



Short-term daily teriparatide improve postoperative functional outcome and fracture healing in unstable intertrochanteric fractures



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ABSTRACT

Background: There has been heightened interest in the effect of osteoanabolic agents on acceleration of fracture healing.

Objectives: The purpose of this study was to identify whether short-term daily teriparatide prescribed for osteoporosis treatment would improve postoperative outcomes including clinical scores, radiographic healing, and complication rates.

Methods: Between 2014 and 2017, we retrospectively assessed 112 patients who underwent closed reduction and internal fixation with proximal femoral nail (PFN) for unstable intertrochanteric fractures. In 60 of 112 patients, patients were treated with a PFN alone (group I). These patients were compared with 52 patients for whom the same device was used and a daily subcutaneous injection of teriparatide (1–34 PTH, Forsteo®) was prescribed postoperatively (group II). Teriparatide was administered by nurses during a hospital stay and then self-injection was monitored by follow-up visits to the outpatient clinic after discharge. Questionnaire surveys were conducted and patients completed a self-report Harris hip score (HHS) and visual analog scale (VAS) scores.

Results: Teriparatide therapy significantly increased HHS ($p=0.02$) and decreased VAS pain scores ($p=0.008$). The mean time to fracture healing post-operatively was 14.8 weeks (SD 7.1) and 12.1 weeks (SD 6.4) in group I and II, respectively ($p=0.002$). The frequency of patients reporting postoperative complications was also markedly reduced in the teriparatide-treated groups ($p=0.028$).

Conclusions: Short-term daily teriparatide used for osteoporosis treatment improved radiographic fracture healing of a hip fracture and reduced complication rates. However, because of the limited power of the study, additional randomized placebo-controlled trials are needed to determine the potential benefit of PTH as an adjunct to enhance fracture healing and its efficacy in broader populations with varying comorbidities and fracture types.

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Introduction

Hip fracture contributes to high mortality and adverse outcomes in the geriatric population. The annual number of cases has been estimated worldwide to be as high as 4.6 million by 2025 and 6.26 million by 2050 [1,2]. Approximately 1 in 6 women in North America will experience a hip fracture in their lifetime [3]. With the advancing age of the general population, complications during bone healing cause a burden for the individuals and health system [4,5]. When performing osteosynthesis for osteoporotic hip fracture, excessive sliding of the lag screw caused by insufficient abutment at the fracture may shorten the femur. Moreover, varus

collapse of the proximal fragment and penetration of the screw into the hip joint or loosening within the femoral head may occur [6]. Thus, there is medical need to improve fracture healing and functional recovery after hip fracture.

Teriparatide is a recombinant 1–34 fragment of human parathyroid hormone (PTH) and has been shown to stimulate the formation and action of osteoblasts, which are the cells responsible for bone formation, thereby promoting increases in bone tissue [7]. In contrast to antiresorptive drugs, direct stimulation of bone formation may not only increase bone strength but also facilitate fracture healing [2]. Teriparatide proved to be an attractive agent to enhance fracture healing and limit the risk of nonunion when human trials on fracture healing were performed [8,9]. Several published case reports and systematic review suggest that teriparatide accelerates bone healing and improves functional recovery after fracture at various skeletal sites [8,10–12]. However, to our knowledge, no previous studies have

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evaluated whether the administration of short-term daily PTH could improve radiographic signs of fracture healing of unstable intertrochanteric fractures treated with intramedullary (IM) nail fixation.

The aim of this study was to evaluate whether the administration of short-term daily PTH prescribed for osteoporosis could improve postoperative outcomes including clinical scores, radiographic healing, and complication rates. We wished to test the hypotheses that postoperative PTH treatment used for osteoporosis treatment would improve functional recovery after intertrochanteric fractures.

