Low-intensity pulsed ultrasound for non-union treatment: A 14-case series evaluation

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KEYWORDS
Pulsed ultrasound; Non-union; Non-invasive; Fracture healing

Summary
Introduction: Non-union is presently managed exclusively by surgery, but alternative treatments are under evaluation.

Objective: To assess the benefit of external ultrasound stimulation in surgically treated lower-limb long-bone non-union.

Patients and methods: A retrospective series of 14 patients were treated using the Exogen® ultrasound stimulator (Smith & Nephew Inc., Memphis, TN, USA) as part of management of surgically treated long-bone non-union. They received 20 min stimulation daily over a period of 3 months. Regular clinical and radiological follow-up checked treatment efficacy.

Results: The mean interval to initiation of Exogen® treatment after initial surgery was 361 days (range, 6, 38 months). Bone consolidation was obtained in 11 of the 14 cases (79%), and within 3 months of initiation of Exogen® treatment in 27% (3/11), within 6 months in 27% (3/11) and within 9 months in 46% (5/11). There were no treatment-linked complications. There was no significant correlation between interval to initiation of ultrasound treatment and bone consolidation. Associated sepsis or atrophy did not significantly impact treatment efficacy.

Discussion: The reference treatment strategy in non-union is surgical revision, with consolidation rates ranging from 85 to 100% according to the series. This attitude entails risk of complications, notably infection and postoperative pain. The present results were comparable to those of the literature, with 79% bone consolidation and no complications. Ultrasound stimulation proved an effective and non-invasive treatment for non-union.

Level of evidence: Retrospective study, level IV.

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Introduction
The evolution of healing in fracture depends on a number of factors: lesion type, patient age, fracture level, the affected
bone, and the type of surgical treatment. In the specific case of long-bone non-union, the reference treatment is surgical revision, usually associating osteosynthesis and autologous bone graft. As an alternative to the various surgical strategies, several modes of osteogenesis stimulation are presently recommended as accelerating and promoting bone consolidation: induced currents, pulsed electromagnetic fields, or low-intensity pulsed ultrasound. Non-surgical management of non-union has the advantage of avoiding all risk of morbidity, and is of particular interest in at-risk patients. Low-intensity pulsed ultrasound is little used in non-union, although several studies have shown its interest in stimulating bone consolidation. Dyson and Brookes [1], followed by Pilla et al. [2] reported an increase in callous tissue and accelerated bone consolidation in animals. One of the first randomized human studied was published in 1994 by Heckman et al. [3]. Comparing two populations with orthopedically managed fracture of the tibial shaft, they reported significantly shorter consolidation times with the use of their ultrasound system.

Other authors, such as Kristiansen et al. and Mayr et al. [4,5], confirmed this radioclinical impression, although Emami et al. [6] found no significant associated difference in consolidation time following tibial shaft fracture treated by intramedullary nailing.

All types of equipment represent a costly investment and have to be specifically ordered from the manufacturer. In June 2007, the French Health Authority (HAS) set up a commission to assess the Exogen® 4000 + low-intensity pulsed ultrasound generator (Decision dated June 27, 2007, available at http://www.has-sante.fr/portal/jcms/c_671298/exogen-4000). The commission examined the interest of the system for the treatment of non-union, excluding vertebral and cranial locations, with and without prior surgical treatment. Interest, however, could not be established, due to the poor methodological quality of the clinical data available: study populations tend to be heterogeneous, preventing precise argument for the indication of this procedure.

The present study assessed bone stimulation induced using the Exogen® low-intensity ultrasound system (Smith & Nephew Inc., Memphis, TN, USA) in case of failed consolidation in surgically stabilized long-bone fracture.

**Patients and methods**

**Inclusion criteria**

The study included patients treated in our department by Exogen® (Smith & Nephew Inc., Memphis, TN, USA) (Fig. 1) as part of management of lower-limb long-bone non-union between September 2006 and January 2008. All underwent surgery, and the non-union site was mechanically and radiologically stable (osteosynthesis by intramedullary nailing, plate or external fixator) in all cases (Table 1).

For patients 1 to 7, non-union was primary (i.e., following initial fracture surgery); for patients 8 to 14, it was a second or third non-union (i.e., following failure of surgical revision for non-union).

Non-union was defined by limp or pain on mobilization of the fracture site and absence of radiologic consolidation at least 6 months after the last surgical procedure (initial fracture surgery for patients 1 to 7, and last surgical revision for patients 8 to 14).

Patients having had ultrasound stimulation at another bone location or treated orthopedically were excluded. Cases in which stimulation was adjuvant (concomitant to non-union surgery) were also excluded.

