Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials
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CRD summary
This review aimed to determine the efficacy of low intensity pulsed ultrasonography for healing of fractures. Overall, this was a well conducted review and the authors’ conclusion that whilst results are promising further research is required is likely to be reliable.

Authors' objectives
To determine the efficacy of low intensity pulsed ultrasonography for healing of fractures.

Searching
MEDLINE, EMBASE, CINAHL, HealthSTAR, and the Cochrane Central Registry of Controlled Trials were searched from inception to September 2008. Search terms were reported. The manufacturer of low intensity pulsed ultrasonography devices was contacted in order to locate any additional studies or ongoing trials. References of all relevant papers were also checked.

Study selection
Randomised controlled trials (RCTs) comparing low intensity pulsed ultrasonography with a control group in patients presenting with any form of fracture were eligible for inclusion in the review. Patient important outcomes were considered, in particular functional recovery.

The active ultrasound device in the majority of trials was the Sonic Accelerated Fracture Healing System, one trial used the Theramed 101-B ultrasound device. In all but two trials the comparator was sham ultrasound. Fracture location varied between studies: clavicle, distal radius, lateral malleolus, mandible, scaphoid and tibia. Duration of low intensity pulsed ultrasonography varied across trials. Most of the trials used imaging methods to assess bone healing. Participants were grouped into five clinical categories by two experienced surgeons: non-operatively managed fresh fractures, stress fractures, distraction osteogenesis, bone-grafting for non-union, and operatively managed fresh fractures.

A variety of outcomes were reported across the trials, the majority of which were considered to be surrogate endpoints. Only five studies reported patient important outcomes (time to return to active duty, time to full weight bearing, time to patient reported fracture healing and resumption of household activities, work or sports).

Two reviewers independently selected papers for inclusion in the review and any disagreements were resolved by discussion.

Assessment of study quality
The methodological quality of the included studies was assessed against the following criteria: allocation concealment, blinding, handling of withdrawals, co-interventions, compliance, similarity of timing of outcome assessment, and adherence to the intention-to-treat (ITT) principle.

Three reviewers independently assessed the methodological quality of the included studies and any disagreements were resolved by discussion.

Data extraction
Reduction in healing time and associated confidence intervals (CIs) were calculated from radiographic mean healing time. Mean time to return to active duty and time to full weight bearing were also calculated. Attempts to contact the authors of the included studies were made if clarification of details was required.

Three reviewers independently extracted data from the included studies and any disagreements were resolved by...
Methods of synthesis
Studies were combined in a meta-analysis using a random-effects model. Optimal information size was calculated (details provided in paper); if the sample size in any meta-analysis was less than the optimal information size then the result was considered to be imprecise. Statistical heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic ($I^2$ greater than 50% was considered to reflect substantial heterogeneity). Subgroup analysis was performed; fracture location, clinical category, and the technical specifications and application of ultrasound devices used. Tests of interaction were used to assess whether subgroups differed significantly from each other. Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria was used to assess the quality of evidence by outcome.

Results of the review
Thirteen RCTs were included in the review (n=563). Overall, the included trials were deemed to be of limited quality; limitations included lack of blinding of all relevant parties and substantial loss to follow-up in some studies (range 0 to 47%).

Pooled analysis suggested an overall benefit of low intensity pulsed sonography in mean reduction in healing time (33.6%, 95% CI: 21.4, 43.8); evidence of substantial heterogeneity was found ($I^2$=76.9%). Tests of interaction did not indicate a different treatment effect across clinical presentations. Of the five trials reporting patient important outcomes, only one trial found a positive effect of low intensity pulsed sonography (time to full weight bearing, p<0.05).

Low quality evidence from three trials suggested a benefit of low intensity pulsed ultrasonography in non-operatively managed fractures (faster radiographic mean healing time 36.9%, 95% CI: 25.6, 46.0%; $I^2$=41.6%). Low quality evidence from one trial found a benefit of low intensity pulsed ultrasonography in accelerating healing of established non-unions managed by bone graft (38 days, 95% CI: 26.3, 49.7), representing a 40.4% (95% CI: 30.8, 48.7) reduction in healing time. Four trials provided low quality evidence for acceleration of healing of operatively managed fresh fractures. Results from a pooled analysis (based on two trials) found no statistically significant difference in radiographic healing time between low intensity pulsed ultrasonography and controls on operatively managed tibial shaft fractures (16.6%, 95% CI: -76.8, 60.7; $I^2$=90.0). One trial of moderate quality found no effect of low intensity pulsed sonography on return to function in non-operatively managed stress fractures. Also, very low quality evidence from three trials suggested accelerated functional improvement after distraction osteogenesis.

Authors' conclusions
The evidence for low intensity pulsed ultrasonography for fractures is moderate to very low in quality and provides conflicting results. While overall results are promising further research with large well conducted trials is required.

CRD commentary
The review question was supported by clear inclusion criteria. Several sources were searched without language restriction. The authors made some attempts to locate unpublished studies, minimising the likelihood of language and publication bias. Methods used to select studies, extract data and assess validity were likely to have minimised the possibility of reviewer error and bias. Methodological quality was assessed using appropriate criteria and the authors took account of these results in their findings. Statistical methods used to pool the data appeared appropriate and a predefined subgroup analysis was performed. The authors highlighted the inconsistent reporting of outcomes across trials, raising the possibility of selective reporting bias. This was a well conducted review and the authors' conclusions are likely to be reliable.

Three reviewers are involved in a multicentre trial that has received partial funding from Smith and Nephew. Two reviewers are part of the GRADE working group.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that large well conducted trials on the effect of low intensity pulsed ultrasonography for the treatment of fractures, and in particular operatively managed fresh fractures, which measure patient important outcomes, such as quality of life and return to function, are needed.

Funding
None.

Bibliographic details

PubMedID
19251751

Original Paper URL
http://www.bmj.com/cgi/content/abstract/338/feb27_1/b351

Additional Data URL
http://www.ejbjs.org/cgi/content/abstract/90/11/2322

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Bone Transplantation; Fracture Healing; Fractures, Bone /therapy; Humans; Osteogenesis /physiology; Randomized Controlled Trials as Topic; Treatment Outcome; Ultrasonic Therapy /methods

AccessionNumber
12009102557

Date abstract record published
31/03/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.