one in the placebo group) Grade I fractures. The most common cause of fracture was a simple fall on the same level or from a low height in seven patients in each treatment group. Sports injuries, mostly from playing soccer, was the second most common activity at the time of fracture, with seven patients in the active group and five patients in the placebo group. Traffic accidents caused five fractures in the placebo group and one in the active treatment group.

Surgery was performed by one of six experienced fracture surgeons. The size of the nail was determined after reaming the medullary canal until the reamer touched the cortical bone at the isthmus: a nail with a diameter of 0.5 to 1.0 millimeter smaller than the final reamer was inserted. The average nail diameter was 11.5 millimeters, with a range of ten to thirteen millimeters in both groups. Twenty-eight patients were allowed to bear weight as tolerated immediately after surgery, and four patients were recommended to bear partial weight for six weeks.

Once the patient had been included in the study, a permanent marker was used to indicate the exact fracture site. During the daily treatment sessions, an alignment fixture was used to ensure that the treatment head module was consistently placed at the marked spot on the anteromedial side of the tibia.

Ultrasound treatment was started within three days after surgery and consisted of one twenty-minute period each day for seventy-five days, for a maximum total treatment time of twenty-five hours. The treatment head module was positioned at the mark on the skin of the lower leg after application of a small amount of ultrasonic coupling gel. The treatment head module was attached to a main operating unit that monitored the proper use and function of the treatment head module. A signal was sounded if there was not enough coupling gel on the skin or if there were any problems with the connection between the treatment head module and the main operating unit during the treatment session. A timer in the main operating unit monitored treatment times and made it possible to measure patient compliance. To measure compliance further, all patients were asked to fill out a daily treatment log. After twenty minutes of treatment, the unit was turned off automatically by a timer, and a visual and an audible signal simultaneously indicated to the patient that the daily treatment period was completed.

All devices (SAFHS 2A Sonic Accelerated Fracture Healing System, Exogen Inc., Piscataway, NJ, U.S.A.) were identical in every way except for the presence or absence of an emitted ultrasound signal. The ultrasound signal could not in any way be felt by either the patients or the investigators. All devices were coded, and the study fulfilled the criteria for being double blinded with placebo controls.

The treatment head module of the active devices emitted an ultrasound signal that was composed of a burst width of 200 microseconds containing 1.5-megahertz sine waves, with a repetition rate of one kilohertz and a spatial average temporal intensity of thirty milliwatts per square centimeter.

All patients were scheduled to return for clinical and radiographic follow-up every third week until healing and at twenty-six and fifty-two weeks whether or not the fracture had healed prior to those visits. Standardized anteroposterior (AP) and lateral radiographs were taken with similar exposure settings and similar leg position at every examination. Two films, twenty by forty centimeters, were used for each projection; the two proximal films were true AP and lateral projections of the knee but were centered approximately fifteen centimeters below the knee joint space, and the distal films were AP and lateral projections of the ankle centered approximately fifteen centimeters above the joint space. There were approximately twenty centimeters of overlap of proximal and distal films, with approximately 10 degrees of inward rotation of the distal pair relative to the proximal pair because of the orientation of the joints. The overlap and the slight rotation provided four, somewhat different, views of most fractures, which was advantageous for evaluation of the four cortices, particularly when the fibula was projected over the fracture in the tibia on one of the lateral images. Thus, the risk for misjudging cortical overlapping at the fracture site as cortical bridging, i.e., a healed fracture, was reduced by the use of these two images in each projection.

All radiographs were assessed separately in independent blind reviews by a musculoskeletal radiologist (M.P.M.) and an orthopaedic trauma surgeon (S.L.). On each evaluation at each time point, four cortices were evaluated for the amount of bridging. Cortical bridging was defined as the disappearance of the cortical interruption at the fracture site as a result of callus formation. The preoperative radiographs were used to classify the fractures according to the AO classification (11). Two time points in relation to the fracture event were evaluated. The first time point was the time in days from the fracture event until the first visible callus could be identified on the radiographs. The second time point, defined as the healing time in days, was set as the time when three

of four cortices were bridged.

The active and placebo groups were compared with regard to important characteristics of the fractures and to the patients to detect any appreciable differences between the group of patients or fractures treated with an active device and the patients or fractures treated with an inactive, i.e., placebo device. At each visit at the outpatient clinic, an assessment of the weight-bearing status of the patient was done by the investigator.

Statistical Analysis^

The Mann-Whitney nonparametric test, Fisher's exact test, and nonparametric survival analysis (log-rank test) were used for analysis. Statistical significance was determined at $p < 0.05$. Mean and standard error of the mean are given.

