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● *Original Contribution*

LOW-INTENSITY PULSED ULTRASOUND: EFFECTS ON NONUNIONS

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Abstract—To study the efficacy of low-intensity pulsed ultrasound (US), or LIPUS, of 85 treated nonunion cases with a minimum fracture age of 8 months, 67 cases met the study criteria. These were: no surgical intervention during 4 months before US treatment and radiographically ceased healing for 3 months before US. In a self-paired control study, the mean fracture age of the 67 patients was 39 ± 6.2 months. After a daily 20-min US treatment at home for an average of 168 days, 85% (57 of 67) of the nonunion cases were clinically and radiographically healed. The study did not include any cases that were malaligned, grossly instable, actively infected or that had extensive bone loss. The results demonstrate that the specific US can effect heal rates similar to those achieved by surgical means, without the associated risks and complications, and to those achieved by electrical bone growth stimulation or by extracorporeal shock-wave therapy. (E-mail: dieter.gebauer@lva-landshut.de) © 2005 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Nonunion, Low-intensity, Pulsed ultrasound, Bone healing stimulation.**

INTRODUCTION

This study was aimed at assessing whether or not low-intensity pulsed ultrasound (US), or LIPUS, is an alternative to surgery, electrical bone growth stimulation and extracorporeal shock-wave therapy for treating nonunions.

Open surgical intervention with debridement of the nonunion site and application of internal or external fixation, in most cases with bone grafting, is considered to be the "gold standard" of nonunion treatment. The range of treatment methods available to the surgeon varies from conservative cast immobilization to one or more surgical procedures with heal rates ranging from 68% to 96%, depending on the bone location and surgical method (Table 1).

Several different treatment methods have been proposed in recent years to achieve a heal rate similar to that of surgery in nonunion cases where surgery may not be required because there is acceptable alignment and limb length discrepancy. These choices include electrical stimulation, extracorporeal shock-wave therapy and, recently, low-intensity pulsed US.

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Electrical stimulation can be induced by direct current (Brighton et al. 1981), pulsed electromagnetic fields (PEMFs) (Gossling et al. 1992) and capacitive couplings (Scott and King 1994). For nonunions, extracorporeal shock-wave therapy is usually performed as middle- or high-energy shock-wave therapy, but the application parameters, such as energy flux density, impulse rate, frequency, etc. are different.

The efficacy of LIPUS has been demonstrated in accelerating fresh fracture healing (Heckman et al. 1994; Kristiansen et al. 1997). For nonunions, some clinical studies were published (Duarte 1983; Xavier and Duarte 1983; Frankel 1998; Mayr et al. 1999). More detailed inclusion/exclusion criteria of the studies were introduced in recent reports (Mayr et al. 2000; Nolte et al. 2001). A study of more cases using more rigorous inclusion criteria, especially for the time between last surgical treatment and US, seemed to be reasonable, to ensure that the successful treatment of the nonunion can be attributed to LIPUS. The problem of nonunion studies is that the studies cannot be realized as placebo-controlled studies. In Germany and Austria, it would be unethical to have a placebo group in a study of nonunions because it would result in denying treatment of a nonunion for a further 6 to 12 months. In the USA, the U.S. Food and Drug Administration (FDA) guidance document for bone

Table 1. Surgical treatment of nonunion: Results from the reference literature

Author	Year publ.	Location/procedure	n	Healed (n)	Healed (%)	Average heal time (d)	Fracture age (months)
Ballmer et al.	(1992)	Femoral intertrochanter/neck/valgus osteotomy	30	21	70%	na*	10
Webb et al.	(1986)	Femoral shaft/IM nailing	105	101	96%	140	10
Barquet et al.	(1989)	Humeral shaft/ORIF and bone graft	25	24	96%	180	13
Ackerman and Jupiter	(1988)	Distal humerus	20	17	85%	na	20
Healy et al.	(1987)	Humeral shaft	26	24	92%	168	15
Healy et al.	(1990)	Proximal humerus with fixation	25	17	68%	144†	14
Boyd et al.	(1961)	Bone graft alone or with internal fixation	122	99	81%	na	na
Boyd et al.	(1965)	Bone graft alone or with internal fixation	842	741	88%	na	na
Marsh et al.	(1997)	Ilizarov fixation	46	40	87%	276‡	18
Watson et al.	(1993)	Scaphoid/dorsal approach bone graft	36	32	89%	na	30
Cooney et al.	(1980)	Scaphoid/Bone graft (volar, dorsal)	90	68	76%	132	>12
Vossman et al.	(1983)	Scaphoid/percutaneous screw	65	62	95%	na	na
Webb et al.	(1981)	Scaphoid/bone graft with volar approach	13	11	85%	150	22
Broderson and Sim	(1981)	Tibia/Bone graft alone or with fixation	126	88	70%	220	>10
Fromm and Niethard	(1992)	Tibia/fibula osteotomy	32	28	88%	na	na
Rosen	(1979)	Long bone and clavicle/most w/compression plates	122	113	93%	8.2 mos.	18
Mandt and Gershuni	(1987)	Tibia	21	20	95%	210	10
Sakkelarides and Freeman	(1964)	Tibia/bone graft w/ plate or rod	100	85	85%†	261§ 368‖	6 mos. to 22 yrs.
Spier et al.	(1983)	Tibia/IM nail	128	118	92%	na	na
Wu and Shih	(1996)	Tibia/intramedullary reaming and external fixation	17	13	76%	156	22
Zaslav and Meinhard	(1988)	Tibia/IM rod; plate and bone graft; External fixation and bone graft	15	13	87%	105	23
Jupiter and Leffert	(1987)	Clavicle (dynamic compression plate)	19	16	84%	na	19
Ebraheim et al.	(1997)	Clavicle (ORIF and bone graft)	16	15	94%	na	30
Total			2041	1766	–	Approx. 200 days	Approx. 15 months
Average			–	–	86%		

