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Effect of low dose pamidronate in the treatment of thalassemia-induced osteoporosis

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Abstract

Introduction: Thalassemia is the most common genetic defect, globally affecting about 200 million individuals. Increased longevity in transfusion-dependent thalassemia patients is accompanied by complications such as osteopenia, osteoporosis and skeletal disabilities. In this regard, increased bone reabsorption in beta-thalassemia has led to the administration of bisphosphonates for these patients.
Objectives: Although there is growing consensus on the effectiveness of pamidronate in thalassemia osteoporosis, the findings about the dosage and duration of pamidronate are inconsistent. Accordingly, the present study aimed to assess the impact of low-dose pamidronate on the bone mineral density (BMD) of major beta-thalassemia patients.
Patients and Methods: In this study, the participants encompassed 20 transfusion-dependent major thalassemia patients with Z-score< -2.5 in bone mineral densitometry. Bone density was determined in the lumbar vertebras and hip by using dual X-ray absorptiometry. Pamidronate was administered intravenously in monthly dosage of 1 mg/kg over six months.
Results: According to the findings, the participants' mean age was 16.55±3.15 years (Range: 10-25 years). The baseline mean of Z-score for lumbar vertebras was -2.92±1.14 and reached -1.95±1.2 after six months ($P<0.001$). Moreover, the baseline mean of Z-score for the hip region was -2.00 (0.65) and reached -1.55 (0.77).
Conclusion: The dosages of 1 mg/kg over six months had a statistically significant effect on bone density and improved Z-scores of lumbar vertebrae and hip bone density by 45% and 20%, respectively.

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Introduction

Thalassemia is the most common genetic defect, globally affecting about 200 million persons. The mechanism by which this disease is presented depends on several factors (1). Beta thalassemia refers to a group of hemoglobin-related disorders inherited through an autosomal recessive pattern, as Lee and Cooley first described. The decreased production of the beta-globulin chains is the main pathogenesis of these diseases (2). The life expectancy of those suffering from beta-thalassemia has gradually increased in recent years due to regular blood transfusions and new generations of iron-chelating agents. However, increased longevity has also been accompanied by complications such as osteopenia and osteoporosis, resulting in remarkable morbidities and disabilities in the adult population affected by major thalassemia (3, 4). Generally, untreated major thalassemia patients experience significant bone alterations at younger age (5). Decreased hormone release, specifically sex hormones, the widespread involvement of the bone marrow, iron overload, iron chelator side effects and calcium and also vitamin D deficiency seem to be the main factors significantly compromising regular bone function in thalassemia patients (6).

Some treatment regimens have been developed to target one or some of the abovementioned factors (7). Increased bone reabsorption in beta-thalassemia has led to the administration of bisphosphonates in these patients. Inhibiting bone reabsorption by osteoclasts, bisphosphonates increase bone mineral density (BMD) and prevent

Key point

Thalassemia is the most common genetic defect worldwide. Increased bone reabsorption in beta-thalassemia results in osteoporosis. Bone density is determined in the lumbar vertebras and hip by employing dual X-ray absorptiometry. Accordingly, the low-dose of pamidronate is effective in the osteoporosis among major beta-thalassemia patients. During six months, the dosage of 1 mg/kg had a statistically significant effect on bone density and remarkably improved Z-scores.

pathologic fractures in osteopenic bones (8). In this regard, intravenous pamidronate is superior to other oral bisphosphonates administered to children daily (1). However, the impact of pamidronate administration has not been addressed in children suffering from major thalassemia and subsequent osteoporosis (7).

Objectives

The present study aimed to assess the impact of pamidronate on the BMD of major beta-thalassemia patients to improve the quality of life in these individuals and facilitate future and further research.

Patients and Methods

Study design

In this qausi-experimental study, for all of the transfusion-dependent thalassemia major patients in Motahary center in Urmia, Bone density was measured in the lumbar vertebra and hip joint, using dual X-ray absorptiometry. Patients who bone mineral density was osteoporotic (Z-score <-2.5 in BMD), after acquiring primary clinical and lab examinations according to the specified protocol, were recruited with the observance of inclusion and exclusion criteria. Each patient was comprehensively informed about the study and also their rights to withdraw from the study whenever they wished. Patient follow-up was performed in accordance with the therapeutic monitoring.

Study Protocol

Inclusion criteria were as follows; Z-score <-2.5 in BMD, ferritin level >1000 mg/dL, more than of 10 blood infusions, more than 100 cc/kg of blood infusion per year and normal creatinine level and blood counts. Exclusion criteria included the positive history of bone-related disorders, leukemia or neoplastic disorders, gastrointestinal disorders and chronic inflammatory diseases.

