Effect of Pamidronate on Osteoporosis in Patients with β-Thalassemia Major

Naderi M, Zakeri Z*, Dorgalaleh A, Alizadeh SH, Tabibian SH, Bamedi T

1. Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
2. Clinical Research and Development Center, Ali Ebn-e Abitaleb Hospital, Zahedan University Of Medical Sciences, Zahedan, Iran.
3. Allied Medical School, Tehran University of Medical Sciences, Tehran, Iran.

*Corresponding Author: Zakeri Z, Email: naderifactorxiii@yahoo.com

Submitted: 04-12-2013, Accepted: 29-04-2014

Abstract

Background: β-thalassemia major is a hereditary life threatening anemia which requires regular blood transfusion. Clinical symptoms of the disease are growth retardation, pallor, jaundice and skeletal alternations. The variety of bone disease in thalassemia major is manifested by diffuse bone pain or deformity, spontaneous and pathologic fractures and osteopenia or osteoporosis. This study aimed to evaluate the effect of Pamidronate on beta thalassemia major induced osteoporosis.

Patients and Methods: This cross sectional study was conducted on 20 patients with β-thalassemia major with osteoporosis. Patients received Pamidronate injections (30 mg in equal intervals of one month) for one year. At the beginning and the end of study period (after twelve months of treatment) patients’ BMD and Z score of lumbar spine and Hip were determined.

Results: The mean baseline BMD of lumbar spine and hip among patients were 0.97±0.720 (gr/cm²) and 0.83±0.684 (gr/cm²) respectively which at the end of the study these numbers reached to 1.00±0.783 (gr/cm²) (p<0.001) and 0.97±0.713 (gr/cm²) (p=0.015) respectively. The mean baseline Z score of lumbar spine and hip for patients were /0±98-2-956 and 727/0±96-1- before treatment (one full year of treatment) that reached 886/0±44/2- (p=0.001) and 856 /0±47/1- (p=0.003) respectively. The baseline alkaline phosphatase was 94/89±85/385 µg/dl and after treatment this value decreased to 66/113±95/251µg/dl (p<0.001).

Conclusion: The Pamidronate is effective in increasing the bone mineral density and improving the osteoporosis condition in patients with β-thalassemia major.

Keywords: Osteoporosis, BMD (Bone Mineral Density), β-thalassemia major, Pamidronate.

Introduction

The term thalassemia stems from the Greek, thalassa (sea) and hemia (blood). This disorder is classified into two major types, α-thalassemia and β-thalassemia. β-thalassemia syndromes are a group of hereditary blood dysfunctions characterized by unbalanced β-globin chain synthesis, resulting in decreased Hb, diminished RBC production and anemia with ineffective erythropoiesis and increased peripheral hemolysis. It consists of three main forms: thalassemia major, thalassemia intermedia and thalassemia minor.

β-thalassemia major (TM) is a hereditary hemolytic anemia that requires regular blood transfusions and most affected people are Mediterranean. Clinical symptoms of thalassemia major occurs between 6 and 24 months after the birth and affected infants are identified by growth retardation, pallor, jaundice, hepatosplenomegaly, progression of masses from extra medullary hematopoiesis, and skeletal alternations resulting from expansion of the bone marrow. The variety of bone diseases in thalassemia major patients are manifested by diffuse bone pain or deformity, fail to thrive, scoliosis, nerve compression, spinal deformities, spontaneous and pathologic fractures and osteopenia or osteoporosis.

Osteopenia and osteoporosis are one of the common complications, especially in adult TM patients and they are prominent causes of morbidity in patients of both genders who...
survive longer as a result of better treatment methods. The pathogenesis of osteoporosis in TM is very complicated and several genetic and acquired factors are implicated in the incidence of bone diseases among TM patient, including hypogonadism, growth hormone (GH) and insulin growth factor-(IGF)-1 deficiency, hypothyroidism, ineffective haemopoiesis with progressive marrow expansion and direct iron toxicity on osteoblasts.

