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ORIGINAL ARTICLE

The effect of teriparatide to alleviate pain and to prevent vertebral collapse after fresh osteoporotic vertebral fracture

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Abstract Vertebral fracture is often seen in osteoporotic patients. Teriparatide is expected to promote bone union. Therefore, we evaluated the action of vertebral collapse prevention by administering teriparatide to vertebral fracture patients. Thirty-four patients with fresh vertebral fracture (48 vertebrae) participated in this study. They were administered either teriparatide (daily 20 μg/day or weekly 56.5 μg/week) or risedronate (17.5 mg/week): ten patients (20 vertebrae) received teriparatide daily (Daily group), 11 patients (15 vertebrae) received teriparatide weekly (Weekly group), and 13 patients (14 vertebrae) received risedronate (RIS group). We compared some laboratory examination items, visual analogue scale (VAS) of low back pain, vertebral collapse rate and local kyphotic angle, and the cleft frequency. In addition, we evaluated 22 vertebral fracture patients (24 vertebrae) who did not take any osteoporotic medicines (Control group). There was no significant difference in any of the scores at the start of treatment. At 8 and 12 weeks after the initial visit, VAS scores in the Daily and Weekly groups were significantly lower than in the RIS group ($p < 0.05$). At 8 and 12 weeks, the vertebral collapse rate and local kyphotic angle in the Daily group were significantly lower than in the RIS and Control groups ($p < 0.01$ and $p < 0.05$, respectively), and those in the Weekly group were significantly lower than in the Control group ($p < 0.05$). The cleft frequency in the Daily group was significantly lower than in the RIS group ($p < 0.05$). Teriparatide is promising for the prevention of vertebral collapse progression after vertebral fracture.

Keywords Teriparatide · Risedronate · Vertebral fracture · Vertebral collapse · Osteoporosis

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Introduction

Osteoporosis is characterized by a low bone mass and microarchitectual deterioration of the bone structure, resulting in bone fragility. Osteoporotic fractures often occur in cancellous bones, such as the femoral neck, distal radius, and vertebrae [1]. Vertebral fracture is often seen in aged osteoporotic patients. If an elderly person develops an osteoporotic vertebral fracture, they will show body movement difficulty due to pain and be forced to rest in bed. This leads to lower-limb muscle weakness and dementia, and causes a decline in activities of daily living. Although low back pain decreases over time in many patients with vertebral fracture, severe kyphotic deformities caused by vertebral collapse progression and pseudoarthrosis in the fractured vertebrae occur in some patients, and marked low back pain may persist in these cases [2, 3]. Therefore, it is difficult to improve the symptoms with conservative treatment, and surgical intervention is necessary.

Teriparatide (human parathyroid hormone (1–34)) has been shown to exhibit a potent anabolic effect on bone in various animal models and humans. It can increase the bone mass in osteoporotic humans and rats with osteopenia with various causes [4–6]. Several studies have reported that teriparatide also enhances fracture healing of cortical

Table 1 Characteristics of vertebral fracture patients at the time of injury in the Daily, Weekly, RIS, and Control groups

	Daily	Weekly	RIS	Control
Number/vertebrae	10/20	11/15	13/14	22/24
Age (years)	81.9 ± 6.7	83.0 ± 6.4	80.3 ± 6.7	81.7 ± 4.5
Male/female	1/9	1/10	2/11	4/18
Laboratory examinations				
BAP (U/L)	18.5 ± 6.9	17.3 ± 11.5	16.4 ± 8.6	–
Serum NTX (nmol BCE/L)	22.6 ± 8.9	22.0 ± 6.5	19.8 ± 5.6	–
Ca (mg/dL)	9.3 ± 0.6	9.0 ± 0.5	9.2 ± 0.5	–
IP (mg/dL)	3.2 ± 0.8	3.0 ± 0.6	3.3 ± 0.6	–
BMD (g/cm^2)				
Lumbar spine	0.69 ± 0.09	0.71 ± 0.11	0.68 ± 0.12	–
Proximal femur	0.46 ± 0.08	0.50 ± 0.06	0.56 ± 0.12	–
VAS (0–100 mm)	79.3 ± 17.0	86.0 ± 11.3	74.5 ± 19.1	–
Vertebral collapse rate (%)	71.1 ± 14.1	69.3 ± 11.2	68.1 ± 11.2	75.0 ± 8.9
Local kyphotic angle (degrees)	9.4 ± 6.5	10.2 ± 4.8	11.8 ± 5.2	9.7 ± 5.9

All values are mean ± standard deviation

Daily daily administration of teriparatide, *Weekly* weekly administration of teriparatide

BAP bone-specific alkaline phosphatase, *BMD* bone mineral density, *IP* inorganic phosphorus, *NTX* cross-linked N-telopeptide of type I collagen, *RIS* risedronate, *VAS* visual analogue scale

and cancellous bones in animals [7, 8]. Furthermore, it has been reported to promote bone union in fracture treatment for humans [9], and it is expected to promote bone union after fracture.

