Ultrasound and shockwave therapy for acute fractures in adults (Review)

Griffin XL, Smith N, Parsons N, Costa ML

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 2

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Ultrasound and shockwave therapy for acute fractures in adults

Xavier L Griffin[1], Nick Smith[1], Nick Parsons[1], Matthew L Costa[1]

[1]Warwick Orthopaedics, Warwick Medical School, University of Warwick, Coventry, UK

Contact address: Xavier L Griffin, Warwick Orthopaedics, Warwick Medical School, University of Warwick, Clinical Sciences Building, Clifford Bridge Road, Coventry, CV2 2DX, UK. x.griffin@warwick.ac.uk. xgriffin@mac.com.

Editorial group: Cochrane Bone, Joint and Muscle Trauma Group.
Publication status and date: New, published in Issue 2, 2012.
Review content assessed as up-to-date: 12 December 2011.

Citation: Griffin XL, Smith N, Parsons N, Costa ML. Ultrasound and shockwave therapy for acute fractures in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008579. DOI: 10.1002/14651858.CD008579.pub2.

ABSTRACT

Background

The morbidity and socioeconomic costs of fractures are considerable. The length of time to healing is an important factor in determining a patient's recovery after a fracture. Ultrasound may have a therapeutic role in reducing the time to union after fracture.

Objectives

To assess the effects of low intensity ultrasound (LIPUS), high intensity focused ultrasound (HIFUS) and extracorporeal shockwave therapies (ECSW) as part of the treatment of acute fractures in adults.

Search methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (December 2011), the Cochrane Central Register of Controlled Trials (in *The Cochrane Library* 2011, Issue 4), MEDLINE (1950 to November Week 3 2011), EMBASE (1980 to 2011 Week 49), trial registers and reference lists of articles.

Selection criteria

Randomised controlled trials evaluating ultrasound treatment in the management of acute fractures in adults. Studies including participants over 18 years of age with acute fractures, reporting functional outcomes, time to union, non-union, secondary procedures such as for fixation or delayed or non-union, adverse effects, pain, costs or patient adherence were included.

Data collection and analysis

Two authors independently extracted data from the included studies. Treatment effects were assessed using mean differences or risk ratios and, where there was substantial heterogeneity, pooled using a random-effects model. Results from 'worst case' analyses, which gave more conservative estimates of treatment effects for time to fracture union, are reported in preference to those from 'as reported' analyses.

Main results

Twelve studies, involving 622 participants with 648 fractures, were included. Eight studies were randomised placebo-controlled trials, two studies were randomised controlled trials without placebo controls, one study was a quasi-randomised placebo controlled trial and the remaining study was a quasi-randomised controlled trial without placebo control. Eleven trials tested LIPUS and one trial tested

ECSW. Four trials included participants with conservatively treated upper limb complete fractures and six trials included participants with lower limb complete fractures; these were surgically fixed in four trials. The remaining two trials reported results for conservatively treated tibial stress fractures.

Very limited data from two complete fracture studies showed no difference between ultrasound and placebo control in functional outcome. Pooled estimates from two studies found LIPUS did not significantly affect the time to return to training or duty in soldiers or midshipmen with stress fractures (mean difference -8.55 days, 95% CI -22.71 to 5.61).

Based on a 'worst case' analysis, which adjusted for incomplete data, pooled results from eight heterogeneous studies showed no statistically significant reduction in time to union of complete fractures treated with LIPUS (standardised mean difference -0.47, 95% CI -1.14 to 0.20). This result could include a clinically important benefit or harm, and should be seen in the context of the highly significant statistical heterogeneity (I^2 = 90%). This heterogeneity was not explained by the *a priori* subgroup analyses (upper limb versus lower limb fracture, smoking status). An additional subgroup analysis comparing conservatively and operatively treated fractures raised the possibility that LIPUS may be effective in reducing healing time in conservatively managed fractures, but the test for subgroup differences did not confirm a significant difference between the subgroups.

Pooled results from eight trials reporting proportion of delayed union or non-union showed no significant difference between LIPUS and control. Adverse effects directly associated with LIPUS and associated devices were found to be few and minor, and compliance with treatment was generally good. One study reporting on pain scores found no difference between groups at eight weeks.

One quasi-randomised study (59 fractures) found no significant difference between ECSW and no-placebo control groups in non-union at 12 months (risk ratio 0.56, 95% CI 0.15 to 2.01). There was a clinically small but statistically significant difference in the visual analogue scores for pain in favour of ECSW at three month follow-up. The only reported complication was infection, with no significant difference between the two groups.

Authors' conclusions

While a potential benefit of ultrasound for the treatment of acute fractures in adults cannot be ruled out, the currently available evidence from a set of clinically heterogeneous trials is insufficient to support the routine use of this intervention in clinical practice. Future trials should record functional outcomes and follow-up all trial participants.

PLAIN LANGUAGE SUMMARY

Does ultrasound treatment of broken bones in adults help improve bone healing times and reduce complications?

Broken bones (fractures) are a major cause of disability in adults. The time taken for a bone to heal (achieve "union") is an important factor in determining recovery after an injury. A minority of fractures fail to heal at all or in an appropriate period of time. This review set out to find out whether treatment with ultrasound, in a variety of forms, accelerates fracture healing and reduces complications associated with fresh (acute) fractures. A related intervention, shockwave therapy, was also examined. Typically, ultrasound treatment involves placing a special device in contact with the skin overlying the fracture site for around 20 minutes on a daily basis.

Twelve studies, involving 622 participants with 648 fractures, were included in this review. Most participants had suffered a fresh complete fracture of a single bone. The participants of two trials had incomplete or stress fractures, resulting from heavy exercise. Four trials tested the effects of ultrasound on healing of upper limb fractures and the other trials, on lower limb fractures. The most commonly investigated bone was the tibia (shin bone). Eleven trials tested low intensity pulsed ultrasound and one trial tested shockwave therapy.

Most trials compared a working ultrasound device with a sham device and thus protected against placebo effects. However, the results of many trials were probably biased because of missing data from several trial participants. Additionally, the trials were very varied; for example, in the bone that was broken and that some fractures were treated surgically. Based on analyses that adjusted for these missing data, the review found that the available evidence did not confirm that ultrasound speeded up bone healing or prevented non-union. The results from one low quality trial testing shockwave therapy were inconclusive. Few complications were reported and these were not related to the ultrasound or shockwave therapy.

BACKGROUND

Description of the condition

The morbidity and socioeconomic cost of fractures (broken bones) is considerable. Whilst most fractures unite, between 5% and 10% of long bone fractures are associated with delayed or non-union, resulting in significant morbidity, loss of independence and loss of productivity (Aaron 2004). The length of time to healing is also an important factor in determining recovery after a fracture (Heckman 1997). Several interventions, including ultrasound, have been proposed to enhance and accelerate bone healing, and potentially reduce the incidence of the complications associated with fractures and their treatment (Einhorn 1995; Hadjiargyrou 1998).

Description of the intervention

Ultrasound, comprising high frequency sound waves, is a form of mechanical stimulation that is delivered via a special device to the fracture site. For closed fractures (where the overlying soft tissue envelope remains intact), the device is typically placed in contact with the skin overlying the fracture site and left in position for around 20 minutes on a daily basis.

There are three modalities of ultrasound used in clinical practice:

- Low intensity pulsed ultrasound (LIPUS)
- High intensity focused ultrasound (HIFUS)
- Extracorporeal shock wave therapy (ECSW)

How the intervention might work

It is known that bone formation and fracture healing are influenced by mechanical factors. It is possible that ultrasound might work by reproducing the effect of functional loading by inducing low level mechanical forces at the fracture site. The mechanisms have not been fully elucidated (Hadjiargyrou 1998) but it is likely that ultrasound influences healing at multiple points during the fracture healing process.

Although it is thought that all three ultrasound modalities work in a similar way in the body, the effectiveness of each modality does appear to be different (Reher 1997; Wang 1994). Thus, these three modalities will be considered separately in this review.

Why it is important to do this review

The ability to improve fracture healing would have a large clinical and socioeconomic impact. Whilst there is currently no consensus on the role of ultrasound, its use is becoming increasingly widespread (Victoria 2009). A recent systematic review has identified a broad evidence base concerning the use of ultrasound in the management of acute fractures (Griffin 2008). This review updates the summary of the available best evidence on the use of ultrasound for acute fractures in order to inform practice and highlight areas in need of further research.

OBJECTIVES

To assess the effects of any ultrasound therapy used as part of the treatment of acute fractures in adults.

We planned to make the following comparisons:

1. Low intensity pulsed ultrasound (LIPUS) versus control (sham ultrasound or none)

2. High intensity focused ultrasound (HIFUS) versus control (sham ultrasound or none)

3. Extracorporeal shockwave therapy (ECSW) versus control (sham ultrasound or none)

Participants might additionally receive a standard-of-care treatment which would be the definitive treatment routinely used in clinical practice for the treatment of the fracture. This might include, but not be limited to, non-surgical treatment, such as plaster cast immobilisation, or surgical treatment such as external or internal fixation, using various devices such as intramedullary nailing.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised (a method of allocating participants to a treatment which was not strictly random; e.g. by date of birth, hospital record number, alternation) controlled clinical studies evaluating any type of ultrasound treatment in the management of acute fractures in adults.

Types of participants

Any skeletally mature adults, over the age of 18 years, with acute fractures. Trials evaluating treatment for delayed or non-union were excluded.

Types of interventions

Trials of all three types of ultrasound (low intensity pulsed ultrasound (LIPUS), high intensity focused ultrasound (HIPUS), and extracorporeal shock wave therapy (ECSW)) were eligible provided the treatment was compared with either no additional treatment or a placebo (sham ultrasound). Ultrasound could be the only treatment, but would more usually be an adjunct to a standard-of-care treatment applied to all trial participants. The standard-of-care treatment could be non-surgical or surgical. Trials comparing ultrasound with other interventions were excluded. Each modality of ultrasound treatment was considered in a separate comparison as described in the Objectives.

Types of outcome measures

Functional recovery, including return to former activities, was the prime focus of the review. However, we anticipated that most trials would not report patient-reported outcome measures but would focus instead on fracture healing outcomes.

The definition of a healed fracture is contentious. For the purpose of this review we adopted the widely accepted definitions in the literature. A fracture is healed when callus is present bridging three of four cortices on orthogonal radiographs or there is an absence of pain and movement at the fracture site or both. It was expected that most studies would report the time to union for each participant. These are the most frequently reported statistics when studies are published in this field. However, it was possible that some studies might have presented a proportional analysis of healed fractures at a number of fixed time points after treatment.

Primary outcomes

The primary outcomes assessed were:

- Overall quantitative functional improvement of the participant using recognised patient-reported outcome measures and the return to normal activities, including work
- Time to fracture union

Secondary outcomes

The secondary outcomes assessed were:

- Confirmed non-union or secondary procedure, such as for failure of fixation or for delayed or non-union
- Adverse effects
- Pain using validated pain scores
- Costs
- Patient adherence

Timing of outcome assessment

We anticipated that some studies might have reported proportional incidence of union at several time points rather than a time-to-event analysis. We planned to try to group these assessments into three categories: short (up to three months), medium (between three and twelve months) and long-term follow-up (greater than one year) (*see* Unit of analysis issues). These time points were a necessary compromise to encompass data from studies which included different bones with different typical healing times.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (December 2011), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2011, Issue 4), MEDLINE (1950 to November Week 3 2011) and EMBASE (1980 to 2011 Week 49). There were no constraints based on language or publication status.

In MEDLINE, the subject-specific search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials: sensitivity-maximising version (Lefebvre 2009). In EMBASE, the subject-specific search was combined with the SIGN strategy for randomised controlled trials (*see* Appendix 1 for all strategies).

Current Controlled Trials and the WHO International Clinical Trials Registry Platform were also searched in order to identify ongoing and recently completed trials.

Searching other resources

We searched reference lists of articles retrieved from the electronic search. We contacted experts in the field for any additional or unpublished articles.

Data collection and analysis

Selection of studies

Two authors (XG and NS) independently selected the studies for inclusion in the review based upon the criteria defined above. Initially the titles and abstracts of all the retrieved studies were reviewed to determine potential eligibility. The full text of each study in this shortlist was then reviewed to determine which studies were eligible for inclusion in the review. Any disagreement was settled by consensus between all authors of the review.

Data extraction and management

Two authors (XG and NS) independently extracted data from the included studies using a pre-piloted version of the Cochrane Bone, Joint and Muscle Trauma Group's data extraction form. The review statistician (NP), who was independent from study selection, collated and processed the extracted outcome data.

Assessment of risk of bias in included studies

The included studies were each assessed for the risk of bias using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2008). This tool incorporates assessment of randomisation (sequence generation and allocation concealment), blinding (trial participants and personnel, and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias. Other sources of bias included selection bias, where we assessed the risk of bias from imbalances in key baseline characteristics (age, sex and smoking behaviour). We assessed the risk of bias associated with a) blinding and b) completeness of outcomes for patient-reported outcomes and objective outcomes separately. Different considerations apply to the primary outcome of fracture healing, which is variably defined in the literature. We anticipated that studies may define healing clinically and radiographically. We anticipated that bias might be introduced by inter and intra-observer error in the reading of radiographs. We ascribed a low risk to studies in which a blinded panel of specialist radiologists or orthopaedic surgeons read the radiographs. Studies employing other methodologies, such as multiple independent observers, were ascribed a high risk of bias.

Measures of treatment effect

We had intended to assess time to fracture union after treatment using a (log) hazard ratio and 95% confidence intervals. However, as we had anticipated, fracture union was either reported as a proportion of fractures healed at each follow-up time-point, or the mean time to union. Where studies reported a proportion of fractures healed we calculated the mean time to union (and standard deviation) assuming that each fracture had healed at the end of the interval between follow-up time-points. From the reported and calculated mean times to union we calculated standardised mean differences and 95% confidence intervals. This reflected the widely differing mean times to union in different studies including different bones. Risk ratios with 95% confidence intervals were used to express the intervention effect for dichotomous outcomes. For continuous data, such as pain scores, we calculated mean differences with 95% confidence intervals.

Unit of analysis issues

It was expected that most studies would report functional improvement scores at a number of follow-up times; for example, at six and twelve weeks. Dependent on the nature of reporting, separate analyses were to be made at each of the commonly reported occasions, representing perhaps, short, medium and long-term follow-up. It was expected that all studies would report simple parallel group designs. However, if other designs were reported (e.g. cluster randomised designs) generic inverse variance methods were to be used to combine data where appropriate.

Dealing with missing data

We sought additional information from the authors of the included studies where the published information or data were incomplete. Where standard deviations were not specifically reported, we attempted to determine these, if available, from standard errors, confidence intervals or exact P values. We did not expect there to be substantial missing data for studies in this research area. Where small amounts of data were missing for proportional outcomes, that could not be reliably determined from the authors, then these outcomes were initially classed as treatment failures and a sensitivity analysis conducted to test the effect of this assumption. For continuous measures, in order to determine a conservative estimate of any treatment effect, we assumed that healing times of participants in the treatment group for whom data were missing lay at the extreme of the distribution (two standard deviations from the reported mean). Conversely, for participants in the control group we assumed the distribution was unaffected by the missing data. Pooled effect sizes were presented with and without these adjustments to check the effect of these assumptions. We refer to the adjusted analyses as 'worst case' analyses and the unadjusted as 'as reported' analyses.

