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Acceleration of Tibial Fracture-Healing by Non-Invasive, Low-Intensity Pulsed Ultrasound*

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ABSTRACT: Sixty-seven closed or grade-I open fractures of the tibial shaft were examined in a prospective, randomized, double-blind evaluation of use of a new ultrasound stimulating device as an adjunct to conventional treatment with a cast. Thirty-three fractures were treated with the active device and thirty-four, with a placebo control device. At the end of the treatment, there was a statistically significant decrease in the time to clinical healing (86 ± 5.8 days in the active-treatment group compared with 114 ± 10.4 days in the control group) (p = 0.01) and also a significant decrease in the time to over-all (clinical and radiographic) healing (96 ± 4.9 days in the active-treatment group compared with 154 ± 13.7 days in the control group) (p = 0.0001). The patients' compliance with the use of the device was excellent, and there were no serious complications related to its use. This study confirms earlier animal and clinical studies that demonstrated the efficacy of low-intensity ultrasound stimulation in the acceleration of the normal fracture-repair process.

Ultrasound has many medical applications, including therapeutic, operative, and diagnostic procedures[23]. Both ultrasound therapy and operative ultrasound subject tissue to power levels that are capable of causing considerable heating and biological effects. In conventional ultrasound therapy, ultrasonic intensities of one to three watts per square centimeter are used to decrease joint stiffness, reduce pain and muscle spasms, and improve muscle mobility[6]. The operative application of ultrasound employs intensity levels of five to more than 300 watts per square centimeter to fragment calculi and to ablate diseased tissues such as cataracts[20]. These relatively high ultrasound intensities are employed to generate heat within the tissues, through which the ultrasound signal passes[15]. Diagnostic applications of ultrasound include examination of vital organs, evaluation of fetuses, vascular and peripheral flow studies, and ophthalmic echography. The diagnostic applications of ultrasound use much lower intensities, typically five to fifty milliwatts per square centimeter, to avoid excessive heating of tissues[19].

Xavier and Duarte[21] reported the acceleration of the normal fracture-repair process in humans with use of low-intensity (diagnostic-range) ultrasound and also indicated that low-intensity ultrasound can induce healing of ununited diaphyseal fractures[22]. With use of a rabbit fibular osteotomy model and a second model that employed a drill-hole in the cortex of the femur of a rabbit, Duarte demonstrated acceleration of the normal fracture-repair process with use of ultrasound. Pilla et al., with use of a slightly different fibular osteotomy model, also demonstrated that non-invasive, low-intensity pulsed ultrasound accelerated fracture-healing in the rabbit. Klug et al. used a scintigraphic technique to demonstrate quicker maturation of the callus and earlier healing in experimentally induced closed fractures in a rabbit model after ultrasound stimulation with intensity levels that were an order of magnitude higher than those used by Duarte or by Pilla et al. Because we believe that these preliminary studies clearly showed a positive effect of ultrasound on the rate of osseous repair, we designed the present study to investigate the effect of specifically programmed, low-intensity pulsed ultrasound on the rate of healing of cortical fractures when used in patients as an adjunct to conventional orthopaedic management.

Materials and Methods

The study was multi-institutional, prospective, randomized, double-blind, and placebo-controlled. There were co-investigators from sixteen sites in various geographical areas of the United States and from one site in Israel.

An opportunity to participate in the study was offered to all skeletally mature men and non-pregnant

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women seen at our institutions between September 1986 and December 1990 who were at most seventy-five years old and who had a closed or grade-I open tibial diaphyseal fracture that was primarily transverse, short oblique, or short spiral and that could be treated effectively with closed reduction and immobilization in a cast.

Anteroposterior and lateral radiographs were made immediately after the reduction. We excluded patients if either the anteroposterior or the lateral radiographs showed that the length of the fracture line was more than twice the diameter of the diaphyseal shaft (a long spiral or long oblique fracture), the displacement was more than 50 per cent of the width of the shaft, or the fracture gap was more than 0.5 centimeter. Other exclusion criteria were open fractures, except grade I as defined by Gustilo and Anderson; fractures of the tibial metaphysis; fractures with persistent shortening of more than one centimeter after reduction; fractures that were not sufficiently stable (recurrent or persistent angulation of 10 degrees or more in any plane) for treatment with immobilization in an above-the-knee cast; fractures with a large butterfly fragment (larger than two times the diameter of the tibial shaft); pathological fractures; and comminuted fractures (comminution with fragments of less than one centimeter in length was acceptable). Patients were also excluded if they had stated that they could not comply with the protocol; were receiving steroids, anticoagulants, prescription non-steroidal anti-inflammatory medication, calcium-channel blockers, or diphosphonate therapy; had a history of thrombophlebitis or vascular insufficiency; or had a recent history of alcoholism or nutritional deficiency, or both.

