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LIPUS: An Effective Alternate Option to Treat Nonunions of Fractures and Surgical Fusions in Trauma and Orthopaedic Surgery

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Abstract

Background: *Limited studies have been conducted to evaluate the use of exogen in different patient groups. We aim to determine the rate of radiological union and symptom resolution following use of Low Intensity Pulsed Ultrasound (LIPUS) therapy, to analyse the efficacy of LIPUS therapy in comparable patient groups, and to determine the cost effectiveness of LIPUS therapy.*

Materials and Methods: *32 adult patients with nonunions of fractures and surgical fusions who were treated with LIPUS over 3 years were identified from the clinic database. Data were recorded retrospectively. Patients were divided into 3 subcategories to provide a meaningful analysis of comparable groups: foot and ankle versus other regions, surgical versus conservative management, and atrophic versus hypertrophic nonunion. A statistical calculator was employed for statistical analysis.*

Results: *Clinical symptoms of nonunion resolved in 19 (59%) patients and radiological union was achieved in 18 (56%) patients post LIPUS use. The foot and ankle group demonstrated the best outcome, with union rates of 73% when compared to other fractures at 44% union. Significant potential cost savings of £3150 per patient have been calculated (p=0.006) when compared to surgical management of nonunion.*

Discussion: *Overall, we achieved just under 60% resolution of clinical symptoms and/or radiological improvement, without the need for further intervention. In our study we observed particularly better outcomes in the foot and ankle group compared to other fractures; this could provide guidance for future targeting of LIPUS therapy to specific patient cohorts based on their anatomical regions of nonunion.*

Keywords: *LIPUS; Exogen; Fracture; Nonunion*

Introduction

The healing of bone following fractures and surgical fusion procedures is a complex biomechanical process[1]. Around 98% of fractures undergo primary unification, while the remaining 2% transition into delayed union or nonunion[2]. Patients affected by this complication can experience persistent pain, impairment of function, and inability to carry out their normal daily activities, leading to significant personal and socioeconomic burden. It also poses considerable cost to the National Health Service (NHS), with a range of values estimated between £7,000 and £30,000 for the treatment of nonunion fractures[3-5].

There are several treatment options available for the management of a nonunited fracture. Typically, the traditional method is surgical fixation using an autologous bone graft at the site of nonunion[6]. This, however, requires fulfilment of specific conditions for use, and may carry significant surgical risks with potential for further complications[7]. In an attempt to avoid these risks, several non-invasive treatment options have emerged, such as pulsed electromagnetic field, direct current, high energy extracorporeal shock wave therapy, and Low Intensity Pulsed Ultrasound (LIPUS)[8-11]. Each employ a different mechanism of producing a stimulating effect at the nonunion site to provoke a cellular reaction and promote bone healing.

LIPUS is believed to work on nonunion by inducing nanometric movement at the fracture site, resulting in micromechanical stress. This mechanical stress transiently increases the membrane expression of integrins, leading to the expression of cyclooxygenase-2 (COX-2). This in turn triggers an increased production of prostaglandin E2 (PGE2), which promotes maturation of osteoblasts and results in endochondral ossification in the soft callus[12].

We aim to review the clinical outcomes and efficacy of the use of LIPUS (Exogen, Bioventus LLC, Durham, NC, USA) for established nonunions of fractures and surgical fusions in trauma and orthopaedic surgery.

Material and Methods

Adult patients who were treated with Exogen in a level 1 major trauma centre from September 2016 to September 2019 were identified from the clinic database. Demographic and clinical data were retrospectively recorded from the trust's Electronic Patient Record, PACS imaging software, and hospital case notes. The data included demographic details, diagnosis, initial treatment modality, nonunion gap size, smoking status, diabetic status, atrophic or hypertrophic appearances, time from injury/ surgery to the diagnosis of nonunion, duration of Exogen therapy, clinical resolution of symptoms, and radiological union post-Exogen treatment. Any complications following therapy or further treatments required post-Exogen use were also noted.

Data were recorded and analysed using Excel software (Microsoft Excel®, Redmond, WA, USA). In order to provide a meaningful analysis of comparable groups, patients were divided into the following subcategories:

1. Foot and ankle versus other regions
2. Surgical versus conservative treatment
3. Atrophic versus hypertrophic nonunions

A statistical calculator was employed for statistical analysis. Categorical data were analysed using the Chi-squared test for independence. The variables included clinical resolution of symptoms and presence of radiological union. Continuous data, which included duration of Exogen therapy, were found to be abnormally distributed, therefore the Mann-Whitney test was used to calculate the p value. The p value was set at a significance level of 0.05 for all statistical analysis.

