

Original Research Article

Effect of teriparatide in fracture healing of intertrochanteric fracture: a prospective study

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ABSTRACT

Background: Intertrochanteric fracture is a relatively common and serious medical issue in geriatric trauma result in serious health problems and decrease health related quality of life. Faster time-to-union is important for early return to daily activities and reduction of complications. Teriparatide has been shown to accelerate fracture-healing. The purpose of the present prospective, randomized, controlled study was to evaluate the effect of teriparatide on the course of intertrochanteric fracture-healing.

Methods: Forty patients of intertrochanteric fractures who underwent surgical intervention between June 2016 and May 2017 were enrolled in this prospective study and followed for minimum of six months. Group A included patients who received only calcium supplementation; patients in Group B received teriparatide along with calcium supplementation postoperatively.

Results: The mean time to fracture healing was between 8-12 weeks for the treatment group, compared with 12-16 weeks for the control group. There was also significant effectiveness with regards to Parker and Palmer mobility score at 6 months.

Conclusions: Postoperative use of teriparatide for 6 months appears to be an effective adjunct therapy in the treatment of patients with intertrochanteric fractures. However, because of the limited power of the study a large-scale cohort study is still required for determining the efficacy of teriparatide.

Keywords: Teriparatide, Fracture healing, Intertrochanteric fracture

INTRODUCTION

Hip fractures related to osteoporosis are a serious medical problem and a burden on the healthcare system.¹⁻³ Complications after osteoporotic hip fractures 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 2050.⁴⁻⁷ In many patients osteoporosis and hip fractures both leads to significant functional loss, poor health-related quality of life and higher mortality rate.⁸⁻¹⁰ Fast union is important for early return of daily activities and reduction of complications.

Usually surgery is indicated, but pain relief, early weight-bearing and an early return to daily activities is of critical importance to avoid complications in geriatric patients remains a challenge for orthopaedic surgeons.⁶⁻⁷

Fixation with an extramedullary or intramedullary device is the standard treatment for these fractures but stability of fixation depends on the quality of bone.^{11,12} Even after achieving good reduction and optimal positioning of the implant, failure rate in osteoporotic bone is higher than those in normal bone because of age-related decreases in bone regenerative capacity and poor bone stock.^{6,7,13,14} Recombinant parathyroid hormone (Teriparatide) is the

only anabolic medication that has a proven efficacy in stimulating bone formation in addition to promoting growth factors production for fracture healing. Studies have shown that Teriparatide can play an important role in the treatment of these fractures.^{6,15-17} In some human trials; it appears to lessen the risk of nonunion and enhance fracture healing.^{18,19-21}

Aim of this study is to assess whether teriparatide accelerates fracture healing in cases of osteoporotic intertrochanteric femur fractures using a prospective analysis of 2 groups of elderly patients, one that received only calcium supplementation and another that received teriparatide with calcium supplementation therapy.

METHODS

This prospective randomized controlled study was hospital based and was conducted at Department of Orthopaedics, Maharaja Agrasen Hospital, New Delhi. Patients were selected from those who attended the emergency and outpatient department. Written informed consent was obtained from all the patients or their family for participation in the study. For this study we recruited 40 patients of intertrochanteric fracture presented to our hospital between June 2016 to May 2017 and followed for minimum six months. Patients were enrolled based on inclusion and exclusion criteria. Patients of intertrochanteric fracture of age of 50 years and above with mental status consistent with completing the study protocol were included. They were excluded if they have diseases other than primary osteoporosis that affect bone metabolism or responses to therapy, known allergy to teriparatide, who are unfit for surgery due to the associated comorbidities and patients who are taking any antiresorptive drug like bisphosphonate prior to fracture. After enrolment, group assignments were determined by a computer-generated number sequence and were contained in sequentially numbered opaque envelopes to ensure blinding. Two groups (A and B) were made each of twenty patients. Group A patients received only calcium supplementation postoperatively while Group B patients were given teriparatide therapy along with calcium supplementation. Participants had to be willing to satisfactorily use a pen-type delivery system or be willing to receive daily subcutaneous injections from a care partner trained to use the injector.

