Effects of Weekly Teriparatide Administration for Vertebral Stability and Bony Union in Patients with Acute Osteoporotic Vertebral Fractures

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Study Design: An open-label, non-randomized prospective study.

Purpose: Teriparatide (TPTD) is known to be an antiosteoporotic agent that may accelerate the healing of fractures. This study was designed to investigate the effect of once-weekly TPTD administration on vertebral stability and bony union after acute osteoporotic vertebral fracture (OVF).

Overview of Literature: Once-weekly TPTD administration can lead to early vertebral stability and promote bony union of fractured vertebrae in patients with severe osteoporosis.

Methods: Forty-eight subjects with acute OVF were assigned to receive activated vitamin D3 and calcium supplementation or once-weekly subcutaneous injection of TPTD (56.5 µg) in combination with activated vitamin D3 and calcium supplementation for 12 weeks. Vertebral stability was assessed using lateral plain radiography. Vertebral height at the anterior location (VHa) and the difference in VHa {ΔVHa=VHa (supine position)–VHa (weight-bearing position)} were measured at baseline and 12 weeks after starting treatment. Bony union was defined as the absence of a vertebral cleft or abnormal motion (ΔVHa >2 mm).

Results: Although not significant, ΔVHa, indicating vertebral stability, tended to be lower in the TPTD group at 12 weeks (p=0.17). As for subjects with severe osteoporosis, ΔVHa at 12 weeks was significantly lower in the TPTD group than in the control group (mean ΔVHa: control group, 3.1 mm (n=15); TPTD group, 1.4 mm (n=16); p=0.02). The rate of bony union was significantly higher in the TPTD group than in the control group (control group, 40%; TPTD group, 81%; p=0.03).

Conclusions: Once-weekly TPTD administration may facilitate early bony union after acute OVF accompanied by severe osteoporosis.

Keywords: Vertebral fracture; Osteoporosis; Bony union; Teriparatide; Vertebral height

Introduction

Osteoporotic vertebral fracture (OVF) is the most fre- quent fragility fracture among patients with osteoporosis. OVF causes acute back pain, and secondary vertebral deformity after OVF results in chronic back pain. Poor

postural deformity, dysfunction in digestive organs, and pulmonary hypofunction caused by progressive vertebral kyphotic deformity result in decreased participation in the activities of daily living and reduced quality of life among elderly patients [1-3]. The majority of OVF cases are successfully treated with a conservative regimen of bed rest and spinal orthosis. However, delayed vertebral union or nonunion may occur. Delayed union or nonunion leads to long-term physical deterioration [4,5]. The most extreme cases may result in osteoporotic vertebral collapse with neurological deficit [6].

Teriparatide (TPTD), which became available for use in Japan in 2010, promotes cortical and cancellous bone formation and has been widely used for the treatment of severe osteoporosis with high risk of fracture. This agent also garnered a great deal of attention in the field of fracture treatment [7,8]. The administration of TPTD to patients with acute OVF may prevent subsequent osteoporotic fractures and promote the healing of fractures. However, few reports have investigated the effects of TPTD for fracture repair in humans [9-11]. No previous report has investigated the effects of TPTD on the healing of fractures after acute OVF because no clear criteria or definitions have been established for bony union after acute OVF using plain radiographs [7,8].

The purpose of the present study was to investigate the effect of once-weekly TPTD administration on vertebral stability and bony union after acute OVF using quantitative criteria.

Materials and Methods

1. Study design and subjects

This was an open-label, non-randomized prospective study. With our protocol, subjects with acute OVF were assigned to the control group and received activated vitamin D3 and calcium supplementation. Control subjects did not receive any antiosteoporotic drugs during the investigation period. Therefore, considering ethical aspects, we recommended once-weekly TPTD administration to all subjects at the time of their initial examination and assigned those who refused TPTD administration to the control group.

