

**Busse JW, Kaur J, et al. Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials. BMJ 2009;338:b51.**

Design: meta-analysis of randomized clinical trials

Study question: does low-intensity ultrasonography reduce the time to fracture healing?

PICOS:

- Patient population: Patients with one of five types of bone fracture
  - o Nonoperatively managed fresh fractures
  - o Nonoperatively managed stress fractures
  - o Distraction osteogenesis
  - o Bone grafting for nonunion
  - o Operatively managed fresh fractures
- Interventions: low intensity pulsed ultrasonography (LIPUS)
- Comparisons: Sham treatment with visually indistinguishable devices
- Outcomes: Fracture healing time by radiographic or patient-centered measures
  - o Radiographic bridging of three cortices or appearance of third callus
  - o Patient-centered outcomes such as return to full participation, pain, time to full weight-bearing, disappearance of tenderness at the fracture site
- Study types: Randomized controlled trials

Study selection:

- Databases included CINAHL, EMBASE, MEDLINE, HealthSTAR, and the Cochrane Central registry from inception through Sept. 2008
- Two authors independently assessed articles for inclusion and graded risk of bias by appraising randomization method, allocation concealment, blinding, handling of withdrawals, co-interventions, compliance, similarity of timing of outcome assessment, and intention to treat analysis of outcomes
- Overall quality of evidence was assessed with GRADE criteria, which begin by assuming that randomized trials are of high quality but which may deduct points for several criteria
  - o Risk of bias by above criteria
  - o Lack of consistency between studies (treatment effects in different directions, widely differing treatment effects whose ranges do not overlap)
  - o Indirectness (outcomes of surrogate measures only, such as radiographic healing rather than return to function)
  - o Imprecision (treatment effect measures having wide confidence intervals which include both benefit and harm, preventing the clinician from knowing whether a treatment is effective)

- A treatment effect of 20% reduction in healing time was considered clinically important and meaningful
- Reporting bias (selective outcome reporting or publication bias)

#### Results:

- 564 potentially eligible articles were screened, 18 were retrieved in full text, and 15 trials met inclusion criteria; two trials reported on a shared group of patients, leaving 13 unique trials for analysis
- Most studies reported only surrogate end points and were downgraded for indirectness; five studies did report outcomes of importance to patients
- For nonoperatively managed fresh fractures, one study with good control of bias and good directness, but with an imprecise treatment estimate, provided moderate quality evidence that LIPUS does not lead to faster return to function (1.4 days, 95% confidence interval was from 0.56 days slower to 3.36 days faster)
- Three trials of nonoperatively managed fresh fractures with poor control of bias yielded low quality evidence for the indirect outcome of reduced time to radiographic fracture healing by 37% (95% CI 25.6% to 46%)
- A single trial of nonoperatively managed stress fractures, with good control of bias and a direct outcome, but an imprecise estimate of treatment effect, produced moderate quality evidence suggesting no effect on return to function (0.4 days, 95% CI was from 13.1 days slower to 13.9% faster)
- Three trials with serious limitations in terms of bias provided very low quality evidence for accelerated functional improvement in fractures managed with distraction osteogenesis
- One trial with good control of bias provided low quality evidence for the indirect outcome of reduced time to radiographic healing
- Two trials of operatively managed fresh fractures with serious methodological limitations and inconsistent results yielded low quality, imprecise evidence for faster return to full weight bearing by 3.4 weeks, but the confidence intervals were from 2.1 weeks slower to 8.9 weeks faster return to weight bearing
- Two additional trials of operatively managed fresh fractures with serious methodological limitations and inconsistent results yielded very low quality evidence of a 16.6% reduction in radiographic healing, but again the confidence intervals spanned the possibility of slower radiographic healing

#### Authors' conclusions:

- There is moderate to very low quality evidence for LIPUS in accelerating functional recovery among patients with fractures
  - However, the two studies with the highest quality evidence showed no difference in functional outcome

- The studies which did show positive results for LIPUS used a surrogate outcome of radiographic healing, and also had methodological limitations such as lack of blinding and dubious allocation concealment
  - o Reduction in healing time shown on plain films may not translate into patient important benefit
- Nevertheless, LIPUS may provide important benefits to patients with fracture, but large trials of high methodological quality and patient-important outcomes are needed to establish whether this is the case

Comments:

- The authors' conclusion that LIPUS may provide important benefits should be read as saying that these benefits are within the realm of possibility and have not been ruled out, rather than to suggest that the benefits are likely to exist
  - o This reading is necessary because the better studies of functional outcome did not show a benefit of LIPUS, with wide confidence intervals and the point estimates being slightly positive, but falling short of a clinically meaningful difference; 0.4 days faster return to duty is essentially no difference)
- LIPUS is used as an acronym for low-intensity pulsed "ultrasonography;" this is probably not the best usage of that term, which is mainly for imaging; it should be called "ultrasound" instead
- The use of the GRADE system for rating evidence is useful because it downgrades studies with surrogate outcomes and with imprecise results, as well as evaluating them for control of bias as with the Cochrane reviews
- The authors undertook a later pilot study (Busse et al 2014) of LIPUS for fresh tibial fractures, but found difficulties with recruitment; the recruitment rate was 10.5%
  - o Even though compliance with LIPUS was acceptable, the patients did offer feedback to the authors that some of the questionnaires were burdensome to complete
  - o The results from the 51 patients who were eventually randomized did not show that LIPUS improved physical function as measured on the SF-36 or two other health status questionnaires
- Overall, the results do not suggest that LIPUS is likely to be very effective for fracture healing

Assessment: A high quality systematic review and meta-analysis which supports a statement that there is a lack of evidence that LIPUS has clinical efficacy in returning fracture patients to normal activities, and that the estimates of effectiveness in accelerating radiographic fracture healing are likely to be biased and inaccurate

Reference:

Busse JW, Bhandari M et al. Trial to re-evaluate ultrasound in the treatment of tibial fractures (TRUST): a multicenter randomized pilot study. *Trials* 2014;15:206