Efficacy and Safety of Bisphosphonate Therapy in Patients with Osteogenesis Imperfecta

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ABSTRACT

Objective: To determine the efficacy and safety of bisphosphonate therapy in patients with osteogenesis imperfecta.

Methods: 36 patients were included in this study, were of either gender with osteogenesis imperfecta (OI type I, II, III & IV). Patients with hypersensitivity to bisphosphonates, with extra-skeletal complications like pulmonary complications and poor tolerability to bisphosphonates were excluded. Informed written consent was taken. Patients were treated as outpatients on day care basis. Patients were subjected to intravenous BPs (alendronate) weight-dependent (0.5 mg-0.1mg/kg) per dose every 12 weeks. Patients were called for a follow up visit at 3rd and 6th month. The clinical evaluation of efficacy and safety was determined in terms of no fracture and no side effects respectively. Findings were recorded on a predesigned proforma and analyzed using SPSS v23.0. This was a descriptive case series study, conducted at the department of orthopedic surgery from Dec 2022 to May 2023.

Results: The mean alkaline phosphate levels were 470.81±465.09 SD prior to BPs therapy and decreased to 226.92±79.35 SD after three months of BPs therapy. The comparison of means before and after BPs therapy showed significant results (p 0.003). Three months following BPs therapy, 17 (56.7%) males and 13 (43.3%) females had effective results (p 0.764) whereas BPs therapy was safe in 20 (57.1%) males and 15 (42.9%) females and only 01 (100.0%) patient showed mild symptoms of abdominal pain (p 0.257).

Conclusion: Bisphosphonates therapy in children with osteogenesis imperfecta (OI) was effective and safe with a significant reduction in alkaline phosphate levels and decrease in the number of fractures post BPs therapy.

Keywords: Bisphosphonates (BPs), Children, Osteogenesis Imperfecta (OI), Metabolic Changes

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INTRODUCTION

Bone fragility and skeletal abnormalities are hallmarks of osteogenesis imperfecta (OI), a genetic skeletal abnormality that affects 1 in 10,000 to 20,000 newborns. OI also causes hearing loss, muscle weakness, respiratory problems, and heart problems. [1] It can also cause dental and craniofacial abnormalities. From almost asymptomatic individuals with a normal life span to severe bone abnormalities, mobility handicap, and even foetal mortality, OI is classified clinically as a spectrum from type I to type V.[4]

Supportive and symptomatic treatment for OI is difficult and may involve medication, physical therapy, or even orthopedic treatments to boost bone density, lessen the likelihood of fracture, and restore mobility. The appropriate length of bisphosphonate (BP) therapy in patients with osteoporosis is uncertain, despite the fact that BPs are the most widely prescribed drugs for OI because of their ability to boost BMD, lower fracture risk, and cause vertebral remodelling.[6] The therapeutic effects of BP medication for OI patients have been shown to be most evident in the first two to four years of

treatment.[7] Otherwise, excessive treatment has been linked to the development of iatrogenic osteopetrosis, and long-term Bisphosphonates therapy is linked to an increased risk of atypical femoral fracture in OI patients.[8]

In a study by Zhang and colleagues, patients had reduction in overall fractures after receiving treatment with bisphosphonates and only 12.7% patients experienced fractures after treatment completion.[9]

Concerns exist about the risk of skeletal fractures during treatment with bisphosphonates in patients with osteogenesis imperfecta; however, the problem has never been quantified before, not even on a global scale, so this study was conducted to determine the efficacy and safety of bisphosphonate therapy in patients with osteogenesis imperfecta. To help decide who and how to treat patients with OI, and to better prepare patients and their families for the effects of current fracture prevention regimes, knowledge of fracture rates in patients with OI under the present treatment regimen is crucial.

METHODOLOGY

Sample Size: The calculated sample size was 36 by using WHO sample size formula considering anticipated 12.7%[9] frequency of post-treatment fractures with 7% margin of error.

Sampling Technique: Non-Probability Consecutive Sampling Technique

Operational Definitions:

Osteogenesis Imperfecta (OI): A group of congenital defective skeletal disorders of variable severity, characterized by recurrent non-traumatic fractures, bowing of the legs, barrel shaped rib-cage, bluish discoloration of the sclera and X-ray revealing severe loss of bone substance, cortical thinning, coarse calcifications kyphoscoliosis, vertebral compression with flat bodies, acetabular protrusion and curving of the bones were called osteogenesis imperfecta.

Fracture: It was confirmed on X-ray. X-ray revealing a pathological breach in the continuity of the bone evident by a dark line separating the bone into two or more halves was deemed as fracture.

