Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline

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Does low intensity pulsed ultrasound (LIPUS) accelerate recovery in adults and children who have experienced bone fractures or osteotomy (cutting of a bone)? An expert panel rapidly produced these recommendations based on a linked systematic review triggered by a large multi-centre randomised trial in adults with tibial fracture.

Fracture is common (see box on p 3). Bones can also be broken for medical reasons; osteotomy is a procedure whereby a bone is cut to shorten, lengthen, or to change its alignment. Following osteotomy, the bone has similar healing problems as traumatic fractures, and may require more extensive recovery.

Irrespective of age, location, and mechanism of the broken bone, whether it is managed with or without surgery, and whether it heals as expected or with delay, the idea of speeding or enhancing this healing to minimise symptoms and inconvenience for the patient is appealing. Bone stimulators such as LIPUS and electromagnetic field therapy might promote bone healing by stimulating bone growth (osteo genesis) in long or other bones.

Guidance from independent organisations on use of LIPUS for bone healing is scarce, but data suggest the device is commonly used in clinical practice (see box on p 3). Prices vary across countries, each device costing between US$1300 and $5000 (based on US and UK).

The TRUST randomised controlled trial published in *The BMJ* on 25 October 2016 found that the addition of LIPUS to standard care in 501 adult patients undergoing surgery for fresh tibial fracture did not improve functional recovery or accelerate radiographic healing at one year follow up compared with a sham device. The *BMJ* Rapid Recommendations team believed that the TRUST trial, if considered in a new systematic review and meta-analysis, could change practice. Previous systematic reviews had concluded that potential benefits of LIPUS on bone healing were highly uncertain, with calls for trials with safeguards against bias and a focus on outcomes important to patients. The linked publications in this package (see “Linked articles” box) synthesise the latest evidence and translate it for clinical care.
RAPID RECOMMENDATIONS

Population

Adults and children with a fracture or osteotomy

Choice of intervention

- **LIPUS**
  - Low intensity pulsed ultrasound, used to stimulate bone growth (ostegenesis)

  or

- **No ultrasound**
  - Standard care without ultrasound

Recommendations

**Comparison of benefits and harms**

<table>
<thead>
<tr>
<th></th>
<th>Favours LIPUS</th>
<th>No important difference</th>
<th>Favours no ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to radiographic healing</td>
<td>147</td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>Days to return to work</td>
<td>205</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td>Days to full weight bearing</td>
<td>73</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Pain score (0–100, lower better)</td>
<td>39</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Subsequent operations</td>
<td>128</td>
<td></td>
<td>160</td>
</tr>
<tr>
<td>Device-related adverse effects</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Evidence quality**

- Moderate
- High

**Key practical issues**

**LIPUS**

- Usually used for 15-20 minutes each day for 14 to 140 days
- Device can be cumbersome to travel with
- Health insurance may not cover cost

**No ultrasound**

- No practical issues

**Preferences and values**

The panel unanimously agreed that all or nearly all informed patients would elect not to apply LIPUS.

**Resourcing**

LIPUS is a costly device which does not represent a wise use of health resources.

**Other considerations**

LIPUS may be burdensome to use. This is reflected in the TRUST trial, in which many patients reported limited compliance.

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RAPID RECOMMENDATIONS

Background information

Bone fracture

• More than one in three people have a fracture at some point in their life
• Each year around four per 100 people of all ages experience a fracture
• Some 5-10% of these experience delayed healing or non-union of the fracture

LIPUS

• Guidance
  – 1994 US Food and Drug Administration (FDA) approved LIPUS for fracture healing and, in 2000, for treatment of established non-unions
  – 2010 UK National Institute for Health and Care Excellence (NICE) issued a statement supporting the use of LIPUS to reduce fracture healing time and to provide clinical benefit, particularly in circumstances of delayed healing and non-union

• Data on use
  – A Canadian survey of 450 trauma surgeons in 2008 found that nearly half of respondents were using bone stimulators to manage tibial fractures. Of those, about half used electro-magnetic field therapy and the other half used LIPUS
  – Global revenues for bone stimulators were about US$400m 2004. In 2007, sales from LIPUS were around $250m in the US
  – We found no data to describe whether use has changed over time

The evidence

Evidence requested from the panel to inform recommendations:

• A new rapid systematic review of the effects of LIPUS added to standard care for a variety of fractures and osteotomies
• A systematic literature search on patients’ values and preferences, which did not identify any relevant studies (see appendix 4 on bmj.com).

Systematic review of LIPUS for all fracture healing

The data from the TRUST trial were included in a linked systematic review of randomised trials of LIPUS compared with sham device or no device on patient-important outcomes in patients with a fracture or osteotomy. Fig 1 shows details about the trials and characteristics of included patients.

We judged that the systematic review provides evidence of moderate to high certainty that LIPUS has little or no impact on time to return to work, time to full weight bearing, pain, the number of subsequent operations, or time to radiographic healing (see infographic on p 2). We were confident that there was little risk of adverse events from the device, based on nine trials that reported this outcome.

