

The efficacy of osteoporotic treatment in patients with new spinal vertebral compression fracture pain, ADL, QOL, bone metabolism and fracture-healing - In comparison with weekly teriparatide with bisphosphonate

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ABSTRACT

We conducted a randomized control study to compare the effects of pain, QOL, bone metabolism and fracture healing by administering bisphosphonate (BP) or weekly teriparatide preparation (W-TPTD) to 43 patients (5 males and 38 females) with fresh spinal vertebral compression fractures for osteoporosis.

The patients were aged between 61 and 93 years old (mean 78.1 years). In principle, a MRI was used for any diagnosis of new vertebral fractures.

From this study, lumbar spine bone mineral density (BMD), after 24 weeks of administration, showed a significant increase ($p < 0.05$) in both the BP group (mean 5.3%) and in the W-TPTD group (mean 4.9%).

The W-TPTD group showed a better Roland-Morris disability Questionnaire (RDQ) improvement throughout the whole period of the study compared with the BP group, the difference was statistically significant after 24 weeks of administration ($p < 0.05$). The EuroQol 5 dimensions (EQ-5D) and visual analogue scale (VAS) score significantly improved over time in both groups ($p < 0.05$).

The fracture-healing rate was observed in 45% of the BP group and 73% of the W-TPTD group at Week 12, and a statistically significant higher fracture-healing rate was obtained in the W-TPTD group compared to the BP group ($p < 0.05$). The mean time of fracture-healing was 3.9 months for the BP group and 2.8 months in the W-TPTD group. Statistically significant faster fracture-healing was observed in the W-TPTD group ($p < 0.05$).

At Week 12 and Week 24, P1NP was significantly higher in the W-TPTD group compared to that of the BP group ($p < 0.05$). TRACP-5b showed no major fluctuations during the study period in either group.

These results suggest that W-TPTD may promote better fracture healing of any new osteoporotic vertebral compression fractures compared with a BP.

1. Introduction

The most frequently occurring fracture in patients with osteoporosis is compression fracture of the spinal vertebra. 1.4 million new cases of vertebral compression fractures are reported each year (Fujiwara et al., 2003). Less than 20% of patients with osteoporosis are continuously treated after vertebral fracture or proximal femoral fracture (Hagino et al., 2012), which is a major obstacle for the extension of a healthy life span in Japan. A vertebral body compression fracture has a large adverse effect on the patient's life prognosis equal to or more than a femoral proximal fracture (Cauley et al., 2000). Patients with preexisting vertebral fractures have a several times greater risk of subsequent

vertebral fractures than those without any prior fractures (Klotzbuecher et al., 2000). An earlier start of therapeutic intervention of osteoporosis for those patients with vertebral compression fracture is considered extremely important.

Parathyroid hormone formulation (teriparatide: TPTD) has been approved and administered clinically as a daily subcutaneous injection for osteoporosis in Japan since 2010, when severe osteoporosis with a high risk of fracture is observed. Once weekly subcutaneously administered TPTD, which was developed in Japan, has a characteristic that differs from daily TPTD in bone metabolic markers transition (P1NP, uNTX) in the trough state, while being the same teriparatide. In particular, bone resorption marker increase continuously in the daily

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TPTD, but its increase cannot be recognized in W-TPTD (Nakamura et al., 2012; McClung et al., 2005). Nakamura et al. also reported that the relative risk reduction for new vertebral fractures after 72 weeks is 80% for the W-TPTD group versus the placebo group. It was reported that the vertebral fracture inhibition effect of W-TPTD is almost equal to that of daily TPTD, and W-TPTD has also improved the femoral bone structure (Ito et al., 2014). In addition, it has also been reported that once weekly administration of teriparatide results in an improvement of abnormal collagen crosslinking in the lumbar spine and vertebral anterior wall structure in OVX monkeys (Saito et al., 2011; Fujihara et al., 2019).

In patients with preexisting vertebral fractures, TPTD administration is given in the event of new spinal vertebral fracture and considered meaningful for the prevention of secondary fractures. Since the osteogenesis promoting effect of TPTD is characterized by a strong bone mass increasing effect, as compared with conventional bone resorption inhibiting drugs, TPTD is also useful for repairing fracture sites which have been reported several times (Chaldis et al., 2007; Dempster et al., 2001). Although TPTD has not been proven to have any clear analgesic effect, or early bone healing, due to the fracture healing promotion effect and accompanying pain mitigation effect, an analgesic effect, is expected at the same time.

