

The Role of Postoperative Bisphosphonates Therapy in Union Time and Functional Outcome in Intertrochanteric Fracture of Femur

Khan N,¹ Pradhan RL,² Pandey BK,² Khanal KR,² Rijal KP,² Manandhar RR,² Sharma S,² Prasai T,² Gautam S²

¹Department Of Orthopaedic Surgery

Lumbini Provincial Hospital,

Butwal, Rupandehi, Nepal.

²Department of Orthopedic Surgery,

Kathmandu Medical College Teaching Hospital,

Sinamangal, Kathmandu, Nepal.

Corresponding Author

Nazir Khan

Department of Orthopedic Surgery,

Lumbini Provincial Hospital,

Butwal, Rupandehi, Nepal.

E-mail: drkhannazir@gmail.com

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ABSTRACT

Background

Intertrochanteric fracture of femur is one of the commonest injuries sustained by elderly people. It comprise approximately half of all hip fractures caused by low energy trauma in elderly population while in case of younger patients, it is due to high energy trauma. At present, surgical fixation of fracture is the primary treatment for intertrochanteric fractures. However, many studies have shown that anti-osteoporosis therapy like bisphosphonates may be better for postoperative rehabilitation, functional outcome and long-term survival. We analyzed the clinical results of bisphosphonate therapy in surgically treated intertrochanteric fractures.

Method

A Prospective comparative hospital based clinical study was conducted at Department of Orthopedic Surgery, Kathmandu Medical College Teaching Hospital from January 2018 to July 2019. A total of 36 patients (14 male and 22 female) with surgically treated intertrochanteric fracture of femur were enrolled. Patients were randomly divided into study or control groups (18 cases in each group) according to the even or odd date of admission as per Nepali calendar. Patients in both groups were treated by proximal femoral nail (PFN). In the study group, patients received 5 mg zoledronic acid intravenously on 3rd postoperative day. The functional outcome and union was evaluated at 3 weeks, 6 weeks, 3 months and 6 months with Harris hip score and RUSH score.

Result

Fracture healed more quickly in patients treated with zoledronic acids than those in control group [(12.77 ± 1.89) vs (15.86 ± 0.94) weeks, p=0.040]. No significant differences were found between the two groups in regard of HHS scores at any period of follow-up. The RUSH score of the patient in between two groups at 3 months follow-up [(23.16 ± 0.85) vs (20.33 ± 3.32), p=0.000] and 6 months follow-up [(29.11 ± 1.23) vs (26.88 ± 2.51), p=0.002] were statistically significant. Two cases of influenza like symptoms in study groups but no other major complications.

Conclusion

Zoledronic acid injection is a safe and effective treatment option for the elderly patients with osteoporotic intertrochanteric fracture who are treated surgically. It can improve functional outcome and promote earlier fracture healing with few complication.

KEY WORDS

Functional outcome, Injection zoledronic acid, Intertrochanteric fracture, Proximal femoral nail, Union

INTRODUCTION

Intertrochanteric (IT) fracture of femur is one of the commonest injuries sustained by elderly people.¹ The IT fracture of femur comprise approximately half of all hip fractures caused by low energy trauma in elderly population while in case of younger patients, it is due to high energy trauma.^{2,3} Intertrochanteric fractures are of intense interest globally as it has led to high morbidity, mortality and disability rates with high degree of pain and an overall negative impact on quality of life.⁴⁻⁷ They are the most operated fracture type and have the highest postoperative fatality rate among the surgically treated fractures. Due to the high cost of care required after the injury, IT fractures have become a serious extensive healthcare resource consuming fracture.^{4,8,9} Management of IT fractures of femur has been recognized and considered as a major challenge faced by the Orthopedic community, especially when elderly patients with osteoporosis have a high prevalence of unsatisfactory functional results not solely for achieving fracture union, but also for restoration of optimal function in the shortest possible time and with minimal complications.^{10,11} The aim of management accordingly has drifted to achieving early mobilization, rapid rehabilitation and quick return of individuals to pre-morbid home and work environment as a functionally and psychologically independent person.¹² At present, surgical fixation of fracture is the primary treatment for intertrochanteric fractures. However, many studies have shown that anti-osteoporosis therapy like bisphosphonates may be better for postoperative rehabilitation, functional outcome and long-term survival.⁵

Bisphosphonates are the most commonly used drug in patients suffering from and at higher risk of developing osteoporosis, as well as less common conditions affecting bone turnover.^{7,13,14} Bisphosphonates are most popular and powerful anti-resorptive and anti-fracture agent used in osteoporosis. They work by inhibiting osteoclast mediated bone resorption and subsequently inducing osteoclast apoptosis.¹⁵ They have been shown to reduce bone turnover rate, increase bone mineral density and promote fracture healing. They are preferentially incorporated into sites of active bone remodeling and inhibit apoptosis of osteocytes and osteoblast.¹⁵⁻¹⁸ It has been shown to relieve bone pain, increase bone density, improve quality of life and promote fracture healing and longtime survival.⁵

The objective of this study was to observe the role of the postoperative bisphosphonates therapy in terms of union time and functional outcome in intertrochanteric fracture of the femur.

