Treatment of thalassemia-induced osteoporosis with intermittent pamidronate infusions: Two-year follow-up

Talasemiye bağlı osteoporoz tedavisinde intermittent pamidronat infüzyonu: İki yıllık takip sonuçları

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Abstract

Objective: The purpose of this study was to evaluate the bone mineral density (BMD) in 23 patients aged 7-14 years with thalassemia major and to assess the alterations in bone density in a two-year follow-up study.

Method: BMD of the lumbar spine and femoral neck was determined by dual-energy X-ray absorptiometry (DXA) at baseline, after 12 months of treatment and two years later. Pamidronate treatment (15 mg/dose, every 3 months for 1 year) was given to 23 osteoporotic (Z score below -2.5) and osteopenic (Z score -1 to -2.5) patients. After 12 months of treatment, all patients received only calcium and vitamin D supplements. After the two years of follow-up, BMD of the lumbar spine and femur was measured using DXA.

Result: Administration of pamidronate resulted in a significant increase in BMD of the femoral neck. Lumbar spine BMD after pamidronate treatment was slightly higher than at baseline, but this was statistically non-significant. After two years, femoral neck and lumbar BMD had significantly increased compared to baseline.

Conclusion: In view of the present findings, longer follow-up studies to determine long-term treatment are fully warranted.*(Turk J Hematol 2008; 25: 79-82)*

Key words: Osteoporosis, pamidronate, thalassemia.

Özet

Amaç: Bu çalışmanın amacı 7-14 yaşlarında talasemi major tanısı alan 23 hastanın kemik mineral dansitesini ve iki yıllık takip sonrası kemik dansitesindeki değişiklikleri (KMD) değerlendirmektir.

Yöntem: Lumber vertebra ve femoral boyun Dual enerji X-ray absorbsiyometri (DXA) ile başlangıçta, tedaviden 12 ay ve 2 yıl sonra değerlendirildi. Pamidronat tedavisi (15mg/doz, bir yıl süreyle 3 ayda bir) 23 osteoporotik (Z skoru -2,5 altında) ve osteopenik (Z skoru -1 ile -2,5 arası) hastaya verildi. Tedaviden 12 ay sonra tüm hastalara sadece kalsiyum ve vitamin D verildi. İki yıl sonra lumber vertebra ve femur KMD'si DXA ile ölçüldü.

Bulgular: Pamidronat verilmesi femur boyun KMD'sinde önemli bir artış sağladı. Lumber vertebra KMD'si pamidronat grubunda başlangıç grubuna göre hafif yüksekti ama bu istatistiksel olarak anlamlı değildi. İki yıl sonra femur boynu ve lumber vertebra KMD'sinde artış vardı.

Sonuç: Bu bulgular doğrultusunda, uzun dönem tedaviyi belirlemek için daha uzun dönem takip çalışmalarına ihtiyaç vardır. *(Turk J Hematol 2008; 25: 79-82*

Anahtar kelimeler: Osteoporoz, pamidronat, talasemi

Introduction

Beta-thalassemia represents a group of recessively inherited hemoglobin disorders first described by Cooley and Lee and characterized by reduced synthesis of the beta-globin chain [1]. The homozygous state results in severe anemia, which requires regular blood transfusion. The life expectancy of patients with beta-thalassemia has greatly improved over the

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last years as a result of regular transfusions and increased compliance with iron chelation therapy. However, this increase is often accompanied by a series of serious complications including osteopenia and osteoporosis [1,2].

As a rule, untreated thalassemia major patients present with severe bone deformities very early in life [3]. The etiology of bone disease in thalassemia is multifactorial and is still under investigation. Factors such as hormonal deficiency, especially gonadal failure, bone marrow expansion, increased iron stores, desferrioxamine (DFX) toxicity and calcium/vitamin D deficiency all seem to have a serious impact on the impaired bone metabolism of the disease [4-10].

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

In this study, BMDs of a pediatric age group with thalassemia major are reported. Also presented are the changes in BMD without any special treatment for osteoporosis during a two-year follow-up.