Assessment of heterogeneity

The degree of statistical heterogeneity between studies was assessed graphically using the Chi^2 test and I^2 statistic (Higgins 2003). A conservative P value for Chi^2 of < 0.1 was set to indicate significant heterogeneity between studies. If the heterogeneity statistic indicated significant heterogeneity and one or more studies appeared to be clear outliers, then data for these studies would be checked carefully for errors or other methodological reasons why they might differ from the other studies. We planned that if good reason was found why the studies differed from the majority then this would be noted and reported and the studies removed from the main meta-analyses; however all analyses would be performed with and without outlier studies in the event that any were excluded (sensitivity analysis).

Assessment of reporting biases

Our search strategy attempted to reduce the risk of missing relevant studies. We planned to complete a funnel plot if a sufficient number of studies had been available.

Data synthesis

Treatment effects from studies reporting proportional outcomes were summarised using risk ratios and combined using the Mantel-Haenszel method. Continuous outcome measures were converted to standardised mean differences to assess the treatment effect and generic inverse variance methods were used to combine data. Confidence intervals were reported at the 95% level and initially the fixed-effect model was used for meta-analyses. Where there was significant heterogeneity, we used the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis to explore possible sources of heterogeneity when significant heterogeneity was present. Two possible subgroup analyses were identified *a priori*:

1. Upper versus lower limb fractures. This was a pragmatic proxy for weight bearing versus non-weight bearing bones.
2. Smokers versus non-smokers.

Sensitivity analysis

We conducted *post hoc* sensitivity analyses to explore the causes of statistical heterogeneity. We also explored the effect of excluding studies because they appeared to differ markedly from the majority of studies. For each of these analyses, a pooled estimate of the effect size was reported with and without these studies.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

A total of 954 references were retrieved using the search strategy. Thirty-six references were thought to be relevant after screening the abstracts and the full text article was retrieved for each. Some of these references were reports of the same study. From these, 12 studies were included in the review and three were excluded. Searches of study reference lists, trials registers and contact with experts, revealed three further studies, one of which is ongoing (*see* Characteristics of ongoing studies), and two, one of which was located after the main search, are awaiting assessment (*see* Studies awaiting classification).

Included studies

Twelve studies, involving 622 participants with 648 fractures, were included in the review. Details of the individual studies are shown in the Characteristics of included studies.

Design

Eight studies were randomised placebo-controlled trials and two studies (Mayr 2000; Strauss 1999) were randomised controlled trials without placebo controls. Of the two quasi-randomised studies, one was placebo-controlled (Leung 2004) and the other (Wang 2007) was not.

Cook 1997 reported a subgroup analysis by smoking status of participants recruited in the trials reported by Heckman 1994 and Kristiansen 1997. These data were not doubly entered into the analyses but have been used to inform an *a priori* subgroup analysis in this review.

Sample sizes

Each of the included studies included relatively few participants:

- Emami 1999: 30 participants (15:15, ultrasound:control).
- Handolin 2005: 30 participants (15:15, ultrasound:control).
- Handolin 2005a: 22 participants (11:11, ultrasound:control).
- Heckman 1994: 97 participants (48:49, ultrasound:control).
- Kristiansen 1997: 85 fractures in 83 participants (40:45, ultrasound:control).
- Leung 2004: 30 fractures in 28 participants (16:14, ultrasound:control).
- Lubbert 2008: 120 participants (61:59 ultrasound:control).
- Mayr 2000: 30 fractures in 29 participants (15:15, ultrasound:control).
- Rue 2004: 58 fractures in 40 participants (21:19, ultrasound:control).
- Strauss 1999: 20 participants (10:10, ultrasound:control).
- Wang 2007: 59 fractures in 56 participants (28:31, ECSW:control).
- Yadav 2008: 67 participants (39:28, ultrasound:control).

Settings

The studies that reported outcomes in participants with complete fractures were set in hospital Trauma and Orthopaedic Departments. These studies were based in a wide variety of countries: Sweden (Emami 1999), Finland (Handolin 2005; Handolin 2005a), USA (Heckman 1994; Kristiansen 1997; Strauss 1999), China (Leung 2004), Netherlands (Lubbert 2008), Germany (Mayr 2000) and Taiwan (Wang 2007). The study reported by Kristiansen 1997 was a multi-centre study. Rue 2004 reported

outcomes in American midshipmen with stress fractures presenting to a military clinic. Yadav 2008 reported outcomes in Indian soldiers with stress fractures presenting to a military clinic.

Participants

The majority of studies reported outcomes from participants with conservatively managed fresh fractures; of these, Heckman 1994 reported data from fractures of the tibia, Strauss 1999 fractures of the fifth metatarsal, and the remainder from upper limb fractures (Kristiansen 1997: distal radius; Lubbert 2008: clavicle; Mayr 2000: scaphoid). Three studies reported outcomes from participants with operatively managed fractures of the tibia (Emami 1999; Leung 2004) or tibia and femur (Wang 2007), and two reported results from participants following internal fixation of lateral malleolus (ankle) fractures (Handolin 2005; Handolin 2005a).

Two studies reported outcomes from participants with acute stress fractures of the tibia (Rue 2004; Yadav 2008).

Interventions

All the included studies reported the use of LIPUS except Wang 2007, which tested ECSW therapy. The nine placebo-controlled LIPUS trials used a sham ultrasound machine, which was deactivated.

The LIPUS treatments were very similar across the included studies. Participants given the test treatment received ultrasound treatment for 20 minutes each day for a total cumulative time of approximately 24 hours. The ultrasound signal was composed of a 200 μs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2.

All 10 studies of participants with complete fractures reported the effectiveness of the test treatment in addition to a method of bony stabilisation. In five studies, stabilisation was achieved with either a plaster or a brace (Heckman 1994; Kristiansen 1997; Lubbert 2008; Mayr 2000; Strauss 1999). Internal fixation was used in the remaining studies (Emami 1999; Handolin 2005; Handolin 2005a; Leung 2004; Wang 2007).

Outcomes

A mixture of outcomes was reported. The majority of studies reported time to radiographic union using plain radiographs as the primary measure of efficacy (Emami 1999; Handolin 2005a; Heckman 1994; Leung 2004). Mayr 2000 used computed tomography to determine fracture union. Each of these studies measured union at multiple time points at various intervals (related to fracture site) from which mean time to union was derived. Wang 2007 and Strauss 1999 reported the proportion of radiographic union only. Handolin 2005, Lubbert 2008, Rue 2004 and Yadav 2008 presented patient-reported outcomes: a region-specific functional score, subjective fracture union and return to work (Rue 2004 and Yadav 2008) respectively.

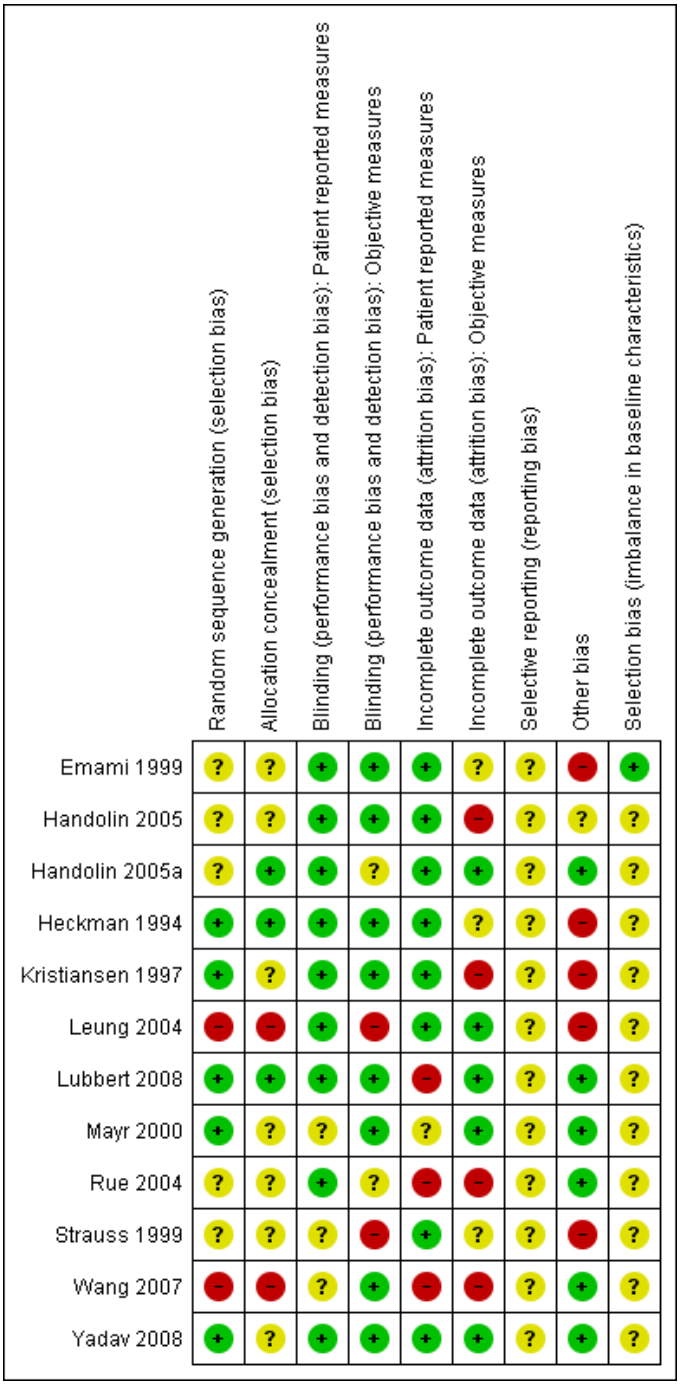
Excluded studies

The reasons for exclusion of three studies are detailed in the Characteristics of excluded studies. Two studies reporting on costs were excluded because the data for the economic analysis were not obtained from a randomised trial (Busse 2005; Heckman 1997). Basso 1998, a quasi-randomised trial, did not focus on fracture healing nor report relevant outcomes to this review.

Risk of bias in included studies

The quality of reporting of the studies was varied. A summary of the assessment of the risk of bias in each study can be found in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The majority of studies were randomised, although the sequence generation and methods of allocation were frequently poorly reported. Only two studies (Heckman 1994; Lubbert 2008) were rated at low risk of selection bias. The two quasi-randomised studies (Leung 2004; Wang 2007) were considered as being at high risk of selection bias.

Blinding

The majority of studies used a deactivated ultrasound unit to blind the allocation. However, the unit used by Leung 2004 was externally dissimilar to the intervention unit and therefore the blinding in this study may have been compromised. Three studies (Mayr 2000; Strauss 1999; Wang 2007) were not placebo-controlled. However, blinded outcome assessment was reported in Wang 2007.

Incomplete outcome data

None of the included studies explicitly reported, or justified where absent, all of the outcome data. We were successful in contacting authors of three trials (Heckman 1994; Kristiansen 1997; Lubbert 2008) for missing data. In general the proportion of missing data was sufficiently low, so that 'as reported' and 'worst case' analyses were similar. We judged three studies at high risk of attrition bias: Handolin 2005a because of the high (47%) and unaccounted loss to follow-up at 18 months follow-up; Rue 2004 because of a high and attrition rate (35%), in part resulting from post-hoc selection decision to limit their analysis to tibial stress fractures; and Wang 2007 because of inappropriate handling of participants with adverse events.

Selective reporting

The overall quality of the reporting of the included studies was poor. No protocols were available for comparing with the trial reports. The reporting of the methods and results was frequently mixed so that determining the risk of bias from selective reporting of outcomes was very difficult. However, there was no clear evidence of selective outcome reporting.

Other potential sources of bias

It was clear from all of the studies that, for obvious practical reasons, it was impossible to assess healing in each participant every day. Typically, participants were assessed at fixed follow-up intervals that varied between studies. This inevitably led to a lack of precision in estimates of healing times. However, we see no reason why this process should have differed between treatment groups in any study, so would not expect there to be any bias in estimates of the treatment effects. However, this may, at least in part, explain the significant heterogeneity in observed healing times between studies.

There were often insufficient data, in particular relating to smoking status, to judge whether there were major imbalances between the treatment and control groups in baseline characteristics. Only Emami 1999 was considered at low risk for this item.

Effects of interventions

Low intensity pulsed ultrasound versus control

Primary outcomes

Functional outcomes

Complete fractures

Only Lubbert 2008 provided data for return to work. There was no significant difference between the treatment and control groups using either 'as reported' data (mean difference (MD) 1.95 days, 95% CI -2.18 to 6.08 days) or when based upon a 'worst case' analysis (MD 1.42 days, 95% CI -2.40 to 5.24) (*see* Analysis 1.1). Handolin 2005 reported no significant difference in the Olerud-Molander score between treatment and control groups in 16 participants (53% of the 30 randomised participants) at 18 months follow-up. However, insufficient data were reported to be able to confirm this report and efforts to contact the authors were unsuccessful.

Stress fractures

Rue 2004 and Yadav 2008 both reported time to the return to training or duty in midshipmen and military recruits respectively. There was no significant benefit of LIPUS in the treatment of stress fractures of the tibia using 'as reported' data (MD -8.55 days, 95% CI -22.71 to 5.61) (*see* Analysis 1.2). There were insufficient baseline data from Rue 2004 to conduct a 'worst-case scenario' analysis. There was considerable heterogeneity in the pooled estimate (I^2 = 78%); the difference in the findings of the two trials is also clearly visible in the analysis.

Time to union

Although time to union data were available in most studies, the definition of union, timing of assessment and statistical analysis were variable. Efforts made to contact authors from each study in order to carry out appropriate intention-to-treat analyses were partly successful.

Four studies defined union radiographically (Emami 1999; Handolin 2005a; Kristiansen 1997; Mayr 2000). Where data were presented from surgeons and radiologists, we report only those based upon radiologists' opinions. Three studies defined union as a combined clinical and radiographic finding with similar definitions of radiographic union (Heckman 1994; Kristiansen 1997; Leung 2004). Lubbert 2008 defined union based upon participants' self-reports.

Each of the studies reporting this outcome only reported a per-protocol analysis, where the reported data are for those participants who complied with the protocol, including follow-up. These 'as reported' data are presented in Figure 2 (Analysis 1.3). Those authors who were successfully contacted explained that such an analysis was necessary because the data were missing due to the haphazard follow-up of some participants. This 'as reported' analysis demonstrated a significant benefit from LIPUS therapy (standardised mean difference (SMD) -0.69, 95% CI -1.31 to -0.07). However, the highly significant and substantial heterogeneity overall and for the upper and lower limb subgroups is also evident ($P < 0.00001$; $I^2 = 86\%$). A conservative, or 'worst case' analysis, which attempted to include the missing data is presented in Figure 3 (Analysis 1.4; details of the imputation method described in Dealing with missing data), shows no significant difference between the treatment and control groups (SMD -0.47; 95% CI -1.14 to 0.20). The subgroup analysis by upper and lower limb fracture location did not significantly alter this finding.

