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Is there a role for low intensity pulsed ultrasound (LIPUS) in delayed or nonunion following arthrodesis in foot and ankle surgery?

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ABSTRACT

Background: Delayed union and nonunion following foot and ankle arthrodesis is a disabling complication for patients. There are no clinical studies looking at whether there is a role for use of low-intensity pulsed ultrasound (LIPUS) following this. The aim of this study is to investigate the efficacy of LIPUS in this cohort of patients in our centre.
Methods: This was a retrospective observational study reviewing the use of LIPUS in patients who had arthrodesis of a number of different foot and ankle joints diagnosed with delayed or non-union.
Results: Over a 5 year period, 18 patients (71st MTPJ fusion, 2 subtalar joints, 2 triple fusion, 4 ankle fusions and 3 isolated midfoot joint) with radiologically confirmed delayed union, were treated with a standardised LIPUS therapy. Twelve patients (67%) were treated successfully with full radiological union confirmed. 4 patients required further surgical revision surgery while 2 were treated conservatively. Isolated small foot joints demonstrated a higher incidence of fusion (9/10; 90%) after LIPUS in comparison to larger or multiple joint arthrodesis (3/8; 38%).
Conclusions: There may be a role for the use of LIPUS as a treatment option in delayed union of isolated, small foot joint arthrodesis. However, we would not recommend its use in large or multiple F&A joint arthrodesis. Large multicentre series are required to confirm our findings.
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1. Introduction

Multiple disease processes ranging from primary osteoarthritis, posttraumatic osteoarthritis, inflammatory arthropathies to neuromuscular conditions such as cerebral palsy, can cause foot and ankle joint pain and deformity [1]. The initial management is always conservative with analgesia, activity modification and orthotics. Arthrodesis of the joint can decrease pain, improve function and restore stability of the foot and ankle once conservative measures fail. The incidence of arthrodesis in foot and ankle surgery has increased by 146% in the United States between 1994 and 2006 [4]. An important complication of arthrodesis in foot and ankle (F&A) surgery is delayed union or non-union, ranging from 8% nonunion rate for the first metatarsophalangeal joint to 27% for triple fusion in one series which looked at rate union for joint arthrodesis of the foot and ankle [5,6].

Mandt and Gershuni describe non-union as “a state in which there is a failure to heal within the expected time and the fracture will not heal without intervention” [7]. Previously non-union was treated with surgical intervention to promote fracture healing. More recent research has suggested a role for low intensity pulsed ultrasound (LIPUS). The use of ultrasound was initially described in the 1960s, with research suggesting a positive effect on fractures from the application of a continuous ultrasound of high intensity 500 mW/cm^2. The treatment could only be utilised for a few minutes to avoid bone necrosis. Later a pulsed low intensity ultrasound was discovered with advantages including application for extended time periods and little temperature increase, latterly known as LIPUS. LIPUS produces high frequency acoustic pressure waves causing micromechanical pressure on bone tissue. LIPUS acts upon cells in soft tissue including osteoclasts, osteoblasts and mesenchymal stem cells, which in turn causes the production of proteins and growth factors that facilitate bone healing [8].

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LIPUS has been shown to be a useful adjunct in the treatment of delayed fractures and non-unions and is currently approved for use in the United Kingdom by the National Institute for Health and Care Excellence (NICE) [9].

It appears to promote bone healing by stimulating the removal of old bone, increasing the production of new bone and increasing the rate of conversion of fibrous matrix to mineralised bone. It is known to be safe and non-invasive, since it uses low intensity mechanical energy thereby avoiding tissue damage. The use of LIPUS in delayed union or non-union following arthrodesis in foot and ankle surgery (F&A) in unknown to the authors' knowledge. Our study aims to evaluate whether there is any benefit with the use of LIPUS bone healing device in delayed union or non-union in patients following F&A arthrodesis. We hypothesised that the use of LIPUS would promote arthrodesis and improve both clinical and radiological outcomes (Figs. 1–3).

2. Materials and methods

We undertook a large retrospective cohort (level IV) examination of our foot and ankle arthrodesis database, identifying those patients who had a delayed or non-union following arthrodesis in our centre and used LIPUS as part of their treatment between 2011–2015.

The clinical notes and radiographs of this cohort of patients were reviewed. The decision to commence LIPUS was made by the treating surgeon following an informed discussion with the

Fig. 1. (a & b) Patient 16. Coronal and Sagittal CT at 5 months confirmed a delayed union of ankle arthrodesis and LIPUS was started. She completed 6 months of LIPUS treatment and Coronal and Sagittal CT (c & d) at 11 months confirmed union.

