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Evaluation of Two Different Pamidronate Treatment Protocols in Children with Osteogenesis Imperfecta

Osteogenezis İmperfekta Olan Çocuklarda İki Farklı Pamidronat Protokolünün Değerlendirilmesi

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ABSTRACT

Purpose: Osteogenesis imperfecta is an inherited disorder of connective tissue. Children with this condition suffer from recurrent fractures, deformities, osteoporosis and pain. Over the recent years, pamidronate became the standard treatment choice. However the optimal dose and interval have not been defined yet. The main of this study was to compare of two different pamidronate regime.

Materials and Methods: 12 patients aged 42.3 ± 37.4 months were studied. At the beginning patients had received pamidronate infusion at a dose of 1.5 mg/kg/day once, every two months with duration of 23.5 ± 9.0 months (first protocol), than switched to a dose of 1mg/kg/day for three consecutive days, every three months with duration of 18.5 ± 5.1 months (second protocol). The bone mineral density Z-score was evaluated yearly.

Results: Annual fracture rate decreased from 6.3 ± 5.5 to 1.1 ± 1.3 (p=0.001) in the first and from 1.1 ± 1.3 to 0.0 ± 0.0 (p<0.001) in the second protocol. Bone mineral density Z-scores increased from -3.9 ± -1.4 to -2.5 ± -1.3 (p<0.05) in the first, and from -2.5 ± -1.3 ± -1.2 ± -1.1 (p<0.05) in the second protocol.

Conclusion: Our study demonstrated that higher yearly doses in 3 consecutive day administration of pamidronate did not provide any additional beneficial effects. Furthermore, higher doses of treatment and longer duration of hospitalization led to the loss of school hours and work hours of parents and was more costly.

Key Words: Osteogenesis imperfecta, pamidronate, children.

ÖZET

Amaç: Osteogenezis imperfekta bağ dokusunun kalıtsal bir hastalığıdır. Bu durumdaki çocuklar tekrarlayan kırıklar, deformiteler, osteoporosis ve ağrıdan yakınırlar. Son yıllarda pamidronat standart tedavi tercihi olmuştur. Ancak, optimal doz ve aralık henüz tam olarak belirlenmemiştir. Bu çalışmada amaç, iki farklı pamidronat tedavi rejiminin karşılaştırılmasıdır.

Materyal ve Metod: Yaşları 42.3 ± 37.4 ay arasında değişen toplam 12 hastada yapıldı. Başlangıçta her iki ayda bir defa 1.5 mg/kg/gün dozunda 23.5 ± 9.0 ay pamidromat infüzyonu uygulandı (ilk protokol), daha sonra üçer aylık aralarla 3 gün üstüste 1 mg/kg/gün 18.5 ± 5.1 ay dozuna geçildi (ikinci protokol). Kemik mineral dansitesi z-skoru yıllık değerlendirildi.

Bulgular: Yıllık kırık oranı ilk protokolde 6.3 ± 5.5'den 1.1 ± 1.3'e (p=0.001), ikinci protokolde 1.1 ± 1.3'den 0.0 ± 0.0'a (p<0.001) düştü. Kemik mineral dansitesi z-skoru ilk protokolde -3.9 ± -1.4'den -2.5 ± -1.3'e (p<0.05), ikinci protokolde -2.5 ± -1.3 ±'den -1.2 ± -1.1'e (p<0.05) yükseldi.

Tartışma: Çalışmamızda pamidronatın 3 gün üst üste yıllık yüksek doz uygulamasının herhangi bir ek yarar sağlamadığı gösterilmiştir. Ayrıca, yüksek doz tedavi, uzun süre hastanede yatışa, okul saatlerinde ve ebevenylerin zaman kaybına ve böylece fazla maliyete neden olmaktadır.
Anahtar Kelimeler: Osteogenesiz imperfekta, pamidronat, çocuklar

INTRODUCTION

Osteogenesis imperfecta (OI) is a complex hereditary disease which diseases characterized by delicacy to bone fractures with variable severity and, in most cases, with presumed or proven defects in collagen type I biosynthesis[1,2]. Other clinical manifestations include blue sclerae, hearing loss, dentinogenesis imperfecta, and short stature[3]. OI has a birth prevalence of 6–7/100,000[4]. The prevalence and incidence of the OI types are different from each other, with OI type I and OI type IV accounting for considerably more than half of all OI cases[2,4]. Sillence et al. proposed a numerical classification of OI into four types based on clinical and genetic findings in OI patients[5]. These heterogeneous disorders, with an estimated 90% of cases due to a causative variant in the *COL1A1* or *COL1A2* genes and new genetic causes as *CRTAP*, *LEPRE1*, *PPIB*, *SERPINH1*, *FKBP10*, *PLOD2*, *SP7, SERPINF1*[6-17].