After they had agreed to participate in the study and gave informed consent, the patients were randomized into groups of four at each study site to receive an active or a placebo-treatment device according to a predetermined computer-generated code. The code was broken only after the radiographic reviews had been completed.

Ninety-six patients, who had a total of ninety-seven fractures, were entered into the study. Forty-eight of the fractures were randomized to the active-treatment group and forty-nine, to the placebo-treatment control group. Thirteen patients (thirteen fractures [13 per cent]) were lost to follow-up, leaving eighty-four patients (eighty-five fractures [88 per cent]) in whom the healing status of the fracture was known. An additional seventeen patients (seventeen fractures [18 per cent]) were excluded from the study because of deviations from the protocol.

Of the thirteen patients (four who had active treatment and nine, placebo treatment) who were lost to follow-up and for whom the final healing status was not known, seven had withdrawn from the study, five had been withdrawn by the site investigator, and one had died of unrelated causes seven weeks after the fracture. Of the five patients who were withdrawn by the site investigator, one had had an open reduction and internal fixation of the fracture and the remaining four had not complied with the outlined treatment protocol.

Of the seventeen patients (eleven who had active treatment and six, placebo treatment) who were excluded because of deviations from the protocol, six (two who had active treatment and four, placebo treatment) had had an operative procedure within six weeks after the injury because of severe angulation of the fracture after treatment had begun, seven were excluded because the fracture did not meet the inclusion criteria of the protocol, and four were withdrawn by the investigator because of failure to comply with the treatment protocol. These seventeen patients were still followed and the outcomes of treatment were obtained.

The remaining sixty-seven fractures (thirty-three that were treated with an active unit and thirty-four, with a placebo unit) represent the core group of fractures in patients who adhered to the study protocol and had sufficient follow-up data. It is this group from which the clinical and statistical inferences were drawn.

There were sixty-four closed fractures (thirty-one in the active-treatment group and thirty-three in the placebo-treatment group) and three grade-I open fractures (two in the active-treatment group and one in the placebo-treatment group). The fractures were treated conventionally with closed reduction and immobilization in an above-the-knee cast. The three grade-I open fractures were treated with initial débridement, and the wounds were allowed to heal by secondary intention. A retaining and alignment fixture made of molded plastic was inserted into a window centered over the anteromedial surface of the cast, at the site of the tibial fracture. This fixture held the treatment head module in place during the daily twenty-minute treatment period. Between treatment periods, a circular, felt plug was inserted in the fixture and a cap was placed over it to maintain an even pressure on the skin and to minimize the risk of edema at the site of the window.

Treatment was started within seven days after the fracture and consisted of one twenty-minute period each day. The treatment head module was positioned in the window after removal of the felt plug and the application of a small amount of ultrasonic coupling gel to the surface of the head. It was attached to a portable main operating unit that contained the necessary circuitry to drive the treatment head module and to monitor the proper attachment of the module in the cast fixture. A warning signal was sounded by the main operating unit if there was not proper coupling to the skin. In addition, the main operating unit contained an integral timer that monitored treatment times and automatically turned the unit off after twenty minutes. A visual and audible signal alerted the patient that the treatment was complete. The patients' compliance with instructions for use of the device was measured by both a timer inside the main operating unit and a patient-maintained

daily treatment log. The active and placebo devices were identical in every way (they had the same visual, tactile, and auditory signals) except for the ultrasound signal emitted.

Treatment was continued for twenty weeks or until the clinical investigator believed that the fracture was healed sufficiently to discontinue the active or the placebo ultrasound therapy.

The treatment head module delivered 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 average intensity of thirty milliwatts per square centimeter.

The regimen for treatment of the fracture was identical for all patients. Immobilization in an above-the-knee cast was maintained until the investigator thought that the fracture was sufficiently stable for application of a short cast or a brace. After immobilization in a cast was discontinued, additional protection with either a splint or a brace was at the discretion of the investigator. Cast changes were permitted as clinically indicated. Weight-bearing was controlled on the basis of the investigator's clinical judgment and the tolerance of the patient. The only difference in the common protocol of fracture management was the initiation of weight-bearing. The first forty-two patients (forty-two fractures) enrolled in the study were instructed not to bear weight during the first eight weeks after the fracture, and the remaining fifty-four patients (fifty-five fractures) were allowed to bear weight as tolerated.

