Enhanced bone healing and decreased pain in sacral insufficiency fractures after teriparatide treatment: retrospective clinical-based observational study

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Summary

The purpose of this retrospective clinical-based observational study was to evaluate the effects of teriparatide (TPTD) on clinical outcomes and radiologic findings of sacral insufficiency fractures (SIFs). Seven elderly women with SIFs received TPTD for at least 6 months. We evaluated the symptoms, pain, and radiological findings. At their initial clinic visit, 86% patients could not walk or sit. Computed tomography (CT) images revealed sacral wing fracture in 6 patients, and bone scintigram showed H-shaped uptake over the bilateral sacral wings in 1 patient. After the treatment, 5 patients could walk. Mean visual analog scale score was significantly lower after (12.9 mm) than before (87.4 mm) TPTD treatment (p < 0.0001). CT images revealed bone union (four patients) and sclerotic changes (three patients) at the fracture sites. Seven elderly women with SIFs had significant improvement in pain and demonstrated bone union or sclerotic changes at fracture sites by TPTD.

KEY WORDS: sacral insufficiency fracture; teriparatide; low back pain; fracture healing; bone union; mobility.

Introduction

Sacral insufficiency fractures (SIFs) often occur, either spontaneously or after minor trauma, in the elderly persons with advanced osteoporosis. The incidence of SIFs has increased with the rapid increase in the size of the elderly population (1). Sacral fractures are a well-defined subgroup of pelvic insufficiency fractures. The mortality rate of pelvic insufficiency fracture patients, reported to be 16.3%, is comparable to that of hip fracture patients (2). Treatment of SIFs is very important for recovering patients' ability to perform activities of daily living. However, the treatment of SIFs is complicated by severely osteoporotic sacral bone, and the incidence of such fractures is increasing.

There is no established best treatment for SIFs. Conservative treatment with bedrest and pain medication is common (3). However, patients cannot recover their mobility in the early stage, and risk of complications increases with long-term bedrest (4). Teriparatide (TPTD) (1-34 parathyroid hormone [PTH]), which has been prescribed to stimulate bone formation in cases of severe osteoporosis, may prevent these problems. Several studies have reported that TPTD enhanced bone healing or bone union after fracture or osteosynthesis surgery (5, 6); however, the effects of TPTD treatment of SIFs on pain, fracture healing, and mobility are still unclear. Therefore, the purpose of this study was to evaluate the clinical and radiological findings of SIFs treated with TPTD in 7 elderly women with osteoporosis.

Methods

Patients

Beginning in April 2012, 7 women with osteoporosis (mean age, 76 years [range, 66-83 years]) with SIFs were treated with TPTD at our institution, which is part of the Akita Bone and Osteoporosis Network (A-BONE). Written consent for inclusion in this study and its publication was obtained from all patients. This study was approved by the ethical committee of Akita University Graduate School of Medicine (No. 1509). Patients' clinical backgrounds, including comorbidities, treatment for osteoporosis, chief complaint at first visit, time to diagnosis, frequency of TPTD administration, combined therapy, and follow-up periods were recorded (Table 1).

TPTD treatment

Following the diagnosis of SIFs, subcutaneous injection of TPTD 20 μg daily (Forsteo®, Eli Lilly and Company, Indianapolis, IN, USA) or 56.5 μg weekly (Teribone ™, Asahi Kasei Pharma Corp. Tokyo, Japan), was used depending on patients’ choice and convenience. 6 patients (86%) received combined treatment (non-steroid anti-inflammatory drugs were used for 4 patients; activated vitamin D was prescribed for 2 patients; and vitamin K, elcatonin, or tocilizumab for rheumatoid arthritis was treated for 1 patient, respectively).

Evaluations

Patients’ mobility and visual analog scale (VAS) pain score
Teriparatide for sacral insufficiency fractures