Data Collection Procedure:

Study was conducted from Dec 2022 to May 2023. Patients having age range 5 to 25 years, of either gender with osteogenesis imperfecta (OI type I, II, III and IV) were included. Patients with hypersensitivity to bisphosphonates, with extra-skeletal complications like pulmonary complications and poor tolerability to bisphosphonates were excluded. They were fully explained about the purpose, procedure, risks and the benefits of study and informed written consent was taken. Approval was taken from the ethical committee. OPD patients were selected and dealt on day care basis. All cases were done using strict sterile measure and were performed under supervision of consultant orthopedic surgeon.

Every parent was counselled regarding intravenous bisphosphonate therapy (Injection Zoledronic acid). All patients had a radiographic examination and baseline biochemistry, including serum calcium, phosphorus, and alkaline phosphatase, before treatment began. When necessary, further radiographs were taken. Patients were subjected to intravenous BPs (alendronate) weight-dependent (0.5 mg-0.1mg/kg) per dose every 12 weeks. Patients were called for a follow up visit at 3rd month and 6th month. During follow up visit, patients were examined for number of fractures and side effects like abdominal pain or skin irritation etc. Final clinical evaluation of efficacy and safety was determined at 6th month in terms of no fracture and no side effects respectively. Findings including age, gender, OI type, pre and post therapy metabolic changes, pre and post therapy number of fracture, efficacy and safety were recorded on a predesigned proforma. Inclusion and exclusion criteria were strictly followed to control biasness and confounders.

Statistical Analysis:

23rd Version of Statistical Package of Social Sciences was used for analyzing the data. Qualitative data like gender, type of OI, pre and post BPs therapy, number of fractures, efficacy, and safety were presented as frequencies and percentages. Quantitative variables like age, pre and post therapy metabolic changes were presented as mean $\pm$ SD. Efficacy and safety was stratified with gender to see effect modifiers. To test significance for quantitative variables, paired t test was applied and to test significance for qualitative variables, chi-square test was applied keeping p value $\leq$ 0.05 as significance level.

RESULTS

This study comprised a total of 36 patients, out of which 20 (55.6%) were males and 7 (19.4%) were females. Mean age was 4.95 years and mean number of doses received was 2.03 n. 17 (47.2%) patients had Type I OI, 7 (19.4%) patients had type II OI, 02 (5.6%) patients had type III OI and 10 (27.8%) patients had type IV OI. 22 (61.1%) patients had

blue sclera and 14 (38.9%) had normal sclera. In 09 (25.0%) patients dentinogensis imperfecta was present and in 27 (75.0%) patients dentinogensis was absent. As per number of fractures before initiation of therapy, 7 (19.4%) patients had < 3 or no fractures, 13 (36.1%) patients had 3-5 fractures and 07 (19.4%) patients had > 5 fractures. As per number of fractures after therapy, 30 (83.3%) patients had no fracture or < 3 fractures, 05 (13.9%) patients had 3-5 fractures and 01 (2.8%) patient had > 5 fractures. Overall, bisphosphonate therapy was effective in 30 (83.3%) and safe in 35 (97.2%) patients (Table 1).

Mean alkaline phosphate levels before and after therapy were 470.91U/L and 226.92 U/L respectively. The comparison of alkaline phosphate levels before and after BPs therapy was examined using Paired Samples t-test, which revealed statistically significant findings ($p < 0.003$). Mean calcium levels before and after therapy were 9.60 mg/dL and 9.95 mg/dL.

The comparison of calcium levels before and after bisphosphonate therapy was examined using Paired Samples t-test, which revealed statistically insignificant findings (p 0.126). Mean serum vitamin D levels before and after BPs therapy was 36.14 ng/dL and 33.00 ng/dL respectively. The comparison of serum vitamin D levels before and after BPs therapy using Paired Samples t-test, which revealed statistically insignificant findings (p 0.502) (Table 2).

In terms of efficacy and safety, six months after BPs therapy, 17 (56.7%) males and 13 (43.3%) females achieved effective results (p 0.764). BPs therapy was safe in 20 (57.1%) males and 15 (42.9%) females, only 01 (100.0%) patient showed mild symptoms of abdominal pain (p 0.257) (Table 3).

