Low-intensity pulsed ultrasound to repair insufficiency fractures occurring adjacent to osteonecrosis caused by long-term steroid administration

Kaori Suto,1 Ken Urabe,1 Kouji Naruse,1 Masaki Ueno,1 Kentarou Uchida,1 Mitsutoshi Suto,1 Takeaki Yamamoto,1 Moritoshi Itoman2

1 Department of Orthopaedic Surgery, Kitasato University School of Medicine
2 Kyushu Rosai Hospital

Background: Low-intensity pulsed ultrasound stimulation (LIPUS) has been known to accelerate fracture healing by mechanical stimulation.

Objective: We report a case in which we used LIPUS to treat an insufficiency fracture of the lateral femoral condyle due to glucocorticoid-induced osteoporosis.

Methods: The patient was a 40-year-old woman who had received steroid therapy for 2 years and 6 months as treatment for systemic lupus erythematosus. She complained of severe left knee pain 2 or 3 days after jumping rope. Plain radiographs showed a radiolucent line at the weight-bearing area of the lateral femoral condyle. Magnetic resonance imaging at the time of diagnosis revealed low signal intensity lines indicating a subchondral fracture at the weight-bearing area of the lateral femoral condyle on T1-weighted and short T1 inversion recovery images. The fracture in this case, caused by normal or physiologic stress, was classified as an insufficiency fracture and treated with LIPUS for 14 months.

Results: The patient's condition remarkably improved within 1 month of beginning LIPUS treatment. Final radiographs revealed that the fracture healed without any displacement.

Conclusions: This case demonstrated the possibility that LIPUS was effective in the treatment of insufficiency fractures.

Key words: low-intensity pulsed ultrasound stimulation (LIPUS), insufficiency fracture, glucocorticoid-induced osteoporosis

Introduction

Long-term administration of steroids is one of the causes of osteoporosis. Steroid-induced osteoporosis causes insufficiency fracture,1,2 and many investigators have reported harmful effects of corticosteroids on fracture healing in rabbits.3,5 Various methods to accelerate fracture healing by mechanical stimulation, such as pulsed electromagnetic field stimulation and low-intensity pulsed ultrasound stimulation (LIPUS), are currently used in clinical therapy. In particular, a number of reports providing a high level of clinical evidence in support of the use of LIPUS have been published.6,7 We have previously reported that LIPUS increases production of prostaglandin E2 (PGE2), mediated by cyclooxygenase-2 (COX2), and of growth factors, such as insulin-like growth factor (IGF)-I, II, and transforming growth factor (TGF)-β1, and also stimulates osteogenesis.8,9 We also reported that LIPUS accelerated periosteal bone formation in an in vitro organ culture system.10

We applied LIPUS to the treatment of an insufficiency fracture of the lateral femoral condyle due to glucocorticoid-induced osteoporosis and report here that LIPUS accelerates the repair of insufficiency fracture.

Case report

A 40-year-old woman complained of severe pain in the left knee 2 or 3 days after jumping rope. She had been receiving steroid therapy for 2 years and 6 months as a treatment for systemic lupus erythematosus. Treatment
A. Posteroanterior view in the standing position
There is a radiolucent line (arrow) on the left lateral femoral condyle.

B. Lateral view, in the standing position
There were no abnormal findings.

Figure 1. Initial plane radiographs of the left knee

A. T1-weighted image
MRI reveals multiple necrotic lesions in the medial and lateral femoral condyles and the lateral tibial plateau (open arrows). The adjacent low-intensity line of the necrotic lesion represents the fracture (white solid arrow). In the bone marrow, the low signal intensity area represents medullary edema and hemorrhage (arrowheads).

B. STIR image
Intermediate to high signal intensity areas in the medial and lateral femoral condyles and the tibial plateau (open arrows) are necrotic lesions. The adjacent line of the necrotic lesion in the lateral femoral condyle represents the fracture (white solid arrow). The high signal intensity area adjacent to the fracture line indicates medullary edema and hemorrhage (arrowhead).

Figure 2. MRI of the left knee, coronal view at the time of diagnosis
### Table 1. Changes in three scores assessing health status and pain