Results

32 patients who completed Exogen treatment were included in the analysis. There were 14 (44%) male and 18 (56%) female patients. Average age was 52 years (25-82 years). 27 (84%) cases were post-traumatic nonunions, while 5 (16%) patients have undergone elective joint fusion surgery. The list of diagnoses is presented in Table 1. There were 8 (25%) smokers, 5 (16%) ex-smokers, and 2 (6%) diabetics amongst the cohort. The average nonunion gap was 4mm (2 to 8mm), as best as it could be recorded on plain radiographs or the computed tomography (CT) scans at the time of establishing the diagnosis of nonunion.

Table1. *List of diagnoses amongst patient cohort*

Diagnosis	Number of cases
Subtalar fusion	2
Ankle fusion	2
1st MTPJ fusion	1
Metatarsal fracture	5
Distal fibula (ankle) fracture	3
Stress fracture (metatarsal, distal fibula)	3 (2, 1)
Pilon fracture	1
Femur (distal third, intertrochanteric fracture)	2 (1, 1)
Humerus fracture (shaft, distal)	5 (4, 1)
Open tibia/fibula fracture	2
Closed tibia/fibula fracture	3
Distal radius	2
Patella fracture	1

The average time from injury or surgery to the time of commencement of Exogen therapy was 6 months (3 to 24 months). 18 (56%) patients had CT scan performed and 3 (9%) underwent magnetic resonance imaging (MRI) to confirm the diagnosis. 28 (86%) patients had an accurate record of the duration of use of Exogen in their medical notes. The average duration of use of Exogen was 17 weeks (5 to 31 weeks).

Clinical symptoms of nonunion resolved in 19 (59%) patients post-Exogen use. We observed radiological union in 18 (56%) patients with the use of Exogen (Tables 2 and 3). CT scan after Exogen treatment was done in 10 (31%) patients as it was not ethically justifiable to perform CT scans in patients who had sufficient resolution of symptoms following the use of Exogen.

Table2. *Comparison of duration of treatment, symptom resolution, and radiological union in time to diagnosis of nonunion groups.*

Time to diagnose nonunion	Number of cases (%)	Average duration of treatment in weeks	Symptom resolution (%)	Radiological union (%)
<6 months	16 (50)	21	10 (63)	10 (63)
≥6 to 8 months	9 (28)	13	5 (56)	5 (56)
≥9 months	7 (22)	13	4 (57)	3 (50)
p value			*0.935*	*0.855*

Table3. *Comparison of duration of treatment, symptom resolution, and radiological union in the subgroup analysis*

	Number of cases (%)	Average duration of Exogen used in weeks	Symptom resolution (%)	Radiological union (%)
Foot and ankle nonunions	16 (50)	16	11 (69)	11 (73)
Other fractures	16 (50)	19	8 (50)	7 (44)
P value		*0.298*	*0.280*	*0.095*
Surgical management	14 (44)	15	8 (57)	7 (50)
Conservative management	18 (56)	18	11 (61)	11 (65)
P value		*0.373*	*0.821*	*0.409*
Atrophic	19 (59)	16	10 (53)	11 (58)
Hypertrophic	13 (41)	19	9 (69)	7 (58)
P value		*0.373*	*0.348*	*0.981*

Among the 8 smokers, 7 (88%) reported symptom resolution and demonstrated radiological union on plain radiographs, while one of the smokers failed the treatment. Among the 5 ex-smokers, 2 (40%) reported resolution of symptoms, including 1 with radiological union. Both the diabetic patients had resolution of symptoms as well as radiological union following Exogen therapy.

The interval from the initial fracture or primary surgical procedure until a diagnosis of nonunion was suspected or established was less than 6 months in 16 (50%) patients, 6 to 8 months in 9 (28%) patients, and 9 months or more (9-24) in 7 (22%) patients. Analysis was performed to evaluate the relationship between time to diagnosis of nonunion against the average duration of use of Exogen, symptom resolution, and radiological union. The results are presented in Table 2.