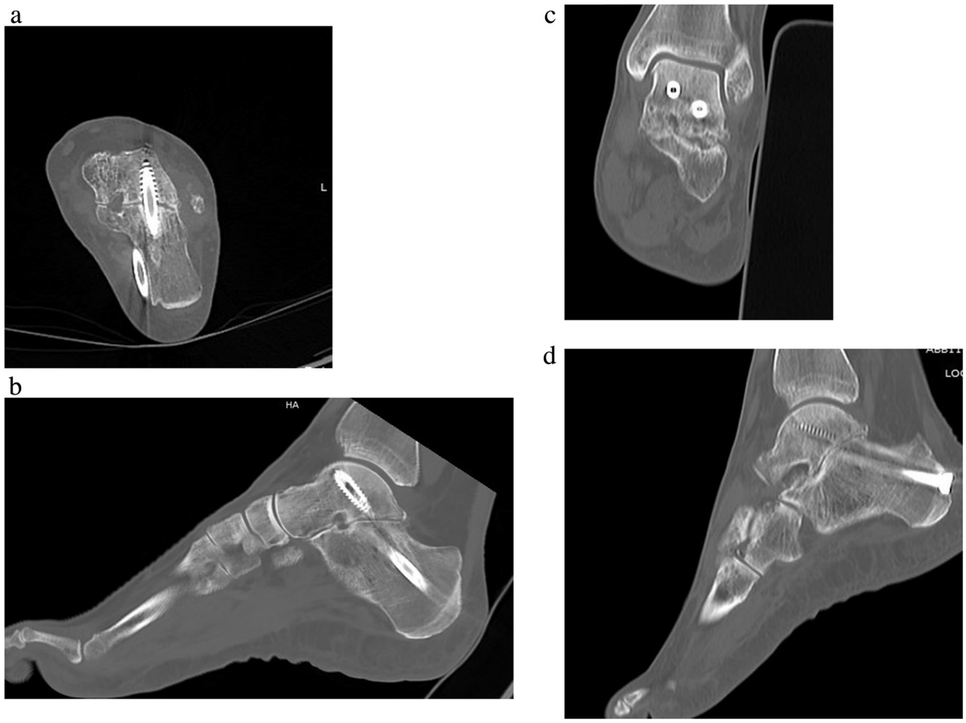

Fig. 2. (a & b) Patient 18. Axial and Sagittal CT at 3 months confirmed a delayed union of subtalar arthrodesis and LIPUS was started. She completed 6 months of LIPUS treatment but Coronal and Sagittal CT (c & d) at 9 months confirmed a nonunion. She went on to have a successful revision surgery with removal of metalwork, bone graft and revision arthrodesis.

Fig. 3. (a & b) Patient 11. AP and oblique radiographs at 3 months confirmed a delayed union at the 1st metatarsophalangeal joint (MTPJ) and LIPUS was started. After 3 months of LIPUS treatment, radiographs (c & d) showed solid union at the 1st MTPJ and she was pain free. LIPUS was discontinued.

patient. Delayed union was defined as lack of clinical and radiological evidence of union, bony continuity or bone reaction at the arthrodesis site if 3 months had elapsed from the index surgery. Non-union was defined as failed arthrodesis for more than 9 months that had not shown any radiographic signs of progressive healing for 3 consecutive months. Data regarding patient demographics, date of initial operation, location of arthrodesis site, type of operation, medical co-morbidities (e.g., smoking history, diabetes, osteoporosis), use of medications (e.g., bisphosphonates, NSAIDs, steroids), date of starting LIPUS, duration of LIPUS treatment and further treatment were collected from patients' records.

2.1. Treatment protocol

Patients in our series were fitted with the EXOGEN Bone Healing System Express (Bioventus, Durham, North Carolina, USA), which delivers a maximum of 150 treatments. This device consists of a main operating unit with a permanently connected transducer. The coupling gel was applied to the transducer head and transducer was secured directly over the marked arthrodesis site by a fixture on the strap. The arthrodesis site was marked in clinic at the onset of treatment using a permanent marker at site of maximal tenderness. The device delivers low intensity pulsed ultrasound in 20-min sessions, which is self-administered by the patient at home once daily. Patients are followed up at 4-week intervals with radiographic imaging of their fusion site. LIPUS treatment was stopped when clinical and radiographic union of the fracture was achieved, at the completion of the 150 cycles or when operative treatment was advised. We also monitored compliance by checking the machine each time the patient came back to clinic for follow up review. We defined union of the arthrodesis joint as the time when the patient reported no bony pain over fusion site or only mild activity-related discomfort and there was radiographic evidence of healing with bridging trabeculae of at least 75% of the cross section. CT was used to determine fusion in all cases.