Patients and methods

Patient cohorts

We performed a retrospective analysis of our institutional hip fracture database between March 2014 and August 2017, and assessed 130 patients (130 hips) who underwent reduction and internal fixation with a short femoral nail for osteoporotic, unstable intertrochanteric fractures. The institutional review board of the ethics committee of our institution approved this single-center retrospective comparative study (approval number: HIRB-2017-008). Written informed consent was waived as this was purely retrospective review without intervention. Inclusion criteria were: (1) patients who were classified as unstable femoral intertrochanteric fractures (AO/OTA type A2, A3 [13]), (2) age more than 65 years, (3) unilateral, low-trauma fracture of the peritrochanteric region, and (4) patients with osteoporosis (T-score of -2.5 or lower). Exclusion criteria were: (1) patients who underwent reduction and internal fixation with a sliding screw (DHS), (2) concomitant mental instability or diseases affecting bone metabolism other than osteoporosis, (3) patients who were prescribed weekly PTH, (4) prior treatment with PTH, and (5) treatment augmented using any type of degradable cement. Among them, 10 patients had incomplete data and 8 patients were lost to follow-up. These patients were excluded. The final study groups were 112 patients (112 hips).

In 60 of 112 patients, patients were treated with a proximal femoral nail (Proximal Femoral Nail Antirotation, AO synthes) alone (group I). These patients were compared with 52 patients for whom the same device was used and a daily subcutaneous

injection of 20 μg teriparatide (Forsteo[®], rhPTH(1–34), Eli Lilly) was prescribed postoperatively for 2 months (group II). To treat osteoporosis, the different osteoporosis medications, the advantages and disadvantages of osteoporosis treatment based on the guidelines for osteoporosis treatment [14] were explained to the patients and the choice of treatments was decided by the patients themselves due to regulatory and financial constraints. Daily supplements of calcium (1000 mg) and vitamin D (400–800 IU) were prescribed in both groups. Patients with history of recent treatments for osteoporosis (including bisphosphonates and selective estrogen receptor modulators) within six months prior to the start of PTH, were not included in our study due to the effects of the drugs on the bone beyond the time of administration. The average age of the patients at the time of surgery was 81 years (range, 66–99 years). There were 42 males and 70 females. Minimum follow-up was 10 months (average, 1.6 years; range, 0.8–3.0 years). Baseline characteristic were well-balanced between treatment groups including age, gender, preoperative clinical scores, affected hip, and osteoporosis at the time of fracture (Table 1).

All patients underwent surgery under general anesthesia and all surgical procedures were performed by a single surgeon. Fixation was deemed to be adequate if the blade was placed central/central (AP/lateral view), inferior/central, or inferior/posterior. The tip apex distance of less than 20 mm was considered to be adequate. After reduction of the fracture, a PFN was inserted using the standard technique. The postoperative protocol was uniform for all patients. Weight-bearing with a walker was allowed within the first 2 weeks after surgery and continued for at least 8 weeks. Subsequently, patients could be advanced to full weight bearing on the basis of the appearance of recanalization or bridging callus on follow-up radiographs. Patients were seen for follow-up at 4, 8, 12, 16, 20, and 24 weeks and then every 6 month thereafter.

Clinical assessment

To compare the differences in functional recovery due to an earlier mature fracture union, clinical assessments were performed with use of the Harris hip score (HHS) [15] and visual analog scale (VAS) [16] scores (pain and stiffness were scored by the patients on a VAS of 0 to 100, with 100 representing maximum pain or stiffness). Questionnaire surveys or telephone interviews

Table 1

The preoperative demographic data for group I and group II (group I, placebo group; group II, teriparatide group).

	Group I (60 hips)	Group II (52 hips)	P value
Age at time of operation (range)	80.2 (67.1 to 99.3)	81.4 (66.2 to 97.9)	0.544
Sex			0.845
Male	22	20	
Female	38	32	
Prior osteoporosis therapy (not within 6 months)	32	23	0.337
bisphosphonates	20	15	
selective estrogen receptor modulators	11	7	
denosumab	1	1	
Body height (cm)	156 (148 to 166)	157 (147 to 164)	0.541
Body weight (kg)	51.2 (37.1 to 82.8)	53.1 (38.1 to 80.8)	0.448
Right/left	33/27	24/28	0.350
Fracture classification			0.775
AO/OTA 31-A2	52	46	
AO/OTA 31-A3	8	6	
Charlson Comorbidity Index	2.7 (1 to 6)	2.86 (0 to 7)	0.522
BMD (T-score)	-3.2 (-5.2 to -2.9)	-3.4 (-4.9 to -2.8)	0.198
Hospital stay (day)	18.5 (12 to 52)	16.2 (10 to 45)	0.348
Duration of surgery (min)	71 (50 to 90)	73 (58 to 92)	0.762

were conducted and patients completed a self-report HHS and VAS scores. Any complications were noted. Data were obtained from medical records and radiographs. The pain scores and functional scores were reviewed and analyzed by a research associate.