The primary objective of the study was to evaluate the difference in rate of fracture union amongst post-operative intertrochanteric fracture patients with or without teriparatide therapy. Since the study was time bound, all consecutive patients meeting the eligibility criteria during the study period were enrolled. It was expected from the previous experience that 20 per group would be enrolled.

The formula for calculated sample size is given below:

$$n = \frac{[z_{1-\frac{\alpha}{2}} \sqrt{2P(1-P)} + z_{1-\beta} \sqrt{\{P_1(1-P_1) + P_2(1-P_2)\}}]^2}{(P_1 - P_2)^2}$$

Where P_1 = Anticipated proportion of union rate with teriparatide therapy;

P_2 = Anticipated proportion of union rate without teriparatide therapy;

On admission to the institution, thorough history about mode of injury, associated injuries, previous medical and surgical history and pretrauma ambulation were documented for each patient. Clinical examination, neurovascular status and radiological assessment of the fractured limb was done. The injured extremity was splinted in a Thomas splint with skin traction. Patients were investigated further depending on the general condition and co-morbidity of the patient and routine pre-operative protocol was followed as per our hospital guidelines. Preoperatively, all patients had radiographic examinations including antero-posterior (AP) view of pelvis and AP and lateral views of the affected hip. Fractures were classified according to AO classification for proximal femoral fractures. Osteosynthesis with intramedullary device was chosen as it is the standard treatment for fixation of intertrochanteric fractures in our institute. In our study we used proximal femoral nail (PFN) as intramedullary implant. In order to minimize the implant related confounding factors patients treated with extramedullary devices such as dynamic hip screw (DHS) were not included in this study. To minimize drug related variables, patients who were taking antiresorptive drugs prior to fracture were excluded. Patients were operated following the surgical principles including fracture reduction and Tip apex distance (TAD). Group A patients received calcium supplementation postoperatively and Group B patients were advised to take daily subcutaneous injections of 20 micro gram teriparatide for 6 months starting from 2nd post op day along with calcium supplementation.

Follow up

Patients were followed at 2 weeks of surgery for stitch removal and clinical assessment, at 4 weeks and then at 4 weeks interval till 6 months. During the follow up radiographic examinations done including anteroposterior (AP) view of pelvis, AP and lateral views of the affected hip at 4 weeks and then at every follow up visit until fracture united. Assessment of functional status done by Parker and Palmer hip mobility scoring at 6 months post op and assessment and analysis of any complications observed.

Fracture union was defined as recanalization of the trabeculae or visible bridging callus on both radiograph views; delayed union is defined as no signs of fracture healing for 24 weeks; and nonunion is defined as the absence of bone union 36 weeks postoperatively.¹² The

tip-apex distance was measured using AP and lateral radiographs of the affected hip.¹²

Parker and Palmer hip scoring system

This mobility score consider three specific factors, which include the patient's ability to ambulate within their place of residence, the ability to ambulate outside, and the ability to go shopping. Independence of walking at 6 months (using Parker and Palmer mobility scoring system) was used for the assessment of functional status in the post operative period (Table 1).

Statistical method

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean \pm SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test. Categorical variables were analyzed using either the chi

square test or Fisher's exact test. For all statistical tests, a 'P' value less than 0.05 was taken to indicate a significant difference.

RESULTS

The study consists of 40 patients of intertrochanteric fractures treated with intramedullary nailing (Proximal femoral nail) divided into 2 groups of 20 each. Post operatively, 20 patients (Group A) were given only calcium and other 20 patients (Group B) were given Teriparatide therapy along with calcium.