2.2. Statistical analysis

Two-tailed Student t tests were used to evaluate differences in continuous variables while Fisher exact test or chi-square test was used to evaluate differences in categorical data. There was no a posteriori calculation. Fisher exact test was used in proportion comparisons where values in any cells fell below 5. Chi-square test was used in proportion comparisons where values in all cells were above 5. Significance was defined as $p \leq 0.05$. Data were analyzed using SPSS Statistics Software 20.0 (IBM, Armonk, NY, USA).

3. Results

There were 18 patients, comprising of nine male and nine female patients, which received LIPUS as an adjunctive treatment for their F&A arthrodesis following a diagnosis of delayed or non-union. The average age was 57.6 (range: 41–76) years. Eight patients underwent CT prior to LIPUS treatment whilst all patients underwent CT imaging after treatment to confirm bony healing. All diagnoses of non-union were atrophic in type. Twelve of 18 patients successfully completed 150 cycles of LIPUS treatment. The average duration of LIPUS treatment was 4.8 (3–6) months. Table 1 shows demographic data and arthrodesis sites.

LIPUS treatment was commenced at an average 21 weeks (12–35 weeks) from the initial arthrodesis operation. 12/18 patients (67%) were treated successfully with evidence of both clinical and radiological union. The average time to successful radiological consolidation from initial operation was 36.5 (range: 24–60) weeks. Patients were followed up for an average of 41 (range: 18–75) months. Table 2 shows a further breakdown of our results.

There was no correlation between union and age ($p = 0.24$) gender ($p = > 0.05$) or duration of treatment ($p = 0.32$). Furthermore there was no correlation between smoking status and union ($p = 0.79$). There was no correlation between completion of all 150 cycles of LIPUS and union ($p > 0.05$)

Table 1
Demographic data and arthrodesis sites.

Patient	Sex	Age	Arthrodesis Site	Side	Smoker	Diabetic	NSAID	No of cigarettes/day	Comorbidities
1	M	76	Ankle	Left	Ex smoker	No	No	40	Hypertension,TIA Foot drop, Previous lumbar discectomy
2	M	51	Triple arthrodesis	Right	No	No	No	N/A	Congenital talipes causing degeneration of 3 joints
3	M	57	Ankle	Right	No	No	No	N/A	Previous pilon fracture
4	M	41	Triple arthrodesis	Left	Yes	No	No	10	Nil
5	F	68	Navicular cuneiform	Right	No	Yes	No	N/A	IDDM, Retinopathy, Chronic Kidney Disease, Hypertension
6	M	39	First Metatarsophalangeal	Left	No	No	No	N/A	Rheumatoid arthritis
7	F	63	First Metatarsophalangeal	Left	Ex smoker	No	No	N/A	Depression
8	F	67	First Metatarsophalangeal	Right	No	No	Yes	N/A	None
9	F	63	Talonavicular	Left	Yes	No	No	10	None
10	M	47	Calcaneocuboid	Right	Yes	No	No	10	None
11	F	50	First Metatarsophalangeal	Left	No	No	No	N/A	Asthma
12	F	70	First Metatarsophalangeal	Left	No	No	No	N/A	None
13	M	76	Subtalar	Left	No	No	No	N/A	Bladder tumour. obesity
14	M	48	First Metatarsophalangeal	Left	Yes	No	No	20	None
15	F	70	First Metatarsophalangeal	Right	Ex smoker	No	Yes	N/A	Hypertension, Rheumatoid arthritis
16	F	45	Ankle	Right	No	No	No	N/A	None
17	M	58	Ankle	Right	Yes	No	No	15	Asthma, depression
18	F	48	Subtalar	Left	Yes	Yes	No	5	Depression, asthma, IDDM

Table 2
Number of patients,arthrodesis site and percentage of successful arthrodesis.

Arthrodesis site	Number of patients	Number of successful arthrodesis following LIPUS	Percentage
First metatarso-phalangeal	7	6	86%
Subtalar	2	0	0%
Triple	2	0	0%
Ankle	4	3	75%
Talonavicular/Calcaneocuboid/Naviculocuneiform (isolated midfoot)	3	3	100%
	18	12	67%

3.1. Nonunion group (n = 6)

Four patients (triple arthrodesis n = 2; subtalar; 1st MTPJ) went on to have further revision surgery with removal of metalwork, revision arthrodesis with bone graft. Three of them have since fused with no further complication. However, one patient who had further failed revision triple arthrodesis surgery elected to have a below knee amputation. He was a young patient (41 years old at time of initial triple arthrodesis surgery) who had a previous open Gustilo Anderson 3 B pilon fracture and had an ankle arthrodesis in 2008 previously for post traumatic osteoarthritis in the same limb. He had multiple pain issues for years and felt this was the best option for him.