Table 1 - Patient backgrounds.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Comorbidity</th>
<th>Treatment for osteoporosis before fracture</th>
<th>Chief complaint at first visit</th>
<th>Time to diagnosis (days)</th>
<th>Teriparatide dose frequency</th>
<th>Combined therapy</th>
<th>Follow-up periods (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>78</td>
<td>HT</td>
<td>None</td>
<td>Low back pain</td>
<td>23</td>
<td>Weekly</td>
<td>NSAIDs</td>
<td>24</td>
</tr>
<tr>
<td>Case 2</td>
<td>76</td>
<td>RA</td>
<td>Vit D, Vit K</td>
<td>Low back pain</td>
<td>11</td>
<td>Daily</td>
<td>Vit D, Vit K, NSAIDs</td>
<td>21</td>
</tr>
<tr>
<td>Case 3</td>
<td>83</td>
<td>HT</td>
<td>None</td>
<td>Buttock pain</td>
<td>30</td>
<td>Daily</td>
<td>Elcatonin</td>
<td>21</td>
</tr>
<tr>
<td>Case 4</td>
<td>78</td>
<td>DM</td>
<td>None</td>
<td>Low back pain</td>
<td>21</td>
<td>Daily</td>
<td>None</td>
<td>6</td>
</tr>
<tr>
<td>Case 5</td>
<td>78</td>
<td>MD</td>
<td>Ris, Vit D</td>
<td>Buttock pain</td>
<td>8</td>
<td>Daily</td>
<td>NSAIDs</td>
<td>16</td>
</tr>
<tr>
<td>Case 6</td>
<td>66</td>
<td>RA,DM,CRF</td>
<td>Vit D</td>
<td>Right hip pain</td>
<td>3</td>
<td>Weekly</td>
<td>Vit D, Bio (tocilizumab)</td>
<td>18</td>
</tr>
<tr>
<td>Case 7</td>
<td>76</td>
<td>HT</td>
<td>SERM, Vit D, Vit K</td>
<td>Left hip pain</td>
<td>20</td>
<td>Daily</td>
<td>NSAIDs</td>
<td>16</td>
</tr>
</tbody>
</table>

Mean ± SD 76.4 ± 5.2 16.5 ± 9.5 17.4 ± 5.8

Notes: Vit. D = Activated Vitamin D, Vit. K = Vitamin K, NSAIDs = Non-steroidal Anti-Inflammatory Drugs, Bio = Biologics, HT = Hypertension, RA = Rheumatoid Arthritis, DM = Diabetes Mellitus, MD = Muscle Dystrophy, CRF = Chronic Renal Failure, Ris = Risedronate, SERM = Selective Estrogen Receptor Modulator, SD = Standard Deviation

were evaluated at their first visit to our institution and after 1, 3, and 6 months of TPTD treatment. Computed tomography (CT) (Discovery CT750 HD; GE Healthcare, Wauwatosa, WI, USA) or bone scintigraphy (Symbia E Dual Head System, Siemens AG, Munich, Germany) was performed to evaluate the condition of the fracture site before TPTD treatment. At least 3 months after initiating TPTD treatment, CT was taken to check the status of fracture healing. Pre- and post-treatment bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry at the forearm (Osteometer, DTX-200, Toyo Medic, Tokyo, Japan) or lumbar spine (QDR-4500 Delphi Bone Densitometer; Hologic, Inc., Bedford, MA, USA). Levels of cross-linked N-telopeptide of type I collagen (NTX; mmolBCE/L) were measured in 4 patients and tartrate-resistant acid phosphatase-5b (TRACP-5b; μU/dL) was evaluated in 1 patient as a marker of bone resorption before and after treatment. Pre- and post-treatment serum concentrations of bone alkaline phosphatase (BAP; μU/L) or intact N-telopeptide of type I pro-collagen (P1NP; μg/L) were measured as markers of bone formation in all patients.

Statistical analyses
Results are shown as mean ± standard deviation (SD). Paired t-tests were used to compare pre- and post-treatment VAS, BMD, and bone-turnover markers. A probability of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Biosciences (SPBS), Version 9.54 (7).

Results
Mobility and VAS pain scores
Table 2 presents results of mobility evaluation at the first visit and after 3 and 6 months of TPTD treatment. Six of 7 patients had improvement in mobility and 1 showed no change from the initial level of mobility at 6 months’ treatment with TPTD. As shown in Table 2, VAS pain scores after 1, 3, and 6 months’ treatment with TPTD were all significantly lower than that of first visit (p < 0.0001 for all).

MRI, CT and bone scintigraphy
Magnetic resonance imaging (MRI) was performed in 4 patients. The fracture sites were seen as low-intensity changes on T1-weighted images and high-intensity changes on T2-weighted images (Table 3). CT revealed bilateral sacral wing fractures in 4 patients (Table 3 and Figure 1A) and right sacral wing fracture in 2 patients (Table 3 and Figure 1B). Only 1 patient showed no clear sacral fracture on CT. Bone scintigraphy was performed in 3 patients and revealed high uptake and H pattern at the sacrum (Figure 2). Based on these image findings, all patients were diagnosed with SIFs. CT revealed bony union of fractures in four patients between 6 and 12 months after initiating treatment with TPTD (Table 3 and Figure 1C). Sclerotic changes at the fracture sites of the other patients were seen from 3 to 12 months after beginning treatment with TPTD (Table 3 and Figure 1D).

