Low-intensity pulsed ultrasound in the treatment for fracture

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Abstract

Introduction
Low-intensity pulsed ultrasound (LIPUS) has been reported, by various authors, to promote bone healing. The aim of our review was to review the available literature and evaluate the effectiveness of LIPUS in the treatment of various types of complicated fracture union.

Materials and methods
Different search engines including MEDLINE, EMBASE and the Cochrane Library were used, and the trials adopting LIPUS in the treatment of fractures were included. Data concerning functional outcomes, time to union, delayed or nonunion and adverse effects were extracted. Few complications were reported.

Results
The results of many trials were probably biased as the data collection was not complete. The study method and materials recruited varied between studies.

Conclusion
Based on the literature, the available evidence did not support LIPUS as a mean to speed up bone healing.

Introduction
Low-intensity pulsed ultrasound (LIPUS) has been reported to promote bone healing in different stages from injury to solid union. LIPUS up-regulates macrophages, which engulf bacteria and foreign body during haematoma formation phase of bone healing. It also stimulates the differentiation of mesenchymal cells into chondrocytes and osteoblasts. Moreover, LIPUS stimulates fibroblast proliferation and migration, enhances cells’ sensitivity to vitamin D3, stimulates extracellular matrix synthesis as well as stimulates proteoglycan synthesis from chondrocytes.

LIPUS is also shown to promote the expression of various genes that are essential for osteogenesis. Alkaline phosphatase, an enzyme associated with osteoblast differentiation, is shown to have raised activities after LIPUS treatment. Elevated vascular endothelial growth factor (VEGF) level was also reported with the use of LIPUS. VEGF is a key growth factor and regulator of angiogenesis and endochondral bone formation.

The ability to improve fracture healing would have a large clinical impact, as well as the socioeconomic aspect. Shortening in the time required for fracture union would imply shorter medical care and better utilization of resources. The cost benefit was enormous. Despite the proposed advantages of application of ultrasound as part of the treatment of fracture healing, there is no consensus on its role.

Different literatures have been published throughout the years describing the efficacy of application of ultrasound. However, the quality of studies varied. Each of the studies varied from one another in terms of treatment plan and outcome measure. The diversity of the study design hence gives rise to limited support in using ultrasound as part of the daily routine practice.

This review summarizes the available best evidences on the use of ultrasound, including the treatment outcome and other parameters including the need for second procedure or the presence of any adverse effects.

Materials and methods
Electronic searches were performed through different databases including Cochrane Library, EMBASE, MEDLINE and also reference lists of the searched articles. Those studies of acute fracture of the lower limb in adults being managed with ultrasound treatment were selected.

Studies with randomized controlled trials were preferred. The inclusion criteria included participants who were over 18 years of age presenting with acute fractures of the lower limbs. The assessment of outcome could be the time to union, the functional outcome, any delayed or nonunion and need for secondary procedures and possible adverse effects.

The selected studies were reviewed. Studies other than randomized controlled trial design were excluded. Also studies involving fractures of upper limb were not under the scope of this review. Two studies were excluded as they were dealing with stress fractures.

Results
Based on the selection criteria of randomized controlled studies, application of LIPUS in treating acute fractures of the lower limbs in participants above 18 years old, five studies were included.

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treatment was in 1994 by Heckman JD et al.\textsuperscript{7}. Being carried out in the University of Texas Health Science Centre, 97 patients with diaphyseal fracture of the tibiae that could be treated with closed reduction and cast immobilization were included. After excluding those patients who either violated the protocol or lost to follow-up, 33 patients with ultrasound treatment and 34 patients with treatment by sham device were included. Clinical examinations and radiographs were taken at different time intervals up to 1 year to assess the outcome.

Strauss et al.\textsuperscript{7} published another paper in 1999 concerning the usage of ultrasound in Jones fracture. This was another study of lower limb fractures that was managed nonoperatively. Twenty fractures were recruited in this study and were divided into two groups. All participants were initially given a short leg cast and weight bearing as tolerated for a mean of 10 days. One group received LIPUS therapy while the other group did not. However, the exclusion criteria were not clearly stated. The primary outcome was the time to clinical and radiographic union, and the proportion of union within 20 weeks was the secondary outcome, but inadequate data were presented.