All patients were scheduled to return for follow-up radiographs at four, six, eight, ten, twelve, fourteen, twenty, thirty-three, and fifty-two weeks after the fracture. Anteroposterior and lateral radiographs were made and standardized whenever possible, with use of the same x-ray machine at each site, the same exposure setting, and a leg-positioning device that was furnished to each site investigator. Clinical follow-up evaluations were performed by the site investigator at the time of any cast change (usually at six and ten weeks) and at the follow-up visit when radiographic evaluation indicated that the fracture had healed sufficiently to allow removal of the cast.

The end-point of the study was a healed fracture, as judged both on clinical examination and on radiographic examination (three of four cortices bridged). In addition to the healed-fracture end-point, intermediate stages of the fracture-healing process were assessed for the difference between the active-treatment and the placebo-treatment groups.

With regard to the intermediate clinical stages of healing, two parameters were evaluated: the time to clinical healing was defined as the time at which the individual site investigator thought that, on clinical examination, the fracture was stable and was not painful to manual stress, and the time to discontinuation of the cast was documented as the time at which the site investigator discontinued use of the cast.

With regard to the intermediate radiographic signs of healing, two parameters were evaluated. The first, cortical bridging, was defined as the gradual disappearance of the interruption of the cortex at the fracture site as a result of callus formation. The amount of cortical bridging was quantified as none (no change at the cortical interruption compared with that seen on a radiograph made in the immediate post-reduction period), initial (when a periosteal reaction at the cortical interruption of the fracture site was first noted), intermedi-

TABLE I
ASSESSMENT OF TREATMENT-GROUP COMPARABILITY

Parameter	Treatment Group		P Value
	Active	Placebo	
No. of fractures	33	34	
Sex			0.37*
Male	25	29	
Female	8	5	
Fracture grade			0.64*
Closed	31	33	
Grade-I open[8]	2	1	
Type of fracture			0.49*
Transverse	4	8	
Short oblique	17	15	
Short spiral	11	11	
Comminuted	1	0	
Location of fracture			0.60*
Proximal	1	3	
Middle	15	15	
Distal	17	16	
Comminuted fracture			0.43*
No	31	29	
Yes	2	5	
Butterfly fracture			0.77*
No	26	28	
Yes	7	6	
Fibular fracture			0.13*
No	9	4	
Yes	24	30	
Age† *(yrs.)*	36 ± 2.3	31 ± 1.8	0.09‡
Displacement *(per cent)*			
Before reduction†	33 ± 4.7 (n = 30)	38 ± 4.9 (n = 31)	0.48‡
After reduction†	23 ± 2.5	23 ± 2.7	0.98‡
Angulation *(degrees)*			
Before reduction†	6 ± 1.0 (n = 30)	6 ± 0.8	0.74‡
After reduction†	4 ± 0.5	4 ± 0.4	0.80‡
Maximum fracture gap† *(mm)*	4 ± 0.3	4 ± 0.3	0.92‡
Length of fracture† *(cm)*	4 ± 0.2	4 ± 0.2	0.55‡
Days until start of treatment†	4 ± 0.3	4 ± 0.3 (n = 33)	0.89‡
Duration of follow-up† *(days)*	250 ± 18.1	284 ± 19.2	0.21‡
Range	92-438	142-586	
Days to start of weight-bearing†	45 ± 4.9 (n = 33)	49 ± 5.9	0.62‡

*With the Fisher exact test or chi-square test.
†The values are given as the mean and the standard error of the mean.
‡With analysis of variance.

TABLE II
INTERMEDIATE RADIOGRAPHIC HEALING STAGES

	Days after Fracture		P Value†		
	Active Treatment* (N = 33)	Placebo Treatment * (N = 34)‡	ANOVA	Kruskal-Wallis Rank ANOVA	Log-Rank
3 bridged cortices					
Principal investigator	89 ± 3.7	148 ± 13.2	0.0001	0.0001	0.0001
Independent radiologist	102 ± 4.8	190 ± 18.3	0.0001	0.0001	0.0001
Complete cortical bridging (4 bridged cortices)					
Principal investigator	114 ± 7.5	182 ± 15.8	0.0002	0.0001	0.0001
Independent radiologist	136 ± 9.6	243 ± 18.4	0.0001	0.0001	0.0001
Endosteal healing					
Principal investigator	117 ± 8.5	167 ± 13.9	0.002	0.0004	0.0004
Independent radiologist	171 ± 13.6	271 ± 19.6	0.0001	0.0001	0.0001

*The values are given as the mean and the standard deviation of the mean, as calculated with analysis of variance.
†ANOVA = analysis of variance.
‡No clinical data were available for one fracture that was treated with the placebo device.

ate (an increase in the density or size of the initial periosteal reaction) or complete (the periosteal reaction completely bridged the cortical interruption). On each radiographic evaluation at each time-point, four cortices (two on the anteroposterior radiograph and two on the lateral radiograph) were evaluated for the amount of cortical bridging.

