

Intermittent Pamidronate Treatment in Thalassaemia-induced Osteoporosis

Talasemiye Bağlı Osteoporoz Tedavisinde İntermittant Pamidronat Tedavisi

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Abstract

Purpose: In this study, we determined osteoporosis by Dual Energy X-Ray (DXA) and the effectiveness of pamidronate treatment in 24 thalassaemic patients in the Pediatric Hematology Unit of Erciyes University.

Material and Methods: Twenty-four thalassaemic patients with an age range of 6-22 years (14 girl, 10 boy, mean age: $11.20 \pm 3,9$) were included in the study. Bone mineral densities of lumbar vertebrae L1-L4 and femur neck were measured by DXA method. Z score of bone mineral densities of vertebrae L1-L4 was below -2.5 in 9 patients (37.5 %), -1 to -2.5 in 14 patients (58.3%) and was normal in one patient. Pamidronate treatment (15 mg/dose for patients at age 15 below, 30 mg/dose at age above 15, per three months for one year) was given to 23 osteoporotic (Z score below $-2,5$) and osteopenic (Z score -1 to $-2,5$) patients with bone pain and history of bone fracture.

Results: The mean Z score of L1-L4 was -2.34 ± 0.77 (Mean BMD: 0.555 ± 0.106) at the beginning and -2.17 ± 0.88 (Mean BMD: 0.587 ± 0.107) after one year. There was a statistically significant difference between results of BMD at the beginning and after 12 months.

Conclusion: Pamidronate treatment is effective in thalassaemia-induced osteoporosis.

Key Words: **Osteoporosis; Pamidronate; Thalassaemia.**

Özet

Amaç: Bu çalışmada Erciyes Üniversitesi Pediatrik Hematoloji bölümünde takip edilen 24 talasemik hastada pamidronate tedavisinin etkinliği Dual Energy X-Ray (DXA) yöntemi ile belirlenmiştir.

Gereç ve Yöntem: Bu çalışmaya yaşları 6-22 arasında (14 kız, 10 erkek, ortalama yaş: $11,20 \pm 3,9$) 24 talasemik hasta dahil edildi. Lomber L1-L4 vertebra ve femur boynu kemik mineral dansitesi (KMD) DXA yöntemi ile ölçüldü. Lomber L1-L4 vertebra KMD Z skoru 9 hastada $-2,5$ altında (%37,5), 14 hastada -1 ile $-2,5$ arası (%58,3) ve 1 hastada normal idi. Pamidronat tedavisi (15 yaşın altında 15mg/doz, 15 yaşın üstünde 30mg/doz, bir yıl süre ile üç ayda bir) osteoporotik (Z skoru $-2,5$ altında) ve kemik kırık hikayesi ve kemik ağrısı olan osteopenik 23 hastaya verildi.

Bulgular: L1-L4 vertebra başlangıçta ortalama Z skoru $-2,34 \pm 0,77$ (ortalama KMD: $0,555 \pm 0,106$), bir yıl sonra Z skoru $-2,17 \pm 0,88$ (ortalama KMD: $0,587 \pm 0,107$) idi. Başlangıç ve 12 ay sonraki KMD arasında istatistiksel olarak önemli fark vardı.

Sonuç: Pamidronat tedavisi talasemiye bağlı osteoporozda etkilidir.

Anahtar Sözcükler: **Osteoporoz; Pamidronat; Talasemi.**

Introduction

Thalassemia is a hereditary anemia resulting from defects in hemoglobin production. Beta-Thalassemia, which is caused by a decrease in the production of beta-globin chains, affects multiple organs and is associated with considerable morbidity and mortality (1). As treatment with transfusion programmes and chelation therapy has significantly prolonged survival in thalassaemia patients, osteopenia and osteoporosis represent prominent causes of morbidity in young adults of both gender with thalassaemia major or thalassaemia intermedia (2, 3). The etiology of bone disease in thalassaemia is multifactorial and is still under investigation. Several factors may affect bone metabolism and turnover in β -thalassaemia patients, such as hormone deficiency, vitamin deficiency, iron overload and chelation therapy (4-10).