* na, not available;
† 12 open reduction internal fixation cases only;
‡ median time; n = total number of cases; average healed rate = weighted calculation using number of healed cases;
§ based on 49 cases with only bone graft;
‖ based on seven cases with bone graft and rod.

growth stimulator studies accepts a study design where the control is the patient's own history of failed treatments (US FDA 1998). The state of nonunion, because of the previous failure to unite and the intervention necessary to obtain healing, does present the ideal example of paired comparison analysis because there is a basis for assessing comparative effectiveness when the patient serves as his or her own control. This self-pairing offers the advantage of controlling extraneous sources of variability, minimizes biologic and other sources of variability and, thereby, permits an accurate comparison between treatment and control.

In the orthopedic literature, the various authors variably define the time when nonunion can be declared; at 15 weeks with no callus or no callus that has bridged (Sarathy et al. 1994), at 3 to 5 months (Healy et al. 1990; Silva 1972), at 6 months (Barquet et al. 1989; Rosen 1979; Sakellarides and Freeman 1964; Trotter and Dobozi 1986; Tucker et al. 1990), at 8 to 9 months (Garland et al. 1991) or at 12 or more months from injury (Sarmiento et al. 1989; Slatis and Rokkanen 1967; Urist et al. 1954). The US FDA requires a minimum period of 9 months from initial injury for nonunion studies. Although the time at which nonunion is declared varies, as shown above, nearly all of the above authors require that all repair processes have stopped in addition to meeting the time requirements. Brashear (1965), Mandt and Gershuni (1987), Nicoll (1964) and Forsted et al. (1978) all indicate that an established nonunion will not heal without intervention.

MATERIALS AND METHODS

In this study, an established nonunion was defined as being a minimum of 8 months from the fracture date using a German reference book for orthopedic trauma (Rüter et al. 1995). There were two more inclusion criteria: radiographic assessments before and at the start of LIPUS indicate that the fracture healing process had not progressed or had stopped for at least 3 months before the start of LIPUS, the fracture line was clearly visible on radiographs and follow-up radiographs were assessed for an independent determination of a healed or failed outcome. The third inclusion criterion was a minimum period of 4 months without surgical intervention before LIPUS. This additional requirement (the US FDA minimum period is 3 months) essentially removed bias that might be introduced by a surgical procedure near the start of LIPUS.

The initial injury or fracture management was not a consideration in study inclusion criteria. In addition, the study did not include patients who were not skeletally mature, women who were pregnant or nursing, patients who could not comply with their physicians' instructions and cases that were malaligned, grossly unstable, actively infected or had extensive bone loss. The study nonunions were a subgroup of a consecutively entered German and Austrian population of fractures, of all fracture ages, who had been prescribed the use of LIPUS by one of the three principal investigators (PIs), D. Gebauer., E. Mayr, E. Orthner, or other prescribing physician investigators during the period of July 1995 to April 1997 as an alternative to surgery, based on the patient's decision.

There was no selection process. All the fractures treated by the PIs and the other physicians that turned into a nonunion, were consecutively entered into the study, provided that the patient did not decide for a surgical revision of the nonunion. There were 85 nonunions who met the time postfracture criterion of 8 months. Of the 85 cases, 5 were excluded because 1 patient was deceased, 2 were noncompliant with device use or orthopedic management instructions and 2 were early withdrawals from treatment. The balance of 80 patients completed treatment with an outcome of healed or failed. In addition, 13 patients were excluded because their last surgical procedure was less than 4 months before the start of LIPUS (all 13 cases healed during the treatment period). The remaining 67 nonunion cases in 66 patients were considered to be the study group nonunions, whose only change in fracture management in the prior 4 or more months was the initiation of LIPUS. Therefore, there were no surgical or physician techniques that could affect the response to US therapy.

The PIs reviewed the radiographs of the prior failed treatment period and the follow-up radiographs after the start of US and were able to validate that all the additional inclusion criteria were met for 72% (48 of 67) of the study group cases. These were considered to be the completely validated subset A of the study group. The remaining 28% (19 of 67), who could not be completely validated with available radiographs, were placed in subset B. For subset B, the PIs were able to document that the case was an established nonunion based on the prescribing physician records or the fracture age of the case. In addition, the PIs documented a healed or failed outcome of treatment from the case records and verified a healed outcome by long-term follow-up with the patient showing that the fracture remained healed. Clinically relevant information relating to the initial fracture treatment and subsequent surgical or other interventions during the prior period to achieve union are presented for the 67 study group cases in Table 2. The demographics section includes gender and age. The prior orthopedic and surgical history data section includes the initial injury type, involved bone and the location within the bone, the treatment record from the initial procedure at the time of fracture and all subsequent surgical procedures to the start of US (a semicolon separarates each procedure). Furthermore, the table presents the smoking status, the nonunion type, the interval in days from the last failed surgery to the start of US (last surgical interval) and the fracture age (time in days from the initial injury date to the start of US treatment). The outcome section of the table records the outcome of healed and failed and the time to a healed fracture.

