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The effects of low-intensity pulsed ultrasound on fresh fracture
A meta-analysis

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Abstract

Background: Low-intensity pulsed ultrasonography (LIPUS) is a form of mechanical stimulation that is delivered via a special device to the fracture site for the acceleration of fracture healing. We conducted a meta-analysis to assess the effect of LIPUS for fresh fractures in adults.

Methods: MEDLINE, EMBASE and the Cochrane Library searched between Jan 1980 and Nov 2016. Studies should be quasi-randomized and randomized controlled trials (RCTs) comparing treatment with LIPUS to placebo or no treatment in adults with fresh fractures, reporting outcomes such as function; time to union; delayed union or non-union. Summary standard mean difference (SMD) and the risk ratio (RR) with their 95% confidence interval (CI) calculated with a random effects model. I^2 statistic was used to assess the heterogeneity. Risk of bias was assessed by the Cochrane risk-of-bias tool. The GRADE system was used to evaluate the evidence quality.

Results: A total of 12 trials with 1099 patients were included. The pooled results showed that LIPUS significantly reduced the time to fracture union (SMD: 0.65, 95% CI: 1.13 to 0.17), improved the quality of life (SMD: 0.20, 95% CI: 0.03–0.37) without affecting the time to full weight bearing (SMD: 0.76, 95% CI: 1.92 to 0.4), the time to return to work (SMD: 0.06, 95% CI: 0.14 to 0.27), or the incidence rate of delayed union and nonunion (RR: 1.02, 95% CI: 0.60–1.74).

Conclusions: Moderate-to-high quality evidence shows that LIPUS treatment reduces the time to fracture union and improves the quality of life without affecting functional recovery and incident rate of delayed union and nonunion, suggesting that LIPUS treatment may be a good treatment modality for adults with fresh fractures. However, there are some methodological limitations in the eligible trials, further studies are needed to determine the clinical circumstances under which LIPUS is truly valid and to examine the optimal approach for the use of this adjunctive therapy.

Abbreviations: CI = confidence interval, CT = computed tomography, FDA = US Food and Drug Administration, GRADE = Grading of Recommendations Assessment, Development and Evaluation, LIPUS = low-intensity pulsed ultrasonography, RCT = randomized controlled trial, RR = risk ratio, SDC = supplemental digital content, SF-36 = short form-36, SMD = standard mean difference.

Keywords: fracture, fracture healing, meta-analysis, ultrasonic therapy

1. Introduction

Fractures are common. In the United States, approximately 5.6 million fractures occur each year.[1] In England, the fracture incidence for all age groups is 3.6% every year.[2] Moreover, it is suggested that >33% of people will experience a fracture in their life time.[3] Meanwhile, 5% to 10% of these fractures show delayed healing or nonunion.[4] The delay unions or nonunions often require further intervention and may cause serious complications, such as pain and functional limitations.[5] Reoperation is usually necessary to promote bone healing, and it is invasive and expensive. To reduce the substantial risk of disability and the socioeconomic costs, the development of a method for accelerating fracture healing is becoming more and more important.[6,7]

Low-intensity pulsed ultrasonography (LIPUS) is a safe and effective noninvasive adjunctive therapy used to promote the bone healing process.[8–10] Although the underlying mechanism of LIPUS treatment on fracture healing remains unclear,[11] it is suggested that LIPUS accelerates fracture healing through multiple avenues,[12] such as stimulating signal transduction, blood flow, angiogenesis, and osteogenic gene expression.[13] Now, we do know that LIPUS can cause pressure waves at the fracture site, and this mechanical signal converts to a biochemical signal inside the cells, through the expression of cyclooxygenase-2 gene,[14] induces the production of cyclooxygenase-2.[15] The

enhanced cyclooxygenase-2 level further induces the production of prostaglandin E2.[16] Accordingly, this drives the expression of osteogenic genes, such as c-fos[17] and aggrecan.[18] These osteogenic genes help to heal the fracture by enhancing endochondral ossification. The US Food and Drug Administration (FDA) approved the use of LIPUS for accelerating healing of fresh fractures in 1994.[19] Since then, several clinical trials have been designed to investigate the effect of LIPUS on bone healing. However, its effectiveness is controversial. Recently, several meta-analyses published on this topic determined that that LIPUS reduces the time to fracture healing.[20–25] However, none of these meta-analyses offered definitive conclusions. All these meta-analyses identified the need for additional trials. Moreover, a number of the prior meta-analyses focusing on the effectiveness of LIPUS on fracture treatment were limited by loose inclusion criteria, inappropriate evaluation techniques, and a focus only on radiographic healing over other patient-important outcomes, such as functional recovery and the incident rate of delayed union and nonunion.

To provide a high-quality evidence for the use of LIPUS in clinical practice, we conducted a meta-analysis of quasi-randomized and randomized controlled trials (RCTs), comparing the different effects between LIPUS treatment and placebo (sham LIPUS or none), for fresh fractures in adults, with the time to fracture union, functional recovery, the incidence rate of delayed union and nonunion, the time to full weight bearing, and the time to return to work as the outcomes.