The other parameter, endosteal healing, was defined as the gradual disappearance or obliteration of the fracture line and its replacement by a zone of increased density formed by endosteal callus. The amount of endosteal healing was quantified as none (no change in the fracture line compared with that on the post-reduction radiograph), initial (the fracture line had become less distinct), intermediate (there was marked consolidation of the fracture line), and complete (the fracture line had been replaced by a zone of increased density formed by endosteal callus). A judgment as to the extent of endosteal healing was made on both the anteroposterior and the lateral radiographs at each follow-up visit.

To minimize the effect of subjective interpretation of the radiographs by the individual investigators, all radiographs were assessed in independent, blind reviews by the principal investigator (J. D. H.) and, separately, by the independent radiologist (R. F. K.). The principal investigator's assessment of radiographic healing was used for purposes of statistical analysis to compare the efficacy of treatment with the results of use of the placebo device. The site investigator's assessment of clinical healing was used for analysis of the clinical components of fracture-healing. Time to response was calculated as the number of days after the fracture to the first occurrence of the specified event.

The active and the placebo-treatment groups were compared with regard to important characteristics of the fractures and patients. A statistical analysis[7] was performed with use of the Fisher exact test (or the chi-square test if there were more than two category levels) for the sex of the patient; the grade, type, and location (proximal, middle, or distal) of the fracture; the presence of minor comminution; the presence of a butterfly fragment; and the presence of a fibular fracture (Table I). Statistical analysis was performed by the analysis of variance for the mean age of the patients in years, mean pre-reduction and post-reduction displacement, mean pre-reduction and post-reduction angulation in degrees, maximum fracture gap in millimeters, maximum length of the fracture in centimeters, mean number of days after the fracture before the start of treatment, mean number of days of follow-up, and mean number of days to the start of weight-bearing (Table I).

Patient compliance was measured as the adherence to the scheduled follow-up visits as dictated by the protocol and the frequency of use of the device as measured by the internal device clock and a written log kept by the patient. Adverse reactions, patients' complaints, and complications were specifically sought by each site investigator at each visit and were recorded if found.

Previous animal and clinical studies[5,9,16,21,22] clearly showed a positive effect of ultrasound on the rate of osseous repair. Therefore, an accelerated time to healing for the active-treatment group was hypothesized at the protocol-design phase of this study. Consequently, one-sided statistical tests of hypothesis and one-sided p values were calculated to assess the superiority of treatment with the active device compared with treatment with the placebo, control device. The null hypothesis that the time to response for fractures treated with the active device was the same or worse than the time to response for those treated with the placebo device was tested against the alternate hypothesis that the time to response was superior for the fractures treated with the active device. Superior was defined as an accelerated (shorter) time to the attainment of a specific healing response, such as a healed fracture status. The result was significant when the p value was 0.05 or less in favor of the active-treatment group.

Three statistical approaches are presented for all

TABLE III
NUMBER AND CUMULATIVE NUMBER OF FRACTURES FOR DAYS AFTER THE FRACTURE TO THE START OF WEIGHT-BEARING

	Active		Placebo*	
Days after Fracture	No.	Cumulative	No.	Cumulative
0-14	5	5	4	4
15-28	5	10	4	8
29-35	6	16	7	15
36-49	3	19	5	20
50-63	7	26	5	25
64-77	3	29	1	26
>77	4	33	7	33

*No data were available on the start of weight-bearing for one fracture in the placebo-treatment group.

analyses. Analysis of variance[18] was used to calculate the mean time and the standard error of the mean, in days, to the attainment of a healed fracture status for the active-treatment and placebo-treatment groups. Analysis of variance, Kruskal-Wallis analysis of variance by ranks[3,12], and log-rank life-table analysis[4,13,14] were used to compare the mean times to healing for the two groups. The Kruskal-Wallis analysis was used because it does not make the statistical assumptions of a Gaussian distribution or homogeneity of variances. The log-rank life-table analysis was used because it analyzes right censored observations as censored observations and uses days to the last follow-up visit as the time-to-event value (one fracture that had active treatment and one that had the placebo treatment had right censored estimated values for the time to a healed fracture).

In addition, Cox regression analysis was used to assess whether potential covariates, such as the sex and age of the patient, the days to the start of weight-bearing, and the grade, type, or location of the fracture, had an effect on the healing response in the active compared with the placebo-treatment group. If an effect was observed because of the covariate, the results of active treatment compared with those of placebo treatment were statistically adjusted for the covariate in order to determine whether the superiority of the active-treatment group compared with the placebo-treatment group was maintained in the presence of the covariate effect.