Radiographic assessment

Digital radiographs of all the patients were retrieved from the picture archiving and communication system for analysis. The primary outcome comprised radiographic findings of fracture healing and callus formation at each follow-up. Radiological union was defined as bridging at the fracture site by a callus or a cortical continuity involving at least three cortices in the hip using AP and lateral views of the femur [17–19]. Malunion was defined as varus collapse of more than 15 degrees after comparison with the opposite side [5]. To assess the quality of the reduction, the position of implants were compared between groups. All the radiographs were studied by two observers and were tested for concurrence and reproducibility by interobserver studies.

Statistical analysis

All data were recorded into an Excel spreadsheet (Microsoft Corp, Redmond, WA) and subsequently copied to a statistical analysis software SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). Various radiographic indices (radiologically defined union) were described by a mean \pm SD. Student's *t*-test was used to compare the clinical parameters of group I to those of group II. The χ^2 test was used to compare the radiological assessment (fracture healing times) with the treatment given and to evaluate differences in the complication rates between groups. Statistical analysis was performed by an independent statistician blinded to group allocations. Significance was reported at the 95% confidence level ($p < .05$).

Results

Reliability

Radiographic parameters were tested for reproducibility by intraobserver and interobserver studies using Pearson correlation coefficients; correlation coefficients ranged from 0.890 to 0.925, indicating good reliability.

Clinical parameters

At the final follow-up, the HHS average score was 60.4 and 70.4, in groups I and II, respectively and the difference between the two groups was statistically significant ($p = 0.02$) (Table 2). Also, VAS pain was significantly better in PTH-treated groups at six months

Table 2

Clinical outcomes for group I and group II (group I, placebo group; group II, teriparatide group; HHS, Harris hip score; VAS, visual analog scale).

	Group I (60 hips)	Group II (52 hips)	P value
HHS score			
after 2 months	45.2 (10 to 80)	60.5 (10 to 80)	0.005
after 4 months	55.4 (20 to 86)	65.4 (20 to 90)	0.04
after 6 months	60.4 (20 to 86)	70.4 (24 to 90)	0.02
VAS pain score			
after 2 months	52.4 (10 to 90)	35.2 (10 to 80)	0.001
after 4 months	41.5 (10 to 80)	28.4 (5 to 70)	0.005
after 6 months	32.8 (10 to 80)	21.2 (5 to 70)	0.008
VAS stiffness score			
after 2 months	50.6 (20 to 90)	40.8 (20 to 90)	0.022
after 4 months	44.8 (10 to 90)	35.9 (10 to 80)	0.04
after 6 months	32.8 (10 to 90)	30.2 (10 to 80)	0.148

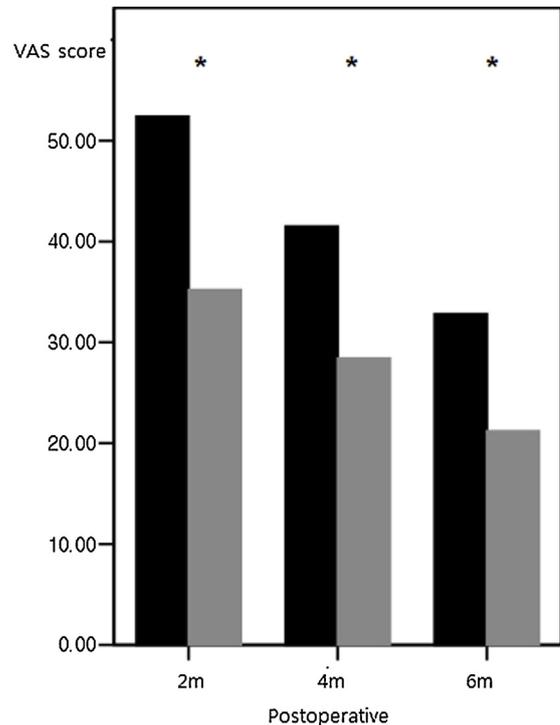


Fig. 1. Mean Visual Analog Scale (VAS) pain scores over time. Asterisks indicate significant differences between groups.

after surgery. ($p = 0.008$) (Fig. 1). With regard to VAS stiffness score, it was lower in group II at the time of the final follow-up but not reached to a statistical significance.