2. Methods

This study did not involve human or animal experiments, and thus, ethical approval was not necessary. Two authors (SHL and HCL) independently performed the meta-analysis. Any disagreements were resolved through discussion and sometimes by seeking an independent third author (LCZ).

2.1. Protocol and registration

This meta-analysis was performed according to the recommendations of the Cochrane Handbook, was reported on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[26] and was registered on the PROSPERO International prospective register of systematic reviews (CRD42016042068).

2.2. Eligibility criteria
2.2.1. Participants.
Adults with all types of fresh fractures were included. Fresh fractures were fractures within 2 weeks. Patients with post-corticotomy (eg, osteotomy and distraction osteogenesis) were excluded.

2.2.2. Interventions.
The intervention was LIPUS with a precise definition, and the LIPUS had to meet the following conditions[27]: frequency: 1.5 MHz; form: pulsed; impulse length: 200 μs; signal repetition frequency: 1 kHz; and intensity: 30 mW/cm^2. We also included trials where LIPUS was used as an adjunctive therapy to nonsurgical or surgical treatments.

2.2.3. Comparators.
LIPUS could be the only treatment or an adjunctive therapy, and the comparison was a placebo (sham ultrasound) or no additional treatment. Trials comparing LIPUS with other interventions were excluded.

2.2.4. Outcomes.
The outcomes included the time to fracture union (days), functional recovery (score), the incidence rate of delayed union (%) and nonunion (%), the time to full weight bearing, and the time to return to work (days).

2.2.5. Study design.
All of the relevant RCTs and quasi-RCTs were included. The quasi-RCTs were trials using a quasi-random method (eg, allocation by date of birth, day of the week, medical record number, or month of the year) of allocating the participants to the different interventions.

2.2.6. Time.
Studies of any duration conducted at any time were included.

2.2.7. Other.
Unpublished and published studies that were written in any language were included. For our study, unpublished data means data not published as an article. The unpublished data include meeting abstracts, supplementary materials, and data published on ClinicalTrials.gov.

2.3. Search strategy

We systematically searched MEDLINE, Embase, and the Cochrane Library from January 1, 1980 until November 1, 2016, with no language restrictions. We also searched Google scholar (www.scholar.google.com), ClinicalTrials.gov registry, (www.clinicaltrials.gov) and screened the references of both retrieved articles and relevant reviews to further identify potentially eligible trials. The search strategies were developed using text words as well as medical subject headings (MeSH) associated with the terms relevant to "fracture healing," "fracture," "ultrasonic therapy," and "ultrasonography" together with "randomized control trial." The full search strategies used in the MEDLINE, Embase, and the Cochrane Library databases are provided in Supplemental Digital Content (SDC) 1, http://links.lww.com/MD/B889.

2.4. Study selection

Our search records were imported into ENDNOTE X7 reference management software, and the duplicate records were removed both electronically and manually. After excluding the duplicate and apparently irrelevant articles, the remaining studies were further reviewed by reading the full text to assess the eligibility for inclusion. After completion, both of the authors met and reviewed their selections for agreement.

2.5. Data extraction

A standard data extraction form was created using Microsoft Excel 2016 to collect the data of interest. The major categories of the variables to be coded were as follows: study characteristics, participant characteristics, and outcome characteristics.

2.6. Risk of bias assessment

The risk of bias of the individual studies was assessed by the Cochrane risk-of-bias tool.[28] The Cochrane risk-of-bias tool is an evaluation scale that is recommended by the Cochrane handbook for RCTs, and it assesses the bias across the following 7 aspects: random-sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other biases. Each aspect could further be classified as a

low, high, or unclear risk. For the study design, we assessed random-sequence generation, allocation concealment, blinding of the participants, and outcome reporting. For each outcome, we assessed blinding of the outcome assessors and loss to follow-up.

2.7. Outcomes

The outcomes of this study included the time to fracture union, quality of life, functional recovery, and the incidence rate of delayed union and nonunion. For the outcome of the time to fracture union, both the radiographic and the clinical union were used to define a healed fracture, which are the widely acceptable definitions in the literature. In our study, fracture union[29] was defined as follows: a callus is present bridging at least 3 of 4 cortices on orthogonal radiographs (radiographic union) or there is no pain, tenderness, or movement at the fracture site (clinical union). The outcome of quality of life was measured by the short form-36 (SF-36) physical component summary scores.[30–33] The outcome of function recovery was measured by the time to return to work and the time to full weight bearing. The time to return to work was defined as the time to return to work without limitations (return to the level before their injury). The time to full weight bearing was defined as when the patients were able to place all their weight on the operated extremity. The incidence rate of the delayed union and nonunion was diagnosed according to the guidelines of the different fractures.

