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Comparison of Calcitonin and Pamidronate Treatments in Children with Osteogenesis Imperfecta

Ostegenezis İmperfekta Olan Çocuklarda Pamidronat ve Kalsitonin Tedavilerinin Karşılaştırılması

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ABSTRACT

Purpose: The main objective of this study was to compare the treatments of calcitonin and pamidronate by clinical, biochemical, and radiological findings in children with osteogenesis imperfecta and evaluate the efficiency of pamidronate treatment.

Materials and Methods: A total of 12 patients, aged 41±38 (1-120) months were studied. Group 1 was consisted of six patients who had received intranasal calcitonin at a dosage of 4-6 U/kg three times a week before switching to pamidronate treatment. Group 2 was also consisted of six patients who had received only pamidronate infusion at a dosage of 0.5-2 mg/kg every two months.

Results: Annual fracture rates decreased from 2.72 ± 0.80 to 0.40 ± 0.70 ($p<0.05$) in group 1, from 3.50 ± 0.54 to 0.40 ± 0.49 ($p<0.001$) in group 2, and from 4.50 ± 3.30 to 0.32 ± 0.41 ($p<0.001$) in total 12 patients. The Z-score of bone mineral density increased from -4.12 ± -0.60 to -3.80 ± -1.0 in calcitonin group ($p>0.05$), and from -3.08 ± -0.61 to -2.29 ± -0.56 in pamidronate group. The difference between the Z-scores of bone mineral density after calcitonin and pamidronate treatments was statistically significant ($p<0.05$). The Z-scores of pre (-3.44 ± -0.96) and post (-2.47 ± -0.60) pamidronate treatments of whole 12 patients were significantly different ($p<0.001$).

Conclusion: Pamidronate was significantly more effective in reducing pain, annual fracture rate, and increasing bone mineral density and mobility than calcitonin without any severe adverse effects even in the neonatal period and severe forms of osteogenesis imperfecta.

Key Words: Osteogenesis imperfecta, calcitonin, pamidronate, children.

ÖZET

Amaç: Bu çalışmanın temel amacı osteogenezis imperfekta olan çocuklarda klinik, biyokimyasal ve radyolojik bulgular ile pamidronat ve kalsitonin tedavisinin karşılaştırılması ve pamidronat tedavisinin etkinliğinin değerlendirilmesidir.

Materyal ve Metod: Yaşları 41±38 (1-120) ay arasında değişen toplam 12 hasta çalışmaya alındı. Grup 1 pamidronat tedavisine geçmeden önce 4-6 U/kg haftada üç defa intranazal kalsitonin tedavisi alan altı hasta oluşturdu. Grup 2, iki ayda bir sadece tek doz 0.5-2 mg/kg dozunda pamidronat alan altı hasta idi.

Bulgular: Yıllık kırık oranları Grup 1'de 2.72 ± 0.80'den 0.40 ± 0.70'e ($p<0.05$), Grup 2'de 3.50 ± 0.54'den 0.40 ± 0.49'a ($p<0.001$) ve toplamdaki 12 hastada 4.50 ± 3.30'dan 0.32 ± 0.41'e ($p<0.001$) geriledi. Kemik mineral dansitesi z skoru kalsitonin grubunda -4.12 ± -0.60'dan -3.80 ± -1.0'a ($p>0.05$), pamidronat grubunda -3.08 ± -0.61'den -2.29 ± -0.56'ya yükseldi. Pamidronat ve kalsitonin tedavisi arasında kemik mineral dansitesi z skoru anlamlı olarak farklıydı ($p<0.05$). Pamidronat tedavisi öncesi (-3.44 ± -0.96) ve sonrasında (-2.47 ± -0.60) z skoru 12 hastada anlamlı olarak farklıydı ($p<0.001$).

Sonuç: Pamidronat tedavisi herhangi bir ciddi yan etkiye neden olmaksızın, yenidoğan döneminde olsa bile osteogenezis imperfektanın ciddi formlarında ağrıları, yıllık kırık oranını azaltmada ve kemik mineral dansitesini arttırmada anlamlı oranda daha etkilidir.