Emami et al.\textsuperscript{4} and Leung et al.\textsuperscript{5} reported outcomes from participants with operatively managed fractures of the tibia. Thirty participants were recruited in Uppsala University Hospital in Sweden who had closed or Gustilo and Anderson grade 1 open fracture of the tibial diaphysis treated with closed reduction and fixation with a reamed, intramedullary locking nail. Half of the participants received ultrasound treatment with specific protocol within 3 days of fixation and was continued for 75 days. For the control group, the sham ultrasound treatment, which made use of the deactivated device, was started at the same time as the study group with the same protocol. All cases were followed up every 3 weeks until union. Time to union as well as time to first radiographic evidence of callus and any adverse events were documented. The study by Leung et al. was carried out in the Chinese University of Hong Kong. Patients with closed or Gustilo grade 1 or 2 open diaphyseal fracture of tibia were treated by internal fixation with reamed, locked intramedullary nail, while patients with Gustilo grade 3 open fractures or fractures in metaphysis were treated with an external fixator. All the wounds were treated with emergency debridement and delayed closure as well. Among the 30 fractures, 16 were put into the test group and 14 were in the control group. For the test group, LIPUS was started once the soft tissues were closed for a total of 90 days with specific protocol. For the control group, a sham device that was externally identical to the LIPUS machine was given as soon as the soft tissues were closed. Follow-up was carried out every 3 weeks for the first 3 months, every 6 weeks for the next 3 months and every 8 weeks for the last 6 months. Radiographs were taken to assess union status.

Ankle fracture was another study entity. Handolin et al.\textsuperscript{5,11} conducted the study in Helsinki University Central Hospital in Finland. Participants with displaced Weber B fractures of the lateral malleolus were included. They underwent open reduction and internal fixation with self-reinforced screws. Postoperatively, the ankle was immobilized for 6 weeks with a removal soft cast brace. Partial weight bearing was allowed at 2 weeks and full weight bearing at 4 weeks. Of the total 30 patients, 15 participants self-administered daily ultrasound treatment with standardized protocol from third to ninth postoperative weeks. The control group was given a sham machine with a similar treatment regimen. The patients were followed up at 2, 6, 9 and 12 weeks. Clinical and radiographic outcomes were assessed. At 18 months, apart from physical examination, the Olerud-Molander score was used to assess the clinical outcome. Multi-detector computed tomography and dual-energy X-ray absorptiometry scans were performed postoperatively and at 18 months.

Apart from the different studies, there was a recent publication by Griffin et al. about ultrasound and shockwave therapy for acute fractures in adults in the Cochrane Collaboration in 2012\textsuperscript{12}, which assess the result of ultrasound treatment in fracture healing and evaluate if it should become a mandatory part of the fracture management. In this review, the authors recruited all randomized controlled trials evaluating the use of ultrasound in treating acute fractures in adults of either upper or lower limbs. They collected and analysed the data. Eleven out of the 12 studies recruited tested LIPUS and the remaining tested the extracorporeal shockwave. There were a total of 622 participants with 648 fractures. Among them, eight studies were randomized placebo-controlled trials and two were randomized controlled trials without placebo. One was a quasi-randomized placebo controlled trial and the remaining study was a quasi-randomized controlled trial without placebo control. Upper limbs were under investigation in four trials, while six trials were about lower limb fractures. The two remaining trials reported the result in stress fractures. With great heterogeneity in the study design and very limited data collection, no difference could be demonstrated between ultrasound and placebo control in functional outcome. There was no significant reduction in time to union of complete fractures treated with LIPUS. Pooled results also showed no significant difference between LIPUS and control in dealing with delayed or nonunion cases. The authors concluded that there was insufficient evidence to support...
the routine use of ultrasound in daily clinical practice.

