A Retrospective Study on Bisphosphonate abuse

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Abstract

\textbf{Background:} Bisphosphonates are common drugs used for the treatment of postmenopausal osteoporosis. Short term benefits of the bisphosphonates are well known. However, there are concerns regarding their long term use. \textbf{Objectives:} The aim of the study was to analyze the association between bisphosphonate treatment and atypical femoral fractures.

\textbf{Material and methods:} The records of nine patients from a tertiary care hospital in Bhopal were reviewed for evaluating the association between bisphosphonate use and atypical femoral fractures. The retrospective analysis was done for the indications, duration of bisphosphonate use, and configuration of associated fractures, management and outcome of the fractures.

\textbf{Results:} All the nine patients were females with mean age of 71 years. The mean duration of bisphosphonate use was 7.2 years. Bisphosphonate treatment was given without significant risk factors before the start of treatment in all the patients. A total of 12 fractures were seen in these patients. Management was successful in all the patients who were treated conservatively. Two patients required revision surgery. \textbf{Conclusion:} Indiscriminate use of bisphosphonates seen in many cases and could be hazardous to the patients. There is need for improved awareness among physicians about the correct use of bisphosphonates including its indication, appropriate duration of use, need for follow up and management of associated complications.

\textbf{Key words:} Bisphosphonates, Fractures, Abuse

Introduction

Antiresorptive agents are widely used for the treatment of postmenopausal osteoporosis. These drugs are shown to improve bone mineral density, prevent bone loss and reduce the risk of spinal and non spinal fractures [1]. Bisphosphonates inhibit osteoclastic activity and therefore bone turnover. The short term efficacy of these agents is well known, however there are concerns regarding their long term use. With the use of these drugs, there is potential risk of impairment of some of the biomechanical properties of the bone [2].

It inhibits normal repair of microdamage which may lead to approximately twenty percent reduction in bone toughness [3-5]. Due to reduced bone turnover, secondary mineralization continues which may lead to the formation of hypermineralised bone [6] with abnormal mechanical properties like reduced stiffness, strength and higher brittleness, ultimately leading to increased risk of fracture [7,8]. The last decade has witnessed better research and understanding in the field of osteoporosis. In developing Nine patients who were world, increased awareness, investigation facilities and easy availability of anti-osteoporotic drugs have helped many patients to avoid fragility fractures and lead a better quality of life. However there are no universally accepted treatment protocols for management of postmenopausal and senile osteoporosis which may be the cause of an excessive use or abuse of bisphosphonates as a main line of treatment for prolonged duration. Various reports of atypical femoral fractures secondary to bisphosphonate use have been published in last few years [9-12].

There is no sufficient data regarding misuse of bisphosphonates in Indian patients. The objective of this study was to review the cases of atypical femoral fracture associated with bisphosphonate use and study their indications, duration of bisphosphonate therapy, association with atypical emoral fractures, treatment of fractures and clinical outcome.

Material and methods

receiving bisphosphonate treatment and diagnosed with either complete or incomplete atypical femoral fractures between January 2010 and August 2012 in Gandhi
Medical College Bhopal (MP) were included in the study. Those with active malignancy, bone metastasis, metabolic bone disorder or renal impairment were excluded from the study. Radiographs of the patients were studied by radiologist and orthopaedic surgeon to confirm atypical fracture characterized by the presence of cortical stress reaction, dreaded black line on the lateral cortex of femur, thickening and flaring of lateral cortex [13]. The duration of bisphosphonate therapy, T score in DEXA scan at initiation of treatment and follow up scans, timing of the insufficiency fracture, treatment given and involvement of contralateral hip/femur were studied. Delay in treatment after recognition of stress fracture as well as any delay in surgery after displaced fractures was noted. Operative records were screened for understanding the mode of reduction; implant used, bone graft and any intraoperative complications. Medical records and radiographs were reviewed to assess postoperative medical treatment, time of union and implant failure requiring revision surgery if any. This study was approved by institutional review board of the hospital.

Results

In this retrospective study all the patients were females, with mean age of 71 years (range: 54 to 85 years). None of the patients had history of corticosteroid use, alcohol or smoking. The mean duration of oral bisphosphonate therapy was 7.2 years (range 4 to 10 years). Initially all patients were on alendronate out of which two were switched to ibandronate after alendronate (table 1). Only one patient had a drug holiday of six months.

