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ORIGINAL ARTICLE

Safety and efficacy of bisphosphonates in thalassemia patients with osteopenia/osteoporosis

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Abstract

Background: Osteoporosis in Thalassemia Major (TM) represents a prominent cause of morbidity. Calcium is important for bone health throughout the life. If not well transfused, the medullary as well as extramedullary erythropoiesis is stimulated. This leads to thinning of the cortices of long bones and marked dilatation of the medullary cavities. *Aims and Objectives:* To evaluate the efficacy of bisphosphonates in thalassemia patients with osteopenia/ osteoporosis and to study the safety profile of bisphosphonates. *Material and Methods:* The prospective interventional study was conducted from January 2019-March 2020 at thalassemia day care centre of a tertiary care hospital after approval from Institutional Ethics Committee. Of the 150 thalassemia patients, 40 diagnosed with B-thalassemia major with more than 7 years of age, who were on regular transfusion and with Dual X-Ray Absorptiometry (DEXA) scan showing osteopenic/osteoporotic changes were exclusively included in the study. Age appropriate consent, history, clinical examination and biochemical investigations were done. All patients whose Bone Mineral Density (BMD) was showing osteoporosis were started on Alendronate 25 mg/week orally in the morning on empty stomach. The patients were followed up monthly for one year, after which they were evaluated with repeat biochemical tests and DEXA scan. *Results:* Majority of children were in the age group of 10-15 years (50%) with male predominance (55%). At pre-treatment, 24 (60%) and 20 (50%) patients had backache and bone pain respectively which significantly reduced to 4 (10%) each at post-treatment. Mean serum calcium improved from 8.27 g% before treatment to 9.26 g% post-treatment. Of the 40 patients, 8 (20%) had osteopenia and 32 (80%) had osteoporosis before starting the therapy. Post-treatment, there was significant increase in bone mass, 10 (25%) patients had normal Z score, 14 (35%) patients had osteopenia and only 16 (40%) had osteoporosis with improved BMD. Only 2 (5%) children had developed twitching secondary to hypocalcemia. *Conclusion:* DEXA scan must be done routinely in all thalassemia patients. Bisphosphonates along with adequate calcium can effectively reduce bone related morbidity in thalassemics with good safety profile.

Keywords: Osteopenia/Osteoporosis, Thalassaemia major, Calcium, Bisphosphonates, Dual X-Ray Absorptiometry Scan, Hypocalcaemia

Introduction

Thalassemia is a group of inherited anemia caused by mutations affecting the synthesis of hemoglobin chains. Well managed thalassemia patients now survive into fifth decade [1]. However, with prolonged survival there are new problems which cause severe morbidity and affect the quality of life in the form of bony abnormalities, short stature, iron overload, endocrinopathies, etc. If thalassemia patients are not well transfused to maintain optimal age appropriate haemoglobin levels, the medullary as well as extramedullary erythropoiesis is stimulated. This leads to thinning of the cortices of long

bones and marked dilatation of the medullary cavities. Dietary deficiency of calcium, vitamin D and endocrinopathies hamper the mineralisation of bones. Accordingly, they become extremely fragile and prone to pathologic fractures. Among the bone abnormalities, pathological fractures, and osteoporosis are seen in almost 33% of regularly transfused patients [2]. As the first fracture increases the risk and chances of subsequent fractures, it is very important to prevent osteoporosis. Thus, early detection and treatment will substantially reduce the morbidity and help in a healthy, productive, and enjoyable lifestyle [3].

Bone Mineral Density (BMD) is a good index of bone status and the most important predictor of fracture risk [4]. Dual Energy X-ray Absorptiometry (DEXA) is an excellent noninvasive choice for repeated measurements of any temporal changes of BMD because of low radiation exposure [5]. The newest approach, third generation DEXA may be quicker, noninvasive, and more precise to detect these bony abnormalities [5].