2.8. Synthesis of the results

We pooled the treatment effects of LIPUS with same outcomes across the included trials. The continuous outcomes are expressed as the standardized mean differences (SMD) and the 95% confidence interval (CI), using the generic inverse variance methods. The dichotomous outcomes are expressed as the risk ratios (RRs) and the 95% CI, using the Mantel-Haenszel method.

For the dichotomous outcomes, we extracted the original data regarding the events (n_e) and the total number (n_t) in both the experimental group and the control group. For the continuous outcomes, we extracted the original data, including the mean, standard deviation (SD), and the total number (n) in both the experimental group and the control group. If the original data was not available, we calculated the data through the available coefficients. For example, we computed the mean from the median and the SD for the standard error (SE), the interquartile range (IQR) or the P values, according to the methods described in the Cochrane Handbook.

The meta-analysis was performed using a random-effects model, which provided more conservative estimated effects. Cochrane Q statistic, the I^2 statistic ($I^2 > 50\%$ as a threshold indicates significant heterogeneity), and P values ($P < .10$ as a threshold indicates significant heterogeneity) were used to assess the heterogeneity.[34] Review Manager (version 5.3) and Comprehensive Meta-Analysis (version 2.0) were used for the statistical analysis.

As different fracture types were pooled for analysis in this study, we further performed preplanned subgroup analyses to explore the sources of heterogeneity according to the following categories: upper versus lower limb fractures, operative versus conservative management, and radiographic versus clinical union. Subgroup analyses were also used to evaluate the relationship between the duration of the treatment and the outcomes. Sensitivity analyses were performed to examine the robustness of our analysis by omitting specific trials from the overall analysis. Publication bias

was assessed by funnel plots and the Egger test,[35] when sufficient trials (no less than 10) were identified.

The quality of the evidence for the outcomes was assessed according to the guidelines of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[36] for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each assessment result was rated as very low, low, moderate, or high. Summary tables were constructed using the GRADE Profiler (version 3.6).

3. Results

3.1. Search results

A total of 925 articles were obtained through electronic and hand searches. After 59 duplicates were removed, the titles and abstracts of 866 records were reviewed, 844 records were excluded for not meeting the inclusion criteria, and thus, the remaining 22 articles were retrieved for further assessment. Two trials[37,38] were excluded because the treatment was not LIPUS but was high-intensity focused ultrasound. Two trials[39,40] were excluded because the fracture was a stress fracture and not a fresh fracture. The other 6 trials[41–46] were excluded because these trials reported the same data. Finally, 12 trials[47–58] fulfilled our inclusion criteria and were included in our meta-analysis (Fig. 1).

3.2. Study characteristics

The main characteristics of the included trials are summarized in Table 1. These trials were published between 1994 and 2016. The sample sizes ranged from 20 to 501, with a total of 1099 patients.

The duration of the LIPUS treatment lasted from 28 to 365 days. The LIPUS treatment was used for 20 minutes a day except in 2 trials.[48,58] In one of these trials,[48] the LIPUS treatment was used for 15 minutes every day, and in the other one,[58] the LIPUS treatment was used 2 times a day for 20 minutes each. All of the included studies demonstrated good compliance with the LIPUS treatment. No trials reported complications or adverse events associated with the LIPUS treatment. The start time of LIPUS treatment varied in the different studies. Most of the included trails did not report the specific time, whereas in clinical practice, most patients received LIPUS within 7 days. Moreover, previous studies have proved that the effect of LIPUS showed no significant differences within 6 weeks.[59]

For the included trials, 5 trials[48,50,54,56,57] used the conservative treatment, and the conservative treatment for these 5 trials used plaster of Paris to maintain reduction. The plaster was not removed when LIPUS was used. A cast window was created in the dorsal area of the cast over the site of the fracture, and an ultrasonic probe was applied on the fracture site though the window. The fracture could remain stable during the LIPUS treatment. For operative cases, the LIPUS device was applied to the area of the fracture using a probe directly on the skin.

