

Effects of Teriparatide on Clinical and Radiologic Long-Term Outcomes after Fixation of Pertrochanteric Hip Fractures

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Abstract

Background: Pertrochanteric hip fractures are common and among serious injuries of the old population with considerable mortality and morbidity. The aim of this study was to evaluate long-term effects of recombinant human parathyroid hormone on postoperative clinical and radiologic outcomes in elderly patients with pertrochanteric hip fractures.

Materials and Methods: Between 2016 and 2019, we prospectively assessed 80 patients with pertrochanteric hip fractures who underwent reduction and internal fixation with a dynamic hip screw. Patients were divided randomly into two groups. About 40 patients in the control group who received supplementary calcium (1000 mg/day) and vitamin D (800 UI/day), and 40 others who were treated additionally with 20–28 mg daily teriparatide for three months post-operatively. The functional and radiologic assessment was done using visual analog scale (VAS), Harris hip score (HSS), and standard radiographs of the hip.

Results: At the final follow-up, there was a significant difference between the two groups regarding average HSS (68.38 in the control group versus 74.12 in the treatment group, P -value <0.001). VAS score was also significantly lower in the treatment group (P -value <0.001). Regarding radiographic evidence of union, the results were not statistically different between the two groups.

Conclusions: The current study illustrated that short-term daily administration of teriparatide improves long-term functional outcome after pertrochanteric hip fracture fixation and can reduce the pain but does not affect union and callus formation.

Keywords: Bone, drug therapy, fractures, hip fractures, hip injuries, parathyroid hormone, teriparatide, vitamin D

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INTRODUCTION

Petrochanteric hip fractures are frequent and serious injuries of the old population with considerable mortality and morbidity. The annual number of cases are predicted to reach 4.6 million cases worldwide by 2025.^[1-4] Early weight-bearing and pain control are essential for a return to functional levels before an injury to prevent complications, but remains a challenge for orthopedic surgeons.^[2,3] As the age of the general population advances, postoperative complications waste significant

resources of the health care system. Thus, things that are more likely to help faster recovery and quicker return to the initial level of activity are of particular importance.

Petrochanteric hip fracture fixation is done using either intramedullary or extramedullary devices such as a dynamic hip screw (DHS)^[5,6] In osteoporotic patients, loss of proximal fixation and protrusion or cut-out of the nail occurs more frequently.^[7] On the other hand, because of osteoporosis, there

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is a potential shortage of femoral neck during the healing process of the fracture site which will cause shortening of abductor lever arm and functional impairment.^[8]

Along with surgical treatment, many medications have a beneficial effect in accelerating fracture healing and may have a positive effect on fracture union.^[2,9,10] Fracture union is a complex process that is regulated by multiple genes and is influenced by cytokines, growth factors, and other chemical molecules.^[11-13] One of the things that helps to strengthen bone, prevent bone loss, and probably accelerate fracture recovery is the parathyroid hormone.^[14] teriparatide is a recombinant product of human parathyroid hormone (PTH) and has been shown to increase the activity of osteoblasts. These cells do the main job of producing and increasing bone mass.^[15] Several studies have shown the positive effect of teriparatide on fracture healing in different parts of the skeleton.^[10,16]

We hypothesized that the positive effect of teriparatide on fracture healing may be able to improve the function of the patients with pertrochanteric hip fracture after surgery and help them to return to daily activities more quickly which is important to reduce mortality and morbidity rates after surgery. The purpose of this study was to evaluate the short-term administration of teriparatide on postoperative long-term clinical and radiologic outcomes in patients with pertrochanteric hip fractures who underwent fixation with DHS.

MATERIALS AND METHODS

Between 2016 and 2019, we prospectively studied 80 patients who had pertrochanteric hip fractures and underwent reduction and internal fixation with a DHS in our academic orthopedic hospital. This study was a cohort with approval from the local medical ethics committee (IR.SBMU.REC.1396.240) and was conducted in accordance with the Declaration of Helsinki with Good Clinical Practice. Informed consent was obtained before the study procedures from all patients. Inclusion criteria included the ability to walk before surgery and no prior hip surgery at the same side. Exclusion criteria were pathologic fractures (including cysts, primary tumors, and metastatic tumors), metabolic bone disease, high energy trauma, multiple injuries, rheumatoid arthritis, and mental disorders such as dementia. Patients who received more than two pack cells during the surgery were also excluded from the study.

