Schofer MD, Block JE, et al. Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. BMC Musculoskelet Disord. 2010;11:229.

Design: randomized clinical trial

Purpose of study: In the setting of delayed union in a tibial fracture, does low-intensity pulsed ultrasound (LIPUS) increase the rate of fracture healing:

Population/sample size/setting:

- 101 patients (24 women, 77 men, mean age 44) treated for delayed tibial union at 6 hospitals in Germany
    - Delayed union defined on the basis of standard AP and lateral x-rays with a lack of bony continuity or bone reaction at the fracture site for no less than 16 weeks after the injury or after the most recent intervention
- Exclusion criteria were pregnancy, revision or reoperation of the fracture within the past 16 weeks, deep wound infection, or excessive malalignment

Interventions:

- Randomization was to either LIPUS (n=51) or sham control (n=50), used by the patients for 20 minutes per day for 16 weeks
    - LIPUS device was set to 1.5 MHz frequency, 1 kHz repetition rate, 200 microsecond pulse duration, and 30mW/cm^2 spatial density
    - Sham device emitted acoustic pressure waves but was otherwise inactivated

Outcomes:

- Primary outcomes were bone mineral density (BMD) and gap area at the fracture site, all assessed by CT which was evaluated at a central radiology lab 16 weeks after the beginning of the initiation of LIPUS or sham LIPUS
    - BMD was assessed at the fracture site, 2-3 mm proximal to the fracture site, and 2-3 mm distal to the fracture site, and was also assessed in a healthy reference area
    - BMD was estimated using the mean CT attenuation coefficients, or Hounsfield Units (HU)
    - Gap area was estimated directly from CT images
- AP and lateral x-rays were also taken at 1, 2, and 3 month followup intervals and read by blinded physicians for healing status (healed/not healed) at 16 weeks [sic]
- There was a difference in attrition rate between groups: 24% (12 od 50) sham LIPUS patients had missing outcome data, compared to 9.8% (5 of 51) LIPUS patients

    - Multiple statistical imputation were used to minimize bias from differential dropouts
- Compliance with device use, taken from records embedded in the devices, was very high, with 91% of the expected number of minutes having the devices in actual active use
- The gain in BMD was greater for LIPUS (0.87 HU) than for sham LIPUS (0.57 HU); the standardized mean difference between groups was 0.53 SD, which is considered a moderate effect size
    - This represents the effect size in completers, who had followup outcome data; the multiple imputation analysis which was done to compensate for missing data yielded nearly the same effect size
- The standardized effect size for the gap area at the fracture site also favored LIPUS over sham LIPUS, with a standardized mean difference of 0.47
- Based on log-transformed data, the adjusted mean improvement in BMD was 1.34 times greater for LIPUS than for sham LIPUS
- At the end of 16 weeks, the blinded physicians looking at AP and lateral films judged fracture healing to be present in 65% of LIPUS and in 46% of sham LIPUS patients
- Additional analyses, which adjusted for such variables as time since fracture, also estimated greater BMD gain with LIPUS than with sham LIPUS

Authors' conclusions:

- LIPUS accelerates the healing process and probably improves the odds of achieving a solid union in patients with delayed union of tibial fractures
- Long times since fracture (more than 48 weeks) are associated with poorer radiographic outcomes regardless of treatment group, and LIPUS should be done at the earliest interval when delayed union is detected

Comments:

- The differential dropout rate, which was higher in the sham than the LIPUS group, is not likely to have greatly biased the results, even though multiple imputation methods can be difficult to execute and interpret
- The CT data were analyzed centrally at one location; it is likely, but not explicitly stated, that these reports were done without information as to treatment group
- BMD and fracture gap area are surrogate measures of solid union
    - There were blinded physicians who evaluated the plain AP and lateral films at 16 weeks, and LIPUS appeared to have higher union rates; these presumably were different physicians from those who were involved in looking at the CT scans

- The plain x-rays were done at 1, 2, and 3 months, but the fracture union was evaluated at 16 weeks, which is about 4 weeks after the 3 month films were done; the reasons for this are not clear from the text of the study
- LIPUS was estimated to have very low quality concerning fracture healing in a systematic review (Busse 2009), and one of the concerns was that surrogate measures of fracture healing may not translate into patient benefit
- The LIPUS devices, which saved data on time of actual use, showed high rates of adherence to treatment, which may have been greater for the study population than for other populations; this could be related to the fact that they were participating in a randomized trial, where followup is often more frequent and systematic than in the setting of daily clinical practice

Assessment: adequate for some evidence that in the setting of tibial fractures which have delayed union at 16 weeks, low-intensity pulsed ultrasound may accelerate gains in bone mineral density and fracture gap area when used daily for 16 weeks

Reference:

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