Among these factors are hypogonadism and delayed puberty causing enhanced resorption of bone and interference with bone reconstruction by inhibiting osteoblast activation and/or increasing osteoclast function. Neoplastic disorders, gastrointestinal disorders, inflammatory conditions, and drugs may also cause osteoporosis. Genetic factors seem to play an important role in the pathogenesis of postmenopausal osteoporosis and osteoporotic fractures. In TM patients, heightened markers of bone resorption such as serum alkaline phosphatase (sALP), osteocalcin (OC), serum levels of tartrate-resistant acid phosphatase isoform 5b (TRACP-5b), pyridinoline, deoxypyridinoline, urinary levels of N-telopeptides of collagen type I (NTX) and elevated ratio of (receptor activator of nuclear factor-kappa B ligand)/OPG (osteoprotegerin) that seem to account for increased osteoclastic activity, diminished bone mineral density and consequently bone diseases, are observed.

Pamidronate, a second generation of amino bisphosphonates has been used intravenously at a monthly dose of 30 mg depending on patient’s condition with minimal side effects for prevention and treatment of osteoporosis. Bisphosphonates are strong inhibitors of osteoclastic bone resorption with high affinity for bone minerals that attach to sites of elevated bone resorption or production and act by inhibiting osteoclastic recruitment, intercepting the development of monocyte precursors into osteoclasts, evolving osteoclast apoptosis and discontinuing of their attachment to the bone and thus, increasing the BMD, diminishing the markers of bone resorption and prevention of bone fractures.

Along with previous studies this investigation aimed to evaluate the effect of Pamidronate on thalassemia major-induced osteoporosis.

**Patients and Methods**

**Study population**

This clinical trial study was conducted on 20 patients with thalassemia major disease during April 2012 to May 2013. Written consent was obtained from each participant and the study was approved by the medical ethics committee of Zahedan University of Medical Science.

**Study protocol**

Inclusion criteria for the present study were having B-thalassemia major, BMD< -2.5, serum ferritin level > 1000 mg/dl, more than 10 sessions of blood transfusion or having received more than 100 cc/kg of blood up to the study time, normal serum creatinine level and also normal complete blood count (CBC). Exclusion criteria were history of bone diseases, leukemia or other neoplastic disorders, gastrointestinal disorders or inflammatory conditions during the study.

All patients were first interviewed by a trained staff to complete a detailed questionnaire regarding

<table>
<thead>
<tr>
<th>Region</th>
<th>Analysis</th>
<th>Before treatment</th>
<th>After twelve months of treatment</th>
<th>Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar</td>
<td>BMD(gr/cm²)</td>
<td>0.720±0.097</td>
<td>0.783±0.100</td>
<td>-0.060</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>spine</td>
<td>Z score</td>
<td>-2.98±0.956</td>
<td>-2.44±0.886</td>
<td>-0.53</td>
<td>0.001</td>
</tr>
<tr>
<td>Hip</td>
<td>BMD(gr/cm²)</td>
<td>0.684±0.083</td>
<td>0.713±0.097</td>
<td>-0.029</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Z score</td>
<td>-1.96±0.727</td>
<td>-1.47±0.856</td>
<td>-0.48</td>
<td>0.003</td>
</tr>
</tbody>
</table>
demographic data and previous medical history including age, gender, height, weight, duration and frequency of blood transfusion. In addition, all participants were questioned about any symptoms like bone pain and life quality changes during clinical examinations every two months. Selected patients were under regular blood transfusion once about every 3 to 4 weeks and all were on chelation therapy by standard protocol. Patients with BMD score (measured by dual energy X-ray absorptiometry (DXA) method) of less than -2.5, at the beginning of study, were considered osteoporotic. All patients regularly received three-hour intravenous (IV) infusion of Pamidronate (Caspian Pharmaceutical Companies, Tehran, Iran) in doses of 30 mg in equal intervals of one month for one year. All patients also received calcium and vitamin D supplementary treatment and patients with hypogonadism also underwent hormone replacement therapy (HRT). During the entire period of the study, patients were regularly checked by physical examination and also by hematological (CBC) and biochemistry (Alkaline phosphatase, ferritin and serum iron) laboratory analysis. For evaluation of treatment efficacy, BMD and Z-score of patients’ hip and lumber regions were measured at the beginning and at the end of the study. The Z-score is the number of standard deviations above or below the average for age- and sex-matched control subjects.