All patients underwent surgery for open reduction and internal fixation using DHS under spinal anesthesia. Side plate length was considered according to the surgeon's decision and tip-apex distance was considered below 25 mm after checking with the image intensifier. Just after reduction and internal fixation with DHS, patients were randomly assigned to the control or treatment group at a 1:1 ratio. Eight patients in the control group refused to be visited one year post-operatively and were excluded. The final study population was 72 patients. 32 patients who did not receive any medication except supplementary vitamin D (800 UI/day) as

the control group, compared with 40 patients in the treatment group who additionally were treated with 20–28 mg daily teriparatide biosimilar (Cinnopar®, CinnaGen pharmaceutical company, Karaj, Iran) for three months post-operatively. After surgery, the patients were allowed to bear weight as tolerated. Postoperative programs, such as physiotherapy for weight-bearing and increasing range of motion were performed in the same manner for all patients.

One year after the surgery, functional assessment was performed using the visual analog scale (VAS) ranging between 0 and 10 as no pain and the maximum imaginable pain, respectively. Clinical outcome was assessed by Harris hip score (HHS) which ranges between 0 and 100 and was graded on a scale: (90–100) excellent, (80–89) good, (70–79) fair, (<70) poor.

Radiographic union of the fracture was defined as bridging at the fracture site by a callus or cortical continuity involving at least two cortices, visible on both Anteroposterior (AP) and lateral radiographic views after 3 months. Reduction failure was defined as varus collapse of more than 15 deg, penetration of femoral head, lag extrusion more than 20 mm, or when a patient underwent a second operation as the reason for implantation failure. Hip axis length (HAL) was measured immediately after surgery and one year post-operatively. HAL is defined as the distance in millimeters from the inferolateral aspect of the greater trochanter to the pelvic inner rim along the long axis of the femoral neck.

Data were analyzed by an independent statistician who was blinded to the group allocation and surgical outcomes. Quantitative data will be presented as mean \pm SD and qualitative data as number and percentage. Student's *t*-test and Chi-square test were used to compare the quantitative and qualitative data between the two groups, respectively. In this study, *P*-value <0.05 was considered as the level of significance.

RESULTS

From September 2016 to October 2019, we prospectively studied 47 females and 33 males who had pertrochanteric hip fractures and underwent reduction and internal fixation with a DHS. Among the participants, eight patients, all in the control group, refused to complete the study. The remaining participants were 32 patients in the control group and 40 ones in the treatment group. The mean age was 66.6 years, ranging from 58 to 83 years. Table 1 shows baseline characteristics including age, sex, body mass index, duration of hospital stay, and stability of the fracture according to Evans classification. There was no significant difference between groups regarding these variables.

At the final follow-up, there was a significant difference between the two groups regarding HHS average score which was 68.38 and 74.12 in control and the treatment groups respectively (*P*-value <0.001). Besides better Harris hip score (HSS) in the treatment group, HSS improvement was also significantly better in the treatment group, one year

post-operatively. VAS score was significantly worse after one year in the control group [Table 2].

Regarding radiographic evidence of union, 26 of 32 (78%) patients in the control group had a good result of bone trabeculation at the last follow-up compared with 28 of 40 (70%) in teriparatide-treated patients that were not statistically different.

Six patients (18%) had reduction failure in the control group which was not statistically different in comparison to the treatment group with eight (20%) reduction failure. Femoral head penetration was not reported in any groups. Lag extrusion was encountered in two patients both in the control group. Varus deformity was reported from four and six patients in treatment and the control group, respectively. The magnitude of femoral shortening based on the HAL index was not significantly different between groups. The magnitude of femoral shortening in those with stable fractures was statistically less than unstable fractures (HAL: 0.87 in unstable versus 0.35 in stable fractures; $P = 0.005$). During the follow-up period no specific complications, such as deep infection, non-union, delayed union or nail cut-out were reported.

DISCUSSION

We showed the positive effect of biosimilar recombinant PTH on pain scores and functional scores in a long-term after surgery. One year after the surgery, there was a significant

difference between the two groups regarding HHS average score which was better in the treatment group. VAS score was significantly worse after one year in the control group.

Since the early return to prior functional levels after pertrochanteric hip fracture is necessary to reduce complications, there is much interest in medical therapies that improve weight-bearing and pain control after surgery.^[17] Many animal studies have demonstrated teriparatide benefits in terms of more rapid fracture healing and callus formation.^[18] Liu *et al.*^[19] reported that subcutaneous injection of Parathyroid hormone-related protein (PTHrP) plays an important role in upregulation of osteoblastic gene and protein expression, increasing endochondral bone formation, osteoblastic bone formation, and osteoclastic bone resorption. The effect of teriparatide in fractures healing in other parts of the body has been studied.