Anahtar Kelimeler: Osteogenezis imperfekta, kalsitonin, pamidronat, çocuklar

INTRODUCTION

Osteogenesis imperfecta (OI) comprises a heterogeneous group of diseases characterized by susceptibility to bone fractures with variable severity and, in most cases, with presumed or proven defects in collagen type I biosynthesis[1]. As a result of defective collagen biosynthesis, the osteoblasts produce less bone than is required. The balance between bone resorption and formation, which normally favors formation, is tipped toward resorption. This results in osteoporosis, and increased risk of fractures[2-4]. Clinical manifestations include fractures, pain and reduced mobility, deformities, short stature, blue sclera, dentinogenesis imperfecta, and hearing loss. Sillence et al.[5] developed a four-type classification, which is still in use for classification. Type I is characterized by bone fragility, blue sclera, growth retardation, and hearing loss. Type II, is the lethal form of disease. Type III is the most severe form in children, surviving the neonatal period defined with a specific phenotype including extremely short stature, growth palate abnormalities, and progressive limb and spine deformities secondary to multiple fractures. In 2004, types V and VI were added to this classification[6,7]. OI comprises a group of heterogeneous disorders, with an estimated 90% of cases due to a causative variant in the *COL1A1* or *COL1A2* genes[8-17]. With the discovery of new genetic causes of OI (*CRTAP*, *LEPRE1*, *PPIB*, *SERPINH1*, *FKBP10*, *PLOD2*, *SP7, SERPINF1*), it was proposed to extend the classification with OI types VII and VIII[1]. The classification of different types of OI is still under discussion[1].

With the discovery of defects in collagen type I biosynthesis as a cause of OI and with the usage of bisphosphonate in treatment, the clinical status improved in this disease. In the past, physical therapy, corrective orthopedic surgery, oral calcium salts, vitamin D, fluoride, anabolic steroids, magnesium oxide, and calcitonin were employed in the treatment[18,19]. Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts[20]. For several years synthetic salmon calcitonin was used to treat patients with OI. Some studies showed an improvement in fracture rate and in bone mineral density[21,22]. Over the recent years bisphosphonate therapy has became the standard mode of treatment. Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and osteoclast survival which are a group of pyrophosphate analogs. Decreased bone turnover by bisphosphonates leads to increased bone mineral density with resultant reduced bone pain, fracture rate, deformity, and immobilization[2,23,24]. Several studies demonstrated a reduction in fracture rate and improvement in bone mineral density with pamidronate[25-29]. The bisphosphonate pamidronate has a beneficial effect in children and adolescents with severe OI[18]. It has been reported that this treatment increases lumbar spine areal bone mineral density (BMD) and metacarpal cortical width, decreases fracture rates, and improves mobility, even though a recent small placebo-controlled trial on low-dose pamidronate was unable to reproduce some of these results[30]. In this study, we evaluated the effectiveness of bisphosphonate (pamidronate: 3-amino-1-hydroxy propylidene-bisphosphonate) by clinical findings, serum alkaline phosphatase levels and bone mineral density measurements in children with OI and compare the results of this drug with calcitonin. To the best of our knowledge, there are no other reports in the literature comparing the efficiency of calcitonin and pamidronate in children with OI.

MATERIALS AND METHODS

There were total 12 patients (six girls and six boys) with an age of 41 ± 38 (1-120) months. According to the classification four patients were diagnosed as OI type II, six were type III, and two were type IV. Patients were divided into two groups. There were six patients in group 1 (three girls and three boys), aged 81 ± 58 (10-104) months, who had received intranasal calcitonin before switching to pamidronate treatment. There were also six patients in group 2 (three girls and three boys), aged 37 ± 29 (1-98) months, who had received only pamidronate treatment. 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.

Parental consanguinity was positive in seven (58.3 %) patients and five (41.6 %) patients had a family history for OI. The 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 (41.6 %) patients. Five (41.6 %) patients 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. Eight (66.6 %) patients had limb deformities due to malunion of late or non detected fractures.

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

Patients in group 1 received intranasal calcitonin (Calcitonina Hubber 50IU, ICN Iberica S A Spain) at a dosage of 4-6 U/kg, three times a week for 42.0±18.6 (25-62) months before switching to pamidronate treatment. Patients in group 2 received pamidronate only. Disodium pamidronate (Aredia, Novartis Pharma AG, Basel, Switzerland) was administered at a dose of 1.5 mg/kg, infused over 4-6 hours in 100-250 ml of 0.9% saline solution, once every two months (expected cumulative dose 9 mg/kg per year). Mean duration of pamidronate treatment was 17 ± 5 (12-22) months.