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption by their action on osteoclasts [6]. Despite hormone replacement therapy, calcium and vitamin D administration, effective iron chelation and normalization of hemoglobin levels are the most common standards of treatment. Patients with thalassemia major continue to lose bone mass and increased bone turnover rate observed justifies the use of powerful anti-resorption drugs, such as bisphosphonates. To date, Alendronate, Pamidronate and Zolidronate seem to be effective in increasing BMD and normalizing bone turnover [7]. Calcium alone has not been shown to be that effective in established osteopenia/osteoporosis. With this background the present study is designed to evaluate the role of calcium with or without bisphosphonates in improving the bone status of multiple transfused children. The aim of the study was to evaluate the efficacy of bisphosphonates in thalassemia patients with osteopenia/osteoporosis. The objectives were to evaluate the demographic profile, degree of osteoporosis and biochemical changes related to bone mineralisation along with symptomology before and after consumption of bisphosphonates with calcium. The safety profile of bisphosphonates in these patients was also evaluated.

Method and Materials

The prospective interventional study was conducted from January 2019-March 2020 at thalassemia day care centre of a tertiary care hospital after approval from Institutional Ethics Committee. After age appropriate consent of adolescent thalassemia patients and parents of children registered at thalassemia day care centre who were regularly receiving packed cell transfusion were evaluated. Of the 150 patients registered at thalassemia day care centre, 40 diagnosed with B-thalassemia major, with age more than seven years and DEXA scan showing osteopenic/osteoporotic changes were included in the study. Children with history of fractures, renal dysfunction and HIV infection were excluded from the study.

All patients were subjected to detailed history including bone pains, backache and fractures, age, sex, number of years of transfusion, chelation therapy, clinical examination, and routine and specific laboratory investigations and were entered in a pre-designed proforma.

Routine investigations like complete blood count with Red Blood Cell (RBC) indices, Liver Function Test (LFT) and Renal Function Test (RFT) were done. Specific investigations (biochemical tests) like serum calcium, phosphorus, alkaline phosphatase, Random Blood Sugar (RBS), urinary calcium/creatinine ratio, urinary phosphorus/creatinine ratio, mean pre – transfusion haemoglobin, amount of packed red cell requirement per year, BMD scan (> 7 years of age) were done.

BMD was evaluated by DEXA scan. BMD of distal forearm, femoral neck and lumbar spine were determined by DEXA on prodigy DF+14230 (third generation version) expressed as exact value in g/cm^2 and as Z scores which represent the patients BMD as compared to the peak bone mass in age matched individuals' reference mean calculated from manufacturer's database for various ethnic population. Level of osteoporosis was scored as per WHO criteria as in Table 1.

All the thalassemia patients whose BMD was showingosteoporosis were started on Alendronate (25 mg/week orally in the morning on empty stomach with full glass of water). Those patients who were taking Alendronate were explained to not to lie down till 60 minutes after taking Alendronate. Those patients who had normal DEXA scans were given only dietary and exercise counselling. Out of 40 cases, 8 (20%) children with osteopenia were given calcium at the dose of 600 to 800 mg per day, dietary counselling, and exercise. Whereas 32 (80%) with osteoporosis were given Alendronate along with diet, exercise and calcium.

The normal values of serum calcium at our laboratory is 8.4-10.6 mg% hence it was taken as normal levels for this study and <8.4 mg% was considered low while>10.6 was considered as high. Normal range for alkaline phosphatase at our laboratory is 108-306 IU/L. Urinary calcium/creatinine ratio> 0.2 and urinary phosphorus/creatinine ratio >0.6 is considered as a risk factor for osteoarthropathy. The patients were followed up monthly for one year andafter one year repeat clinical examination, biochemical tests and DEXA scan and any patient having side effects of Alendronate such as pain in abdomen, dyspepsia, musculoskeletal pain, heart burn and pain in the jaw were documented. Then analysis of the obtained data was done.

Statistical analysis

Statistical analysis was done using SPSS version 21. Symptomatology and various biochemical markers were compared pre-treatment and post-treatment. Student't' test and Chi-square test were used wherever applicable.

Table 1: WHO criteria for osteoporosis

Category	Z score
Normal	At or above -1 SD
Osteopenia	Between -1 and -2.5 SD
Osteoporosis	At or below -2.5 SD
Established Osteoporosis	At or below -2.5 SD (with fractures)

Results

As shown in Table 2, out of 40 children, 22 (55%) were males and 18 (45%) were females. Most of the children were in the age group of 10 to 15 years (50%). Among the clinical features, 24 (60.0%) of them had backache at pre-treatment which significantly reduced to only 4 (10.0%) after the treatment. Also 20 (50.0%) of the total cases had bonepain at pre-treatment which had significantly reduced to 4 (10.0%) after the treatment. None had fractures.