Table 1: Duration of Bisphosphonate Use and Configuration of Fractures

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Age in yrs</th>
<th>Bisphosphonate</th>
<th>Duration of therapy</th>
<th>Affected side</th>
<th>Contralateral side</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>Alendronate 6 yrs</td>
<td>10 years</td>
<td>Left subtrochanteric fracture – Displaced</td>
<td>-</td>
<td>Open reduction</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Alendronate</td>
<td>10 years</td>
<td>Midshaft fracture femur right – Displaced</td>
<td>Left Cortical stress reaction – ST</td>
<td>Conservative :left side Open reduction: Right side</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>Alendronate</td>
<td>4 years</td>
<td>Cortical stress reaction – ST</td>
<td>Cortical stress reaction - ST</td>
<td>Conservative :left side Open reduction: Right side</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>Alendronate</td>
<td>4 years</td>
<td>Left -ST – Displaced</td>
<td>-</td>
<td>Open reduction</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>Alendronate</td>
<td>6 years</td>
<td>Left Side - Dreaded black line - Undisplaced - ST</td>
<td>Cortical stress reaction - ST</td>
<td>Closed procedure – left side Conservative – right side</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>Alendronate</td>
<td>10 years</td>
<td>Right - ST –Displaced</td>
<td>-</td>
<td>Closed procedure</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>Alendronate 4 yrs</td>
<td>7 years</td>
<td>Left - ST – Displaced</td>
<td>-</td>
<td>Open reduction</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Alendronate</td>
<td>5 years</td>
<td>Right - ST –Displaced</td>
<td>-</td>
<td>Open reduction</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>Alendronate</td>
<td>4 years</td>
<td>Left - ST – Displaced</td>
<td>-</td>
<td>Open reduction</td>
</tr>
</tbody>
</table>

ST - Subtrochanteric fractures

DEXA Scans: DEXA scan was done before starting bisphosphonate in eight patients while in one patient it was never done. The results show osteopenia (mean worse T score -1.6) in six patients. Only two patients had osteoporosis before starting the treatment. Repeat DEXA scans were available for all the nine patients at their last follow up visit which showed osteopenia with a mean worse T score of -1.4. Eight patients had prodromal
symptoms of thigh pain with mean duration of 4.8 months (range: 8 days-1 year).

Fractures associated with bisphosphonate use: A total of twelve fractures in nine patients were available for the analysis. Four of the fractures were on left, two on right side while remaining three had bilateral involvement. Two of the fractures had involvement of contralateral side with subtrochanteric area cortical stress reaction. One patient was treated with intramedullary nail for fracture of femur shaft due to bisphosphonate induced insufficiency elsewhere. There was no history of fall in any of the patients who sustained these fractures. Six patients (66%) felt a give way sensation in the thigh while walking just before the fracture.

None of the patients had significant risk factors before initiation of bisphosphonate treatment. There was no evidence of fragility fractures in any of the study patients. Configurations of fractures are shown in table 1.

Management was successful in all the patients who were treated conservatively. Revision surgery was required in two patients who were treated with intramedullary nailing. The revision surgery was performed because of non union and failure of implant.

In one patient, exchange nailing was done from a short PPFN to long PFNA nail with iliac crest bone graft. Healing occurred seven months after the revision surgery. In other patient, the implant was changed to condylar blade plate because of implant failure at six months.

Discussion

Bisphosphonates are commonly used as a treatment for osteoporotic patients because of its effectiveness in reducing the risk of fractures [14-16]. They are one of the approved agents for the treatment of osteoporosis. According to National Osteoporosis Foundation [17], treatment for osteoporosis should be started for patients with hip or vertebral fractures, those with T-scores < -2.5 at the femoral neck, total hip or lumbar spine by dual-energy x-ray absorptiometry (DEXA), after appropriate evaluation, and for postmenopausal women and men ≥50 years with low bone mass at the femoral neck, total hip or lumbar spine by DEXA and a 10-year hip fracture probability > 3% or a 10-year major osteoporosis-related fracture probability > 20% based on the U.S.-adapted WHO absolute fracture risk model. We observed ‘abuse’ of bisphosphonates as per the WHO (1969) definition ‘Persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice [18] especially in the patients where use was not indicated initially. In our study group, only two patients had T score of < -2.5 and started on bisphosphonate therapy. Seven other patients did not have any associated risk factors like early menopause, fragility fractures, use of steroid therapy, malignancy or long term chemotherapy treatment before starting on bisphosphonate therapy.

According to NOF [17] and NICE [19] guidelines, seven out of nine patients (78%) from our study did not require bisphosphonate therapy.

It is reasonable to stop use of bisphosphonates after five years of use because of the scanty evidence for use after five years [20]. Many papers have been published demonstrating occurrence of atypical femoral fractures in patients on long term bisphosphonate therapy [12,21-23].

