Does Bisphosphonate Delay Bone Healing After Proximal Femoral Nail Anti-Rotation

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Abstract

Background

Bisphosphonates are widely used for osteoporotic patients to decrease the rate of osteoporotic fractures and they have been shown to reduce the mortality rate in clinical trials. A yearly intravenous zoledronic acid in a clinical study (The HORIZON-RFT) significantly reduced any new clinical fracture and also secondary prevention of hip fracture while bisphosphonates are known to delay remodeling of bone raising the risk that they may delay fracture healing. However, current studies lack data demonstrating whether bisphosphonate (BPs) delays bone healing after hip fracture treatment in clinical practice. Purpose of study was to determine whether treating elderly patients with Bisphosphonate (BP's) after proximal femoral nail fixation (PFNA) for intertrochanteric fractures delays fracture healing compared to similar patients not treated with BP's. A secondary goal was to compare the functional outcome, complications and mortality between the two treatment groups.

Methods

One hundred ninety-six elderly patients underwent PFNA fixation for intertrochanteric fracture between 2015 and 2017 with age > 60 years and minimum 1-year follow-up inclusive of functional scores and complications.

Intervention: Surgical treatment of intertrochanteric fracture plus calcium and vitamin D supplementation.

Main Outcome Measurements: Time to clinical union and radiographic union (weeks), the functional outcome (Harris Hip Score) and complications including mechanical failure and mortality rate.

Setting: Level 1 Trauma Center

Results

There were comparable functional class and comorbidity between those with BP's and not treated BP's. In addition, there was no different in mortality rate (4.0%% vs 6.6%, $p=0.537$), time to clinical union (6.0 weeks vs 6.0 weeks, $p=0.822$), radiographic union (11.8 weeks vs 12.0 weeks, $p=0.849$), and functional outcome (Harris Hip Score) (74.4 vs 69.9, $p=0.177$) between two groups.

Conclusions

BP's can be used after surgical treatment of an osteoporotic hip fracture without concern that fracture healing will be delayed.

Level of Evidence: Prognostic level III.

Tables

Table 1. Demographic data/comorbidities between treated and untreated group

Demographic data and Comorbidities	Treated (n=75) (38.3%)	Untreated (n=121) (61.7%)	p-value
Female, n (%)	64 (85.3%)	81 (66.9%)	0.004
Age (Years) Mean $\pm$ SD	80.4 $\pm$ 8.0	79.9 $\pm$ 8.7	0.678 ‡
ASA classification, n (%) #			0.139
Class I	11 (14.7%)	11 (9.1%)	
Class II	45 (60.0%)	64 (52.9%)	
Class III	19 (25.3%)	46 (38.0%)	
Metabolic equivalence (METs) #			0.780
Low METs (1-4)	58 (77.3%)	98 (81.0%)	
Moderate to high METs (>4)	17 (22.7%)	23 (19.0%)	
Hypertension, n (%)			0.272
No	24 (32.0%)	30 (24.8%)	
Yes	51 (68.0%)	91 (75.2%)	
Type II DM, n (%)			0.532
No	54 (72.0%)	82 (67.8%)	
Yes	21 (28.0%)	39 (32.2%)	
Dyslipidemia, n (%)			0.788
No	43 (57.3%)	67 (55.4%)	
Yes	32 (42.7%)	54 (44.6%)	
Heart disease, n (%)			0.728
No	64 (85.3%)	101 (83.5%)	
Yes	11 (14.7%)	20 (16.5%)	
Chronic kidney disease, n (%)			0.07
No	66 (88.0%)	94 (77.7%)	
Yes	9 (12.0%)	27 (22.3%)	
Lung disease, n (%)			0.383

