Does Low-Intensity Pulsed Ultrasound Reduce Time to Fracture Healing? A Meta-Analysis

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Abstract

We conducted a meta-analysis of randomized controlled trials to obtain a more precise estimate of the effect of low-intensity pulsed ultrasound (LIPU) versus placebo on the acceleration of fracture healing in skeletally mature persons and to determine if any serious adverse events are associated with LIPU when used to accelerate fracture healing.

In the United States, 5.6 million fractures occur each year, corresponding to a 2% incidence. Simple fractures require at least 6 to 8 weeks to heal, and patients often require several more weeks of rehabilitation to recover full function. Nonetheless, 5% to 10% of fractures demonstrate delayed healing, or nonunion, necessitating further orthopedic management.[1] Fracture healing represents a significant disability in which even the normal reparative process accounts for a significant period of lost productivity and associated health care costs.[2]

Several interventions have been proposed to facilitate fracture healing by both decreasing overall healing time and reducing associated sequelae. Low-intensity pulsed ultrasound (LIPU) has been found to promote accelerated fracture healing in animal and human studies, though many reviews and texts on fracture management fail to recommend use of therapeutic ultrasound. The therapy is given in daily 20-minute sessions with an ultrasound signal having a burst width of 200 µs, 1.5-MHz sine waves, a repetition rate of 1 kHz, and spatial mean temporal intensity of 30 mW/cm^2.[1] The exact mechanism by which ultrasonography promotes fracture healing is unknown but is most likely mediated through cellular mechanotransduction pathways of ossification.[3]

In a 2002 meta-analysis of 3 studies, Busse and colleagues[1] determined that LIPU significantly reduced time to fracture healing for nonoperatively managed fractures. Since then, several more validated studies have been completed, and a Cochrane protocol has called for an updated meta-analysis.[4]

We conducted a meta-analysis of randomized controlled trials to obtain a more precise estimate of the effect of LIPU versus placebo on the acceleration of fracture healing in skeletally mature persons and to determine if any serious adverse events are associated with LIPU when used to accelerate fracture healing.

Methods

Search Strategy

Databases, Search Terms, Limits, Special Strategies. We searched MEDLINE (1950–October 2, 2008) using the 2008 Cochrane highly sensitive search strategy, sensitivity-maximizing version,[5] combined with MeSH terms *fracture fixation, fracture healing, bone fractures, bone and bones, bony callus, bone remodeling, bone regeneration, osseointegration, ultrasonic therapy, ultrasonics,* and *ultrasound.* Using a combination of the terms *fractur$* and *ultraso$,* we also searched 3 databases through the Cochrane library (2008, issue 4): Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we used the same combination of terms to search (from inception to October 2, 2008) Cumulative Index to Nursing and Allied Health Literature (CINAHL, excluding MEDLINE records), National Library of Medicine (NLM) Gateway, ProQuest Dissertations & Theses, and Physiotherapy Evidence Database. Language restrictions were not applied. Please see the Appendix for the detailed search strategies used for each database.

Additional Search Methods. Further attempts to locate studies were made by contacting experts (eg, Dr. Jason W. Busse),[1] using the search terms *fractur$* and *ultraso$* at Clinicaltrials.gov (inception to October 2, 2008), and manually reviewing the references of the selected studies.

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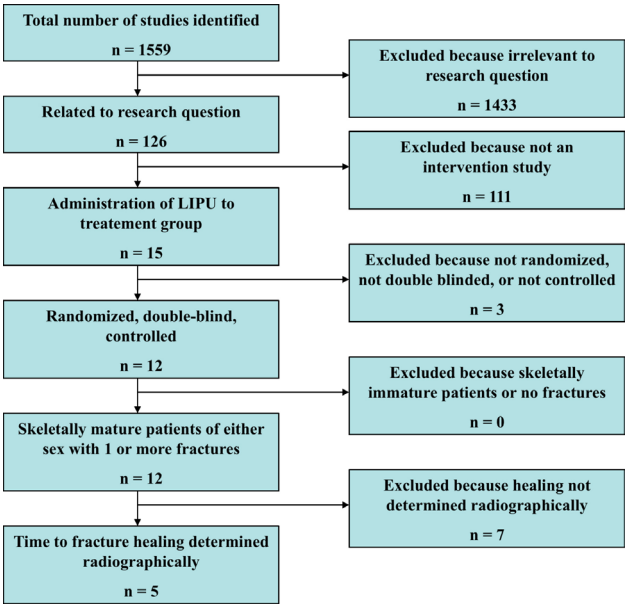