Average age of patients with intertrochanteric fractures was 74 years. It was found that age distribution between the two groups was comparable and there was no statistically significant difference between two groups. Majority of patients in our study were females (29 out of total 40 patients =72.5%) and rest 11 patients were male. In group A, 75% (15) of patients were females while in group B, 80% (16) of patients were females. The difference in gender distribution in between two groups was not significant (Table 2).

Table 1: Parker and Palmer hip scoring system.

| Mobility | No aid | With an aid | With help from another person | Not at all |
|------------------------------|--------|-------------|-------------------------------|------------|
| Able to get about the house | 3 | 2 | 1 | 0 |
| Able to get out of the house | 3 | 2 | 1 | 0 |
| Able to go shopping | 3 | 2 | 1 | 0 |

Table 2: Demographic profile of patients.

| | Group A | | Group B | | P value |
|---------------------------|-----------|----|-----------|----|---------|
| | Frequency | % | Frequency | % | |
| Age groups (years) | | | | | |
| <70 | 7 | 35 | 9 | 45 | 0.867 |
| 71-80 | 7 | 35 | 7 | 35 | |
| 81-90 | 4 | 20 | 3 | 15 | |
| >90 | 2 | 10 | 1 | 5 | |
| Gender | | | | | |
| Female | 15 | 75 | 16 | 80 | 1.000 |
| Male | 5 | 25 | 4 | 20 | |

Table 3: Fracture union time.

| Union in weeks | Group A | | Group B | | P value |
|----------------|-----------|-----|-----------|-----|---------|
| | Frequency | % | Frequency | % | |
| <8 | 0 | 0 | 3 | 15 | 0.008 |
| 8-12 | 2 | 10 | 9 | 45 | |
| 12-16 | 11 | 55 | 6 | 30 | |
| 16-24 | 7 | 35 | 2 | 10 | |
| Total | 20 | 100 | 20 | 100 | |

Out of 40 patients, 36 were due to simple fall, 2 were due to fall from height and 2 were due to road traffic accident.

All of them were closed injury. The distribution in two groups was also comparable. We classified

Intertrochanteric Fracture according to the AO Group Classification. Maximum numbers of patients were classified in Group A2 (24 patients out of 40). The distribution of the fracture pattern in between two groups was comparable and there was no significant difference in between the groups.

In our prospective study, union time in majority of the patients of Group A (55%) was 12-16 weeks while in majority of the patients of Group B (45%), it was less, i.e. 8-12 weeks. It was found that the difference in fracture union time between two groups was statistically significant (Table 3).

In some patients, we observed complications which were either related to surgery, implant related or fracture healing. Pulling out of screw from neck was observed in one patient of group A. Post op shortening of 0.5 - 1.5cm was found in 4 patients of Group A and 3 patients of Group B. Varus collapse was seen in 2 patients of Group A. Overall, the difference in complications between two groups was not statistically significant.

Parker and Palmer mobility scores at 6 month

In our study, mean mobility score at 6 months in Group A came out 5.5, while in Group B mobility score was 7.15. The difference of the Parker mobility score at 6 months between the two groups was statistically significant (Table 4).

Table 4: Parker and Palmer mobility scores at 6 month.

| | Group A | Group B | P value |
|------------------------------|-----------|-----------|---------|
| | Mean±SD | Mean±SD | |
| Parker mobility score | 5.50±1.51 | 7.15±1.31 | <0.001 |

DISCUSSION

Proximal femoral fractures are the frequent injuries affecting elderly patients with osteoporosis and are a burden for the individual, their family, and the health-care system.^{4,5} Pain and immobility due to these fractures lead to a loss of functioning in daily activities and loss of quality of life and are associated with high morbidity and mortality.^{6,7} The primary goals in treating intertrochanteric fractures in these patients are pain relief, improvement of mobilization, and prevention of complications associated with comorbidities. Non operative treatment has little or no role in definitive treatment of these fractures and has high mortality rate; hence surgical fixation is the treatment of choice.²²⁻²⁵