No	74 (98.7%)	121 (100.0%)	
Yes	1 (1.3%)	0 (0.0%)	
Cerebrovascular accident, n (%)			0.596
No	67 (89.3%)	105 (86.8%)	
Yes	8 (10.7%)	16 (13.2%)	
Charlson Comorbidity Index (CCI)	5 (2-10)	5 (2-9)	0.211
Median (Min-Max)*			
‡Independent t-test; * Mann-Whitney U-test; #Chi-square test; the others: Fisher's exact test			

Table 2. Fracture pattern assessed by modified AO/OTA 2017 between treated and untreated group

Fracture pattern	Treated (n=75) (38.3%)	Untreated (n=121) (61.7%)	p-value
Stable type			0.400
A1.1, n (%)			NA
No	75 (100.0%)	121 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)	
A1.2, n (%)			0.333
No	69 (92.0%)	106 (87.6%)	
Yes	6 (8.0%)	15 (12.4%)	
A1.3, n (%)			0.893
No	68 (90.7%)	109 (90.1%)	
Yes	7 (9.3%)	12 (9.9%)	
Unstable type			0.383
A2.2, n (%)			0.106
No	32 (42.7%)	66 (54.5%)	
Yes	43 (57.3%)	55 (45.5%)	
A2.3, n (%)			0.385
No	66 (88.0%)	101 (83.5%)	
Yes	9 (12.0%)	20 (16.5%)	
A3.1, n (%)			0.055†
No	72 (96.0%)	121 (100.0%)	
Yes	3 (4.0%)	0 (0.0%)	
A3.2, n (%)			0.410†
No	74 (98.7%)	116 (95.9%)	
Yes	1 (1.3%)	5 (4.1%)	
A3.3, n (%)			0.432
No	70 (93.3%)	109 (90.1%)	

Yes	5 (6.7%)	12 (9.9%)
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Almost parameters: Chi-square tests, †Fisher's exact test

Table 3. Postoperative fracture displacement (Gap and Step), Neck Shaft Angle, and Tip Apex Distance during admission between treated and untreated group

Postoperative radiography	Treated (n=75) (38.3%)	Untreated (n=121) (61.7%)	p-value
<u>During admission</u>			
1.Fracture displacement (mm.) (Mean±SD)			
-Gap (AP view)	1.42±2.17	0.89±1.85	0.079
-Gap (Lateral view)	0.42±1.18	0.42±1.12	0.973
-Step (AP view)	1.42±2.21	1.37±2.87	0.907
-Step (Lateral view)	1.73±2.78	2.25±2.48	0.181
2.1 Neck Shaft Angle (NSA) (Degree) (Mean±SD)	129.46±4.42	130.71±5.24	0.087
2.2 Neck Shaft Angle (NSA) (n) (%)			0.173†
-Coxa vara (<120°)	0 (0.0%)	2 (1.7%)	
-Normal (120-135°)	68 (90.7%)	97 (81.5%)	
-Coxa Valga (>135°)	7 (9.3%)	20 (16.8%)	
3.Tip Apex Distance (TAD) (mm.) (Mean±SD)			
-AP view	10.16±3.08	9.98±3.04	0.696
-Lateral view	10.80±2.97	11.04±3.28	0.601
-Summation of AP and Lateral #	20.96±5.88	21.03±5.81	0.937
TAD <20 mm (n=86) (43.9%)			
TAD 20-30 mm (n=99) (50.5%)			
TAD >30 mm (n=11) (5.6%)			
# No significant correlation between TAD and mechanical failure			
Independent t-test; †Fisher's exact test; significant if p<0.05			

Table 4. Time to union, Functional outcome assessed by Harris Hip Score (HHS), and Complications including Mortality rate between treated and untreated group