METHODS

Under ethical approval from institutional review committee (IRC) of Kathmandu medical college teaching hospital (KMCTH), a prospective comparative hospital based clinical

study was conducted at Department of Orthopedic Surgery, KMCTH from January 2018 to July 2019.

We used prevalence of cases of intertrochanteric fracture of femur treated with Proximal Femoral Nail (PFN) in our hospital. In a month, there were total 3 cases of IT fracture treated operatively meeting criteria and hence total 36 cases in study time period (18 cases each in study group and control group).

All patients with stable intertrochanteric fracture of femur (Boyd and Griffin type I and type II), age 50 year and above fixed with Proximal Femoral Nail (PFN) were included in study. Patient hypersensitive to bisphosphonates, treated with dynamic hip screw (DHS), not giving informed consent, deranged RFT, abnormal calcium and phosphorous level, poly-trauma were excluded from study.

Patients admitted on the odd day of Nepali calendar were taken into study group and even day were taken into control group.

Patients in both groups were treated by proximal femoral nail (PFN). All the patients were engaged in joint motion and muscle strength exercise in bed on the first day after surgery. Three day later, walking assistance were recommended. Weight-bearing exercise depends on the fracture type and the stability after reduction. In the study group, given a normal renal function test (RFT) and normal calcium level, patients received zoledronic acid 5 mg/100 ml via intravenous drip on 3rd postoperative day. The patients took tablet paracetamol 1 gm prior to infusion and continuing 6 hourly into the next day after the infusion. A 1000 ml normal saline solution was given over 15-30 minutes before the zoledronic acid injection and next 500 ml of normal saline solution over 30 minutes after zoledronic acid. The functional outcome was evaluated with Harris hip score and union was evaluated with RUSH score at 3 weeks, 6 weeks, 3 months and 6 months.

Harris hip score (HHS) is used to measure the function at the hip joint. The domains of HHS covered are pain, function, absence of deformity, and range of motion. Standard scores of > 90, 80-90, 70-79, and < 70 were indicative of excellent, good, acceptable, and poor function respectively.^{19,20}

The Radiographic Union Score for Hip (RUSH) score is designed to describe radiographic healing of fracture around hip such as femoral neck fractures and intertrochanteric fracture.^{6,21} It is a checklist-based system that quantifies four measures of healing which includes cortical bridging, cortical disappearance, trabecular consolidation, and trabecular disappearance.¹² The overall RUSH score ranged from a minimum of 10 to a maximum of 30 and scores below 18 were 10 times more likely to undergo a nonunion reoperation than individuals with higher scores.^{6,22,23}

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 23 for Windows. Independent sample t-test was applied to assess the

statistical significance of resultant variables. The p value < 0.05 was considered statistically significant.

RESULTS

The study cohort consists of 36 cases, 14 males and 22 females. Comparison of the pretreatment baseline data are shown in Table 1.

Table 1. Pre-treatment baseline data

Baseline data	Control group (n=18)	Study group (n=18)	P-value
Age (years)	81.44 ± 13.395	74.61 ± 10.711	0.612
Gender (Male/Female)	12/6	10/8	0.230
Fracture classification			
Boyd and Griffin I	4	4	
Boyd and Griffin II	14	14	
Involved side (Right/Left)	9/9	8/10	
Mechanism of injury			
Fall from height	8	3	
Fall from standing height	7	11	
Fall from bed	2	4	
RTA	1	0	

At any post-operative follow up period, no significant difference was found between the two groups in terms of HHS (table 2). Likewise, in terms of the grade of the HHS, there was no significant difference between two groups (table 3).

Table 2. Mean Harris Hip Score

HHS	Control group (Mean ± SD)	Study group (Mean ± SD)	P-value
3 weeks	22.33 ± 0	22.55 ± 0	0.266
6 weeks	43.61 ± 2.22	44.11 ± 2.98	0.544
3 months	68.22 ± 4.79	73.11 ± 5.18	0.758
6 months	81.38 ± 5.28	87.05 ± 5.75	0.247

Table 3. Grade of HHS

Group	Follow-up	Poor	Fair	Good	Excellent	Total	P-value
Control group	3 months	10 (55.6)	8 (44.4)	0 (0)	0 (0)	18 (100.0)	0.427
Study group	3 months	5 (27.8)	12 (66.7)	1 (5.6)	0 (0)	18 (100)	
Control group	6 months	0 (0)	7 (38.9)	9 (50)	2 (11.1)	18 (100.0)	1.000
Study group	6 months	0 (0)	2 (11.1)	9 (50)	7 (38.9)	18 (100.0)	

After 3 months of follow-up, the study group showed significantly higher RUSH score than that of the control group (table 4).

