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Review of the Latest Evidence for Use of Low Intensity Pulsated Ultrasound (LIPUS) for Fracture Healing

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ABSTRACT

Introduction: LIPUS can be used for fractures to promote bone healing. Established for non-union and delayed union fractures, it has the advantage of avoiding the risks associated with surgery and can speed up healing time.

LIPUS works by accelerating all the stages of bone healing. National institute of clinical excellence has evaluated LIPUS and recommended it for non-union, but rejected it for delayed union due to cost. Aim of this review is to look at the latest evidence regarding LIPUS.

Pubmed and Scopus were searched for relevant articles on LIPUS and bone healing since 2008. Four relevant articles were found which were reviewed and analysed.

Discussion: There is benefit in using LIPUS for non-unions and delayed unions and a potential benefit in sepsis. No benefit for LIPUS was found in fresh clavicle fractures or for surgically treated fractures of the lower extremity. There is a potential benefit for LIPUS in comminuted fractures.

Conclusion: LIPUS is useful in non-union and delayed union fractures. Effectiveness in fresh fractures possibly depends on fracture site but further research is needed. LIPUS may have a role in comminuted fractures but further robust research is needed in this subject.

KEYWORDS: LIPUS, Non-union fractures, Mal-union fractures

Introduction

Low intensity pulsated ultrasound (LIPUS) at a fracture site can be used to encourage bone healing [1]. It is used mainly for mal-union and delayed union fractures. The advantages of using LIPUS include the non-invasive nature of the treatment, avoidance of surgery and associated healthcare costs, convenience of the treatment, quicker recovery and weight bearing [2].

The way that LIPUS works is by stimulating growth factors and cytokines, Increasing angiogenesis and blood flow to the site of the fracture and by increasing mineralisation of bone matrix[3, 4]. It is said to work at every stage of the fracture healing process (Inflammation, soft callus formation, hard callus formation and remodelling) [3].

The ultrasound waves are transmitted to the affected bone and their motion is detected by the receptors of trans-membrane cell adhesion molecules called integrins [3]. These molecules are involved in cellular signalling. They stimulate the expression of cylcooxygenase 2. Cyclooxygenase 2 enzyme leads to the production of prostaglanding E2 (PGE2). This release of PGE2 can occur within 24 hours after the dose treatment of the fracture with LIPUS[5]. The release of PGE2 and increase of intracellular calcium aids the mineralisation of the soft callus. Speeding up of this process in the fracture healing produces quicker stabilisation of the fracture which will lead to quicker healing of the fracture [3-5].

In addition the micro-motion, which results from the action of the ultrasound waves on the tissues, causes increased permeability of cells and flow of the extracellular fluid. This increases the amount of blood and nutrients reaching the fracture site. The ultrasound waves also raise the local temperature by 1^{o}c. This will also increase the blood supply to the fracture area as the blood dissipates away. Angiogenesis is stimulated by the activation of various cytokines such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and interleukin 8. This increase in blood supply to the fracture site is especially important since it can aid tissue healing and blood supply is especially reduced in co-morbidities[6].

The latest national institute for clinical excellence (NICE) guidance has concluded that for non-union, the LIPUS system is effective and is more cost effective than the current treatment, autologous iliac crest bone graft. However, for delayed union, treatment with observation and

surgical intervention was deemed more cost efficient than the use of LIPUS[2].

Since this new treatment has a role in fracture healing, it is important to look at the latest evidence regarding LIPUS to assess its suitability and potential clinical usage. In order to do this, a literature search was conducted to look at the latest evidence regarding LIPUS. This evidence was then reviewed and analyzed.

Aims

The aim of this article is to review the most recent evidence for LIPUS and compare this with the NICE guidance[2].

Method

A literature search was conducted using Scopus and Pubmed. The terms searched for were "low intensity pulsed ultrasound" and "fracture healing". The search looked at original research since 2008. Exclusions were:foreign language articles and non-human research.

The remaining articles were then scanned. Articles not reporting on fracture healing as an end point and non-original research articles were excluded. The resulting articles were then analysed and their evidence reviewed.

Results

The Pubmed search produced 39 results, while scopus produced 111 results using the criteria above. After selective scanning, 4 articles were found. Reasons for exclusion were: duplicity between the 2 search engines, not meeting the criteria above in terms of end point, the report being a case study and one study was excluded due to the cause of the fracture being operative.