The objective of this study was to investigate post fracture pain and QOL when administering bisphosphonate (BP) or weekly teriparatide (W-TPTD) to patients with new spinal compression fractures and who have completed a patient questionnaire. At the same time, to compare and investigate the effect of both drugs on bone metabolism and the final fracture healing effect after a new spinal vertebral fracture.

2. Target patients and study methods

The number of cases registered with osteoporotic and new spinal vertebral compression fracture was 43 patients (5 males and 38 females). The range of patients' ages was between 61 and 93 years old (mean 78.1 years).

Target patients had new spinal vertebral compression fractures that required osteoporosis treatment, regardless of menopause, sex, presence or absence of previous treatment, and < 80% of young adult mean (YAM) value in bone mass measurement of the lumbar vertebra or femoral proximal. Patients of 85 years or over, who had difficulty in completing the questionnaire, on subjects such as pain and QOL, were excluded from this study. In principle, a MRI was used for the diagnosis of new spinal vertebral fracture. The vertebral body which showed low intensity change at T1 and high intensity change at STIR was diagnosed as a new fracture.

This study was conducted with the approval of the hospital ethics committee and targeted only those patients who gave their informed consent for participation in the study, before any treatment was administered. Patients were randomized and treatment was arranged for both the BP and W-TPTD groups (prospective randomized controlled study).

For the treatment of compression fracture, a rigid brace was made in principle for the purpose of resting the trunk. The brace was worn as early in the day as possible, and used as a support when lying in bed. The study period was 1 year, and the final evaluation of fracture healing was carried out at 6 months.

The patient's pain was evaluated by the pain experienced at the back of the lumbar region, using a visual analogue scale (VAS) at the initial examination, Week 2, Week 4, Week 8, Week 12, and Week 24, during resting time (supine position or sitting position), and at the time of operating (raised from the supine position, or sitting position, and walking). QOL was evaluated by using the Roland-Morris Disability Questionnaire (RDQ) and EuroQol 5 dimensions (EQ-5D).

The vertebral body deformation of the fractured part was measured using the Cobb angle. The CT was examined in three directions (axial, sagittal, and coronal) to check the continuity of the trabecular bone,

presence or absence of fracture healing, and presence or absence of any new fracture. The judgment of fracture healing was evaluated using function shots from X-rays and CT scans, which were evaluated by numerous doctors under blind conditions. From the CT examinations, those cases with clear intervertebral cleft formation were not judged as fracture healing. Even if there was a bone formation at the fracture site, when there was deterioration of vertebral body deformation over time (compared to the final CT scan taken 1 year after injury), it was not judged as fracture healing. The survey was made at the initial visit, 1 month, 2 months, 3 months, 6 months and one year later. We also examined the number of vertebral fractures (presence or absence of new fractures and previous fractures).

Bone mass measurements were made using the DXA method and the lumbar vertebrae (L2-L4) and proximal femur (cervical and proximal) were both measured at the initial visit and 6 months later. Serum Ca, and ALP were used for biochemical examinations, and serum TRACP-5b and PINP were used as bone metabolism markers. The survey was made at the initial visit, 1 month, 3 months, and 6 months later.

Statistical analysis of the change between the two groups was made using the Mann-Whitney's *U* test. Wilcoxon's signed-rank test was used for the observation of any statistical analysis changes from the initial visit. In the case of $p < 0.05$, it was judged that there was a statistically significant difference.

3. Results

Patients with previous fractures amounted to 31 cases (72%). This study was a prospective randomized comparative study, and there was a statistically significant difference in mean age only between the BP group and W-TPTD group (BP group: 80.2 years old, W-TPTD group: 75.6 years old, $p < 0.05$) (Table 1). The administered BP was once-weekly Alendronate (35 mg), once-weekly (17.5 mg) or monthly (75 mg) Risedronate, and the dosage administered was in the amount that is approved in Japan.

In the W-TPTD group, 3 patients dropped out due to nausea or vomiting, and in the BP group, there was 1 patient with medical complications and 1 patient who left the study.

There were no cases of new vertebral fractures occurring in the follow-up period of 6 months in either group.