Table 3 reveals that mean serum calcium was 8.27 mg% at pre-treatment which was significantly low as compared to 9.26 mg% at post-treatment. Urine calcium/creatinine ratio was 0.15 which was significantly more as compared to 0.06 at post-treatment. Mean urine phosphorous/creatinine ratio was 0.74 at pre-treatment, which was significantly more as compared to 0.46 at post treatment. Mean serum inorganic phosphorous and ALP were comparable between pre and post treatment.

Of the 40 thalassemia patients at pre-treatment, 8 (20%) had osteopenia and 32 (80%) had osteoporosis. Post-treatment however there was significant increase in bone mass – 10 (25%) patients had normal Z score, 14 (35%) patients had osteopenia and only 16 (40%) had osteoporosis with improved BMD (Figure 1).

Table 2: Demographic profile of the patients

Age group (years)	**Male**	**Female**	**Total**
10 to 15	12 (60%)	08 (40%)	20 (50%)
15 to 20	06 (43%)	08 (57%)	14 (35%)
20 to 28	04 (66.67%)	02 (33.33%)	06 (15%)
Total	22 (55%)	18 (45%)	40 (100%)
Parameters	**Mean**	**SD**	**Range**
Age (years)	16.15	3.45	12-23
Weight (kg)	32.78	7.26	24.5-48
Height (cm)	137.80	11.33	120-159
Symptomatology	**Pre-treatment**	**Post-treatment**	***p***
Backache	24	4	0.0001
Bone pains	20	4	0.00095
Fractures	None	None	

**p< 0.05 Significant*

Table 3: Profile of biochemical parameters

Biochemical parameters	Pre-treatment	Post-treatment	*p*
Serum calcium	8.27 ± 00.77* (7.5-9.04)	9.26 ± 1.11 (8.15-10.37)	0.0001
Serum inorganic phosphorus	4.47 ± 01.07 (3.4-5.54)	4.70 ± 0.41 (4.29-5.11)	0.2080
Alkaline phosphatase	389.40 ± 309.04 (80.36-698.44)	426.45 ± 168.10 (258.35-594.55)	0.85
Urine calcium / creatinine ratio	0.15 ± 00.13* (0.02-0.28)	0.06 ± 0.06 (0.0-0.12)	0.0002
Urine phosphorus / creatinine ratio	0.74 ± 0.43* (1.17-0.31)	0.46 ± 0.33 (0.13-0.79)	0.0016

**p< 0.05 Significant*

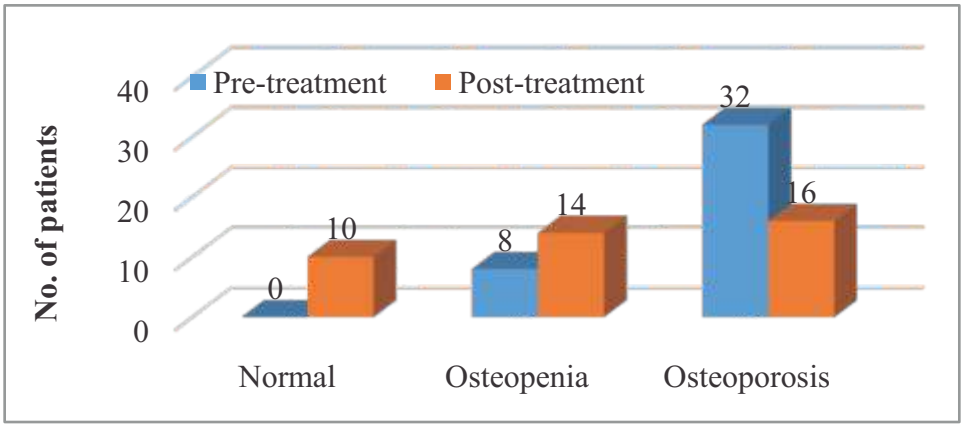

Figure 1: Comparison of mean BMD at spine, femur, and radius between pre and post treatments

Discussion

Bone diseases are one of the major causes of morbidity. As the first fracture increases the risk of subsequent fractures, it is important to prevent the occurrence of first fracture. Various biochemical and radiological parameters have been studied to detect bone loss in thalassemia patients. Bone scan by DEXA is more precise and is a well-accepted modality in patients with diseases of bone loss. These issues have been inadequately addressed in developing countries, though there are some studies from western world on thalassemia [8]. However, it will be inappropriate to extrapolate western literature to our population due to extreme diversity of dietary habits, physical life, stress,

demographic characteristics, socioeconomic status, and other compounding problems. With this background, the present study was therefore, designed to study the role of third generation DEXA to evaluate the efficacy of calcium with or without bisphosphonates in thalassemia patients with osteopenia/ osteoporosis.