We enrolled subjects with acute OVF registered between January 1, 2014 and December 31, 2016 at two facilities associated with the Department of Orthopedics at Osaka University Graduate School of Medicine. OVF was diagnosed in cases with no history of trauma or a result of low-energy trauma such as a fall on the ground. Acute OVF was defined as occurring within 1 week after injury or the onset of symptoms. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethics review boards of all participating facilities (approval no., 12410-2; Osaka University Graduate School of Medicine). All subjects in the study provided written informed consent.

During the investigation period, subjects in the control group received daily oral alfacalcidol 0.5 μg and oral calcium lactate 2 g (or oral calcium aspartate 600 mg). Those in the TPTD group also received once-weekly TPTD acetate (Teribone; Asahi Kasei Pharma Co. Ltd., Tokyo, Japan) 56.5 μg, which was administered subcutaneously. All subjects were hospitalized and instructed to remain at rest in a lateral decubitus position, rather than a supine position. After their pain was alleviated and they were able to move in bed, they were fitted for a spinal brace and forced to continuously wear a spinal brace for approximately 3 months during the study period.

2. Inclusion and exclusion criteria

Subjects with acute OVF were eligible for the study, regardless of having undergone prior treatment for osteoporosis. All subjects who were hospitalized with acute back pain underwent whole-spine magnetic resonance imaging (MRI). The presence of low T1 signal intensities on T1-weighted images and high signal intensities on short-tau inversion recovery sequences were diagnosed as acute OVF. To ensure that all subjects exclusively had primary osteoporosis, subjects with secondary osteoporosis, including rheumatoid arthritis or glucocorticoid-induced osteoporosis, were excluded from the study. No subjects enrolled in this study had pathological fractures with primary spinal tumors, metastatic spinal tumors, myeloma, spinal infections, or metabolic bone diseases such as osteomalacia and hyperparathyroidism. Subjects with acute burst fracture with injury to the posterior wall were also excluded.

3. Clinical assessment

Within 3 days of admission to the hospital, all subjects underwent bone mineral density (BMD) measurements,

whole-spine MRI, and biochemical examination of blood and bone turnover markers. BMD measurements were performed using dual-energy X-ray absorptiometry (GE Lunar Prodigy, Bedford, MA, USA) on lumbar spine (L2–4) and femoral neck. A BMD T-score was calculated for all measured sites. Blood samples were collected, and routine serum chemistry determinations were performed with standard automated techniques. We measured levels of serum calcium, alkaline phosphatase, creatinine, estimated glomerular filtration rate, and intact parathyroid hormone. Serum intact N-terminal propeptide of type I procollagen and tartrate-resistant acid phosphatase 5b were also assessed, as markers of bone turnover.

4. Assessment of vertebral stability and bony union

Previous studies comparing plain radiographs of subjects with acute OVF in weight-bearing (standing or seating) and non-weight-bearing positions (lateral decubitus or supine position) have reported that a comparison of ver-

tebral morphology and vertebral height at the anterior location (VHa) in each position is effective in diagnosing acute OVF [12-15] and assessing bony union [16].