3.3. Risk of bias assessment

Figure 2 summarizes the details of the risk of bias. One trial[58] was published only as a structured abstract with no sufficient information to assess the risk of bias, and thus, most of the 7 domains were classified as an unclear risk. For the other 11 trials,[47–57] we carefully assessed the risk of bias. Random sequence generation was reported in all of the trials except 1[53] that was a quasi-RCT. One trial[53] had a high risk of allocation concealment because of the quasi-RCT design, and 2 trials[48,54]
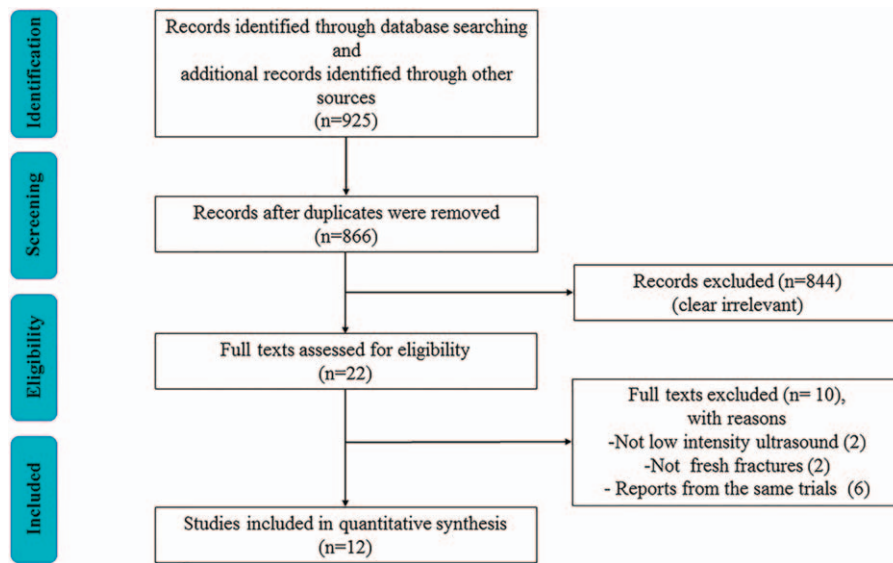
Figure 1. Flow diagram showing the process of literature selection.

did not adequately report the allocation concealment. The treatment was not blinded to the participants[48,54] and was not adequately reported by 1 trial,[53] which might lead to a potential performance bias. However, whether or not the participants were blinded had a limited impact on the time to fracture union. Blinding of the outcome assessment was adequately reported in all of the 8 trials except 1.[53] Three trials[51,56,57] had a high risk of attrition bias because of a high loss of follow-up (over 20%). Only two trials[47,49] had a low risk of reporting bias, because most of the included trials did not have protocols. Most of the included trials[48,50–54,56–58] had a potential risk of other biases because of the fact that the baseline age, the gender, or the smoking status were not clearly reported.

3.4. Time to fracture union

Eleven trials,[47–57] including 887 patients, reported the time to fracture union. Both radiographic and clinical unions were used to define the fracture union. Nine trials[47,49,51–57] reported the time to radiographic union, and the radiographic union was measured by radiography[47,51,53,55–57] or computed tomography (CT).[52,54] Two trials[48,50] reported the time to clinical union. There were significant differences in the time to fracture union between the LIPUS and placebo groups (SMD: −0.65, 95% CI: −1.13 to −0.17, $P < .01$, $I^2 = 89\%$; Fig. 3). Sensitivity analyses were performed to examine the robustness of our analysis by omitting each study in turn, and the pooled SMD was not affected (Fig. S1, http://links.lww.com/MD/B889).

The first subgroup analysis was performed using the different treatments (Fig. 3A). The LIPUS treatment was effective for fractures treated with conservative management (SMD: −1.08, 95% CI: −1.82 to −0.34, $P < .01$, $I^2 = 90\%$) but not for those treated with operative management (SMD: −0.25, 95% CI: −0.78 to 0.28, $P = .35$, $I^2 = 78\%$). However, the tests for the subgroup differences did not indicate that the results of conservatively managed fractures and operatively managed fractures were statistically significantly different from each other ($P = .07$ for interaction).

The second subgroup analysis was performed based on the upper limb and lower limb (Fig. 3B). The results suggested that

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Table 1

Characteristics of the included RCTs.

| Study | Fracture location | Number of patients (analyzed) | | Treatment method | Duration of LIPUS, d |
		Control	LIPUS		
Heckman et al[57]	Tibia	49 (34)	48 (33)	Conservative treatment	140, or until healed
Kristiansen et al[56]	Distal radius	45 (31)	40 (30)	Conservative treatment	70
Strauss[58]	Fifth metatarsal	10 (10)	10 (10)	Conservative treatment	Until healed
Emami et al[55]	Tibia	17 (17)	15 (15)	Operative treatment	75
Mayr et al[54]	Scaphoid	15 (15)	15 (15)	Conservative treatment	Until the cast was removed
Leung et al[53]	Tibia	14 (14)	16 (16)	Operative treatment	90
Handolin et al[52]	Lateral malleolus	11 (11)	11 (10)	Operative treatment	42
Handolin et al[51]	Lateral malleolus	15 (15)	15 (15)	Operative treatment	42
Lubbert et al[50]	Clavicle	59 (49)	61 (52)	Conservative treatment	28
Busse et al[49]	Tibia	28 (22)	23 (21)	Operative treatment	365, or until healed
Liu et al[48]	Distal radius	40 (40)	41 (41)	Conservative treatment	Until healed
Busse et al[47]	Tibia	250 (240)	251 (241)	Operative treatment	365, or until healed

RCT = randomized controlled trial.

Figure 2. Risk of bias graph. Risk of bias summary. "+" means low risk; "?" means unclear risk and "-" means high risk.