All data observations were entered into a computer file and then the computer printout was proofread carefully against the case-record form. An independent, thorough comparison of all data used in the statistical analyses with those in the case-record form was done before the statistical analysis, to ensure the accuracy of the data further. All analyses were performed with the Statistical Analysis System software (SAS Institute, Cary, North Carolina) on an IBM 3081 mainframe computer.

All of the fractures that were randomized into each study group were analyzed for the time to healing in an intention-to-treat log-rank life-table analysis. Each fracture was considered to be healed only at the time of a scheduled follow-up visit (for example, at ten, twelve, fourteen, twenty, thirty-three, or fifty-two weeks) and no interim visit (planned or otherwise) was used to assign a healing time. The number of days to the last completed follow-up examination was used for the time to healing for the fractures that had not reached a healed status by the last follow-up visit. This intention-to-treat analysis evaluated whether exclusion of the withdrawn and non-protocol-compliant patients biased the results obtained in the analysis of the time that the fractures in the core group took to heal.

Results

With regard to the seventeen patient and fracture parameters that were studied (Table I), we could not detect any appreciable differences between the thirty-three fractures in the active-treatment core group and the thirty-four fractures in the placebo-treatment core group, with the numbers studied. Therefore, we believe that the placebo-treatment group was quite similar to the active-treatment group.

The patients' compliance with the follow-up protocol was analyzed by calculation of the ratio of actual clinical visits to the expected (scheduled) number of clinical visits for each group. The patients who received active treatment returned for the scheduled follow-up visits 89 per cent of the time (245 of 276 visits), and the patients who were treated with the placebo, 90 per cent of the time (256 of 283 visits). Usage of the device was comparable between the active-treatment and the placebo-treatment core groups, as recorded by both the device timer and the patient log, and all of the patients in the active-treatment group used the unit for at least thirty-six treatment sessions.

The total duration of follow-up, in days, was comparable in the active and the placebo-treatment groups; it was 250 ± 18.1 days (mean and standard error of the mean [analysis of variance]) (range, ninety-two to 438 days) for the active-treatment group compared with 284 ± 19.2 days (range, 142 to 586 days) for the placebo-treatment group ($p = 0.21$) (Table I). One patient in the active-treatment group sustained a fracture in the same area of the tibia seven months after the initial fracture was considered to be healed both clinically and radiographically. The second fracture occurred during a soccer game, from simultaneous kicks to the tibia by two other players. This fracture healed four months later.

A subsequent, long-term follow-up was done at the request of the Food and Drug Administration to determine whether all healed fractures in both groups in the study remained healed at a minimum of two years after the injury. Fifty-five patients (fifty-six fractures) of the sixty-six patients (sixty-seven fractures) who had been enrolled in the protocol were contacted. All fifty-six of the fractures were still healed. The duration of follow-up for twenty-three fractures was more than four years and for thirty-three fractures, it was two to four years.

TABLE IV

SUMMARY OF THE COX REGRESSION ANALYSES FOR ASSESSMENT OF THE SIGNIFICANCE OF POTENTIAL COVARIATES ON THE TIME TO A HEALED FRACTURE

Potential Covariate	Core-Group Fractures		
	Log-Likelihood Chi-Square	P Value	Significant Covariate
Sex	0.01	0.92	No
Age	1.78	0.18	No
Days to start of weight-bearing	4.55	0.03	Yes
Adjusted difference*	17.97	0.0001	—
Fracture grade	1.38	0.24	No
Type of fracture	0.10	0.76	No
Location of fracture	1.27	0.26	No

*The active compared with the placebo p value, when adjusted for the start of weight-bearing, compared favorably with the analysis of variance and log-rank p values of 0.0001.

Analysis of variance showed that the mean time to the end-point of the study (a healed fracture), as judged both clinically by the site investigator and radiographically (three of four bridged cortices) by the principal investigator, was 96 ± 4.9 days for the active-treatment group compared with 154 ± 13.7 days for the placebo-treatment group ($p < 0.0001$ [analysis of variance, Kruskal-Wallis rank analysis of variance, and log-rank life-table analysis]) (Fig. 1). At 120 days after the fracture, 88 per cent of the fractures in the active-treatment group were healed compared with 44 per cent in the placebo-treatment group; at 150 days, 94 per cent of the fractures in the active-treatment group were healed compared with 62 per cent in the placebo-treatment group (Fig. 2).