After the diagnosis OI, the patient should be evaluated by a multidisciplinary team[4]. Management consists of pharmacological, orthopedic, physical, and dental treatment. On pharmacological treatment, oral and intravenous bisphosphonates are commonly prescribed for all OI types[18]. Bisphosphonates, a group of pyrophosphate analogs, are potent inhibitors of osteoclast-mediated bone resorption and osteoclast survival. The primary rationale for bisphosphonate therapy is leads to increased bone mineral density with resultant reduced bone pain, fracture rate, deformity, and immobilization[1,2,19-22]. After the report from Glorieux et al. significant clinical experience with the use of short-term bisphosphonates in children with OI[18], causes a reduction in fracture rate and improves bone mineral density[1,19-22]. The most widely used bisphosphonate in children, is typically prescribed in a dosage of 1 mg/kg intravenously daily for 3 consecutive days, three times a year (i.e., 9 mg/kg/year). Several studies have shown although the most optimal, practical, safe and effective regimen of pamidronate has not been defined yet. However, lower doses (i.e., 4 mg/kg/year) have successfully reduced fracture rates and improved bone mineral density (BMD) in children with OI[23-26].

In this study, we evaluated the effectiveness of two different bisphosphonate (pamidronate: 3-amino-1-hydroxy propylidene-bisphosphonate) protocols by clinical, biochemical, and radiological findings in children with OI.

MATERIALS and METHODS

In this study, there were total 12 patients (seven girls and five boys) with an age of 42.3±37.4 (14-120) months. According to the Sillence classification four patients were diagnosed as OI type II, six were type III, and two were type IV. Parental consanguinity was positive in seven patients (58.3 %) and five patients (41.6 %) had a family history for OI. Pretreatment fractures were localized to upper limbs in two (16.6 %), lower limbs in five (41.6 %), and both upper and lower limbs in five patients (41.6 %). Five patients (41.6 %) had intrauterine fractures, and two (16.6 %) of them had costae fractures. Ten (83.4 %) patients had blue sclera, seven (58.3 %) patients had chest deformities, and three (25.0 %) had scoliosis. Six (50.0 %) patients had limb deformities due to malunion of late or non detected fractures.

All patients had a daily intake of vitamin D of 600U/day and calcium intake was at least 600 mg/day. All patients underwent physiotherapy and corrective orthopedic surgery was performed when needed.

The study was approved by the ethics committee of Cukurova University Faculty of

Medicine. Written consent was obtained from all patients or their legal guardians if under age.

TREATMENT

In the beginning patients received the first protocol of pamidronate (Aredia, Novartis Pharma AG, Basel, Switzerland) at a dose of 1.5mg/kg/day, infused over 4-6 hours in 100-250 ml of 0.9% saline solution, once, every two months in the outpatient clinic of hospital. Mean duration of this treatment was 23.5 ± 9.0 (min:14-max:29) months and expected cumulative dose was 9 mg/kg per year. Then we switched to the second protocol consisted of pamidronate infusions at a dose of 1mg/kg/day, for three consecutive days, every 3 months. Patients were hospitalized three days for this protocol. Mean duration of this treatment was 18.5 ± 5.1 (min:13-max:24) months and expected cumulative dose was 12 mg/kg per year.

Laboratory and radiological investigations

Each treatment protocols before and after serum calcium, phosphorus and alkaline phosphatase (ALP) levels were measured by colorimetric method. Twenty-four hour urinary calcium excretion was calculated in both protocols every three months and renal ultrasonography was performed yearly. Radiological changes were evaluated every six months. Areal bone mineral density of the second to fourth lumbar spine (L_2-L_4) including gender and age corrected score (Z-score) was measured using dual energy X-ray absorbtiometry (DEXA) (Norland DEXA model XR-46-USA, coefficient of variation 1 %) at baseline and yearly in both protocols. Fracture data was collected as recounted by the subjects and confirmed by review of radiographs.