Figure 1. Study selection flow diagram

Study Selection

In assessing the studies, we used 4 predetermined inclusion criteria: (1) randomized, double-blinded, placebo-controlled trial; (2) skeletally mature study participants with at least 1 fracture, traumatic or surgically induced; (3) LIPU intervention with control arm receiving sham (placebo) ultrasound; and (4) time to fracture healing determined by radiography, specifically bridging of 3 or more cortices according to radiography or computed tomography (CT), which has been shown to be the best objective measure of fracture healing.[6] Dr. Snyder, a nonexpert reviewer, applied these inclusion criteria to the potentially eligible studies. He was not blinded to the studies.

Data Collection

Dr. Snyder and Mr. Conley independently extracted the data from the eligible studies. A standardized electronic data collection form was used to facilitate accurate and timely data retrieval. Any discrepancies were resolved by mutual agreement or by obtaining Dr. Koval's confirming decision. Studies missing data were excluded from the meta-analysis.

Quality Assessment

Dr. Snyder and Mr. Conley independently examined the methodologic quality of the eligible studies to assess for any bias. Assessment was based on criteria adapted from a list published by Van Tulder and colleagues[7] (Cochrane Collaboration Back Review Group):

- Was the randomization method adequate?
- Was the treatment allocation concealed?
- Were the groups similar at baseline regarding the most important prognostic criteria?
- Was the patient blinded to the intervention?

Study	Randomization adequate?	Patient/ Outcome Assessor blinded?	Drop-out rate described/ acceptable?	Allocation concealed	Timing of outcome assessment in all groups similar?	Similar baseline characteristics?	Compliance acceptable in all groups?	Intention-to-treat analysis?
Heckman (1994)	Yes	Yes	Yes	Unknown	Yes	Yes	Yes	Yes
Kristiansen (1997)	Yes	Yes	Yes	Unknown	Yes	Yes	Unknown	Yes
Enami (1999)	Yes	Yes	Yes	Unknown	Yes	Yes	Yes	No
Leung (2004)	No	Yes	Yes	Unknown	Yes	Unknown	Unknown	Yes
Ricardo (2006)	Unknown	Unknown	Yes	Unknown	Yes	Unknown	Unknown	Yes

Figure 2. Methodological quality of the studies included in the meta-analysis.

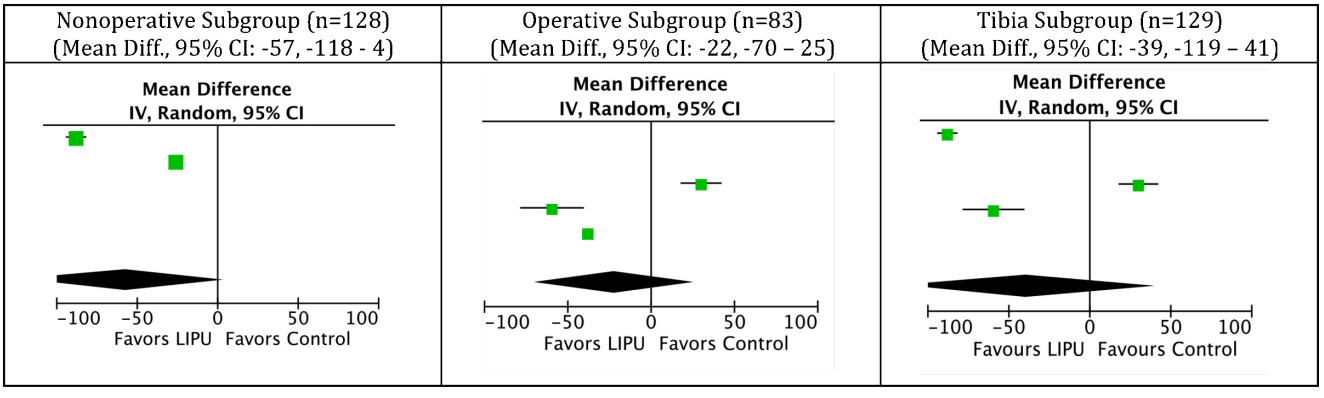


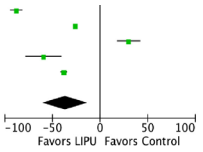
Figure 3. Subgroup analyses of selected studies (LIPU, low-intensity pulsed ultrasound).