The mean time to clinical healing, as assessed by the site investigator, was 86 ± 5.8 days for the active-treatment group compared with 114 ± 10.4 days for the placebo-treatment group ($p = 0.01$, 0.03, and 0.01 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis, respectively]). The mean time to discontinuation of the cast was 94 ± 5.5 days for the active-treatment group compared with 120 ± 9.1 days for the placebo-treatment group ($p = 0.008$, 0.005, and 0.01). The time to clinical healing was not recorded for one patient in the placebo-treatment group.

The intermediate stages of radiographic healing were determined by the principal investigator for all sixty-seven patients. Analysis of variance of the time to complete healing for the first, second, third, and fourth cortices demonstrated an increased rate of bridging in the active-treatment group compared with that in the placebo-treatment group. There was a significant increase (according to analysis of variance, rank analysis of variance, and log-rank life-table analysis) in the differences between the groups with regard to the number of days after the fracture that bridging had occurred; these differences were thirty, fifty-nine, and sixty-eight days for the second, third, and fourth cortices, respectively (Fig. 3).

The radiographic assessments of the principal investigator and the independent radiologist for the time to cortical bridging for three and four cortices and the time to complete endosteal healing produced comparable statistical results, with the radiologist's assessments reflecting more conservative evaluations (Table II). The

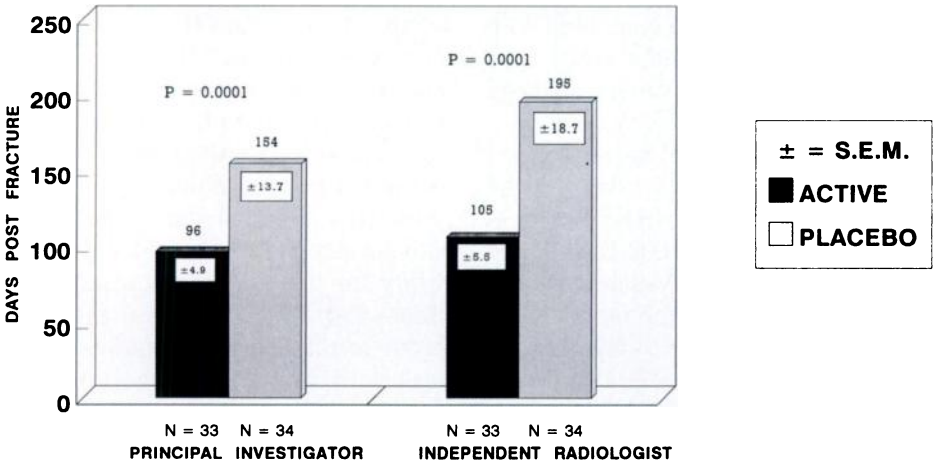

FIG. 1

Graph showing the days to healing of the fracture (clinically and radiographically) as assessed by the principal investigator and the independent radiologist. S. E. M. = standard error of the mean.

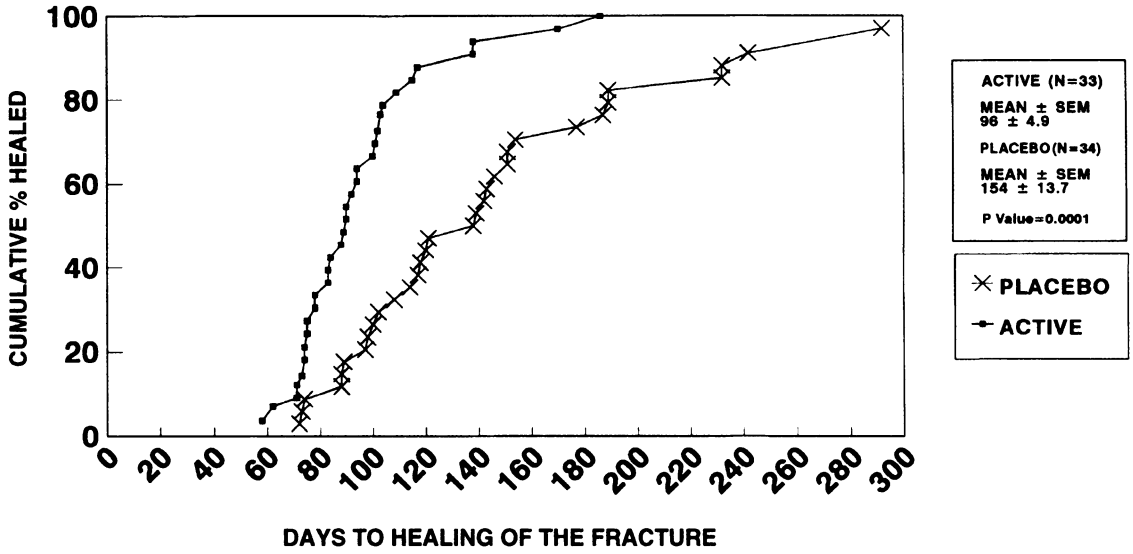

FIG. 2

Graph showing the cumulative percentage of clinically and radiographically healed fractures in the core group as a function of time. The superiority of the active-treatment group is seen, with 56 per cent of the fractures healed compared with 18 per cent of the fractures in the placebo-treatment group, at ninety days after the fracture. One fracture in the placebo-treatment group healed at 465 days after the fracture, and no clinical data were available for one fracture in this group. The p value is for analysis of variance, rank analysis of variance, and log-rank life-table analysis. SEM = standard error of the mean.