Two patients did not have revision surgery. One patient (subtalar arthrodesis, in her late 70s) was happy to live with the pain whilst the final patient (ankle arthrodesis) is being treated conservatively and was not offered further surgery due to patient non-compliance with LIPUS treatment and continuation to smoke heavily at 40/day.

4. Discussion

This study is the first to report the outcome of LIPUS following a diagnosis of delayed union or non-union following foot and ankle (F&A) arthrodesis. It confirms our hypothesis of a role for LIPUS in the treatment of non-union in arthrodesis in the foot and ankle patient demonstrating a radiological union in 12 patients (67%). Our study cannot confirm a correlation between any patient factors and non-union, which is somewhat surprising in the case of smoking. It is most likely that this is due to the low number of subjects in the study

The study is limited in that it is a small retrospective series, in a heterogeneous group of patients. We also evaluated the efficacy of LIPUS treatment without comparing it to a parallel control group (Level IV case series). It may be argued the delayed unions may have united without LIPUS treatment. However, this limitation is similar with other reported treatments of delayed/non-unions in the literature. A larger series or a prospective well-designed study is required to confirm our findings. With that said, the practicality of this type of study would be limited by recruitment of a homogeneous series of patients, as delayed union can be affected by a variety of factors. This difficulty in conducting meaningful comparative studies (and specifically randomized controlled trials) to collect data on healing rates was also specifically stated in The National Institute for Health and Care Excellence (NICE)‘s report on LIPUS treatment [20]. The authors also acknowledge compliance using the LIPUS machine could also be a factor but we checked the number of cycles at each clinic visit to ensure patients were using it.

Our success rate is low compared to the high success rates previously quoted for delayed and nonunion of fractures. A review of the literature reveals healing ranging from 70 to 100% in nonunion fractures whilst a large series of delayed union fractures demonstrated a healing rate of 89% [10]. Owing to the nature of the fracture nonunion and fracture delayed unions, most of the evidence is reliant upon case series. Leighton et al. present a systematic review and meta analysis on the use of LIPUS in fracture nonunion. 13 papers, 1441 fracture non-unions, were evaluated. The paper finds in favour of LIPUS with a pooled estimate of effect size of 82% for any anatomical region, with fracture age of 3 months. With a definition of fracture nonunion as 8 months, pooled estimate of effect size was 84%. However 6 of the papers are retrospective cohort studies, 1 RCT is included and multiple different bones are evaluated [11].

However the use of LIPUS is not always so favourable. Biglari et al. describe the use of LIPUS in 61 long bone non-unions. Subjects were divided into those that responded successfully to treatment and those that did not [12]. The study found that only 32.8% of non-unions were healed. The authors suggested that the cause for this was likely the high number of “difficult” non-unions. The cohort had an elevated NUSS (non union scoring system) score. LIPUS was also presented as an alternative therapy following multiple unsuccessful surgical interventions. Biglari suggested that success was more likely in patients with small gap in terms of the defect between fractures and a low NUSS score [12].

In our series, there appears to be a limited role in the use of LIPUS following delayed union for the arthrodesis of larger F&A joints and arthrodesis of multiple F&A joints with the exception of the ankle joint. None of the subtalar joint arthrodesis and the triple arthrodesis fused with LIPUS as an adjunct. One in four (25%) ankle arthrodesis failed to fuse. It may be argued in light of Biglaris findings that larger joints may not successfully arthrodese as a larger surface area is required to be reduced and be in close contact for successful union [12]. The use of LIPUS for the treatment of isolated, smaller joints was far more successful with 9/10 (90%) patients demonstrating clinical and radiological union. This is more in line with the reported rate of success in other LIPUS series for fractures [13,14].

The definition for delayed union or nonunion remains vague with authorities diagnosing a non union from 15 weeks [15] to 12 months [16], in those fractures in which the reparative process has ceased. The causes for delayed or nonunion are multifactorial and can be categorised according to patient dependent and patient independent factors. The former include medical comorbidities, smoking, the use of non steroidal anti inflammatory drug use whilst the latter are dependent on the pattern of bone injury, degree of comminution and the presence of infection amongst others [17] Our study evaluated the patient dependent factors (Table 1) but found no difference. This is likely due to our small numbers.

