

Original Research Article

Effect of zoledronic acid on functional outcome in cases of pertrochanteric femoral fractures in elderly patients operated with proximal femoral nailing

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Received: 08 April 2023

Revised: 17 May 2023

Accepted: 31 May 2023

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ABSTRACT

Background: Osteoporosis is a very common problem in geriatric population and postmenopausal women. Zoledronic acid injection is a very convenient and effective treatment option available for osteoporosis. Our study aimed to study the effect of zoledronic acid on functional outcome and fracture related complications in elderly patients with low energy pertrochanteric femoral fractures who were operated with proximal femoral nail.

Methods: This was a case control study. Elderly patients who underwent surgery in the form of proximal femoral nailing for low energy pertrochanteric femoral fractures were included. Injection zoledronic acid was given to every alternate patient who underwent surgery. Radiological healing was evaluated at six weekly intervals for six months and then 12 weekly intervals for one year. The Harris hip score was used to measure the functional outcome of the patient.

Results: Effective study population consisted of total 49 patients (25 cases and 24 controls). The mean union time in the cases and the control was 8.76±9.12 weeks and 7.04±1.57 weeks respectively. The mean Harris hip score was 86.742±7.55 in the cases and 84.339±11.20 in the control group. The p value was 0.3815. This study concluded that the two groups had no statistically significant difference between functional outcome and fracture related complications.

Conclusions: Zoledronic acid in patients admitted for surgery with osteoporotic fracture does not improve the functional outcome of the patients. It does not affect the mortality of the patients.

Keywords: Functional outcome, Harris hip score, Low-energy pertrochanteric fractures Osteoporosis, Zoledronic acid

INTRODUCTION

Osteoporosis is a metabolic bone disease which is characterized by low bone mineral density (BMD) and microstructure damage to bone tissue. This results in increased bone fragility thereby increasing the risk of fractures, specifically the risk of low energy fractures that occur following trivial trauma.¹⁻³ Primary osteoporosis mainly occurs in postmenopausal women and elderly men. Osteoporosis can be effectively treated even after the first fracture has occurred, so that the risk of further fractures

can be minimised. Hip (pertrochanteric region) fractures are the most common among osteoporotic fractures next to the vertebral fractures. Hip fractures are associated with an 8 to 36% excess mortality within 1 year.^{2,4,5} They are also associated with a 2.5 times increased risk of future fractures. In low-income countries like India where people are less aware of underlying osteoporosis DEXA scan is not available at most places and cost related is not borne by all, patients usually do not consult physician unless fractures occur.^{2,6-8} Thus it is better to empirically treat all the elderly patients with fractures for underlying

osteoporosis. Zoledronate is the most potent bisphosphonate with a long-lasting effect. Several studies have shown that bisphosphonates increase the BMD and reduce the risk of vertebral, non-vertebral, and hip fractures.^{9,10} Nevertheless, bisphosphonates are not recommended in patients with acute fractures because they have been found to delay the process of fracture healing and suppress remodelling of the callus in some studies.¹¹ However, some clinical studies have shown no negative influence of bisphosphonates on fracture repair rather they showed to produce larger and stronger callus. Intravenous zoledronic acid 5 mg given once a year for 1 year after a hip fracture reduces secondary fracture rates and mortality but its effect on the functional outcome has not been well studied.¹² Aim of this study was to assess the effects of injection zoledronic acid supplementation on the functional outcome of patients with low energy pertrochanteric fractures undergoing proximal femoral nailing.

METHODS

This is a case-control study. This study was conducted in the department of orthopedics of Sanjay Gandhi Memorial Hospital and Shyam Shah Medical College, Rewa, Madhya Pradesh, India from August 2018 to February 2021. The authors declare that this submission was in accordance with the principles laid down by the responsible research publication position statements as developed at the 2nd world conference on research integrity in Singapore, 2010. Prior to commencement of the study ethical approval was obtained from the following ethical review board: institute ethics committee, SS Medical College, Rewa, Madhya Pradesh. with approval number 04/SS/MC/18 Rewa, dated 26.02.2018. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2008. Informed written consent was obtained from all patients for being included in the study. Consent was obtained from patients for the use of clinical photographs and these images were adequately anonymized.

Elderly patients who underwent surgery in the form of proximal femoral nailing after a well-informed consent for osteosynthesis of low energy pertrochanteric femoral fractures were considered as study subjects. The fractures are classified using the AO (Arbeitsgemeinschaft für Osteosynthesefragen) system (AO/OTA 31-A1, A2 and A3). The patients who met the inclusion criteria were enrolled in the study. The documentation protocol of each case included demographic data of each patient along with the main features of the fracture, details of the surgery and of the immediate postoperative radiological images. Preoperatively, written and informed consent about surgery and medication was obtained from the patients. Closed or minimal open reduction and internal fixation of fracture with proximal femoral nail was performed under image intensifier guidance. The operation was performed

by the same surgical team. At 1st postoperative week, an infusion of zoledronic acid (5 mg intravenously) was given to every alternate patients (to about half of all patients). A 1000 ml balanced salt solution was given before the zoledronic acid injection (5 mg/100 ml, infusion time 15 minutes). Postoperatively, oral 1200 mg calcium citrate + calcitriol 0.25µg/ day supplementation was started and continued for 3 months.