Figure 2. Forest plot of comparison: 1 LIPUS versus control, outcome: 1.3 Time to fracture radiographic union (days): 'as reported' analysis.

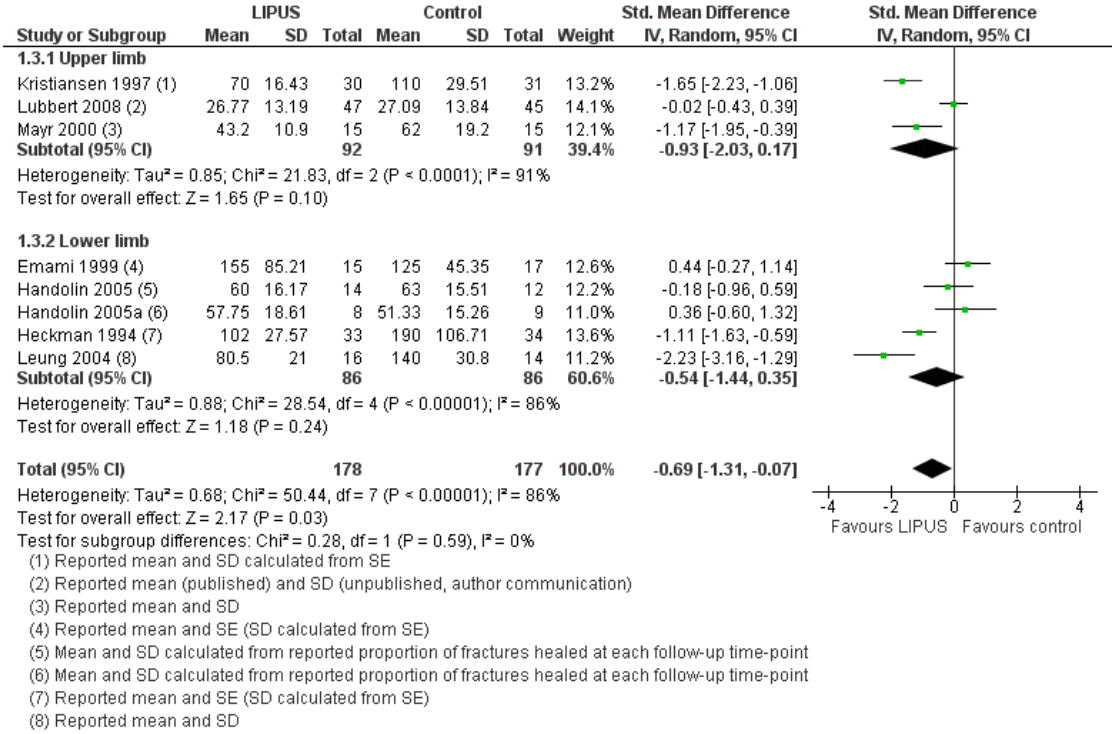
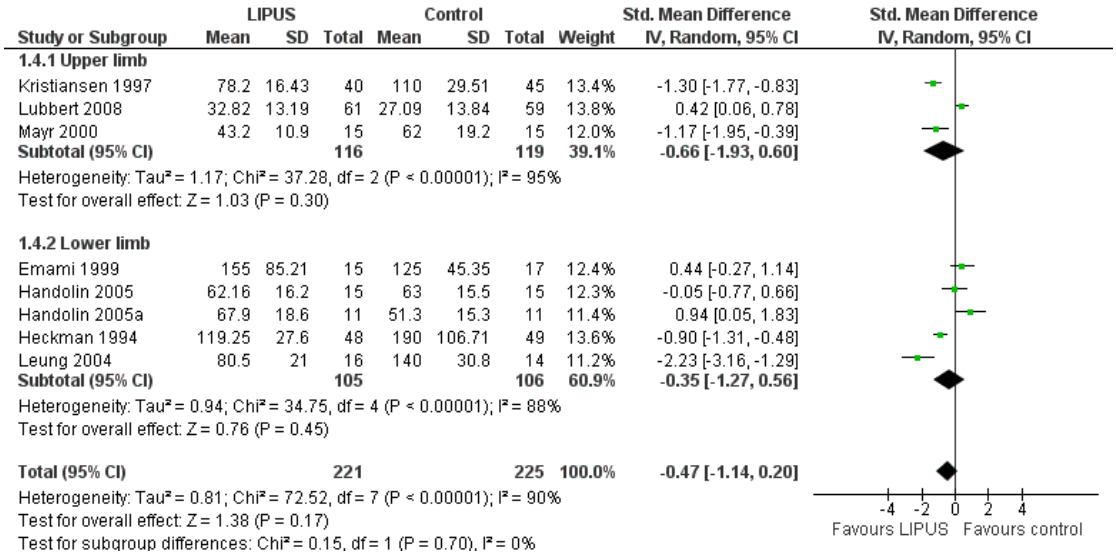
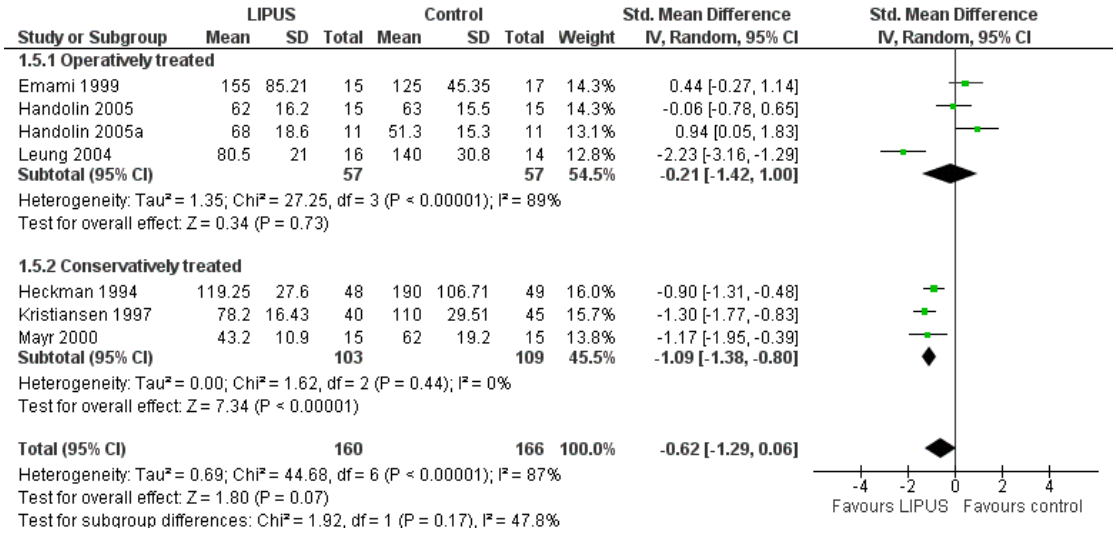


Figure 3. Forest plot of comparison: 1 LIPUS versus control, outcome: 1.4 Time to fracture radiographic union (days): worst case analysis.



As reported above, there was very substantial statistical heterogeneity both in the pooled estimate of effect from all the studies and in the subgroup analyses (I^2 = 90% for worst case analysis). We considered that this may be explained by the clinical variation in the treatment (operative versus conservative) of the participants between studies. We thus subgrouped the worst case analysis data by operative and conservative management (Figure 4; Analysis 1.5). The effect estimates from studies of participants with operatively treated fractures were substantially heterogenous and the precision of the estimate poor. The majority of the data from participants whose fractures were managed conservatively was consistent, excepting those from one study (Lubbert 2008). Importantly, Lubbert 2008 defined union quite differently from the other studies based upon participants' self-reports and this may be a reason for the observed heterogeneity in the estimate of effect. Excluding these data from Lubbert 2008 suggested a significant treatment effect due to ultrasound in this subgroup (SMD -1.09, 95% CI -1.38 to -0.80). However, the test for subgroup differences did not indicate that the findings of the two subgroups were statistically significantly different from each other (Chi^2 = 1.92, df = 1 (P = 0.17), I^2 = 47.8%).

Figure 4. Forest plot of comparison: 1 LIPUS versus control, outcome: 1.5 Time to fracture union (days) subgrouped by operation: worst case analysis.



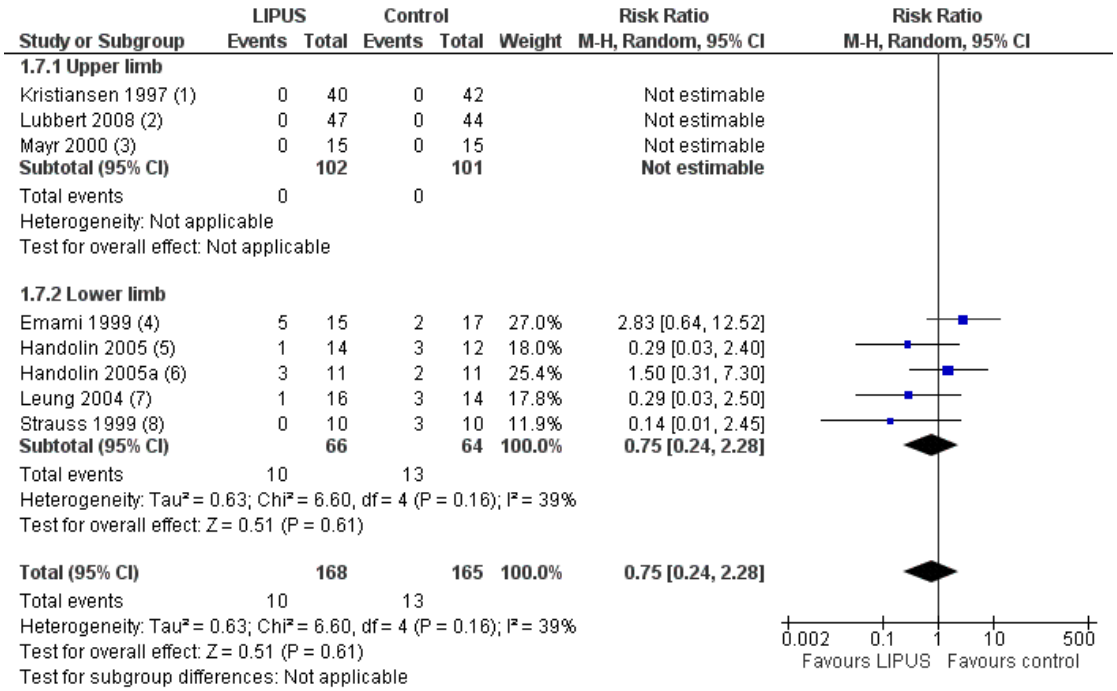
The trial reports of the included studies failed to present adequate data to conduct the two described *a priori* subgroup analyses in this review. However, Cook 1997 reported a retrospective subgroup analysis split by smoking status of the data from Heckman 1994 and Kristiansen 1997 (*see* Analysis 1.6). These results show that the effects of LIPUS were similar in both smokers and non-smokers (test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), I^2 = 0%).

Secondary outcomes

Delayed union and non-union

Figure 5 (Analysis 1.7) shows the available data for delayed or non-union. The different follow-up times and definition of this outcome are shown in the footnotes. The available data for all three upper limb fracture trials indicated that all fractures had eventually healed. Overall, the pooled data from five lower limb studies showed no significant difference between the treatment and control groups in this outcome (10/168 versus 13/165; RR 0.75; 95% CI 0.24 to 2.28).

Figure 5. Forest plot of comparison: 1 LIPUS versus control, outcome: 1.7 Delayed or non-union (as reported analysis).



Adverse events

Seven studies reported on adverse events. Emami 1999 reported no difference in the numbers of participants developing compartment syndrome (1 versus 2) or deep infection (0 versus 2), or requiring the removal of locking screws (revision dynamisation: 2 versus 1). Several venous thromboembolic events were reported. Handolin 2005 found four deep vein thromboses, three of which were in the placebo group, Handolin 2005a reported one deep vein thrombosis in the placebo group and one participant suffered a pulmonary embolus in Heckman 1994. Three studies (Heckman 1994; Leung 2004; Lubbert 2008) reported a low incidence of self-resolving conditions (skin irritation, erythema and swelling), which did not lead to any trial protocol violations, and occurred in both treatment and placebo groups. Kristiansen 1997 reported that there had been no adverse reactions or complications attributable to the device reported during their study.

Pain

Lubbert 2008 reported visual analogue scores for pain (Analysis 1.8). An estimate from both the 'as reported' analysis and 'worst case' analysis showed no significant treatment effect (worst case analysis: MD -0.02, 95% CI -0.54 to 0.50) (Analysis 1.8).

Cost

None of the studies reported a health economics analysis.

Adherence

Several studies reported the recordings from both internal timers, contained within the devices, and participant treatment diaries. Emami 1999 reported good adherence to the trial protocol, with no significant difference between the treatment and placebo

groups' usage or diary records, both of which closely matched the protocol requirements (ultrasound: mean 23.4 hrs, SD 0.8; placebo: 22.3 hrs SD 1.0; participant diary: mean 24.6 hours). Kristiansen 1997 reported similar findings (ultrasound: mean 62 hours; placebo 64 hours) which compared favourably with the trial protocol requirement. Other studies (Handolin 2005; Heckman 1994) reported adherence less formally but did highlight good participant compliance. For instance, Handolin 2005 reported comparable duration of use of the ultrasound device (mean: 40.7 days versus 39.9 days). Participants of Rue 2004 were administered treatments by trial personnel so that adherence was easily determined. Both LIPUS and control groups missed a similar proportion of treatments, which was less than approximately 20% of all treatments in each group.

Extracorporeal shock wave therapy (ECSW) versus control

ECSW was tested only in Wang 2007, which compared ECSW with no ECSW in 56 patients with 59 fractures of the tibia or femur. Results in this trial were reported for fractures instead of participants; however, it was not possible to correct for the unit of analysis discrepancy.

Primary outcomes

Wang 2007 did not report on functional outcome or time to union.

Secondary outcomes

Delayed union and non-union

Wang 2007 found there was no significant effect of ECSW on non-union (all cases involved fractures of the femur) at 12 months (*see* Analysis 2.1: RR 0.56; 95% CI 0.15 to 2.01). A sensitivity analysis where the fractures of the two excluded participants were assumed not to have united at 12 months gave similar results (RR 0.63, 95% CI 0.21 to 1.93).

Adverse events

Wang 2007 reported one case of deep infection and osteomyelitis in each group (both patients were excluded from the final analyses) and five cases of superficial infection (2/27 versus 3/30), all of which resolved with antibiotics and wound care. There were no other complications, including those directly related to shockwave treatment.

Pain

Wang 2007 found a clinically small but statistically significant difference in visual analogue scores for pain in favour of ECSW, from both the 'as reported' analysis (MD -0.87, 95% CI -1.31 to -0.43) and the 'worst case' analysis (MD -0.80, 95% CI -1.23 to -0.37) (Analysis 2.2). Similarly, pain scores were significantly lower in the ECSW group at six (1.19 versus 2.47) and 12 months (0.15 versus 0.77).