Basic science studies have shown favourable results for in the use of LIPUS in arthrodesis. One study describes the use of LIPUS in rats, undergoing single level unilateral posterior spinal arthrodesis with the use of a freeze-dried bone allograft. One cohort received LIPUS treatment, administered for 20 min each day whilst the other received a sham treatment. The post mortem evaluation included the use of micropalpation, radiology and histology. The

LIPUS groups demonstrated an increase in the number of osteoblasts (12.02 ± 3.03 vs. 8.01 ± 2.47, $p < 0.01$) compared to that of the control. Additionally there was also an increase in the level of angiogenesis surrounding the allograft with mean vascular densities in the LIPUS and control groups were $5.42 \pm 0.58\%$ and $3.73 \pm 0.87\%$ ($p < 0.01$) [18]. Others also describe similar successful outcomes in other animal model experiments. Hui et al. investigated the use of LIPUS in enhancing bone fusion rate in posterior spinal fusion in a rabbit model. The LIPUS group demonstrated a statistically significant increase in clinical fusion (86%) by manual palpation in the LIPUS group compared to control groups (0 and 14%) [19].

There is currently limited clinical evidence regarding the benefits of the use of LIPUS in arthrodesis and none regarding delayed or nonunion in particular. One study evaluated the beneficial effect of LIPUS following hindfoot arthrodesis. A cohort of 15 patients undergoing primary subtalar arthrodesis received an adjunct of LIPUS post operatively. The LIPUS cohort was compared to an older cohort not receiving LIPUS treatment. Those receiving LIPUS demonstrated significantly improved radiographic outcomes, with a statistically significant faster healing rate on plain radiographs at 9 weeks ($p = 0.034$) and CT scan at 12 weeks ($p = 0.017$). Clinically 100% of patients attained fusion whilst the AOFAS (American Orthopaedic Foot and Ankle Society score also improved at 12 months, ($p = 0.026$) [20].

Coughlin's group also describes the adjunctive use of LIPUS in revision arthrodesis for hindfoot non-union in 19 joints. Nonunion was confirmed preoperatively with radiographs revealing a frank nonunion in 3 whilst a further 6 underwent a CT scan. Postoperatively patients received a daily session of LIPUS treatment. The patients were assessed with clinical and radiological outcomes. A grading system was devised from the postoperative CT scan. A ratio of the sum total of the widths of fused area was divided by sum total of the width of the potential arthrodesis site. Union was defined in terms of a percentage and categorised according to cumulative improvement. A full non-union was 0%, some union between 0–33%, partial union 34–66% and complete union 67–100%. 10 isolated subtalar revision arthrodeses demonstrated a mean fusion of 65.1%. There was also a statistically significant associated improvement in hindfoot AOFAS score from 45.3 pre operatively to 72.3 postoperatively ($p < 0.005$) as well as improved pain scores [21]

For fractures, LIPUS is a proven alternative therapy to surgical intervention and is recommended by the NICE in the UK [22]. Faced with a delayed union or impending non-union of F&A arthrodesis, it might be worth considering LIPUS as an adjunct treatment to promote union rather than an operation immediately to revise the arthrodesis as this would cause more morbidity for the patient. Revision arthrodesis surgery would normally also include supplementary bone graft being harvested to promote union. The most common site for bone grafts is the iliac crest, but the proximal tibia and calcaneum are also common sites. However, the harvesting of iliac crest bone incurs considerable donor-site morbidity and there is a significant incidence of pain at the donor site. Minor complications occur in up to 10% of cases and major complications include deep infection, vascular injury, deep haematoma, nerve injury, abdominal hernia and fracture of the iliac wing. The other option would be to use biologics which are increasingly popular but expensive. It is hard to cost revision surgery for our heterogenous group but a LIPUS machine cost £1000 in our centre and this would likely be cheaper than revision surgery. Some patients may prefer alternatives to revision surgery and seek conservative options. A revision surgery would likely mean further cast immobilisation, which will affect their activities of daily living and work.

This is the first study to date to examine the use of LIPUS in delayed or nonunion following F&A arthrodesis. The authors acknowledge that there are several limitations of this study which we have addressed above in our discussion.

5. Conclusion

Our series demonstrates an overall success rate of 67% with the use of LIPUS in delayed or nonunion following F&A arthrodesis. There may be a role for the use of LIPUS as a treatment option in delayed union of isolated, small foot joint arthrodesis. However, we would not recommend its use in large or multiple F&A joint arthrodesis. Large multicentre series will be required to confirm our findings.

Conflict of interest

The authors would like to state that they have no declarations of interest.

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