

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

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Abstract

Background: The effect of low-intensity ultrasonography on fracture healing is controversial, and current management of fractures does not generally involve the use of ultrasound therapy. We describe a systematic review and meta-analysis of randomized controlled trials of low-intensity pulsed ultrasound therapy for healing of fractures.

Methods: We searched 5 electronic databases (MEDLINE, EMBASE, Cochrane Database of Randomised Clinical Trials, HealthSTAR and CINAHL) for trials of ultrasonography and fracture healing, in any language, published from 1966 to December 2000. In addition, selected journals published from 1996 to December 2000 were searched by hand for relevant articles, and attempts were made to contact content experts in the area of ultrasound therapy and fracture healing as well as primary authors of reviewed trials. Trials selected for review met the following criteria: random allocation of treatments; inclusion of skeletally mature patients of either sex with 1 or more fractures; blinding of both the patient and the assessor(s) as to fracture healing; administration of low-intensity pulsed ultrasound treatments to at least 1 of the treatment groups; and assessment of time to fracture healing, as determined radiographically by bridging of 3 or 4 cortices. Two reviewers independently applied selection criteria to blinded articles, and selected articles were scored for methodologic quality. The internal validity of each trial was assessed with the use of a 5-point scale that evaluates the quality of trial method on the basis of description and appropriateness of randomization and double-blinding, and assessment of study withdrawals and likelihood of bias.

Results: We identified 138 potentially eligible studies, of which 6 met our inclusion criteria. Agreement beyond chance of quality assessments of the 6 trials was good (intraclass correlation coefficient 0.77, $p = 0.03$). One trial was a repeat analysis of previously reported data, and 2 trials appeared to report on a shared group of subjects. Three trials, representing 158 fractures, were of sufficient homogeneity for pooling. The pooled results showed that time to fracture healing was significantly shorter in the groups receiving low-intensity ultrasound therapy 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.

Interpretation: There is evidence from randomized trials that low-intensity pulsed ultrasound treatment may significantly reduce the time to fracture healing for fractures treated nonoperatively. There does not appear to be any additional benefit to ultrasound treatment following intramedullary nailing with prior reaming. Larger trials are needed to resolve this issue.

Of the estimated 5.6 million fractures that occur annually in the United States, 5% to 10% demonstrate delayed healing or nonunion.¹ In an effort to reduce the substantial associated disability and socioeconomic costs,² a variety of interventions have been proposed, including the use of low-intensity pulsed ultrasonography.^{1,3,4}

Research

Recherche

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This article has been peer reviewed.

CMAJ 2002;166(4):437-41

Historically, fracture sites have been considered an absolute contraindication for the use of therapeutic ultrasonography. This is largely due to early animal studies showing that ultrasound treatment delayed, or even damaged, healing bone,^{5,6} despite some contradictory findings by other groups.^{7,8} However, more recent work has shown that the effect of therapeutic ultrasonography on healing bone is dictated by the intensity used. A high-intensity (1.0 W/cm²) continuous-wave ultrasound signal, as was applied in earlier animal studies, appears to be harmful;^{9,10} however, a low-intensity (30 mW/cm²) pulsed ultrasound signal appears to promote accelerated healing.^{11,12} This notion has been reinforced by positive findings (i.e., shorter time to fracture healing) in controlled animal trials^{3,13,14} and uncontrolled human trials.^{15,16} The exact mechanism by which therapeutic ultrasonography effects bone repair is unknown.^{4,17}

Recent controlled trials involving treatment of fractures in humans with therapeutic ultrasonography have yielded conflicting results.¹⁸⁻²² Furthermore, many commonly used teaching texts in physiotherapy on the use of therapeutic ultrasonography continue to list treatment over fracture sites as a contraindication²³⁻²⁵ or remain ambivalent about its usefulness,^{26,27} with few exceptions.²⁸ Many reviews on fracture management also neglect to recommend use of therapeutic ultrasonography,²⁹⁻³¹ with some exceptions.^{1,4,32} Current management of fractures or nonunion does not generally involve the use of ultrasound therapy.^{33,34}

Given the increased number of small randomized placebo-controlled trials comparing the effect of ultrasonography on fracture healing and the controversy regarding its use in fractures, we conducted a systematic review and meta-analysis of relevant randomized controlled trials to determine whether low-intensity pulsed ultrasonography affects the time to fracture healing.