Initially, 65 patients were enrolled in the study. Out of these 65, a total of 10 patients (5 cases and 5 controls) died during the follow up period of the study. Also, 2 patients from the case group and 4 patients from the control group were lost to follow-up. Thus, the effective study population consisted of total 49 patients (25 cases and 24 controls), where cases are defined as patients who have received zoledronic acid and controls are the patients who have not received zoledronic acid. Study duration was of 3 years including treatment phase of 18 months, follow-up phase of 12 months and 6 months of analysis and study submission.

Inclusion criteria

Inclusion criteria of the study was (1) Patients above 60 years of age; (2) patients with low energy pertrochanteric femoral fractures (AO type- 31-A1, A2 and A3) that occur after trivial trauma and are willing to undergo proximal femoral nailing with or without subsequent supplementation of zoledronate (3) patients operated within 3 weeks of a fracture and (4) normal kidney function tests and (5) normal blood calcium levels.

Exclusion criteria

The exclusion criteria of the study was (1) non-osteoporotic pathological fractures; (2) high energy fractures; (3) chronic use of glucocorticoids; (4) patients receiving hormone replacement therapy and (5) conditions associated with low bone density (e.g. rheumatoid arthritis, cystic fibrosis, Parkinson's disease etc.).

Radiological healing was evaluated at six weekly intervals for six months and then twelve weekly intervals for 1 year. The progress of union was evaluated based on the presence of bridging callus and cortical continuity in antero-posterior and lateral radiographs of the fracture site. Radiographic union is defined as the presence of bridging of trabeculae or osseous bone in three of four (medial, lateral, anterior, and posterior) cortices. In each evaluation of the union of intertrochanteric femur fractures, the images were interpreted by two orthopedic surgeons. In cases where no agreement could be reached on the union by the two observers, the mean union time was used as a representative value.

The Harris hip score was used to measure the functional outcome of the hip joint. Standard scores of ≥ 90 , 80-90, 70-79, and ≤ 70 were indicative of excellent, good, acceptable, and poor function, respectively. Statistical

analysis is done using GraphPad Prism. Data was represented as the mean±standard deviation, and Student’s t-test was used to conduct between-group comparisons. The Chi-square test was used to examine differences between categorical variables. Any result with a p value below 0.05 was deemed statistically significant.

RESULTS

This study consisted of effective population of total 49 patients (25 cases and 24 controls), out of which there were 10 males and 15 females in cases and 8 males and 16 females in control group. In age wise distribution 15 patients of cases and 10 of the control group were of age between 60 to 69 years. 7 patients of cases and 6 of the control group were of age between 70 to 79 years. 3 patients in cases and 8 in control group were of more than

80 years old. 6 patients of cases and 3 of control had AO type 1 pertrochanteric fracture, 15 patients of cases and 12 of control had AO type 2 fracture and 4 patients of cases and 9 of control had AO type 3 fracture.

The functional outcome of the patients of both the groups was compared at the end of 1 year using the mean Harris Hip score which was 86.742±7.55 in the cases and 84.339±11.20 in the control group. The difference in the functional outcome is not significant with a p value of 0.3815. At the end of 6 months, all the patients in both the groups showed signs of union on the radiographs except 1 patient from the case group who showed delayed union and the fracture eventually united by the end of 1 year. The mean union time in the cases and the control was 8.76±9.12 weeks and 7.04±1.57 weeks respectively with a p value of 0.3676.

Table 1: Comparison of two groups in different variables.

Parameter	Case (N=25)	Control (N=24)	P value
Age (Mean ± SD)	67.40±7.44	73.58±7.78	0.0066
No. of patients in each age group	60-69	15	10
	70-79	7	6
	80 Above	3	8
Sex	Male	10	8
	Female	15	16
AO Type	A1	6	3
	A2	15	12
	A3	4	9
Harris hip score	86.742±7.55	84.33±11.20	0.3815
Union time in weeks	8.76±9.12	7.04±1.57	0.3676
Harris hip score categorization	Poor	1	4
	Fair	6	4
	Good	6	8
	Excellent	9	8

Table 2: Correlation between AO type and functional outcome.

