The effect of low-intensity pulsed ultrasound therapy on time to fracture healing: a meta-analysis

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Authors' objectives
To determine whether low-intensity pulsed ultrasonography affects the time to fracture healing.

Searching
MEDLINE, EMBASE, the Cochrane Controlled Trials Register, HealthSTAR and CINAHL were searched for trials of ultrasonography and fracture healing, published in any language from 1966 to December 2000. In addition, selected journals published from 1996 to December 2000 were handsearched, and attempts were made to contact content experts in the fields of interest and the primary authors of the reviewed trials. The bibliographies of the retrieved trials and other relevant publications, including reviews and meta-analyses, were examined for additional articles. The first two stages of the search strategy of the UK Cochrane Centre (see Other Publications of Related Interest no.1) were used to identify randomised controlled trials (October 1996). This strategy was combined with the following terms: 'physical therapy', 'physiotherap$' 'ultraso$', 'bone remodeling' 'callus' 'fracture healing' and 'fractur$'.

Study selection
Study designs of evaluations included in the review
Only randomised trials were included in this review. The trials also had to blind both the patient and the assessor(s) as to fracture healing.

Specific interventions included in the review
The interventions had to include the administration of low-intensity pulsed ultrasound treatments to at least one of the treatment groups. In all six included studies, the participants received daily 20-minute sessions with an ultrasound signal that was composed of a burst width of 200 microseconds (plus or minus 10%) containing 1.5-MHz (plus or minus 5%) sine waves, with a repetition rate of 1 kHz (plus or minus 10%) and a spatial average temporal intensity of 30 mW/cm2 (plus or minus 30%).

Participants included in the review
Patients of either sex needed to be skeletally mature with one or more fractures. The three trials in the meta-analysis included patients with tibial shaft, distal radius and scaphoid fractures.

Outcomes assessed in the review
The outcome assessed was time to fracture healing, as determined radiographically by the bridging of three or four cortices.

How were decisions on the relevance of primary studies made?
Two reviewers independently applied the inclusion criteria to the potentially eligible studies.

Assessment of study quality
The reviewers assessed the quality of each trial using the scale of Jadad et al. (see Other Publications of Related Interest no.2). This is a 5-point scale that evaluates the quality of the trial methodology on the basis of description and appropriateness of randomisation and double-blinding, and assessment of study withdrawals and likelihood of bias. In addition, the reviewers assessed whether the trial reports described efforts to ensure that randomisation codes had been concealed at least until treatment allocation occurred. Information on the identity and affiliation of the authors, the journal and date of publication, acknowledgements and sources of funding were deleted from each of the copies. The masked copies were independently assessed by two reviewers. Trials that received a score of two or less on the Jadad scale were regarded as being of a low quality and likely to yield biased estimates of treatment effects. The reviewers resolved any disagreements by discussion to achieve consensus.
Data extraction
Two reviewers independently abstracted the data from each eligible study. The data abstracted included demographic information, method, treatment groups, interventions and time to fracture healing (the primary outcome). For each study, the reviewers calculated the effect size as the mean difference in healing time between the treatment and control groups, divided by the pooled standard deviation (SD).

Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis. A random-effects model was used for all analyses. The effect sizes were weighted by the inverse of the SD and combined to compute an overall weighted mean effect size. The effect size was calculated as a weighted mean difference. The methods of Hedges and Olkin (see Other Publication of Related Interest no.3) were used to test for statistical significance.

How were differences between studies investigated?
The methods of Hedges and Olkin (see Other Publication of Related Interest no.3) were used to test for homogeneity. The three studies pooled involved the treatment of different fracture sites (scaphoid, tibial shaft and distal radial fractures). The authors stated that, as the process of fracture healing is consistent across all fractured bones, the effect of ultrasonography versus placebo on the time to fracture healing should also be similar. Their view was that in pooling trials with the same intervention directed toward fractures of different bones, the generalisability and usefulness of the meta-analysis would be considerably improved. However, they did exclude two studies since they felt that prior operative treatment with an intramedullary nail was an important difference between the methods in these trials and the other studies.

Results of the review
Six studies met the inclusion criteria for the review, of which three (158 patients) were included in the meta-analysis. One analysed previously presented data and two used reamed intramedullary nailing before application of the intervention.

The pooled results from the 3 studies showed that time to healing was significantly shorter in the groups receiving low-intensity pulsed ultrasound treatment than in the control groups. The weighted average effect size was 6.41 (95% confidence interval: 1.01, 11.81), which converts to a mean difference in healing time of 64 days between the treatment and control groups. The 2 studies that evaluated ultrasound therapy following reamed intramedullary nailing of tibial shaft fractures were limited in size, and showed no difference in mean time to healing between the treatment and control groups: 155 (SD=22) days versus 125 (SD=11) days (p=0.76) in one study, and 155 (SD=22) days versus 129 (SD=12) days (p>0.05) in the other.

There was absolute agreement between the reviewers on the quality score for 4 trials, and a difference of one point for 2 trials (intra-class correlation coefficient 0.77; p=0.03).

Authors' conclusions
Ultrasound therapy may be beneficial to fracture healing. Treatment with a low-intensity pulsed ultrasound signal may reduce healing time, and could yield substantial cost-savings and decreases in disability associated with delayed union and nonunion of fractures.

CRD commentary
This was a well-conducted review with clear inclusion criteria in terms of the study design, participants, intervention and outcome. The search was comprehensive with no language restrictions. The review process was thorough. The selection of trials, validity assessment and data extraction were all performed independently by two reviewers. Heterogeneity was assessed and appropriate reasons were given for pooling just three of the six included studies. However, the review has limitations as expressed by the authors. The three studies pooled involved the treatment of...
different fracture sites (scaphoid, tibial shaft and distal radial); the authors' rationale for this has been explained previously. Despite these limitations, the review presents important results and paves the way for further clinical trials in this area.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors state that further clinical trials are needed to determine the optimal role of ultrasound therapy in fracture healing.

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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.