LIPUS treatment was effective on upper limb fractures (SMD: −1.08, 95% CI: −2.05 to −0.11, P=.03, I^2=92%), but not for lower limb fractures (SMD: −0.39, 95% CI: −0.91 to 0.13, P=.14, I^2=83%). However, the test for subgroup differences indicated that the findings from the upper and lower limb subgroups were not statistically significantly different from each other (P=.22 for interaction).

Moreover, a subgroup analysis was performed to determine whether the different definitions of fracture union could affect the results (Fig. 3C). Although the effect of the LIPUS treatment was different between the time to radiographic union (SMD: −0.55, 95% CI: −1.01 to −0.09, P=.02, I^2=83%) and the time to clinical union (SMD: −1.07, 95% CI: −3.14 to 1, P=.31, I^2= 97%), the test for subgroup differences did not indicate that the

results were statistically significantly different from each other (P=0.63 for interaction).

Finally, we performed a subgroup analysis to evaluate the relationship between the duration of the LIPUS treatment and the time to fracture union (Fig. 3D). The results demonstrated that when the duration was <6 months, the LIPUS treatment reduced the time to fracture union (SMD: −0.87, 95% CI: −1.72 to −0.02, P=.04, I^2=91%). However, when the duration assessed was the time until healing, the effect of the LIPUS treatment was not statistically significant (SMD: −0.39, 95% CI: −0.92 to 0.14, P=.15, I^2=82%). In addition, a test for subgroup differences indicated that the duration of treatment did not affect the effect of LIPUS (P=.34 for interaction).

3.5. Quality of life (SF-36 physical component summary scores)

Two trials[47,49] reported the functional recovery by the SF-36 physical component summary scores. Compared with placebo, LIPUS enhanced the SF-36 physical component summary scores (SMD: 0.2, 95% CI: 0.37–0.02, P=.02, I^2=0%, Fig. 4A).

3.6. Functional recovery
3.6.1. Time to full weight bearing. Three trials[47,53,55] reported the time to full weight bearing. The results showed that LIPUS did not reduce the time to full weight bearing (SMD: −0.76, 95% CI: −1.92 to 0.4, P=.2, I^2=91%; Fig. 4B).

3.6.2. Time to return to work. Two trials[47,50] reported the time to return to work. LIPUS treatment did not reduce the time to return to work (SMD: 0.06, 95% CI: −0.14 to 0.27, P=.56, I^2= 0%; Fig. 4C).

3.7. Incident rate of delayed union and nonunion

Eight trials,[47,49–53,55,58] consisting of 773 patients, provided the available data about the incident rate of delayed union and nonunion. The results showed that LIPUS did not reduce the incident rate of delayed union and nonunion (RR: 1.02, 95% CI: 0.60–1.74, P=.94, I^2=14%; Fig. 5). Sensitivity analyses were performed to examine the robustness of our analysis by omitting each study in turn, and the data showed that the pooled RR was not affected (Fig. S2, http://links.lww.com/MD/B889).

Based on the results of the subgroup analyses, there were 2 different groups of treatment based on the duration, including <6 months (RR: 0.76, 95% CI: 0.34–1.69, P=.5, I^2=0%) and time until healing (RR: 1.16, 95% CI: 0.49–2.73, P=.73, I^2=33%) and that the duration of the treatment did not affect the effect of the LIPUS treatment (P=.48 for interaction; Fig. 5A).

Meanwhile, the subgroup differences did not indicate that the findings from the upper (RR: 0.94, 95% CI: 0.29–3.01, P=.91, I^2=0%) and lower limb subgroups (RR: 0.96, 95% CI: 0.49–1.89, P=.92, I^2=25%) were statistically significantly different from each other (P=.96 for interaction; Fig. 5B).

Similarly, we found that there were no significant differences between the operative (RR: 1.12, 95% CI: 0.61–2.06, P=.71, I^2=15%) and conservative management (RR: 0.57, 95% CI: 0.11–3.01, P=.51, I^2=34%; P=.45 for interaction; Fig. 5C).