Others

Wang 2007 reported neither measures of cost nor adherence.

DISCUSSION

Summary of main results

The review presented evidence from 11 trials comparing low intensity pulsed ultrasound (LIPUS) versus control, and one trial comparing extracorporeal shock wave therapy (ECSW) versus control. We found no trials evaluating high intensity focused ultrasound. The included trials form a clinically heterogeneous group of studies, which included participants with a range of acute fractures, treated in a variety of ways. The fractures were complete in 10 trials and stress fractures in two trials.

Low intensity pulsed ultrasound versus control

Primary outcomes

Neither of the two studies of complete fractures reporting functional outcomes found a difference between LIPUS compared with placebo control. Pooled results from two studies found that LIPUS had no significant effect on the time to return to training for soldiers or midshipmen with tibial stress fractures.

Data were pooled from eight small studies that reported the time to union of a complete fracture as a primary outcome following LIPUS. While the 'as reported' analysis indicated a significant benefit of LIPUS on time to union, a purposefully conservative 'worst case' analysis showed there was no statistically significant reduction in healing time of fresh fractures treated with LIPUS. However, a potential for greater benefit than harm from LIPUS should not be ruled out and the highly significant heterogeneity in the results indicates this potential may apply for some categories of patients. The two prespecified subgroup analyses by upper and lower limb fractures and smoking status did not show any differences between the subgroups. An additional subgroup analysis, comparing conservatively with surgically treated fractures, raised the possibility that LIPUS may be more effective in reducing healing time in conservatively managed fractures. However, while the

results from the subset of the three trials of conservatively treated fractures (that measured time to union radiographically) were homogeneous, the test for differences between the conservative and surgical treatment subgroups was not statistically significantly different.

Secondary outcomes

Several studies reported the proportion of participants going on to develop delayed union or non-union. However, the reporting, measurement and definition of these outcomes varied. We found no significant difference between the treatment and control groups in the pooled result.

Importantly, the compliance with LIPUS treatment was found to be good and the adverse effects directly associated with its use (or associated devices) were found to be few and minor. Thus this review provides reasonably good evidence that such a treatment would be acceptable to patients in general clinical practice.

Only one study reported pain scores using visual analogue scales, finding no difference between groups at eight weeks. There were no data on costs.

Extracorporeal shock wave therapy (ECSW) versus control

The small quasi-randomised trial evaluating ECSW, for tibia and femur fractures, did not report on functional outcomes nor time to union. It found no significant improvement in the proportion of people achieving union following ECSW at 12 months. There were, however, clinically small but statistically significant differences in the visual analogue scores for pain in favour of ECSW at three, six and 12 month follow-ups. The only reported complication was infection, with no significant differences between the two groups.

Overall completeness and applicability of evidence

Completeness of the evidence

This review includes data from 11 studies, conducted in seven countries, testing the use of ultrasound for acute fractures in a total of 566 adults. Nine studies concerned the treatment of complete fractures; Rue 2004 and Yadav 2008 reported the outcomes in participants with stress fractures. The evidence for ECSW therapy was restricted to that from one small study involving 56 adults (Wang 2007). We found no trials evaluating high intensity focused ultrasound. While the total population represents a minute proportion of the acute fractures occurring annually, the fractures included in the studies are some of those characterised by higher incidences of delayed and non-union.

Few of the studies reported functional patient reported outcome measures or return to limb function or work. There was a considerable proportion of data missing for time to union, the other primary outcome of this review. This in part may reflect the difficulties in measuring this outcome. There was little evidence regarding pain or adverse events. Participant adherence to the treatment protocols was reported to an extent.

Application of the evidence to current practice

The included studies reported the use of ultrasound in a wide variety of settings and participants. Most settings were typical hospital settings, such as in Europe and the United States. The participants included those with fractures of the upper or lower limbs, which were treated either surgically or conservatively. Although these populations were highly heterogeneous, they are still representative of the type of fracture populations, generally at higher risk of delayed healing and non-union, for which treatment adjuncts might be considered.

Clinical practice varies worldwide but LIPUS remains a specialist treatment usually only considered for, or administered to, patients with fractures at risk of delayed union or non-union. The evidence from this review would not seem to encourage the wider clinical application of LIPUS at this time. It does, however, support the widely held view that LIPUS is safe and acceptable to patients.

Quality of the evidence

Sources of systematic error

The quality of reporting of the included studies was moderate only, with insufficient details to judge risk of bias. All bar two studies were randomised, but in only three could we assign a low risk of selection bias relating to allocation concealment. Most trials were blinded through the use of sham devices but even so, the lack of identical devices in Leung 2004 put this quasi-randomised trial at high risk of performance and detection bias.

All of the studies were small and therefore the likelihood of an imbalance in the baseline characteristics is high. This could be unknown or not reported; for example, only three studies adequately report the baseline smoking behaviour of the participants (Emami 1999; Heckman 1994; Kristiansen 1997).

There was also a considerable proportion of data missing. Several of the lead authors of the studies were contacted during this review and each reported that they had struggled to maintain participant compliance with the demanding follow-up schedule required to determine time to union. We have chosen to handle the missing data in such a way to make a conservative estimate of any treatment effect.

Other sources of error

The individual studies reported here are small and often underpowered. This is reflected in the imprecision and heterogeneity of the study estimates of treatment effects. The largest pool of data concerned the time to fracture union. Reported data from 355 participants were available to determine the effect of LIPUS on the time to fracture union. This might be sufficient to detect a large, clinically relevant effect, although the problem of missing data cannot be ignored. The number of participants included in the other reported pooled analyses is lower, and therefore the conclusions about these important outcomes are necessarily even more tentative.

The primary outcome of fracture healing is variably defined in the literature. As anticipated, we found that studies defined healing clinically and radiographically. This reflects the difficulty that is inherent in the assessment of union. The choice of measurement tool and the timing of assessments of union varied between studies. Radiographic union commonly follows behind clinical union and can be difficult to determine from plain radiographs. None of the included studies used a panel of independent radiologists to assess radiographic union.

Potential biases in the review process

None of the authors of this review have been involved in any of the included trials or have any commercial or other conflict of interest.

We predominantly searched the published literature. Despite efforts to contact experts we have not found any unpublished data. Given that trial registration was limited during the period over which most of these studies were conducted, it is possible that commercially sponsored negative trials were not published. We have also not searched conference abstracts. It is therefore possible that there are other trials and trial data that have not been included in this review. It is not possible to estimate the potential effects of these on the review findings. However, some reassurance can be gained from the finding that a recent systematic review by Busse 2009 found no additional studies that fulfilled our inclusion criteria.

There was significant heterogeneity in the meta-analyses. We conducted a *post hoc* sensitivity analysis to try to explore the sources of heterogeneity between the studies. We made these decisions through consensus with a view to dealing with the available data in a pragmatic manner. However, the decisions regarding the pooling of data were necessarily subjective and may be a cause of bias. The rational for our conjecture of a difference between conservatively and operatively (where rigid fixation methods are used) treated fractures is that in the former, ultrasound might cause micromotion at the fracture site leading to accelerated union, whereas in the latter such micromotion might be impossible and any benefit of ultrasound lost. This hypothesis was not confirmed by the data available so far to this review.

We have attempted to contact the authors of included studies to retrieve missing data with mixed success. There may be a systematic difference between those authors who we have been able to contact and those that we have not. Some existing data have therefore been excluded or not retrieved by this review.

Agreements and disagreements with other studies or reviews

The findings of this review are in keeping with a recent systematic review on the effects of LIPUS for fractures (Busse 2009). Busse 2009 also included trials testing the effects of LIPUS on non-union (one trial) and 'distraction osteogenesis' (three trials). In keeping with our review, Busse 2009 observed the conflicting results from the included trials and concluded that the evidence, while promising, was not enough to establish the role of LIPUS in the management of fractures.

AUTHORS' CONCLUSIONS

Implications for practice

This review highlights the limitations of the available evidence on therapeutic ultrasound for acute fractures in adults. Currently, the best assessment of the clinical effectiveness of LIPUS for complete or stress fractures in adults does not support the routine use of this intervention in clinical practice.

Implications for research

The identification of three unpublished trials, the largest of which is ongoing, points to importance of both the timely publication of the results of these trials and the regular updating of this review. Two of these trials involve surgically treated tibial fractures and one involves conservatively treated tibial fractures. While conclusive evidence on time to union may result from the largest trial (TRUST (Full)) should it recruit 500 participants, it is regrettable that the opportunity to collect patient-reported outcome measures appears to have been overlooked. Any future research, which should involve secure randomisation and placebo controls, on the use of ultrasound for acute fractures should focus on patient-reported outcome measures to determine if the possible benefit of ultrasound in terms of fracture healing translates into a tangible benefit to patients. Trials should conform to reporting standards as set out in the CONSORT statement, including reporting the results of all trial participants (Boutron 2008).

ACKNOWLEDGEMENTS

We would like to thank the trial authors Jason Busse, Joan McCabe, James Heckman and Pieter Lubbert, each of whom responded positively to our requests for further information about their studies. We would also like to thank Anette Bluemle and Juliane Ried from the German Cochrane Centre for their help in translation of one of the studies.

The authors would like to thank Prof William Gillespie, Dr Helen Handoll, Dr James D Heckman, Prof Peter Herbison and Dr Vicki Livingstone for valuable comments on the protocol and review. We also acknowledge the help of Mrs Lesley Gillespie in developing the search strategies, and the editorial base staff for their help in the processes of writing the protocol and review.

REFERENCES

References to studies included in this review

Emami 1999 ***{published data only}***

Emami A, Petren-Mallmin M, Larsson S. No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. *Journal of Orthopaedic Trauma* 1999;**13**(4): 252–7.

Handolin 2005 ***{published data only (unpublished sought but not used)}***

Handolin L, Kiljunen V, Arnala I, Kiuru MJ, Pajarinen J, Partio EK, et al. No long-term effects of ultrasound therapy on bioabsorbable screw-fixed lateral malleolar fracture. *Scandinavian Journal of Surgery* 2005;**94**(3):239–42.

* Handolin L, Kiljunen V, Arnala I, Pajarinen J, Partio EK, Rokkanen P. The effect of low intensity ultrasound and bioabsorbable self-reinforced poly-L-lactide screw fixation on bone in lateral malleolar fractures. *Archives of Orthopaedic and Trauma Surgery* 2005;**125**(5):317–21.

Handolin 2005a ***{published data only (unpublished sought but not used)}***

Handolin L, Kiljunen V, Arnala I, Kiuru MJ, Pajarinen J, Partio EK, et al. Effect of ultrasound therapy on bone healing of lateral malleolar fractures of the ankle joint fixed with bioabsorbable screws. *Journal of Orthopaedic Science* 2005;**10**(4):391–5.

Heckman 1994 ***{published and unpublished data}***

Cook S, Ryaby JP, Heckmann JD, Kristiansen TK. Low-intensity pulsed ultrasound accelerates tibia and distal radius fracture healing in smokers. *Hefte zur der Unfallchirurg* 1996;**262**:336.

Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fracture healing in patients who smoke. *Clinical Orthopaedics & Related Research* 1997;**(337)**:198–207.

Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Low intensity pulsed ultrasound accelerates tibia and distal radius fracture healing in smokers [abstract]. *Orthopaedic Transactions* 1996;**20**(1):56.

Heckman JD. Personal communication September 2 2010.

* Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *Journal of Bone and Joint Surgery - American Volume* 1994;**76**(1):26–34.

Kristiansen 1997 ***{published and unpublished data}***

Cook S, Ryaby JP, Heckmann HD, Kristiansen TK. Low-intensity pulsed ultrasound accelerates tibia and distal radius fracture healing in smokers. *Hefte zur der Unfallchirurg* 1996;**262**:336.

Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fracture healing in patients who smoke. *Clinical Orthopaedics & Related Research* 1997;**(337)**:198–207.

Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Low intensity pulsed ultrasound accelerates tibia and distal radius fracture healing in smokers [abstract]. *Orthopaedic Transactions* 1996;**20**(1):56.

Kristiansen TK, Ryaby JP, McCabe J, Frey J. Controlling loss of reduction in distal radius fractures in an randomized, double-blind study using low-intensity ultrasound. Hefte zur der Unfallchirurg. 1996; Vol. 262:369.

Kristiansen TK, Ryaby JP, McCabe J, Frey J. Controlling loss of reduction in distal radius fractures with low intensity pulsed ultrasound [abstract]. *Orthopaedic Transactions* 1997;**21**(1):141.

* Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound: A multicenter, prospective, randomized, double- blind, placebo-controlled study. *Journal of Bone and Joint Surgery - American Volume* 1997;**79**(7):961–73.

McCabe J. Personal communication September 22 2010.

Leung 2004 ***{published data only}***

Leung KS, Lee WS, Tsui HF, Liu PPL, Cheung WH.

Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. *Ultrasound in Medicine and Biology* 2004;**30**(3):389–95.

Lubbert 2008 ***{published and unpublished data}***
Lubbert PH. Personal communication November 7 2010.
* Lubbert PHW, van der Rijt RHH, Hoorntje LE, van der Werken C. Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: A multi-centre double blind randomised controlled trial. *Injury* 2008;**39**(12):1444–52.

Mayr 2000 ***{published data only}***
Mayr E. Accelerated healing of scaphoid fracture - a randomized study [abstract]. *Journal of Bone and Joint Surgery - British Volume* 1999;**81 Suppl 2**:206.
Mayr E, Rudzki M, Borchardt B, Ruter A. Accelerated healing of scaphoid fractures - A randomized study [abstract]. *Journal of Orthopaedic Trauma* 1999;**13**(4):310.
* Mayr E, Rudzki M-M, Rudzki M, Borchardt B, Hausser H, Ruter A. Does Pulsed Low-Intensity Ultrasound Accelerate Healing of Scaphoid Fractures? [Beschleunigt niedrig intensive, gepulster Ultraschall die Heilung von Skaphoidfrakturen?]. *Handchirurgie Mikrochirurgie Plastische Chirurgie* 2000;**32**(2):115–22.

Rue 2004 ***{published data only}***
Rue JP, Armstrong DW 3rd, Frassica FJ, Deafenbaugh M, Wilckens JH. The effect of pulsed ultrasound in the treatment of tibial stress fractures. *Orthopedics* 2004;**27**(11): 1192–5.

Strauss 1999 ***{published data only (unpublished sought but not used)}***
Strauss E, Ryaby JP, McCabe J. Treatment of Jones' fractures of the foot with adjunctive use of low-pulsed ultrasound stimulation. *Journal of Orthopaedic Trauma* 1999;**13**(4): 310.

Wang 2007 ***{published data only}***
Liu HC, Fu TH. Effects of shockwave on acute high-energy fractures of the femur and tibia [abstract]. American Academy of Orthopaedic Surgeons Annual Meeting. Febuary 2007.
* Wang CJ, Liu HC, Fu TH. The effects of extracorporeal shockwave on acute high-energy long bone fractures of the lower extremity. *Archives of Orthopaedic and Trauma Surgery* 2007;**127**(2):137–42.