The low-intensity pulsed US device (Fig. 1a, b) has both the CE (Council of European Communities quality designation) and GS (German product safety) marks of approval (Exogen GmbH, Diessen, Germany). The device consists of the three components, these are a plastic retaining and alignment fixture (RAF), a battery-operated treatment module (TM) that supplies the US signal to the skin at the fracture site and a 110/220 V AC powered main operating unit (MOU).The RAF was used with a strap arrangement to position the TM on the skin over the fracture site. The TM and the MOU were connected by fiberoptic cables that allowed for communication of control and sensing signals by means of light pulses and, in addition, provided electrical isolation for the patient from the electrical line-operated MOU. The prescribing physician indicated the treatment site based on radiographic evaluation. Patients applied approximately one teaspoon (5 ml) of ultrasonic coupling gel to the transducer surface of the TM before placing it on the treatment site. Coupling gel is necessary to ensure the proper transmission of US. Audible and visual signals alerted the patient if the device was not operating properly. The effective radiating area of the transducer is 3.88 cm^2. The US pressure wave signal is characterized by a 200-μs burst of 1.5-MHz acoustic sine waves that repeats at a modulation frequency of 1 kHz. The intensity of the pressure wave, applied to the skin at the nonunion site, was 30 mW/cm^2 (spatial average-temporal average or SATA). This intensity is equal to a force of less than 3 mg/cm^2 (peak pressure of 0.3 pascals). The main operating unit monitored treatment time and automatically turned off the treatment session after 20 min. The device incorporated a patient-compliance monitor that registered each use in a microprocessor module. The patients used their

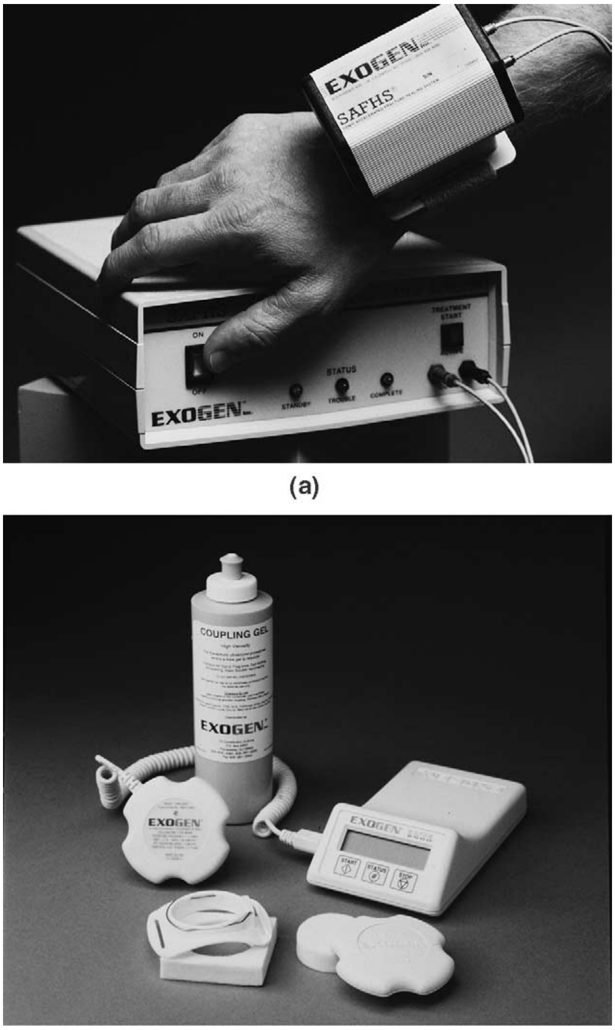
Table 2. Patient, fracture and nonunion characteristics

