West of England Medical Journal

Formerly Bristol Medico-Chirurgical Journal

WEMJ Volume 114 No. 3 Article 1 September 2015

The e-journal of the
Bristol Medico-Chirurgical Society

An overview of the use of the EXOGEN™ Ultrasound Bone Healing system for non-union of long bone fractures.

Nathan Richard Walker *
Medical Student, Bristol University

INTRODUCTION

The EXOGEN™ low intensity pulsed ultrasonic system (LIPUS) is currently being investigated for bone healing enhancement and callus formation in non-unions. Non-union treatment is an intense research area as currently most treatment options available are surgically limited and economically unappealing. This review aims to briefly summarise the disease manifestations, illustrate the latest knowledge on EXOGEN™ as a non operative therapy including NICE guidelines, and review the clinical outcomes from research compared with operative strategies. This paper will also consider the economics of the device and the relative cost: benefit ratio versus surgery. To assess the efficacy of EXOGEN™ versus surgery for non-union, the author conducted a MEDLINE search and reviewed NICE guidelines with reference to EXOGEN™ .

BACKGROUND

Non-union.

Definition, Diagnosis and Management

The term non-union is defined as a fracture with no apparent signs of healing. This manifests as persistent fracture lines, a hypertrophic or missing callus with sclerotic fracture ends and a well defined fracture site division, 6-8 months post injury[1]. The aetiology of non-unions are multifactorial, such as mechanical (unstable fractures; many causes), biological (vascular insufficiency, infection) and patient factors (smoking, age, malnutrition, medications, co morbidities) which prevent local growth factors from developing bone[2]. The classification of non-union (see appendix 1), is based on the aetiology.

Diagnosis comprises of clinical suspicion with a previous fracture history combined with radiological information. Factors such as non-union position and type, previous treatment and reason for failure need consideration to tailor treatment. Conventional management involves surgical removal of fibrotic material from the site, an autogenous bone graft (usually from the iliac crest) to induce osteoinduction, osteoconduction and osteogenesis[3]. This is followed by internal/external fixation. Post-operative healing times are longer than normal fracture healing by internal fixation. Delayed unions up to three months are generally not operated upon unless the fracture is complex. Surgery typically takes place between 3-9 months, however this is an individual based clinical decision[4].

** Declaration*

This project is all my own work unless otherwise stated. All text, figures, tables, data or results which are not my own work are indicated and the sources acknowledged.

EXOGEN™ TECHNOLOGY

EXOGEN™ is a unique low intensity pulsed ultrasonic system (LIPUS) due to the transducer design and defined signal boundaries allowing emission of an exclusive wavelength of ultrasound[5]. The system comprises a main operating unit connected to an ultrasound transducer within a strap which fixes on the skin at the fracture site (see appendix 2). Gel is applied before fixing the transducer to improve conduction. The device's simplicity allows self administration of treatment at home.

The theory behind EXOGEN™ is the 1.5MHz ultrasonic wave induces a nano-movement in the bone's intracellular matrix which is recognised by cell surface integrins on the cell membrane. This induces protein synthesis of factors in bone remodelling, osteogenesis and angiogenesis[6] (not primary data). From this the fracture site is expected to radiologically and clinically unite.

NICE GUIDELINES

The evidence for reviewing the efficacy of EXOGEN™ was based on 17 studies (3 randomised control trials (RCTs), 13 case series and one prospective comparison). Side effects of EXOGEN ™ reported by the US FDA were three cases of irritated skin from the ultrasound gel and one case of chest pain due to potential interference with a patient's pacemaker. This was over a one year peiod during which over 55000 EXOGEN™ devices were used in the US[7].

Important uncertainties to consider are whether result findings can be attributed to natural patient variation in bone healing or whether patients used in the studies were hindered in bone healing compared to the general population. However currently there is little evidence to support this so it can be disregarded. Efficacies of EXOGEN™ varied between sites but was particularly effective on tibial non-union (the most common long bone non-union) and clinical experts estimate that a third of tibial non-unions are suitable for EXOGEN™ treatment[8]. Overall EXOGEN™ was seen as suitable treatment for non-union, providing the fracture is stable and aligned.

ECONOMICAL IMPLICATIONS

One of the main benefits of EXOGEN™ is it is relatively inexpensive and thus appealing to UK clinical governors. LIPUS allows patients to not only avoid surgery and its associated costs, but also outpatient follow up appointments. Surgery is an expensive process, and was on average in a systematic review (SR) by Kanakaris et al (2007) in the "best case scenario" £15566, £17200 and £16330 for humeral, femoral, and tibial non-unions[9]. According to NICE the EXOGEN™ 4000+ for non-uniting fractures costs £2562.50 for 191x20 minute treatments which equates to over 6 months demonstrating its cost effectiveness[10].