Lateral plane radiographs were taken, with a focus on the fractured vertebral body in weight-bearing (standing or seating if subjects were unable to stand) and non-weight-bearing (supine) positions. On the lateral radiograph, two points were hand selected and marked on each vertebra. These two points were placed at the most anterior-superior and anterior-inferior endplate margins, respectively. VHa was set as the distance in millimeters between identical points on the superior and inferior endplates at the anterior location (Fig. 1). VHa in both positions was measured at baseline and 12 weeks after starting the treatment. The difference in VHa {ΔVHa=VHa (supine position)–VHa (weight-bearing position)} was calculated. The difference in VHa was taken as a measure of vertebral stability and compared between groups. The rate of vertebral collapse {VHa (weight-bearing position, baseline)–VHa (weight-bearing position, 12 weeks after
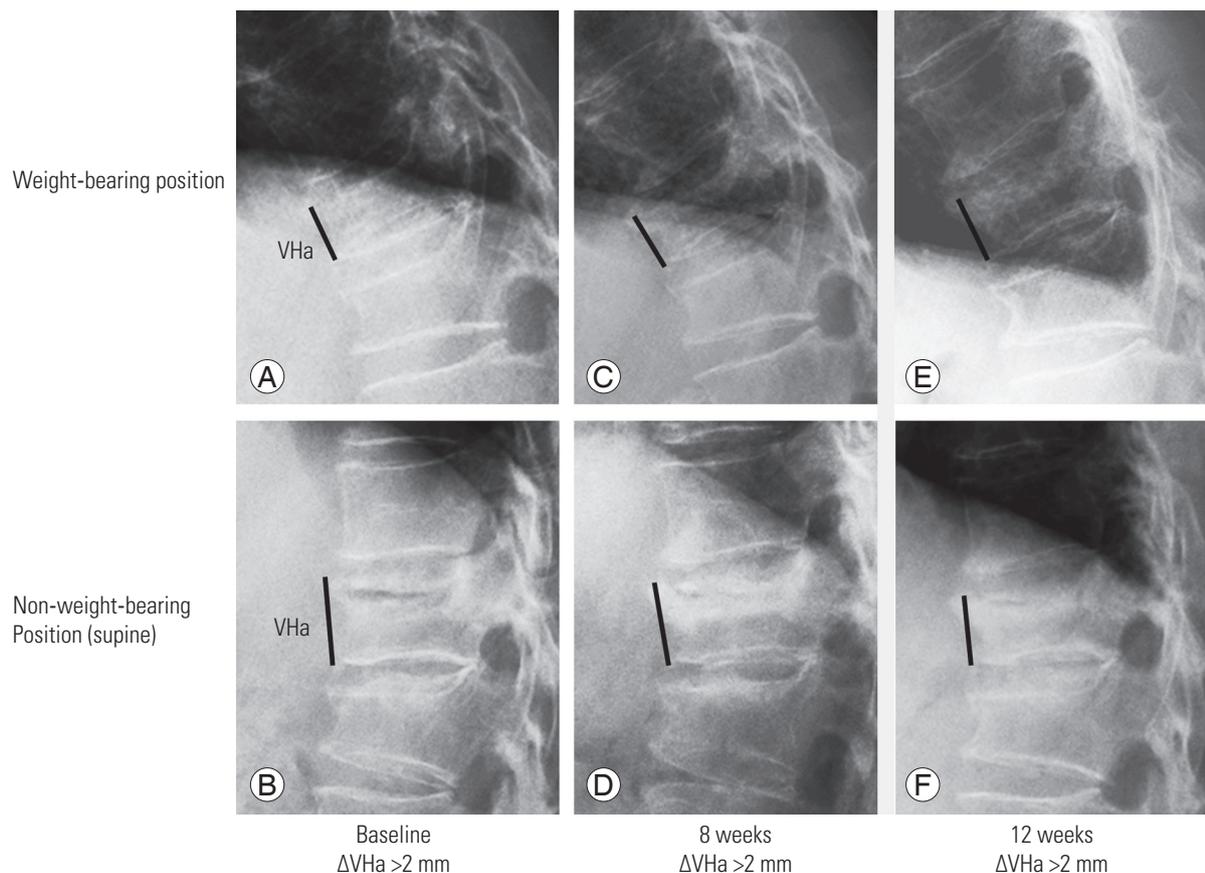

Fig. 1. Chronological assessment of vertebral stability and bony union after acute osteoporotic vertebral fracture. VHa was measured in both weight-bearing and non-weight-bearing positions at baseline **(A, B)** as well as after 8 **(C, D)** and 12 weeks **(E, F)**. The difference in VHa was calculated. VHa, vertebral height at the anterior location.

starting treatment) divided by VHa (weight-bearing position, baseline)} was also calculated.