Among older women, treatment with a BPs for more than 5 years has been shown to be associated with an increased risk of subtrochanteric or femoral shaft fractures.[24] Although there was a high prevalence of current BPs among patients with atypical fractures, the absolute risk was small.[25]

Patients in our study received bisphosphonates for mean duration of 7.2 years which shows inappropriate use of these agents by many orthopaedic surgeons and rheumatologists. Increased awareness about the right indications and criteria for the use of bisphosphonates in the management of osteoporosis is necessary.

Wang et al [23] reported 8 cases of atypical femoral fractures with cortical stress reaction on the contralateral femurs of three patients. Egolet al [26] reported outcomes of patients with incomplete bisphosphonate related femoral fractures. They studied 31 patients with 43 fractures of which 13 patients had bilateral femur fractures. In our study, three patients had bilateral involvement of femur and none of this was picked up by the initial treating surgeon.

One of the three patients underwent prophylactic intramedullary nailing due to the presence of dreaded black line which healed without any complications. Patients with atypical femoral fractures should be screened for the contralateral side and treated accordingly.

In a study of non-operative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures, Banffyet al [27] emphasised the importance of
orthopaedic surgeons recognizing incomplete bisphosphonate related femur fractures. Incomplete fractures often resemble stress or insufficiency fractures and may be missed clinically and radiographically.

Radiographs of patients treated with bisphosphonates for five years or longer and have sustained low-energy subtrochanteric and diaphyseal femoral fractures show characteristic imaging features such as focal lateral cortical thickening or transverse orientation of the proximal femoral fracture line which was noticed in all the study patients. If displaced, a medial cortical spike or beak, superior displacement of the distal fragment and varus angulation at the fracture site are seen [28].

All our study patients with cortical stress reaction healed with conservative management by six months. Patients with undisplaced or displaced fractures or with the dreaded black line underwent surgical intervention. Most of the fractures (6/8) were treated with open reduction, freshening of the fracture edges and intramedullary nailing. Six out of eight fractures healed at a mean duration of seven months.

Two of eight fractures had non-union which required further surgery and autologous bone graft. Our findings suggest that surgical treatment, in these cases with intramedullary nailing for the most part, improves clinical and functional outcomes for patients who have sustained bisphosphonate related femur fractures.

Our results corroborate those of Bannfly et al [27] who suggested that non-operative management of bisphosphonate associated stress fractures has a high likelihood of failure with the majority of fractures progressing to fracture completion. Egolet al [26] have also shown that the average time of union is higher in these types of fractures. In our study, probably bisphosphonates were not indicated in most of the patients. Follow up was also not regular.

Fractures were not detected early and surgery was delayed in spite of detection of incomplete fractures. Bisphosphonates were continued despite the improvement in DEXA. In fact in one patient with displaced fracture surgery was delayed for two years. Excessive use of bisphosphonates in these patients indicates its abuse.

We strongly recommend avoiding the indiscriminate use of bisphosphonates. Similarly, after stopping the therapy of bisphosphonates, the patients should be carefully followed for assessment of bone turnover.

The study has some limitations including retrospective study design and small sample size with relatively less number of fractures. However such type of fractures are relatively less common and hence we believe it is worth reporting. The statistical comparison between different groups was not possible due to small sample size.

<table>
<thead>
<tr>
<th>Caveats of bisphosphonate abuse</th>
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<tbody>
<tr>
<td>Bisphosphonates were not indicated in most of the patients</td>
</tr>
<tr>
<td>Published data of atypical femoral fractures on long term bisphosphonate therapy[12,21-23]</td>
</tr>
<tr>
<td>Patients with atypical femoral fractures should be screened for the contralateral side</td>
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<td>Patients with cortical stress reaction healed with conservative management</td>
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<td>Non-operative management of bisphosphonate-associated stress fractures has a high likelihood of failure</td>
</tr>
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<td>Average time of union is higher in these types of fractures</td>
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</table>

### Conclusion

Bisphosphonates are inappropriately used in many patients. Misuse of bisphosphonates can be harmful to the patients. Increased awareness among healthcare practitioners about the right indications, duration and need of follow up is required to avoid complications associated with use of bisphosphonates.

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### References


3. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically


16. Felsenberg D, Miller P, Armbricht G. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone 2005; Nov;37(5): 651-4


19. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended). January 2011

20. Ott SM. What is the optimal duration of bisphosphonate therapy? Cleveland Clinic Journal of Medicine. Sep 2011; 78;9: 619-630


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