A total of 13 patients failed Exogen therapy with persisting symptoms and no radiological progression of union. 7 of these patients underwent revision surgery. Details including initial diagnosis, initial management, smoking status, radiological appearances, and type of revision surgery performed are presented in Figure 3. Among the remaining 6 patients, 2 were planned for revision surgery; however, one died due to other known medical co-morbidities before the planned surgery could go ahead. The other patient refused to undergo surgery as the residual symptoms were manageable. A further 2 of these patients were commenced on another course of Exogen and both achieved 50% radiological union and symptom resolution after an average therapy duration of 10 months, at which point they were discharged from further care. The last 2 of these 6 patients reported some resolution of symptoms without any further intervention despite lack of radiological union.

2 patients who had radiological evidence of union reported persisting symptoms. They both were suspected to have developed an adverse reaction to Exogen treatment in the form of complex regional pain syndrome (CRPS). The diagnosis included a distal fibula Weber A fracture nonunion and a tibia and fibula fracture nonunion. These were referred for physiotherapy and were managed for CRPS.

The average time taken to diagnose nonunion amongst the patients who failed Exogen treatment was 8 months (3 to 24 months). Average duration of Exogen therapy in this group was 16 weeks (5 to 31 weeks). Ten (67%) patients had atrophic nonunion. There was one smoker and no diabetic patients amongst the failed treatment group.

3 sub-analyses were performed to compare the following groups: foot and ankle fractures and fusions versus other regions; fractures managed surgically versus conservatively; and atrophic versus hypertrophic nonunions based on pre-treatment plain x-rays and CT scan appearances. Data compared included duration of Exogen treatment, symptom resolution, and radiological union. Table 4 presents the results of this analysis.

Table 4. *Details of patients who underwent revision surgery following failed Exogen treatment*

Diagnosis	Initial treatment	Revision surgery	Smoking status	Radiological appearances of nonunion
Distal femur comminuted fracture	External fixation followed by ORIF	Bone grafting	Ex-smoker	Hypertrophic
Humeral shaft fracture	Conservative in plaster of Paris	ORIF	Non smoker	Atrophic
Distal humerus fracture	ORIF	Bone grafting	Non smoker	Hypertrophic
Humeral shaft fracture	Humeral brace	Bone grafting and ORIF	Non smoker	Hypertrophic
Open tibia-fibula fracture	ORIF	Bone grafting	Non smoker	Atrophic
Humeral shaft comminuted fracture	Humeral brace	ORIF	Smoker	Hypertrophic
Ankle fusion for osteoarthritis	Conservative in plaster of Paris	Revision ankle fusion	Non smoker	Atrophic

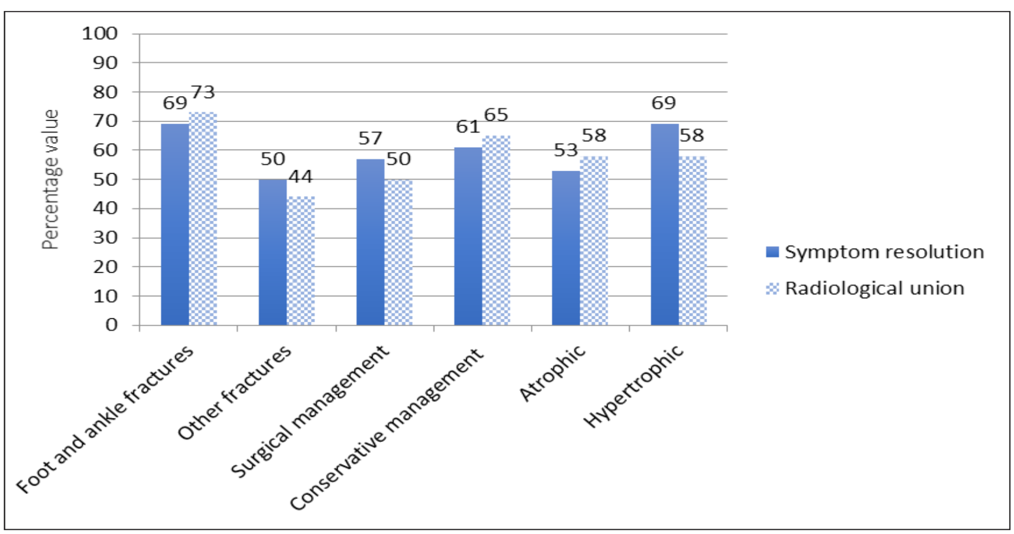


Fig1. *Symptom resolution and radiological union in each subgroup*

Discussion

Our study demonstrated a 56% radiological union rate, and 59% clinical union after LIPUS therapy. Figure 1 demonstrates the rates of symptomatic resolution and fracture union in the subgroups which are discussed below in more detail.