Functional Outcome and Complications	Treated (n=75) (38.3%)	Untreated (n=121) (61.7%)	p-value
<u>Time to union (weeks).</u>			
1.Clinical union (weeks)*	6.00±1.35	6.04±1.17	0.822
2.Radiographic union (weeks)*	11.77±2.95	11.99±9.80	0.849
<u>Functional Outcome (at one year) and Follow up Time (months).</u>			
1.Harris Hip Score (HHS) (Mean±SD)*			
1.1 Pre-fracture HHS	79.09±16.37	80.64±13.80	0.640
1.2 HHS at 1 year follow up	74.44±13.52	69.90±16.97	0.177
1.3 Difference of HHS	4.65±22.13	10.74±18.16	0.189
2.HHS improvement †(n=175)			0.361
2.1 Worse than pre-fracture #	48 (67.6%)	77 (74.0%)	
2.2 Same as pre-fracture	2 (2.8%)	8 (7.7%)	
2.3 Better than pre-fracture	21 (29.6%)	19 (18.3%)	
3.Time for follow up (months) (Median)(Min-Max) ††	29 (12-48)	30 (12-50)	0.640
<u>Complications</u>			
1.Mechanical failure	4 (5.3%)	2 (1.7%)	0.205
1.1 PFNA blade cut through	1 (1.3%)	2 (1.7%)	
1.2 PFNA blade cut out	1 (1.3%)	0 (0.0%)	
1.3 Varus collapse	2 (2.7%)	0 (0.0%)	
2.One year mortality rate (%) †††			0.042
No	71 (94.7%)	98 (85.2%)	
Yes	4 (5.3%)	17 (14.8%)	

*Independent t-test; †Fisher's exact test; †† Mann-Whitney U test;

††† Chi-square test; significant if p<0.05

Almost patients (125 out of 175) (71.4%) are using gait aid at 1 year follow up

Background

Osteoporosis represents a major problem in public health because it is associated with fractures from low-energy mechanisms. Hip fracture has been recognized as the most serious complication of osteoporosis because of its consequences including disability, poor quality of life, increased risk of mortality, and health care costs [7,9,15,17]. The incidence of hip fracture has been increasing around the world as a result of the aging population from 1.66 million in 1990 to 6.26 million by 2050 [8]. Bisphosphonates are widely used for osteoporotic patients to decrease the rate of osteoporotic fractures and they have been shown to reduce the mortality rate in clinical trials [4,11]. Animal studies demonstrated that a delayed single dose of zoledronic acid (1 or 2 weeks after fracture) produced significantly increasing bone strength and fracture repair [1] while a yearly intravenous zoledronic acid in a clinical study (The HORIZON-RFT) significantly reduced any new clinical fracture and also secondary prevention of hip fracture [6]. BP's are known to delay remodeling of bone raising the risk that they may delay fracture healing. However, current studies lack data demonstrating whether bisphosphonate (BPs) delays bone healing after hip fracture treatment in clinical practice. The purpose of this study is to determine whether treating elderly patients with BPs after proximal femoral nail fixation (PFNA) for intertrochanteric fractures delays fracture healing compared to similar patients not treated with BP's. A secondary goal was to compare the functional outcome, complications and mortality between the two treatment groups

Methods

After Institutional Research Board Approval, 249 elderly patients (age more than 60 years old) with intertrochanteric fractures from low energy trauma who underwent PFNA fixation from January 2015 until December 2017 were prospectively collected. Demographic data, comorbidity including Charlson Comorbidity Index (CCI), ASA classification (American society of anesthesiologist), Metabolic equivalence (METs), time to union, functional outcome and complications were collected. Hip fracture patients were excluded when they had followed up time of less than one year, they were referred to a different hospital, poly trauma, pathologic fracture, or they had previous history of bisphosphonate intake. There were 196 elderly hip fractures treated with PFNA fixation that met these criteria. Patients were further classified into 2 groups: 75 patients taking bisphosphonate [70 milligrams per oral alendronate once weekly (70.7%, 53 patients), 150 milligrams per oral risedronate once monthly (21.3%, 16 patients), and 150 milligrams per oral ibandronate sodium once monthly (8.0%, 6 patients)] at two weeks after surgical fixation of fracture and those who did not receive bisphosphonate (121 patients). All patients in both groups received supplemental vitamin D and calcium. The primary outcome was measured prospectively by time to clinical union and radiographic union (weeks). The secondary outcome was the functional outcome (Harris Hip Score) and complications including mechanical failure and mortality rate. All outcomes were compared between the two groups.