Case no.	Gender	Age	Initial fracture type	Bone	Fracture location	Prior failed surgical procedures	Smoking status	NU type	Last surg interval (d)	Fracture age (d)	Treatment outcome	Heal time (d)
11	F	45	Osteotomy	Tibia	Plateau	Cast; Ost; BG; Ext fix	Never	A	240	1189	Healed	275
21	F	17	Closed	Clavicle	Middle	Brace	Never	H	349	349	Healed	140
31	M	28	Closed	Femur	Distal	DCS; BG	Smoker	A	125	264	Healed	126
51	F	51	Osteotomy	Metatarsal	Middle	Plate; Plate; BG	Never	H	970	1476	Healed	129
61	M	56	Open	Tibia	Middle	IM rod; IM rod; Ext fix	Never	A	651	1012	Healed	184
71	M	23	Closed	Tibia	Middle	IM rod; Dynam; Shockwave	Smoker	H	316	324	Healed	119
81	F	22	Closed	Ulna	Epicondyle	Cast; Screws	Smoker	A	313	4740	Failed	572
91	F	42	ns	Femur	Middle	ns	Never	ns	1767	1767	Failed	334
101	M	31	Open	Tibia	Proximal	Ext Fix; IM rod	Smoker	ns	208	398	Healed	88
111	F	35	Open G-I	Tibia	Distal	IM rod	Never	A	301	301	Healed	97
121	M	41	Closed	Ulna	Proximal	Plate; BG	Smoker	H	163	277	Healed	121
131	M	42	Open	Tibia	Distal	IM rod; BG	Stopped	H	193	239	Healed	137
141	F	66	Closed	Ulna	Proximal	Plate	Never	ns	558	559	Healed	319
161	F	32	Open comm.	Tibia/Fibula	Middle	Cast; Plate; Ext fix	Smoker	A	283	376	Healed	258
171	M	53	Closed	Humerus	Subcapital	Cast	Smoker	ns	269	269	Healed	99
181	M	46	Arthrodesis	Ankle	na	ns; Screws; BG; Plate	Smoker	ns	204	452	Failed	121
191	F	73	Closed transv.	Metatarsale	Middle	Cast	Never	A	275	278	Healed	222
201	M	49	Closed	Ulna	Proximal	Plate; BG;	Stopped	A	247	429	Healed	238
221	F	67	Closed	Fibula	Distal	Cast	Never	A	354	354	Healed	200
231	M	26	Closed-seg.	Tibia	Proximal	ns; IM rod	Smoker	A	278	4737	Healed	194
232	M	26	Closed-seg.	Tibia	Distal	ns; IM rod	Smoker	A	278	4737	Healed	315
241	M	62	ns	Humerus	Middle	ns	Never	ns	272	272	Failed	222
261	F	39	Closed	Metatarsal	Proximal	Cast; Screws;	Never	A	155	257	Healed	88
271	F	62	Open	Ulna	Proximal	Plate; Wires; BG	Never	A	124	263	Healed	369
311	M	39	Open comm.	Femur	Proximal	IM rod	Stopped	A	399	399	Healed	182
321	F	62	ns	Tibia	Middle	ns	Never	ns	1079	1079	Healed	117
331	M	33	Closed	Femur	Middle	IM rod; BG	Never	A	503	1158	Healed	212
341	M	25	Closed	Metatarsal	Proximal	Cast; Orthotic	Smoker	H	246	246	Healed	98
351	M	54	Osteotomy	Femur	Middle	ns	Never	ns	298	298	Healed	114
361	M	59	ns	Tibia	Plateau	Cast; Antibiotic; Debridement	ns	ns	642	1478	Healed	150
371	F	46	Closed	Fibula	Distal	Plate; Plate; BG; Ext fix; BG	Never	A	129	719	Healed	145
381	M	42	Open comm.	Tibia/fibula	Middle	Ext Fix; BG	ns	ns	778	778	Healed	143
391	M	24	Closed	Scaphoid	Proximal	ns; BG; Screws	Smoker	A	235	485	Failed	213
401	M	37	Osteotomy	Femur	Intertroch.	Plate; Plate; BG; Plate	Smoker	H	178	407	Healed	96
411	M	44	Arthrodesis	Ankle	na	ns	Smoker	ns	991	991	Healed	133
421	M	32	Closed	Scaphoid	Proximal	Cast	Stopped	A	3690	3690	Failed	232
431	M	27	Open G-III	Tibia/Fibula	Distal	Ext Fix; BG; Ext fix; Ext fix; BG	Smoker	ns	261	585	Failed	118
441	M	54	Closed	Tibia	Distal	IM rod	Smoker	H	269	497	Healed	210
451	M	86	Stress	Femur	Middle	Cast	Never	ns	1415	1415	Healed	296
461	M	41	Open	Tibia/Fibula	Distal	IM rod; IM rod; Curretage; IM rod	Smoker	ns	224	4067	Healed	375
481	M	33	Closed	Scaphoid	Distal	Cast	Smoker	A	5093	5893	Failed	141
491	M	41	Open G-II	Humerus	Distal	Plate; BG; Plate	Never	H	319	474	Healed	118
501	M	37	Closed	Scaphoid	Waist	Cast	Never	A	4808	4808	Failed	280

Table 2. Continued...

Case no.	Gender	Age	Initial fracture type	Bone	Fracture location	Prior failed surgical procedures	Smoking status	NU type	Last surg interval (d)	Fracture age (d)	Treatment outcome	Heal time (d)
511	F	45	Closed	Tibia	Distal	Cast; Brace	Never	A	252	252	Healed	188
531	M	55	Closed	Femur	Trochanter	Nail; THR; Reconstruction	Stopped	A	158	420	Healed	280
541	M	64	Closed	Tibia	Plateau	Ext Fix	Stopped	ns	3006	3006	Failed	178
551	F	46	Osteotomy	Femur	Proximal	Plate	Smoker	A	1290	1290	Healed	249
561	F	47	Closed	Pelvis	Acetabulum	Cast	Stopped	ns	6011	6011	Healed	92
581	M	33	Open	Fibula	Middle	ns	Smoker	A	506	506	Healed	105
601	F	14	Osteotomy	Femur	Distal	Plate	Never	ns	240	240	Healed	98
611	F	61	Open	Tibia	Middle	IM rod; Dynamization; IM rod	Never	H	125	310	Healed	182
621	M	54	Closed comm.	Calcaneus	Middle	Plate	Never	ns	316	323	Healed	118
631	M	26	Closed	Scaphoid	Middle	ns; BG; Cast; Screws	Smoker	A	132	298	Healed	157
641	M	60	Closed	Rib	Anterior	Cast	Never	A	511	511	Healed	148
661	F	71	Open	Knee	na	TKR; Arthrodesis; Ext fix	Never	ns	149	255	Healed	108
671	F	55	Open comm.	Tibia	Distal	Ext Fix; Plate	Smoker	A	314	421	Healed	211
681	F	62	Closed	Metatarsal	Metaph-prox	Screws; Cast	Never	A	232	521	Healed	57
691	M	59	Closed	Tibia	Distal	Plate; Plate; Ext fix; IM rod; BG; our tage; Ext fix	Smoker	A	122	490	Healed	245
711	F	67	Closed	Knee	na	ns	Never	ns	417	417	Healed	69
721	M	48	Closed	Femur	Middle	IM rod; BG; IM rod; BG; shockwave; IM rod; BG	Stopped	A	463	1263	Healed	216
731	M	49	Closed	Scaphoid	Waist	Cast	Never	A	402	402	Healed	180
751	M	24	Open	Tibia/fibula	Middle	IM rod; Dynamization	Never	H	992	992	Healed	230
761	F	73	Closed	Femur	Middle	ns	Never	ns	1111	1111	Healed	113
771	M	37	Closed	Clavicle	Middle	Brace	Smoker	A	256	356	Healed	117
791	M	35	Open	Radius/ulna	Middle	Plate; BG; Plate; BG	Never	A	132	431	Healed	90
801	F	76	Closed	Clavicle	Middle	Brace	Never	A	553	553	Healed	102
811	F	59	Open	Tibia/Fibula	Distal	Screws; BG; Screws; BG; BG; IM rod	Never	A	308	4752	Healed	86