Radiographic parameters

There was no difference in the positioning of the blade between the groups as assessed on the immediate post-operative radiographs. The positioning of the implant was considered to be adequate in 54/60 (90%) of groups I, and 46/52 (92%) of group II. The mean TAD was 16 mm (SD2) in groups I and 18 mm (SD2) in group II, and the difference was not statistically significant. Postoperatively, the mean time to radiographically defined union was 14.8 weeks (SD 7.1) and 12.1 weeks (SD 6.4) in group I and II, respectively ($p = 0.002$). A few fractures were radiographically healed at the first and second examination (at 4 and 8 weeks) (Table 3). However, there was significant difference between two groups with respect to radiographic fracture healing at 12–16 weeks postoperatively. Two 4-part fractures took several months to heal completely even in the treatment Group II (Table 3).

Postoperative complications

A total of 17 complications (28%) were encountered in group I and 6 complications (11%) in group II. This result was statistically

Table 3

Fracture healing times for group I and group II (group I, placebo group; group II, teriparatide group).

Fracture healing	Group I (60 hips)	Group II (52 hips)	P value
Week 4	4 (6 %)	4 (7 %)	0.834
Week 8	25 (41 %)	30 (57 %)	0.091
Week 12	47 (78 %)	50 (96 %)	0.006
Week 16	53 (88.0 %)	52 (100 %)	0.011
Week 20	59 (98.0 %)	52 (100 %)	0.350
Week 24	60 (100 %)	52 (100 %)	

Table 4

Postoperative complications for group I and group II (group I, placebo group; group II, teriparatide group).

Categories	Group I (60 hips)	Group II (52 hips)	P value
Lateral screw migration requiring further intervention	2	1	
Varus collapse with screw sliding	2	0	
Deep wound infection	1	0	
Superficial wound infection	2	1	
Malunion	8	3	
Superior cut-out of lag screw	2	1	
Nonunion	0	0	
Avascular necrosis	0	0	
Overall complication	17 (28 %)	6 (11 %)	p = 0.028