<table>
<thead>
<tr>
<th></th>
<th>0M</th>
<th>1M</th>
<th>3M</th>
<th>6M</th>
<th>9M</th>
<th>1Y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function</td>
<td>15.0</td>
<td>30.0</td>
<td>60.0</td>
<td>50.0</td>
<td>70.0</td>
<td>80.0</td>
</tr>
<tr>
<td>&quot;Role Physical&quot;</td>
<td>25.0</td>
<td>6.3</td>
<td>25.0</td>
<td>43.8</td>
<td>62.5</td>
<td>75.0</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>22.0</td>
<td>22.0</td>
<td>84.0</td>
<td>74.0</td>
<td>74.0</td>
<td>100.0</td>
</tr>
<tr>
<td>General Health</td>
<td>25.0</td>
<td>30.0</td>
<td>42.0</td>
<td>42.0</td>
<td>37.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Vitality</td>
<td>18.8</td>
<td>25.0</td>
<td>50.0</td>
<td>56.3</td>
<td>50.0</td>
<td>43.8</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>50.0</td>
<td>0.0</td>
<td>25.0</td>
<td>62.5</td>
<td>50.0</td>
<td>75.0</td>
</tr>
<tr>
<td>&quot;Role Emotional&quot;</td>
<td>25.0</td>
<td>0.0</td>
<td>25.0</td>
<td>62.5</td>
<td>50.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Mental Health</td>
<td>5.0</td>
<td>30.0</td>
<td>50.0</td>
<td>60.0</td>
<td>65.0</td>
<td>70.0</td>
</tr>
<tr>
<td>VAS</td>
<td>8.9</td>
<td>1.7</td>
<td>0.7</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>JKOM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain and stiffness in knee</td>
<td>29</td>
<td>16</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Condition in daily life</td>
<td>32</td>
<td>25</td>
<td>20</td>
<td>18</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>General activities</td>
<td>18</td>
<td>25</td>
<td>21</td>
<td>16</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Health conditions</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>87</td>
<td>72</td>
<td>56</td>
<td>50</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

SF-36, Short Form 36-Item Health Survey; VAS, Visual Analog Scale; JKOM, Japanese Knee Osteoarthritis Measure; M, month; Y, year

---

**Figure 3.** Coronal MRI of the left knee 3 months after treatment

A. T1-weighted image

The low-intensity area surrounding the necrotic lesion in the lateral femoral condyle has decreased in size (arrowheads).

B. STIR image

The brightness of the high signal intensity in the lateral femoral condyle has been reduced (arrowhead).
LIPUS to repair insufficiency fractures

was started with prednisolone at 30 mg per day, and the
dose was reduced to 7 mg per day when she came to our
hospital. At the first visit, the physical examination
showed tenderness of the left lateral femoral condyle.
There was no joint effusion or instability. She felt pain
on motion but had a normal range of motion. The pain
increased when standing, and she was unable to walk
without any aids.

Plain radiographs showed a radiolucent line at the
weight-bearing area of the lateral femoral condyle (Figure
1). Magnetic resonance imaging (MRI) at the time of
diagnosis (Figure 2) revealed multiple foci of necrotic
lesions in the medial and lateral femoral condyles and
the lateral tibial plateau. They were defined by a
serpiginous low signal intensity halo, which was of a low
to intermediate signal intensity on T1-weighted images.
On STIR (short T1 inversion recovery) images, the areas
were of intermediate to high signal intensity defined by a
high-intensity signal halo. There were low signal intensity
lines indicating a subchondral fracture at the weight-
bearing area of the lateral femoral condyle on T1-
weighted and STIR images. The area adjacent to the
fracture line in the marrow space with low signal intensity
on T1-weighted images and high signal intensity on STIR
images represented medullary edema and hemorrhage.

The patient was treated with LIPUS generated by a
Sonic Accelerated Fracture Healing System (SAFHS
2000J® TEIJIN, Japan) for 1 year and 2 months. The

A. Radiograph 4 months after beginning
treatment
The fracture line is still visible in the lateral
femoral condyle.

B. Radiograph 7 months after beginning
treatment
The fracture line in the lateral femoral
condyle is indistinct. The trabecular structure
in the subchondral bone of the lateral femoral
condyle shows improvement.

C. Radiograph 1 year and 2 months after
beginning treatment
The fracture line in the lateral femoral condyle
is no longer visible. The trabecular structure
in the subchondral bone of the femoral lateral
condyle has greatly improved. The joint space
has not been narrowed, and there is no
displacement of fractured fragments and no
evidence of subchondral bone sclerosis of
the lateral joint.

Figure 4. Plane radiographs of the left knee, posteroanterior view, in the standing position
LIPUS signal and treatment times per day were as clinically recommended. A transducer 3.8 cm² in area (2.2 cm in diameter) was placed on the tender point on the lateral cortex of the lateral femoral condyle that corresponded to the fracture line confirmed by MRI. In addition to LIPUS, the patient was allowed to gradually increase partial weight-bearing as long as she remained pain-free, but she did not use nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular injections. The function and pain of the knee joints and overall health status were assessed using the visual analog scale (VAS), the Japanese Knee Osteoarthritis Measure (JKOM), and the Short Form 36-Item Health Survey (SF-36) version 2. The JKOM is a self-administered, disease-specific measure. It consists of 25 items that include assessment of patient pain on level walking, standing, and climbing stairs, physical functions related to activities of daily living, and social functions including participation. The intention was that items selected for the questionnaire reflected the contemporary lifestyles of Japanese people. The SF-36 is a self-reported general health status questionnaire comprised of 8 subscales: physical function, "role physical" (RP), body pain, general health, vitality, social function (SF), "role emotional" (RE), and mental health (MH). The SF-36 is used to evaluate quality of life, with a higher score indicating a better quality of life.