principal investigator determined the time needed for bridging of three cortices to be 89 ± 3.7 days for the active-treatment group compared with 148 ± 13.2 days for the placebo-treatment group (p = 0.0001 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis]), and the independent radiologist's assessment was 102 ± 4.8 days for the active-treatment group compared with 190 ± 18.3 days for the placebo-treatment group (p = 0.0001 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis]).

The time to complete cortical bridging (all four cortices), as assessed by the principal investigator, was 114 ± 7.5 days for the active-treatment group compared with 182 ± 15.8 days for the placebo-treatment group (p = 0.0002, 0.0001, and 0.0001 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis]), and the independent radiologist's assessments were 136 ± 9.6 days for the active-treatment group compared with 243 ± 18.4 days for the placebo-treatment group (p = 0.0001 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis]).

The time to complete endosteal healing, as assessed by the principal investigator, was 117 ± 8.5 days for the active-treatment group compared with 167 ± 13.9 days for the placebo-treatment group (p = 0.002, 0.0004, and 0.0004 [analysis of variance, Kruskal-Wallace analysis, and log-rank life-table analysis]), and the independent radiologist's assessment was 171 ± 13.6 days for the active-treatment group compared with 271 ± 19.6 days for the placebo-treatment group (p = 0.0001, 0.0001, and 0.0001).

A smoking history was obtained from thirty-seven core-group patients (thirty-eight fractures). Among the fourteen fractures in thirteen patients who had never smoked, nine were treated with the active device and healed in a mean of 87 ± 3.9 days, compared with 132 ± 11.2 days for the five that were treated with the placebo device (p = 0.002). Among the fractures in the remaining patients, who were ex-smokers or who were smoking during the treatment period, eleven that were treated with the active device healed in a mean of 115 ± 11.2 days, compared with a mean of 158 ± 28.6 days for thirteen fractures that were treated with the placebo device (p = 0.09).

As mentioned previously, the only difference with regard to the management of the patients was the time to the start of weight-bearing. The justification for the combination of all core-group fractures in the efficacy analysis was the essentially identical pattern of fracture and mean time after the fracture to the start of weight-bearing in the active-treatment and placebo-treatment groups (Tables I and III) and on the statistical analysis by Cox regression of the effect of the start of weight-bearing on the efficacy results of the active treatment compared with the placebo treatment. The Cox regression analysis established that when the active-treatment and the placebo-treatment groups were statistically adjusted to a common start of weight-bearing effect, the active-treatment group maintained a significant superiority for the time to a healed fracture (p = 0.0001) (Table IV). This result is identical to the p value of 0.0001 in the analysis of variance, Kruskal-Wallis rank analysis of variance, and log-rank life-table analysis (Fig. 1) and confirms that the day that weight-bearing started did not significantly affect the efficacy results of time to a healed fracture.

In addition, the Cox regression analysis established that other clinically relevant covariates, such as the sex