BMD and bone-turnover markers
BMD was measured in 5 patients, at the forearm in 1 and at the lumbar spine in 4. Comparison of BMD pre- and post-treatment with TPTD is presented in Table 4. Bone-turnover markers were also measured in 5 patients (Table 5). Mean NTX value was higher after treatment with TPTD than before treatment, but it was not statistically significant. The bone-formation markers BAP and P1NP were evaluated in 6 patients and in 1 patient, respectively. By 6-12 months after TPTD treatment, mean BAP value had decreased, but not significant, in 4 patients.
**Discussion**

In the present case series, TPTD treatment significantly and rapidly decreased low back, buttock, and hip pain caused by SIFs after 1 month of treatment. Following the decrease in symptoms, patients’ mobility was also notably improved (e.g., from wheelchair or bedrest to walking with a cane) after 3 months’ treatment. CT revealed bony union at half of the fracture sites with 6 to 12 months of TPTD treatment and sclerotic changes in the remainder of fracture sites with 3 to 12 months of treatment.

Conservative treatment such as bedrest and pain medication has typically been used for SIFs (4, 8). However, because SIFs often occur in patients with severe osteoporosis, not only the pain, but also the osteoporosis, should be treated in these patients. Bisphosphonates are widely used for the treatment of osteoporosis but can have an inhibitory action on bone turnover, and bisphosphonate treatment immediately after fracture may delay healing by affecting normal bone metabolism and turnover at the fractures site (9). There is no report regarding the usefulness of bisphosphonates in healing SIFs. Several studies have reported surgical treatment such as sacroplasty or percutaneous screw fixation for SIFs (10, 11), but the optimal surgical techniques and long-term

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**Table 2 - Mobility and visual analog scale (VAS) score before and after treatment.**

<table>
<thead>
<tr>
<th>Teriparatide dose</th>
<th>Mobility</th>
<th>3 months</th>
<th>6 months</th>
<th>VAS score (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequency</td>
<td>First visit</td>
<td>1 month</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Case 1 Weekly</td>
<td>Wheel chair</td>
<td>Walk with cane</td>
<td>Walk</td>
<td>69</td>
</tr>
<tr>
<td>Case 2 Daily</td>
<td>Stretcher</td>
<td>Wheel chair</td>
<td>Wheel chair</td>
<td>90</td>
</tr>
<tr>
<td>Case 3 Daily</td>
<td>Wheel chair</td>
<td>Walk with cane</td>
<td>Walk</td>
<td>82</td>
</tr>
<tr>
<td>Case 4 Daily</td>
<td>Stretcher</td>
<td>Walk with cane</td>
<td>Walk</td>
<td>96</td>
</tr>
<tr>
<td>Case 5 Daily</td>
<td>Stretcher</td>
<td>Wheel chair</td>
<td>Walk with support</td>
<td>95</td>
</tr>
<tr>
<td>Case 6 Weekly</td>
<td>Wheel chair</td>
<td>Wheel chair</td>
<td>Walk chair</td>
<td>100</td>
</tr>
<tr>
<td>Case 7 Daily</td>
<td>Walk with cane</td>
<td>Walk with cane</td>
<td>Walk</td>
<td>80</td>
</tr>
</tbody>
</table>

Mean ± SD 87.4 ± 11.0 42.3 ± 18.1* 24.6 ± 15.6* 12.9 ± 14.9*

Notes: VAS = Visual Analog Scale, SD = Standard Deviation, *; p < 0.0001 vs VAS at first visit by paired t-test.