Bisphosphonates increase bone mineral density (BMD) and prevent bone fractures in patients with osteoporosis (11). The effect of the pamidronate administration in pediatric thalassaemic osteoporosis has not been properly evaluated to date (12-14).

The aim of our study was to investigate the effects of pamidronate on BMD in a group of thalassaemic patients with low bone mass.

Patients and Methods

This study was prospectively conducted in Pediatric Hematology Department of Erciyes University Medical Faculty. The study group of 24 transfusion-dependent thalassaemic patients aged between 6 and 22 years (14 female, 10 male). All had been treated with monthly blood transfusion aiming for and overall mean pretransfusion hemoglobin of 9.5-10g/dl. Two out of 24 patients were splenectomized.

Body mass index (BMI) was calculated with the following formula; $BMI (kg/m^2) = \text{weight} / \text{height}^2$. All patients were under regular blood transfusion once every 3 weeks and all of them had chelation therapy. The patients received subcutaneous desferrioxamine (DFX) 40mg/kg over 10-12h five to six times per week, aiming to keep the serum ferritin level 1000 and 1500 $\mu\text{g/l}$ (normal reference range 14-300 $\mu\text{g/l}$). Their weight, height and pubertal stage were measured. The patients were evaluated prior to starting the drug and on a monthly basis thereafter. Serum levels of calcium and ionized calcium, magnesium, phosphorus, alkaline phosphates (ALP), albumin, urine calcium and creatinin were analysed using standard biochemical

methods. Serum intact paratiroid hormon (iPTH) concentrations were measured by an IRMA (B-14400 Niueller, Belgium). Serum ferritin concentration was determined using a microparticle enzyme immunoassay (Imx Ferritin assay, Abbot Diagnostics). The ferritin level was determined as the mean value of four measurements.

Bone density measurement by DXA of the lumbar spine and femoral neck is recommended as one of the most reliable and non-invasive techniques (15). The bone mineral density (BMD) of the anteroposterior lumbar spine (L1-L4) and femoral neck was determined by DXA (DXA; Hologic, QDR 4500 W, Hologic Inc., Waltham, MA, USA) before and 12 months after treatment in all patients. Osteopenia is defined as Z score between -1 to -2.5 and osteoporosis below -2.5 by WHO (1994) criteria. The patients were questioned about any symptoms at clinical examination every 3 months. Standard clinical evaluations and laboratory analyses were performed every 3 months.

The study was conducted with the approval of the Ethical Committee of the hospital. Written informed consent was obtained from all patients. Compliance with treatment and drug tolerability were good.

Treatment groups. The patients received 3-hour iv infusion of pamidronate over 12 months. Two were included: One because of history of fractures and osteopenia, and the other because of osteoporosis. Children 15 years old received 15 mg/dose of pamidronate, whereas older patients received 30 mg/dose. The dosage range was based on data from children studies that used pamidronate infusion for treatment of juvenile osteoporosis (13). No treatment-related side effects were observed.

Statistical analyses. Data were analyzed using the SPSS program (SPSS 10.0; SPSS Inc.; Chicago, IL, USA). Results are presented as mean \pm SD. The paired t test was used to compare between the baseline values and at 12 months after starting and completing the therapy. A p value of 0.05 was considered to be statistically significant.

Results

Twenty-four patients with transfusion dependent beta-thalassaemia were enrolled in our study. Ten patients were male and 14 were female, with a mean (\pm standard deviation) age of 11.2 ± 3.9 years. Nine patients had severe osteoporosis (Z -score of BMD lower than -2.5).

