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Cochrane in *CORR*®: Ultrasound and Shockwave Therapy for Acute Fractures in Adults (Review)

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Importance of the Topic

Fractures cause considerable morbidity and often result in pain, loss of function, and decreased productivity [8]. Delayed union and nonunion complicate approximately 5% to 10% of fractures and often require further surgical or nonsurgical intervention [7]. A number of adjunct methods have been proposed to accelerate fracture healing, including low-intensity pulsed ultrasound (LIPUS).

Ultrasound therapy delivers noninvasive soundwaves, which are believed to induce low-level micromechanical forces at the fracture site, stimulating the molecular and cellular responses in fracture healing [5, 13]. The first successful application of LIPUS for human nonunions was demonstrated in 1983 in a study that reported healing in 70% of 26 fractures [15]. In 1994 and 2000, the FDA approved ultrasound for accelerating the healing of acute fractures and existing nonunions [11].

This Cochrane Review systematically reviewed the best available evidence on LIPUS, high-intensity pulsed ultrasound, and extracorporeal shockwave therapy for acute fractures in adults. After evaluating 12 studies that enrolled a total of 622 patients with 648 fractures, no meaningful reductions with LIPUS in time to

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We are pleased to publish the next installment of Cochrane in CORR®, *our partnership between* CORR®, *The Cochrane Collaboration*®, *and McMaster University's Evidence-Based Orthopaedics Group. In it, researchers from McMaster University and other institutions will provide expert perspective on an abstract originally published in The Cochrane Library that we think is especially important.*
(Griffin XL, Parsons N, Costa ML, Metcalfe D. Ultrasound and shockwave therapy for acute fractures in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD008579. DOI: 10.1002/14651858.CD008579.pub3).

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Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library (http://www.thecochranelibrary.com) should be consulted for the most recent version of the review.
This Cochrane in *CORR*® column refers to the abstract available at: DOI:10.1002/14651858.CD008579.pub3.

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union of acute fractures, fractures with delayed unions, or nonunions were found when compared to controls.

Upon Closer Inspection

Heterogeneity in systematic reviews should be explored and explained. Exploration may reveal poor study design, inconsistent reporting, or reliability of outcome measures or "real" sources of variation related to patient or fracture characteristics, interventions, and outcome measures [6]. The authors reported considerable statistical heterogeneity (I^2 = 90%) for the outcome of fracture healing with LIPUS, which was explored but not explained by two subgroup analyses a priori: Upper- versus lower-limb fractures and smoking status. An additional subgroup analysis comparing nonoperatively with surgically-treated fractures likewise found no benefit to LIPUS. Posthoc sensitivity analyses, in which outlier studies were excluded, also did not explain heterogeneity. The authors did not explore the assessment of fracture union, a potentially important source of heterogeneity in fracture studies.

Although adjudication of outcomes has been shown to provide a more reliable and valid outcome assessment in fracture healing [12], only one of the included studies [10] used a blinded panel to adjudicate outcomes. Furthermore, the method and timing of assessing radiographic union varied widely, with no consistent measure of radiographic union used across studies. Standardized assessments of union, such as the Radiographic Union Scale for Tibial (RUST) fractures [14] or the Radiographic Union Score for Hip [4] have been shown to substantially improve agreement of fracture-healing assessment [1, 9].

Take-home Messages

Despite the apparent lack of benefit, a survey of 450 Canadian trauma surgeons in 2008 [3] (response rate: 79%) showed that 45% of surgeons used either LIPUS or electrical stimulators as part of their treatment strategies for managing acute tibial fractures in adults, divided almost equally between electrical stimulators and ultrasound therapy. Most respondents (80%) considered a reduction in healing time due to a bone stimulator of 6 weeks to be clinically important. The current available evidence, however, does not support this practice.

The Trial to Re-evaluate Ultra-Sound in the treatment of Tibial (TRUST) fractures [2] is a concealed, blinded randomized trial engaging 25 trauma centers comparing LIPUS versus placebo for operatively treated tibial fractures using primarily patient-important functional outcomes (Physical Component Summary Score of the SF-36). Radiographic assessment of healing is assessed using the RUST score, which was found to exhibit improvements in reliability compared to previously published scores [14].

By addressing many of the methodological issues inherent in previous trials, particularly issues of clinical heterogeneity, small sample size, risk of bias, and limited assessment of patient-important outcomes, TRUST aims to definitively elucidate the role of ultrasound therapy in fracture healing.

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Appendix

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

Griffin XL, Parsons N, Costa ML, Metcalfe D

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[Intervention Review]

Ultrasound and shockwave therapy for acute fractures in adults

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ABSTRACT

Background

The morbidity and socioeconomic costs of fractures are considerable. The length of time to healing is an important factor in determining a person's recovery after a fracture. Ultrasound may have a therapeutic role in reducing the time to union after fracture. This is an update of a review previously published in February 2012.