**Stimulation equipment and technique**

The Exogen® stimulator was held against the limb by hook-and-loop tape, or directly incorporated in the cast in some cases, with a transducer connected to the ultrasound generator (Fig. 2). Ultrasound transfer to the soft tissue was ensured by coupling gel. Patients were required to use the stimulator for 20 min in a single daily session. The Exogen® stimulator delivered low-intensity ultrasound (30 mW/cm² mean spatiotemporal intensity), which could not be modified by the patient or the physician. The equipment was shipped directly to the patient on reception and checking of the order documents. All patients had received directions for using the Exogen® system in the supplier’s brochure and during consultation with the physician. The equipment was used for a period of 3 months maximum.

**Revision methods**

All patients were followed up by the surgeon in consultation, with complete X-ray assessment every 3 months. Radiologic consolidation was defined as continuity in all planes between the two cortical shapes, and in two orthogonal planes on x-ray examination or on CT in case of doubt. Clinical consolidation was defined as absence of pain in the limb on weight-bearing and on fracture site mobilization.

Statistical analysis used SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Qualitative data (sepsis, open fracture, type of non-union and revision for non-union) were assessed with a significance threshold set at \( P < 0.05 \). In the specific framework of the use of the Exogen® system in non-union, a randomized comparative study did not seem feasible, and we therefore used self-paired analysis, with patients serving as their own control. The probability of non-union showing favorable evolution without surgical treatment was estimated to be zero; each patient was therefore compared before and after initiation of ultrasound stimulation.
## Table 1  
Detail of fracture types and consolidation after ultrasound stimulation.

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient Gender and age</th>
<th>Type of fracture</th>
<th>Initial treatment</th>
<th>Sepsis</th>
<th>Previous treatment of non-union</th>
<th>Type of non-union</th>
<th>Interval before stimulation (months)</th>
<th>Consolidation time after stimulation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M 20</td>
<td>Mid-third femur</td>
<td>IMN</td>
<td>No</td>
<td>No</td>
<td>Hyper</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>F 50</td>
<td>Mid-third femur</td>
<td>IMN</td>
<td>No</td>
<td>No</td>
<td>Hyper</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>F 16</td>
<td>Inf. third tibia</td>
<td>EF</td>
<td>Yes</td>
<td>No</td>
<td>Hyper</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>M 62</td>
<td>Inf. third tibia</td>
<td>EF</td>
<td>No</td>
<td>No</td>
<td>Hyper</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>M 58</td>
<td>Mid-third femur</td>
<td>IMN</td>
<td>No</td>
<td>No</td>
<td>Hyper</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>M 42</td>
<td>Sup. third tibia</td>
<td>IMN</td>
<td>Yes</td>
<td>No</td>
<td>Atrophic</td>
<td>7</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>M 26</td>
<td>Inf. third tibia</td>
<td>Plate</td>
<td>Yes</td>
<td>No</td>
<td>Hyper</td>
<td>6</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>F 36</td>
<td>Inf. third tibia</td>
<td>EF</td>
<td>Yes</td>
<td>Early debridement, EF removed at 6 months, Tibio-talar arthrodesis at 7 months</td>
<td>Atrophic</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>M 49</td>
<td>Mid-third tibia</td>
<td>IMN</td>
<td>No</td>
<td>Nail removal, rereaming and new IMN at 8 months</td>
<td>Hyper</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>M 52</td>
<td>Inf. third tibia</td>
<td>Plate</td>
<td>No</td>
<td>Plaque removal and ITPG at 8 months</td>
<td>Hyper</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>M 32</td>
<td>Sup. third tibia</td>
<td>Plate</td>
<td>Yes</td>
<td>Early debridement, rereaming and IMN at 7 mo</td>
<td>Atrophic</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>M 31</td>
<td>Inf. third tibia</td>
<td>Plate</td>
<td>No</td>
<td>Curettage, graft and plate at 6 months, then tibio-talar arthrodesis at 18 months</td>
<td>Hyper</td>
<td>28</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>M 36</td>
<td>Sup. third tibia</td>
<td>IMN</td>
<td>Yes</td>
<td>Early debridement, rereaming and new IMN at 8 months, then curettage, graft and plate at 15 months</td>
<td>Hyper</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>14</td>
<td>M 38</td>
<td>Mid-third tibia</td>
<td>IMN</td>
<td>No</td>
<td>Removal of IMN and curettage, graft and plate at 9 months</td>
<td>Hyper</td>
<td>38</td>
<td>9</td>
</tr>
</tbody>
</table>

M: male; F: female; hyper: hypertrophic non-union; N/A: non-applicable (no bone consolidation); IMN: intramedullary nailing; EF: external fixator; ITPG: intertibial peroneal graft; Inf.: inferior; Sup.: superior.
Results

Patients

The series comprised 11 males and three females. Mean age at trauma was 39 years (range, 16–62 yrs). Table 1 shows fracture sites and demographic data. Postoperative course was complicated by infection in six patients, all of whom had presented with open fracture.

