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

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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, malnourishment, 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 osteogenesis3. 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 decision4.

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.5 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).6

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.7 Shofe er al published a study of 101 tibial delayed unions at 4 months post trauma treated using EXOGEN™.8 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.9

Dijkman et al systematically reviewed 8 publications assessing LIPUS for non-unions.10 The exclusion criteria included 9 months post fracture with no progression in the last 3 to establish true non-union, with an impressive self healing rates. 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.11 Similarly, Khalil et al (2010) showed that 90% of ulna non-unions resolved through surgical contoured plating.12 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™.
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 management¹.

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

APPENDIX 2

Image of EXOGEN™ 4000+ for a metatarsal non-union. Annotations added by the author.
An overview of the use of the EXOGEN™ Ultrasound Bone Healing system for non-union of long bone fractures.

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.

Initial Search

- 39 Papers
  - Title Review
    - 16 not relevant
  - Abstract Review
    - 15 poor quality/case studies/primary outcomes irrelevant
  - Full Paper Review
    - 3 excluded for bias

PAPERS USED: 5
An overview of the use of the EXOGEN™ Ultrasound Bone Healing system for non-union of long bone fractures.

APPENDIX 4

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

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Patient Number</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanakaris et al⁵</td>
<td>SR</td>
<td>9 papers - N.A</td>
<td>Non-union surgery cost identification</td>
<td>£15566 (humeral), £17200 (femoral) and £16330 (tibial)</td>
<td></td>
</tr>
<tr>
<td>Taylor et al¹¹</td>
<td>Economic evaluation</td>
<td>N.A</td>
<td>Non union treatment cost identification</td>
<td>Conservative + US = $4704, Conservative = $5488, Surgery = $15060, Surgery +US = $14390</td>
<td></td>
</tr>
<tr>
<td>Roussignol et al⁶</td>
<td>Retrospective Cohort</td>
<td>59</td>
<td>Bone consolidation (clinically/radiologically)</td>
<td>88% consolidation</td>
<td>23% non adherence at 12 weeks, study design, low patient numbers.</td>
</tr>
<tr>
<td>Shofer et al¹³</td>
<td>RCT</td>
<td>101</td>
<td>Bone Mineral Density (BMD) changes</td>
<td>LIPUS increased BMD 1.34(1.14-1.57) c.f. placebo</td>
<td>Small time between treatment and system application.</td>
</tr>
<tr>
<td>Dijkman et al¹⁴</td>
<td>SR</td>
<td>594</td>
<td>Healing rate</td>
<td>87% average</td>
<td>7/8 studies n=100, heterogenous in non-union location</td>
</tr>
<tr>
<td>Rubin et al¹⁵</td>
<td>SR</td>
<td>1546</td>
<td>Recovery time</td>
<td>172 days average</td>
<td>Little description of methodology</td>
</tr>
<tr>
<td>Khalil et al¹⁶</td>
<td>Prospective Cohort</td>
<td>21</td>
<td>Union Rate</td>
<td>19/21 (90%)</td>
<td>Low patient numbers.</td>
</tr>
</tbody>
</table>

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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REFERENCES