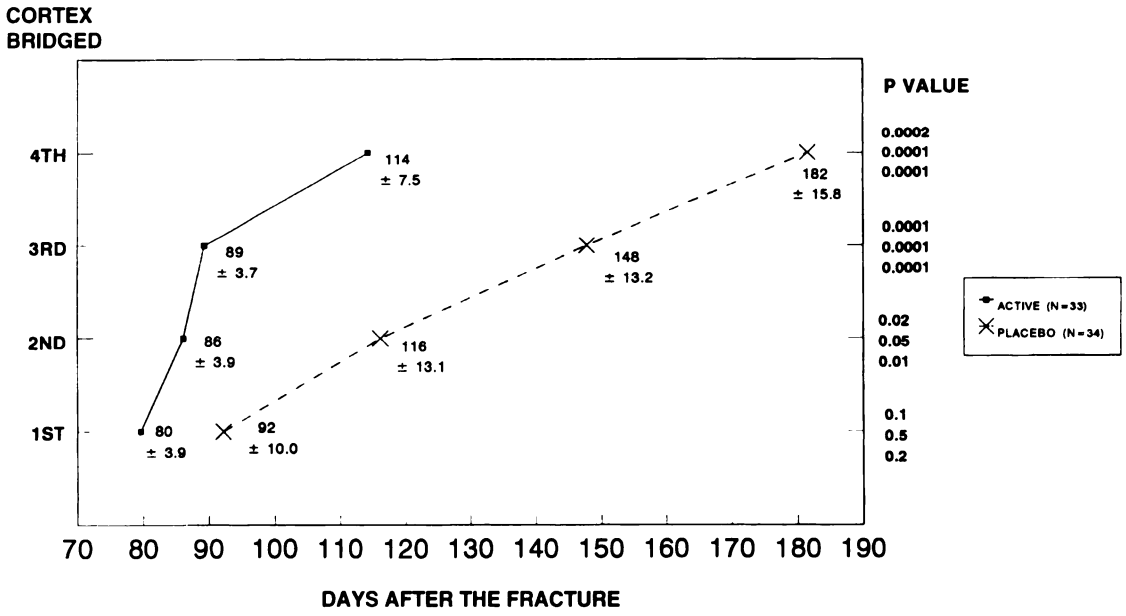

FIG. 3

Graph showing the rate of progression of healing by the amount of cortex bridged. The values are given as the mean and the standard error of the mean. P values are given for analysis of variance, rank analysis of variance, and log-rank life-table analyses.

and age of the patient and the grade, type, and location of the fracture, also had no significant effect on the efficacy results of time to a healed fracture (Table IV).

Log-rank life-table analysis was used in an intention-to-treat analysis for all fractures randomized into the study. The time to a healed fracture was significant for the active-treatment group at the 0.005 probability level, which compares favorably with the analysis of variance, Kruskal-Wallis, and log-rank p values for time to a healed fracture in the core group. This result confirms the validity of the use of the core group of protocol-compliant patients for clinical and statistical inferences.

There were two adverse reactions and one complication in the sixty-six patients in the core group. One patient (who had active treatment) reported muscle-cramping at one week. The cramping resolved, without treatment, by the second week. One patient (who had placebo treatment) had swelling in the cast at the six-week follow-up visit. This problem had resolved by the next visit. No other adverse reactions were reported. One patient who used a placebo device had a pulmonary embolus at the four-week follow-up visit. The patient was managed successfully with anticoagulant therapy and remained in the study.

Discussion

The intriguing clinical findings of Xavier and Duarte[21], supported by placebo-controlled animal studies by Duarte and by Pilla et al., demonstrated that ultrasound accelerates the normal fracture-repair process in diaphyseal bone. These findings led us to design a prospective, randomized, double-blind, placebo-controlled study to assess both the safety and the effectiveness of the use of low-intensity ultrasound to accelerate healing of fresh fractures in humans. The randomization process created two very similar groups of patients and therefore permitted an unbiased assessment of the effect of the active-treatment device. When these two groups were compared, the time to a healed fracture was found to be significantly accelerated when the active-treatment device was applied for one twenty-minute period each day for as many as twenty weeks in the immediate post-fracture period in patients who had a closed or grade-I[8] open tibial diaphyseal fracture.

The treatment regimen was tolerated well by the patients, and no serious complications attributable to the treatment were identified. No patient had noticeable edema at the site of the window or skin irritation as a consequence of use of the device. The patients found the portable unit easy to use and were able to achieve adequate coupling contact between the skin and the treatment head surface. No specific mechanical or technical problems were encountered during the study.

The specific mechanism by which low-intensity pulsed ultrasound accelerates the normal diaphyseal fracture-repair process is unknown. The present study does not address this question. Other authors have reported on biological effects caused by static mechanical forces[1] and by the pressure waves of ultrasound's mechanical perturbation[2,17]. These pressure waves may mediate biological activity directly by mechanical deformation of the cell membrane or indirectly by an electrical effect caused by cell deformation.

Kristiansen reported on the acceleration of the time to a healed fracture and on other radiographic parameters of healing of metaphyseal bone in a similar double-blind, randomized, placebo-controlled study with use

of the same ultrasound treatment on Colles fractures. Knoch and Klug reported an increased rate of healing of fractures at various locations in humans with use of ultrasound treatment with signal intensities that were one order of magnitude more than the signal intensities used in the present study.

Beyond the preliminary clinical studies of Xavier and Duarte[21,22], Kristiansen, and the present study, we are not aware of any other studies that document the effectiveness of low-intensity, pulsed ultrasound in the acceleration of the fracture-healing process in humans. We believe that additional clinical corroboration of the acceleration of healing of fresh fractures with use of specifically programmed, pulsed, low-intensity ultrasound treatment may lead to its useful application in the treatment of fractures.

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