Initial management was by intramedullary nailing in seven cases, external fixator in three and screwed plate in four. All patients showed fracture site non-union; seven had already undergone revision surgery (patients 8 to 14).

Bone consolidation

Exogen® treatment was initiated 6–7 months after surgery (primary fracture or secondary non-union surgery) in 10 of the 14 cases (71%), and was delayed in four (11, 26, 28 and 38 months after last surgical procedure, respectively), because the patient either was lost to follow-up or had been referred late, at the non-union stage.

Consolidation was obtained in 11 of the 14 cases (79%): within 3 months of beginning Exogen® treatment in 27% (3/11), within 6 months in 27% (3/11) and within 9 months in 46% (5/11) (Fig. 3). Mean time to consolidation was 5.3 months (158 days) in initial non-union and 6.4 months (192 days) after revision for non-union (P = 0.41). Three patients (cases no 6, 7 and 12) failed to respond to treatment, with no radiologic improvement in consolidation in the 6 months following the ultrasound treatment; two underwent surgical revision, with decortication, bone graft and osteosynthesis (cases 6 and 7) and one preferred the radical solution of trans-tibial amputation, due to his history (case 12).

No postoperative complications occurred. Two patients showing consolidation required surgical revision: 1 case of arthrolysis and 1 of calcaneal tendon lengthening.

Statistical analysis

Treatment of non-union in surgically stabilized long bone by the ultrasound stimulator was significantly effective (P < 0.0001; Table 2).

There was no significant correlation between the interval from surgery to Exogen® treatment and treatment efficacy. Patients not showing consolidation had undergone ultrasound treatment at a mean 13.6 months (407 days) after surgery (initial or for non-union), compared to a mean 11.6 months (348 days) for those who responded favorably (P = 0.776). Nor was there any significant link between efficacy and age, gender or fracture location. Four of the six patients who developed sepsis showed consolidation after ultrasound treatment; there was no significant correlation, however, between failure of ultrasound treatment and previous sepsis (P = 0.385). Three patients showed atrophic non-union and 11 hypertrophic non-union: bone consolidation was not significantly affected by type of non-union (P = 0.412).

Discussion

Three months’ ultrasound stimulation was applied systematically in the present series, and enabled consolidation of non-union in 79% of cases at a mean 5.8 months (173 days).

The limitations of the present study mainly lie in its retrospective design, and in the small size and lack of homogeneity of the series. Statistically, no definite conclusion could be drawn as to the efficacy of this type of treatment for non-union. As stressed by Busse et al. [7] in their meta-analysis, further randomized double-blind studies on larger series will be needed in order to assess treatment efficacy.

Mode of action of low-intensity ultrasound

Ultrasound, when used therapeutically on soft tissue, induces thermal effects within the tissue, which may be harmful for bone tissue, especially in the growth phase, if intensity is high (3000 mW/cm² mean intensity). The Exogen® bone-growth stimulator uses low-intensity ultrasound with an energy level comparable to that employed in radiology (30 mW/cm²), low enough not to induce thermal effects or any obvious adverse effects [8]. The benefit of ultrasound in bone tissue remains poorly determined:

<table>
<thead>
<tr>
<th>Bone consolidation</th>
<th>Surgery</th>
<th>Ultrasound</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td>14 (100%)</td>
<td>3 (21%)</td>
<td>0.000069</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Hadjiargyrou et al. [9] suggested different modes of action as possibly explaining the observed effects. The energy of ultrasound is absorbed proportionally to the density of the tissue it passes through. These differences in absorption probably play a role in bone stimulation, as bone tissue is denser than muscle or hematoma. Absorbed energy is converted into heat, and this heat effect (< 1°C) may facilitate the enzymatic process of collagenase. In a second mode of action, absorbed energy may induce acoustic stimulation, particularly in a liquid environment. Oscillation in little air bubbles, which are not normally found in healthy tissue but do appear in the fracture area, may accelerate consolidation.

Thirdly, the physical change in cell response induced by ultrasound may lead to a molecular biochemical change at cell level. Ryabi [10], in an in vitro experiment, found elevated intracellular calcium when chondrocytes, in culture in a favorable medium, were subjected to low-intensity ultrasound stimulation (50 mW/cm²). This theory of micromovement is the most widely accepted [11].