Data collection and outcome

A total of 196 elderly patients with low energy intertrochanteric fracture underwent PFNA fixation and were included in the study. Patient demographic information, comorbidities, pre-operative and postoperative status, history of prior fracture and treatment, cause of injury, medication at hospital admission and discharge, and radiological reports were also obtained from the medical record review. Patient's comorbidities were reviewed from the medical record: (1) Diabetes mellitus was grossly classified into two major types (Non-Insulin Dependent Diabetes Mellitus and Insulin Dependent Diabetes Mellitus). (2) Hypertension. (3) Dyslipidemia (4) Lung disease (Pulmonary disease) (5) Heart disease was classified into 5 types (coronary artery disease, valvular heart disease, cardiomyopathy, arrhythmias, and heart infection). (6) Liver disease (7) Kidney disease (8) Dementia.

Additionally, all hip fracture patients had the Charlson Comorbidity Index (CCI) calculated. A single MET is defined to be the resting metabolic rate, or the amount of oxygen consumed while sitting at rest (approximately $3.5 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for a person weighting 70 kg). METs are the ratio of the work metabolic rate to the resting metabolic rate and can be used to quantify an individual's maximal functional aerobic capacity [11]. METs were stratified as follows: (1) 1-4 (low intensity), and (2) >4 (moderate to high intensity).

All patients received standard medications of calcium and vitamin D supplements. In this study, patients who received any bisphosphonate was classified as the "treated group" and those who did not receive anti-osteoporosis drugs were classified as the "untreated group". The enrollment of subjects and their allocation of treatment including the outcome was shown in CONSORT diagram.

All patients were prospectively identified for clinical union and radiological union at 2, 4, and 6 weeks, 3, 6, 9, and 12 months consequently. Clinical union was defined by clinical and radiographic measurement: patient can partially bear weight without pain and the radiograph demonstrates incomplete obliteration of the fracture line. Radiographic union was defined by complete obliteration of the fracture line on the radiograph [10]. However, fracture patterns based on modified AO/OTA classification were retrospectively categorized into AO/OTA 31 A1.1, A1.2, A1.3, A2.2, A2.3, A3.1, A3.2, and A3.3. The quality of reduction was measured by neck-shaft angle (degree), displacement between cortices of proximal and distal fragments: gap and step in Anteroposterior (AP) and lateral view (millimeters; mm), and Tip Apex Distance (TAD) (millimeters; mm).

Operative procedure

Fractures were all fixed with a titanium PFNATM nail (Synthes). All patients were operated on the fracture table in supine position. Closed reduction was done under fluoroscopy. After anatomical reduction, a guide wire was inserted into the tip of greater trochanter, proximal reaming was done, diameter of nail was measured under fluoroscopy, and a standard-proximal femoral nail with 200

millimeters length was placed into the medullary canal and the guide wire was removed. Before the application of the helical blade into the femoral head, a guide wire was inserted into the femoral head and the exact position and length of helical blade in AP and lateral views was measured. The helical blade was inserted into the femoral head and it was tightened in the final step.

Postoperative management

Appropriate pain control was provided for all patients, they were allowed weight bearing as tolerated, and deep vein thrombosis prophylaxis was applied during hospital admission.

Outcome measurement

All patients were followed up in clinic at 2 weeks, 4 weeks, 6 weeks, 3 months, 6 months, 9 months, and 1 year. Radiographic measurements were done by two orthopedic training surgeons who did not participate in the operative procedures. Mean of these measurements were calculated. Anteroposterior (AP) and lateral radiographs were assessed by PACS software and were used for assessment of quality of reduction: neck-shaft angle (NSA), displacement between cortices of proximal and distal fragments: gap and step in AP and lateral views (mm), Tip Apex Distance in AP and lateral views (TAD, mm).