Lumbar spine BMD showed a mean increase of 5.3% in the BP group and 4.9% in the W-TPTD group at 24 weeks after administration, and both groups showed a statistically significant increase. BMD increased by 1.4% on average in the femoral neck area of the BP group, but in the W-TPTD group, both the femoral neck and proximal area showed a decreasing trend (Fig. 1).

Fracture healing was observed in 45% of the BP group and 73% of the W-TPTD group at the early stage, by Week 12, and statistically significant fracture healing was obtained in the W-TPTD group compared with the BP group ($p < 0.05$). Whereas, at Week 24 observation, the fracture healing rate was 68% in the BP group and 80% in the W-

Table 1
Patients' demographic characteristics.

	BP (n = 24)	W-TPTD (n = 19)
Age (year)	80.2	75.6 ^a
Sex: male, female	4, 20	1, 18
Patients with prior fracture (n)	16	15
Patients with prior fracture (n): Vertebral, non-vertebral	14, 5 ^a	14, 3 ^b
Patients with prior fracture (%)	66.7	78.9
BMD vertebral body (g/cm ²)	0.717	0.720
BMD femoral neck (g/cm ²)	0.535	0.526
BMD femoral proximal (g/cm ²)	0.666	0.643

a: 3 patients had both b: 2 patients had both.

^a $p < 0.05$ vs BP (Student's *t*-test).

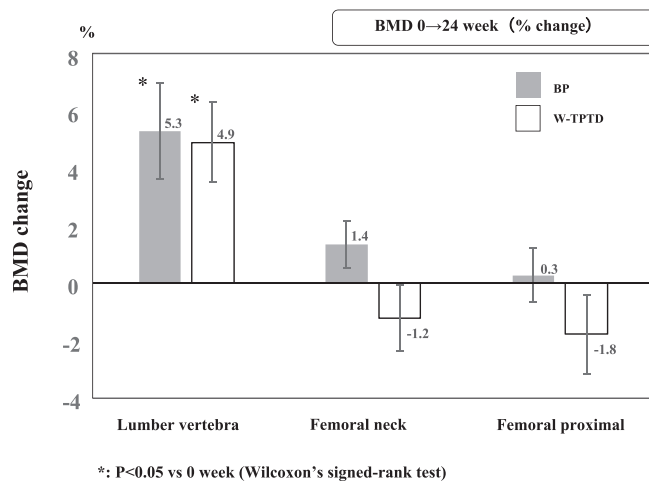


Fig. 1. BMD change.

BMD = bone mineral density.

TPTD group, and there was no statistical significance observed (Fig. 2). The mean time for fracture healing was 3.9 months in the BP group and 2.8 months in the W-TPTD group. Statistically significantly earlier fracture healing was observed in the W-TPTD group ($p < 0.05$) (Fig. 3).

A significant improvement was observed in RDQ from 12 weeks after administration to the BP group and 4 weeks after administration to the W-TPTD group. The W-TPTD group's reaction was better throughout the whole period of testing, and the difference was considered significant ($p < 0.05$) (Fig. 4). EQ-5D significantly improved over time in both groups. The VAS score of patients' pain significantly improved from the early stage in both groups in all cases when a subject was in a laying position, sitting position or in operation, and no significant difference was observed between either group.

Serum Ca remained within the reference value throughout the study period in both groups and showed no significant change. ALP and TRACP-5b showed no significant change throughout the study period in either group. P1NP significantly increased after 4 weeks of administration in the W-TPTD group and then decreased. At Week 12 and Week 24, P1NP was significantly higher in the W-TPTD group compared to that of the BP group (Fig. 5).

4. Discussion

By the osteogenesis promoting action of TPTD, the lost bone structure is actively repaired, the trabecular continuity is increased, the

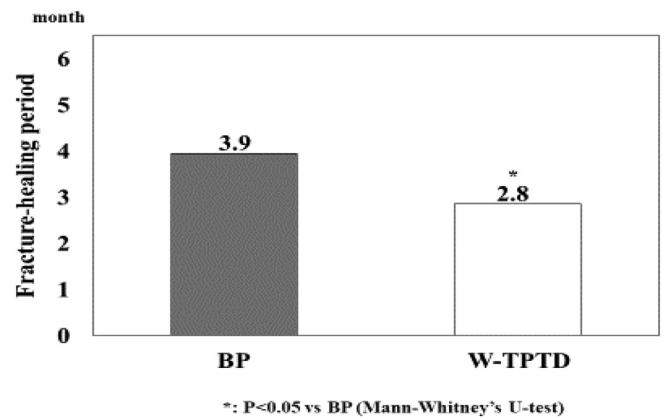


Fig. 3. Time to fracture-healing.