ns = not specified; na = not applicable; BG = bone graft; TKR = total knee arthroplasty; Ost. = osteotomy; Ext fix = external fixator; DCS = dynamic condylar screw; THR = total hip replacement; Seg. = segmental; comm. = comminuted; Shockwave = electrical shockwave therapy; IM rod = intrameduallary nail; NU = nonunion; A = atrophic; H = hypertrophic.



(a)

(b)

Fig. 1. (a) US device with the transducer fixed at a nonunion site of the radius. (b) The new version of the device with a battery-powered, instead of 110/220 VAC powered, main operating unit.

device for one continuous 20-min treatment per day at home. Anterior/posterior and lateral radiographs were taken at 1- to 2-month intervals after the start of LIPUS. Oblique views sometimes were necessary for more fracture details. Clinical examination of the level of pain upon palpation, and weight-bearing if applicable, and motion at the fracture site were performed at each follow-up visit to determine the extent of healing, by the prescribing physician.

The nonunion was judged as healed when the fracture was both clinically (no pain or motion upon gentle stress, and weight-bearing if applicable) and radiographically healed (three of four bridged cortices for long bones and bridging callus for flat bones). Clinical and radiographic assessments were performed by the prescribing physician. The PIs independently assessed and validated the final outcome and the date of that outcome in a radiographic review, except for those subset B cases where the prescribing physicians' records and the long-term follow-up were used to determine final outcome of healed or failed. Nonunions were categorized as a failure of LIPUS when it was apparent to the prescribing physician that they were not responding to LIPUS; the PIs concurred with all determinations of failed outcome.

The patient demographics for the study group show a distribution by gender of 39% (26 of 67) women and 61% (41 of 67) men. At the start of the US treatment period, the average patient age was 46 ± 1.9 years. The mean fracture age was 39 ± 6.2 months (median of 15.9 months), with a range of 8 to 198 months. The mean months without surgery before the start of low-intensity US therapy was 24.2 ± 4.9 (median of 10.1 month), with a range of 4 to 197 months. The study group had a mean of 2.0 ± 0.3 prior failed surgical procedures.

An analysis between subsets A and B for patient and fracture characteristics demonstrated no clinically meaningful differences. Combining the data from the prescribing investigators for evaluation of safety and efficacy was justified, based on this analysis that did not identify systematic differences across investigators; it was also justified because of the common inclusion/exclusion criteria and uniform evaluation definitions that were used by all investigators. In addition, the PIs confirmed the presence of an established nonunion at the start of treatment and confirmed the outcome determinations; and long-term follow-up established that the nonunion remained healed.

The statistical significance of the LIPUS treatment vs. the paired comparison control of prior failed orthopedic treatment was determined by computing the *p* value to assess the superiority of treatment with the US device for the percent of nonunions healed. Because nonunion cases have essentially a zero probability of achieving a healed state without intervention, we assumed that the heal rate without US therapy during the time period of this study was 5% rather than 0%. Therefore, the null hypothesis was that the heal rate was less than or equal to 5% and the alternative hypothesis was that the heal rate was greater than 5%. This one-sided test (Conover 1980) could be used because a nonunion can only remain failed or heal and because the effectiveness of US therapy was hypothesized *a priori* based on the nonunion clinical studies of Xavier and Duarte (1983) and Duarte (1983). Fisher's exact test (Fisher 1934; Fleiss and Everitt 1971) was used to contrast the strata in Table 5. All times to a specific response or event were calculated in the number of days. Months, if reported, were calculated by dividing days to event by 30.44. This paper reports averages as the mean ± standard error of the mean (SEM). All statistical analyses were performed with Proc-Stat Xact statistical software and statistical analysis systems software (SAS Institute, Cary, NC, USA).

RESULTS

Table 3 presents the statistical analysis assessing the primary efficacy of the low-intensity US treatment for all of the completed study cases with a 0% (0 of 67) heal rate in the control period of prior orthopedic treatment vs. 85% (57 of 67) heal rate for the same nonunions treated by US, a highly significant ($p < 0.00001$) effect. Table 3 also presents the secondary efficacy parameter of heal time for the 57 healed nonunions, with a mean heal time of 168 ± 10.2 days, a median of 143 days and a range of 57 to 375 days. Of the patients, 25% were healed by 108 days and 75% were healed by 212 days. The fracture age for the healed cases was an average of 31.2 months, with a median of 14.1 month and a range of 8 to 197 months. Of the healed cases, 10% had fracture ages of greater than 48.6 months, and 25% had fracture ages of greater than 33.2 months. In addition, Table 3 presents the same analyses for the failed cases. Table 4 shows the healed results for the 67 completed cases (85%) and compares it with the 85% (41 of 48) heal rate for subset A and to 84% (16 of 19) heal rate for subset B. Table 4 also presents the results of an intention-to-treat analysis that combined the 10 failed cases with the 5 excluded cases (1 deceased, 2 withdrawals and 2 noncompliant) into a group as "not healed." The intention-to-treat heal rate for all nonunion cases was 82% (70 of 85). Of 10 ten failures, 4 were scaphoid nonunions (average fracture age of over 10 years), 2 were tibia nonunions (average fracture age of 4.9 years) and the remaining 4 were an ulna epicondyle nonunion (fracture age of 13.9 years), a femoral nonunion (fracture age of 4.8 years), a nonunion of an ankle arthrodesis (fracture age of 1.2 years), and a humerus nonunion (fracture age of 9 months).