Taylor et al (2009) showed that EXOGEN™ combined with conservative treatment was the cheapest ($4704 USD per patient) versus conservative alone ($5488), surgery alone ($15060) and surgery with ultrasound ($14390). Costs were calculated through diagnosis, surgery if applicable, rehabilitation, follow up and cost of any osteomyelitis[11]. After considering the evidence and assessing the most appropriate cost model available NICE summarised that EXOGEN™ was associated with a £2310 saving per patient versus surgery for non-unions (£4647 versus £6957)[12].

ASSESSMENT OF CLINICAL EVIDENCE OF EXOGEN™

Methods

See appendix 3.

Results

A 2011 study by Roussignol et al examined the efficacy of EXOGEN™ , assessing patients clinically and radiologically after a mean treatment time of 151 days (90-240 range). The study was well conducted despite low patient numbers with no loss to follow up and radio-clinical control groups at 3 and 6 months for comparison. Bone consolidation occurred in 88% of cases with 7/59 failures, however due to the study type, differences between treatment initiation and bone consolidation were clinically significant between groups. Factors such as smoking (p=0.38) and age (P=0.68) were statistically insignificant to bone consolidation[6].

Shofer et al published a study of 101 tibial delayed unions at 4 months post trauma treated using EXOGEN™ . This significantly improved bone mineralization (P=0.002) and reduced fracture gaps (P=0.014), however the time between treatment and system application was arguably too small to qualify for non-union and therefore apply the results[13].

Dijkman et al systematically reviewed 8 publications assessing LIPUS for non-unions[14]. The exclusion criteria included 9 months post fracture with no progression in the last 3 to establish true non-union, with an impressive self appraisal. The review reported on average bone healing in 87% and a recovery time of 146.5 days which is comparable to Rubin et al of 1546 non-unions averaging 172 days[15]. Similarly, Khalil et al (2010) showed that 90% of ulna non-unions resolved through surgical contoured plating[16]. The two studies however cannot be directly compared as the Dijkman study includes non-unions at various sites whilst the Khalil study is directed towards the ulna. Therefore recovery time similarities could be accounted for by the relative healing variation of different bones and not similar treatment efficacies. A review summary of the papers was conducted in appendix 4.

Local audits are increasing in UK hospitals since NICE guidance on EXOGEN™ was released. Appendix 5 shows a case report summary from an audit at the Great Western Hospital (GWH) in Swindon (UK), of a candidate who was treated with EXOGEN™ .

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CONCLUSIONS AND DISCUSSION

EXOGEN™ has many advantages that contend with surgery for the treatment of non-union. The system is claimed to be of a comparable efficacy with a hastier recovery, return to normal living and a reduced cost. Based on the evidence presented in this review, it would be appropriate to assume the previous statement is accurate to at least some extent. Evidence for LIPUS versus surgery is limited as most studies performed are cohorts. However RCTs clinically are difficult to directly compare EXOGEN™ and surgery, with blinding and ethical issues raised as treatment would be denied for 6 months.

There are several limitations of this review that need consideration. Non-union healing rates are difficult to interpret due to the number of different assessment methods, with no standard way to quantify bone healing which can be subjective. Assessment with X-ray is common, CT and MRI are sensitive but too expensive to justify in an average case. Some of these studies also contain low patient numbers, therefore the power of the result becomes diluted.

To summarise, EXOGEN™ is an easy to use, inexpensive, self-administering non operative management option for stable, well aligned, aseptic diaphyseal non-unions. Studies show similar efficacies to surgery through ultrasonic induction of bone synthesis whilst avoiding the costs and complications associated, however more high quality research must be performed to give a definitive answer as to a place in management. NICE guidelines published in 2013 recognise high fracture healing rates combined with cost saving initiatives compared to surgery by EXOGEN™ for non-union long bone fractures.