They were given pamidronate IV at a dose of 15-30 mg every 3 months over 12 months. The effects were monitored by measuring the BMD of the lumbar spine, femoral neck, alkaline phosphatase (ALP), as a marker of osteoblast function and iPTH, as a marker of osteoclast function.

The dosing regimen applied in our study seemed to be effective in the treatment of beta- thalassaemia- associated osteoporosis.

The clinical and hematological characteristics of all patients are shown in Table I. No association was demonstrated between the ages of the patients, overall mean pretransfusion hemoglobin and the age at which transfusion started.

Table I. Clinical Characteristics of the patients

No. of patients	24
Gender (male/ female)	10/14
Age (years)	11.2 ± 3.9
BMI (kg/m ²)	17.8 ± 2.1
Patients below 3P	11
Age started transfusion (months)	18.71 ± 16.99
Hemoglobin (g/dl)	9.0 ± 0.7
Serum ferritin (ng/dl)	1672 ± 949.3
DFX (mg/kg/day)	32.05 ± 10.35

Data are expressed as mean ± SD.

Administration of pamidronate was followed by a significant decrease in iPTH and a significant increase in the BMD of the lumbar spine and femoral neck. Serum iPTH was significantly higher in pamidronate treatment than at the beginning. Serum Ca, phosphorus (P) and

ALP did not display any significant differences between baseline and after 12 months of pamidronate treatment (Table II). Administration of pamidronate resulted in a significant increase in the BMD of the lumbar spine and the femoral neck in all patients (Table II).

Table II. Biochemical parameters and BMD at baseline and after Pamidronate treatment (Bold numbers denote statistical significance)

Parameter	Baseline	Pamidronate	P-value
Serum Ca (mg/dl)	9.79 ± 0.47	9.8±0.28	>0.05
Serum P (mg/dl)	4.7 ± 0.88	4.66±0.79	>0.05
ALP (IU/L)	445 ± 142	403 ± 127	>0.05
iPTH	39.34 ± 20.17	32.32 ± 15.58	<0.05
Lumbar spine L1-4 (g/cm ²)	0.555 ± 0.106	0.587 ± 0.107	<0.05
Lumbar spine Z score	-2.34 ± 0.77	-2.17 ± 0.88	<0.05
Femoral neck (g/cm ²)	0.628 ± 0.116	0.677 ± 0.138	<0.05

Data are expressed as mean ± SD.

Compared with DFX dose >40mg/kg/day and serum ferritin level >1500mg/ml, lumbar spine bone mineral density were significantly elevated in DFX dose

40mg/kg/day and serum ferritin level 1500mg/ml (P<0.05, Table III).

Table III. Serum ferritin levels/ DFX dose and lumbar BMD at baseline

	L1-4 BMD	P-value
Ferritin		
>1500 mg/ml	0.540 ± 0.128	>0.05
< 1500mg/ml	0.571 ± 0.117	<0.05
DFX		
>40mg/kg/day	0.545 ± 0.135	>0.05
< 40mg/kg/day	0.557 ± 0.110	<0.05

Discussion

The pathogenesis of bone disease in thalassaemia is multifactorial; underlying mechanisms include bone marrow expansion, iron overload, desferrioxamine toxicity, calcium/ vitamin D deficiency, genetic factors, and hormonal deficiency (1, 2, 16).

Several genetic and acquired factors are implicated in bone destruction in thalassaemia. The typical delay in sexual maturation, presence of diabetes and hypothyroidism, parathyroid gland dysfunction, ineffective haemopoiesis with progressive marrow expansion, direct iron toxicity on osteoblasts and deficiency of growth hormone (GH) or insulin like growth factor I (IGF-I) have been indicated as possible causes for thalassaemia-induced osteoporosis (2, 3, 5, 15-17). The therapeutic approaches, which have so far been proposed to prevent or to manage osteoporosis in thalassaemia, aim to correct one or more of the above disturbances.