Table I. Characteristics of Studies Included in the Meta-Analysis (Randomized, Double-Blinded, Placebo-Controlled Trials With Low-Intensity Pulsed Ultrasound as Active Group and Placebo as Control Group)

Study	Year	Setting	Fracture Details	No. of Fractures	Participant Characteristics: Male:Female Ratio	Participant Characteristics: Mean (SD) Age, y	Follow-Up, wk	No. of Fractures Lost to Follow-Up
Heckman & colleagues[12]	1994	US/Israel	Tibia, nonoperative	97	54:13	33 (3)	52	30
Kristiansen & colleagues[15]	1997	US/Israel	Radius, nonoperative	85	10:51	56 (3)	16	24
Emami & colleagues[11]	1999	Sweden	Tibia, operative	33	24:8	37 (15)	52	1
Leung & colleagues[13]	2004	China	Tibia, operative	30	25:3	35.3	52	0
Ricardo[14]	2006	Cuba	Scaphoid, operative	21	21:0	26.7	208	0

Table II. Summary Table and Forest Plot for Results of Studies Included in the Meta-Analysis[a]

Study	Year	Time to Healing, days: LIPU Mean	LIPU SD	LIPU Total	Placebo-Control Mean	Placebo-Control SD	Placebo-Control Total	Weight, %	Mean Difference, days IV, Random	95% CI	Year	Mean Difference, days IV, Random 95% CI
Heckman & colleagues[12]	1994	102	4.8	33	190	18.3	34	20.5	–88.00	[–94.37, –81.63]	1994	
Kristiansen & colleagues[15]	1997	51	4	30	77	5	31	20.8	–26.00	[–28.27, –23.73]	1997	
Emami & colleagues[11]	1999	155	22	15	125	11	17	19.7	30.00	[17.70, 42.30]	1999	
Leung & colleagues[13]	2004	80.5	21	16	140	30.8	14	18.3	–59.50	[–78.64, –40.36]	2004	
Ricardo[14]	2006	56	3.2	10	94	4.8	11	20.7	–38.00	[–41.46, –34.54]	2006	
Total (95% CI)	—	—	—	**104**	—	—	**107**	**100.0**	**–36.30**	**[–59.66, –12.94]**	—	



Abbreviation: LIPU, low-intensity pulsed ultrasound; IV, inverse variance; CI, confidence interval.
[a]Heterogeneity: $T^2 = 681.86$; $\chi^2 = 439.46$; df = 4 ($P<.00001$); $I^2 = 99\%$. Test for overall effect: $Z = 3.05$ ($P = .002$).

Table III. Cumulative No. of Adverse Events in Studies Included in the Meta-Analysis

Treatment Group	Delayed Union	Infection	Swelling	Reflex Sympathetic Dystrophy	Acute Compartment Syndrome	Pulmonary Embolism
LIPU (n = 104 fractures)	8	0	4	1	1	0
Control (n = 107 fractures)	12	4	1	1	2	1

Abbreviation: LIPU, low-intensity pulsed ultrasound.

- Was the outcome assessor blinded to the intervention?
- Were co-interventions avoided or similar?
- Was adherence acceptable in all groups?
- Was the dropout rate described and acceptable?
- Was the timing of the outcome assessment in all groups similar?
- Did the analysis include an intention-to-treat analysis?

Discrepancies in quality assessment were resolved by mutual agreement or, when agreement could not be reached, by Dr. Koval. The results of these methodologic quality assessments were not summed; the yes/no/unknown answer to each question was tabulated so that readers could assess each quality component as they interpret the findings of our meta-analysis.

Outcome Measures

Primary Outcome. The primary outcome assessed in this meta-analysis was time to fracture healing as determined radiographically, specifically the bridging of 3 or more cortices measured by radiography or CT. To ensure standardization across studies, we included only radiographically documented cases of fracture healing. For documentation, we used bridging of 3 out of 4 cortices because this is the best accepted radiographic measure of fracture healing in the orthopedic literature.[6] Bridging may also be determined using bone density scans, such as dual-energy absorptiometry or ultrasound, but these measures are less common, and their validity remains questionable.