RESULTS^

There was no significant difference between the two treatment groups with regard to any of the patient- or fracture-related parameters measured (Table 1). There were only two smokers among the patients, one each in the two treatment groups. Therefore, we believe that the randomization produced comparable treatment groups for the efficacy evaluation.

TABLE 1. Clinical characteristics of patients with tibial fractures treated with intramedullary nailing and either active low-intensity ultrasound or placebo

Most patients could take full weight on the fractured leg prior to radiologic healing because of the stability achieved by the locked intramedullary nail. For the active treatment group, the average time from the fracture event until patients could walk without crutches and apply full weight on the affected leg was 6.5 ± 0.7 weeks and 7.1 ± 0.8 weeks for the placebo group ($p = 0.59$).

There was no significant difference between the two groups with respect to type and rate of complication during the course of treatment. Three patients, one in the active treatment group and two in the placebo group, developed an acute compartment syndrome within the first days following the fracture event and nailing. They were reoperated with fasciotomy as soon as the compartment syndrome had been verified. Secondary closure of the skin was done five days later in two patients, and split-thickness skin grafting was done in one patient. None of those patients developed any sequelae. There were two deep infections, both in the placebo group. One infection was treated with saline irrigation, drainage, and antibiotics with the nail left in place until the fracture had healed, after which the nail was removed. The other infection was diagnosed about twelve weeks after surgery when the fracture had already healed; this patient was treated with nail extraction followed by saline irrigation and antibiotics locally and systemically. Both infections were successfully treated, with no signs of any sequelae at the one-year follow-up. In three patients, two in the active group and one in the placebo group, the nail was dynamized due to delayed healing by removal of the locking screws.

Compliance data as defined by the total time the patients had used the ultrasound device were comparable between the two treatment groups, as recorded by the timer in the main operating unit and the patient log. The timer showed a usage time of 23.4 ± 0.8 hours in the active group, and the corresponding average time for the placebo group was 22.3 ± 1.0 hours, i.e., an insignificant difference of about one hour. In the patient log, the average reported user time was 24.6 hours for both groups. In twenty-three of the thirty-two patients, the discrepancy between the total usage time as reported by the patient and the actual time using the device as indicated by the timer was less than thirty minutes. In six patients, two in the active group and four in the placebo group, the usage time as reported by the patient was more than two hours longer than the actual usage time indicated by the timer.

The mean time from the fracture event until the first visible callus seen on the radiographs as assessed by the radiologist was 40 ± 3 days in the active treatment group and 37 ± 3 days in the placebo group ($p = 0.44$). The corresponding time as assessed by the orthopaedic surgeon was 37 ± 3 days and 33 ± 3 days, respectively ($p = 0.20$; Fig. 1). All fractures healed, although in seven patients, five in the active treatment group and two in the placebo group, the time to bridging of three cortices as assessed by the radiologist exceeded six months, i.e., a time span usually regarded as delayed union. The mean time from the fracture event to radiographic healing (three of four cortices bridged) as assessed by the radiologist was 155 ± 22 days (median 113 days) for the active treatment group and 125 ± 11 days (median 112 days) for the placebo group ($p = 0.76$, Mann-Whitney test; $p = 0.33$, log-

rank test; Figs. 2 and 3). The corresponding time for the assessment done by the orthopaedic surgeon on the same radiographs was 128 ± 13 days for the active treatment group and 114 ± 9 days for the placebo group (p = 0.40, Mann-Whitney test; Fig. 2).

FIG. 1. Time to the first visible callus in the group treated with active ultrasound and the group treated with placebo as assessed by a radiologist and an orthopaedic trauma surgeon. Mean ± standard error of the mean.

FIG. 2. Time to healing of the fracture (bridging of three cortices) in the group treated with active ultrasound and the group treated with placebo as assessed by a radiologist and an orthopaedic trauma surgeon. Mean ± standard error of the mean.

FIG. 3. Cumulative percentage of radiographically healed fractures as a function of time. There was no significant difference between the two treatment groups (p = 0.33, log-rank life analysis).

DISCUSSION^

In two previous double-blinded, randomized, and placebo-controlled clinical studies, low-intensity ultrasound significantly reduced the overall healing time in cast-treated tibial fractures (7) and cast-treated distal radial fractures (9). In the present study, in which we applied exactly the same low-intensity pulsed ultrasound device as in the previous two studies, there was no visible positive effect of ultrasound on the healing time. In fact, the average healing time was longer, albeit insignificantly, in the active treatment group than in the placebo group.