Methods

Two of us (J.W.B. and E.T.) independently identified relevant randomized trials, in any language, by means of a systematic search of several electronic databases: CINAHL (1982 to December 2000), MEDLINE (1966 to December 2000), HealthSTAR (1975 to December 2000) and EMBASE (1983 to December 2000). We used the first 2 stages of the search strategy of the UK Cochrane Centre (October 1996)³⁵ to identify randomized controlled trials. This strategy was combined with the following terms: "physical therapy," "physiotherap\$", "ultraso\$", "bone remodeling," "callus," "fracture healing" and "fractur\$." We used the wild card term "\$" to increase the sensitivity of our search strategy by allowing the capture of any term that shared the letters preceding the "\$." For example, a search for "ultraso\$" would capture "ultrasound," "ultrasonics" and so on. We searched the Cochrane Database of Randomised Clinical Trials³⁶ using the terms "ultrasound" and "fracture healing." We reviewed the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analyses, for additional relevant articles. In addition to bibliography searches, one of us (J.W.B.) searched by hand 7 journals known to publish in the

area of interest to this study (*Clinical Orthopaedics and Related Research*, *Physiotherapy*, *Journal of Bone and Joint Surgery* [American and British volumes], *Physical Therapy*, *Archives of Physical Medicine and Rehabilitation* and *The Journal of Orthopaedic Trauma*) from 1996 to December 2000. We sent letters to the principal authors of all relevant retrieved randomized controlled trials as well as to content experts, in an effort to identify further published or unpublished trials or any research efforts in progress pertinent to this review.

Two reviewers (M.B. and A.V.K.) independently applied a priori inclusion criteria to the methods section of each potentially eligible study. Each of the following criteria had to be met: random allocation of treatments; inclusion of skeletally mature patients of either sex with 1 or more fractures; blinding of both the patient and the assessor(s) as to fracture healing; administration of low-intensity pulsed ultrasound treatments to at least 1 of the treatment groups; and assessment of time to fracture healing, as determined radiographically.

To assess trial validity, we obtained hard copies of trials identified for inclusion in the review. 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 given to 2 reviewers (M.B. and A.V.K.), both of whom are surgeons with graduate degrees in clinical epidemiology. The reviewers independently assessed the quality of each trial using the Jadad scale,³⁷ a 5-point scale that evaluates the quality of trial method on the basis of description and appropriateness of randomization and double-blinding, and assessment of study withdrawals and likelihood of bias. Trials that received a score of 2 points or less were regarded as being of low quality and likely to yield biased estimates of treatment effects.³⁸ In addition, the reviewers assessed whether the trial reports described efforts to ensure that randomization codes had been concealed at least until treatment allocation occurred.³⁹ There was absolute agreement between the reviewers on the score for 4 trials and a difference of 1 point for 2 trials (intraclass correlation coefficient 0.77; $p = 0.03$). The reviewers resolved disagreements by discussion to achieve consensus.

The time to fracture healing, as defined by radiographic evidence of cortical bridging of 3 or 4 cortices, for each treatment arm was extracted from the studies. Two of us (M.B. and A.V.K.) independently abstracted data from each eligible study. Data abstracted included demographic information, method, treatment groups, interventions and time to fracture healing (the primary outcome). All discrepancies were resolved by discussion to achieve consensus.

For each study we calculated the effect size as the mean difference in healing time between the treatment and control groups divided by the pooled standard deviation (SD). We used a random effects model for all analyses. 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 used to test for statistical significance and homogeneity were those of Hedges and Olkin.⁴⁰ Our decision to pool results across studies was based on a nonsignificant test of heterogeneity and clinical sensibility. For example, we would pool data if, across the range of populations, interventions, outcomes and methods, we would expect, more or less, the same treatment effect. For the outcome measure — time to fracture healing — we reported the estimate of effect size and 95% confidence interval.

Results

We identified 138 potentially eligible studies, of which 6 (5 in English and 1 in German) met our inclusion criteria and underwent review (Fig. 1). Of the 6 studies 3 were excluded from the final analysis:^{18,19,41} one⁴¹ was a repeat analysis of previously presented data,^{20,21} and the others^{18,19} made use of reamed intramedullary nailing before the ultrasound signal was applied and appeared to report on a shared group of 30 subjects. We reached this conclusion following examination of demographic information of the respective study populations. Because sex and age were reported in one study¹⁸ and age, weight and height were reported in the other,¹⁹ we were able to compare subjects by age within allocation groups (treatment v. control). This comparison showed that 30 subjects had an identical match for age and allocation between the 2 studies. In addition, according to