The LIPUS-treated cases were also stratified by covariates of patient and fracture characteristics (Table 5). With the numbers of cases available, no significant differences were found for the comparisons of gender, age groups, number of prior surgical procedures, displaced at the start of therapy, long bone type, initial injury type, fixation present at the start of and during treatment, prior failed shockwave therapy and smoking status. A significant comparison was found across fracture age strata where the heal rates were 95%, 86% and 93% for the three fracture age strata of ≤ 1 year, > 1 year to ≤ 2 years, and ≥ 2 years to ≤ 5 years, respectively; however, cases with fracture ages of over 5 years had a healing rate of 50% (5 of 10) and, therefore, the

Table 3. Efficacy of low-intensity pulsed ultrasound for the treatment of nonunions

Primary efficacy parameter: outcome, number (and %) of cases (n = 67)				Secondary efficacy parameter: heal time and descriptive parameter of fracture age			
				Healed cases: *n* = 57		Failed cases: *n* = 10	
Outcome	Prior orthopedic treatment period	US treatment period	Exact (one sided) *p* value*				
Healed	0 (0%)	57 (85%)		time (d)	Fracture age (months)	time (d)	Fracture age (months)
Failed	67 (100%)	10 (15%)	0.0001	Mean ± SEM: 168 ± 10.2	Mean ± SEM: 31.2 ± 5.6	Mean ± SEM: 241 ± 42.7	Mean ± SEM: 84.4 ± 22.1
Total	67	67		Median: 143 d	Median: 14.1 months	Median: 218 d	Median: 78.4 months
				Range: 57 to 375 d	Range: 8 to 197 months	Range: 118 to 572 d	Range: 9 to 194 months
				Percentile heal time:	Percentage fracture age	Percentile outcome time:	Percentage fracture age
				25% : 108 d	10% : 48.6 months	25% : 141 d	10% : 175.8 months
				50% : 143 d	25% : 33.2 months	50% : 218 d	25% : 155.7 months
				75% : 212 d	50% : 14.1 months	75% : 280 d	50% : 78.4 months
				90% : 280 d	75% : 10.2 months	90% : 453 d	75% : 15.9 months

* Binomial test of the null hypothesis that the US treatment period healed rate was less than or equal to 5%. The average fracture age (time from fracture date to the start of the US treatment period) of the 67 ununited fractures was 39.2 ± 6.2 months (median = 15.9 months), with a range of eight to 198 months.

Table 4. Effectiveness summary for the study group and its subsets A and B and for the intention-to-treat analysis

	Total	Healed	Failed	% Healed	*p* value*
Study group:	67	57	10	85	0.00001
Subset A (completely validated by Pls from radiographs)	48	41	7	85	0.00001
Subset B (documented by Pls with clinical records, fracture age, and long-term follow-up)	19	16	3	84	0.00001
Intention-to-treat analysis (all cases including excluded cases)	85	70	15[†]	82	0.00001

* *p* value for comparison against prior orthopedic treatment results of 100% failed cases;
[†] Combines 10 failed and 5 incomplete cases into "Not healed" outcome for intention-to-treat analysis.

comparison across fracture age strata was significantly different at $p = 0.015$. The last procedure interval (time from the last surgical procedure to the start of LIPUS therapy) was stratified and the 120 to 365 days and 366 to 730 days strata had similar heal rates at 88% (37 of 42) and 100% (11 of 11), respectively; these heal rates, when compared across strata with the 64% (9 of 14) of the ≥ 731 days stratum, show a significant comparison at $p = 0.04$. The significant comparisons for fracture age, last surgical procedure interval, for bone ($p = 0.02$) and long bones vs. other bones ($p = 0.05$), were a result of the failed scaphoid cases, 3 of which were atrophic, with each having a fracture age and last surgical procedure interval of over 10 years. Nonunions of the tibia and femur accounted for 55% of the study nonunions and had a 92% heal rate. Although there was not a significant comparison across smoking strata, smokers and past smokers had the lowest heal rates at 79% and 75%, respectively, vs. 91% for those patients who never smoked.

The microprocessor (patient compliance monitor) that stored the compliance data in the US device was downloaded for a printout of daily use when the devices were returned upon completion of treatment. The average 20-min daily device use for the returned devices was 143 ± 9.4 days; that is an average of 89% of the time the cases were treated with US.

The long-term healed status of all healed patients was verified in a telephone follow-up conducted in February and March of 1998. Long-term follow-up, verifying a still healed status, was obtained for 52 of the 57 healed patients, with only 5 who could not be reached for long-term follow-up. The average long-term follow-up time from the date that the patient was healed to the date of the verification of a still-healed status was 402 ± 20.8 days (median = 381 days), with 25% over 469 days, 50% over 381 days and 25% over 289 days.

There were no reports of any device-related adverse effects in this study.