Bone disease in patients with thalassaemia major is a multifactorial and still poorly understood process. An increased bone resorption, as shown by high levels of urinary bone resorption markers, had been demonstrated in previous studies (18). However, in previous studies, not all thalassaemic patients had elevated urinary bone resorption markers (18, 19).

Earlier studies of bone mineral metabolism in thalassaemic patients concentrated mainly on the paediatric and adolescence age groups (20-22). Recent advances in the field of bone mineral metabolism, including precise measurements of bone mass, the assessment of bone turnover by biochemical indices and the introduction of new therapeutic modalities such as the bisphosphonates, may have clinical utility in thalassaemic osteoporotic patients.

Voskaridou et al. reported that markers of bone resorption were significantly increased, while those reflecting bone formation were not; this observation supports that treatment with agents possessing anti-osteoclastic activity, such as bisphosphonates, may be of benefit for the patients (23).

Bisphosphonates have been considered as a first line treatment for postmenopausal and male osteoporosis as well as for steroid-induced bone loss (11).

Pamidronate, a second-generation aminobisphosphonate given intravenously, has produced a clear increase of BMD in postmenopausal and steroid-induced osteoporosis (14, 23-25). Intravenous pamidronate also has several advantages over daily oral bisphosphonate administration in many pediatric patients, including overcoming the poor absorption of oral bisphosphonates, the relative ease of administration, the lack of gastrointestinal side effects (particularly in the presence of gastroesophageal reflux), and ensured compliance (13, 23).

Firstly, Wonke (26) evaluated the effect of pamidronate on the BMD of 39 thalassaemia major patients. Pamidronate i.v. was given at doses of 15–60 mg, in a 40 minute infusion, with monthly intervals. A significant improvement in BMD was observed in most adult patients.

The group compared the effects of two different doses of pamidronate, 30 mg vs. 60 mg, on BMD of the lumbar spine, the femoral neck and the forearm and on markers of bone remodelling and osteoclast function in 26 patients with thalassaemia and osteoporosis (23). Thirteen patients with thalassaemia major and five patients with thalassaemia intermedia were given pamidronate at a dose of 30 mg in a 2-h i.v. infusion, once a month for 12 months; another eight patients (four with thalassaemia major and four with thalassaemia intermedia) received a dose of 60 mg/month,

in an attempt to explore whether increasing the dose of pamidronate might have any additional effect. Finally, Voskaridou et al. (23) found no differences between the two doses of pamidronate in terms of the reduction of bone resorption markers or improvement of the lumbar BMD, suggesting that 30 mg of pamidronate seems to be as effective as 60 mg in thalassaemia patients with osteoporosis. Voskaridou et al. (23) have shown that the increase in lumbar BMD was not accompanied by a comparable increase in the femoral neck BMD. In the present trial, we explored the effect of pamidronate on bone remodelling and BMD in patients with beta-thalassaemia and osteoporosis; to this effect we evaluated three month doses of intravenous pamidronate, 15- 30 mg.

Administration of pamidronate in our thalassaemic patients reduced bone resorption and increased lumbar and femoral neck BMD. To our knowledge, this is the first study in which pamidronate was utilized to treat osteoporosis in thalassaemic pediatric patients.

In conclusion, patients with beta-thalassaemia have increased bone resorption, which results in low BMD. Pamidronate, at a monthly dose of 15-30 mg, i.v., is very effective in reducing osteoclast activity and bone resorption. We found significant improvements in the bone density of our patients treated for at least a year with pamidronate. Clinical evidence supporting the beneficial effects of pamidronate is the apparent increase of the lumbar BMD. The data reported here indicate that intravenous infusion of pamidronate is efficacious and well tolerated in pediatric patients with symptomatic osteoporosis. However, more trials must be conducted in order to clarify the exact role of biphosphonate in thalassaemic pediatric patients. Future research should focus on ways of monitoring and treating children in order to preserve normal patterns of growth and bone mineralization, thus preventing the problems of pain and disability in the later life.

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