Based on the results of previous studies, bony union was defined as the absence of a vertebral cleft or abnormal motion (ΔVHa >2 mm) [12,13,16]. Rates of bony union were compared between groups at 12 weeks. X-ray measurements and grading via the semi-quantitative (SQ) method were performed by a single spine surgeon [17], who was blinded to each subject's group. The number of prevalent OVFs from T4 to L4 was investigated with the use of spinal MRI images. Acute burst fracture with a protruding bony fragment was excluded.

5. Reproducibility of the vertebral height at the anterior location

To assess the reproducibility of measurements of VHa and ΔVHa, intraobserver and interobserver intraclass correlation coefficients (ICC) were calculated. For analysis of intraobserver reliability, a spinal surgeon measured both VHa and ΔVHa in 15 patients with vertebral fractures (30 fractured vertebral bodies), in the supine position and the weight-bearing position. Measurements were obtained twice, with a 2-week interval. For the analysis of interobserver reliability, two spinal surgeons and a general orthopedic surgeon measured these vertebral fractures

once in the same way. Intraobserver and interobserver ICC for VHa were 0.988 (95% confidence interval [CI], 0.976–0.994) and 0.983 (95% CI, 0.96–0.992), respectively. Intraobserver and interobserver ICC for ΔVHa were 0.925 (95% CI, 0.798–0.925) and 0.903 (95% CI, 0.788–0.963), respectively. The standard error for VHa and ΔVHa (intraobserver) was 0.48 mm and 0.66 mm, respectively.

6. Statistical analysis

Statistical analysis was performed using IBM SPSS software ver. 22.0 (IBM Corp., Armonk, NY, USA). All data reported here are expressed as means and standard error (SE). Statistical analysis of comparisons between groups was performed using Mann–Whitney's U-test, chi-square test, and Fisher's exact test. Changes from baseline were statistically analyzed using Wilcoxon's signed-rank test. Probability values lower than 0.05 were considered significant.

Results

We obtained consent from 71 subjects with acute OVF (36 and 35 in the control and TPTD groups, respectively). Subjects who transferred to a different hospital during the study period and those who discontinued treatment with once-weekly TPTD due to adverse effects were excluded
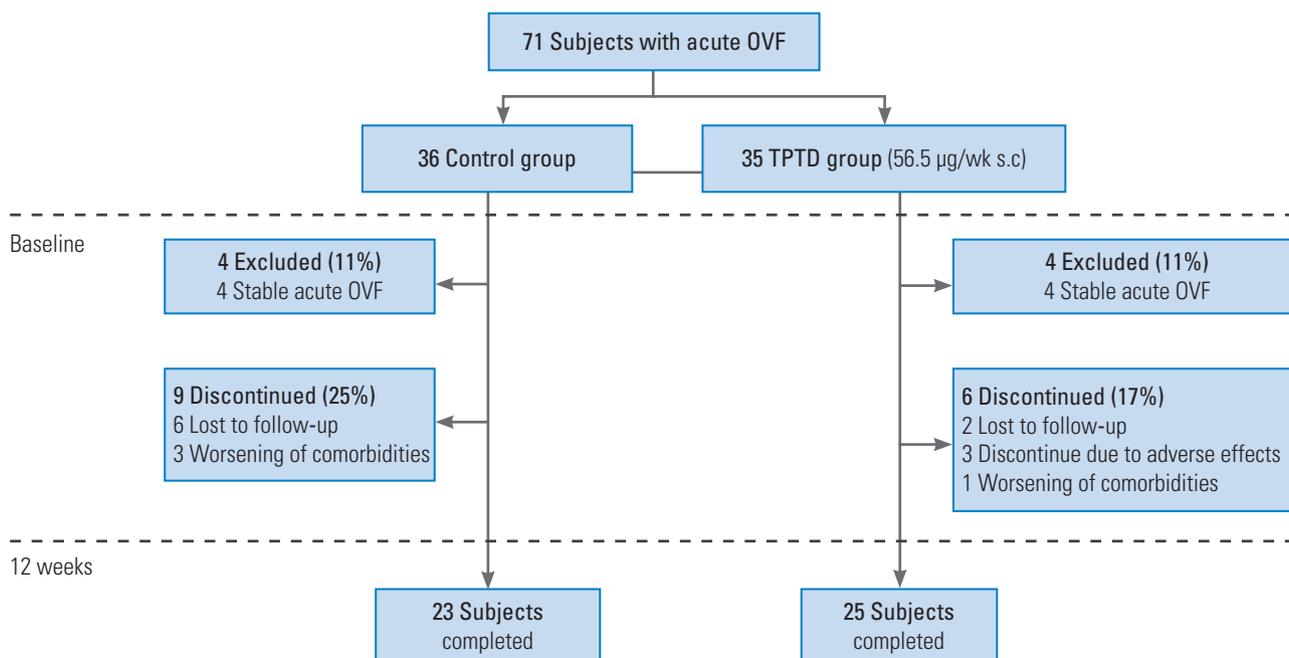