Several studies have also reported that teriparatide can reduce low back pain and prevent the progression of vertebral body collapse [10–13]. These studies have suggested some mechanisms of pain relief, such as resolving bone micro-damage and acting on the central nervous system. Although we can use two types of teriparatide preparations in Japan, i.e., daily or weekly injection, no study has compared them.

The aim of this study was to examine analgesic action and vertebral collapse prevention by administering teriparatide to fresh vertebral fracture patients. In addition, we examined the difference in the effect of these two types of teriparatide.

Materials and methods

Subjects (Table 1)

A total of 34 consecutive patients with fresh osteoporotic vertebral fracture (48 vertebrae) hospitalized for treatment in our hospital between April 2012 and March 2014 were included in this study. They were all primary osteoporosis patients. There were four males and 30 females, with a mean age of 82 years (range 68–94). We explained to the patients that the treatment of osteoporosis was required, and they were administered any one of the following: daily 20-μg teriparatide injection (Forteo®, Eli Lilly Japan Co., Ltd., Kobe, Japan), once per week 56.5-μg teriparatide injection (Teribone®, Asahi Kasei Pharma Co., Ltd., Tokyo, Japan), or once per week 17.5 mg risedronate for internal use (Actonel®, Eisai Co., Ltd., Tokyo, Japan) for osteoporosis treatment (the dose of risedronate is for Japanese, being half of the standard international dose), based on their choice. The daily teriparatide group (Daily group) included ten patients (20 vertebrae), consisting of one male and nine females with a mean age of 82 years (range 71–91); the weekly teriparatide group (Weekly group) included 11 patients (15 vertebrae), consisting of one male and ten females with a mean age of 83 years (range 68–91); and the risedronate group (RIS group) included 13 patients (14 vertebrae), consisting of two males and 11 females with a mean age of 80 years (range 68–94). Regarding taking osteoporotic medicines before vertebral fracture, three Daily group patients, three Weekly group patients, and four RIS group patients took bisphosphonate orally, and one Weekly group patient took selective estrogen receptor modulator (SERM) orally. In addition, we retrospectively enrolled some fresh osteoporotic vertebral fracture patients who did not take any osteoporotic medicines before or after hospitalization and who were hospitalized for treatment in our hospital between April 2009 and March 2012, and we set them as a Control group. Twenty-two fresh osteoporotic vertebral fracture patients (24 vertebrae) were included in this Control group. There were four males and 18 females, with a mean age of 82 years (range 73–90). We excluded patients who had been unable to walk by themselves before the vertebral fracture.

We performed bone mineral density (BMD) measurement and laboratory examinations of bone metabolic markers within 3 days after hospitalization in all patients. We measured anteroposterior (AP) views of the lumbar spine from L2 to L4 and the femoral neck. They were diagnosed with vertebral fracture by magnetic resonance imaging (MRI), and prescribed a spinal brace. After wearing the brace, standing and gait training were begun in

rehabilitation, depending on the level of pain. Patients wore the spinal brace for up to 3 months after injury.

Assessment of pain and vertebral collapse change

We asked patients to use the visual analogue scale (VAS) to evaluate their pain at the time of injury, and 2, 4, 8, and 12 weeks after injury, and we compared VAS scores between Daily, Weekly, and RIS groups. We evaluated the vertebral collapse rate, dividing the height of the most collapsed vertebral region by the height of the vertebral posterior height, and local kyphotic angle set by the vertebral body endplates of the fractured vertebrae to assess the fractured vertebral compression change (Fig. 1) [14]. We compared the vertebral collapse change and local kyphotic angle change to deduce parameters at the time of injury among Daily, Weekly, RIS, and Control groups at 4, 8, and 12 weeks. We also compared the frequency of cleft formation in the fractured vertebrae at 12 weeks after injury among the four groups. These parameters were measured by one medical doctor who was blinded to each patient's prescription, in order to minimize the error. In addition, we compared their hospitalization periods.

Statistical analysis

All values are expressed as the mean ± standard deviation (SD). A one-factor analysis of variance (ANOVA) was used to test for significance. Significant differences in VAS, the vertebral collapse change, local kyphotic angle change, hospitalization period, age, laboratory data, and BMD among the four groups were compared using Scheffe's method for multiple comparisons. The χ^2 test was used to compare the frequency of cleft formation among the four groups. Probability (p) values less than 0.05 were considered significant.