Secondary Outcomes. Rates of delayed union and other reported adverse events were assessed as secondary outcomes. Studies that did not measure these secondary outcomes were not excluded. Including rates of reported adverse events will help clarify the therapeutic benefit or harm in using LIPU to heal bone fractures—especially considering that LIPU is purported to reduce rates of delayed union and other adverse events after bone fractures.[8]

Subgroup Analyses

To evaluate the effect of LIPU on fracture healing according to varying indications, we performed subgroup analyses on 3 types of studies: those in which fracture reduction required open operative fixation (operative subgroup),

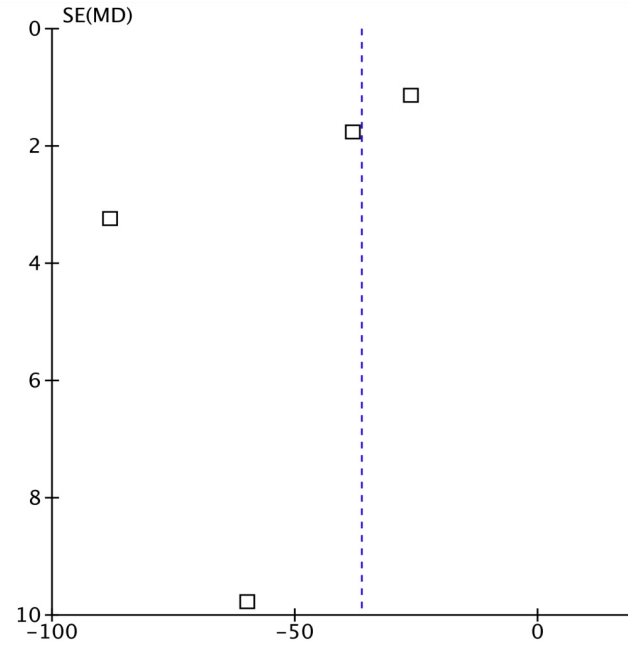


Figure 4. Funnel plot of studies included in meta-analysis.

those in which reduction required only closed treatment (nonoperative subgroup), and those in which the fracture model was tibia fractures only (tibia subgroup).

Quantitative Data Synthesis

Summary Measure Used for Dichotomous and Continuous Variables. Our quantitative data synthesis benefited from consistent reporting of the primary outcome and time of fracture healing—measured as a continuous variable in days or weeks—across all studies. Therefore, we pooled these results using the statistical measure of weighted mean difference. Given the variation in the secondary outcomes (ie reported adverse events), we summarized these data in a table without formal pooling. All statistical summarization was performed using Review Manager Version 5.0 (RevMan 5).[9]

Fixed Versus Random Effects. Although each study included was conducted to assess the effect of LIPU on fracture healing times for skeletally mature adults, inevitably, the populations and methodology used in each trial varied. To account for these unavoidable differences, we used random effects models to generate summary estimates in RevMan 5, as the treatment effects being measured in each study varied to some degree and resulted in heterogeneity.[9]

Dealing With Missing Data. Studies for which adequate data for the primary outcome could not be obtained were excluded from the meta-analysis because time to fracture healing (primary outcome) was the only outcome that was pooled using meta-analysis statistics.

Dealing With Heterogeneity. Statistical variability among the studies contributing to the primary outcome summary estimate was assessed using RevMan 5, which calculates a heterogeneity test on the basis of both χ^2 P and I^2 threshold.[9] Heterogeneity was determined to be statistically significant when $P<.10$ and $I^2>.50$.[10] When heterogeneity was present, we reviewed the results of each study to determine the study or studies responsible and then examined study characteristics for possible explanations. We performed subgroup analyses to identify potential sources of heterogeneity.

Sensitivity Analyses. Sensitivity analyses were not performed, but, as already mentioned, 3 subgroup analyses were completed to investigate sources of heterogeneity.

Assessing for Publication Bias. Careful assessment for publication bias involved using RevMan 5 to generate a funnel plot of the primary outcome and organizing the studies by sample size.[9] The plot was evaluated for presence of an upside-down funnel shape, which would suggest little to no publication bias. Potential variations in this shape may indicate publication bias.