Fig. 2. Study flow-chart and disposition of subjects in the control group and the weekly TPTD use group. OVF, osteoporotic vertebral fracture; TPTD teriparatide.

from the study. We also excluded eight subjects with stable OVF with a ΔVHa of 2 mm or less at baseline (four subjects in each group). The remaining cohort comprised 23 subjects in the control group and 25 in the TPTD group (Fig. 2). The baseline characteristics in both groups are shown in Table 1. Although the trend was not significant, the TPTD group tended to have a higher rate of prevalent OVFs with severe vertebral deformity and a higher percentage of women. Rates of osteoporosis treatment at baseline tended to be higher in the TPTD group (control, 17%; TPTD, 40%; $p=0.09$), and oral bisphosphonate were administrated in many subjects.

Vertebral morphology after fracture was assessed. The results showed that non-weight-bearing VHa in both groups had significantly decreased at 12 weeks compared with baseline, and VHa at 12 weeks had decreased to nearly the weight-bearing VHa observed at baseline (Table 2). At 12 weeks, weight-bearing VHa in both groups had also significantly decreased, compared with baseline. ΔVHa, indicating vertebral stability, tended to be lower in the TPTD group at 12 weeks ($p=0.17$), but there were no significant difference between groups. Although not significant, the rate of bony union tended to be higher in the TPTD group (control, 48%; TPTD, 68%; $p=0.16$).

In accordance with the diagnostic criteria for primary osteoporosis [18], subjects with severe osteoporosis were categorized as having a 'lumbar spine BMD T-score below −3.0,' 'at least two prevalent OVFs,' or 'a prevalent OVF with SQ grade 3 vertebral deformity.' Further analysis was performed on subjects with severe osteoporosis as described above. Fifteen subjects in the control group and 16 subjects in the TPTD group were found to have severe osteoporosis (Table 3). Baseline characteristics in both groups with severe osteoporosis indicated that the TPTD group had significantly lower lumbar spine BMD T-scores, despite significantly lower mean age (Table 3). At baseline, there were no significant differences in the rates of osteoporosis treatment between groups.

VHa (weight-bearing position) for subjects with severe osteoporosis in both groups had significantly decreased at 12 weeks, compared with baseline (Table 4). Progressive vertebral collapse was significantly more common in the control group, compared with the TPTD group (control, 26%; TPTD, 12%; $p=0.03$). Moreover, despite no significant differences in ΔVHa between groups at baseline, ΔVHa was significantly smaller in the TPTD group than in the control group at 12 weeks (control: mean±SE, 3.1±0.6 mm; TPTD: mean±SE, 1.4±0.5 mm;