Results (Tables 1, 2, and 3)

At the start of treatment, there was no significant difference in the age, laboratory examination items (bone-specific alkaline phosphatase, serum cross-linked N-telopeptide of type I collagen, calcium, and inorganic phosphorus), BMD (the lumbar spine and proximal femur), VAS, vertebral collapse change, local kyphotic angle change, frequency of cleft formation, or hospitalization period among the four groups (Table 1). Most of the fractured vertebrae in the four groups were in the thoracolumbar region (Table 2). At 8 and 12 weeks after the initial visit, the VAS score in the Daily group was significantly lower than in the RIS group ($p < 0.05$), and that in the Weekly group was significantly lower than in the RIS group at 12 weeks (Table 3). At 8 and 12 weeks after the initial visit, the difference in the vertebral collapse change in the Daily group was significantly lower than in the RIS and Control groups ($p < 0.05$ and $p < 0.01$, respectively), and that in the Weekly group was significantly lower than in the Control group ($p < 0.01$ and $p < 0.05$, respectively). At 8 and 12 weeks after the initial visit, the difference in the local kyphotic angle change in the Daily group was significantly lower than in the RIS and Control groups ($p < 0.05$ and $p < 0.01$, respectively),

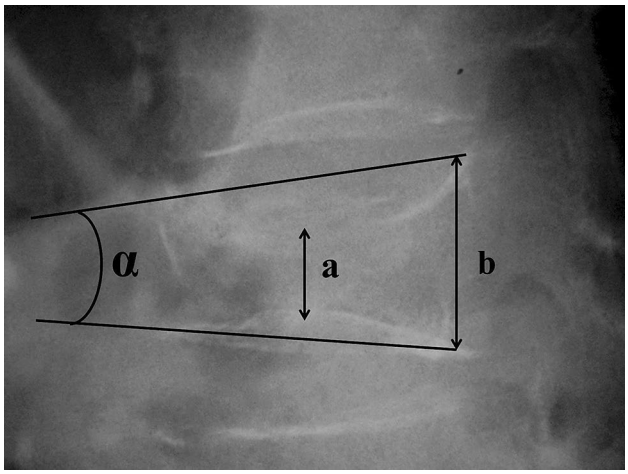

Fig. 1 Imaging methods to evaluate the vertebral collapse rate and local kyphotic angle. The vertebral collapse rate was calculated by dividing the height of the most collapsed vertebral region (**a**) by the vertebral posterior height (**b**). The local kyphotic angle was the angle set by the vertebral body endplates of fractured vertebrae (**α**)

Table 2 The number of fractured vertebrae in the Daily, Weekly, RIS, and Control groups

	Daily	Weekly	RIS	Control
Thoracic vertebrae				
8	1	2	0	0
9	0	0	0	0
10	0	1	1 (1)	0
11	3	0	0	1
12	3	3 (1)	2	5 (1)
Lumbar vertebrae				
1	3 (1)	4	6 (2)	6 (1)
2	4	3	2 (2)	7 (1)
3	4	1	2 (1)	2
4	1	1	0	3 (3)
5	1	0	1	0
Total vertebrae	20	15	14	24

The values in parentheses are the number of patients with cleft formation in the fractured vertebrae on radiography

Daily daily administration of teriparatide, *Weekly* weekly administration of teriparatide, *RIS* risedronate

Table 3 The results of VAS, vertebral collapse rate, local kyphotic angle, frequency of cleft formation, and hospitalization period in the four groups

	Daily	Weekly	RIS	Control
Number/vertebrae	10/20	11/15	13/14	22/24
VAS (0–100 mm)				
2w	46.5 ± 20.8	51.7 ± 25.4	50.7 ± 20.8	–
4w	27.7 ± 15.8	20.3 ± 14.3	35.7 ± 19.5	–
8w	15.2 ± 10.8[a]	20.5 ± 13.8	34.5 ± 18.2	–
12w	11.7 ± 8.0[b]	12.6 ± 10.3[b]	31.8 ± 20.0	–
Vertebral collapse change				
4w	0.005 ± 0.047	0.005 ± 0.083	0.027 ± 0.124	0.075 ± 0.071
8w	0.007 ± 0.061[c,d]	0.025 ± 0.084[d]	0.089 ± 0.054	0.114 ± 0.083
12w	0.017 ± 0.059[e,f]	0.048 ± 0.085[f']	0.129 ± 0.079	0.143 ± 0.095
Local kyphotic angle change (degrees)				
4w	0.55 ± 1.57	1.47 ± 2.85	2.29 ± 2.95	2.53 ± 4.06
8w	0.75 ± 2.12 [g,h]	2.20 ± 2.48 [h']	3.93 ± 2.76	5.21 ± 3.98
12w	0.55 ± 2.37[i]	2.54 ± 2.70	3.80 ± 4.08	5.96 ± 4.89
Cleft formation (number)	1/20 (5 %)[j]	1/15 (6.7 %)	6/14 (42.9 %)	6/24 (25 %)
Hospitalization period (days)	34.6 ± 21.0	38.1 ± 11.5	43.2 ± 18.2	46.2 ± 18.5