National Institute for Health and Clinical Excellence in United Kingdom published a medical technology guidance in 2013 concerning the EXOGEN ultrasound bone healing system for long bone fractures with nonunion or delayed healing.15 Seventeen clinical studies were retrieved with a total of 1,710 patients. Three of them were randomized controlled trials, 13 were case series and 1 was a prospective comparison. Nonunion was described in 13 of the studies, delayed healing in 2 and the other 2 studies reported on both types of fractures. After reviewing all the studies by the expert committee, they recognized that high rates of fracture healing were noted in adopting EXOGEN to treat long bone fractures with nonunion. Despite the absence of direct evidence on avoiding surgery, it was associated with an estimated cost saving of £1,164 per patient compared with current management through avoiding surgery. EXOGEN usage in treatment of long bone fractures with nonunion was supported.

Discussion
When comparing different studies, the LIPUS treatments were very similar. Participants in the study group were given ultrasound treatment for 20 minutes each day for a total cumulative time of around 24 h. The ultrasound signal was composed of 200 μs burst of 1.5 MHz sine waves, with a repetition rate of 1 kHz and a spatial average intensity of 30mW/cm².

For the outcome measurements, a wide diversity can be observed. The majority of the studies made use of plain radiograph as the primary measure of the efficacy to the time of radiographic union.10,11 However, each study measured union at multiple time points of various intervals from which mean time to union was derived without standardization.

In this review, the studies being selected were randomized controlled trials. There was no documentation on the randomization process. There may be the possibility of selection bias during the generation of random sequences. The majority of studies used a sham device (deactivated ultrasound unit) as theblinding procedure, but not all the studies used the same device, which would lead to the performance bias. There was also no specific mention of whether the assessors were aware of different groups of participants during their clinical or radiographic evaluation of fracture healing.

The number of participants in all the above randomized controlled trials was relatively small; hence there would be a chance of imbalance in the baseline characteristics. Concerning the primary functional outcomes in fractures treated with LIPUS, the current studies were more favourable to the use of LIPUS as an adjunct treatment of lower limb fractures; however there was no clear significant difference between the study and control groups. Moreover, there were no clear criteria to define fracture union and so the time to bone union. Also, the timing and way of assessment varied between studies. The statistical analysis methods employed were also different in different studies.

For the secondary outcomes of delayed union and nonunion, the overall pooled data from the lower limb fracture studies showed no significant difference between the treatment and the control groups. For the adverse events, Emami et al.12 reported no difference in the number of participants developing deep infection, or compartment symptoms, or removal of the implant. Handolin et al.11 reported four deep-vein thromboses. Three of them were in the control group. Heckman et al.13 reported that one patient suffered from pulmonary embolism. None of the studies touched on economic analysis.

The highly significant heterogeneous results about primary outcome between the control group and the study group indicated that LIPUS might be a good option to apply to specific categories of patients. There was no significant difference between the control group and the study group concerning the secondary outcome of the adverse events.

As there is a considerable natural interparticipant variation in healing rates, the different healing rates as reported in different studies may be expected. Moreover, there were no controlled or randomized studies in which ultrasound treatment was compared directly with surgery as the treatment of fractures.

The Cochrane Library Review actually gives a clearer and more comprehensive summary about the use of ultrasound in treatment of acute fractures in adults. In this review, the authors performed a very extensive yet systematic search for all the relevant articles regarding ultrasound treatment in acute fractures in adults, not just limited to lower limb as in our review. This review clearly breaks down all the potential bias in each step of the study design and adopted a “worst case” analysis, which would give more conservative estimates of treatment effects for time to fracture union. Treatment effects were assessed using mean differences or risk ratios. It also included the ongoing research data. All these give valuable information on the use of LIPUS in the acute fracture management.

The NICE guideline, however, puts more emphasis on cost consideration. Fracture management has great socioeconomic influences, including length of hospitalization, resource management for all different kinds of management and the medical expense, subsequently affect the duration before an individual can return to work or normal activities of daily living, which affects the productivity. The ability to improve fracture healing would have a huge clinical and socioeconomic impact.
Review

Conclusion
From the above reviews, limited evidence was available to prove the efficacy of therapeutic ultrasound for the treatment of acute fractures in adults; despite this there was support that LIPUS was safe and acceptable to patients. The best evidence available did not support the routine use of LIPUS in daily clinical practice. Further investigation and research should be continued and focused on more secure randomization and placebo control, and the outcome measurement should focus on patient-reported entities.

Abbreviations list
LIPUS, low-intensity pulsed ultrasound; VEGF, vascular endothelial growth factor

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