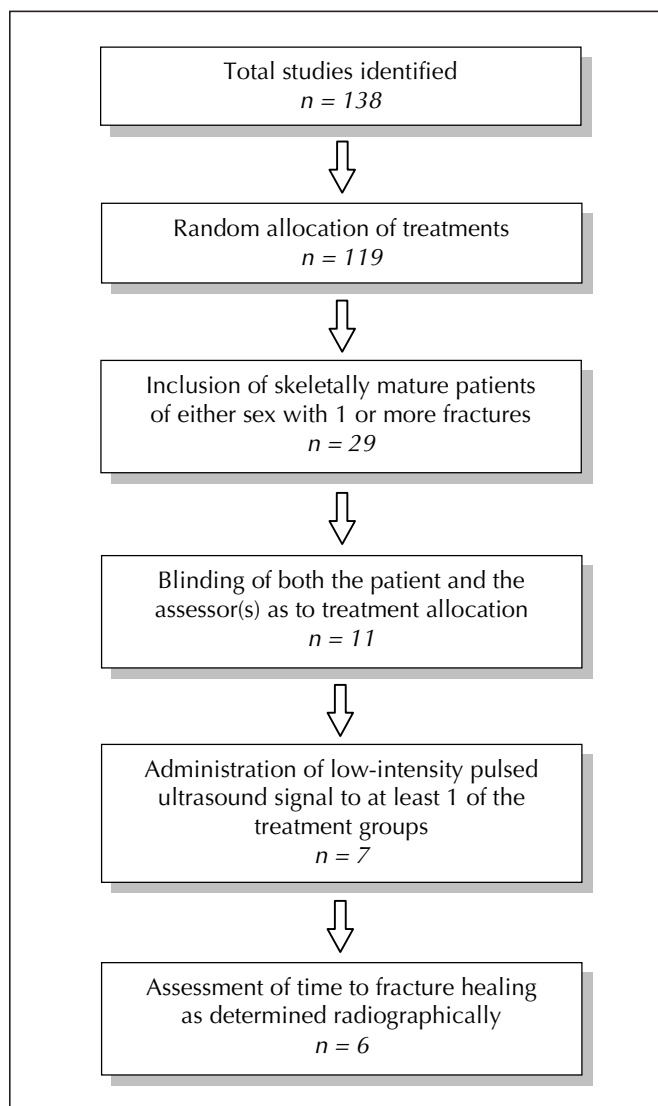


Fig. 1: Process of screening retrieved studies for inclusion in overview, according to predefined eligibility criteria.

the methods sections, these subjects were recruited at the same institution over the same study period. Neither study referenced the other or indicated that the results for fracture healing had been reported elsewhere. Attempts to contact the authors of the 2 studies to clarify this issue were unsuccessful. From 10 letters sent out (4 to content experts and 6 to the principal authors of the included trials), 2 responses were received, 1 of which identified a trial in progress, the results of which were unavailable for analysis at the time this article was prepared.

Baseline characteristics of the studies selected for review

In all 6 studies the investigators required their treatment groups to receive daily 20-minute sessions with an ultrasound signal that was composed of a burst width of 200 μ s ($\pm 10\%$) containing 1.5-MHZ ($\pm 5\%$) sine waves, with a repetition rate of 1 kHz ($\pm 10\%$) and a spatial average temporal intensity of 30 mW/cm² ($\pm 30\%$). To ensure a standardized signal, each group made use of the Sonic Accelerated Fracture Healing System (SAFHS 2A) (Exogen, Piscataway, NJ). In each study the treatment provided to the control group was indistinguishable from that provided to the treatment group. Identical units were used, with consistent setup, and both the subjects and the investigators were blinded as to treatment allocation. Ultrasound unit settings could not be modified, a warning signal was sounded if there was not proper coupling to the skin, and the patient's compliance with the device was measured by an elapsed-time recorder inside the unit and by a daily log book maintained by the subject. In addition, clinicians assessing radiographs were also blinded as to whether ultrasound therapy had been provided.

Among the 3 studies excluded from the final analysis, the repeat analysis of trials by Cook and colleagues⁴¹ examining the effect of ultrasound therapy on tibial and radial shaft fractures ($n = 111$) showed that the healing time for tibial fractures was reduced by 41% among smokers ($p < 0.006$) and by 26% among nonsmokers ($p < 0.05$). Healing time for distal radial fractures was reduced by 51% among smokers ($p < 0.003$) and by 34% among nonsmokers ($p < 0.0001$). Ultrasound treatment also resulted in a trend toward a reduced incidence of tibial delayed union, although this difference did not reach significance except for a subgroup of subjects who were smokers at the time of the study or had been smokers within the previous 10 years ($p = 0.02$). Emami and associates^{18,19} ($n = 32$ and 30 respectively) examined the effect of ultrasound treatment on intramedullary fixed tibial fractures and noted equivocal results. We identified an additional study that did report on the effect of ultrasound therapy on distal radial fractures; however, the authors used range of motion as their outcome and did not provide data on time to healing.⁴² Attempts to contact the principal author to determine whether such data were available were unsuccessful.

The 3 studies retained in the final analysis²⁰⁻²² displayed nonsignificant heterogeneity ($p = 0.56$) and similar point estimates, and their results were pooled ($n = 158$ fractures) (Table 1). These studies, in which a total of 89 men and 69 women were enrolled, examined the effect of low-intensity ultrasound treatment of scaphoid,²² distal radial²¹ and tibial shaft²⁰ fractures.