Foot and Ankle Vs other Regions

Foot and ankle group showed better rates of symptom resolution (73% vs 44%) and radiological unions (69% vs 50%) compared to other anatomical regions (p=0.095). It was observed that only 20% (1/5) of the humerus fracture nonunions achieved radiological and symptomatic union following the Exogen treatment. Gabr et al [13] reported a similar trend in their study and demonstrated a 20% lower rate of union in upper limb fractures compared to the lower limb with the use of LIPUS (75% vs 55%). One hypothesis to explain this trend considers the inherent instability of the fracture site as it is more difficult to maintain stability of a humeral fracture and allow for accurate transducer placement. Furthermore, of the 7 patients that required revision surgery after failed Exogen treatment, 6 involved a long bone fracture, suggesting there may be an issue with the stability of such fractures affecting the ultimate outcome of LIPUS therapy.

Another contributing factor is the potential impact of the thickness of subcutaneous tissues on effective LIPUS therapy. The ultrasound transducer of Exogen device has a near field length of 118mm and a diameter of 22mm that provides a direct beam on the target area without any divergence of the waves. Fractures of the foot and ankle are more subcutaneous than other regions of the body where the presence of excessive soft tissue may potentially lower the accuracy of placement, intensity and efficacy of the beam[14]. However, at the time of this study, excessive body mass index (BMI) or limb circumference did not constitute an exclusion criteria to commencing Exogen therapy[15].

Hypertrophic vs Atrophic

The majority of patients (59%) in our cohort had atrophic nonunions. However, both groups had similar rates of radiological union following Exogen treatment (58%, p=0.98). The hypertrophic group demonstrated a greater proportion of symptom resolution in comparison to the atrophic group (69% vs 53%, p=0.35). Among the failed Exogen treatment group (13), 10 had atrophic nonunion. Among the 7 patients who underwent revision surgery, 3 had atrophic nonunions.

Atrophic nonunions have significantly lower quantity of blood vessels in comparison to normal healing groups and may also be characterised by dysfunctional mesenchymal stem cells at the fracture site[16]. These factors may explain relatively poor outcomes of Exogen treatment in atrophic nonunions compared to the hypertrophic nonunions reported in the literature. Although in our study radiological union rates were equal in the two groups, the significant majority of patients who failed Exogen therapy had atrophic nonunion. Similar findings were reported by Leighton et al[17] who found that hypertrophic nonunions had a greater benefit from LIPUS therapy as opposed to atrophic nonunions. Failure of LIPUS therapy associated with atrophic nonunion has further been demonstrated by Watanabe et al[18]. Among a group of 101 patients with delayed union, they found a statistically significant ($p < 0.001$) relative risk of 23.72 of failure of therapy in atrophic compared to hypertrophic nonunion. Atrophic nonunion may therefore be a predictive risk factor for unsuccessful Exogen therapy.

