ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Retrospective Evaluation of Patients Diagnosed with Osteogenesis Imperfecta

Osteogenezis İmperfekta Tanısı Alan Hastaların Retrospektif Olarak Değerlendirilmesi

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Abstract

Introduction: Osteogenesis imperfecta (OI) is a hereditary disease that impairs the quality of life by frequent bone fractures. The objective of our study is to retrospectively evaluate patients diagnosed with OI and to come up with helpful data that will assist developing new diagnosis and treatment protocols.

Materials and Methods: Twenty-eight cases with OI who were followed-up in our clinic were retrospectively evaluated. Clinical classification of OI was done. Age, sex, and oxologic data were evaluated. Height, weight and body mass index (BMI) data was given as standard deviation score (SDS). Family history of fracture and consanguineous marriage was sought. Blue sclera and presence of deformity was evaluated on physical examination.

Results: Out of the 28 cases in our study, 14 (50%) were boys, 14 (50%) were girls, and mean age was 7.48±5.09 years. Mean age of diagnosis was 25.59±39.59 months. Ten cases (47.6%) had OI, and 7 cases (25%) had consanguineous marriage in their family history. The cases were separated into autosomal dominant 4 clinical types according to Sillence classification as follows; 13 cases (46.4%) type 1, 10 cases (35.7%) type 3, and 5 cases (17.9%) type 4. The mean average basal dual energy X-ray absorptiometry Z score, mean height SDS, mean weight SDS and BMI SDS significantly increased for the cases after treatment ($p<0.001$).

Conclusions: Treatment of OI with pamidronate was observed to increase bone mineral density, decrease number of fractures and pain, and improve the patient's quality of life with inreasing mobility. Pamidronate is one of the most effective treatments of OI until a more effective treatment is found. On the other hand, since the long-term side effect of pamidronate on bones is not well-known, we think that randomised controlled studies still need to be done to determine the optimal time, interval and dose for bisphosphonate use.

Keywords
Osteogenesis imperfecta, pamidronate, dual energy X-ray absorptiometry

Öz

Giriş: Osteogenezis imperfekta (Oİ) tekrarlayan kemik kırıklarının yaşam kalitesini bozduğu kalıtsal bir hastalıktır. Çalışmamızın amacı Oİ tanısı almış hastalarının retrospektif değerlendirilip, Oİ'de yeni belirlenebilecek tanı ve tedavi protokollerine yardımcı olabilecek veriler sağlayabilmektir.

Gereç ve Yöntem: Kliniğimizde Oİ tanısı ile takip edilen 28 olgu retrospektif olarak değerlendirildi. Oİ'nin klinik sınıflandırması yapıldı. Yaş, cinsiyet ve oksolojik veriler değerlendirildi. Boy, kilo ve vücut kitle indeksi (VKİ) verileri standart sapma skoru (SSS) olarak verildi. Ailede kırık öyküsü ve akraba evliliği araştırıldı. Fizik muayenede, mavi sklera ve deformite varlığı değerlendirildi.

Bulgular: Çalışmaya alınan 28 olgumuzun 14'ü erkek (%50), 14'ü kız (%50), ortalama yaş 7,48±5,09 yıl idi. Olguların ortalama tanı yaşı ise 25,59±39,59 ay

Anahtar kelimeler
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idi. On olguda (%47,6) ailesinde başka bireylerde de Oİ tanı öyküsü, yedi olguda (%25) ise akraba evliliği öyküsü vardı. Olgular Sillence sınıflamasına göre otozomal dominant geçen dört klinik tipe ayrıldığında; 13 olgu (%46,4) tip 1, 10 olgu (%35,7) tip 3, 5 olgu (%17,9) tip 4 olarak sınıflandırıldı. Olguların tedavi sonrası ortalama bazal çift X ışınlı absorpsiyometri Z skoru, ortalama boy SSS'si, ortalama ağırlık SSS'si ve VKİ SSS'si anlamlı olarak yükseldi (p<0,001).