3.8. Publication bias

For the time to fracture union outcome, the publication bias was assessed through a visual inspection of the funnel plots and the
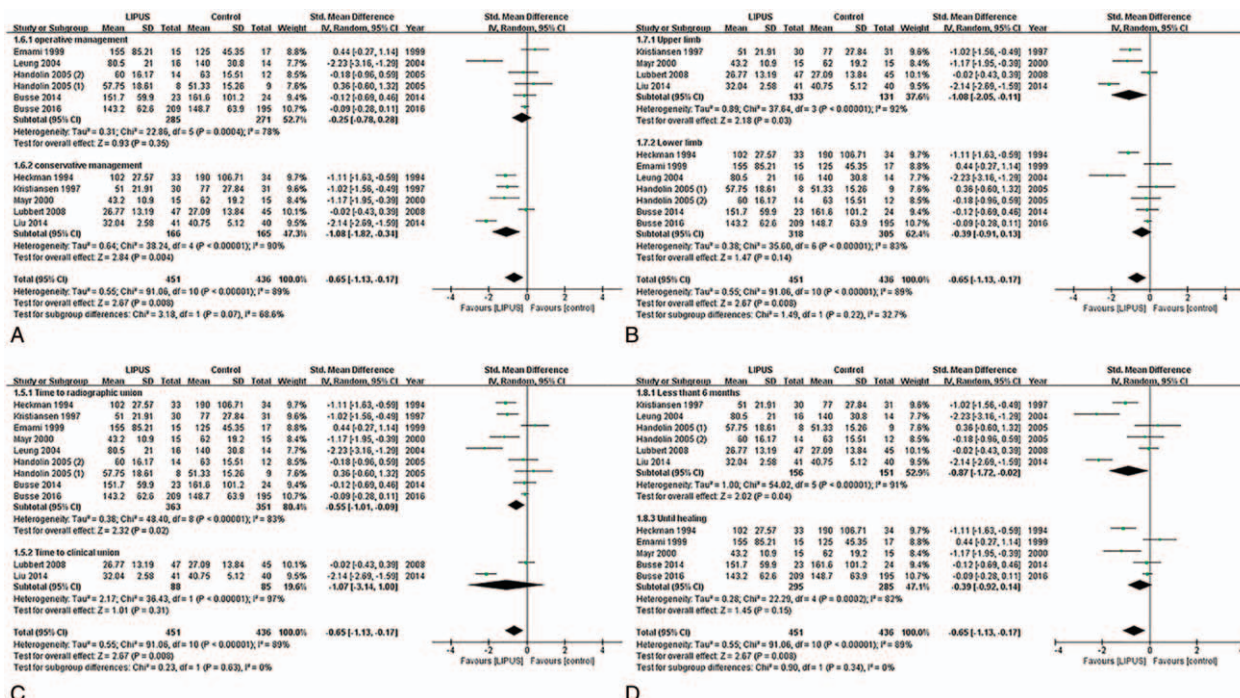
Figure 3. Forest plot for the time to fracture union. (A) Operative and conservative management; (B) upper and lower limb; (C) radiological union and clinical union; (D) time less than 6 mo and time until healing.

Egger test. Both the funnel plot and the Egger test suggested there was no significant publication bias ($P = .18$ for Egger test; Fig. S3, http://links.lww.com/MD/B889). For the incident rate of delayed union and nonunion outcome, the funnel plot was symmetrical, suggesting that there was no significant publication bias (Fig. S4, http://links.lww.com/MD/B889).

3.9. GRADE profile evidence

GRADE evidence profiles for each outcome are shown in Table 2. All of the included trials were quasi-RCTs or RCTs and had no serious inconsistencies, indirectness, or significant publication bias. A risk of bias existed in
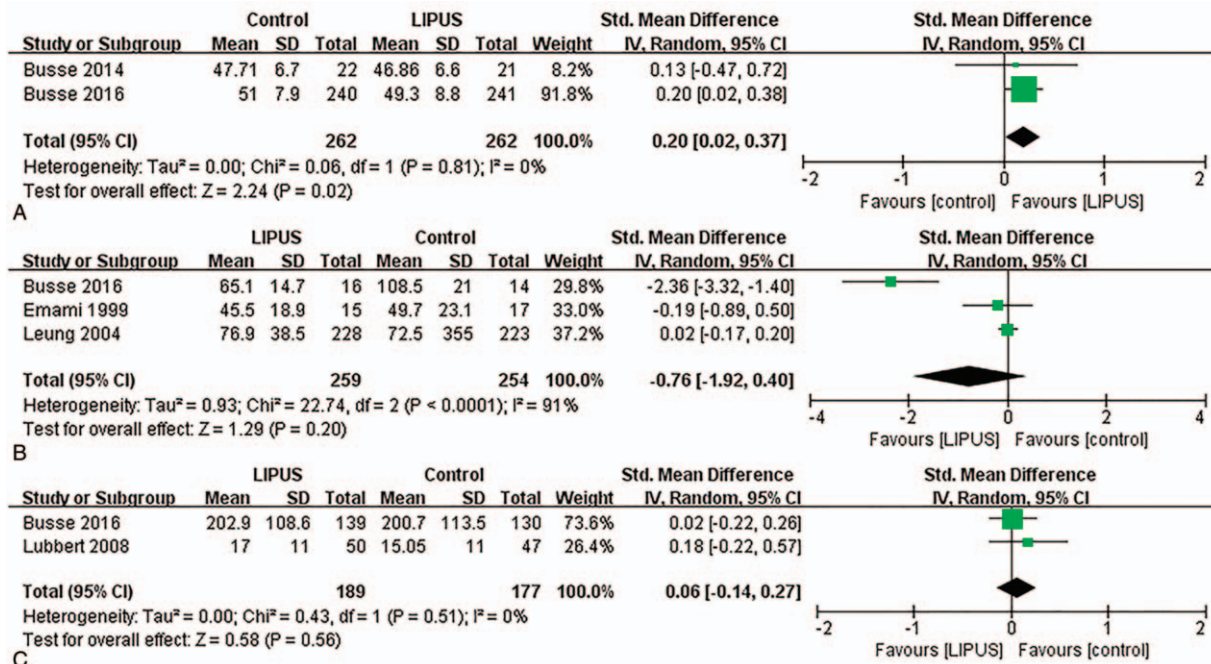