Yadav 2008 ***{published data only}***
Yadav YK, Salgotra KR, Banerjee A. Role of ultrasound therapy in the healing of tibial stress fractures. *Medical Journal Armed Forces India* 2008;**64**(3):234–6.

References to studies excluded from this review

Basso 1998 ***{published data only}***
Basso O, Pike JM. The effect of low frequency, long-wave ultrasound therapy on joint mobility and rehabilitation after wrist fracture. *Journal of Hand Surgery - British Volume* 1998;**23**(1):136–9.

Busse 2005 ***{published data only}***
Busse JW, Bhandari M, Sprague S, Johnson-Masotti AP, Gafni A. An economic analysis of management strategies for closed and open grade I tibial shaft fractures. *Acta Orthopaedica* 2005;**76**(5):705–12.

Heckman 1997 ***{published data only}***
Heckman JD, Sarasohn-Kahn J. The economics of treating tibia fractures: The cost of delayed unions. *Bulletin of The Hospital for Joint Dieases* 1997;**56**(1):63–72.

References to studies awaiting assessment

ISRCTN90844675 ***{unpublished data only}***
Seifert J. Pulsed ultrasound to speed-up healing after intramedullary nailing of tibia fractures (PUSH-IT). http://controlled-trials.com/ISRCTN90844675/ISRCTN90844675 (accessed 9 December 2011).

TRUST (Pilot) ***{unpublished data only}***
* Bhandari M, Busse J, Guyatt G. Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST). http://www.controlled-trials.com/ISRCTN98682811 (accessed 14 June 2011).
Busse J. personal communication 20 December 2011.

References to ongoing studies

TRUST (Full) ***{unpublished data only}***
Bhandari M. Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST). http://www.clinicaltrials.gov/ct2/show/NCT00667849 (accessed 7 December 2011).

Additional references

Aaron 2004
Aaron RK, Ciombor DM, Simon BJ. Treatment of nonunions with electric and electromagnetic fields. *Clinical Orthopaedics & Related Research* 2004;**(419)**:21–9. [PUBMED: 15021127]

Boutron 2008
Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Annals of Internal Medicine* 2008;**148**(4):295–309.

Busse 2009
Busse JW, Kaur J, Mollon B, Bhandari M, Tornetta P 3rd, Schunemann HJ, et al. Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials. *BMJ* 2009;**338**:b351.

Busse 2011
Busse J. personal communication 20 December 2011.

Cook 1997
Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fracture healing in patients who smoke. *Clinical Orthopaedics & Related Research* 1997;**(337)**:198–207.

Einhorn 1995
Einhorn TA. Enhancement of fracture healing. *Journal of Bone & Joint Surgery - American Volume* 1995;**77**(6): 940–56. [MEDLINE: 7782368]

Griffin 2008

Griffin XL, Costello I, Costa ML. The role of low intensity pulsed ultrasound therapy in the management of acute fractures: a systematic review. *Journal of Trauma-Injury Infection & Critical Care* 2008;**65**(6):1446–52. [PUBMED: 19077640]

Hadjiargyrou 1998

Hadjiargyrou M, McLeod K, Ryaby JP, Rubin C. Enhancement of fracture healing by low intensity ultrasound. *Clinical Orthopaedics & Related Research* 1998; **(355 Suppl)**:S216–29. [PUBMED: 9917641]

Handolin 2005b

Handolin L, Kiljunen V, Arnala I, Kiuru MJ, Pajarinen J, Partio EK, et al. No long-term effects of ultrasound therapy on bioabsorbable screw-fixed lateral malleolar fracture. *Scandinavian Journal of Surgery* 2005;**94**(3):239–42.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [MEDLINE: 12958120]

Higgins 2008

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons, 2008.

Lefebvre 2009

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Reher 1997

Reher P, Elbeshir el-NI, Harvey W, Meghji S, Harris M. The stimulation of bone formation in vitro by therapeutic ultrasound. *Ultrasound in Medicine & Biology* 1997;**23**(8): 1251–8. [PUBMED: 9372573]

Victoria 2009

Victoria G, Petrisor B, Drew B, Dick D. Bone stimulation for fracture healing: What's all the fuss?. *Indian Journal of Orthopaedics* 2009;**43**(2):117–20.

Wang 1994

Wang SJ, Lewallen DG, Bolander ME, Chao EY, Ilstrup DM, Greenleaf JF. Low intensity ultrasound treatment increases strength in a rat femoral fracture model. *Journal of Orthopaedic Research* 1994;**12**(1):40–7. [PUBMED: 8113941]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Emami 1999

Methods	Randomised, placebo-controlled study.
Participants	Setting: Uppsala University Hospital, Sweden. Size: 30 participants in total, with 15 in each arm. Baseline characteristics: mean (range) age 39 years (19 to 73), 21 males and 9 females Inclusion criteria: patients aged over 16 years with a closed or Gustillo and Anderson grade I open fracture of the tibial diaphysis treated with closed reduction and fixation with a reamed, intra-medullary, locked nail Exclusion criteria: history of alcohol or drug dependency; current steroid, anticoagulant, NSAID or bisphosphonate use; past medical history of neuropathy, arthritis, malignant disease; radiographs that showed severe comminution or open physes
Interventions	Participants underwent closed reduction and reamed, intra-medullary nailing of the fracture. Surgery was performed by one of six experienced trauma surgeons. The fracture site was marked with a permanent skin marker. **Test:** ultrasound treatment was started within three days of fixation and was continued for 75 days. The treatment consisted of one 20 minute period daily with a maximum exposure of 25 hours. The transducer head was coupled to the skin with a standard gel. The ultrasound signal was composed of a 200 µs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2 **Control:** sham ultrasound treatment was started within three days of fixation and was continued for 75 days. The treatment consisted of one 20 minute period daily with a maximum exposure of 25 hours. The sham device was a deactivated, identical model to that provided to the test group
Outcomes	Follow-up schedule: every third week until union. Additional follow-up at 26 and 52 weeks irrespective of union status Primary: time to radiographic union. Secondary: time to first radiographic evidence of callus, proportion of fractures united at six months, adverse events
Notes	Outcomes were assessed by a single blinded radiologist and an orthopaedic surgeon independently, but were not pooled

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was ... randomized" Comment: No specific report of how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	The allocation method was not reported.

Emami 1999 (*Continued*)

Blinding (performance bias and detection bias) Patient reported measures	Low risk	No patient reported measures included in the study.
Blinding (performance bias and detection bias) Objective measures	Low risk	Quotes: "The codes were not broken for any device until the radiographic reviews for all patients had been completed." "...devices were identical in every way..." Comment: All measures were adequately blinded.
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	No patient reported measures included in the study.
Incomplete outcome data (attrition bias) Objective measures	Unclear risk	Quote: "In one patient, it became obvious during the course of the study that he did not fulfil the inclusion/exclusion criteria." Comment: No data were reported for this single participant and he was excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Quote: "All radiographs were assessed separately in independent blind reviews by a musculoskeletal radiologist...and an orthopaedic trauma surgeon." Comment: These outcomes are not pooled but rather presented separately. The data used in this review is that derived from the single independent radiologist
Selection bias (imbalance in baseline characteristics)	Low risk	Baseline data for age, sex and smoking status are reported and show a balanced distribution of these confounders between groups

Handolin 2005

Methods	Randomised, placebo-controlled study.
Participants	Setting: Helsinki University Central Hospital, Finland. Size: 30 patients in total, 15 in each arm. Baseline characteristics: mean age 41.4 years (5 male/10 female) in intervention group and 39.4 years (8 male/7 female) in the control group Inclusion criteria: patients aged between 18 and 65 years with displaced Weber B fractures of the lateral malleolus Exclusion criteria: widening of the distal tibiofibular joint; open fracture; inability to co-operate with the requirements of the trial

Handolin 2005 (*Continued*)

Interventions	Participants underwent open reduction and internal fixation with a 4.5 mm self-reinforced poly-L-lactic acid screw. Surgery was carried out by one of two surgeons. The fracture was approached through a lateral incision. Post-operatively the ankle was immobilised for six weeks with a removable Soft Cast brace. Partial weight bearing was allowed at two weeks and full weight bearing at four weeks **Test:** participants self-administered daily ultrasound treatment for 20 minutes from the third to ninth post-operative weeks directly over the fracture marked an intra-operatively placed marker. Appropriate contact between the probe and the skin was maintained with standard ultrasound coupling gel. The ultrasound signal was composed of a 200 µs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm² **Control:** participants in the control group were given a similar treatment regimen but had an externally similar sham machine instead
Outcomes	Follow-up schedule was 2, 6, 9 and 12 week and, in a separate publication, 18 months At 18 months, the clinical outcome was assessed using the Olerud-Molander scoring as well as clinical examination; this was reported in a separate article for 16 (8 versus 8) participants Plain radiographic assessment at 2, 6, 9 and 12 weeks and at 18 months. Multi detector computed tomography (MDCT) at 18 months and dual-energy X-ray absorptiometry (DEXA) scan post operatively and at 18 months
Notes	Based on overlapping, but not matching, dates of recruitment we have assumed that a publication (Handolin 2005b) reporting 18 month results for 16 participants is a long-term follow-up of this trial. These reports share a common methodology and reporting framework. Efforts to contact the authors were unsuccessful

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...prospective, randomised ... study." Comment: The method of sequence generation is not reported.
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment is not reported
Blinding (performance bias and detection bias) Patient reported measures	Low risk	None reported.
Blinding (performance bias and detection bias) Objective measures	Low risk	Quote: " double blind; half of the devices were active ... half were sham." Comment: Likely to be the same device but placebo devices were deactivated

Handolin 2005 (*Continued*)

Incomplete outcome data (attrition bias) Patient reported measures	Low risk	None reported
Incomplete outcome data (attrition bias) Objective measures	High risk	All outcome data reported up to 12 weeks, but data from only 16 participants reported at 18 months
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	It is not reported how the radiographic outcomes were assessed
Selection bias (imbalance in baseline characteristics)	Unclear risk	Age and sex similarly distributed, but smoking status not reported

Handolin 2005a

Methods	Randomised, placebo-controlled study.
Participants	Setting: Helsinki Unversity Central Hospital, Finland. Size: 22 patients, 11 in each arm. Baseline characteristics: mean (range) age 37.5 years (18 to 54), 9 males and 2 females in intervention group. Mean (range) age 45.5 years (26 to 59), 6 males and 5 females in the control group Inclusion criteria: patients aged between 18 and 65 years with displaced Weber B fractures of the lateral malleolus Exclusion criteria: widening of the distal tibiofibular joint; open fracture; inability to co-operate with the requirements of the trial
Interventions	Participants underwent open reduction and internal fixation with a 4.5 mm self-reinforced poly-L-lactic acid screw. Surgery was carried out by one of two surgeons. The fracture was approached through a lateral incision. Post-operatively the ankle was immobilised for six weeks with a removable Soft Cast brace. Partial weight bearing was allowed at two weeks and full weight bearing at four weeks **Test:** participants self-administered daily ultrasound treatment for 20 minutes from the third to ninth post-operative weeks directly over the fracture marked an intra-operatively placed marker. Appropriate contact between the probe and the skin was maintained with standard ultrasound coupling gel. The ultrasound signal was composed of a 200 μs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2 **Control:** participants in the control group were given a similar treatment regime but had an externally similar sham machine instead
Outcomes	Fracture healing was assessed by anterior and lateral radiographs taken immediately and at 2, 6, 9 and 12 weeks postoperatively In addition, fracture healing was assessed by multiplanar computed tomography and 2 and 9 weeks postoperatively

Handolin 2005a (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "..prospective, randomized, double-blind and placebo controlled study". No comment on sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The patients were randomly provided with either an active or sham ultrasound device in a double-blind manner"
Blinding (performance bias and detection bias) Patient reported measures	Low risk	None reported.
Blinding (performance bias and detection bias) Objective measures	Unclear risk	Quote: "The patients were randomly provided with either an active or sham ultrasound device in a double-blind manner" Comment: Likely to be the same device but placebo devices were deactivated
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	No patient reported outcome measures.
Incomplete outcome data (attrition bias) Objective measures	Low risk	None.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	
Selection bias (imbalance in baseline characteristics)	Unclear risk	Smoking status not reported.

Heckman 1994

Methods	Randomised, placebo-controlled study.
Participants	Setting: University of Texas Health Science Centre, USA. Size: 97 patients were enrolled. Of the 48 patients in the test group, 11 violated the protocol and 4 were lost to follow-up, leaving 33 patients completing the study. Of the 49 patients in the control group, 6 violated the protocol and 9 were lost to follow up, leaving 34 patients completing the study Baseline characteristics: mean age was 36 years, with 25 males and 8 females in the intervention group, and mean age 31 years with 29 males to 5 females in the control

Heckman 1994 (*Continued*)

	group Inclusion criteria: skeletally mature men and non-pregnant women aged less than 76 years with closed or grade I open, transverse or short oblique/spiral, fractures of the tibial diaphysis that could be treated with closed reduction and cast immobilisation Exclusion criteria: post-reduction findings of long oblique/spiral fracture, length of fracture line greater than twice the diameter of the diaphysis; fracture displacement greater than 50%; fracture gap greater than 0.5 cm or persistent shortening; persistent angulation greater than 10 degrees; metaphyseal fracture; large butterfly fragment; pathological fracture; comminution; participant inability to comply with trial procedures; current prescription of NSAID, calcium channel blockers, bisphosphonates; history of thrombophlebitis, vascular insufficiency, alcoholism or nutritional deficiency
Interventions	Participants were treated with closed reduction and above-knee casting. An alignment window was placed in the cast at the level of the fracture over the antero-medial aspect of the leg. Reduction of the casting to a below-knee cast, any subsequent splintage and weight bearing status was at the discretion of the clinician **Test:** participants underwent ultrasound treatment for 20 minutes each day from the second to twentieth week, or earlier if the clinician believed there was adequate evidence of union. The ultrasound signal was composed of a 200 µs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2 **Control:** participants in the control group were given a similar treatment regimen but had an externally similar sham machine instead
Outcomes	Follow-up schedule: plain radiographs at 4, 6, 8, 10, 12, 14, 20, 33 and 52 weeks. Clinical examination at times of cast change and at the time of union Outcomes: time to combined radiographic and clinical union.
Notes	The weight bearing status of the patients was strictly described initially but subsequently handed over to the discretion of the treating clinician part way through the trial It was confirmed in personal communication with James Heckman that there was no time to union data on participants who violated protocol Cook 1997 describes a subgroup analysis of the study by Heckman 1994. Smoking status was collected prospectively during the study for half the participants and retrospectively for the other half. There were 33 participants in the active group and 34 in the control group. These numbers correspond with the numbers of participants that successfully completed the study by Heckman 1994. Of these smoking status was not determined in 7 participants due to loss to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...predetermined computer generated code." Comment: Likely to have been a robust method.