All values are mean ± standard deviation

w week, *Daily* daily administration of teriparatide, *Weekly* weekly administration of teriparatide, *RIS* risedronate

[a] $p < 0.05$ vs. RIS 8w group

[b] $p < 0.05$ vs. RIS 12w group in each evaluation

[c] $p < 0.05$ vs. RIS 8w group

[d] $p < 0.01$ vs. Control 8w group in each evaluation

[e] $p < 0.01$ vs. RIS 12w group

[f] $p < 0.01$ and [f'] $p < 0.05$ vs. Control 12w group in each evaluation

[g] $p < 0.05$ vs. RIS 8w group

[h] $p < 0.01$ and [h'] $p < 0.05$ vs. Control 8w group in each evaluation

[i] $p < 0.01$ vs. Control 12w group

[j] $p < 0.05$ vs. RIS group

and that in the Weekly group was significantly lower than in the Control group at 8 weeks ($p < 0.05$). The frequency of cleft formation in fractured vertebrae in the Daily group was significantly lower than in the RIS group ($p < 0.05$). There was no significant difference in the hospitalization period.

Discussion

Although several studies have reported that bisphosphonate has an analgesic effect [15, 16], the current study shows the possibility that teriparatide has an even stronger analgesic effect. In this study, there were some significant differences in the VAS score at 2 and 3 months after the initial visit. However, no significant difference was noted in the early stage after the initial visit. Thus, the teriparatide group showed no shortening of the hospitalization period. Preventing micromovement due to early bone-healing effects, rather than a direct analgesic effect on the central nervous system, may primarily influence the analgesic effects.

This study shows that teriparatide administration to fresh osteoporotic vertebral fracture patients significantly prevented vertebral collapse. In addition, vertebral collapse was prevented from the start of treatment to 12 weeks after the initial visit, being independent of the time. Teriparatide promotes bone formation, so we can consider that vertebral collapse is prevented by early formation of bone tissues at the fracture site. However, it is difficult to prevent vertebral collapse in the early stage solely through this. Cancellous bone repair is due to endochondral ossification. Some recent reports state that the effect of accelerated bone union by intermittent teriparatide administration is related to the accelerated formation of cartilage tissue [17–19]. It may prevent vertebral collapse in the early stage because of these effects. Furthermore, this early bone union effect and reducing back muscle stress through preventing vertebral collapse may cause analgesic effects.

In this study, we did not show any significant difference of the effect of preventing vertebral collapse between Daily and Weekly teriparatide groups, although a tendency toward stronger effects was observed in the Daily group. Teriparatide administered by daily injection enhances both bone formation and bone absorption. However, the bone-forming effect is much stronger than the bone-absorbing effect, and so it enhances bone formation overall. On the other hand, the weekly injection of teriparatide weakly enhances bone formation and suppresses bone absorption, and finally, the bone-forming effect is expressed overall [19–21]. Differences among teriparatide medicines regarding the strength of the bone-forming effect may influence the effect of preventing vertebral collapse, and we need to perform further detailed studies with a larger number of fresh osteoporotic vertebral fracture patients.

The limitations of this study were the small number of fresh osteoporosis vertebral fracture patients who matched the inclusion criteria, and the short follow-up period. Although fresh osteoporosis vertebral fracture patients are not rare, hospitalized patients are limited. Because the level of pain due to fresh vertebral fracture differs from patient to patient, we targeted only hospitalized patients whose symptoms were marked. Therefore, eligible patients for this study were limited, and so we need more time to increase patient numbers. Also, symptoms of vertebral fracture are mainly resolved 3 months after injury, and so patients who are administered injections like teriparatide often hope to discontinue them as soon as possible. Because of the short follow-up period, we could not examine the BMD and bone turnover markers after the treatment. In addition, as another limitation, anti-osteoporosis medicines were chosen based on the patients' decisions, and so this study was not a randomized controlled trial. Although the local kyphotic angle changes at 8 weeks in the Daily and RIS groups were slightly larger than those at 12 weeks, these changes may have been due to postural and X-ray angle differences. Reproducibility of these radiographic evaluations may be a little poor in this study, and we should consider a more accurate method of radiographic evaluation. Although there are some limitations, this is the first study comparing the two forms of teriparatide.

In conclusion, the present study showed that teriparatide is promising for the prevention of vertebral collapse progression after fresh osteoporotic vertebral compression fracture. In addition, this is the first study to compare the two forms of teriparatide. We need to perform further detailed studies with a larger number of fresh osteoporotic vertebral fracture patients.

Conflict of interest All authors have no conflict of interest.

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