DISCUSSION

In clinical applications, low-intensity pulsed US therapy was first reported by Xavier and Duarte (1983), with results that demonstrated a 70% heal rate in a series of 28 nonunions. In a review paper of LIPUS use, Duarte et al. (1996) reported an 85% heal rate in 380 nonunions with an average healing time of 77 days. A similar heal rate of 86% was noted by Mayr et al. (1999). Romano et al. (1999) presented the results in 15 patients with septic nonunions of 10 tibias, 2 femurs and 1 each of the humerus, ankle and ulna. They reported a 90% heal rate (9 of 10) in the completed cases, with the remaining 5 patients demonstrating progressive signs of healing. Frankel (1998) assessed the overall heal rate in nonunions at different bone sites and reported a heal rate that was 70% in the humerus, 86% in the femur, 81% in the metatarsal, 96% in the radius, 86% in the scaphoid and 83% in the tibia. Mayr et al. (2000) assessed the effect of comorbidity factors on the heal rate when using LIPUS in treating nonunions. They demonstrated a heal rate reduction of 5% to 10% in patients taking calcium channel blockers, nonsteroidal anti-inflammatory drugs and steroids, in patients under renal treatment and in patients with vascular insufficiency at the nonunion site. Smokers also had heal rates that were several percent lower than the overall result that was found in the presented study. In the same report, a study group of 16 cases had the inclusion criterion of last change of treatment 2 months before beginning US, to exclude healing influences other than US. The heal rate was 94% (15 of 16). Nolte et al. (2001) reported a study with 41 cases of nonhealing fractures. The criteria used to define a nonunion were a failure of fracture to unite at a minimum of 6 months from fracture, the fracture line is visible in two orthogonal views, radiographic healing had not progressed or had stopped for a minimum period of 3 months and the last surgical procedure had to be performed prior 3 months before the start of US treatment. Of the 41 cases, 29 met these inclusion criteria. Comparing the report of Nolte et al. (2001) with the study presented here, the number of those analyzed cases was 85. All the fractures, consecutively treated by the investigators that turned into a nonunion were suitable for the study on principle. The inclusion criterion to minimize the possible bias of the effects of surgery on the resulting heal rate was no surgical procedure during the 4 months before the start of

Table 5. Stratification of patient and fracture characteristics (67 study cases)

Strata	Healed	Failed	% Healed	*p* value	Mean heal time (d)	Healed cases mean fx. age (months)
Bone						
Tibia/tibia-fibula	23	2	92		185	42.9
Femur	11	1	92		180	24.7
Radius/radius-ulna	5	1	83	0.02	227	12.9
Humerus	2	1	67		109	12.2
Metatarsal	5	0	100		119	18.3
Ankle	1	1	50		133	32.6
Scaphoid	2	4	33		169	11.5
Other	8	0	100		111	39.7
Long bones vs. other bones						
Long bones	46	5	90	0.05	178	31.2
Other bones	11	5	69		124	31.2
Nonunion type						
Hypertrophic	11	0	100		144	11.5
Atrophic	30	5	86	0.32	185	31.7
Initial fracture type						
Closed	32	8	80		164	31.0
Open	17	1	94	0.32	174	31.0
Arthrodesis	1	0	50		133	32.6
Osteotomy	6	2	100		160	21.8
Stress	1	0	100		296	46.5
Fixation in place at start and during US treatment						
IM rod (only for long bone cases = 51)						
No	33	5	87		174	20.0
Yes	13	0	100	0.32	187	59.8
Open reduction, internal fixation						
No	42	7	86		163	36.4
Yes	15	3	83	1.00	181	16.6
External fixation (only for long bone cases = 51)						
No	40	4	91		173	32.2
Yes	6	1	86	0.54	208	25
Conservative (cast)						
No	42	7	86		174	32
Yes	15	3	83	1.00	150	29.1
Patient age						
17	2	0	100		119	9.7
18–29	7	3	70		177	54.4
30–49	24	5	83	0.53	164	31.4
50–64	16	2	89		169	29
65	8	0	100		179	20.3
Gender						
Males	33	8	81	0.30	171	31.9
Females	24	2	92		163	30.7
Smoking status: (missing = 2)						
Smoker	19	5	79	0.30	175	36.2
Never smoked	30	3	91		160	24.4
Stopped prior to start	6	2	75		191	48
Fracture age						
9 mos–1 year	20	1	95		145	9.5
>1 year to <2 years	19	3	86	0.015	165	15.4
>2 to <5 years	13	1	93		188	38.5
>5 years	5	5	50		212	160
Days from last surgical procedure to start						
120–365 days	37	5	88		167	27.4
366–730 days	11	0	100	0.04	170	24.7
>731 days	9	5	64		167	53.3

US. The required minimum fracture age for inclusion as nonunion was 8 months. With these more-rigorous criteria, 57 of the 67 established nonunion cases healed, which means nearly the same heal rate of 85%, in comparison with 86% in the study of Nolte et al. (2001). Another difference between the two studies is that the presented study reports about 67 surgically treated fractures but, in Nolte and colleagues' study, 8 cases of 29 were treated conservatively and 21 fractures were operated.