The number of patients in our study was about half the number of fractures included in the study by Heckman et al. (7). With a smaller number of patients, the power of the study is reduced and the risk that a nonsignificant result may be due to a statistical Type II error increases. Considering that the only tendency between the two groups was toward a shorter healing time in the placebo group, we are convinced that, even with a larger number of patients, there would not have been any difference in healing time between the two groups.

There are several similarities between the present study and the study by Heckman et al. (7). Both studies were performed in patients with a single tibial shaft fracture with inclusion of closed or Grade I open fractures. In both studies, fairly similar exclusion and inclusion criteria were applied, which means that the patient population and the fracture characteristics should have been fairly similar between the two studies. In the present study, 75 percent of the patients were men; in the study by Heckman et al. (7), the proportion of men was approximately 80 percent. We have not been able to detect any major difference between the two studies when comparing the proportion of different fracture types or fracture locations or the proportion of patients with a fibular fracture. The time from the fracture event until start of ultrasound treatment was about four days in both studies.

Considering the disagreement in results, it seems important to focus on the differences between the studies to find a plausible explanation. The most obvious dissimilarity is the type of treatment, with nonoperative treatment versus surgery. The surgical method used in the present study, i.e., a reamed statically locked nail, includes several steps that could influence the fracture healing process. Excessive reaming was avoided, but even so, the reaming itself may cause endosteal and cortical tissue damage that, at least under experimental conditions, has been shown to impair fracture healing (3). However, reaming has also been considered to be osteogenic due to osteoinductive bone marrow and small bone fragments being pushed out at the fracture site during reaming, as could be seen in several of our cases. The average healing time in the placebo group in the study by Heckman et al. (7) was considerably longer than the corresponding healing time in the placebo group in the present study. This difference may be related to the differences in the type of treatment, including reaming, used in our patients. The ultrasound did not seem to provide any additive effect in reducing the healing time in our patients.

The exact mechanism by which low-intensity ultrasound works during bone healing is unknown. One theory has stated that it acts by creating low-level mechanical forces at the fracture site (7) that stimulate the healing process by acting on the cellular system as a mechanical load that can regulate bone formation during the early phase of fracture healing (1,5). Even if intramedullary fixation

does not create a completely stable fixation construct, it still provides much more stability compared with a cast.

Axial loading at the fracture is considered beneficial for fracture healing (8). When using a statically locked nail, the load during weight-bearing is to some extent taken by the locking screws, especially in unstable fractures or in cases without good apposition of the fractured bone ends. This is a difference when compared with the loading conditions at tibial fractures treated with a cast.

Thus, the differences in fixation rigidity, fracture movement, and loading at the fractured bone ends are possible explanations for the observed differences in outcome between studies. However, considering that low-intensity ultrasound with thirty milliwatts per square centimeter is equivalent to a force of just a few milligrams per square centimeter, it seems highly unlikely that such a low-intensity signal would work by changing the gross mechanical input on the fractured bone as a structure. It seems more likely that the difference in results may be due to differences at the cellular level and not to differences related to fracture motion and loads at the fracture site. However, the positive effect of ultrasound in previous studies could be due to the signal acting on the cellular level, e.g., by causing microstrain in chondrocytes, as previously described.

The presence of metal in the fracture area is also an obvious difference between the studies, and to our knowledge this is the first randomized trial in humans in which metal was at the fracture site when using ultrasound. In the animal study by Wang et al. (15), a small Kirschner wire was used as intramedullary fixation to stabilize experimentally created femoral fractures in rats. Even in the presence of such a metal wire, they could show that rat femora exposed to low-intensity ultrasound treatment were stronger than fractured femora not subjected to ultrasound. Thus, from the animal study, the presence of metal does not seem to diminish the ultrasound effect. It is important to realize that the stabilization achieved by a Kirschner wire is poor compared with the stabilizing effect of a reamed statically locked intramedullary nail, as used in the present study.

The length of treatment is another difference between the present study and the study by Heckman et al. (7). The patients in the present used the ultrasound device daily for seventy-five days; in the study by Heckman et al., the patients used the treatment device for about twenty weeks or until fracture healing. We do not believe that the outcome of the study would have been different if we had applied such a long treatment period. If ultrasound had had any effect on the healing process in the present study, it seems reasonable that there should have been a measurable difference between the treatment groups with regard to the time until the first visible callus was observed. However, there was no such difference in callus formation between the two groups during the early phase of the healing process.