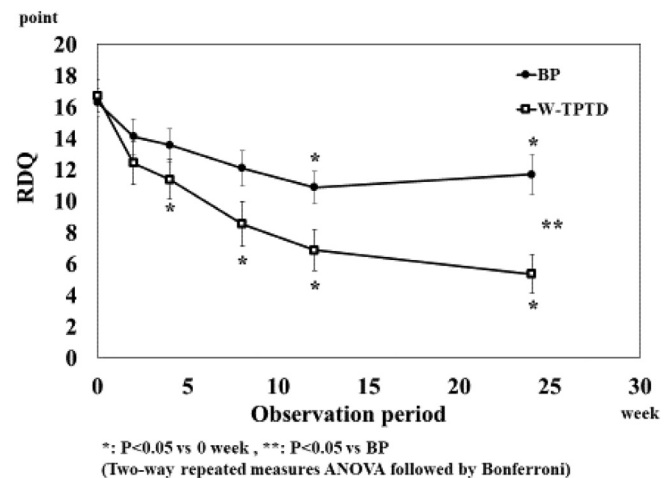


Fig. 4. Transition of RDQ.

RDQ = Roland-Morris Disability Questionnaire.

trabecular structure is shifted to a plate-like structure, and bone strength rises (Jiang et al., 2003). In spinal vertebral bodies, a remarkable increase in bone density and the reconstruction of bone microstructure is obtained. In addition, the effect of suppressing the occurrence of vertebral fracture is also obtained. At the same time, osteoblast activity is selectively stimulated, promotion of differentiation into osteoblasts, suppression of apoptosis of osteoblasts, and osteoblast bone formation function are enhanced. As a secondary effect thereof, the frequency of bone activation is also increased, thereby

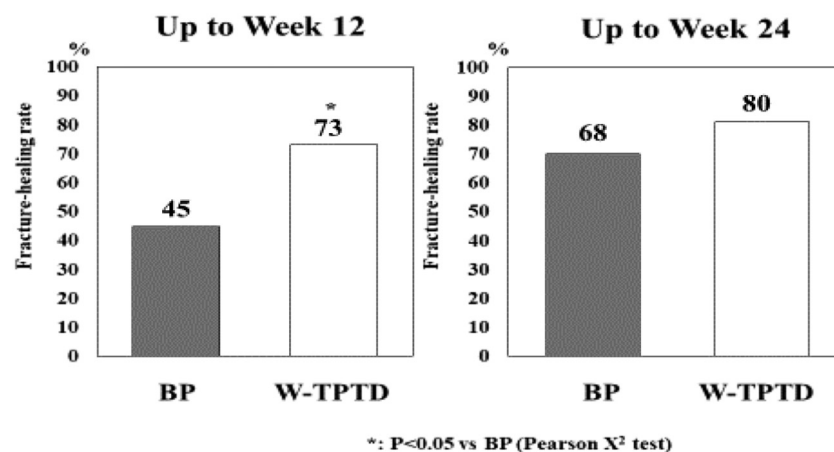


Fig. 2. Fracture-healing rate.

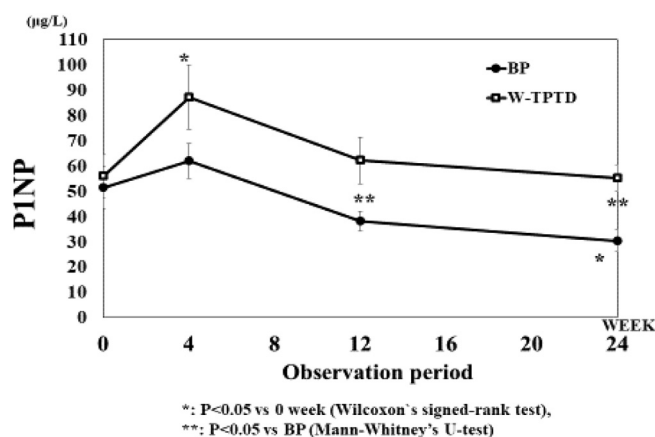


Fig. 5. Transition of serum P1NP.

accelerating an increase in the amount of bone tissue and the promotion of fracture-healing.