Harris Hip score (HHS) is composed of many aspects: Pain (44 points), Limp (11 points), Support (11 points), Distance walked (11 points), Sitting (5 points), Enter public transportation (1 point), Stair (4 points), Put on Shoes and Socks (4 points), Absence of Deformity (4 points), and Range of Motion (5 points). Zero points means the lowest hip score while one hundred points means the maximal hip score. HHS was measured into two aspects in all patients: pre-fracture state by interview and postoperative state at one year follow up by examination in clinic. Surgical complications (mechanical failure including PFNA blade cutout, blade cut through, and varus collapse) and mortality rate were compared between groups.

Statistical analysis

All patient's information was compared between the treated and untreated groups to identify any differences. Data were summarized using descriptive statistics (mean $\pm$ SD and number of patients). Comorbidities were compared using Fisher's exact test. Age of patient,

Distance between proximal and distal fragment (gap and step in AP and lateral views) (mm), Tip and Apex Distance (TAD) (AP and lateral views, mm), and Neck Shaft Angle (degree) between groups were compared by independent T-test. ASA class, METs, and Fracture pattern (AO/OTA classification 31 A1, 2, and 3) were compared by Chi-Square test while the others were compared by Mann-Whitney U test. P-value less than 0.05 were considered a significant difference.

Results

Demographic data and comorbidities including Charlson Comorbidity Index (CCI) are reported in Table 1. There was no difference in the average age between groups, but female gender in the treated group was significantly higher than in the untreated group (85.3% and 66.9%, $p=0.004$, respectively). For ASA classification, METs, any underlying diseases, and CCI there were no significant difference between groups.

Fracture pattern assessed by modified AO/OTA 2017 are demonstrated in Table 2. There were no significant differences in fracture pattern (Stable and Unstable type) between groups. There was comparable fracture displacement (gap in lateral view and step in both AP and lateral views) between both groups although the gap in AP view in treated group was almost significantly higher than untreated group (1.42 ± 2.17 and 0.89 ± 1.85 , $p=0.079$). There was no significant difference in the neck shaft angle (NSA), NSA ratio, and Tip Apex Distance (TAD) following PFNA fixation between groups as shown in Table 3. The average TAD was 20.9 mm in the treated group and 21.0 mm in untreated group which fall within the recommended range (20-30 mm). There was no significant correlation between TAD and mechanical failure.

The average time to clinical union and radiographic union (weeks) were similar in both groups. Even though pre-fracture HHS and HHS at one year follow up were not significantly different between groups, in most patients in both groups the HHS was lower when compared with pre-fracture HHS (67.7% in treated group and 74.0% in untreated group). Mechanical failure after PFNA fixation was not significantly different between groups including mortality rate in both groups (4.0% vs 6.6%, $p=0.537$) (Table 4).

Discussion

Bisphosphonates (BP's) are widely used for osteoporotic patients and they have been shown to decrease the fracture rate and reduce mortality in clinical trials [4,11]. However, there is concern that BP's delay bone healing and this may be relevant in clinical practice after hip fracture repair a scenario in which BP's are frequently utilized. The purpose of this study was to assess whether elderly patients treated with BP's after proximal femoral nails (PFNA) for intertrochanteric fractures have delayed fracture repair compared to similar patients not treated with BP's and to compare the functional outcomes between the two groups.