Laboratory and radiological investigations

Before and after pamidronate treatment and once every three months after calcitonin treatment regimens serum calcium, phosphorus and alkaline phosphatase (ALP) levels were measured by using colorimetric method. Twenty-four hour urinary calcium excretion was calculated in both protocols. Areal bone mineral density (BMD) of the second to fourth lumbar spine (L_2-L_4) including gender, age, and height 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 every six months after the treatment in both protocols. Fracture data were collected as recounted by the subjects and confirmed by review of radiographs and hospital records.

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) (18).

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 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

After calcitonin treatment, in group 1 we detected a statistically nonsignificant increase in BMD from -4.12 ± -0.60 to -3.80 ± -1.00 ($p>0.05$),

in parallel with a statistically nonsignificant decrease in annual fracture rate from 3.81 ± 3.3 to 2.72 ± 0.80 (p>0.05) (Table-1). All six children had new fractures on treatment. After pamidronate treatment, first we observed a remarkable reduction in bone pain. However the most impressive effect of pamidronate treatment was seen in annual fracture rate, which decreased from 2.72 ± 0.80 to 0.40 ± 0.70 (p<0.001) in group 1 (Table-2), from 3.50 ± 0.54 to 0.40 ± 0.49 (p<0.001) in group 2 (Table-3), and from 4.5 ± 3.3 to 0.32 ± 0.41 (p<0.001) in all patients (Table-4). Eight children had no fractures after treatment. Additionally, appearance of dense lines parallel to the growth plates in the bones of distal forearms were noted without evidence of rickets.

Table 1. Evaluation of calcitonin treatment in group 1.

	Before calcitonin	After calcitonin	P
Serum ALP (IU/L)	657 ± 162 (528-775)	600 ± 239 (307-1059)	>0.05
Bone mineral density (L_2-L_4) Z-score	-4.10 ± -0.60	-3.80 ± -1.0	>0.05
Annual fracture rate	2.40 ± 1.20	1.70 ± 1.0	>0.05

Table 2. Comparison of calcitonin and pamidronate treatments in group 1.

	After calcitonin	After pamidronate	P
Serum ALP (IU/L)	600 ± 239 (307-1059)	608 ± 123 (304-731)	>0.05
Bone mineral density (L2-L4) Z-score	-3.80 ± -1.0	-2.49 ± -0.85	<0.05
Annual fracture rate	2.72 ± 0.80	0.40 ± 0.70	<0.001

Table 3. Evaluation of pamidronate treatment in group 2.

	Before pamidronate	After pamidronate	P
Serum ALP (IU/L)	547 ± 126 (428-742)	509 ± 137 (454-542)	>0.05
Bone mineral density (L2-L4) Z-Score	-3.08 ± -0.61	-2.29 ± -0.56	<0.05
Annual fracture rate	3.50 ± 0.54	0.40 ± 0.49	<0.001

Table 4. Evaluation of pamidronate treatment both in groups 1 and 2.

	Before pamidronate	After pamidronate	P
Serum ALP (IU/L)	600 ± 113 (474-710)	560 ± 116 (420-765)	>0.05
Bone mineral density (L2-L4) Z-score	- 3.44 ± - 0.96	- 2.47 ± - 0.60	<0.001
Annual fracture rate	4.50 ± 3.30	0.32 ± 0.41	< 0.001

When we compared the Z-scores after calcitonin (-3.80 ± -1.0) and after pamidronate (-2.49 ± -0.85) treatments the difference was statistically significant (p<0.05). The pretreatment Z-score was -3.08 ± -0.61 and increased to -2.29 ± -0.56 (p<0.05) in group 2. When we evaluated the Z-score of whole 12 patients pre (-3.44 ± -0.96) and post (-2.47 ± -0.60) pamidronate treatment values were statistically significant (p<0.001).

Calcitonin and pamidronate did not provide a significant reduction in serum ALP levels.

Ambulation was assessed according to the children's degree of independence and mobility[4]. Before calcitonin treatment five children were

confined to a bed or a wheel-chair from group I, and six children from group II (grade 0 or 1). Ambulation scores improved from 0 to 1 in two children and from 1 to 2 in one child after calcitonin treatment. However, these 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 pamidronate treatment. Remaining two children were both currently 14 months-old.

We did not observe any severe adverse effect of pamidronate or calcitonin treatments. As expected a short term fever up to 38.3°C and limb and back pain was seen in five (41.6 %) patients only after the first infusion of pamidronate. Before and after calcitonin and pamidronate treatments all children had normal concentrations of serum calcium, phosphate, and 24 hours urinary calcium excretion. All children were short for age before and after two treatment protocols; although their height Z-scores increased nonsignificantly from -4.10 ± -1.11 to -3.80 ± -0.80 with pamidronate treatment ($p>0.05$).