A total of 40 thalassemia patients were included in the study and majority of them were in the age group of 10-15 years (50%) with male predominance (55%). Study done by Voskaridou *et al*. showed progression of osteoporosis with decreased physical activity [9], which is not the case in current study. Jansen *et al*. also reported no relationship between low bone mass and the age of the patient [10]. However, Skordis *et al*. found no significant relation between height and weight with BMD [11] while Voskaridou *et al*. found growth failure to be parallel with osteoporosis [9].

Of the18 females, 4 (22.3%) had osteopenia and 14 (77.7%) had osteoporosis and of the 22 males, 6 (27.3%) had osteopenia and 16 (72.7%) had osteoporosis. Similarly in previous studies [10, 12-13] preponderance of osteoporosis was observed in females.

Of the total cases, 60.0% had bone pain at pre-treatment which was significantly reduced to 10.0% at post treatment. Fifty percent of the total cases had backache at pre-treatment which was significantly reduced to 10.0% at post treatment. Piga *et al*. suggested exercise and dietary measures to treat patients with bone pain and poor DEXA scan [2]. Preliminary data of bisphosphonates were encouraging according to them, which are similar topresent findings.

The mean serum calcium was 8.27 mg% at pre-treatment which was significantly low as compared to 9.26 mg% at post-treatment. Of the 40 thalassemia patients at pre-treatment, 28 (70%) had serum calcium levels less than 8.4 mg%, and only 12 (30%) had normal serum calcium levels (8.4-10.6 mg%). While this data dramatically changed post-treatment when 36 (90%) had normal values, 2 (10%) had low levels and 2 (10%) had high levels. The changes in serum phosphorus levels were not statistically significant after starting on treatment. Tantawy *et al*. found no change in BMD and calcium, phosphorus, and Ca-P related hormone levels [14]. In the current study, urine calcium/creatinine ratio improved from 0.15 at pre-treatment to 0.06 at post-treatment suggesting decreased calcium excretion and better bone mineralisation. Mean urine phosphorous/ creatinine ratio did not vary during the treatment. Mean serum inorganic phosphorous and ALP were comparable. These findings are in accordance with the study done by Voskaridou *et al*. [9] and Tantawy *et al*. [14].

There was significant risein Z score and BMD after starting treatment with calcium and/ or bisphosphonates. Of the 40 thalassemia patients, 8 (20%) had osteopenia and 32 (80%) had osteoporosis. Post treatment however there was significant increase in bone mass – 10 (25%) patients had normal Z score, 14 (35%) patients had osteopenia and 16 (40%) had osteoporosis. These findings are comparable with the study conducted by Voskaridou *et al*. [16].

As far as complication goes, only 2 (5%) children had developed twitching secondary to hypocalcaemia, which had improved on oral calcium supplementation and withholding Alendronate for some time till calcium levels were normal and did not further develop this complication on restarting Alendronate. None had any side effects like gastritis, intolerance, idiosyncrasy, uveitis or thrombocytopenia. Bisphosphonates were stopped once the DEXA scan showed normal bone density.

Osteoporosis in thalassemia mainly results from bone resorption as the bone forming mechanism is intact in these thalassemia children. Further development of osteoporosis is influenced additionally by acquired or genetic elements [17]. Pollak *et al*. also stressed that increased bone resorption is a major mechanism of bone loss in thalassemia patients [18]. Therefore, anti-resorptive agents such as the bisphosphonates may be efficacious in thalassemia patients.

Conclusion

The present study has shown that bisphosphonates (Alendronate, Zolendronate) are effective in reducing osteopenia/osteoporosis in corroboration with other studies with hardly any side effects. Thereby it is recommended to do DEXA scan regularly for all thalassemia patients above the age of 10 years with regular use of bisphosphonates and calcium in those with lower BMD.

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