Smoking has a serious negative effect on bone and fracture healing. In a study by Kyro et al. (10), smokers who had sustained a tibial fracture had a significantly longer time to heal and a higher incidence of delayed union than did nonsmoking patients with similar fractures. Cook et al. (2) reanalyzed the previously presented patients with tibial or distal radial fractures included in the randomized studies by Heckman et al. (7) and Kristiansen et al. (9), with an emphasis on the effect of ultrasound on healing time. The reanalyses by Cook et al. (2) specifically examined the difference in healing time between smokers and nonsmokers. They concluded that the healing time in smokers was longer than that in nonsmokers. However, the healing time in smokers was reduced 40 to 50 percent, and the reduction in healing time in nonsmokers was 26 to 34 percent when subjected to active ultrasound treatment rather than placebo. This finding means that active ultrasound has a more pronounced effect on healing time in smokers than in nonsmokers. In the present study, there were only two smokers, one in each group, which is a marked difference from the 35 percent of patients who were smokers in the study by Heckman et al. (7). The limited number of smokers in the present study obviously makes it impossible to evaluate whether low-intensity ultrasound has any effect on healing time in this specific subgroup.

We are convinced from the present findings that low-intensity ultrasound does not accelerate fracture healing in tibial fractures fixed with a reamed statically locked intramedullary nail. However, considering the convincing results with reduced healing time of tibial fractures and distal radial fractures when treated with a cast, it is important to limit the conclusion of the present trial to the specific type of fracture studied and to the specific surgical treatment used, i.e., statically locked intramedullary nails inserted after reaming.

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REFERENCES^

1. Buckley MJ, Banes AJ, Levin LG, et al. Osteoblasts increase their rate of division and align in response to cyclic, mechanical tension in vitro. *Bone*

Miner 1988;4:225-236. **Bibliographic Links** [Context Link]

2. Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fractures healing in patients who smoke. *Clin Orthop* 1997;337:198-207. **Ovid Full Text** **Bibliographic Links** [Context Link]

3. Danckwardt-Lilliestrom G. Reaming of the medullary cavity and its effect on diaphyseal bone: a fluorochromic, microangiographic and histologic study on the rabbit tibia and dog femur. *Acta Orthop Scand* 1970;170(Suppl):1-153. [Context Link]

4. Duarte LR. The stimulation of bone growth by ultrasound. *Arch Orthop Trauma Surg* 1983;101:153-159. **Bibliographic Links** [Context Link]

5. Goodship AE, Kenwright J. The influence of induced micromovement upon the healing of experimental tibial fractures. *J Bone Joint Surg* 1985;67A:650-655. [Context Link]

6. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analysis. *J Bone Joint Surg* 1976;58A:453-458. **Bibliographic Links** [Context Link]

7. Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg* 1994;76A:26-34. **Bibliographic Links** [Context Link]

8. Kenwright J, Goodship AE. Controlled mechanical stimulation in the treatment of tibial fractures. *Clin Orthop* 1989;241:36-47. **Bibliographic Links** [Context Link]

9. Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. *J Bone Joint Surg* 1997;79A:961-973. **Bibliographic Links** [Context Link]

10. Kyro A, Usenius JP, Aarnio M, Kunnamo I, Avikainen V. Are smokers a risk group for delayed healing of tibial shaft fractures? *Ann Chir Gynaecol* 1993;92(4):254-262. [Context Link]

11. Müller ME, Nazarian J, Koch P, Schatzker J. *Comprehensive Classification of Fractures of Long Bones.* Berlin, Springer-Verlag, 1990. [Context Link]

12. Parvizi J, Parpura V, Kinnick RR, Greenleaf JF, Bolander ME. Low intensity ultrasound increases intracellular concentration of calcium in chondrocytes. *Trans Orthop Res Soc* 1997;42:465. [Context Link]

13. Pilla AA, Figueiredo M, Nasser PR, et al. Effect of ultrasound intensity on accelerated bone repair in a rabbit model. *Trans Orthop Res Soc* 1991;37:452. [Context Link]

14. Pilla AA, Mont MA, Nasser PR, et al. Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit. *J Orthop Trauma* 1990;4:246-253. **Bibliographic Links** [Context Link]

15. Wang SJ, Lewallen DG, Bolander MG, Chao EYS, Ilstrup DM, Greenleaf JF. Low intensity ultrasound treatment increases strength in a rat femoral fracture model. *J Orthop Res* 1994;12:40-47. **Bibliographic Links** [Context Link]

16. Yang KH, Parvizi J, Wang SJ, et al. Exposure to low intensity ultrasound increases aggrecan gene expression in a rat femur fracture model. *J Orthop Res* 1996;14:802-809. **Bibliographic Links** [Context Link]

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