Ambulation scores

The mobility and ambulation of the children were evaluated using a five-point scale as follows: 0 (bed or wheelchair bound), 1 (able to walk with aids, but not functionally mobile) 2 (able to walk in the household, with or without aids), 3 (able to walk short distances, with or without aid), and 4 (able to walk indepently)[27].

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc., Chicago, IL). Differences in mean values were assessed by the Wilcoxon signed ranks test. The value of $p<0.05$ was considered as significant.

RESULTS

During the first pamidronate protocol, we observed a remarkable reduction in bone pain, as well as a significant decrease in annual fracture rate from 6.3 ± 5.5 to 1.1 ± 1.3 ($p=0.001$) parallel with an increase in BMD Z-scores from -3.9 ± -1.4 to -2.5 ± -1.3 ($p<0.05$) (Table 1). Eight children had no fractures during the first protocol. After switching to the second treatment protocol, annual fracture rate decreased from 1.1 ± 1.3 to 0.0 ± 0.0 ($p=0.001$) and all 12 patients had no new fractures. We also detected an increase in BMD Z-scores with second protocol (from -2.5 ± -1.3 to -1.2 ± -1.4) ($p<0.05$) (Table 1). The duration of two pamidronate protocols was not statistically different ($p>0.05$). Appearance of dense lines parallel to the growth plates particularly in the bones of distal forearms without evidence of rickets were noted in all children with both protocols. Number of these lines was increased with every new pamidronate infusion.

Two different pamidronate regimens did not provide a statistically significant reduction in serum ALP levels.

Ambulation scores improved in 10 children and seven of them progressed from being wheel chair-bound (grade 0 or 1) to walking dependently or independently (grade 3-4) with first pamidronate treatment. After the second pamidronate protocol ambulation scores were increased from 3 to 4 in six children and three children were joined to the walkers. However two of them were still not able to walk due to severe limb deformities before treatment.

All children were short for age before and after two treatment protocols, although a nonsignificant increase in height standard deviation score (HSDS) and height velocity standard deviation score (HVSDS) were observed in one day [HSDS from -4.1 ± -1.9 to -3.6 ± -1.8 (p>0.05) and HVSDS from -3.1 ± -1.5 to -2.6 ± -1.4 (p>0.05)] and three days protocols [HSDS from -3.6 ± -1.8 to -2.9 ± -1.7 (p>0.05) and HVSDS from -2.6 ± -1.4 to -2.2 ± -1.5 (p>0.05)].

We did not observe any severe adverse effects of either pamidronate protocols. As expected a short term fever up to 38.3°C and limb and back pain were observed in five (41.6 %) patients only in the first infusion of pamidronate. Before and after both pamidronate regimens all children had normal concentrations of serum calcium, phosphate, and 24-hour urinary calcium excretion.

Table 1. Valuation of first and second protocol regimes

	Before treatment	**After first pamidronate regime**	**p***	**After Switched to second treatment regime**	**p****
Bone mineral density (L_2-L_4) Z-Score	-3.9 ± -1.4	-2.5 ± -1.3	<0.05	-1.2 ± -1.4	<0.05
Annual fracture rate	6.3 ± 5.5	1.1 ± 1.3	0.001	0.0 ± 0.0	0.001

p*: compare before treatment with after first pamidronate regime

p**: compare first pamidronate regime with second pamidronate regime

DISCUSSION

Osteogenesis imperfecta is a genetic disorder characterized with decreased bone mineral density, recurrent fractures resulting in deformities, and restricted ambulation. The goal of treatment is to reduce bone resorption and to increase bone mass for a better lifestyle. Bisphosphonates are used in adults for bone loss and increased fragility and for OI and other childhood osteoporotic conditions[28-30]. Pamidronate is a widely used agent for OI and other childhood osteoporotic conditions[19-22]. The main effect of pamidronate, which is deposited; on the surface of the bone and ingested by osteoclasts during bone turnover, is antiresorbtive. It inhibits the mevalonate pathway in osteoclasts, enhancing apoptosis and inhibiting skeletal resorption[31]. Pamidronate was administered in various doses and dose intervals in different studies for children with OI. But up to today the most optimal and practical dosing regimen has not yet been defined.