Figure 4. Forest plot of the quality of life, the time to full weight bearing and the time to return to work. (A) Quality of life; (B) time to full weight bearing; and (C) time to return to work.
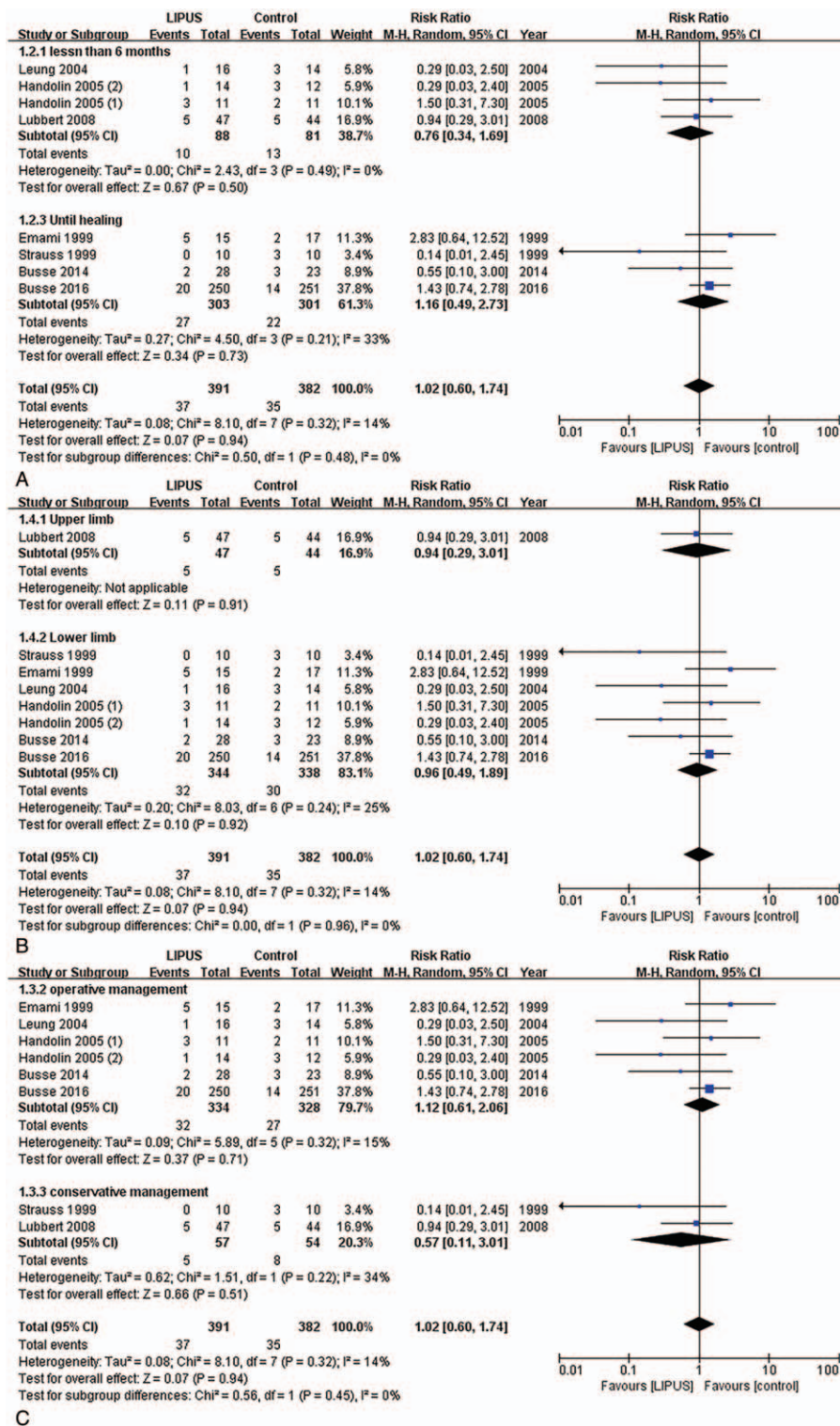
Figure 5. Incident rate of delayed union and nonunion. (A) Time less than 6 mo and time until healing; (B) operative and conservative management; and (C) upper and lower limb.

each outcome except for the outcome from the SF-36 physical component summary scores and the time to return to work. The selection bias, the performance bias, and the attrition bias were major causes of risk of bias. Imprecision existed in the outcome of the time to return to work. Although the included RCTs were considered as high quality evidence, the quality was down rated by the aforesaid limitations. Therefore, the strength of the evidence was limited, and the available evidence of each outcome was high to moderate.