The patient’s condition remarkably improved within 1 month of beginning LIPUS treatment. Although some local tenderness remained, she was able to walk without pain in 2 months. The pain in the knee had completely disappeared 1 year and 2 months later. The VAS score was remarkably decreased after 1 month of treatment and reached zero by 9 months (Table 1). The JKOM score indicated a clear improvement in pain and stiffness in the knee and in conditions of daily life 1 and 3 months after beginning treatment. The SF-36 also demonstrated an obvious improvement in scores of body pain, physical function, general health, and vitality 1 and 3 months after starting treatment. In MRI, the low-intensity area on T1 and the high-intensity area on STIR images were both decreased in size (Figure 3). The radiographs revealed obscuration of the fracture line and restoration of the trabecular structure (Figure 4). There was no displacement of fractured fragments.

Discussion

Our patient had been taking glucocorticoids orally for 2.5 years. At the time of the fracture, her percent of the young adult mean was 88.8%; however, her daily dose of prednisolone was 7 mg. A daily prednisolone dose of more than 5 mg is one of the risk factors for reduced bone mass. In the present case, our patient suffered a femoral condyle fracture even though she had been taking biologically active vitamins D₃ and K₂ orally for 2.5 years.

The fracture in the present case, caused by normal or physiologic stress, was classified as an insufficiency fracture. To our knowledge, this is the first report on LIPUS treatment of insufficiency fracture due to glucocorticoid-induced osteoporosis.

In animal models and in patients with glucocorticoid-induced osteoporosis, glucocorticoid was found to increase the apoptosis of osteoblasts and osteocytes. Accumulation of apoptotic osteoblasts and osteocytes may contribute to a decrease in bone formation. Glucocorticoids also have stimulatory effects on osteoclasts, increasing cell recruitment and differentiation. These effects on osteoclasts are mainly mediated by receptor activator of NF-kappaB ligand and macrophage colony stimulating factor produced by osteoblasts. Glucocorticoids also exert a direct antiapoptotic effect on mature osteoclasts. These effects result in increased osteoclast survival and activity, leading to increased bone resorption.

In animal models, fractures due to glucocorticoid-induced osteoporosis are difficult to heal. Blunt et al. showed that glucocorticoid-treated rabbits had less callus formation than controls. Sissons and Hadfield demonstrated that fractures in glucocorticoid-treated rabbits failed to heal. Their results suggest that fracture healing is likely to be delayed in humans with glucocorticoid-induced osteoporosis.

The normal physiological reaction to fracture is the spontaneous initiation of a sequence of cellular events, which, briefly summarized, includes initial inflammation followed by soft callus formation, hard callus formation, and ultimately bone repair and remodeling. It is known that LIPUS can accelerate repair of fractures at each stage of the fracture repair process. Several studies have already shown that LIPUS exposure promotes fracture healing in both animal fracture models and clinical trials. Duarte reported that ultrasonic energy accelerates the healing of fractures in an osteotomy model in rabbits. Wang et al. showed that LIPUS could stimulate fracture repair and increase bone strength in rat fracture models. Kristiansen et al. reported a significant 38% acceleration in the time to heal of a fresh distal radial fracture in a human case, while Mayr et al. demonstrated that LIPUS can help achieve union in 85% to 90% of cases of delayed-union and nonunion in humans.
In light of these studies, we decided to treat the insufficiency fracture caused by glucocorticoid-induced osteoporosis with LIPUS. Within 1 month of starting treatment with LIPUS, the patient's pain was markedly relieved, function remarkably improved, and her VAS score and some SF-36 scores were significantly improved. These results indicate that the application of LIPUS was useful from the earliest stage of the fracture repair process. In MRI, high-intensity areas were reduced in STIR images 3 months after LIPUS exposure. The radiograph revealed that the fracture line became indistinct 7 months after the treatment began, while the structure of trabecular bone finally improved. Narrowing of the lateral joint space between the femoral and tibial condyles was not seen in the final radiograph taken in the standing position. These healing processes suggest no displacement of fracture fragments due to delayed union or nonunion of the fracture even though the repair ability was most likely reduced due to chronic administration of corticosteroid. This case demonstrated the possibility that LIPUS exposure may be effective in the treatment of insufficiency fracture caused by glucocorticoid-induced osteoporosis.

It is possible that the healing process observed in the present case is an entirely natural healing process. However, Uchiyama et al. reported that LIPUS was useful for the early alleviation of focal pain in fracture. Similarly, as the pain of the fracture decreased early in the present case, LIPUS most likely affected the accelerated healing process that we observed.

References