Comparison with the literature

In the present series, ultrasound stimulation provided a 79% non-union consolidation rate. This was largely comparable to that found in the various series in the literature using low-intensity pulsed ultrasound. Mayr et al. [5] reported 86% consolidation in a series of 153 non-unions managed without surgery. In a similar study, Stein reported 88% consolidation (16 patients out of 18) [12]. Gebaueur et al. [13] and Nolte et al. [14] reported respectively 70% and 87% consolidation. In 2007, Rutten et al. [15] obtained a 70% rate of favorable evolution in follow-up of delayed tibial fracture consolidation. Pigozzi et al. [16] obtained favorable evolution of non-union in all 15 of their athlete patients.

There have been many reports of accelerated consolidation using ultrasound. In the particular case of the present study, focused on non-union, the mean consolidation time after treatment initiation was 173 days. Likewise, Nolte et al. [14] obtained a mean consolidation time of 157 days in eight patients managed by ultrasound; this figure was identical to that obtained by Gebaueur et al. [13] in a series published in 2005. The present relatively long consolidation time may be mainly due to physicians’ caution in claiming consolidation; also the present series consisted of non-union treated by surgery, and certain patients required multiple surgical revision.

In the present series, no correlation emerged between treatment efficacy and type of non-union. Nolte et al. [14] reported 83% consolidation in hypertrophic and 86% in atrophic non-union.

Ultrasound is a non-invasive technique, and there were no treatment-linked complications in the present series. Likewise, a review of the literature found no reports of associated complications (allergy or irritation).

Moreover, the efficacy of ultrasound treatment would not appear to be diminished by sepsis. Four of the six patients showing postoperative sepsis also showed consolidation. Certain authors recommended associating ultrasound bone stimulation to antibiotherapy in case of septic non-union. In 2008, Ayan et al. [17] performed a comparative study between two groups of staphylococcus aureus in test-tubes: tubes stimulated by ultrasound showed significantly fewer bacteria than controls, without change in sensitivity to antibiotics. We were able to retrieve no clinical studies of ultrasound stimulation efficacy specifically in osteo-articular infection: ultrasound stimulation associated to medical treatment or as adjuvant associated to surgery in osteo-articular infection could be an interesting line of research.

Alternative treatment strategies

Despite the satisfactory rate of bone consolidation, the efficacy of ultrasound stimulation in non-union remains lower than that of specific surgical management. Judet et al. [18], in 1967, described bone decortication, which provided a success rate of nearly 94.2%. Beckers [19], in 1992, retrospectively analyzed 26 cases of lower limb decortication, with associated cancellous bone graft in 12 cases, and reported a consolidation rate of 100%. Piriou et al. [20], in 2005, reported a consolidation rate of 94% at a mean 108 days in 18 cases of lower-limb non-union treated by decortication associated to plate osteosynthesis: surgical treatment enabled malunion to be reduced, but not without...
certain complications, notably a 27% rate of pain around the osteosynthesis material.

Some teams used autologous cancellous bone graft, which entails a certain iatrogenic donor-site risk. Younger et Chapman [21] reported an overall 8.6% complications rate, including a 2.6% rate of pain persisting beyond 6 months. Surgical revision, moreover, entails a risk of sepsis, estimated by Christensen [22] at between 7.4 and 13%, with bacterial reactivation in 50% of cases.

Other non-invasive techniques have been used in treating non-union. Wang’s team [23] demonstrated accelerated consolidation with pulsed ultrasound (extracorporeal shock-wave treatment) in animals. Xu et al. [24] studied the efficacy of pulsed waves in 69 cases: consolidation was obtained in 75.4%, but this study failed to demonstrate efficacy in atrophic non-union. Bara et Stnder [25] reported 83% consolidation in a series of 150 patients, and likewise found favorable response to such treatment to be lacking in case of atrophic non-union.

Other authors studied the effect of electromagnetic stimulation on osteogenesis. Scott and King [26] used low-frequency electromagnetic fields in 10 cases of non-union and obtained consolidation in 60% versus zero in a control group of 11. Sharrard et al. [27] obtained consolidation in 71.7% of cases and 86.7% in tibial locations. Meskens et al. [28] reported consolidation in 23 out of 34 patients receiving external electromagnetic stimulation.

Conclusion

Low-intensity pulsed ultrasound is a non-invasive procedure that seems to promote consolidation in case of non-union. The Exogen® system enabled bone consolidation in 11 of the 14 patients of the present series. No treatment-linked complications were observed.

Low-intensity ultrasound showed a favorable effect on both atrophic and hypertrophic non-union, unlike other types of external stimulation. These results are encouraging, but a larger series will be needed to validate the application of low-intensity pulsed ultrasound in the management of non-union.

Conflict of interest statement

None.

References