Heckman 1994 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "...the patients were randomized, in groups of four, at each study site..." Comment: It is likely that the sequence was held centrally and allocations were given to the distant study centres
Blinding (performance bias and detection bias) Patient reported measures	Low risk	None reported.
Blinding (performance bias and detection bias) Objective measures	Low risk	Quote: "The active and placebo devices were identical in every way..." Comment: Likely to have been a robust method.
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	None reported.
Incomplete outcome data (attrition bias) Objective measures	Unclear risk	Quote: "...patients who adhered to the study protocol ... inferences were drawn" Only data from 67 fractures were presented, which represents a loss to follow-up of 31%. [From JDH: 13 lost to follow-up, 17 did not present in a timely manner so only certainty is ultimate successful union, no time to event data available.]
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Quote: "Ninety-six patients, who had ... ninety-seven fractures..." Comment: Per protocol analysis only. Also, there was no adjustment for recruiting related fractures
Selection bias (imbalance in baseline characteristics)	Unclear risk	Smoking status is not reported as part of the baseline characteristics of the participants

Kristiansen 1997

Methods	Randomised, placebo-controlled study.
Participants	Setting: multi-centre trial, USA. Size: a total of 85 fractures in 83 patients. Of the 40 fractures in the test group, there were 10 withdrawn, leaving 30. Of the 45 fractures in the control group, 3 were lost to follow-up and 11 were withdrawn, leaving 31 Baseline characteristics: there were 6 males and 24 females in the intervention group and 4 males and 27 females in the control group

Kristiansen 1997 (*Continued*)

	Inclusion: men and non-pregnant women who were at least 20 years old, who had closed dorsally angulated metaphyseal fractures of the distal radius Exclusion: fracture extending beyond 4 cm proximally from the tip of the radial styloid, failure to satisfactorily reduce closed and immobilise in a below elbow cast, requirement for additional reduction after ultrasound treatment had begun, associated fracture of the ulnar shaft, current prescription of steroids or anticoagulant, any medical history of thrombophlebitis or vascular insuffiencey of the upper limb, current nutritional deficiency or alcohol dependency
Interventions	Patients underwent closed reduction and immobilisation of the limb in a cast with volar flexion and ulnar deviation. A window was created on the dorsal aspect of the cast overlying the fracture and a retaining alignment fixture was placed in the window. The patients were given a device within 7 days of the fracture, were told to use it for 20 minutes a day, until their 10 week appointment **Test:** ultrasound probe that fitted into the retaining fixture was given to each participant. The ultrasound signal was composed of a 200 μs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2 **Control:** a visually and audibly similar device was given to each participant
Outcomes	Follow-up schedule was weekly until week 6 and then 8, 10, 12 and 16 weeks. End point was defined as combined clinical and radiographic healing Primary: time to radiographic union. Secondary: time to early trabecular healing, time to cortical bridging, percentage of organised trabecular healing, loss of reduction
Notes	The protocol specified combined clinical and radiographic healing, but investigators were reluctant to remove casts, therefore no clinical data are reported and radiographic union was used as the primary outcome measure It was confirmed in personal communication with Joan McCabe that multiple reports with similar titles were all from the same study Cook 1997 describes a subgroup analysis of the study by Kristiansen 1997. Smoking status before and during the study was retrospectively collected. There were 30 participants in the active group and 31 in the control group. These numbers correspond with the numbers of participants that successfully completed the study by Kristiansen 1997. There were 10 participants who could not be located for a retrospective analysis of smoking status

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomly assigned...according to a computer generated code, developed by an independent consultant"
Allocation concealment (selection bias)	Unclear risk	Comments: Concealment of the codes is not reported.

Kristiansen 1997 (*Continued*)

Blinding (performance bias and detection bias) Patient reported measures	Low risk	No patient reported measures.
Blinding (performance bias and detection bias) Objective measures	Low risk	Quote: "The placebo device...was identical to the active unit". "The principle investigator and the independent radiologist...were blinded...performed independent central assessments...of the radiographic parameters of union
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	No patient reported measure.
Incomplete outcome data (attrition bias) Objective measures	High risk	Comments: The protocol specified combined clinical and radiographic healing, but investigators were reluctant to remove casts, therefore no clinical data is reported. All patients lost to follow-up accounted for but approximately 30% loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Two patients had bilateral fractures and they were treated with alternate devices. These fractures were analysed as independent events
Selection bias (imbalance in baseline characteristics)	Unclear risk	Gender, age and fracture characteristics were similar. Smoking status is not reported

Leung 2004

Methods	Quasi-randomised, placebo-controlled study.
Participants	Setting: Chinese University of Hong Kong, China. Size: a total of 30 fractures in 28 patients. The test group had 16 fractures in 15 patients and the control group had 14 fractures in 13 patients Baseline characteristics: mean (range) age 35.3 years (22 to 61), 25 males and 3 females Inclusion: patients with open or comminuted tibial fractures Exclusion: simple fractures, fractures of sites other than the tibia
Interventions	Patients with closed fractures or Gustillo grade 1 or 2 open fractures in the diaphysis underwent fixation with reamed, locked intramedullary nail. Participants with fractures in the metaphysis or Gustillo grade 3 open fractures were treated with an external fixator. All open fractures were treated with emergency debridement and delayed closure **Test:** LIPUS machine was given to the patients as soon as the soft tissues were closed. The ultrasound signal was composed of a 200 μs burst of 1.5 MHz sine waves, with a

Leung 2004 (*Continued*)

	repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm² and was given for 20 minutes a day, for 90 days using coupling gel applied directly over the fracture site **Control:** a sham device that was externally identical to the LIPUS machine was given to the participants as soon as the soft tissues were closed
Outcomes	End point was combined clinical and radiographic union. Clinical union was defined as full painless weightbearing. Radiographic union was defined as 3 out of 4 cortices were bridged with bone on plain orthogonal radiograph. Follow-up times were every 3 weeks for the first 3 months, every 6 weeks for the following 3 months and every 8 weeks for the last 6 months. The radiographs were assessed by 3 independent surgeons and a mean time of union was used Primary: time to union. Secondary: bone mineral density and plasma bone specific alkaline phosphatase, adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "...assigned...according to the sequence of admission" Comments: Quasi-randomised.
Allocation concealment (selection bias)	High risk	Quote: "...assigned...according to the sequence of admission" Comments: No list provided. Quasi-randomised.
Blinding (performance bias and detection bias) Patient reported measures	Low risk	None reported.
Blinding (performance bias and detection bias) Objective measures	High risk	Quote: "Control group were given a dummy machine". Comments: Efforts were made to blind the patients, but the assessors were not blind as the machines were not identical and the patients were quasi-randomly allocated
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	None reported.
Incomplete outcome data (attrition bias) Objective measures	Low risk	The complete dataset was presented.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Leung 2004 (*Continued*)

Other bias	High risk	Quote: "Four patients had segmental fractures..." Some participants had two fractures which may have been randomised independently. No statistical adjustments were reported to allow for this
Selection bias (imbalance in baseline characteristics)	Unclear risk	Age, gender and smoking status not separately reported.

Lubbert 2008

Methods	Randomised, placebo-controlled study.
Participants	Setting: multi-centre trial, Netherlands. Size: there were 120 patients. Of the 61 in the test group, 9 were lost to follow-up, leaving 52 patients. Of the 59 in the control group, 7 were lost to follow-up and 3 did not complete the intervention, leaving 49 patients Baseline characteristics: 46 males and 6 females in the intervention group and 39 males and 10 females in the control group Inclusion: over 18 years of age, diaphyseal fracture of the clavicle (Allman group 1), treatment begun within 5 days of trauma Exclusion: multiple trama, re-fracture, pathological fracture, open fracture or threatened soft tissue envelope, metaphyseal fracture
Interventions	All participants were treated non-operatively with a collar and cuff sling for symptom control. Free arm movements within a range allowed by pain were allowed from day 1. Participants maintained a treatment diary **Test:** a LIPUS machine was given to the patients at the first visit. The ultrasound signal was given for 20 minutes a day, for 28 days using coupling gel applied directly over the fracture site. The unit was an Exogen 2000 battery powered Main Operating Unit and a Smith and Nephew Treatment Head Module transducer that delivered an ultrasound signal composed of a 200 μs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30 mW/cm^2 **Control:** a sham device that was externally identical to the LIPUS machine was given to the participants with similar instructions for use
Outcomes	Follow-up schedule: 1, 2, 4, 6, 8 weeks. Primary: patient reported subjective clinical fracture healing Secondary: Pain (VAS and painkiller use), operation, adverse events, resumption of sport/professional activities/sport
Notes	Data from the patients excluded from the study was provided by Pieter Lubbert in personal communication; these allowed an intention-to-treat analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lubbert 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "For each participating hospital consecutive numbered transducers were delivered in packs of four." "Randomisation took place at the site of the manufacturer." Comment: Distant block randomisation.
Allocation concealment (selection bias)	Low risk	Quotes: "Each hospital supply contained two randomly assigned active transducers and two placebo transducers." "The placebo transducers looked identical..." Comment: Allocation was concealed at a distant site.
Blinding (performance bias and detection bias) Patient reported measures	Low risk	Quote: "The placebo transducers looked identical..."
Blinding (performance bias and detection bias) Objective measures	Low risk	Quote: "The placebo transducers looked identical..."
Incomplete outcome data (attrition bias) Patient reported measures	High risk	Trial flow diagram presented clearly. Only a per-protocol analysis was presented
Incomplete outcome data (attrition bias) Objective measures	Low risk	None reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	
Selection bias (imbalance in baseline characteristics)	Unclear risk	Age and smoking status not separately reported.

Mayr 2000

Methods	Randomised controlled trial
Participants	Setting: German emergency outpatient department. Single centre study Size: 29 patients, 30 fractures; 15 fractures in each group. Baseline characteristics: mean age (SD) age 37 (14) years; 5 to 1 male / female ratio Inclusion: skeletally mature adults with a fresh stable scaphoid fracture (AO B1 and B2) Exclusion: unstable fractures, generalised skeletal disease, pathological fracture, fracture more than 10 days old at diagnosis

Mayr 2000 (*Continued*)

Interventions	A forearm plaster splint was applied to include the thumb to the interphalangeal joint. After detumescence, the splint was replaced with a circular restraining forearm bandage to include the thumb to the interphalangeal joint **Test:** after appliance of the circular immobilising forearm bandage, daily 20-minute pulsed low-intensity ultrasound treatment (SAFHS, Exogen, Piscataway, NJ, USA; frequency: 1.5 MHz, pulsed with 1 kHz, signal length: 200 µsec, intensity: 30 mW/cm²) was conducted **Control:** no additional placebo treatment.
Outcomes	Follow-up schedule: CT at 6 weeks and then every 2 weeks until union. Primary outcome: time to union by CT assessment of fracture union Secondary outcome: percentage of ossification of the fracture gap
Notes	The follow-up schedule was changed after six patients had been scanned at 6 weeks, when 3 of them had already achieved union. From that point onwards in the trial, first follow-up was at 4 weeks Translated from German.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated by a random number generator.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Patient reported measures	Unclear risk	No patient reported measures were recorded.
Blinding (performance bias and detection bias) Objective measures	Low risk	CT scans were blinded before reporting.
Incomplete outcome data (attrition bias) Patient reported measures	Unclear risk	No patient reported measures were recorded.
Incomplete outcome data (attrition bias) Objective measures	Low risk	There was no loss of outcome data.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	
Selection bias (imbalance in baseline characteristics)	Unclear risk	Smoking status is not reported.

Rue 2004

Methods	Randomised, placebo-controlled trial
Participants	Setting: US Naval Academy Size: 40 midshipmen with 58 stress fractures; data reported for 26 (14 in the treatment group and 12 in the control group) midshipmen with tibial stress fractures Baseline characteristics: 23 men and 17 women; mean age 19 years; fractures sites were tibia, metatarsal, femur and fibula (74%, 9%, 5% and 5% respectively) Inclusion: new midshipmen sustaining stress fractures diagnosed on radiographic and scintigraphic examinations during initial training. Informed consent. Exclusion: none
Interventions	While not stated explicitly it is likely that all participants received the standard-of-care treatment that included protected weight bearing if normal walking reproduced symptoms, alternative aerobic exercise, a daily multivitamin and calcium supplementation (twice daily 500mg) **Test:** daily 20-minute LIPUS treatment (Exogen Inc, Piscataway, NJ) administered by sports medicine personnel until stress fracture had healed **Control:** similar protocol with a sham unit.
Outcomes	Follow-up schedule: daily treatments until fit to return to duty (work) defined as no pain on palpation, the ability to do a single leg hop on the affected side without pain and radiographic evidence of healing Primary outcome: time to return to duty (work) Secondary outcome: adherence
Notes	Although 40 participants were enrolled with a variety of injured bones only 33 were able to comply with the protocol for a variety of reasons. Of these 33, 7 further participants were excluded from the analysis as only those with fractures of the tibia were analysed (total attrition: 14 of 40). The 26 participants had 43 tibial stress fractures - time to return to duty was based on stress fracture site with the longest duration of symptoms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...and were randomized into one of two treatment protocols..." Comment: No description of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "...and were randomized into one of two treatment protocols..." Comment: No description of allocation concealment.
Blinding (performance bias and detection bias) Patient reported measures	Low risk	Quote: "The placebo group underwent the identical protocol, except that the stimulator unit was non-functional. This study was a double-blind, placebo-controlled investigation."

Rue 2004 (*Continued*)

		Comment: Participants were blinded to intervention.
Blinding (performance bias and detection bias) Objective measures	Unclear risk	Quote: "This study was a double-blind ... investigation." Comment: Trial personnel administered the treatments and documented adherence. It is not explicit that they were also blind to the allocation although the study was 'double-blind'
Incomplete outcome data (attrition bias) Patient reported measures	High risk	Overall attrition proportion was 14 of 40 and the loss was explicitly systematic
Incomplete outcome data (attrition bias) Objective measures	High risk	Overall attrition proportion was 14 of 40 and the loss was explicitly systematic
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	
Selection bias (imbalance in baseline characteristics)	Unclear risk	Smoking status is not reported.

Strauss 1999

Methods	Randomised controlled trial
Participants	Setting: USA hospital. Size: 20 participants, 20 fractures; 10 fractures in each group Baseline characteristics: not reported. Inclusion: patients with a fracture of the fifth metatarsal (zone II) Exclusion: not stated
Interventions	All fractures were initially treated with short leg cast and weightbearing as tolerated for a mean of 10 days. All casts were converted to a hinged ankle foot orthosis and patients continued with weightbearing until fracture union **Test:** participants were given LIPUS therapy for 20 minutes twice each day **Control:** participants were given no additional placebo treatment.
Outcomes	Follow-up schedule: not reported. Primary: time to clinical and radiographic union. Secondary: proportion of union within 20 weeks.
Notes	Inadequate data were presented to include the primary outcome in the analysis in this review
Risk of bias	

Strauss 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...were studied in a prospective randomized setting. The twenty fractures were randomly divided..." Comment: Method of randomisation is unclear.
Allocation concealment (selection bias)	Unclear risk	Quote: "...were studied in a prospective randomized setting. The twenty fractures were randomly divided..." Comment: Method of randomisation is unclear.
Blinding (performance bias and detection bias) Patient reported measures	Unclear risk	None reported.
Blinding (performance bias and detection bias) Objective measures	High risk	Quote: "...Group B (control or no ultrasound treatment)." Comment: Control group received no sham LIPUS machine.
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	None reported.
Incomplete outcome data (attrition bias) Objective measures	Unclear risk	All participants were followed up to the final time point of the study
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	This study was only reported as a poster abstract. The detail contained within this report is minimal and evaluation of the risk of bias is extremely limited
Selection bias (imbalance in baseline characteristics)	Unclear risk	Baseline characteristics were not reported.