Table 6. Comparison of heal rates among study group nonunions, surgery references, electrical references and shock wave references

Nonunion treatment	Total (*n*)	Healed (*n*)	Heal rate for treated nonunions (%)	Mean heal time or range (weeks)	Healed fracture mean fx. age or range (months)
Study group	67	57	85	24.0	39.2
Surgery references (Table 1)	2041	1766	86 (68–96)	27.0	15.0
PEMF					
Hinsenkamp et al. (1985)	272	199	73	ns	ns
Garland et al. (1991)	135	108	80	ns	ns
Gossling et al. (1992)	817	654	80	9–76	2–20
Capacitive coupling					
Brighton and Pollak (1985)	22	17	77	22.5	40.0
Scott and King (1994)	10	6	60	21.0	23.0
Direct current					
Brighton et al. (1981)	178	149	84	ns	33.0
Heppenstall (1983)	40	32	80	ns	26.4
Longo (1997)	84	51	61	25.0	28.8
Extracorporeal shock wave					
Schleberger (1995)	45	41	91	ns	ns
Ekkernkamp (1996)	ns	ns	67	ns	ns
Rompe et al. (1997)	52	27	52	15.0	13.0
Diesch (1997)	172	114	66	ns	ns
Russo et al. (1997)	125	84	67	ns	ns
Wirsching et al. (1998)	115	81	69	24–340	34.0
Beutler et al. (1999)	27	11	41	ns	9.0
Rompe et al. (2001)	43	31	72	18.0	ns
Wang et al. (2001)	72	58	81	ns	ns

ns = not specified.

This study reports on the successful use of low-intensity pulsed US for the treatment of nonunions. A list of surgical reference literature is presented in Table 1 and indicates a range of heal rates for surgical treatment of nonunion from a low of 68% (Healy et al. 1990) to a high of 96% (Barquet et al. 1989; Webb et al. 1986), with the surgical heal rate varying by the bone location and surgical method. For those surgical literature references that provided the data, the mean heal time was approximately 200 days (range of 105 to 368 days) and the mean fracture age was approximately 15 months (range of 10 to 30 months). Table 6 compares the heal rates, average heal time and average fracture age of the surgery references of Table 1 (86%), the study group results of this study (85%), eight electrical bone-growth-stimulator references and nine extracorporeal shock-wave therapy studies.

The results achieved in this study show an equal or better heal rate in comparison with literature reports of electrical bone-growth-stimulator studies that used a similar study design, with each case serving as his/her own control. Gossling et al. (1992), in their review of ununited tibia fractures, compared literature results for treatment of tibia nonunions by surgery vs. pulsed electromagnetic fields. They reported a heal rate of 80% for tibial nonunions treated with pulsed electromagnetic fields and 91% with surgical treatment. Garland et al. (1991) had an 80% success rate (108 of 135) when using a modified PEMF device for 3 h daily. Hinsenkamp et al. (1985) published a European multicenter study of nonunion treatment by pulsed electromagnetic field. Of 272 cases, 199 (73.2%) healed by this type of stimulation. Scott et al. (1994) presented the only double-blind clinical trial of nonunions using electrical stimulation without additional conservative or surgical treatment. Of 21 patients, 11 received a placebo unit and 10 patients were actively managed by an electrical capacitive coupling device. Of the 10 actively managed patients, 6 healed, but none of the placebo group united. Brighton et al. (1981) reported on a heal rate of 84% in treating 178 nonunions by constant direct current. The study of Brighton and colleagues (1985) showed a solid osseous union in 17 of 22 nonunions (77%) after treatment with capacitive coupling. Heppenstall (1983) used direct current and obtained a healed nonunion in 80% (32 of 40) of his established tibial nonunion cases, which compares favorably with the 92% heal rate obtained in this study for tibial nonunions. Longo (1997) reported the results of a larger multicenter study in 116 nonunion cases that were a minimum of 9 months from fracture with no visibly progressive signs of healing for a minimum of 3 months. Of the 84 cases that completed combined magnetic field treatment, only 61% (51 of 84) healed.

Extracorporeal shock-wave therapy has also been proposed as a treatment for nonunion. Schleberger (1995) was the first to report on treating nonunions by extracorporeal shock waves. The heal rate of his study of 45 patients was 91%. Ekkernkamp (1996) reported 67% of nonunions significantly improved by the shock-wave therapy, with some reported side effects. Rompe et al. (1997) did not verify such a high rate and reported 52% in 52 nonunions. The study of Diesch (1997) demonstrated a heal rate of 66% in 172 nonunion cases. Russo et al. (1997) presented a study of various nonunions with a heal rate of 67% in 125 cases, 64 of them concerned with carpal scaphoid. Wirsching et al. (1998) treated 115 nonunions by one to four shock wave applications, with a heal rate of 81%. Beutler et al. (1999) reported a heal rate of 41% in 27 nonunions treated by standardized shock wave therapy. Rompe et al. (2001) described bony consolidation in 31 of 43 (72%) nonunions of fractures and osteotomies. Wang et al. (2001) presented a bony union in 81% of 72 nonunions of long bone fractures treated with specific shock-wave inductions for each bone type.

The nonunion therapy results of the presented LIPUS study have shown healing in different bones, different fracture types, fractures that have had many prior surgical procedures that have failed, in patients who smoked, stopped smoking or never smoked, in fractures with different fixation, in fractures with bone graft, in male and female patients and in all patient age groups. All of these data, including the stratifications by patient and fracture covariates, demonstrate the clinical potential of low-intensity pulsed US. This study also demonstrated that specifically programmed US can affect heal rates similar to those achieved by surgical means, without the associated risks and complications associated with surgery and anesthesia. Of course, surgery may be a requirement because of unacceptable angulation and leg length discrepancy of the nonunion, and low-intensity US should not be expected to replace all surgery. However, low-intensity US treatment can become another important technique in the healing armamentaria that the physician can use in the treatment of challenging nonunions.

In conclusion, this study demonstrated a highly significant treatment effect for low-intensity US by healing 85% of nonunions that had the ideal comparative group (*i.e.*, their own prior failed orthopedic treatments). The use of low-intensity US for the healing of nonunions has no known contraindications, risks or side effects. When appropriately used, this treatment option can be a safe and effective approach for the treatment of nonunions.

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