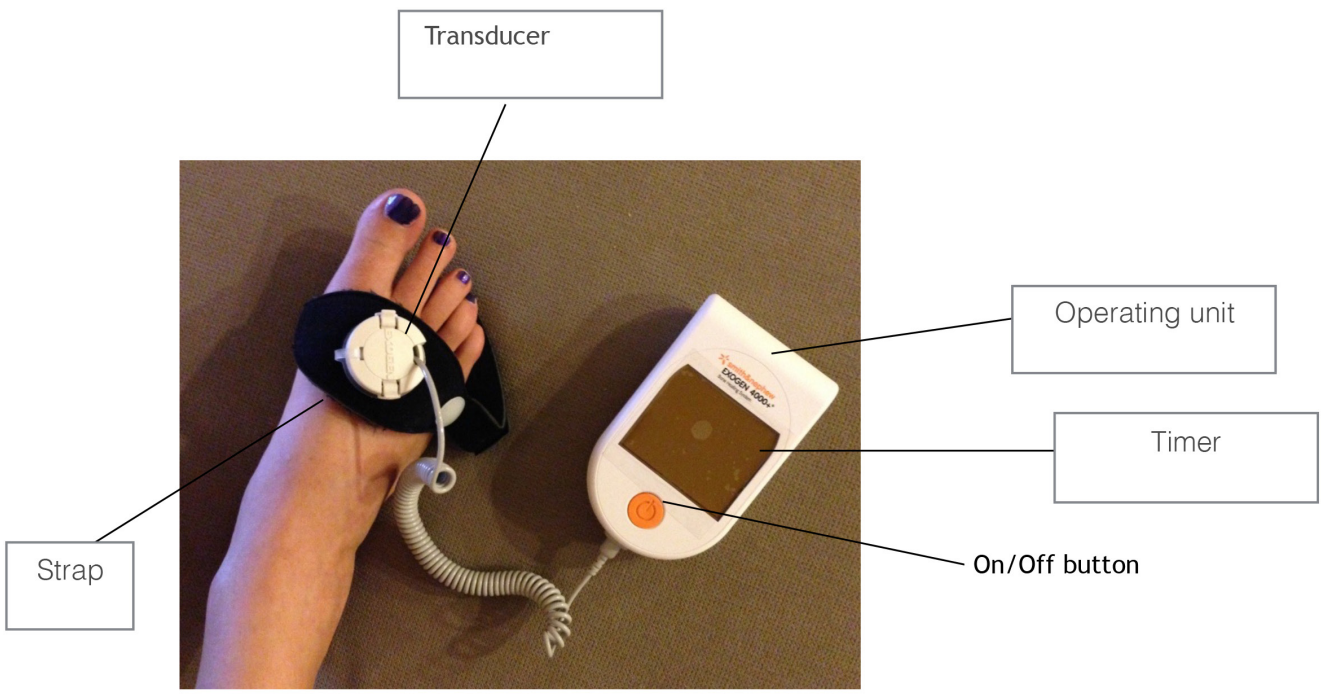
APPENDIX 1

Table 1. A classification summary of aseptic non-unions. Note avascular non-union can be with or without bone loss. Information from AO-Principles of fracture management[1].

	Type of Non-union	Vascularity	Callus formation	Main features
Diaphyseal	Hypertrophic	Hypervascular	Prolific	Instability detaches periosteum increasing bone remodelling
	Avascular	Diminished	Absent	Bone fragments devascularise after injury/surgery
	Atrophic	Normal	Absent	Absence of force transmission leads to bone atrophy, combination of host and injury factors- poor local biology
	Pseudoarthrosis	Normal	Present	Continued fracture site motion forms synovial producing false joint
	Metaphyseal			Cancellous bone - high risk osteoporosis

APPENDIX 2

Image of EXOGEN™ 4000+ for a metatarsal non-union. Annotations added by the author.



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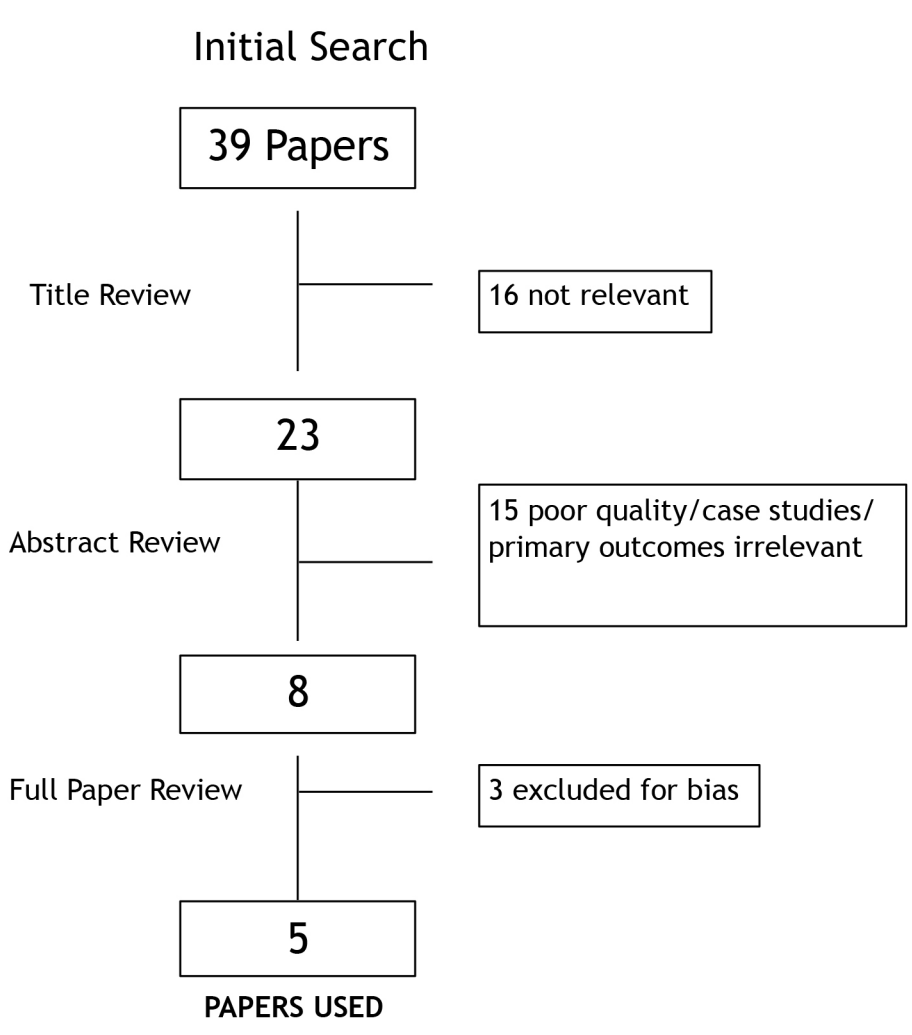
APPENDIX 3