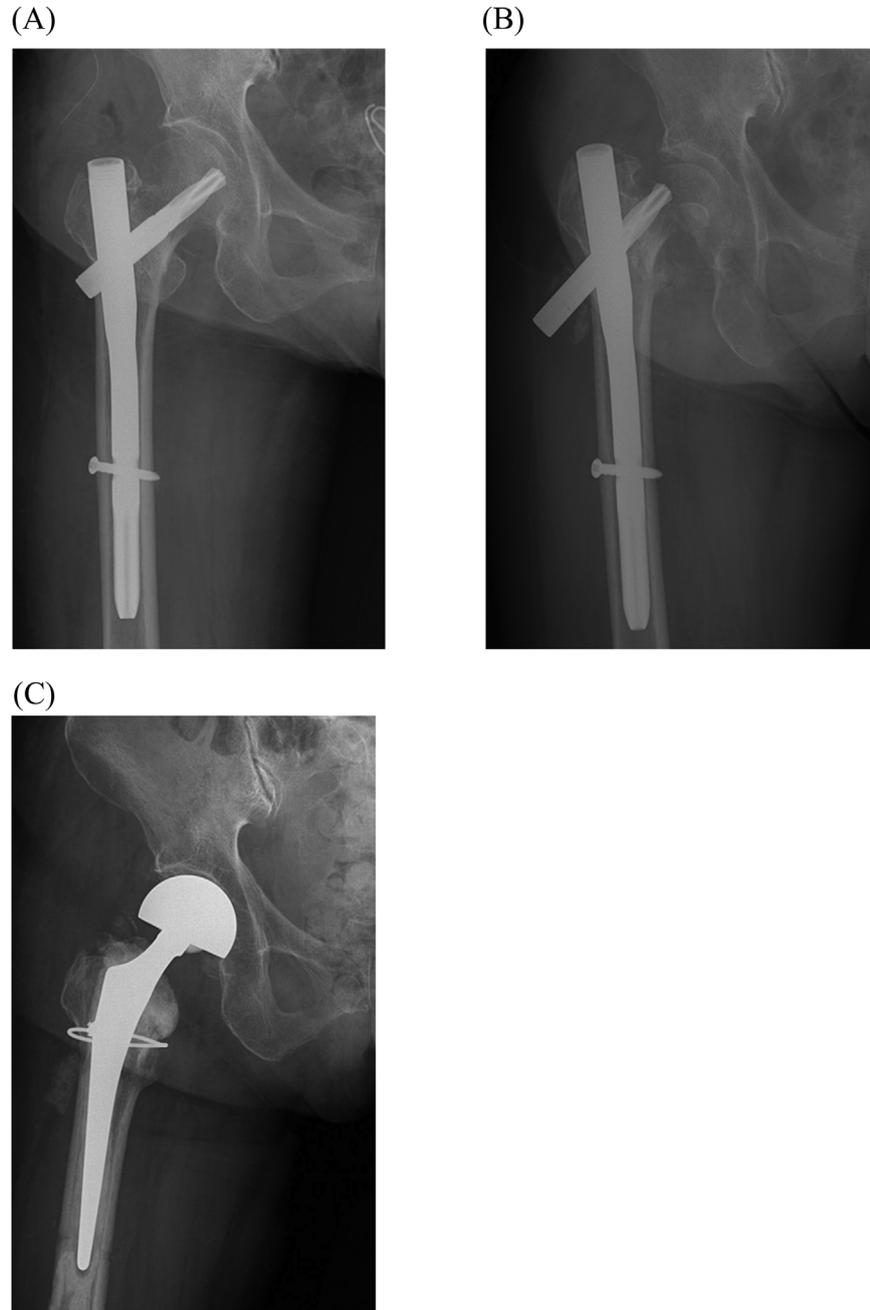


Fig. 2. A–C (A) Postoperative radiograph shows that the fracture was well reduced and fixed with an intramedullary nail. (B) Loss of reduction were noted at 1 months after surgery. (C) The patient was re-operated for cemented bipolar hemiarthroplasty.