Sonuç: Oİ'de pamidronat tedavisi ile kemik mineral yoğunluğunda artış, kırık sayısında, ağrıda azalma ve mobilitede artış sağlanması ile hastaların yaşam kalitesinde ciddi iyileşmeler sağlanabildiği görülmüştür. Daha etkin bir tedavi bulununcaya kadar pamidronat Oİ tedavisinde en etkin seçeneklerden biri olarak görülmektedir. Ancak pamidronatın kemik üzerinde kronik yan etkileri net olarak bilinmediği için bifosfonat kullanımında optimal süre, kullanım aralığı ve dozu konusunda randomize kontrollü daha birçok çalışmaya ihtiyaç olduğunu düşünmekteyiz.

Introduction

Osteogenesis imperfecta (OI) is a genetic disease that leads to increased bone fractures, osteoporosis and other connective tissue disorders. In this disease, bone, tendon, skin, sclera and dentine tissues with type 1 collagen are affected. *COL1A1*, *COL1A2* gene mutations were determined. The patients present with different forms varying from severe form with intrauterine fractures to mild forms without any fractures. Diagnosis is made by patient history, clinic and genetic tests. The disease is divided into four autosomal dominant clinic types according to Sillence classification (1). In addition, autosomal recessive type 2 and type 3 were also reported in articles. Type 1 is the most common and the most mild type, associated with pre-puberty fractures and blue sclera. Type 2 is the most severe type with most severe fractures and these cases are lost in early life (lethal form). Type 3 is slowly progressive with bone deformities, fracture possibility at birth, blue or grey sclera. Dentinogenesis imperfecta, triangular face and short height is observed in this type. Type 4 has normal sclera with clinical severity between type 1, 3. Types 5, 6, 7, 8, 9 have also been identified (2).

OI treatment involves physiotherapy, rehabilitation and orthopedic surgery. However, strengthening the bones should be our first priority. This is why calcitonin, bisphosphonates (alendronate, pamidronate, and zolendronate) are commonly used. Additionally, growth hormone, gene therapy, bone marrow stroma cell transplantation have been experimentally used in adults (3). Bisphosphonates are drugs that reduce osteoclastic activity and have been used for more than 15 years. The introduction of bisphosphonates to therapy decreased the progression of this disease. In this study, we present clinical features and the effect of pamidronate therapy in OI patients followed up in our clinic.

Materials and Methods

Twenty eight cases followed-up with OI in our clinic were retrospectively evaluated after approval by Uludağ University Faculty of Medicine Ethics Comittee (09 December 2014 dated and 2014-23/17 number). Clinical classification of the patients was done (1). Age, sex, and oxologic data were evaluated. Height, weight and body mass index (BMI) data was given as standard deviation score (SDS) (4). Family history of fracture and consanguineous marriage was questioned. On physical examination, blue sclera and presence of deformities was evaluated. Pamidronate therapy was given every 3 months, 1 mg/kg/dose continuously on two cosecutive days, within 4 hours in 100-250 cc normal saline infusion. Serum calcium, phosphorous, alkaline phosphotase, 25-hydroxy vitamin D, and parathormone levels were measured, and bone mineral density (BMD) at lomber vertebrae (L1-4) was assessed by dual-energy X-ray (DEXA) absorptiometry Z score. BMD was evaluated at the beginning and after 12 months. Yearly fractures before and after therapy were compared. Statistical analysis was made by SPSS 16.0 programme. Results were presented as median (minimum-maximum). Meaningful value was given as $p<0.05$. Data was evaluated with Shapiro-Wilk test to identify normal or abnormal distribution. Comparison between two groups showing normal distribution was done with t-test, comparison between more than two groups was done with one way variance analysis. Tukey test was used in the multiple analysis of results found to be meaningful after the one way variance analysis. Illustrative t-test was used in the comparison of related groups. Spearman correlation coefficient was used to identify the relationship between variables.