Even with the improvement in implant design, implant choices, and surgical techniques, intertrochanteric fractures still carry a mortality rate ranging from 2.49%

to 33% at one month to one year and constitute a major socioeconomic problem.^{4,5}

To date, no systemic treatment is approved for fracture healing. Impaired healing of fractures delays the rehabilitation process, which influences life quality of the patients. At the same time, the associated costs cause an economic burden to both the society and the patients. Faster time of union is important for early return of daily activities and reduction of complications. This prospective study demonstrated that Teriparatide fastens the fracture union and improves functional outcome in postoperative patients of intertrochanteric fracture and there was significant difference in between the two groups.

Previously, Teriparatide appeared effective in improving BMD and reducing the rate of subsequent osteoporotic fracture.¹⁸ In past 20 years, many studies on animals and humans have been done regarding role of Teriparatide in fracture union.^{20,26} Only a few studies have been done in India on clinical use of teriparatide in fracture healing, where cost is a major factor. The study done at our institute was a prospective design comprising of 40 patients, of them 29 were females and 11 were males (2.63:1) which was comparable to other studies on intertrochanteric fractures like Gardenbroek et al, Simmermacher et al (3.3:1).^{27,28} Significant female dominance may be attributed to the fact that osteoporosis sets in after menopause in many females and proximal femoral fractures are on rise. The average age of the patients having intertrochanteric fracture in our study was 74 years which was comparable to other studies like Gardenbroek et al (79.1 yrs) and Simmermacher et al (80.6yrs).^{27,28} Majority of patients in our study sustained a fracture due to minor trauma, which is in accordance with other major studies. This may be attributed to poor bone quality in the elderly patients, loss of mental faculties and high stresses in the proximal femur region.

Our study included all the 3 types of fractures according to AO classification with majority of patients in A2 group. This trend of maximum patients in the A2 group is consistent with the international studies like Gardenbroek et al and Simmermacher et al.^{27,28} This may be attributed to the inherent geometry and stress pattern of the proximal femur.

In our study, we analysed that Teriparatide has significantly reduced the time of fracture healing and improved the functional outcome at 6 months compared with that in the control group of patients given only calcium replacement therapy. Huang TW et al in their study also analysed that union time was significantly reduced in teriparatide treated group.²⁹ Lau et al in their study concluded that patients who were treated with teriparatide had statistically significant difference in radiological fracture healing time compared with the control group.³⁰ The overall complication rate was not significantly different in two groups. In our study, there

was a significant difference in the mobility scores in between two groups and showed better functional outcome in teriparatide treated group. Similar results were shown in study by Huang et al.²⁹

As teriparatide therapy can promote osteoporotic fracture healing and improve function outcome, we suspect that teriparatide may prove to be useful in the stimulation of implant anchoring and fixation. Likewise, it may prove to be useful in fractures which have a high risk of delayed union or non-union.

Several limitations in this study must be acknowledged. Sample size and duration of the study was very small. In view of very limited studies on the role of teriparatide in fracture healing of intertrochanteric fractures, the outcome could not be compared with literature. All the patients in our study were treated by proximal femoral nailing. We do not know whether the adding of teriparatide could also benefit the patients treated with extramedullary implant like dynamic hip screw. The strict inclusion criteria for this study were designed to limit the variables in the study, but it also reduced the numbers of subjects and limited the power of the study to detect a clinically significant difference.

CONCLUSION

This prospective randomized controlled study shows statistically significant faster fracture healing and better functional outcome in the intertrochanteric fracture patients group treated with teriparatide therapy. The faster union may be important for elderly patients with intertrochanteric fractures to enable them to return to daily activities and reduce morbidity and mortality. However, a randomized, large-scale cohort study is still necessary to determine the efficacy of teriparatide in intertrochanteric fractures.

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Ethical approval: The study was approved by the institutional ethics committee

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