**Table 3 - MRI, CT, and bone scan before and after the treatment.**

<table>
<thead>
<tr>
<th>Teriparatide dose</th>
<th>MRI</th>
<th>Fracture locations on CT</th>
<th>Bone scintigram</th>
<th>Post-treatment fracture appearance on CT</th>
<th>Time to CT evaluation of union/sclerotic change (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequency</td>
<td>CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1 Weekly</td>
<td>NA</td>
<td>R, L sacral wings R pubis</td>
<td>NA</td>
<td>Union</td>
<td>10</td>
</tr>
<tr>
<td>Case 2 Daily</td>
<td>T1 low, T2 high</td>
<td>L pubis, T11, L1,2</td>
<td>H pattern</td>
<td>Sclerosis</td>
<td>12</td>
</tr>
<tr>
<td>Case 3 Daily</td>
<td>T1 low, T2 high</td>
<td>R, L sacral wings R transverse process of L5</td>
<td>H pattern</td>
<td>Union</td>
<td>9</td>
</tr>
<tr>
<td>Case 4 Daily</td>
<td>T1 low, T2 high</td>
<td>R, L sacral wings</td>
<td>NA</td>
<td>Sclerosis</td>
<td>3</td>
</tr>
<tr>
<td>Case 5 Daily</td>
<td>NA</td>
<td>R sacral wing R ischium</td>
<td>H pattern</td>
<td>Sclerosis</td>
<td>6</td>
</tr>
<tr>
<td>Case 6 Weekly</td>
<td>NA</td>
<td>R, L sacral wings R pubis and ischium</td>
<td>NA</td>
<td>Sclerosis and union</td>
<td>3 and 6</td>
</tr>
<tr>
<td>Case 7 Daily</td>
<td>T1 low, T2 high</td>
<td>R sacral wing L pubis</td>
<td>NA</td>
<td>Sclerosis and union</td>
<td>8 and 12</td>
</tr>
</tbody>
</table>

Notes: MRI = Magnetic Resonance Imaging, CT = Computed Tomography, R = Right, L = Left, NA = Not Applicable
Teriparatide for sacral insufficiency fractures

Figure 1 - Computed tomography images of fracture sites. (A) Pre-treatment bilateral sacral wing fractures (arrows). (B) Pre-treatment right sacral wing fracture (arrow). (C) Bone union of bilateral fractures after 6 months of TPTD treatment. (D) Right sacral wing fracture showing sclerotic change after 6 months of TPTD treatment.

Figure 2 - Posterior-anterior bone scintigraphy. Image reveals high uptake, with H shape at the sacral insufficiency fractures (black arrows). There was also high uptake at L1, T11, and right ribs, indicating osteoporotic fractures of the thoracolumbar lesion and ribs.
The outcomes of these procedures are still unclear (12, 13). In the present case series, the major symptoms of SIFs, which were low back or buttock pain, rapidly decreased after 1 month of treatment with TPTD. Several studies have demonstrated low back pain from vertebral fracture in patients with osteoporosis to be reduced with TPTD treatment (14-18). A meta-analysis showed that TPTD significantly reduced the risk of moderate or severe back pain compared to placebo, alendronate, or hormone replacement therapy in the patients with osteoporosis (15). There are no data suggesting an analgesic effect of TPTD, and whether it possesses a mechanism of pain relief in SIFs remains unclear. It has been reported that intermittent administration of PTH stimulates fracture healing in animal models (19, 20). TPTD treatment (20 μg daily) significantly reduced in time to cortical bone bridging of Colles' fractures in postmenopausal women aged 45-85 years (21). Peichi et al. reported that PTH 1-84 (100 μg daily) accelerated fracture healing of pelvic fractures, as evaluated by CT, and improved functional outcomes such as pain, evaluated using a VAS, and mobility, assessed with a timed up-and-go test, in 65 patients with osteoporosis (22). Recent systematic reviews have indicated that TPTD plays an important role in fracture healing and promotes fracture healing in patients with osteoporosis (23, 24). In the present case series, TPTD did not show significant effects on BMD and bone turnover markers evaluated with NTX and BAP. However, TPTD does stimulate bone formation, even in SIFs, and can thus lead to healing and stabilization of the fracture site and a consequent reduction in pain.

We identified only two case reports describing the treatment of sacral insufficiency fractures with TPTD (25, 26). Both demonstrated that TPTD was effective in callus formation as well as treatment of osteoporosis, and in the present case series, bony union or sclerotic changes were seen at the fracture sites after treatment with TPTD. These previous studies and the present case series suggest that TPTD can be useful in the treatment of SIFs in patients with severe osteoporosis.
Conclusions

In 7 elderly women with osteoporosis, daily or weekly TPTD treatment of SIFs beginning within 30 days of pain onset significantly improved low back, buttock, or hip pain at 1, 3, and 6 months. CT revealed bone union or sclerotic changes at the fracture site in all patients after 6 months of TPTD treatment.

Consent

Written informed consent was obtained from all patients for publication of this case report and any accompanying images.

Competing interests

The Authors declare that they have no competing interests.

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References