Materials and Methods

This study was prospectively conducted in the Pediatric Hematology Department of Erciyes University Medical Faculty between January 2002 - 2005. The study group consisted of 23 transfusion-dependent thalassemic patients aged between 7 and 14 years (12 female, 11 male). Four of 12 females and 3 of 11 males were prepubertal. At the end of the study, all of them were pubertal. All had been treated with monthly blood transfusion aiming for an overall mean pretranfusion hemoglobin of 9.5-10 g/dl. Two out of 23 patients were splenectomized.

Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). All patients were under regular blood transfusion once every three weeks and all had chelation therapy.

The patients received subcutaneous DFX 40 mg/kg over 10-12 h five to six times per week, aiming to keep the serum ferritin level at 1000 and 1500 μg/L (normal reference range 14-300 μg/L). Their weight, height and pubertal staging according to Tanner were measured serially. Bone density measurement by dual energy X-ray absorptiometry (DXA) of the lumbar spine and femoral neck is recommended as one of the most reliable and non-invasive techniques [15]. The BMD of the anteroposterior lumbar spine (L1-L4) and femoral neck was determined by DXA (Hologic, QDR 4500 W, Hologic Inc., Waltham, MA, USA) at baseline, 12 months after treatment and after two years of follow-up in all patients. Osteopenia is defined as Z-score between -1 to -2.5 and osteoporosis as below –2.5 according to the World Health Organization (WHO) (1994) criteria. No matched control group was used for comparison of the results in these patients. The Z-score is the number of standard deviations above or below the average of age- and sex-matched control subjects (available from Hologic). None of them received hormone replacement therapy during the two years. The patients were questioned about any symptoms during clinical examinations every three months. No bone pain or changes in life quality were reported in these patients. Standard clinical evaluations and laboratory analyses were performed every three 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 group

The patients received three-hour intravenous (IV) infusion of pamidronate over 12 months. Two were excluded: One because of history of fractures and osteopenia, and one because of osteoporosis. Pamidronate treatment (15 mg/dose, every 3 months for 1 year) was given to 23 osteoporotic (Z score below -2.5) and osteopenic (Z score -1 to -2.5) patients. The dosage range was based on data from child studies that used pamidronate infusion for treatment of juvenile osteoporosis [13]. After 12 months of treatment, all patients received only calcium and vitamin D supplements. Most of the patients that complained of severe bone pain at the onset of the study reported feeling much better during and after treatment. There were no bone fractures during or after treatment.

Statistical methods

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 10.00. Results are presented as mean±SD and median (minimum-maximum). The changes over time were evaluated by analysis of variance (ANOVA) for repeated measures and then by Friedman test for abnormally distributed data. Dunn's method was used as post-hoc. A value of $p<0.05$ was considered to be statistically significant.

Results

The demographic characteristics of all patients are shown in Table 1. There were no significant differences between the groups.

The BMD values are presented in Table 2. There were significant increases in femoral neck BMD after pamidronate treatment and after two years compared with baseline values ($p<0.05$). Lumbar spine BMD showed no significant difference after pamidronate treatment when compared to baseline value, but after two years, lumbar spine BMD had increased significantly compared to baseline. Lumbar spine Z scores did not change significantly at any time ($p>0.05$).

Discussion

The pathogenesis of bone disease in thalassemia is multifactorial; underlying mechanisms include bone marrow expansion, iron overload, DFX toxicity, calcium/vitamin D deficiency, genetic factors, and hormonal deficiency [1,2,16].

As treatment with transfusion programs and chelation therapy has significantly prolonged survival in thalassemia patients, osteopenia and osteoporosis represent prominent causes of morbidity in young adults with thalassemia major or intermedia

[3,5]. The therapeutic approaches, which have so far been proposed to prevent or to manage osteoporosis in thalassemia, aim to correct one or more of the above disturbances.

The mechanism of reduced bone mass in thalassemic patients is still uncertain. An increased bone resorption, as shown by high levels of urinary bone resorption markers, had been demonstrated in previous studies [17]. However, in the previous study, not all thalassemic patients had elevated urinary bone resorption markers [17,18]. In our study, we did not determine bone metabolic markers of osteoblastic and osteoclastic activity.