Table 1. Characteristics of study subjects

Characteristic	Control group (n=23)	TPTD group (n=25)	p-value
Age (yr)	79.5±1.6	77.8±1.1	0.23
Body mass index (kg/m^2)	21.5±0.8	21.2±0.7	0.85
Gender (male:female)	6:17	2:23	0.09
Rates of osteoporosis treatment at baseline (%)	17	40	0.09
Presence of prevalent OVF (%)	48	56	0.57
Level of the injured vertebra (T10–L2, %)	83	80	1.00
No. of prevalent OVF confirmed by magnetic resonance imaging images (T4–L4)	0.9±0.3	1.1±0.3	0.65
No. of prevalent OVFs with severe vertebral deformity (semi-quantitative method grade 3)	0.2±0.1	0.6±0.2	0.11
Lumbar spine BMD T-score	-2.6±0.3	-3.1±0.3	0.22
Femoral neck BMD T-score	-2.3±0.2	-2.4±0.2	0.67
Estimated glomerular filtration rate (mL/min/1.73 m^2)	61.0±3.6	62.5±3.0	0.42
Intact N-terminal propeptide of type I procollagen (µg/L)	54.3±7.8	46.4±4.0	0.35
Tartrate-resistant acid phosphatase 5b (mU/dL)	455±37	389±34	0.18
Parathyroid hormone (pg/mL)	46.5±4.7	35.1±3.7	0.16

Values are presented as mean±standard error or number. Statistical analysis was conducted using Mann-Whitney U-test or chi-square test or Fisher's exact test: $p<0.05$ was considered a statistically significant difference.
TPTD, teriparatide; OVF, osteoporotic vertebral fracture; BMD, bone mineral density.

Table 2. Changes of VHa and collapse rate in subjects with acute osteoporotic vertebral fracture

Variable	Control group (n=23)	TPTD group (n=25)	*p*-value
Baseline			
Non-weight-bearing VHa (mm)	24.5±2.0	24.3±0.9	0.90
Weight-bearing VHa (mm)	17.7±1.4	18.3±1.0	0.76
ΔVHa (mm)	6.8±0.6	5.8±0.6	0.33
12 wk			
Non-weight-bearing VHa (mm)	17.4±1.5[a]	18.0±1.0[a]	0.85
Weight-bearing VHa (mm)	15.4±1.6[b]	16.0±1.1[b]	0.81
ΔVHa (mm)	2.7±0.5	2.2±0.5	0.17
Vertebral collapse rate (%)	19.9±4.4	14.5±4.0	0.38
Bony union rate (ΔVHa <2 mm)	47.8	68.0	0.16

Values are presented as mean±standard error or %. ΔVHa=VHa (supine position)–VHa (weight-bearing position); vertebral collapse rate=VHa (weight-bearing position, baseline)–VHa (weight-bearing position, 12 weeks after starting treatment)/VHa (weight-bearing position, baseline). Statistical analysis between the control group and the TPTD group was conducted using Mann-Whitney *U*-test or chi-square test: *p*<0.05 was considered a statistically significant difference.
VHa, vertebral height at the anterior location; TPTD, teriparatide.
[a]Significant difference of VHa in non-weight-bearing position (baseline vs. 12 weeks). [b]Significant difference of VHa in weight-bearing position (baseline vs. 12 weeks).

Table 3. Characteristics of study subjects with severe osteoporosis

Characteristic	Control group (n=15)	TPTD group (n=16)	*p*-value
Age (yr)	81.6±1.5	76.8±1.4	0.03*
Body mass index (kg/m^2)	20.6±1.0	20.9±0.8	0.58
Gender (male:female)	2:13	1:15	0.60
Rates of osteoporosis treatment at baseline (%)	20.0	31.3	0.69
Presence of prevalent OVF (%)	66.7	68.8	1.00
Level of the injured vertebra (T10–L2, %)	93	88	0.71
No. of prevalent OVF confirmed by magnetic resonance imaging images (T4–L4)	1.2±0.4	1.2±0.3	0.92
Lumbar spine bone mineral density T-score	-3.3±0.3	-4.0±0.3	0.04*
Estimated glomerular filtration rate (mL/min/1.73 m^2)	58.9±3.0	63.2±4.4	0.32
Intact N-terminal propeptide of type I procollagen (μg/L)	52.2±9.0	53.9±5.3	0.34
Tartrate-resistant acid phosphatase 5b (mU/dL)	486±47	432±46	0.33
Parathyroid hormone (pg/mL)	44.8±5.6	32.4±2.1	0.07