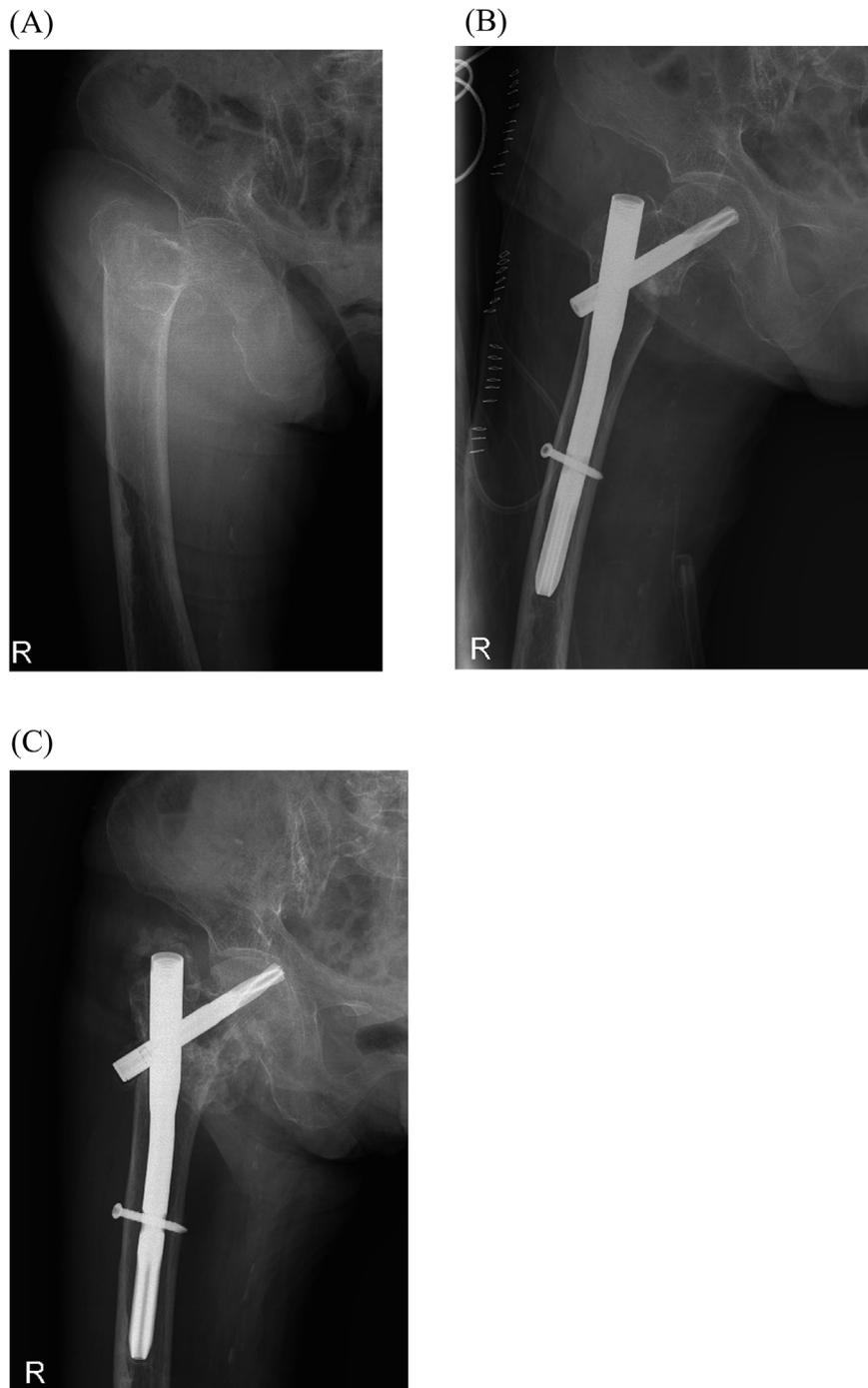


Fig. 3. A–C (A) Preoperative AP radiograph of 94-years old patient with an unstable intertrochanteric fracture. (B) Immediate postoperative AP radiograph (teribone was prescribed). (C) AP radiograph at 3 months after surgery shows that cutting-out of the lag screw from the femoral head occurred with varus collapse. However, the screw was remained because bony union was obtained and the patient had no symptoms.

significant ($p = 0.028$) (Table 4). Lateral screw migration requiring further intervention occurred in two patients in group I, and one patient in group II. For these patients, screws were exchanged because of severe skin irritation. Varus collapse with screw backout occurred in two patients in group I, who were re-operated for a bipolar hip replacement (Fig. 2). In group II, cutting-out of the lag screw from the femoral head occurred in one patient. However, further intervention was not necessary because early bone union was obtained, and the patient had no symptoms (Fig. 3). Other medical complications or serum electrolyte abnormalities with use of teriparatide were not identified.

Discussion

Since osteoporotic hip fracture is a serious medical problem and a notable burden on the healthcare system [20], there is a medical need for therapies that improve hip fracture healing. Recently, there has been heightened interest in using osteoanabolic agents for osteoporosis treatment [21]. However, its effectiveness in patients who have sustained hip fractures is currently unknown. The aim of this study was to evaluate whether the administration of short-term daily teriparatide could improve early postoperative outcomes in hip fractures.

Huang et al [21] reported that teriparatide yields better clinical outcomes of unstable pertrochanteric fractures in 44 patients who underwent DHS fixation at 3 and 6 months postoperatively. Tu et al [22] demonstrated that teriparatide therapy significantly decreased visual analogue scale pain scores, increased functional scores but suggested that therapy should continue for at least six months to ensure it is effective. However, because PTH treatment is more expensive than other medical treatments for osteoporosis and uncomfortable subcutaneous injection remains the only licensed route of administration [23], the greatest challenge of delivering this study was that of identifying a sufficient number of eligible patients. For these reasons, we couldn't recommend the use of expensive injection therapy for patients over three months. The dose, duration and cost effectiveness of treatment remain in question [24]. Nevertheless, in the present study, significant differences between groups regarding the functional endpoints were observed. Two months of teriparatide use after surgery improved functional score and decreased pain compared with conventional treatment. This earlier recovery of function might possibly reflect an earlier mature fracture union due to teriparatide.