Fasting blood samples were collected and submitted to the hospital laboratory to determine biochemical values. The levels of calcium, phosphorus, parathormone hormone (PTH), alkaline phosphatase and vitamin D were determined in the collected samples. Bone density was also assessed in the lumbar vertebras and hip using dual X-ray absorptiometry. The obtained Z-scores values were compared between age and gender-matched groups. In this regard, Z-scores >-1, -2 – -2.5 and <-2.5 were considered normal, osteopenia and osteoporosis, respectively. Pamidronate was administered intravenously in the monthly dosages of 1 mg/kg over six months. Following this period, calcium and vitamin D supplements were administered. Laboratory markers were checked at the baseline and six months after the emergence of pamidronate and consequently, variations were calculated.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) software version 22 was employed to analyse the collected data statistically applying descriptive statistics such as percentages, frequencies, mean ± standard deviation, interquartile range and median. Depending on the distribution of quantitative data, as determined by the Kolmogorov-Smirnov test, the paired-sample *t* test or Wilcoxon tests was used to analyse data statistically. Pearson's coefficient was used to assess the correlation among the research variables. In this study, $P<0.05$ was set as the significance level.

Results

Of 20 participants, 13 persons (65%) were male and 7 individuals (35%) were female, and also the participants' mean age was 16.55 ± 3.15 years (range; 10-25 years). There were statistically significant differences between the baseline and post-treatment phosphorus, PTH and alkaline phosphatase ($P=0.0001$, $P=0.004$ and $P=0.04$, respectively). The baseline and post-treatment values of laboratory variables are summarized in Table 1 and presented as mean ± standard deviation or (interquartile range). The baseline mean of Z-score for lumbar vertebras was -2.92 ± 1.14, and it reached -1.95 ± 1.2 at the end of the study after six months ($P<0.001$). Moreover, the baseline mean of Z-score for the hip region was -2.00 (0.65), and it reached -1.55 (0.77) at the end of the six-month period ($P=0.01$). The baseline and post-treatment Z-scores are summarized in Table 2.

Discussion

This study aimed to assess the impact of pamidronate administration in the monthly dosages of 1 mg/kg over six months on hip and lumbar vertebrae Z-scores in major beta-thalassemia patients. This treatment regimen improved the Z-scores of lumbar vertebrae and hip bone density in patients by 45% and 20%, indicating a

Table 1. Baseline, post-treatment and percentage changes in the values of laboratory variables

	Baseline	Post-treatment	Percentage changes	*P* value
Calcium (mg/dL), Mean ± SD	9.65 ± 0.52	9.53 ± 0.45	0.86	0.26
Vitamin D (IU), Mean ± SD	16.9 ± 6.98	19.92 ± 5.67	29.99	0.06
Phosphorus (mg/dL), Mean ± SD	4.45 ± 1	5.9 [0.85]	20	0.001
Alkaline phosphatase (IU/dL), Mean ± SD	333 ± 118.75	275.5 [167.25]	18.65	0.004
Parathormone (ng/mL), Mean ± SD	25.00 ± 43.37	21.5 [29.98]	10.87	0.04

Table 2. Baseline, post-treatment and percentage changes in the values of Z-score

		Baseline	Post-treatment	Percentage changes	*P* value
Z-score	Lumbar vertebra	-2.92 ± 1.14	-1.95 ± 1.2	<0.001	45.35
	Hip	-2.00 ± 0.65	-1.55 ± 0.77	0.01	2.2

statistically significance difference.

Data on the result of calcium and vitamin D administration in major beta-thalassemia patients are conflicting. For the first time, Wonke studied the impact of 15-60 mg pamidronate administration over six months on BMD in major beta-thalassemia patients (9). Their findings were consistent with our results while a significant improvement was observed in BMD in a majority of the patients. Voskaridou et al examined the positive impact of pamidronate on osteoporosis in beta-thalassemia. In their study, 26 patients received 30-60 mg of intravenous pamidronate per month over 12 months and then their bone marrow density and the markers of osteoclast activity were evaluated to determine the efficacy of the medication. In this study, 30 healthy patients were also assigned to the control group. They concluded that pamidronate administration significantly reduced the markers of osteoclast activity, leading to a considerable improvement in bone density of lumbar vertebrae. No significant difference was noticed between the administration of 30 and 60 mg of pamidronate (10). This finding is in line with those of the present study, especially in terms of significant variations in BMD of lumbar vertebrae following pamidronate administration.

Skordis et al examined 53 patients (namely 22 males and 31 females) from Greece. The cohort was divided into two groups receiving either alendronate (n = 29) or pamidronate (n = 24) for two years. The variations in bone density of lumbar vertebrae and the neck of the femur were analysed. In the pamidronate group, lumbar vertebrae and femoral neck bone density improved from -2.81 and -2.1 to -2.2 and -2, respectively, indicating statistically significant improvement. However, bone density variations were not significant in the alendronate group (11). In a review study by Voskaridou and Terpos, bisphosphonates such as pamidronate could significantly improve bone density in beta-thalassemia patients. However, a study with long-term follow-up is required to confirm these findings (12).

Patıroğlu et al examined 23 major thalassemia patients residing in turkey, whose bone density in lumbar vertebrae and femoral neck were measured at the baseline and two years after pamidronate administration (15 mg every three months for a total period of one year). The findings indicated that this regimen improved bone density in the femoral neck region significantly. After one year, although the variations were observable in the bone density of the lumbar vertebrae, they were not statistically significant. This is, while variations in bone density were statistically significant in both regions after two years (7).