For return to work, time to full weight bearing, and number of subsequent operations, our certainty in the evidence is moderate (rather than high) because of imprecise estimates of effect, where confidence intervals

Fig 1 | Characteristics of patients and trials included in systematic review of LIPUS

Use this information to gauge how similar your patients’ conditions are to those of people studied in the trials

DATA SOURCES

NUMBER OF TRIALS 26

NUMBER OF PATIENTS 1565

TYPES OF FRACTURE OR OSTEOTOMY

Operatively managed femur fractures 7
Nonoperatively managed femur fractures 6
Stress fractures 3
Non-union 3
Osteotomy 8

EXCLUSIONS

Infection 3
Multiple fractures 1
Pathologic fractures 2
Large gap between bone ends after fixation 1

FRACTURE LOCATIONS

Radius 120
Clavicle 7
Fibula 3
Humerus 7
Scaphoid 2
Ulna 2
Lilac 1
Femur 10
Osteotomy 3

PATIENT CHARACTERISTICS

MEAN AGE

0 10 20 30 40 50 60

Males females 52% 48%

SEX  % women

0 20 40 60 80 100

Males females 52% 48%

FUNDING

$ 3 of 26 trials were explicitly free of industry funding

AGENCY PARTICIPATION

No patient involvement reported in trial design

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A particular challenge for the panel was to determine to what extent the most trustworthy evidence—coming from trials of patients with fresh tibial and clavicle fractures managed operatively—could be applied to adults with different types of fracture or osteotomies. Trials including patients with stress fractures, non-union, and osteotomies were either at high risk of bias or did not contribute sufficient outcome data to the systematic review. After extensive deliberations, the panel found no compelling anatomical or physiological reasons why LIPUS would probably be beneficial in these other included potentially important benefit and harm (see forest plots (figs 2-7) in the linked systematic review). The observed heterogeneity in the effect sizes between trials for time to weight bearing, pain, and radiographic healing was explained by considering risk of bias: studies with serious methodological limitations due to lack of blinding (no use of sham device) suggested a benefit, whereas studies without such limitations did not (see subgroup analyses in the linked systematic review). For these outcomes, we therefore based our conclusions on the clinical outcomes of most importance to patients and clinicians a priori, and the systematic review authors focused their reporting on these. The outcomes chosen for LIPUS were:

- Functional recovery (such as time to return to work and time to full weight bearing)
- Pain
- Subsequent operations
- Complications.

The patient representatives judged radiographic healing as a less important outcome. It was included because many clinicians would consider radiographic healing to inform their management decisions. Some patients may feel reassured by observing radiographic healing, with increased confidence in resuming activities such as weight bearing and return to work.

Before seeing the evidence, we agreed on what would constitute an important benefit from using LIPUS for these outcomes, and how patient values and preferences might vary between persons. Guided by patients on our panel, we agreed that most people want at least a possibly important benefit in functional recovery time or pain to make the time and expense of using LIPUS worthwhile. Reduced adherence with the device in the TRUST trial suggests that LIPUS can be burdensome to patients.9 We applied the GRADE system to critically appraise the evidence and move from evidence to recommendations (appendix 3).14 We considered the balance of benefits, harms, and burdens of the procedure; the quality of evidence for each outcome; the typical and expected variation in patient values and preferences; resources; feasibility; and acceptability—details of our reasoning are summarised in the infographic and discussed further in the text.15 Recommendations can be strong or weak, for or against a course of action. We place a low value on speculative benefits of treatments. Thus, when available evidence suggests no benefit, or only very low quality evidence suggests benefit and moderate or high quality evidence shows appreciable adverse effects, burden, or cost, the panel would make a strong recommendation against an intervention.

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patient populations. For example, if LIPUS on fresh fractures does not decrease the incidence of non-unions, it is unlikely to exert a beneficial effect in the conversion of non-unions into healed bones. Furthermore, osteotomies have the same biological response as for traumatic fractures. An additional challenge faced by the panel was that no trials included children. Paediatric fractures typically heal faster and have lower rates of non-union; thus, any potential benefit of LIPUS for children is likely to be even smaller than that for adults. The panel concluded that the evidence was applicable to all of these groups, and did not downgrade their certainty in these evidence.

In response to peer review comments, the panel again considered the applicability to other fractures and populations, in particular non-union fractures. Reviewers pointed to differing healing methods in non-union, and the potential that smaller effect sizes could make a difference to patients. Non-union is the result of impaired bone health, as seen in smokers and diabetics, or due to mechanical reasons such as large bone defects. There was high quality evidence showing a lack of benefit in accelerating healing for fresh fractures, thus it is unlikely that LIPUS would improve outcomes in patients with non-union. Given the panel’s judgment of an implausible benefit of LIPUS for patients with non-union, the panel chose to make a strong recommendation against LIPUS also for these patients.

**Future research**

It is unlikely that new trials will alter the evidence. Fracture research should focus on other interventions that have a greater probability to speed up healing, such as surgical application of adjuvant biomaterials or extracorporeal shock wave therapy. Further trials of treatments for non-union fractures would be better compared with operative stabilisation, with or without autologous bone grafts. Research should also address de-implementation strategies for the use of LIPUS for bone healing.

**Competing interests**

All authors have completed the BMJ Rapid Recommendations interests form. The BMJ Rapid Recommendations team judged that no panel member declared financial, professional, or academic interests that precluded authorship. The declared interests for each panel member are in appendix 2 on bmj.com. No panel members declared any financial conflicts of interest related to this clinical question, specifically no financial ties to the bone stimulation industry. B Mollon uses bone stimulators in practice. T Agrotis, RAC Siemieniuk, B Mollon, S Schendelainer, J Lyphon, and PO Vandvik participated in writing the complementary systematic reviews that formed the evidence base for this guideline. B Mollon was a co-author on a systematic review on this topic published in The BMJ in 2009, for which R Poolman wrote the editorial. No other panel member has previously formally made statements regarding LIPUS. This article was edited by H McDonald at The BMJ who had no relevant financial or intellectual interests.

**Transparency**

Poolman affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

RAPID RECOMMENDATIONS


22 Barreto E. Evaluation of efficacy and safety of autologous MSCs combined to biomaterials to enhance bone healing (OrthoCT1). 2016. https://clinicaltrials.gov/ct2/show/NCT01842477.