Results

Description of Studies

Search Results. Of the 1559 potentially eligible studies identified, 1433 were excluded because their contents were irrelevant to determining whether LIPU altered fracture healing time. The remaining 126 studies were then scrutinized with respect to the 4 primary inclusion criteria. Five studies met these criteria and underwent data abstraction (Figure 1).[11-15]

Characteristics of Included Studies. Five randomized, double-blinded, placebo-controlled trials involving 209 skeletally mature patients (266 fractures) were included in our meta-analysis (Table I).[11-15] Of these studies, 4 used the Sonic Accelerated Fracture Healing System (SAFHS 2A; Smith & Nephew, Exogen; Piscataway, New Jersey) set at 1.5-MHz frequency, 1-kHz repetition rate, 200-μs pulse duration, and 30-mW/cm^2 spatial mean temporal intensity (the fifth study, by Ricardo,[14] used a similar device, TheraMed 101-B, Institute of Cybernetics, Mathematics and Physics, Havana, Cuba). The settings could not be modified by the patient. The transducer head was applied to the skin through a cast window. Coupling gel was added between the transducer and the skin, and a warning signal sounded when there was poor acoustic coupling. Patients were instructed to use the device for 20 minutes a day. Patient adherence was measured with an elapsed-time recorder inside the unit and with a daily patient logbook. A sham device was provided for the placebo-control group in each study, and patients were given identical instructions for daily use. Across all studies, adherence was very good, and it was comparable between LIPU and placebo-

control groups. Patient and investigators were blinded to the patient's randomized treatment allocation. However, none of the studies investigated whether patients were able to determine their allocation. Clinicians who assessed the radiographs were also blinded to treatment allocation.

The studies were conducted between 1994 and 2006 in a variety of settings throughout the world (Table I). Study sizes ranged from 21 to 97 fractures and some studies included individual patients with 2 or more fractures. Heckman and colleagues[12] studied patients with closed or grade I open tibial diaphyseal fractures effectively managed with closed reduction and cast immobilization.

In another study, Kristiansen and colleagues[15] evaluated patients with closed, dorsally angulated metaphyseal fractures of the distal aspect of the radius reduced with closed reduction and cast immobilization. Emami and colleagues[11] included patients with closed or grade I open diaphyseal tibial fractures managed with closed reduction and a reamed and locked intramedullary nail. In 2004, Leung and colleagues[13] included patients with high-energy comminution and open fractures at the tibial shaft fixed with reamed intramedullary locked nails or external fixator. Ricardo[14] studied fractures of the scaphoid with established delayed unions managed with vascularized pedicle bone graft fixed with Kirschner wires and case immobilization.

The studies compared a total of 134 males and 75 females. The only study with more females than males was conducted by Kristiansen and colleagues.[15] Their patient population was significantly older as well, which can be attributed to the fact that the distal radius is primarily cancellous bone, and therefore, more likely to fracture in older, osteoporotic women. The other fracture models, tibia and scaphoid, are more likely caused by traumatic injury, which is more common in younger males. Follow-up ranged from 16 to 208 weeks and depended largely on the expected healing times of the fracture models. Rather than study the healing of simple traumatic fractures, Ricardo[14] investigated the healing of nonunions, which require longer follow-up. Loss to follow-up was more significant in the earlier studies. Heckman and colleagues[12] reported that 13 patients were lost to follow-up because of withdrawal or death and 17 were excluded for deviations from the protocol. Kristiansen and colleagues[15] reported that 11 patients were lost because of withdrawal and another 13 were lost for protocol deviations. Emami and colleagues[11] excluded 1 patient who did not fulfill the inclusion/exclusion criteria.