Statistical analyses

Data was collected during the entire period of the study and analyzed by SPSS statistical software. Paired-t test was applied to compare variable changes before and after treatment. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level of significance.

Results

For a total of 20 patients (all women) the mean age was 23.1±3.3 years (range 18-31 years). The mean weight and height were 42±8 kg and 152±5 cm respectively.

The mean baseline BMD of lumbar spine was 097/0±720/0(gr/cm²) that after one year of treatment with Pamidronate reached 100/0±783/0 (gr/cm²) (p<0.001) (Table 1). The baseline BMD of hip was 083/0±684/0(gr/cm²) that after treatment, reached to 097/0±713/0(gr/cm²) (p=0.015) (Table 1). The baseline Z scores of the hip region was 727/0±96/1- which reached to 856/0±47/1- (p=0.003) (Table 1).

The baseline alkaline phosphatase was 94/89±85/385 µg/dl that after treatment this value decreased to 66/113±95/251µg/dl (p<0.001).

Discussion

Osteoporosis in TM patients is a prominent cause of morbidity in both genders. The etiology of the bone disease in these patients is very complex and multifactorial. It is commonly accepted that its main causes include factors primarily interfering with bone reconstruction, such as aging, genetic abnormalities of osteogenesis especially COLIA1 gene polymorphism, defective certain nutritional elements including vitamin D deficiency or physical activity, elevated iron stores, desferrioxamine toxicity and endocrine disorders mainly estrogen deficiency which cause increased resorption. The primary disease, itself may make a mechanical interruption of bone production through bone marrow expansion, leading to cortical thinning, augmented distortion and fragility of the bones. Moreover, changes in the RANK/RANKL/OPG system in favor of osteoclasts seem to have a serious influence on the impaired bone metabolism in the bone disease. Patients show an enhanced resorptive phase resulting in seriously decreased bone mineral density (BMD), indirectly indicating an increase in osteoclastic activity. One of the therapeutic approaches, which have so far been suggested to prevent or manage osteoporosis in thalassemia, and aims to emend one or more of the above disturbances, is Pamidronate. This medicine results in increased bone mineral density and prevention of bone fractures through inhibiting osteoclastic recruitment and maturation.

In this study we evaluated the effect of Pamidronate treatment on thalassemia major-induced osteoporosis by determination of BMD and Z score of the lumbar spine and the hip region. There are a few similar studies which have assessed the effect of this drug on improvement of osteoporosis in patients with thalassemia.

In our study, prescription of Pamidronate injections with a dose of 30 mg/month caused...
significant increase of BMD that showed the effectiveness of this drug in improving the osteoporosis among thalassemia patients. Our results also indicated that Pamidronate causes significant change in Z score of β-thalassemia major patients with osteoporosis. Measurement of serum alkaline phosphatase also revealed a decrease after administration of Pamidronate that itself was an indicator of osteoporosis improvement.

In a similar study, Terpos et al. have shown the effect of 15 mg of Pamidronate injection per month on increasing the BMD in TM patients with osteoporosis 16. In another evaluation, Voskaridou et al. in 2003 indicated the effect of Pamidronate in thalassemia major-induced osteoporosis and postmenopausal women through increased BMD and diminishing the markers of osteoclast function including TRACP-5b, NTX, OPG, and RANKL. In another study Brumsen et al. in 2002 have shown that Pamidronate administration causes the increase of BMD and decrease of bone fractures in postmenopausal and steroid-induced osteoporosis 20. Also Viereck et al. in 2002 demonstrated that Pamidronate can enhance the production of OPG by primary human osteoblasts, thus antagonizing the osteoclast genetic activity of RANKL and finally increase the BMD. Skeletal assessment is important to determine the risk of fracture in transfusion dependent thalassemia patients. The etiology of increased bone turn over are multifactorial, but bisphosphonates such as alendronate, pamidronate, and zolendronic acid are effective in repairing the bone mineral density. Our study did not have a big sample size and more trials are necessary to compare the efficacy of these products in reducing fracture risks and to produce national guidelines in treatment of osteoporosis among thalassemic patients.

Conclusion

The Pamidronate is effective in increasing the bone mineral density and improving the osteoporosis condition in patients with β-thalassemia major.

References