Methods

Search criteria: The author searched the MEDLINE Ovid SP database with the following terms:
"non-union.mp" (OR "fractures ununited.exp") AND "Ultrasonic therapy.exp" AND "fracture healing.exp".
Inclusion Criteria
Papers were limited to the MEDLINE database with human trials published in English. Papers were required to either test LIPUS or surgery on defined outcomes of non-union (definition above) otherwise excluded.



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APPENDIX 4

An analysis of papers used in the economical implications and evidence sections.

Paper	Design	Patient Number	Primary Outcome	Results	Disadvantages
Kanakaris et al[9]	SR	9 papers - N.A	Non-union surgery cost identification	£15566 (humeral), £17200 (femoral) and £16330 (tibial)	
Taylor et al[11]	Economic evaluation	N.A	Non union treatment cost identification	Conservative + US = $4704 Conservative = $5488 Surgery = $15060 Surgery +US = $14390	
Roussignol et al[6]	Retrospective Cohort	59	Bone consolidation (clinically/ radiologically)	88% consolidation	23% non adherence at 12 weeks, study design, low patient numbers.
Shofer et al[13]	RCT	101	Bone Mineral Density (BMD) changes	LIPUS increased BMD 1.34(1.14-1.57) c.f. placebo	Small time between treatment and system application.
Dijkman et al[14]	SR	594	Healing rate	87% average	7/8 studies n<100, heterogenous in non-union location
Rubin et al[15]	SR	1546	Recovery time	172 days average	Little description of methodology
Khalil et al[16]	Prospective Cohort	21	Union Rate	19/21 (90%)	Low patient numbers.

APPENDIX 5

A case from GWH's Orthopaedic department audit of the use of EXOGEN™ in non-union.
PC : 79 year old female presented in 09/2010 after falling on holiday in Italy.

Background:
Past medical history
Transient Global Ischemia likely TIA 12/2011 – CT old right frontal infarct.
Hypertension
Hypercholesterolaemia
Stroke
Heart murmur
(secondary to aortic stenosis)
E-coli Urinary Tract Infection

Medication and Drug History
Lansoprazole 15mg od
Nebivolol 2.5mg od
Clopidogrel 75mg od
Simvastatin 40mg
Telmisartan 80mg od
Paracetamol prn
Previous low dose Aspirin prior to TIA
Diagnosis - Grade II open fracture left tibia with comminuted proximal fibula fracture.

Follow up:
1) Wound debridement and intra-medullary nail 4/7 post injury in Italy. Admitted to Swindon Intermediate Care Centre for rehabilitation and fracture clinic referral.

2) 02/10/10. Fracture clinic. Wound healed and reasonable range of movement in the knee and ankle. X-rays showing acceptable position.

3) 08/12/10. Fracture clinic - acceptable progress.

4) 09/02/11. Fracture clinic. ?non-union anterior tibia. 1x dynamised nail removed.

5) 09/03/11. Knee clinic. X-ray suggests tibial non-union incorporating > 2/3 tibial circumference, CT confirmed, conservative management.

6) 24/01/12. Knee Clinic. Tibial discomfort. X-rays showed healed fibular fracture but tibial non-union. EXOGEN™ discussed, due to co-morbidities and surgical risk agreed.

7) 17/10/12. EXOGEN™ funding granted, started 06/03/13.

8) 03/07/13. Knee clinic. Tibial tenderness, no pain on stressing site. 80-90% knee/ankle motion. X-rays showed ¾ cortices anterior tibia healed.

9) 15/01/14. Patient discharged. X-ray showed consistent small anteromedial fracture gap, outcome unaffected.

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