Characteristics of Excluded Studies. Initially excluded were 1433 studies, most because of irrelevant use of ultrasound as a diagnostic or imaging modality or because of use of ultrasound in oral hygiene. Of the other 121 excluded studies (Figure 1), 111 did not involve interventions and described basic science principles or reviewed the primary literature, 3 were excluded because they were of inferior quality for meta-analysis, and 7 were excluded because of our use of the most accepted and best objective assessment of fracture healing—bridging of 3 out of 4 cortices.[6]

Methodologic Quality of Included Studies

In assessing the methodologic quality of the included studies, we found that overall study quality was reasonably good (Figure 2). All studies were adequately rigorous in the quality assessment fields of patient blinding, co-interventions, timing of outcome assessment, and described dropout rate. Four of the 5 studies had acceptable randomization, blinding of outcome assessor, dropout rate, and intention-to-treat analysis. The single consistent weakness in methodologic quality across studies was lack of information about allocation concealment, which could introduce selection bias. Another weakness was that acceptable adherence to study protocol was not reported in more than half of the included studies.

Main Results

Time to Fracture Healing (Primary Outcome). The summary estimate from the 5 studies included showed that time to fracture healing, as determined by radiographic bridging of 3 out of 4 cortices, was considerably shorter in the 104 fractures managed with LIPU than in the 107 placebo-control fractures (Table II). Mean effect size was –36 days (95% confidence interval [CI], –60 to –13 days), which translates to a healing time reduction of 36 days in the LIPU group, compared with the placebo-control group.

Heterogeneity. Although the pooled results showed a significant reduction in fracture healing time with use of LIPU, the 5 studies failed the χ^2 ($P<.00001$) and I^2 (99%) tests for heterogeneity (Table II, bottom). Therefore, the fracture healing times of these studies differed significantly, and they varied, as expected, by chance.

Subgroup Analyses. To explore sources of heterogeneity among the 5 studies included, we analyzed the methodologic differences among 3 subgroups (Figure 3). The 128-fracture nonoperative subgroup included the 2 studies[12,15] that did not require operative fracture fixations; there was a reduction in fracture healing time with a mean effect size of –57 days (95% CI, 4 to –118 days). The 83-fracture operative subgroup included the 3 studies[11,13,14] that required operative fracture fixations and often involved metal hardware for securing the fixations; there was a reduction in fracture healing time with a mean effect size of –22 days (95% CI, 25 to –70 days). The 129-fracture tibia subgroup included the 3 studies[11-13] that used tibia fractures as their fracture model; there was a reduction in fracture healing time with a mean effect size of –39 days (95% CI, 41 to –119 days).

Notably, none of the 3 subgroup analyses passed either heterogeneity test, χ^2 or I^2, and all 95% CIs crossed 0 day, indicating potential delay in fracture healing.

Adverse Outcomes. The rate of adverse outcomes was lower in the active LIPU group than in the placebo-control group (Table III). As for the main adverse outcome of interest, 8 fractures (7.7%) in the LIPU group and 12 fractures (11.2%) in the placebo group underwent delayed union. Swelling was the only adverse event reported to have a higher rate in the LIPU group (3.8%) than in the placebo group (0.9%). Notably, all adverse outcomes are events associated with normal fracture healing and are not particular to LIPU. Use of ultrasound is purported to have no adverse side effects.[8]

Publication Bias. Initial evaluation of the funnel plot revealed a shape resembling an inverted funnel (Figure 4). Yet, with only 5 studies meeting the inclusion criteria for this analysis, the data in the plot were insufficient to adequately assess for publication bias.

Discussion

Summary of Main Results

Five randomized, double-blinded, placebo-controlled trials of skeletally mature patients were identified as having examined the effects of LIPU on reducing time to fracture healing as compared with a placebo treatment. According to meta-analytic protocol, we used inclusion and exclusion criteria that we thought would provide the best summary estimate to determine whether LIPU reduced time to fracture healing.[16] Only randomized, double-blinded, sham-controlled designs with discernible outcome measurement were included to reduce the chance for selection bias, detection bias, and potential confounding variables that would compromise the validity of our findings. Skeletally mature patients were required in order to best standardize healing rates across both patients and studies. Radiographic assessment was used as the outcome measure because it is the gold standard that orthopedic surgeons use to objectively determine fracture healing.[6]

According to the pooled summary estimate of the 5 included studies, LIPU reduced mean fracture healing time by 36 days compared with placebo treatment. Although the random-effect model was used to account for variability among studies, the pooled result failed the χ^2 and I^2 tests of heterogeneity, and thus, the findings should be interpreted with caution.[10,16] To explore potential sources of heterogeneity, we performed subgroup analyses based on gross methodologic differences among studies. Subgroup analyses based on nonoperative, operative, and tibial fractures did not reveal the source of heterogeneity. The wide CIs in the operative and tibia subgroups were mainly attributable to the negative results reported by Emami and colleagues,[11] whose study may have been undermined by type II statistical error.[1]

With the exception of swelling, adverse outcomes of fracture healing occurred more often in the placebo-control group than in the active LIPU group. Other studies have demonstrated the positive effect of ultrasound in reducing the incidence of delayed unions and nonunions.[8] A funnel plot failed to reveal a significant publication bias but was limited by the small number of included studies.