Results

Out of the 28 cases in our study, 14 (50%) were boys, 14 (50%) were girls, and median age was 7.48±5.09 years. The mean age at diagnosis was 25.59±39.59 months. Ten cases (47.6%) had a family history of OI, and seven cases (25%) had consanguineous marriage history. When the cases were divided into 4 autosomal dominant clinic types according to Sillence classification; 13 cases (46.4%) was type 1, 10 cases (35.7%) type 3, and five cases (17.9%) type 4. Twenty four cases (85.7%) had repetitive fractures and four cases (14.3%) complained of bone deformities. Intrauterine fracture was identified in four cases. Only four cases (7.1%) had prenatal diagnosis. Nine (32.1%) had orthopedic surgery history. Delivery was by cesarean section in nine (32.1%) and by normal vaginal route in 19 (67.9%) cases. Problems during neonatal period were breathing problems in three (10.7%) cases, jaundice in two (7.1%) cases, prematurity in four (14.3%) cases, meconium aspiration syndrome in one (3.6%) case and bone fracture at birth in two (7.1%) cases. Regarding the complaints of the patients, 24 (85.7%) cases had fractures and four (14.3%) complained of bone deformities. On physical examination, 21 cases had blue sclera (75%) and four cases had a triangular face (14.3%). Deafness was identified in one case (3.6%). Accompanying abnormalities and additional diseases are summarized in Table 1.

The fractured regions of the cases were ulna in one case (3.6%), clavicle in one case (3.6%), radius in three cases (10.7%), metacarpal bones in two cases (7.1%) and multiple fractures in four cases (14.3%).

The anthropometric and biochemical parameters before and after therapy are summarized in Table 2.

Pamidronate therapy was used in all patients. Nineteen cases (67.9%) used vitamin D in addition to pamidronate. The mean age at the beginning of the therapy was 35.45±45.93 months. None of the cases developed severe side effects. Two cases (7.1%) had subfebrile fever and two cases developed asymptomatic hypocalcemia (7.1%). The mean DEXA Z scores and mean annual fracture frequency after therapy were similar in patients who received additional vitamin D compared to those who did not (p=0.14 and p=0.11 respectively).

Mean DEXA Z score change percentages for patients who received vitamin D and who did not were calculated. The mean DEXA Z score change percentage was 47.04±27.37% in patients who received vitamin D and 62.25±21.10% in patients who did not receive vitamin D therapy (p=0.15). Table 3 shows mean DEXA Z scores before and after therapy according to the type of OI. The mean DEXA Z scores were not different between the groups either before

Table 1. Accompanying abnormalities and additional diseases

Abnormality	n	%
Hypospadias	1	3.6
Syndactyly	1	3.6
Undescended testes	1	3.6
Cloacal extrophy	1	3.6
Low-set ears (with no renal anomaly)	1	3.6
Hemangioma	1	3.6
Hypothyroidism	2	7.1
Epilepsy	2	7.1
Growth hormone deficiency	1	3.6

Table 2. The anthropometric and biochemical parameters before and after therapy

Parameter	Before therapy	After therapy	p
Mean height SDS	-2.61±2.78	-1.87±2.34	<0.001
Mean weight SDS	-1.68±2.71	-0.79±2.17	<0.001
Mean BMI SDS	-2.18±2.60	-1.28±2.36	<0.001
Calcium (mg/dL)	9.85±0.53	9.46±0.39	NS
Phosphorous (mg/dL)	5.41±1.02	4.49±0.51	NS
Alkalene phosphatase (U/L)	306.78±143.29	221.64±85.57	NS
25-OH vitamin D (ng/mL)	21.92±14.18	31.79±16.16	NS
Parathormone (pg/mL)	37.16±20.57	39.82±14.45	NS
Mean DEXA Z score	-4.76±1.56	-2.27±1.36	<0.001
Mean fracture frequency	1.95±1.40/year	0.52±0.68/ year	<0.001

SDS: Standard deviation score, DEXA: Dual-energy X-ray absorptiometry, BMI: Body mass index, NS: Non significant

or after therapy. Similarly, the mean DEXA Z score change percentages did not differ between the types of OI. Table 4 shows the mean height, weight and BMI SDS scores in different types of OI.

Table 5 shows the mean annual fracture frequency in different types of OI before and after therapy.