Earlier studies of bone mineral metabolism in thalassemic patients concentrated mainly on the pediatric and adolescent age groups [19-21]. 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 thalassemic osteoporotic patients [22]. Voskaridou et al. [22] 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.

Pamidronate, a second-generation aminobisphosphonate given intravenously, has produced a clear increase in BMD in postmenopausal and steroid-induced osteoporosis [23-25]. IV 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. However, in a recent study of 25 thalassemic patients with osteoporosis, oral alendronate but not clodronate significantly increased BMD [12].

Wonke [26] first evaluated the effect of pamidronate on the BMD of 39 thalassemia major patients. Pamidronate was given at doses of 15–60 mg, in a 40 min infusion, at monthly intervals. A significant improvement in BMD was observed in most adult patients.

One group compared the effects of two different doses of pamidronate, 30 mg vs. 60 mg, on BMD of the lumbar spine, femoral neck and the forearm and on markers of bone remodeling and osteoclast function in 26 patients with thalassemia and osteoporosis. Thirteen patients with thalassemia major and five patients with thalassemia intermedia were given pamidronate at a dose of 30 mg in a 2-h IV infusion, once a month for 12 months; another eight patients (4 with thalassemia major and 4 with thalassemia 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. [22] found no differences between the two doses of pamidronate in terms of reduction in bone resorption markers or improvement in the lumbar BMD, suggesting that 30 mg of pamidronate seems to be as effective as 60 mg in thalassemia patients with osteoporosis. Voskaridou et al. showed that the increase in lumbar BMD was not accompanied by a comparable increase in femoral neck BMD [22]. In the present trial, we explored the effect of pamidronate on bone remodeling and BMD in patients with beta-thalassemia and osteoporosis; in this regard, we evaluated three-month doses of IV pamidronate, 15-30 mg.

Administration of pamidronate in our thalassemic patients increased lumbar and femoral neck BMD. The two-year follow-up proved that vitamin D and calcium supplementation alone in children with thalassemia is important and successful in increasing the BMD. Some investigators believe that peak bone mass is re-

Table 1. Clinical characteristics of the patients

	Patients
No. of patients	23
Gender (female/male)	12/11
Age (years)	
Female*	9.3 ± 1.4
Male*	11.5 ± 2.4
BMI (kg/m^2)*	17.9 ± 2.1 / 18.1± 2.0

* BMI:Body mass index

Table 2. Comparison of the BMD at baseline, 12 months later and after two years

BMD	Baseline	Pamidronate (12 months later)	After two years	Friedman chi-square	P-value*
Femoral neck (g/cm2)	0.63±0.07	0.67±0.09[a]	0.68±0.82[a]	12.08	0.002
	0.62 (0.49 - 0.81)	0.64 (0.55 - 0.93)	0.67 (0.59 - 0.88)		
Lumbar spine L1-4 (g/cm^2)	0.55±0.10	0.58±0.10	0.62±0.12[a]	13.65	0.001
	0.53 (0.39-0.82)	0.56 (0.42 - 0.86)	0.59 (0.45 - 0.88)		
Lumbar spine Z score	-2.33±0.78	-2.20±0.84	-2.45±0.93	1.65	0.44
	-2.18 (-4.29 - -0.85)	-2.20 (-4.49 - -0.96)	-2.35 (-4.29 - -0.69)		

Values are given as mean ± SD and median (minimum-maximum).
* P<0.05, baseline vs. pamidronate vs. after two years (ANOVA-Friedman). Dunn's method was used post-hoc.
a Significantly higher than values at baseline.

ached in adolescence [19]. The skeletal bone mass is the result of a balance between the amount of bone gained during growth and the subsequent bone loss. In thalassemic patients, both these processes would be altered. However, in children BMD increases during growth and reaches peak bone mass in puberty.

In conclusion, pamidronate, at a monthly dose of 15-30 mg IV, is very effective in reducing osteoclast activity and bone resorption. In thalassemic patients, the regular use of calcium/vitamin D supplementation can be useful. In view of the present findings, longer follow-up and bone resorption marker studies, which are needed to determine accurate and long-term treatment, are fully warranted.

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