Wang 2007

Methods	Quasi-randomised controlled trial
Participants	Setting: Taiwan Size: a total of 59 fractures in 56 patients. There was one exclusion in each group, leading to 27 fractures in 27 patients in the test and 30 fractures in 27 patients in the control Baseline characteristics: mean (range) age was 34.2 years (15 to 81), 40 males and 16 females Inclusion: patients with acute, displaced, high energy trauma diaphyseal fractures of the femur and tibia that required reduction and internal or external fixation Exclusion: pathological fracture, active infection, coagulopathy, immunosuppression, pregnancy, cardiac pacemaker, skeletal immaturity, poor compliance

Wang 2007 (*Continued*)

Interventions	All closed fractures were treated with open or closed reduction and internal fixation with intra-medullary nailing or plate fixation. Patients with type III-C open fractures were initially treated with surgical debridement of the wounds and external fixator for fracture stabilization. Delayed open or closed reduction and internal fixation was performed when the soft tissues were optimised. All other open fractures were treated with primary open reduction and internal fixation Postoperative management included early ambulation with no weight bearing allowed through the affected limb; quadriceps and hamstring and lower limb joint range of motion exercises **Test:** participants in the study group received shockwave treatment immediately after surgery under the same anaesthesia. For patients with type III-C open fractures, shockwave treatment was performed after delayed open reduction and internal fixation for the fractures. The source of shockwaves was from an OssaTron (High Medical Technology, Kreulingen, Switzerland). Shockwaves were performed with patients on the fracture table. The fracture site was verified with C-arm X-rays, and the depth of treatment was confirmed with the control guide of the device under C-arm imaging. Surgical lubrication gel was applied to the area of skin in direct contact with the shockwave tube. Each fracture site was treated with 6,000 impulses of shockwave at 28 kV (equivalent to 0.62 mJ/mm^2 energy flux density). Shockwaves were applied in two planes with equal dosage in each plane as a single session **Control:** participants in the control group received open reduction and internal fixation without shockwave treatment after surgery
Outcomes	Follow-up schedule: 1, 3, 6 and 12 months. Primary: proportion of union at 12 months. Secondary: proportion of union at earlier time points, fracture alignment, pain (VAS), weight bearing status, adverse events
Notes	Authors have assumed independence between observations from multiple fractures in a single participant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "[The study group] who had surgery on odd days of the week, and the control group ... who had surgery performed on even days of the week" Comment: Quasi-randomised study.
Allocation concealment (selection bias)	High risk	Quote: "[The study group] who had surgery on odd days of the week, and the control group..who had surgery performed on even days of the week" Comment: Unclear whether method of randomisation known, but would be easy to identify pattern

Wang 2007 (*Continued*)

Blinding (performance bias and detection bias) Patient reported measures	Unclear risk	Quote: "Patients in the control group ... without shockwave treatment after surgery." Comment: It is not reported whether the participants were blind to their allocation
Blinding (performance bias and detection bias) Objective measures	Low risk	Quote: "An independent examiner blinded to the nature of the study protocol performed the examination."
Incomplete outcome data (attrition bias) Patient reported measures	High risk	Quote: "Two patients were excluded from the final analysis because of postoperative deep infection and osteomyelitis." Comment: This was consistent with the eligibility criteria but is an unusual means to handle data from participants developing adverse events
Incomplete outcome data (attrition bias) Objective measures	High risk	Quote: "Two patients were excluded from the final analysis because of postoperative deep infection and osteomyelitis." Comment: This was consistent with the eligibility criteria but is an unusual means to handle data from participants developing adverse events
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	Quote: "56 patients with 59 .... fractures" Some participants had two fractures which may have been randomised independently. No statistical adjustments were reported to allow for this
Selection bias (imbalance in baseline characteristics)	Unclear risk	The distribution of smoking status between the groups is not reported

Yadav 2008

Methods	Randomised, placebo-controlled trial
Participants	Setting: Indian military recruits in training. Size: 67 cases with stress fracture; with 39 in the treatment group and 28 in the control group Baseline characteristics: age not reported, gender data not reported Inclusion: history and examination consistent with a diagnosis of stress fracture Exclusion: none.
Interventions	All participants were managed non-operatively and prescribed paracetamol and ice-packs **Test:** treated with 10 min/day using a ultrasound probe emitting a 3 MHz, 1 W/cm^2 ultrasound signal pulsed with a duty cycle of 50% **Control:** similar treatment with a sham unit which was identical to the test unit

Yadav 2008 (*Continued*)

Outcomes	Time to return to training. No radiological outcome measures assessed	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...were randomly assigned ... by chit method."
Allocation concealment (selection bias)	Unclear risk	Quote: "...were randomly assigned ... by chit method." Comment: It is not clear whether this was done on or off site and who had access to the results
Blinding (performance bias and detection bias) Patient reported measures	Low risk	Quotes: "... nonfunctioning unit identical in appearance." "... patients ... study's researchers were blinded. .."
Blinding (performance bias and detection bias) Objective measures	Low risk	Quotes: "... nonfunctioning unit identical in appearance." "... patients ... study's researchers were blinded. .."
Incomplete outcome data (attrition bias) Patient reported measures	Low risk	There were no missing data.
Incomplete outcome data (attrition bias) Objective measures	Low risk	There were no missing data.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	
Selection bias (imbalance in baseline characteristics)	Unclear risk	Quote: "... matched in terms of age, height, demographics, and delay from symptom onset to diagnosis." Comment: Sex and smoking status not reported.

CT = computed tomography
LIPUS = low intensity pulsed ultrasound

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Basso 1998	This RCT involving a single application of ultrasound to conservatively treated distal radius fractures reported on range of motion and referral for physiotherapy at 8 weeks. It is excluded because its focus was not on fracture healing - it also not did not report any outcome measures pertinent to this review
Busse 2005	This study is a health economic analysis which is informed using data from a systematic review
Heckman 1997	This study is a cost analysis based upon models developed from clinical data and specified assumptions. It is not a formal health economics analysis within a randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ISRCTN90844675

Methods	Randomised controlled multi-centre trial
Participants	Adults with closed or type I open fractures of the tibia that had been treated by reamed or unreamed locking intramedullary nails less than 10 days prior to randomisation. Patients with fractures of the lateral malleolus, fixed by plates, as well as patients with minor concomitant injuries (bruises, sprains) were offered trial participation Intended target population: 250
Interventions	**Test:** pulsed, low-energetic ultrasound (Exogen, Smith & Nephew), applied daily for three months **Control:** standard of care
Outcomes	Follow-up: 1 year Primary: bony union three months (+/- 1 week) after randomisation, as assessed on plain radiographs by independent, blinded raters Secondary (assessed after 6 weeks, 3, 6, and 12 months): 1. Delayed union and non-union rates 2. Health-related quality of life (36-item Short Form Health Survey [SF-36], EuroQoL instrument [EQ-5D]) 3. Functional outcomes (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) 4. Duration of sick leave 5. Cost-utility 6. Serious adverse events (SAE)
Notes	Trial registration identified after preparation of the review. Indicated as a completed trial (01/10/2008 to 01/10/2010). Efforts to find out its current status are ongoing. Contact: Dr Julia Seifert, Berlin (julia.seifert@ukb.de)

TRUST (Pilot)

Methods	Randomised controlled trial
Participants	Patients with conservatively managed fractures of the tibia. Target population = 50
Interventions	**Test:** LIPUS (low intensity pulsed ultrasound) - Exogen (Piscataway, New Jersey) Sonic Accelerated Fracture Healing System **Control:** Sham ultrasound unit
Outcomes	Primary: SF-36 Secondary: 1. Time to radiographic healing of tibial fractures 2. Rates of malunion and non-union of tibial fractures 3. Rates of secondary procedures (operative and non-operative)
Notes	This single-centre trial, funded by the Canadian Institutes of Health, is a pilot study for the other ongoing trial on operatively managed tibia fractures. The study is complete (Busse 2011). The authors have provisionally agreed to provide an unpublished manuscript for this Review once the Steering Committee have released it for submission for publication in 2012 (Busse 2011).

Characteristics of ongoing studies *[ordered by study ID]*

TRUST (Full)

Trial name or title	Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST)
Methods	Randomised controlled trial
Participants	Patients with tibial fractures treated with intramedullary nailing. Target population = 500
Interventions	**Test:** LIPUS (low intensity pulsed ultrasound) - Exogen (Piscataway, New Jersey) Bone Healing System **Control:** Sham ultrasound unit
Outcomes	Primary: radiographs at 6, 12, 18, 26, 38 and 52 weeks Secondary: rates of nonunion of tibial fractures (6, 12, 18, 26, 38 and 52 weeks)
Starting date	01/07/2005 (estimated completion of recruitment 2012)
Contact information	Dr Jason Busse, Toronto (j.busse@rogers.com)
Notes	This multi-centre study, involving centres in USA and Canada, is sponsored by Smith & Nephew. It has the same name as the other trial on conservatively treated tibia fractures

DATA AND ANALYSES

Comparison 1. LIPUS versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to return to work complete fractures (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Resumption of work (as reported)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Resumption of work (worst case scenario)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Time to return to training / duty after stress fracture (days): as reported analysis (days)	2	93	Mean Difference (IV, Random, 95% CI)	-8.55 [-22.71, 5.61]
3 Time to fracture radiographic union (days): 'as reported' analysis	8	355	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.31, -0.07]
3.1 Upper limb	3	183	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-2.03, 0.17]
3.2 Lower limb	5	172	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.44, 0.35]
4 Time to fracture radiographic union (days): worst case analysis	8	446	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-1.14, 0.20]
4.1 Upper limb	3	235	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.93, 0.60]
4.2 Lower limb	5	211	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.27, 0.56]
5 Time to fracture union (days) subgrouped by operation: worst case analysis	7	326	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.29, 0.06]
5.1 Operatively treated	4	114	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-1.42, 1.00]
5.2 Conservatively treated	3	212	Std. Mean Difference (IV, Random, 95% CI)	-1.09 [-1.38, -0.80]
6 Time to fracture union (days) subgrouped by smoking status: worst case analysis	2	111	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.47, -0.65]
6.1 Smokers	2	44	Std. Mean Difference (IV, Random, 95% CI)	-1.17 [-2.09, -0.25]
6.2 Non-smokers	2	67	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.58, -0.53]
7 Delayed or non-union (as reported analysis)	8	333	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.28]
7.1 Upper limb	3	203	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Lower limb	5	130	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.28]
8 Pain at 8 weeks (VAS: 0 no pain to 10 worst pain)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 As reported analysis	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Worst case analysis	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. ECSW versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-union at 12 months follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 As reported analysis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sensitivity analysis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain at 3 months (VAS: 0 no pain to 10 severe pain)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 As reported analysis	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Worst case analysis	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

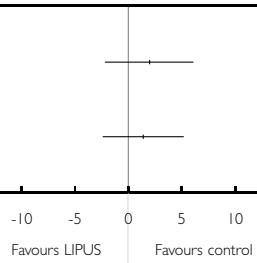
Analysis 1.1. Comparison 1 LIPUS versus control, Outcome 1 Time to return to work complete fractures (days).

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 1 Time to return to work complete fractures (days)

Study or subgroup	LIPUS N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Resumption of work (as reported)						
Lubbert 2008 (1)	52	17 (10.8)	49	15.05 (10.38)		1.95 [-2.18, 6.08]
2 Resumption of work (worst case scenario)						
Lubbert 2008 (2)	61	16.81 (11.05)	59	15.39 (10.3)		1.42 [-2.40, 5.24]



(1) Reported mean (published) SD confirmed (unpublished, author communication)

(2) Reported whole group (unpublished, author communication)

Analysis 1.2. Comparison 1 LIPUS versus control, Outcome 2 Time to return to training / duty after stress fracture (days): as reported analysis (days).

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 2 Time to return to training / duty after stress fracture (days): as reported analysis (days)

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rue 2004 (1)	14	56.2 (19.6)	12	55.8 (15.5)		39.5 %	0.40 [-13.10, 13.90]
Yadav 2008 (2)	39	25.46 (3.84)	28	39.84 (5.36)		60.5 %	-14.38 [-16.70, -12.06]
Total (95% CI)	**53**		**40**			**100.0 %**	**-8.55 [-22.71, 5.61]**

Heterogeneity: $Tau^2 = 84.79$; $Chi^2 = 4.47$, df = 1 (P = 0.03); $I^2 = 78\%$

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable

(1) Reported mean and SD (published)

(2) Reported mean and SD (published)

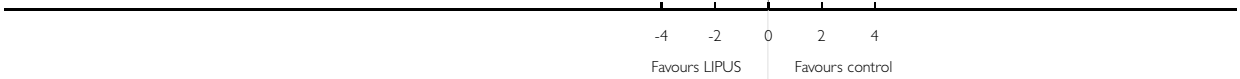
Analysis 1.3. Comparison 1 LIPUS versus control, Outcome 3 Time to fracture radiographic union (days): 'as reported' analysis.

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 3 Time to fracture radiographic union (days): 'as reported' analysis

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Upper limb							
Kristiansen 1997 (1)	30	70 (16.43)	31	110 (29.51)		13.2 %	-1.65 [-2.23, -1.06]
Lubbert 2008 (2)	47	26.77 (13.19)	45	27.09 (13.84)		14.1 %	-0.02 [-0.43, 0.39]
Mayr 2000 (3)	15	43.2 (10.9)	15	62 (19.2)		12.1 %	-1.17 [-1.95, -0.39]
Subtotal (95% CI)	**92**		**91**			**39.4 %**	**-0.93 [-2.03, 0.17]**
Heterogeneity: Tau^2 = 0.85; Chi^2 = 21.83, df = 2 (P = 0.00002); I^2 =91%							
Test for overall effect: Z = 1.65 (P = 0.099)							
2 Lower limb							
Emami 1999 (4)	15	155 (85.21)	17	125 (45.35)		12.6 %	0.44 [-0.27, 1.14]
Handolin 2005 (5)	14	60 (16.17)	12	63 (15.51)		12.2 %	-0.18 [-0.96, 0.59]
Handolin 2005a (6)	8	57.75 (18.61)	9	51.33 (15.26)		11.0 %	0.36 [-0.60, 1.32]
Heckman 1994 (7)	33	102 (27.57)	34	190 (106.71)		13.6 %	-1.11 [-1.63, -0.59]
Leung 2004 (8)	16	80.5 (21)	14	140 (30.8)		11.2 %	-2.23 [-3.16, -1.29]
Subtotal (95% CI)	**86**		**86**			**60.6 %**	**-0.54 [-1.44, 0.35]**
Heterogeneity: Tau^2 = 0.88; Chi^2 = 28.54, df = 4 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 1.18 (P = 0.24)							
Total (95% CI)	**178**		**177**			**100.0 %**	**-0.69 [-1.31, -0.07]**
Heterogeneity: Tau^2 = 0.68; Chi^2 = 50.44, df = 7 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 2.17 (P = 0.030)							
Test for subgroup differences: Chi^2 = 0.28, df = 1 (P = 0.59), I^2 =0.0%							



(1) Reported mean and SD calculated from SE

(2) Reported mean (published) and SD (unpublished, author communication)

(3) Reported mean and SD

(4) Reported mean and SE (SD calculated from SE)

(5) Mean and SD calculated from reported proportion of fractures healed at each follow-up time-point

(6) Mean and SD calculated from reported proportion of fractures healed at each follow-up time-point

(7) Reported mean and SE (SD calculated from SE)

(8) Reported mean and SD

Analysis 1.4. Comparison 1 LIPUS versus control, Outcome 4 Time to fracture radiographic union (days): worst case analysis.