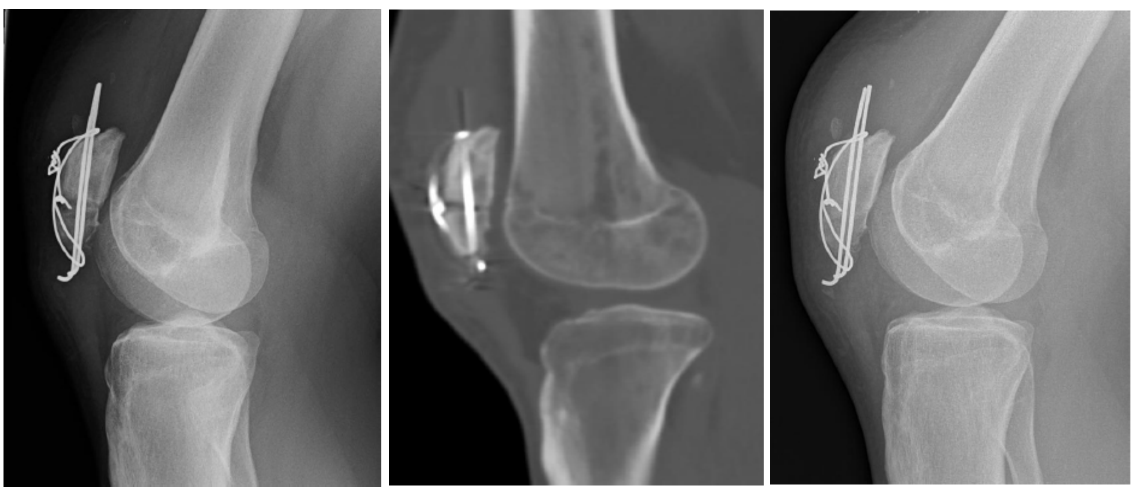
It is well-known that hypertrophic nonunions occur secondary to problems with mechanical instability. It is unclear how LIPUS improves the healing rates of hypertrophic nonunions as it does not address the underlying mechanical instability theorised to cause a hypertrophic nonunion; further research could be conducted to evaluate this.

Conservative vs Surgical Management

In our cohort, 56% patients were managed conservatively prior to developing nonunion and the remainder had nonunion following their primary surgical procedures. The conservatively managed group showed improved radiological union rates with Exogen treatment compared to the surgical group (65% vs 50% respectively, p=0.409). Symptom resolution rates were similar between the two groups (61% vs 57% respectively, p=0.821). Historically, LIPUS studies have reported positive outcomes in both such groups. Hemery et al[19] presented a 79% success rate in a case series of 14 patients with femoral and tibial fracture nonunions managed surgically. A study of 67 cases by Gebauer et al[20] reported 85% heal rate following LIPUS, with no significant difference found between groups with and without surgical fixation present. Figures 2 and 3 demonstrate examples of Exogen being used to successfully treat both conservatively managed and surgically managed nonunion.

2a 2b

Fig2 (a & b). *A 70-years old female with persistent clinical tenderness and radiological non-union 12 weeks after the base of 5th metatarsal fracture (2a). Treated with Exogen for 4 months that led to complete resolution of symptoms and radiological union (2b).*



3a 3b 3c

Fig7 (a, b & c). *A 31-year-old male treated with tension band wire fixation for patella fracture. Persistent pain with radiological confirmed non-union on plain radiographs (3a) and CT scan (3b) 13 months after surgery. Treated with Exogen for 4 months that led to complete resolution of clinical symptoms and radiological progression to union (3c).*

Cost Implications

Cost analysis was performed on these patients who achieved clinical and/or radiological union. NICE estimates the average cost saving associated with eliminating the need for revision surgery in those treated with Exogen to be £2,407 per patient.[21] The total cost of Exogen in our hospital was £2300 for each patient for the duration of its usage. This was compared against the potential cost of revision surgery that ranged from £3034 to £5688, depending on the site of nonunion and the type of revision surgery that could have been required, as identified from figures obtained from Healthcare Resource Group (HRG) coding system. Hence the Exogen treatment led to a total potential cost saving of £103,550 with an average cost saving of £3150 per patient successfully treated with Exogen. Thus, the cost of Exogen treatment was found to be associated with significant cost savings compared to potential surgery (p=0.006). It is also important to consider the potential risks and complications of revision surgery against the use of Exogen, which is considered safe and has no potential complications or known contraindications.

Strengths and limitations

The main strength of our study is an elaborated analysis of different comparable groups. There was variation noted in outcomes, particularly between foot and ankle group and other anatomical regions. This could provide guidance for future targeting of Exogen therapy to specific patient cohorts based on their anatomical regions of nonunion.

We acknowledge limitations of our study. The study was conducted in a retrospective manner, which had implications on the available data. Prospective data collection could have offered a more effective way of capturing all the required data and more control on assessing the outcomes. Furthermore, functional scores were not used as one of the assessed outcomes, which could have provided more objective quantifiable data on clinical outcomes following the Exogen treatment. Nevertheless, our study highlights a valid role of Exogen therapy in treatment of established nonunions in fractures and fusion procedures in nearly 60% cases. The use of Exogen also led to significant cost savings compared to potential surgical intervention that could otherwise have been required to treat these patients.

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