Regarding the promotion of bone fracture-healing by TPTD intermittent administration, the report of Fukuhara, et al. seems to be the first publication. The report confirmed the prolonged healing of femoral fracture in parathyroidectomized rats and bone formation was promoted at the early stages of fracture by the administration of TPTD (Fukuhara and Mizuno, 1989). TPTD daily administration was approved in the US in 2002, and the indication for osteoporosis was approved in the EU in 2003. After a substantial delay, TPTD was approved in Japan in 2010, since then only a few study reports have been published on fracture-healing in patients with osteoporosis (Holzer et al., 1999; Ellegaard et al., 2010; Aspenberg et al., 2010). Aspenberg et al. reported that TPTD promoted fracture repairing in 102 patients with postmenopausal osteoporosis with a distal radius fracture in a prospective randomized double-blind study. Chintamaneni et al. reported that osteogenesis occurred 3 months after the daily administration of TPTD to the fracture nonunion following a sternal fracture, and fracture healing was completed 9 months later (Chintamaneni et al., 2010). In a report of 65 patients with pubic or sciatic fracture, the time required for fracture healing was 7.8 weeks in the TPTD group, and 12.6 weeks in the control group to whom vitamin D and calcium were administered. TPTD required a shorter time to obtain fracture healing than the control group and the difference was statistically significant ($p < 0.05$). The bone healing rate at 8 weeks was 100% in the TPTD group and 9.1% in the control group, and statistically significant and earlier fracture healing was obtained in the TPTD group (Peichl et al., 2011).

The BPs have some clinical concerns as they are agents that inhibit bone resorption, which is an important period for fracture healing. Kates and Ackert-Bicknell (2016) indicated that atypical fracture risk and fracture healing are delayed by BP administration during the long term, but it is safe to use for the treatment of acute fractures in human limb fractures. From the view of secondary fractures prevention etc., the targeted patients were treated and divided into the BP group and W-TPTD group respectively without a control group being set up in this study. With regard to the analgesic effect of BP, Strang et al. reported that it was caused by various mechanisms, and the long-term effect was due to the suppression of osteoclasts, and the effect in the acute phase was to suppress any pain-producing substances (Strang, 1996). In addition, Hadji et al. reported when the effect on pain in postmenopausal osteoporosis patients with lumbar and back pain, due to vertebral body fracture, was compared to daily TPTD and Risedronate in the randomized, double-blind, double-dummy study, both showed pain-relieving activity, and there was no difference in the evaluation of the effect of the VAS score (Hadji et al., 2012).

There is little evidence that has been reported on the use of TPTD for osteoporotic vertebral compression fracture treatment. Park et al.

divided 68 female patients with osteoporotic compression fracture in one vertebra of the thoracolumbar vertebra (T11-L2) into groups for short-term TPTD treatment (32 patients), or in a group treated with a bone resorption suppressant (36 patients), to compare the degree of collapse of the fractured vertebra. In conclusion, mean increments of kyphosis and wedge angle were significantly lower in the TPTD group (4.0° and 3.6°) than in the bone resorption inhibitor group (6.8° and 5.8°). It was reported that TPTD did not prevent, but did decrease the progression of fractured vertebral body collapse (Park et al., 2014). In the case of W-TPTD, there is a report that it is useful for preventing the progress of vertebral collapse progression after vertebral fracture (Tsuchie et al., 2016), and a case report that it may have correction of vertebral fractures without surgical intervention (Miyakoshi et al., 2015).

The present study is the result of a randomized study. It was suggested that W-TPTD had a higher bone healing rate than BP, the mean time to fracture healing was shorter, and the effect of improving QOL was better. However, no statistically significant difference was found between the two groups regarding pain relief.

5. Conclusions

From this study, it is concluded that weekly TPTD and BP both reduced back pain. In addition, in terms of QOL and fracture healing, weekly TPTD tended to improve both conditions faster than BP.

Declaration of Competing Interest

Keiichi Shigenobu, Tomoyuki Hashimoto, Masahiro Kanayama, Humihiro Ohha, and Shigeru Yamane declared they have no conflict of interest.

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