Table 1: search criteria

Keywords	Inclusion criteria	Exclusion criteria
Low intensity pulsed ultrasound	Original research articles	Articles older than 2008
Fracture healing	Articles with the keywords	Non-original research articles
	Research conducted on humans	Foreign language articles
		Research conducted on non-humans
		Case studies

Table 2: Articles chosen for review

Article	Author	Title	Journal
1	X. Hemery, X. Ohl, R. Saddiki, L. Barresi, E. Dehoux	Low-intensity pulsed ultrasound for non-union treatment: A 14-case series evaluation	Orthopaedics and Traumatology: Surgery and Research, 2011. 97(1): p. 51-57
2	Markus D Schofer, Jon E Block, Julia Aigner, Andreas Schmelz	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**: p. 229.
3	Pieter H.W. Lubbert, Rob H.H. van der Rijt, Lidewij E. Hoorntje, Chris van der Werken	Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: A multi-centre double blind randomised controlled trial	Injury, 2008. **39**(12): p. 1444-52.
4	YoKinami,Tomoyuki Noda, Toshifumi Ozaki	Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: multi-center retrospective cohort study	Journal of Orthopaedic Science, 2013. **18**(3): p. 410-418.

Discussion

Article 1: Hemery et al 2011 - Low-intensity pulsed ultrasound for non-union treatment: A 14-case series evaluation[7]:

This research by Hemery et al looked at the use of LIPUS in a small 14-case series study. The patients used in this study were patients who had surgical treatment of their fracture but suffered non-union, considered as failure of the fracture to heal after 6 months since the initial surgical treatment. The patients used LIPUS for a maximum of 3 months. The patients were their own controls, however they were judged to have a zero chance of union without intervention. The participants were assessed in terms of the radiological changes present during their surgical follow up.

One of the main weaknesses of this study is the fact that evidence wise, it is a case series therefore it is not one of the stronger study designs. In addition there were differences in the way that the LIPUS system was applied between the subjects, with some patients having the transducer incorporated in their cast. Also there were variations in the

onset of treatment and the site of treatment. Due to the small sample size used in this study, it would be difficult to extrapolate anything significant. However, this study is useful to look at individual treatment cases.

11 out of the 14 cases responded to the treatment giving a response rate of 78%. This is lower than previous results obtained by Romano et al 2009 [8], from their systematic review of non-union which showed an 85-86% fracture healing rate. Average time to fracture in this study varied from 5.3-6.4 months. This matches the findings from the Romano et al study 2009 [8], which found a mean healing time of 6 months.

The study reported on the cases of sepsis in this case series. 6 of the patients in the study had sepsis, with the conclusion that it did not impair the function of the LIPUS system and that in fact 4 out of these patients showed healing. This could be a topic of further discussion in the future to judge whether this is a potential indication for LIPUS.

Article 2: Schofer et al 2010 - Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial[9]:

This next article by Schofer et al 2010 [9], Looked at the effects of LIPUS in comparison with a sham device for treatment of tibial fractures, in a double blind randomised controlled trial. The end points measured were bone mineral density and fracture gap; measured radiologically. The study was carried out on 101 patients in 6 hospitals in Germany. Delayed union was defined in this study as a lack of clinical or radiological improvement 16 weeks after the last intervention. Each patient was randomised to receive either the LIPUS device or a placebo device. The device was to be used for 20 minutes per day for 16 weeks.

In terms of study design, this study had a robust design. It was in the highest level of evidence and it was a multi-centre trial. In addition there was a standardised treatment period and a strict definition of delayed union which increases the validity of the study, as well as a high compliance rate (quoted as 91%). The problem with this trial was the fact that it only had 101 subjects, which is not a sufficiently high number to be able to generalise with confidence; besides the trial taking place in only one country. However, as the author mentioned it is the first study of its kind to randomise patients receiving the LIPUS treatment with a placebo, therefore it is a useful trial to base larger trials on, with more varied populations worldwide. Another limitation of the study is that despite the randomization, the LIPUS group had a larger time frame between fracture and management with LIPUS. It is also noteworthy that the study is partially funded by Smith & Nephew who produce the LIPUS device.

The study concluded that the study subjects in the LIPUS group had an increase in their BMD, which is 34% larger than the subjects who received the placebo treatment. The outcome of this study adds weight in terms of the effectiveness of LIPUS for delayed union fractures. However, further research comparing this method of treatment with surgical options is needed to affect the guidelines currently available (i.e. NICE). This is important due to the app aren't safety of this treatment and the reduced rate of side effects aside from erythema and swelling [10], which could give it the edge over other treatments [8].

Article 3:lubbert et al 2008 -Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: A multi-centre double blind randomised controlled trial[11]

This study was a multi-centre randomised double-blind study. The study included initially 120 patients from six different hospitals in the Netherlands, who suffered a fresh (< 5 days), closed, mid-shaft fracture of the clavicle. The treatment arm of the study was treated with a LIPUS transducer, while the control arm of the study was managed with a placebo device. The patients were given 20 minutes of LIPUS or placebo treatment per day for 28 days. The outcomes measured were subjective fracture consolidation primarily and as secondary outcomes, operations required, painkillers used, adverse events, non-unions, return to normal activities and pain scores.