DISCUSSION

Osteogenesis imperfecta is a heterogeneous group of disorders principally affecting type I collagen. Children with the severe forms of this condition suffer from recurrent fractures resulting in limb and spine deformities, and restricted ambulation[31]. Bone mineral density is markedly decreased in OI.

Calcitonin has been the most commonly employed therapy for OI for long years[20,32-34]. Bisphosphonate therapy is widely used for OI and other childhood osteoporotic conditions; however, the most optimal and practical dosing regimen has not yet been defined[31,35-37]. As different from the previous studies on the treatment of OI, our study provides clinical, biochemical, and radiological data from the comparison of two different treatment regimens, calcitonin vs. pamidronate, for the first time in the literature. Our study demonstrates that two monthly cyclic infusions of pamidronate for 17 ± 5 months were statistically more efficous to reduce bone turnover and improve bone mineralization than calcitonin and that provide an important decrease in pain and annual fracture rate without any severe adverse effects.

Although we detected a statistically nonsignificant decrease in annual fracture rate with calcitonin, all children experienced new fractures. Beneficial effects of calcitonin treatment in decreasing annual fracture rate, increasing BMD, ambulation, and linear growth have been reported in some studies[32-34]. In our study during pamidronate treatment fractures occurred only after a severe trauma and eight patients had no fractures. Several authors reported a similar decrease in annual fracture rates on pamidronate treatment[2,18,23,31]. In contrast with these results Falk at al[29] noted new fractures with major traumas in all patients within the first two years of cyclic pamidronate infusion due to increased mobilization.

Lee et al.[18] demonstrated a significant decrease in serum ALP levels, with cyclic pamidronate administration. However Gonzalez et al.[31] and we did not detect any significant decrease in serum ALP levels either with pamidronate or calcitonin treatments.

The Z-scores of BMD were significantly different in calcitonin and pamidronate treatment groups in favor of pamidronate. It has been reported that intranasal calcitonin improved BMD by 1% - 2% in two years, although pamidronate increased BMD by 4% - 8%[38]. Pedersen et al.[39] reported an unchanged bone mineral content during 12 month calcitonin treatment. Augst et al.[40] demonstrated any histological changes in OI with calcitonin and but severe complications of this therapy such as vomiting, hypomagnesaemia, hypophosphatemia, hyponatremia, and hypokalemia. Baratelli et al.[41] claimed that calcitonin have no capacity in the treatment of OI as it does not affect the underlying biochemical defect. The Z-scores of BMD were increased from -3.44 ± -0.96 to -2.47 ± -0.60 in all patients with

pamidronate. Significant increases in Z-scores and volumetric BMD of with pamidronate treatment was demonstrated in different studies[18,23].

After the pamidronate therapy, our patients became more active and seven (58.3 %) of them became able to walk. Especially with this treatment a more orderly school life provided a better academic performance in school and gains in social life. Increments in bone mineral density also led more successful corrective orthopedic interventions. Lee et al.[18] reported a significant improvement in mobility with pamidronate in two patients. In one study, Ambulation scores improved in 16 children: 6 gained one grade, 5 gained two, and 1 gained three, and 4 children progressed from being wheelchair-bound (grade 0 or 1) to walking independently (grade 4)[4]. Beneficial effects of pamidronate treatment on mobility were also demonstrated in severe forms of OI (42). The first reduction was the pain, then annual fracture rate reduced and at the end mobility provided important changes in the quality of the life of these children.

Brumsen reported a catch-up growth with pamidronate[43]. We did not detect a significant increase in growth patterns, although a nonsignificant acceleration was observed.

We did not observe any important adverse effects of pamidronate and calcitonin treatments except a flu-like acute reaction in five patients after 48 hours from the first cycle of pamidronate which responded to acetaminophen. In some studies a transient reduction in serum calcium levels were observed[29]. However we did not detect a decrease in serum calcium levels after calcitonin or pamidronate administrations. In this study we used pamidronate treatment in two patients during neonatal period and detected no adverse effects. Guillot et al.[25] used bisphosphonate in a one-month-old child without any adverse effects and with improvement in the clinical status.

In conclusion, cyclic pamidronate infusions appear to be markedly better than calcitonin in increasing bone mineral density and mobility also in decreasing pain and annual fracture rate without any severe adverse effect in all age groups including neonatal period and severe forms of OI.

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