AO type	Case (N=25)	Control (N=24)	SE	95% CI	P value
Harris hip score (mean±SD)					
AO1	86.975±8.898 (N=6)	91.266±2.1939 (N=3)	5.382	-17.0184 to 8.4351	0.4514
AO2	88.667±5.551 (N=15)	79.692±11.993 (N=12)	3.476	1.816 to 16.134	0.0161
AO3	79.175±9.2978 (N=4)	88.2278±9.7089 (N=9)	5.768	-21.7480 to 3.6425	0.1448

Table 3: Correlation between age group and functional outcome.

Age group (in years)	Case (N=25)	Control (N=24)	SE	95% CI	P value
Harris hip score (mean±SD)					
60-69	86.416± 7.970(N=15)	88.880± 10.071 (N=10)	3.614	-9.9392 to 5.0125	0.5023
70-79	89.071± 6.7909 (N=7)	83.7250± 10.2898 (N=6)	4.763	-5.1360 to 15.8288	0.2855
80 and above	82.933± 7.824 (N=3)	79.125± 12.053 (N=8)	7.617	-13.423 to 21.039	0.6291

Table 1 shows the comparison between 2 groups in terms of different characteristics. The correlation between the AO type and mean Harris Hip score is given in Table 2. The correlation between the age distribution and the mean Harris hip score is given in Table 3.

There was a significant difference in the functional outcome of patients belonging to A2 type in both the groups (0.0161) in that the patients who received zoledronic acid did better. P value in all the remaining variables were not significant. Also, all the patients in the study population did not develop any new fracture or re-fracture during the study period.



Figure 1: a) Pre-operative radiograph of a 75 year old female patient who did not receive zoledronic acid showing a A3 type of pertrochanteric femur fracture; b) bridging callus was noted at all the four cortices in antero-posterior (A/P) and lateral projection at the end of 1 year; c) clinical pictures of the same patient who had achieved functional range of motion of the affected hip joint at the end of one year.



Figure 2: a) Pre-operative radiograph of a 66 year old male patient who had received zoledronic acid showing an A2 type of pertrochanteric femur fracture; b) callus noted at all the four cortices in antero-posterior (A/P) and lateral projection at the end of 1 year; c) clinical pictures of the same patient who had achieved functional range of motion of the affected hip joint at the end of one year.

Figure 1a shows the pre-operative radiograph of a 75-year-old female patient who did not receive zoledronic acid.

This radiograph shows that this patient had an A3 type of pertrochanteric femur fracture. Figure 1b shows that at the end of one year, bridging callus was noted at all the four cortices in antero-posterior (A/P) and lateral projection. Her Harris hip score at the end of 1 year was 88.85. Figure 1c represents the clinical pictures of the same patient, which shows that patient had achieved functional range of motion of the affected hip joint at the end of one year.

Figure 2a shows the pre-operative radiograph of a 66-year-old male patient who had received zoledronic acid. This radiograph shows that this patient had an A2 type of pertrochanteric femur fracture. Figure 2b shows that at the end of one year, callus was noted at all the four cortices in antero-posterior (A/P) and lateral projection. His Harris hip score at the end of 1 year was 87. Figure 2c represents the clinical pictures of the same patient, which shows that patient had achieved functional range of motion of the affected hip joint at the end of one year.

DISCUSSION

We have given 5 mg/100 ml zoledronic acid of dosages to every alternative patient selected for the study. We met with a few complications during study proceedings which were managed as per standard protocol and they are briefly described here. 1 patient who had received zoledronic acid developed superficial infection which was treated with regular dressing, debridement and intravenous antibiotics. 2 patients from the case group developed Z effect, but since their fracture had united by the end of one year no active orthopaedic intervention was done. Also, 1 patient developed anaphylactic reaction to zoledronic acid immediately after 10 ml of infusion and therefore the patient's infusion was stopped abruptly. Patient developed sudden dyspnoea with bilateral crepts and hypoxia. Pulmonary edema of the patient was managed by the team of intensivists and the patient's condition improved eventually. In our study we found no significant improvement in Harris hip score in patients who received zoledronic acid. However, patients who had A2 type of fracture and had received zoledronic acid had a significantly better functional outcome than the ones who had A2 type of fracture but didn't receive the zoledronic acid supplementation. Although the mean union time of the fracture in cases was more than that of control, the difference was not significant. There was no difference in the mortality rates of patients amongst both the groups as five patients had died in both the groups within one year of surgery who were then excluded out of the study. Out of these 5 patients who had received zoledronic acid, 1 patient had hypertension, 1 had left ventricle dysfunction and 1 had chronic obstructive pulmonary disease (COPD). 1 patient had diabetes, 1 had COPD, and all five of the patients who passed away and didn't receive zoledronic acid had hypertension.