Values are presented as mean±standard error or %. Statistical analysis was conducted using Mann-Whitney *U*-test, chi-square test, or Fisher's exact test: *p*<0.05 was considered a statistically significant difference.
TPTD, teriparatide; OVF, osteoporotic vertebral fracture.
*p<0.05 (significant difference between control and TPTD group).

p=0.02) (Table 4). The rate of bony union was significantly higher in the TPTD group (control, 40%; TPTD, 81%; *p*=0.03).

Discussion

We investigated the effects of once-weekly TPTD administration on vertebral stability and bony union after acute OVF. Previous studies of bony union after acute OVF had the following issues: (1) methods to assess bony union were often qualitative, and definitions of bony union differed from study to study; (2) previous studies failed to exclude cases of stable OVF, in which bony union is relatively common, regardless of the therapy used. To the best

Table 4. Changes of VHa and collapse rate in subjects with acute osteoporotic vertebral fracture accompanying with severe osteoporosis

Variable	Control group (n=15)	TPTD group (n=16)	p-value
Baseline			
Non-weight-bearing VHa (mm)	24.4±1.4	24.4±1.2	0.74
Weight-bearing VHa (mm)	18.0±1.6	18.7±1.2	0.43
ΔVHa (mm)	6.7±0.7	5.6±0.6	0.24
12 wk			
Non-weight-bearing VHa (mm)	18.0±1.7[a]	18.2±1.4[a]	0.85
Weight-bearing VHa (mm)	15.0±1.6[b]	16.7±1.5[b]	0.81
ΔVHa (mm)	3.1±0.6	1.4±0.5	0.02*
Vertebral collapse rate (%)	25.8±4.3	12.0±4.1	0.03*
Bony union rate (ΔVHa <2 mm)	40.0	81.3	0.03*

Values are presented as mean±standard error or %. ΔVHa=VHa (supine position)–VHa (weight-bearing position); vertebral collapse rate=VHa (weight-bearing position, baseline)–VHa (weight-bearing position, 12 weeks after starting treatment)/VHa (weight-bearing position, baseline). Statistical analysis between the control group and the TPTD group was conducted using Mann-Whitney U-test or chi-square test: p<0.05 was considered a statistically significant difference.

VHa, vertebral height at the anterior location; TPTD teriparatide.

*p<0.05 (significant difference between control and TPTD group). [a]Significant difference of VHa in non-weight-bearing position (baseline vs. 12 weeks). [b]Significant difference of VHa in weight-bearing position (baseline vs. 12 weeks).

of our knowledge, this is the first study to investigate the effect of TPTD on acute OVF using quantitative criteria for the evaluation of bony union after the exclusion of subjects with stable acute OVF. The results of the present study indicated that the effects of once-weekly TPTD administration promoted bony union in fractured vertebrae in patients with severe osteoporosis. This agent therefore appears to prevent further vertebral collapse and contributes to early vertebral stability.

Previous studies regarding bony union after acute OVF had a serious issue: methods used to assess bony union were often qualitative and definitions of bony union differed from study to study. Several authors reported that ΔVHa of 2 mm is the most reasonable cutoff value for diagnosis of acute OVF using lateral radiographs obtained in weight- and non-weight-bearing positions [12,13]. Sato et al. [16] defined union as the absence of abnormal motion (ΔVHa >1 mm) and reported that the rate of bony union 3 months after conservative therapy for acute OVF was 42% (in the case of ΔVHa >2 mm, the rate of bony union was 80%). Niimi et al. [13] showed that precision errors associated with measurements of VHa corresponded to standard deviation of 1.2 mm, and SE VHa and ΔVHa (intraobserver) were 0.48 mm and 0.66 mm, respectively. In order to ensure the accuracy of measurements obtained with plain radiography, we defined bony union as the absence of a vertebral cleft or abnormal mo-

tion (ΔVHa >2 mm) 3 months after starting treatment.