Overall Completeness and Applicability of Evidence

The addition of 3 studies to the original meta-analysis evaluating use of LIPU to accelerate fracture healing was intended to improve the precision of the estimate and the generalizability of the intervention. We believe that the 5 studies total included in this meta-analysis had proper and consistent patient populations and clinical presentations, standardized interventions, and similarly measured and clear outcomes. The summary estimate of this meta-analysis agrees with previous findings that LIPU accelerates healing in a variety of fracture locations. However, the substantial heterogeneity indicates that this summary estimate should be interpreted with caution. Subgroup analyses on fixation intensity and fracture location failed to reveal sources of heterogeneity, and therefore, other sources of clinical or methodologic diversity among the studies need to be investigated. In short, efforts to expand the generalizability of LIPU in managing fractures may contribute to, and ultimately be limited by, substantial heterogeneity.[10]

Quality of Evidence

The 5 included studies were all randomized, double-blinded, placebo-controlled trials. According to Jadad score, the quality of these trials would have been high, averaging above 4, out of 5 possible points.[17] However, Jadad score does not adequately account for allocation concealment, blinding of care provider, co-interventions, and intention-to-treat analyses, which are all underreported in our 5 included studies.[7,17] Attempts to contact the original authors about these methodologic questions were unsuccessful. Therefore, the internal validity of our summary estimate is also limited because of the questionable quality of the studies. Notably, all studies had similar timing of outcome assessment through regular interval radiographs, which helped to standardize outcome assessment across all studies and limit diagnosis time bias.

Potential Biases in Review Process

The scientific strength of this meta-analysis is that its predetermined inclusion criteria required randomized, double-blinded, sham-controlled studies—largely reducing the chance that selection bias, detection bias, and potential confounding variables would compromise the validity of its findings. Another main strength is that steps were taken to prevent bias from occurring in the selection of included studies. Rigorous efforts were made to ensure

that every potential study would be considered for this meta-analysis. We adhered to using the Cochrane highly sensitive search strategy, sensitivity-maximizing version,[5] and attempted to search all eligible databases; EMBASE was excluded due to a lack of funding.

The main limitation of this meta-analysis is the significant heterogeneity in the summary estimate of the primary outcome. To reduce the potential bias introduced through heterogeneity, we used subgroup analyses to find a statistically justifiable combination of included studies. However, no combination of studies resulted in significant homogeneity, and thus, the ability of our pooled results to predict fracture healing time differences between LIPU and placebo therapy[16] was limited.

Although the funnel plot was inconclusive in determining publication bias, the potential for bias is high, given that several of the included studies were partially funded by the ultrasound device manufacturers. In addition, blinding of the outcome assessors in this analysis could have reduced the potential for bias in the selection of included studies.

Agreements and Disagreements With Other Studies or Reviews

Busse and colleagues[1] used similar inclusion criteria in their 2002 meta-analysis and found that, compared with placebo-control treatment, LIPU reduced time to fracture healing by a mean of 64 days, with homogeneity ($P = .56$) between studies. The effect was both larger and homogenous in that meta-analysis because they excluded the negative results reported by Emami and colleagues[11] owing to methodologic differences and heterogeneity. The mean effect represented a subgroup of 3 studies that met the inclusion criteria.[1] Therefore, though our pooled results fail the tests of heterogeneity, the summary estimate is arguably more representative of the true effect size because all studies are included.