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 4 Time to fracture radiographic union (days): worst case analysis

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Upper limb							
Kristiansen 1997	40	78.2 (16.43)	45	110 (29.51)		13.4 %	-1.30 [-1.77, -0.83]
Lubbert 2008	61	32.82 (13.19)	59	27.09 (13.84)		13.8 %	0.42 [0.06, 0.78]
Mayr 2000	15	43.2 (10.9)	15	62 (19.2)		12.0 %	-1.17 [-1.95, -0.39]
Subtotal (95% CI)	**116**		**119**			**39.1 %**	**-0.66 [-1.93, 0.60]**
Heterogeneity: Tau^2 = 1.17; Chi^2 = 37.28, df = 2 (P<0.00001); I^2 =95%							
Test for overall effect: Z = 1.03 (P = 0.30)							
2 Lower limb							
Emami 1999	15	155 (85.21)	17	125 (45.35)		12.4 %	0.44 [-0.27, 1.14]
Handolin 2005	15	62.16 (16.2)	15	63 (15.5)		12.3 %	-0.05 [-0.77, 0.66]
Handolin 2005a	11	67.9 (18.6)	11	51.3 (15.3)		11.4 %	0.94 [0.05, 1.83]
Heckman 1994	48	119.25 (27.6)	49	190 (106.71)		13.6 %	-0.90 [-1.31, -0.48]
Leung 2004	16	80.5 (21)	14	140 (30.8)		11.2 %	-2.23 [-3.16, -1.29]
Subtotal (95% CI)	**105**		**106**			**60.9 %**	**-0.35 [-1.27, 0.56]**
Heterogeneity: Tau^2 = 0.94; Chi^2 = 34.75, df = 4 (P<0.00001); I^2 =88%							
Test for overall effect: Z = 0.76 (P = 0.45)							
Total (95% CI)	**221**		**225**			**100.0 %**	**-0.47 [-1.14, 0.20]**
Heterogeneity: Tau^2 = 0.81; Chi^2 = 72.52, df = 7 (P<0.00001); I^2 =90%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							

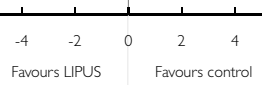
Analysis 1.5. Comparison 1 LIPUS versus control, Outcome 5 Time to fracture union (days) subgrouped by operation: worst case analysis.

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 5 Time to fracture union (days) subgrouped by operation: worst case analysis

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Operatively treated							
Emami 1999	15	155 (85.21)	17	125 (45.35)		14.3 %	0.44 [-0.27, 1.14]
Handolin 2005	15	62 (16.2)	15	63 (15.5)		14.3 %	-0.06 [-0.78, 0.65]
Handolin 2005a	11	68 (18.6)	11	51.3 (15.3)		13.1 %	0.94 [0.05, 1.83]
Leung 2004	16	80.5 (21)	14	140 (30.8)		12.8 %	-2.23 [-3.16, -1.29]
Subtotal (95% CI)	**57**		**57**			**54.5 %**	**-0.21 [-1.42, 1.00]**
Heterogeneity: Tau^2 = 1.35; Chi^2 = 27.25, df = 3 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 0.34 (P = 0.73)							
2 Conservatively treated							
Heckman 1994	48	119.25 (27.6)	49	190 (106.71)		16.0 %	-0.90 [-1.31, -0.48]
Kristiansen 1997	40	78.2 (16.43)	45	110 (29.51)		15.7 %	-1.30 [-1.77, -0.83]
Mayr 2000	15	43.2 (10.9)	15	62 (19.2)		13.8 %	-1.17 [-1.95, -0.39]
Subtotal (95% CI)	**103**		**109**			**45.5 %**	**-1.09 [-1.38, -0.80]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.62, df = 2 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 7.34 (P < 0.00001)							
Total (95% CI)	**160**		**166**			**100.0 %**	**-0.62 [-1.29, 0.06]**
Heterogeneity: Tau^2 = 0.69; Chi^2 = 44.68, df = 6 (P<0.00001); I^2 =87%							
Test for overall effect: Z = 1.80 (P = 0.072)							
Test for subgroup differences: Chi^2 = 1.92, df = 1 (P = 0.17), I^2 =48%							



Analysis 1.6. Comparison 1 LIPUS versus control, Outcome 6 Time to fracture union (days) subgrouped by smoking status: worst case analysis.

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 6 Time to fracture union (days) subgrouped by smoking status: worst case analysis

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Smokers							
Heckman 1994	14	98 (22.4)	18	164 (95.5)		31.2 %	-0.88 [-1.61, -0.14]
Kristiansen 1997	8	51 (12.4)	4	109 (47.4)		7.3 %	-1.91 [-3.44, -0.39]
Subtotal (95% CI)	**22**		**22**			**38.5 %**	**-1.17 [-2.09, -0.25]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.45$, df = 1 (P = 0.23); $I^2 = 31\%$							
Test for overall effect: Z = 2.50 (P = 0.012)							
2 Non-smokers							
Heckman 1994	17	97 (33.4)	11	129 (50.7)		27.2 %	-0.76 [-1.55, 0.03]
Kristiansen 1997	17	67 (21)	22	98 (25.3)		34.3 %	-1.29 [-1.99, -0.59]
Subtotal (95% CI)	**34**		**33**			**61.5 %**	**-1.06 [-1.58, -0.53]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.95 (P = 0.000079)							
Total (95% CI)	**56**		**55**			**100.0 %**	**-1.06 [-1.47, -0.65]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.43$, df = 3 (P = 0.49); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), $I^2 = 0.0\%$							

Analysis 1.7. Comparison 1 LIPUS versus control, Outcome 7 Delayed or non-union (as reported analysis).

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 7 Delayed or non-union (as reported analysis)

Study or subgroup	LIPUS n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Upper limb				
Kristiansen 1997 (1)	0/40	0/42		0.0 [0.0, 0.0]
Lubbert 2008 (2)	0/47	0/44		0.0 [0.0, 0.0]
Mayr 2000 (3)	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**102**	**101**		**0.0 [0.0, 0.0]**
Total events: 0 (LIPUS), 0 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Lower limb				
Emami 1999 (4)	5/15	2/17		2.83 [0.64, 12.52]
Handolin 2005 (5)	1/14	3/12		0.29 [0.03, 2.40]
Handolin 2005a (6)	3/11	2/11		1.50 [0.31, 7.30]
Leung 2004 (7)	1/16	3/14		0.29 [0.03, 2.50]
Strauss 1999 (8)	0/10	3/10		0.14 [0.01, 2.45]
Subtotal (95% CI)	**66**	**64**		**0.75 [0.24, 2.28]**
Total events: 10 (LIPUS), 13 (Control)				
Heterogeneity: Tau^2 = 0.63; Chi^2 = 6.60, df = 4 (P = 0.16); I^2 =39%				
Test for overall effect: Z = 0.51 (P = 0.61)				
Total (95% CI)	**168**	**165**		**0.75 [0.24, 2.28]**
Total events: 10 (LIPUS), 13 (Control)				
Heterogeneity: Tau^2 = 0.63; Chi^2 = 6.60, df = 4 (P = 0.16); I^2 =39%				
Test for overall effect: Z = 0.51 (P = 0.61)				
Test for subgroup differences: Not applicable				

(1) Study reported that all fractures healed eventually (3 placebo group lost to follow-up)

(2) At 8 weeks

(3) At 12 months

(4) At 6 months (delayed union)

(5) At 12 weeks

(6) At 12 weeks (one LIPUS patient had another injury)

(7) Within 12 months (delayed union)

(8) At 6 months (non-union)

Analysis 1.8. Comparison 1 LIPUS versus control, Outcome 8 Pain at 8 weeks (VAS: 0 no pain to 10 worst pain).

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 1 LIPUS versus control

Outcome: 8 Pain at 8 weeks (VAS: 0 no pain to 10 worst pain)

Study or subgroup	LIPUS N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 As reported analysis						
Lubbert 2008	52	3.51 (1.56)	49	3.55 (1.37)		-0.04 [-0.61, 0.53]
2 Worst case analysis						
Lubbert 2008	61	3.53 (1.54)	59	3.55 (1.37)		-0.02 [-0.54, 0.50]

Analysis 2.1. Comparison 2 ECSW versus control, Outcome 1 Non-union at 12 months follow-up.

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 2 ECSW versus control

Outcome: 1 Non-union at 12 months follow-up

Study or subgroup	ECSW n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 As reported analysis				
Wang 2007	3/27	6/30		0.56 [0.15, 2.01]
2 Sensitivity analysis				
Wang 2007	4/28	7/31		0.63 [0.21, 1.93]

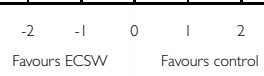
Analysis 2.2. Comparison 2 ECSW versus control, Outcome 2 Pain at 3 months (VAS: 0 no pain to 10 severe pain).

Review: Ultrasound and shockwave therapy for acute fractures in adults

Comparison: 2 ECSW versus control

Outcome: 2 Pain at 3 months (VAS: 0 no pain to 10 severe pain)

Study or subgroup	ECSW N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 As reported analysis						
Wang 2007	27	3.26 (0.94)	30	4.13 (0.73)		-0.87 [-1.31, -0.43]
2 Worst case analysis						
Wang 2007	28	3.33 (0.94)	31	4.13 (0.73)		-0.80 [-1.23, -0.37]



APPENDICES

Appendix 1. Search strategies

The Cochrane Central Register of Controlled Trials (Wiley)

#1 MeSH descriptor Ultrasonics, this term only
#2 MeSH descriptor Ultrasonic Therapy, this term only
#3 MeSH descriptor High-Energy Shock Waves, this term only
#4 (ultraso* or LIPUS or shock wave* or shockwave* or ESWT):ti,ab
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Fractures, Bone explode all trees
#7 MeSH descriptor Fracture Healing, this term only
#8 MeSH descriptor Bone Remodeling explode all trees
#9 MeSH descriptor Bony Callus, this term only
#10 fractur*:ti,ab
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 (#5 AND #11)

MEDLINE (OvidSP interface)

1. Ultrasonics/ or Ultrasonic Therapy/ or High-Energy Shock Waves/
2. (ultraso$ or LIPUS or HIPUS or shock wave$ or shockwave$ or ESWT).tw.
3. or/1-2
4. exp Fractures, Bone/ or Fracture Healing/ or exp Bone Remodeling/ or Bony Callus/
5. fractur$.tw.
6. or/4-5
7. and/3,6
8. (dental or tooth or oral).mp.
9. 7 not 8
10. Randomized Controlled Trial.pt.
11. Controlled Clinical Trial.pt.
12. randomized.ab.
13. placebo.ab.
14. Drug Therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. or/10-17
19. exp Animals/ not Humans/
20. 18 not 19
21. and/9,20

EMBASE (OvidSP interface)

1. Ultrasound/ or Ultrasound Therapy/ or Low Intensity Pulsed Ultrasound/ or Extracorporeal Lithotripsy/
2. (ultraso$ or LIPUS or shock wave$ or shockwave$ or ESWT).tw.
3. or/1-2
4. exp Fracture/ or Fracture Treatment/ or Bone Remodeling/
5. fractur$.tw.
6. or/4-5
7. and/3,6
8. (dental or tooth or oral).mp.
9. 7 not 8
10. Clinical trial/
11. Randomized Controlled Trial/
12. Randomization/
13. Single Blind Procedure/
14. Double Blind Procedure/
15. Crossover Procedure/
16. Placebo/
17. Randomi?ed controlled trial$.tw.
18. Rct.tw.
19. Random allocation.tw.
20. Randomly allocated.tw.
21. Allocated randomly.tw.
22. (allocated adj2 random).tw.
23. Single blind$.tw.
24. Double blind$.tw.
25. ((treble or triple) adj blind$).tw.
26. Placebo$.tw.
27. Prospective Study/
28. or/10-27

29. Case Study/
30. Case report.tw.
31. Abstract Report/ or Letter/
32. or/29-31
33. 28 not 32
34. limit 33 to Human
35. and/9,34

HISTORY

Protocol first published: Issue 7, 2010

Review first published: Issue 2, 2012

CONTRIBUTIONS OF AUTHORS

XL Griffin is responsible for the conception, design and writing of the review. He is the co-guarantor of the review.

ML Costa is involved in conception and design of the review. He is the co-guarantor of the review.

N Parsons is the review statistician. He is responsible for the data management and analysis plan.

N Smith is responsible for study retrieval strategy and writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University Hospital Coventry and Warwickshire NHS Trust, UK.

Provision of salary to NS

- University of Warwick, UK.

Provision of salaries to NP and MC

External sources

- Furlong Charitable Research Foundation, UK.

Provision of salary to XG through a PhD fellowship.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Data analysis

We anticipated that the primary analysis in the included studies was likely to be a survival analysis using the time to fracture union as the outcome measure. Therefore, it seemed likely that the majority of studies would report either log-rank statistics or estimates of hazard ratios, after fitting Cox's proportional hazards regression model, as an estimate of the intervention effect. However, the majority of studies reported mean healing times. We specified that we would deal with such continuous data by estimating the mean differences and 95% confidence intervals. Since the included studies report outcomes from participants with a variety of long bone injuries, which are well understood to have widely varying healing times normally, we chose to combine these data using standardised mean differences.

Dealing with missing data

We altered our method of dealing with missing continuous data where these remained unavailable after attempting to contact trial authors. In order to determine a conservative estimate of any treatment effect, we assumed that the missing data from participants in the treatment group lay at the extreme of the distribution (2 SD from the reported mean). Conversely, for participants in the control group we assumed the distribution was unaffected by the missing data.

Sensitivity analyses

We anticipated that outcomes may have been reported at a number of time points (e.g. six months and twelve months). We planned to include these outcomes in order to provide some sensitivity to the selection of an appropriate follow-up time for assessment of the treatment effect. Given these data were not available, such an analysis was not necessary.