Leung et al examined the impact of pamidronate on bone density in beta-thalassemia patients undergoing three years of continuous administration. In this regard, seven patients were included in the study and received treatment. The Z-scores of lumbar vertebrae at the baseline and endpoint were -3.0 and -2.1, and also the Z-scores of hip were -3.1 and -2.1, respectively. They found, variations in both groups were statistically significant (13). Stefanopoulos et al assessed the impact of pamidronate on osteoporosis or osteopenia in 20 patients suffering from major thalassemia. The patients received 30 mg of pamidronate/month over one year. The mean Z-scores of the lumbar spine and hip shifted from -2.98 and -1.96 to -2.44 and -1.47, respectively, revealing significant differences (14). The aforementioned studies reported that pamidronate administration positively affected osteopenia/osteoporosis in patients suffering from major thalassemia. Additionally, our findings are consistent with the aforementioned reports.

Increased bone reabsorption in beta-thalassemia patients and those requiring regular blood transfusion necessitates the use of reabsorption agents such as bisphosphonates to manage osteoporosis and osteopenia better. Bisphosphonates are a group of medications with remarkable potentials to inhibit bone reabsorption and are used widely in managing osteoporosis (15-17). These agents slow down the bone minerals reabsorption process and at the same time, increase the mineral density of the bones and retain the chemical and structural properties of the bone. Accordingly, they prevent the incidence of pathologic fractures in patients. A body of evidence suggests that bisphosphonates can significantly reduce the risk of fractures in both female and male populations suffering from primary or secondary osteoporosis (18-21). Although the pathogenesis of osteoporosis in beta-thalassemia is complex, increased bone reabsorption is considered a key factor in this process (21-23).

Bisphosphonates are the strong inhibitors of osteoclast-related bone reabsorption. At a cellular level, bisphosphonates are released during reabsorption and absorbed by osteoclasts, thereby inhibiting these cells (15-17). Nitrogen-containing bisphosphonates such as pamidronate cause variations in the skeletal structure of cells, thus inhibiting osteoclasts and activating apoptosis pathways in these cells. This is mainly achieved by synthesizing farnesyl pyrophosphate, a key enzyme within the mevalonate biosynthesis pathway (24). The administration of intravenous bisphosphonates is superior to the ingested forms since complications such as impaired

gastrointestinal uptake, administration difficulty and drug adherence are much less frequent (7).

Although a number of studies have examined the impact of pamidronate on BMD in major thalassemia patients, there are discrepancies amongst clinicians regarding the dosage duration of administration. In a recent study by Bhardwaj et al, the impact of administering intravenous pamidronate in two separate protocols (45 mg/6 weeks; n=91; and 90 mg/4 weeks; n = 36) was assessed in beta-thalassemia patients. It was reported that both protocols revealed increased bone density (lumbar vertebrae) in similar manners. Moreover, the Z-scores of lumbar vertebrae bone density in the first and second groups improved from -2.95 and -2.92 to -2.53 and -2.81, respectively, revealing statistically significant differences in both groups. The recreation of similar results with lower dosages and administration frequency is mandatory due to the medication cost and the administration method (25). This study suggests that the administration of 1mg/kg of pamidronate monthly significantly improves bone density in beta-thalassemia patients.

The minimum duration of 12 months is suggested for the administration of pamidronate (10,24). As mentioned before, the findings of the present study are obtained from six months of intravenous treatment with pamidronate. In this study, in addition to significant improvements in Z-scores in assessed regions, there was a remarkable decrease in serum parathormone and alkaline phosphatase and an increase in serum phosphorus. Serum alkaline phosphatase reflect bone metabolisms, and an inverse relationship is observed between serum alkaline phosphatase and calcium. In other words, increased alkaline phosphatase values represented increased bone metabolism and decreased BMD (26). In patients receiving bisphosphonates, decreased renal phosphate threshold and subsequently, decreased serum phosphorus are observed. This is due to the impact of parathormone on renal tubules in secondary hyperparathyroidism (27). On the other hand, when no increase in parathormone values following bisphosphonate administration is observed due to secondary hyperparathyroidism, a significant and constant increase in serum phosphorus levels is noticed following an increase in renal tubular uptake (28).

Conclusion

According to the current study's findings, the intravenous administration of pamidronate (1 mg/kg/mon over a period of six months) improves bone density in major thalassemia patients and those requiring chronic and regular blood transfusions. Further studies with larger sample sizes and longer follow-up periods are recommended.

Limitations of the study

NM, GF and GS were the principal investigators of the study. NM, GF and GS were included in preparing the concept and design. NM and GF revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that there is not any conflict of interest.

Ethical issues

The research followed the principles of the Declaration of Helsinki. The Ethics Committee of the Urmia University of Medical Sciences approved the study protocols (Code: IR.USBMSU.MSP.REC.13946.133900). Accordingly, written informed consent was obtained from all participants prior to the intervention. This study was extracted from an M.D thesis by Sima Gitifar at the Urmia University of Medical Sciences (94-0-32-1774). Additionally, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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