Table 4. Mean RUSH Score

RUSH score	Control group (Mean ± SD)	Study group (Mean ± SD)	P-value
3 weeks	10 ± 0	10 ± 0	NA
6 weeks	12.83 ± 0.98	15.05 ± 1.35	0.89
3 months	20.33 ± 3.32	23.16 ± 0.85	0.00
6 months	26.88 ± 2.51	29.11 ± 1.23	0.02

The fracture union was greatly expedited in study group with significant difference found between the two groups in term of union time (p = 0.040, table 5).

Table 5. Union time

Time of union (Weeks)	Group	N	Mean ± SD
Time of union (Weeks)	Control group	18	15.86 ± 0.94
	Study group	18	12.77 ± 1.89

There was no significant difference in two groups in terms of complication after the treatment (p=0.148, table 6). Total of 7 patients (19.44%) developed postoperative complications. Among 18 patients in study group, 2 patient developed influenza-like symptoms such as fever, feeling feverish/chills, cough, sore throat, runny or stuffy nose, malaise or body aches, headaches, fatigue (tiredness). During the 6-month follow-up, no new fractures or femoral head necrosis were observed in both the groups.

Table 6. Complications

Complications	Control group	Study group	Total
Anemia required blood transfusion	1	1	2
Superficial infection	2	1	3
Influenza-like symptoms	0	2	2
None	15	14	29

p=0.148

DISCUSSION

Intertrochanteric fracture of femur is a common osteoporotic fracture among the elderly population leading to high morbidity, mortality and disability rates in the elderly population.^{5,8} Second only to cardiovascular and cerebrovascular diseases and far beyond the mortality rate of cumulative malignancies, death related to osteoporotic hip fracture is high on the survey list of mortality rates among the elderly. Because of the high mortality and disability rates pertaining to intertrochanteric fracture of femur, in recent year treatment has been intensified to combination of surgical fixation of fracture along with bisphosphonates therapy. We evaluated the clinical results of bisphosphonate therapy in terms of union time and functional outcome in surgically treated intertrochanteric fractures.⁵

Due to the bone pain, patients with intertrochanteric fracture of femur experience limited physical activity, diminished physical function and decreased ability of self-care. These factors often cause anxiety to the patients and bring a burden to their family. At final (6 months) postoperative follow-up period, no significant difference was found between the two groups in the Harris hip scores of the affected hip (87.05 ± 5.75 vs 81.38 ± 5.28 , $p = 0.247$) in our study which is comparable to study of Li et al. (81.12 ± 7.9 vs 81.62 ± 5.4 , $p = 0.219$) and Cengiz et al.^{5,24} Although there is no significant difference in term of Harris hip score, we found that the study group exhibited more obvious improvement in terms of Harris hip score and grade of Harris hip score in each follow-up period.

In our study, for the patients taking zoledronic acid (study group), the average union time was 12.77 ± 1.89 weeks and for control group 15.86 ± 0.94 weeks ($p = 0.040$). So the union time of fracture in study group decreases by around 20%. Similarly Li et al. found that zoledronic acid reduced fracture union time by 13.5% ($p = 0.02$) and also study by Kim et al. found that zoledronic acid in osteoporotic patients with spinal fusion shortens the time to fusion and improves the fusion rate at 3 months, 6 months and 9 months follow-up comparing to control group ($p < 0.05$).^{5,25} A study by Chen et al. also found that treatment with zoledronic acid in osteoporotic patients with spinal fusion shortens the time to fusion, improves the fusion rate and improves clinical outcomes. They found that Grade A or B bridging bone was more frequently observed in zoledronic acid group at 3, 6, and 9 months post-operation compared to the control group ($p < 0.05$).¹⁶ However, the clinical results and influence of bisphosphonates on fracture healing is controversial.³ A few study had shown about possible negative effect of bisphosphonates therapy on

fracture healing. A study by Molvik et al. did a literature review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines including all relevant articles with information on bisphosphonates effect on fracture healing in humans found via MEDLINE, Cochrane, CINAHL, EMBASE and Google Scholar and found that bisphosphonates significantly prolong union times of distal radius fractures but not femoral fractures.³ Prasarn et al. reports high complications and prolong union time in patients with femur fracture receiving zoledronic acid compare to control group (26 weeks vs 19 weeks).²⁶ We did not find any cases with negative effect of zoledronic acid on fracture healing and prolonged union time. We found it to be promising drug in promoting early fracture healing in surgically treated intertrochanteric fracture.

Influenza like symptoms are known to be complications associated with zoledronic therapy.^{27,28} We also observed 2 cases with such symptoms but no major complications. It has also been shown to have other serious side effects like renal failure, osteonecrosis of jaw, hypocalcemia, gastric intolerance, atypical femur fracture, atrial fibrillation, esophageal cancer, inflammatory eye disorder and impaired fracture healing.^{29,30} We did not find any cases with such complications. We found it to be a safe treatment option provided utmost care be ascertained especially in terms of maintaining hydration to prevent the serious complications associated with zoledronic acid therapy.

CONCLUSION

Zoledronic acid injection is a safe and effective treatment option for the elderly patients with surgically treated osteoporotic intertrochanteric fracture. It can shorten the union time and give good functional outcome.

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