In this prospective study, we evaluated the efficiencies of two different pamidronate treatment protocols by clinical, biochemical, and radiological datas. Gökşen et al. tried the different therapy models (at the beginning 7-10 mg/kg/year monthly and after switching to 3-4 mg/kg/year once daily therapy with 4 cycles/year) in order to decrease bone resorption and assessed the effects of low-dose bisphosphonate treatment (3-4 mg/kg/ year once daily therapy with 4 cycles/year) in osteogenesis imperfecta[32]. They discussed that, low-dose cyclical pamidronate infusions markedly increased bone density and decreased bone fracture rate[32]. In another study, Martinez-Soto et al. described the effects of two different pamidronate treatment regimens (4 mg/kg/year and 9 mg/kg/year) on the bone mineral density (BMD) and fracture rate of these OI children[33]. They found no difference in treatment effect was observed between the two doses[33]. Our study demonstrated that three consecutive days of

pamidronate treatment did not have a significant superiority to one day treatment in reducing annual fracture rate, increasing bone mineral density, and mobility. During one day protocol fractures occurred only after a severe trauma and eight patients had no fractures. Remaining four children's fractures occurred only during the first three cycles of pamidronate. Patients were absolutely free from fractures and two of them joined to the walkers during the second protocol. Although, second protocol may seem more efficious, one can not exclude the lasting effects of the first protocol into the second one, as the patients were switched to the second protocol without a prolonged break. With three consecutive days of pamidronate regimen for 1 to 5 years, a dramatic increase in BMD, mobility and a decrease in annual fracture rate was reported[21,22,34-36]. The cumulative dose of pamidronate was changed from 0.5mg/kg to 1.75mg/kg due to the patients age in these studies. In addition to clinical and radiological beneficial effects of three days pamidronate infusion Rauch demonstrated positive effects with bone histomorphology[21]. Increased fracture rate was noted in all patients with major traumas within the first two years of cyclic pamidronate infusion due to increased mobilization in only one study[37]. With less frequent usage of pamidronate beneficial results were also demonstrated. Gonzalez et al. treated his patients with 30-60 mg pamidronate every 6 months and found a striking improvement in BMD[38]. Glorieux et al. reported that one third of his patients were remained free from fractures on once, in 4-6 months intervals of pamidronate treatment[20]. Gandrud et al. demonstrated reduced fracture rates and increased BMD in osteoporosis of children other than OI with low dose pamidronate once every three months and defends the usage of lower doses and infrequent intervals[23].

The increments in BMD Z-scores of two protocols were not different in our study. All of the authors who used three consecutive days of pamidronate infusion reported a significant increase in BMD Z-scores[21,22,34-36]. However, Gonzalez et al. reported the same increment with more infrequent and lower doses of pamidronate[38]. In some studies, it is recognized that the improvement in BMD may not be parallel to improvement in annual fracture rate, and that pamidronate have a more positive effect on fracture rate than on BMD[39]. The gains in BMD were lesser than the gains in annual fracture rates in both protocols of our study.

Pamidronate treatment provided a more orderly school life, a better academic performance and gains in social life. Increment in BMD lead more successful corrective orthopedic interventions and the reduced bone turnover did not compromise bone growth and fracture healing. All these factors changed the quality of life of the children and their families. Significant improvements in mobility with the second protocol were reported in different studies, although the ambulation was limited in severe forms and late treated OI patients independent of treatment protocol[21,22,34-36].

Some investigators reported a catch-up growth with pamidronate[40,41]. In our study, linear growth proceeded at a slightly better pace (although statistically not significant). We did not detect a significant difference in pre and post treatment levels of ALP with either pamidronate treatment protocols. Decreased levels of ALP were found in a few studies due to the slowing of bone resorption[22,27].

We did not observe any important adverse effects of pamidronate except a flu-like acute reaction in five patients after the first cycle of pamidronate which responded to acetaminophen. In some studies a transient reduction in plasma calcium levels was observed[22,35].

The second protocol was more costly than the first protocol due to the higher cumulative yearly dose and three days of hospitalization. In conclusion, from the point of clinical, biochemical, radiological and cost effectiveness view, three consecutive days of pamidronate every three

months did not have any superiority to one day of pamidronate every two months. Additionally, longer duration of hospitalization may decrease the compliance of patients due to the loss of school hours and work hours of parents.

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