Intertrochanteric fractures of femur are the most complicated type of osteoporotic fractures in the elderly population. Acute bone loss upto 1% of whole body bone

mass was found in bedridden patients because of immobilization leading to secondary osteoporosis.¹³ This results in a significant increase in the degree of osteoporosis, and the BMD will continue to decline in following 3-6 months. This increases the probability of a re-fracture, thus forming a vicious cycle.^{13,14} Bisphosphonates have a potential to control bone loss and reduce the risk of refracture, thereby decreasing the mortality rates and improving the quality of life. It is a third generation bisphosphonate compound, whose unique R side chain containing dinitrogen imidazole heterocyclic structure results in a stronger bonding force between the drug and bone surface thus resulting in stronger inhibition of osteoclasts. The drug gets absorbed by the bone tissue quickly after injection, directly adheres with the bone surface, and enters the osteoclast to inhibit the activity of enzyme farnesyl pyrophosphate (FPP) synthase necessary for the synthesis of cellular structural proteins in osteoclasts by inhibiting the pathway of mevalonate.^{9,13,17} This will cause the apoptosis of osteoclasts and inhibition of bone resorption mediated by osteoclasts. Zoledronic acid has a higher bioavailability and a longer half-life period compared to other bisphosphonates which increases patient compliance after intravenous administration.¹³ Lyles et al reported that in a randomized controlled trial, annual infusions of zoledronic acid after low-trauma hip fractures decreased the risk of new clinical fractures by 35% and also improved the survival of the patients.¹⁴ Liu et al concluded that zoledronic acid administration in the postoperative period of patients with intertrochanteric fracture can relieve acute bone loss, reduce the incidence rate of re-fracture, alleviate pain, and improve bone metabolism and quality of life.¹³ Bergman et al reported that there was a decrease in the relative risk of new fracture during bisphosphonate treatment.¹⁸ Hayer et al reported that bisphosphonates did not adversely affect fracture union radiologically. Also, they found no significant correlations between severity of osteoporosis, age, gender, and time taken to fracture union.¹⁹ Li et al concluded that zoledronic acid injection is a favourable treatment option for the elderly patients with osteoporotic intertrochanteric fracture operated with proximal femoral nail anti-rotation. It can effectively relieve bone pain, increase bone density, improve quality of life, reduce the occurrence of new fractures and promote fracture healing.²⁰ Cengiz et al reported that the use of zoledronic acid after surgical treatment of intertrochanteric femoral fractures in osteoporotic over 65-year-old patients is a safe treatment modality which helps to reduce mortality, improves functional outcomes, and has less side effects with single dose use per year.²¹ Osteoclasts are important for early fracture healing callus remodelling of cortical bone. There is a growing concern of bisphosphonates having a negative effect on fracture healing because of its inhibitory effect on osteoclasts. Savaridas et al reported using animal model that bisphosphonate treatment in a therapeutic dose, as used for fragility fracture risk reduction in osteoporosis, had an inhibitory effect on direct fracture healing.²² Solomon et al reported that the risk of non-union was almost double in elderly patients who used

bisphosphonates after humeral fractures.²³ Lim et al reported that fracture union at three months was delayed in patients previously treated with bisphosphonates, but most of the patients achieved fracture union by six months. However, at one year post surgery, there were no significant differences in fracture healing and clinical scores suggesting that bisphosphonates do not significantly impact clinical outcomes.²⁴

In our study, one patient who had received zoledronic acid showed delayed union. The fracture showed signs of complete union at the end of 1 year post surgery. This delayed rate on union could be attributed to the inhibitory effect of zoledronic acid on direct fracture healing.

The limitation of our study is that we had small sample size and hence the findings need to be confirmed with a larger study population.

CONCLUSION

The functional outcome of the patient depends primarily on the fracture pattern, the age of the patient, the surgical technique used and the post-operative rehabilitation protocol used. Zoledronic acid is a safe drug, when supplemented in the elderly osteoporotic patients with low energy pertrochanteric fractures who undergo proximal femoral nailing, does not improve the functional outcome of the patients. However, patients with A2 type of fracture who received zoledronic acid supplementation did have a better functional outcome. It does not affect the mortality of the patients.

ACKNOWLEDGEMENTS

We would like to thank the nursing staff, operation theatre technician of department of orthopedics of our hospital and staff and laboratory technicians of multi-disciplinary research Unit, who managed all the resources efficiently and helped us carry the work smoothly.

Funding: This study is funded by Department of Health Research, Ministry of Health and Family Welfare, Govt. of India

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee, SS Medical College, Rewa, Madhya Pradesh. with approval number 04/SS/MC/18 Rewa, dated 26.02.2018

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Cite this article as: Lakhtakia PK, Chaurasia AK, Singh V, Verma PK, Vora AK, Shah V, et al. Effect of zoledronic acid on functional outcome in cases of pertrochanteric femoral fractures in elderly patients operated with proximal femoral nailing. *Int J Res Orthop* 2023;9:733-8.