Recombinant teriparatide (Forteo[®], Eli Lilly, USA) has been used in treating osteoporosis and reducing subsequent fracture risk in many studies.^[20,21] Moreover, its beneficial effects on fracture healing have been reported in recent studies.^[17,22-25] Kim *et al.* reported that 2-month daily teriparatide (Forteo[®]) improves HHS as a functional scale and radiographic bone healing especially at 12–16 weeks post-operatively. In addition, it decreased VAS pain scores of hip fractures as well as complication rates.^[25] Tabatabaei-Malazy *et al.*^[26] study demonstrated that there was no difference between the efficacy and safety of teriparatide biosimilar (Cinnopar[®]) to the reference product (Forteo[®]) as an osteoporosis treatment among 104 post-menopausal osteoporotic women. In this study, similar results were obtained one year after using three-month administration of Cinnopar[®] but the study did not show any positive effect of Cinnopar[®] on the union of the fracture site.

In study that examined the weekly use of teriparatide, the short-term use of teriparatide did not improve radiographic signs of fracture healing or functional outcomes.^[24] Huang *et al.*^[17] demonstrated that long-term use of teriparatide (Forteo[®]) for six months is radiologically and functionally effective in pertrochanteric hip fractures of osteoporotic patients. However, due to the high cost of PTH treatment for six month and uncomfortable subcutaneous injection as the only licensed route of administration, the long-term use is encountered with limitations. To overcome this limitation, we used a short-term administration of teriparatide for three months but evaluated the outcomes in a long-term after the surgery: one year post-operatively.

In a systematic review regarding fractures of the pelvis, proximal femur, distal femur, shoulder, wrist, and spine Kim *et al.*^[27] demonstrated that the use of teriparatide had positive effects on radiographic bone healing in six of nine studies. Moreover, on functional recovery, it was related to a decrease in pain or shorter time to mobilization in six studies, but not related with pain numerical scale and mobility in 3. Femoral shortening is a common complication after the operation with DHSs for pertrochanteric hip fractures.^[8,28,29]

Table 1: Age, sex, body mass index, duration of hospital stay, and stability of the fracture according to Evans classification

	Control group (n=32) Mean±SD or n (%)	Treatment group (n=40) Mean±SD or n (%)	P
Sex			
Female	20 (62.5%)	22 (55%)	0.521
Male	12 (37.5%)	18 (45%)	
BMI ¹	29.38±8	29.15±6	0.751
Age (year)	63.56±5	69.70±9	0.103
Hospital stay	4.84±0.4	4.35±0.3	0.163
Evans			
Stable	8 (25%)	8 (20%)	0.612
Unstable	24 (75%)	32 (80%)	
HHS	65.07±3	64.02±6	0.373

¹Body mass index

Table 2: Post-operative clinical and radiologic variables

Variable	Control group (n=32) Mean±SD or n (%)	Treatment group (n=40) Mean±SD or n (%)	P
VAS ¹	3.88±0.08	2.80±0.05	>0.001
HAL change ²	0.52±0.07	0.54±0.08	0.271
HHS ³	75.35±4	85.12±3	>0.001

¹Visual Analog scale, ²Hip axis length, ³Harris hip score

teriparatide (Forteo®) is reported to have an important role in decreasing femoral shortening.^[17] Similarly, in this study the magnitude of femoral shortening was significantly less in those treated with Cinnopar®.

There are some limitations to our study. Though statistically insignificant, we had eight patients who refused to participate in the last follow-up, one year after the surgery and all of them were in the control group. Regarding the only licensed route of Cinnopar administration which is subcutaneous injections, the patients could not be blinded about their medications; because the only route of drug administration for the control group was intramuscular injection for vitamin D. On the other hand, as some of the authors were responsible for post-operative clinical visits, and the patients revealed their use of teriparatide, authors could not be blinded. Hence, we were not able to design a triple-blinded study.

CONCLUSION

In conclusion, the results of this study illustrated that short-term daily administration of Cinnopar® has positive effect on long-term functional outcome after pertrochanteric hip fracture fixation and can be effective in pain reduction but does not have any effect on fracture union and callus formation.

Ethical approval and consent to participant

The authors confirm that they are accountable for all aspects of the work (including full data access, the integrity of the data, and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent to participate

Since this is a retrospective data analysis, hence it does not require any consent of patient participation.

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Conflict of interest

There are no conflicts of interest.

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