Many animal studies have demonstrated an acceleration of fracture healing, and the fracture callus in teriparatide-treated animals formed more rapidly, remodeled more quickly, and possessed superior biomechanical properties compared with placebo-treated animals [25–27]. Holzer et al [28] reported that parenterally administered parathyroid hormone may accelerate normal fracture healing in 3-month-old, Sprague Dawley rats at 3 weeks post fracture. Positive effects on femoral fractures has been demonstrated also in Cynomolgus monkeys, where a treatment for 3 weeks led to a healing process with a better mechanical properties [29]. Despite of the difficulties that are present in monitoring the healing process in human [30], the effects of PTH on normal primary fracture have been investigated [8,31,32]. Peichl et al [32] reported a prospective, randomized, controlled study of 65 patients and concluded that PTH 1–84 accelerates fracture-healing in pelvic fractures and improves functional outcome in elderly patients with osteoporosis. Moon et al [33] demonstrated that two-months teriparatide treatment is considered to be useful to relieve pain rapidly, to allow walk in early stage, and to reduce side effects caused by drug administration in pelvic insufficiency fracture patients with osteoporosis. Recently, Huang et al [21] demonstrated that postoperative use of teriparatide for 6 months appears to be an effective adjunct therapy in the treatment of patients who underwent surgery using a DHS for osteoporotic intertrochanteric fractures. In our study, we confirmed that radiographic outcomes of intertrochanteric hip fractures were improved in the group treated with daily short-term teriparatide. In the present study, plain radiography was used to determine fracture healing. Although CT scans have been found to provide a more accurate healing assessment [34] and a higher correlation with fracture rigidity, their postoperative application is limited by higher costs and greater radiation dosage compared with conventional radiographs [35]. We believe that plain radiography remains the most common method of fracture union assessment. In a review of 122 fracture studies using radiographic criteria, plain radiographs were used by 98% of studies compared with 1% for both CT and ultrasound [19].

Shortening or varus collapse are common postoperative complications in unstable three- and four-part intertrochanteric fractures because of pronounced impaction of the fracture [36]. Cement-augmentation has been widely used for osteoporotic intertrochanteric fractures, it has its own set of failure modes and makes subsequent revision surgeries more complex and technically demanding [5]. On the other hand, significant reduction of sliding of lag screw, femoral shortening, varus collapse, and incidence of cut-out of the lag screw has been reported in patients who received teriparatide [21]. Similarly, in the present study,

there was significant between-group difference in the proportion of patients undergoing revision surgery at 6 months with the numbers available. Although, the mean time to fracture healing was not notably different (14.8 and 12.1 weeks in group I and II, respectively), the mechanism of accelerated fracture healing is likely to diminish the overall rate of late complications and falls [37]. Because slow recovery after hip fracture has been associated with negative consequences and complications, if a pharmacological therapy could improve hip fracture healing, this may reduce the number of revision surgical procedures and potentially improve other aspects important for recovery, such as early ambulation and rapid return to function. We believe that even a slight improvement in union time is important for elderly populations with unstable pertrochanteric fractures, allowing them to return to daily activities sooner and reducing overall morbidity (such as pneumonia and pressure ulcer) and mortality.

The present study had some limitations. Since this was a retrospective study with all the inherent weaknesses and selection biases of such study designs, the conclusions from the results are limited. Other limitations were the sample size and the patient-allocation process. Nevertheless, even though the patients themselves chose medication for osteoporosis, they were not aware of osteoanabolic effects of teriparatide. In addition, in order to decrease the impact of this weakness, strict inclusion and exclusion criteria were applied, and the authors used objective data such as digitized plain radiographs which allowed us to achieve excellent reproducibility, and compared postoperative complication rates.

Conclusions

In conclusion, daily short-term teriparatide used to treat osteoporosis yielded better clinical outcomes, improved radiographic signs of fracture healing, and decreased postoperative complication rate compared with conventional treatment in intertrochanteric fractures. The improvement in union time is important for elderly populations with unstable hip fractures to enable them to return to daily activities and reduce morbidity and mortality. Further multicenter prospective studies are needed to demonstrate the efficacy of teriparatide in osteoporotic intertrochanteric fractures.

Conflict of interest

The authors declare that they have no conflict of interest.

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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