Few previous reports have investigated the effects of TPTD for fracture repair in humans [9-11], and the effects of TPTD for fracture repair remain controversial [7,8]. To the best of our knowledge, no previous study published in English has investigated the effect of once-weekly TPTD administration on bony union after acute OVF. One such study has been published in the Japanese language [19]. The study reported that, 12 weeks after treatment with anti-osteoporosis drugs, bony union was significantly higher in the once-weekly TPTD group than in the bisphosphonate group (at 73% versus 45%) [19]. Our study results in subjects with severe osteoporosis (control, 40%; TPTD, 81%) are compatible with the rate of bony union reported in their study.

When we restricted our investigation to subjects with severe osteoporosis, the ΔVHa was significantly smaller in the TPTD group than in the control group at 12 weeks (control: mean±SE, 3.1±0.6 mm; TPTD: mean±SE, 1.4±0.5 mm; p=0.02). In addition, progressive vertebral collapse was significantly less frequent in the TPTD group, compared with the control group (control, 26%; TPTD, 12%; p=0.03). In control subjects with severe osteoporosis, we observed a vicious cycle of further deformity of injured vertebrae during the post-fracture course. This cycle resulted in increased ΔVHa, persistent instability, and delayed union. However, when compared with the control

group, the TPTD group showed greater suppression in progressive vertebral deformity during the post-fracture course, leading to more rapid achievement of vertebral stability (smaller ΔVHa) and a higher rate of bony union. This result is impressive, given the fact that the TPTD group had significantly lower lumbar-spine BMD, conditions which increase the likelihood of progressive vertebral deformity of the fractured vertebra. Taken together, these results indicate that TPTD increases the rate of vertebral bony union by suppressing vertebral collapse and promoting vertebral stability. Previous studies have reported that TPTD prevents the collapse of fractured vertebral bodies after acute OVF [20-22]. Tsuchie et al. [20] conducted a study similar to ours, in which TPTD was administered to subjects with acute OVF for 12 weeks. Tsuchie et al. [20] reported that, at 4 weeks after TPTD administration, TPTD was effective in preventing collapse of the injured vertebra. The authors suggested the possibility that TPTD administration promoted cartilage formation through endochondral ossification, which prevented early vertebral collapse [22].

The present study has several limitations. As the first limitation, this study was not a double-blind, randomized prospective study. To investigate the issues more precisely, a double-blind, randomized prospective study should be performed. However, in the design of such a study, the control group would be required to interrupt antiosteoporotic drugs for a fixed period of time. Termination of antiosteoporotic drugs could cause additional vertebral fractures and would therefore be ethically unacceptable. The second limitation was the fact that the number of subjects in both groups was relatively small. Unlike previous studies, we excluded cases of stable acute OVF that showed no or little change in ΔVHa, thereby limiting the patient population to those with vertebral instability and decreasing the number of subjects included in the study. The third limitation was the fact that a study period of 3 months is relatively brief. However, pain and other symptoms caused by acute OVF normally resolve within 3 months. Vertebral collapse is most common within 3 months of injury [23]; it is therefore reasonable to investigate the effects of TPTD on vertebral fractures within a 3-month period.

Conclusions

The results of the present study indicate that once-weekly administration of TPTD promotes bony union of fractured vertebra in patients with severe osteoporosis. This approach to treatment appears to promote the stability of fractured vertebrae by preventing further vertebral collapse during the immediate post-injury period.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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