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.1

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 (osteogenesis) 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.7 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.10 11 The linked publications in this package (see “Linked articles” box) synthesise the latest evidence and translate it for clinical care.
### Population

Adults and children with a fracture or osteotomy

### Choice of intervention

- **LIPUS**: Low intensity pulsed ultrasound, used to stimulate bone growth (osteogenesis)
- **No ultrasound**: Standard care without ultrasound

### Recommendations

| Population | Favours LIPUS | Favours no ultrasound |
|------------|---------------|-----------------------|
| All        | Strong        | Strong                |

We recommend against the use of LIPUS

### Comparison of benefits and harms

|                        | Favours LIPUS | No important difference | Favours no ultrasound | Evidence quality |
|------------------------|---------------|--------------------------|-----------------------|------------------|
| Days to radiographic healing | 147           |                          | 150                   | Moderate         |
| Days to return to work  | 205           |                          | 200                   | Moderate         |
| Days to full weight bearing | 73           |                          | 70                    | High             |
| Pain score (0–100, lower better) | 39            |                          | 40                    | High             |
| Subsequent operations  | 128           |                          | 160                   | Moderate         |
| Device-related adverse effects | 0             |                          | 0                     | 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.
RAPID RECOMMENDATIONS

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...
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).16

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).16

For these outcomes, we therefore based our conclusions on the trials with low risk of bias. The estimates for typical (prognostic) outcomes for patients not treated with LIPUS were informed by the control arm of the TRUST trial, which enrolled patients with tibia fractures in the US and Canada and was at low risk of bias.

Understanding the recommendation
We unanimously agreed to issue a strong recommendation against LIPUS for patients with any bone fractures or osteotomy. We have moderate to high certainty of a lack of benefit for outcomes important to patients, and, combined with the high costs of treatment, LIPUS represents an inefficient use of limited healthcare resources.
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 this evidence.20

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,21 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.

Practical considerations
Patients with fractures may experience pain and limited mobility, particularly in the first two to three months. Driving and physical activity are limited during the recovery period. Figure 2 outlines the key practical issues for those considering LIPUS as an adjunct therapy in the management of bone fractures.

Costs and resources
LIPUS does not represent an efficient use of health resources for individuals or health funders, given its lack of benefit on outcomes important to patients and its purchasing costs. Healthcare organisations that currently pay for LIPUS may reasonably choose to stop reimbursements based on best current evidence and our strong recommendation against LIPUS.

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.22,23 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.24

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 stimulators industry. B Mollon uses bone stimulators in practice. T Argintas, RAC Siemieniuk, B Mollon, S Chandreimnit, J Lyysen, 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 MacDonald at The BMJ who had no relevant financial or intellectual interests.

Transparency: R 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.

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