The characteristics of the fracture and the treatment were similar between the two groups of patients. The fracture pattern assessed by modified AO/OTA 2017 was not significantly different (Stable and Unstable type) between groups. The fracture displacement (gap in lateral view and step in both AP and lateral views) between both groups was comparable even though the gap in the AP view in the treated group was almost significantly higher than in the untreated group (1.42 ± 2.17 and 0.89 ± 1.85 , $p=0.079$). There was no significant difference in the neck shaft angle (NSA), NSA ratio, and Tip Apex Distance (TAD) following PFNA fixation in both groups as shown in Table 3. The average TAD in our study was 20.9 mm in the treated group and 21.0 mm in the untreated group which was well within an acceptable range (20-30 mm) as defined in previous studies [2,3,14,16]. The fractures in this study had a low rate of mechanical failure (6 out of 196) (3.1%) and helical blade cutout (3 out of 196) (1.5%).

Previous animal studies demonstrated that a delayed single dose of zoledronic acid (1 or 2 weeks after fracture) produced significantly increased bone strength and improved fracture repair [1] while a yearly intravenous zoledronic acid in clinical study (The HORIZON-RFT) significantly reduced any new clinical fracture and prevented a secondary hip fracture [6]. However, since BP's delay bone remodeling, there is a concern they may delay fracture healing. The current literature has insufficient data to determine whether BP's delay bone healing or increases complications after surgical fixation of an intertrochanteric fracture in elderly patients. This study demonstrated that there was similar average time to clinical and radiographic union between treated and untreated group showing that there was not an effect on fracture repair that we could detect in this study. BP's do not appear to inhibit bone healing after osteoporotic hip fracture fixation in clinical practice.

Pre-fracture HHS and HHS at one year follow up were not significantly different between groups. In both groups HHS was lower following PFNA fixation when compared with pre-fracture HHS (67.6% in treatment group and 74.0% in non-treatment group). Most patients in this study (125 out of 175) (71.4%) had lower functional outcome than pre-injury and walking ability was comparable with previous studies demonstrating a high rate of dependence (80% were using a walking aids at 1 year follow up, 16% were institutionalized, and 11% were bedridden postoperatively) [5,16,18]. Mechanical failure after PFNA fixation was not significantly different between treated and untreated groups further supporting the contention that BP's do not inhibit bone healing after hip fracture fixation to an extent that is detectable in actual clinical practice. The mortality rate in this study was not significantly different (4.0% vs 6.6%, $p=0.537$) even though several studies have been demonstrated reduction of mortality rate after BP's use [4,11,13]. Even though we prospectively measured the time to clinical and radiographic union because these are the primary outcome of this study, some parameters were measured retrospectively, for instance, the fracture pattern assessed by modified AO/OTA 2017 classification that established later after this study had been started. Another limitation was time to bone union evaluated by clinical and plain radiography. These are semiquantitative assessment for complete bone healing, the better tool should be a Computerized Tomography. In addition, the rate of mechanical failure after PFNA fixation was so small. Therefore, there was no actual power to detect a significant difference of mechanical failure between groups.

Conclusion

The data in this study suggests that BP's can be used after surgical treatment of an osteoporotic hip fracture without concern that fracture healing will be delayed.

Abbreviations

BPs: Bisphosphonate; PFNA: Proximal femoral nail fixation; CCI: Charlson Comorbidity Index; ASA: American society of anesthesiologist; METs: Metabolic equivalence; AP: Anteroposterior; TAD: Tip Apex Distance; NSA: neck-shaft angle; HHS: Harris Hip score

Declarations

Ethical review committee statement and consent to participate

On the behalf of the Institutional Review Board, Royal Thai Army Medical Department, our research was approved with code R172h/60. The authors confirm that written informed consent was obtained from all participants.

Competing Interests

The authors declare that they have no competing interests.

No funds were received in support of this study.

The manuscript submitted does not contain information about medical device(s)/drug(s).

No benefit(s) in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Author's contributions

All authors designed the protocol.

O.P. Generating the idea, collecting data, and writing the manuscript

S.T. collecting data and assisting in discussion part.

S.P. collecting data and analyzing the data.

J.L.M. supervised the study and revising manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Figures

Figure 1

CONSORT Diagram