This study had a good and robust design, with a high level evidence due to the use of a randomised double blind placebo controlled trial. In addition there were clear inclusion and exclusion criteria, which should introduce homogeneity to the study and rule out outliers. The shortfalls of the study are the fact that it only included 120 patients, of which 19 were eventually excluded, further weakening the study. The reason for this was explained in depth by the author. Furthermore, the study was not international, which would again prevent worldwide generalisation.

The study chose the clinical signs of fracture healing which is a suitable outcome, since clinical function is the ultimate aim of fracture healing. Also clinical assessments were considered in other detailed reviews ahead of radiological findings such as in the Cochrane review of clavicle fractures[12]. However, due to other review studies on the subject using radiological evidence and reporting it as the most commonly used [13], it would have been useful to carry out both types of assessments.

The study found no differences in the time to clinical healing of the fractures and no significant differences between the study and control group in the secondary outcomes. This differs from the findings of other studies such as the meta analysis by Busse et al 2009 [13], which found a 36.9% reduction in time to fracture healing and the work by Snyder et al 2012 [10], which found a reduction in fracture healing time by 36 days. Considering the differences in the site of the fracture between this study and these other studies further comparative work needs to be done to validate these results and to see if the site of the

fracture could be the cause of the difference between the results of these studies.

Article 4: Kinami et al 2013 - Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: multi-center retrospective cohort study[14]

This research was a multi-centre retrospective cohort study, carried out in Japan. The research was carried out in 14 hospitals, with some hospitals using LIPUS and some hospitals not using LIPUS. Patients from the hospitals who used LIPUS were designated as the study group while patients in the non-LIPUS using hospitals were the controls. The subjects had tibial/femoral diaphyseal fractures and underwent surgery for their fractures. The subjects were treated within 3 weeks of the original injury with LIPUS, in the case of the study group. The patients in the study group had LIPUS for a minimum of 3 months. The outcome was measured using x-ray. The study had 78 cases in the LIPUS group and 63 in the control group.

The limitations of this study were again the fact that this was not an international study. The study design would also not provide the best evidence when compared to better study designs such as randomised double blind control studies. This is especially important when considering that these patients are all post surgery therefore there could be bias resulting from better surgical treatment depending on whether the hospital uses LIPUS, which could affect the results (although the authors took measure to reduce the potential effects of this bias). In addition there were a lot of patients excluded due to a lack of proper follow up, 12 in the study group and 25 in the experimental group.

This study found no significant differences in the time period to fracture healing between the study group and the control group overall but did find a difference in healing time between the study group and the control group in comminuted fracture, with the union period being 30% less in the study group than in the control group. Previous studies have also shown benefit of LIPUS in treatment of comminuted and high energy fractures; studies by Lerner et al 2004 [15] and by leung et al 2004 [16] have reached similar conclusions. This could prove a useful finding, which could identify a new indication for LIPUS in comminuted fractures, and is a potential addition to new guidelines. However more studies with better design looking into this subject are necessary before implementation into guidance.

Conclusion

There was always evidence of the benefits of LIPUS in delayed-union and non-union fractures [8, 17]. The new studies looking at LIPUS for these indications have agreed with these previous findings. They also confirm that this is in fact a safe treatment, which agrees with other reviews [1, 8]. As a non-invasive treatment for delayed unions and non-unions, they are an effective and safe choice; however these new studies do not compare LIPUS directly with surgical treatment, which should be explored further.

The findings from the Lubbert et al study 2008, raise questions against the use of this treatment for fresh fractures. Comparison with previous research shows that despite this study not showing a benefit for LIPUS in fresh fractures, other studies have. This could indicate that LIPUS may have differing effects depending on the site of the fracture. This should be investigated further to see if some types of fractures respond better to LIPUS than others.

With regards to clavicle fractures, the study found no benefit clinically or in terms of pain control or functionally. Considering the fact that the use of a cuff and collar bandage is cheap, there doesn't seem to be any benefit for LIPUS in clavicle fractures.

In terms of surgically managed fresh fractures, the study by Kinami et al 2013, have shown no benefit for LIPUS use in surgically managed fractures. With this study being different from other studies, more investigation of this is warranted but certainly this indication would not be recommended based on these findings.

The Study by Kinami et al 2013 has found a potential benefit for LIPUS in comminuted fractures. This could be a useful addition to the future LIPUS guidelines. A robust randomised controlled double blind study to investigate this is necessary before any changes to guidance are undertaken.

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