Table 1: Demographic and Clinical Characteristics of the Patients

Quantitative Variables	**Mean ± SD**
Age (Years)	4.958 ± 3.97 SD
Number of Doses Received (n)	2.03 ± 0.97 SD
Qualitative Variables	**n (%)**
Gender	
Male	20 (55.6%)
Female	7 (19.4%)
OI Type	
Type I	17 (47.2%)
Type II	7 (19.4%)
Type III	2 (5.6%)
Type IV	10 (27.8%)
Sclera	
Blue	22 (61.1%)
Normal	14 (38.9%)
Dentinogensis Imperfecta	
Present	9 (25.0%)
Absent	27 (75.0%)
Number of Fractures Before Therapy	
0 or < 3	7 (19.4%)
3-5	13 (36.1%)
> 5	7 (19.4%)
Number of Fractures After Therapy	
0 or < 3	30 (83.3%)
3-5	5 (13.9%)
> 5	1 (2.8%)
Efficacy	
Yes	30 (83.3%)
No	6 (16.7%)
Safety	
Yes	35 (97.2%)
No	1 (2.8%)

Table 2: Metabolic Changes Before and After Therapy

Metabolic Changes	Mean ± SD	p-Value
Alkaline Phosphate Level (U/L) (Before)	470.81 ± 465.09	0.003
Alkaline Phosphate Level (U/L) (After)	226.92 ± 79.35	
Calcium Level (mg/dL) (Before)	9.6081 ± 1.04	0.126
Calcium Level (mg/dL) (After)	9.9536 ± 0.85	
Serum Vitamin D Level (ng/dL) (Before)	36.1461 ± 26.70	0.502
Serum Vitamin D level (ng/dL) (After)	33.00 ± 17.16	

Table 3: Stratification of Efficacy and Safety with Gender

		Gender		Total	p-Value
		Male	Female		
Efficacy	Yes	17 (56.7%)	13 (43.3%)	30 (100.0%)	0.764
	No	3 (50.0%)	3 (50.0%)	6 (100.0%)	
Total		20 (55.6%)	7 (19.4%)	36 (100.0%)	
Safety	Yes	20 (57.1%)	15 (42.9%)	35 (100.0%)	0.257
	No	0 (0.0%)	1 (100.0%)	1 (100.0%)	
Total		20 (55.6%)	7 (19.4%)	36 (100.0%)	

DISCUSSION

In this study, BPs therapy showed significant reduction in alkaline phosphate levels, efficacy, and safety as before BPs therapy, the mean alkaline phosphate levels before and after therapy were 470.91U/L and 226.92 U/L respectively after three months of therapy. Overall, bisphosphonate therapy was effective in 30 (83.3%) and safe in 35 (97.2%) patients.

Previous research suggests that between 1 in 10,000 and 20,000 newborns are born with osteogenesis imperfecta (OI), a genetic skeletal dysplasia characterized by bone fragility and skeletal abnormalities. Other problems from traumatic brain injury include changes to the teeth and face, weakened muscles, impaired hearing, and trouble breathing and heart failure. Type I OI is virtually symptom-free and has a normal life expectancy, while severe type II OI causes significant bone abnormalities, mobility handicap, and even neonatal mortality.

To date, no single treatment has been described for the patients with OI and multimodal approach including physical therapy, orthopedic operations, and rehabilitation with avoidance of trauma had been the mainstay of the treatments. Among medical treatment, bisphosphonates (BPs), and the structural analogues of pyrophosphates had been utilised satisfactorily for more than two decades in individuals with osteogenesis imperfecta.[10,11]

As the goal of medical therapy in this disease is to lessen the rate of fracture, reduce bone pain, improve mobility, enhance independence, and decrease levels of bone turnover markers, the results of this study demonstrated that BPs therapy is an effective treatment in children and adolescents with osteoporosis.

Treatment with zoledronic acid significantly decreased the rate of fractures and caused metabolic changes that were equivalent to those seen in trials done in Saudi Arabia and India.[12,13]

A correlational investigation confirmed that the first year of treatment with zoledronic acid resulted in much higher bone mineralization than with any other bisphosphonate medication.[14] This is consistent with the findings of increased bone mineral density in the first 6-12 months in children treated with zoledronic acid (p 0.001).

Consistent with the results of this study, Hogler et al. found a considerable decrease in alkaline phosphate levels following BPs therapy, and they also found that hypocalcemia (74%) and hypophosphatemia (82%).[15] A clinical trial that compared the effectiveness of zoledronate and alendronate in a group of 136 individuals with OI lent further credence to these findings.[16]

Few gastrointestinal, renal, or ophthalmic adverse effects were observed in the study population, despite their presence in numerous trials including the use of oral bisphosphonates and intravenous pamidronate.[17] Children's compliance with oral BPs use may be a difficulty. Some long-term repercussions of delayed remodeling have been described, including poor longitudinal growth of bones, osteopetrosis, and even rare instances of sub-trochanteric femur fractures.[18,19]

Limitation of the study: The small sample size and single centered study were the main limitations of this study, therefore, large multicentered randomized controlled trials shall be carried out across the country in order to generalize its results to the overall population of the area.

CONCLUSION

Bisphosphonates therapy in children with osteogenesis imperfecta (OI) was effective and safe with a significant reduction in alkaline phosphate levels and decrease in the number of fractures post BPs therapy.

Conflict of Interest: None

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