In 2009, Busse and colleagues[18] updated their systematic review of LIPU for fracture repair. Data were compiled from 6 randomized controlled trials and divided into 3 fracture subgroups: conservatively managed fresh fractures, operatively managed fresh fractures, and operatively managed nonunions. One of the included studies by Mayr and colleagues[19] was not part of our meta-analysis because time to bridging of 3 out of 4 cortices was not discernible. Busse and colleagues[18] attempted to adjust variability between the fracture models and assessment modes by calculating the percentage reduction in healing time and creating summary estimates based on these calculations. Overall reduction in healing time was 33.6%, on par with our summary estimate. However, the authors reported an overall I^2 of 76.9% and, in their respective subgroup analyses, I^2 values of 41.6%, 76.9%, and 90%, representing moderate to high levels of heterogeneity and corroborating the results of our tests for heterogeneity.[18] We support their conclusion that LIPU demonstrated promising effects, but more large and high-quality studies are needed.[18]

Conclusions

We identified 5 studies that met our predetermined inclusion criteria representing a variety of fracture models. After 2 independent reviewers extracted the study data, results were combined to show a mean reduction in fracture healing time of 36 days. Despite that positive result, the meta-analysis failed the χ^2 and I^2 tests for heterogeneity, and therefore, the results should be interpreted with caution. Subgroup analyses based on nonoperative, operative, and tibial fractures did not reveal the source of heterogeneity. These results corroborate inconclusive evidence presented by 2 former reviews [1,18] and strengthen the call for further research.

Basic scientists should be invigorated to try to better understand the molecular mechanisms behind ultrasound enhancement of fracture healing and to experiment with combinatorial approaches that may augment the effects of LIPU.[3] Continued clinical research that incorporates larger randomized studies of high methodologic quality is needed to appropriately combine study results and determine the true effect of LIPU on fracture healing. Once this true effect is known, clinical guidelines may shift to increase use of LIPU in situations in which shortening the duration of fracture healing is of utmost importance (eg, athletics, performance arts, media) and can lead to decreased costs (eg, disability insurance, lost job productivity).[2]

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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Appendix

Detailed search strategies for each database.

Ovid MEDLINE (1950 - October 2, 2008)

1. randomized controlled trial.pt.	266806
2. controlled clinical trial.pt.	80365
3. randomized.ab.	174816
4. placebo.ab.	110356
5. drug therapy.fs.	1307066
6. randomly.ab.	126939
7. trial.ab.	182324
8. groups.ab.	880169
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	2362779
10. humans.sh.	10738442
11. 9 and 10	1934906
12. fracture fixation.mp. or exp Fracture Fixation/	37708
13. fracture healing.mp. or exp Fracture Healing/	7503
14. exp Fractures, Bone/	111911
15. exp "Bone and Bones"/	392347
16. bony callus.mp. or exp Bony Callus/	1720
17. bone remodeling.mp. or exp Bone Remodeling/	37495
18. bone regeneration.mp. or exp Bone Regeneration/	12650
19. osseointegration.mp. or exp Osseointegration/	5757
20. or/12-19	482061
21. ultrasonic therapy.mp. or exp Ultrasonic Therapy/	6693
22. ultrasonics.mp. or exp Ultrasonics/	20556
23. ultrasound.mp.	97925
24. or/21-23	115606
25. 11 and 20 and 24	725

Cochrane Database of Systematic Reviews (Cochrane Reviews) (from inception to Oct 2, 2008)
"fractur*" (search all text) and "ultraso*" (search all text) 86

Database of Abstracts of Reviews of Effects (Other Reviews) (from inception to Oct 2, 2008)
"fractur*" (search all text) and "ultraso*" (search all text) 10

Cochrane Central Register of Controlled Trials (Clinical Trials) (from inception to Oct 2, 2008)
"fractur*" (search all text) and "ultraso*" (search all text) 158

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from inception to Oct 2, 2008)
"fractur*" (TX All Text) and "ultraso*" (TX All Text) 439

Limit: Exclude MEDLINE records 258

NLM Gateway (from inception to Oct 2, 2008)
"fractur*" and "ultraso*"

NLM Catalog 16
Bookshelf 116

ProQuest: Dissertations & Theses (from inception to Oct 2, 2008)
"fractur*" and "ultraso*"
All dates; No limits 146

Physiotherapy Evidence Database (PEDro) (from inception to Oct 2, 2008)
"fracture*" and "ultraso*" 24

Clinicaltrials.gov (from inception to Oct 2, 2008)
"fracture" and "ultrasound" 20