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 (2 June 2014), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2014, Issue 5), MEDLINE (1946 to May Week 3 2014), EMBASE (1980 to 2014 Week 22), trial registers and reference lists of articles.

Selection criteria

Randomised and quasi-randomised controlled trials evaluating ultrasound treatment in the management of acute fractures in adults. Studies had to include participants over 18 years of age with acute fractures, reporting outcomes such as function; time to union; non-union; secondary procedures such as for fixation or delayed union or non-union; adverse effects; pain; costs; and patient adherence.

Data collection and analysis

Two authors independently extracted data from the included studies. Treatment effects were assessed using mean differences, standardised mean differences or risk ratios using a fixed-effect model, except where there was substantial heterogeneity, when data were 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.

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Main results

We included 12 studies, involving 622 participants with 648 fractures. Eight studies were randomised placebo-controlled trials, two were randomised controlled trials without placebo controls, one was a quasi-randomised placebo-controlled trial and one 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.

'Risk of bias' assessment of the included studies was hampered by the poor reporting of methods, frequently resulting in the risk of bias of individual domains being judged as 'unclear'. Both quasi-randomised studies were at high risk of bias, including selection and attrition bias. Three studies were at low risk of selection bias relating to allocation concealment the majority of studies were at low risk of performance bias as they employed a form of intervention blinding.

Only limited data were available from three of only four studies reporting on functional outcome. One study of complete fractures found little evidence of a difference between the two groups in the time to return to work (mean difference (MD) 1.95 days favouring control, 95% confidence interval (CI) -2.18 to 6.08; 101 participants). Pooled data from two studies found LIPUS did not significantly affect the time to return to training or duty in soldiers or midshipmen with stress fractures (MD -8.55 days, 95% CI -22.71 to 5.61; 93 participants).

We adopted a conservative strategy for data analysis that was more likely to underestimate than to overestimate a benefit of the intervention. After pooling results from eight studies (446 fractures), the data showed no statistically significant reduction in time to union of complete fractures treated with LIPUS (standardised mean difference (SMD) -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 five of the eight trials (333 fractures) reporting proportion of delayed union or non-union showed no significant difference between LIPUS and control (10/168 versus 13/165; RR 0.75; 95% CI 0.24 to 2.28). 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 (101 participants).

One quasi-randomised study found no significant difference in non-union at 12 months between internal fixation supplemented with ECSW and internal fixation alone (3/27 versus 6/30; RR 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 (MD -0.80, 95% CI -1.23 to -0.37). 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

Ultrasound and shockwave treatment for recently broken bones in adults

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 their healing takes considerably longer than expected. This review set out to find out whether treatment with ultrasound, in a variety of forms, accelerates fracture healing and reduces complications associated with new (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.

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

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This is an update of a review previously published in February 2012. We did a new literature search up till 2 June 2014 but did not find any new studies. There are 12 studies, involving 622 participants with 648 fractures, included in this review. In all the studies we included, participants were assigned randomly to one of two groups, one group receiving treatment by ultrasound and the other group receiving no treatment or sham treatment. Most participants had a recent complete fracture of a single bone. The participants of two trials had 110 incomplete or stress fractures that resulted from heavy exercise. Four trials tested the effects of ultrasound on healing of 203 upper limb fractures and the other trials, on 130 lower limb fractures. The most commonly investigated bone was the tibia (shin bone). Eleven trials tested low-intensity pulsed ultrasound and one trial with 59 fractures tested shockwave therapy.

Most trials compared a working ultrasound device with a sham device and thus protected against placebo effects. The placebo effect is a phenomenon whereby patients experience a treatment effect that is not objectively attributable to the treatment itself. However, studies varied substantially in terms of quality and risk of having biased results. In many cases the quality of reporting was poor, which made it difficult to determine which biases might have affected each study. The risk of bias across many domains therefore had to be judged as 'unclear'. The results of many trials were probably biased because of missing data from several trial participants. Additionally, the trials were very different from each other; for example, they varied in the bone that was broken and whether or not the fractures were also treated surgically. Based on analyses that adjusted for these missing data, the available evidence did not confirm that ultrasound improved the time taken for bone healing or prevented the problem of the bone failing to heal at all (eight trials with 333 fractures). The results from one low quality trial (with 59 fractures) testing shockwave therapy were inconclusive.

Few complications were reported in any of the studies and these were not related to the ultrasound or shockwave therapy.

While a potential benefit of ultrasound for the treatment of acute fractures in adults cannot be ruled out, the currently available evidence from 12 quite different trials is insufficient to support the routine use of ultrasound in clinical practice. Future studies should measure return to full function and normal activity and should try to ensure all participants are followed up.

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

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