4. Discussion

4.1. Main findings

Our meta-analysis provides moderate to high quality evidence that LIPUS treatment reduces the time to fracture union and improves the quality of life, which was measured by the SF-36 physical component summary scores. We also determine that LIPUS treatment does not affect functional recovery, which was measured by the time to return to work and the time to full weight bearing. In addition, LIPUS treatment dose not increase the incident rate of delayed union and nonunion.

4.2. Comparison with other systematic reviews

Our results are consistent with other meta-analyses in the fact that LIPUS treatment significantly reduced the time to fracture union.[23,25,60,61] This meta-analysis, however, was different from previous meta-analyses in several important aspects. First, this meta-analysis adds to the existing literature by not only assessing the outcome of the time to fracture union, but also assessing the outcomes about the quality of life, functional recovery, and the incident rate of delayed union and nonunion, which are also very important for patients. Second, heterogeneity was well explored by subgroup analyses and sensitivity analyses, and the overall quality of the evidence was also assessed by GRADE approach. Third, this study included a greater number of eligible trials for the pooled analysis.

4.3. Implications for clinical practice

Currently, many surgeons use LIPUS as part of their management of fractures.[62] However, LIPUS is a high-energy wave that generates heat energy[9] and the increased heat energy may further aggravate the thermal osteonecrosis caused by bone drilling during the operation.[63] Thus, the situation under which LIPUS is truly valid should be noted. There are important clinical implications to this study's findings. LIPUS treatment might be more suitable for fractures with conservative treatment rather than those with operative treatment. And it might be more suitable for fractures of the upper limb rather than those of the lower limb. In addition, for fresh fractures with potential risks of delayed union or nonunion, LIPUS treatment should not be expected as a method to reduce the incident rate of delayed union and nonunion.

4.4. Limitations

This study has limitations. First, there were some methodological limitations in the included trials, which included the quasi-random method, an inadequate concealment of treatment allocation, a high loss of follow-up, the unclear age baseline and the gender or smoking status. Second, although subgroup analyses and sensitivity analyses were used to explore the heterogeneity, obvious heterogeneity still existed in some of the outcomes. There were too few studies to use subgroup analysis methods to test for variables possibly associated with heterogeneity. We are not sure whether the effectiveness of LIPUS could be affected by treatment methods, fracture location, treatment duration, and other variables. Third, although our study suggested that LIPUS treatment could reduce the time to fracture union and improve the quality of life, the minimum clinically important difference for these outcomes has not been well established, raising questions about the clinical significance of

Table 2

The GRADE evidence quality for each outcome.

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
SF-36 physical component summary scores												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	262	262	N/A	SMD 0.2 lower (0.37 to 0.02 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to full weight bearing												
3	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	259	254	N/A	SMD 0.76 lower (1.92 lower to 0.4 higher)	⊕⊕⊕0 MODERATE	CRITICAL
Time to return to work												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	None	189	177	N/A	SMD 0.06 higher (0.14 lower to 0.27 higher)	⊕⊕⊕0 MODERATE	CRITICAL
Time to fracture union												
11	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	451	436	N/A	SMD 0.65 lower (1.13 to 0.17 lower)	⊕⊕⊕0 MODERATE	CRITICAL
Incident rate of delayed union and nonunion												
8	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	37/391 (9.5%) / N/A	35/382 (9.2%) / 15.6%	RR: 1.02 (0.6–1.74)	2 more per 1000 (from 37 fewer to 68 more) / 3 more per 1000 (from 62 fewer to 115 more)	⊕⊕⊕0 MODERATE	CRITICAL

CI = confidence interval, N/A = not applicable, RR = risk ratio, SMD = standardized mean differences.

LIPUS. Thus, results of this meta-analysis should be interpreted cautiously.

4.5. Implications for future research

To gain a comprehensive understanding and full evaluation of LIPUS treatment, future trials are still needed. The design of the future trials should pay attention to the following points: Trials should use LIPUS treatment with the same duration and frequency. For example, 20 minutes once a day was the most widely used in the literature. Trials should pay attention to the methodological limitations, such as blindness, and a placebo should be used in the design of trials. And trials should report more outcomes, such as functional recovery, pain, and cost-effectiveness.

5. Conclusions

In conclusion, moderate-to-high quality evidence shows that LIPUS treatment reduces the time to fracture union and improves the quality of life without affecting functional recovery and incident rate of delayed union and nonunion. Thus, LIPUS treatment may be a good treatment modality for adults with fresh fractures. However, there is still a need for further studies with large numbers of patients to determine the clinical circumstances under which LIPUS is truly valid and the optimal approach to the use of this therapy.

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