Time to fracture healing

The pooled results from the 3 studies showed that the 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.

Although the 2 studies that evaluated ultrasound therapy following reamed intramedullary nailing of tibial shaft fractures^{18,19} were limited in size, they showed no difference in mean time to healing between the treatment and control groups (155 [SD 22] days v. 125 [SD 11] days [$p = 0.76$] in one study,¹⁸ and 155 [SD 22] days v. 129 [SD 12] days [$p > 0.05$] in the other¹⁹).

Interpretation

We identified 6 human trials that met our inclusion criteria and that examined the effect of ultrasound therapy on fractures.^{18-22,41} Four of the 6 studies reported positive results.^{20-22,41} All 3 studies that met our eligibility criteria for statistical pooling were randomized double-blind placebo-controlled trials.²⁰⁻²² It was not surprising, therefore, that these studies scored high on the Jadad scale,³⁷ which bases 80% of its total score on randomization and blinding. The remaining 2 studies, which appeared to report on a shared subject group, gave equivocal findings but may have suffered from a type II statistical error.^{18,19} Alternatively, the authors suggested that the use of intramedullary nails may have negated the effects of ultrasonography on bone healing reported in other studies. Reaming of fractures is

known to have an osteoblastic effect and may explain their negative results.^{43,44}

Our analysis had limitations. Our results were based on the pooling of studies that involved the treatment of different fracture sites (scaphoid, tibial and distal radial fractures). Although baseline healing time differs by bone size and site of fracture, the process of fracture healing is consistent across all fractured bones,⁴⁵ and the effect of ultrasonography versus placebo on the time to fracture healing should also be similar. We also felt that, by pooling trials with the same intervention directed toward fractures of different bones, the generalizability and usefulness of our meta-analysis would be considerably improved.⁴⁶ The pooled estimate excluded 2 studies owing to heterogeneity. We felt, however, that prior operative treatment with an intramedullary nail was an important difference in these trials' method when compared with the other studies. In addition, caution must be used in generalizing our findings. Although we have confidence in the calibration of the machines used in the studies reviewed, Guirro and coworkers⁴⁷ reported large discrepancies between the intensity setting of therapeutic ultrasound machines and the actual intensity being emitted by the transducer. The SAFHS 2A ultrasound devices used in the pooled trials are recalibrated between uses to maintain their accuracy,⁴⁸ and although we are unaware of any formal reliability studies, the numerous fail-safe measures inherent to the use of the SAFHS 2A device should allow for a high degree of consistency in therapeutic application.

Conclusion

Our analysis suggests that ultrasound therapy may be beneficial to fracture healing. This finding is of considerable importance in that 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.² Further clinical trials are needed in order to determine the optimal role of ultrasound therapy in fracture healing.⁴⁹

Table 1: Summary of the trials included in the meta-analysis

Trial	Location of fracture	Sample size, no. of fractures		Mean age (and SD), yr	Male: female ratio	Fracture		Mean time to healing (and SD), d		Effect size	Quality score†
		Treatment group	Control group			Open	Closed	Treatment group	Control group		
Heckman et al ³⁹	Tibial shaft	33	34	Treatment 36 (2) Control 31 (2)	54:13	3 (grade I)	64	114 (7.5)	182 (15.8)	5.41	5
Kristiansen et al ⁴⁰	Distal radius	30	31	Treatment 54 (3) Control 58 (2)	10:51	0	61	61 (3)	98 (5)	8.82	5
Mayr et al ⁴²	Scaphoid	15	15	37 (14)	25:5	NA	NA	43 (11)	62 (19)*	1.20	4

Note: SD = standard deviation, NA = not applicable.

*Healing time was defined as the time from initiation of treatment to removal of the cast.

†Maximum score 5 (see Methods section).

Competing interests: None declared.

Contributors: Dr. Busse was responsible for conceiving and implementing the study design, collecting and interpreting the study data, and preparing and critically revising the manuscript. Drs. Bhandari and Kulkarni were responsible for designing and implementing the data analysis, interpreting the study data and critically revising the manuscript. Dr. Tunks was responsible for conceiving and implementing the study design, interpreting the study data and critically revising the manuscript.

Acknowledgements: We thank Dr. Wolfram Bosenberg for translating reference 22 into English.

Dr. Kulkarni is supported by the Duncan L. Gordon Fellowship from the Hospital for Sick Children Foundation, Toronto. Dr. Bhandari is supported in part by a Clinical Scientist Fellowship, Department of Clinical Epidemiology and Biostatistics, McMaster University. Oncidium Health Group Inc. is a private incorporated company that consults on and manages long-term disability claims and conducts studies on rehabilitation and issues of disability management; it is funded by employers and insurers.

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