Table 3. Mean (± standard deviation) dual-energy X-ray absorptiometry Z scores before and after therapy in different types of osteogenesis imperfecta

Type of OI	Before therapy	After therapy	Change percentage (%)
Type 1 (n=13)	-4.43±1.43	-2.59±1.78	45.8±33.41
Type 3 (n=10)	-5.00±1.62	-2.29±0.79	53.83±6.12
Type 4 (n=5)	-5.14±1.90	-1.44±0.65	64.37±29.19
p*	>0.05	>0.05	>0.05

OI: Osteogenesis imperfecta, *OI types were compared in groups of two according to ANOVA test, in all comparisons p was >0.05

Table 4. Anthropometric parameters in different types of osteogenesis imperfecta before and after treatment

Parameter	Type of OI	Before therapy	After therapy
Height SDS	Type 1	-2.37±2.83	-1.57±2.31
	Type 3	-3.12±2.88	-2.31±2.36
	Type 4	-2.22±2.78	-1.77±2.80
Weight SDS	Type 1	-1.36±2.72	-0.54±2.00
	Type 3	-3.14±2.81	-1.11±2.56
	Type 4	-1.61±2.93	-0.81±2.10
BMI SDS	Type 1	-2.19±2.88	-1.36±2.00
	Type 3	-2.30±2.41	-1.32±2.29
	Type 4	-1.91±2.77	-0.98±2.55
	p*	>0.05	>0.05

OI: Osteogenesis imperfecta, BMI: Body mass index, SDS: Standard deviation score, *OI types were compared in groups of two according to ANOVA test, in all the comparisons p>0.05

Table 5. The mean annual fracture frequency (mean ± standard deviation) and change percentage (%) in different types of osteogenesis imperfecta before and after therapy

Type of OI	Before therapy	After therapy	Percentage change
Type 1	1.97±1.31	0.63±0.90	54.31±83.82
Type 2	1.67±0.85	0.42±0.39	67.50±31.38
Type 4	2.45±2.45	0.45±0.51	74.17±42.73
p*	>0.05	>0.05	>0.05

OI: Osteogenesis imperfecta, *OI types were compared in groups of two according to ANOVA test, in all comparisons, p was >0.05

Discussion

OI is a genetic defect characterized by reduced bone mass and increased bone fragility. It is seen in one out of 20.000 births (5). While its diagnosis can easily be done by a positive family history, typical clinical presentation, and radiological findings, cases with no evident clinic and family history may not be easy to diagnose. In such cases collagen type 1 gene analysis helps in diagnosis (6). Usage of bisphosphonate, a potent osteoclastic activity inhibitor for treatment was first reported in 1980s (7). Treatment with bisphosphonates such as pamidronate and alendronate has resulted in positive results like increased BMD, increased ability of movement, reduced risk of fractures, and reduced pain (8). Gökşen et al. (9,10) reported that in 16 patients treated with low-dose pamidronate, fracture frequency was reduced from 4/year to 0/year and 10 cases were able to stand on their feet. Andiran et al. (11) found that pamidronate treatment reduced fracture number from 3.5 to 0.83 per year. Adiyaman et al. (12) administered pamidronate at 0.5 mg/kg/dose for 3 days to 8 bedridden OI patients (3.6-13.8 years of age) once in 3 months and reported reduced fracture and evident pain reduction. Self sufficiency was reported by 7 of these patients who were bedridden before treatment. The reasearchers concluded that yearly cyclic palmidronate treatment was reported as a safe and effective treatment (12). In another study performed by Akcay et al. (13), 12 OI cases aged 1.8-15.4 years were given bisphosphonate treatment for approximately 20 months which reduced fracture frequency from 1.2±1.5 to 0.16±0.32 per year. In this study, the DEXA Z score increased from -4.6±1.3 to -2.47±1.52. Our study showed harmony with the literature with reduced fracture rate from 1.95/year to 0.52/year after bisphosphonate treatment. DiMeglio and Peacock (14) investigated the efficacy of bisphosponate therapy in 18 OI patients and reported results of a two year follow up. The DEXA Z score improved from -3.2 to -1.8 in nine patients treated with alendronate, and from -3.2 to -2.1 in nine patients treated with pamidronate. There was no statistical difference between the effectiveness of these two treatments. The authors reported that oral treatment was more effective. We also found that the DEXA Z score of our patients who received pamidronate therapy improved from -4.76 to -2.27 in concordance with the literature. Currently, there

is no consensus regarding optimum therapy period. Andiran et al. (11) in their study gave pamidronate 0.5 mg/kg/day to OI patients with a mean age of 5.1±6.8 for 3 consecutive days once in two months. Six patients had BMD improvement without any fractures for 6 months and the therapy was stopped after 16 months due to family demand. About 1.5 years after stopping therapy, BMD decreased, fracture rate increased, and bone pain began in four patients. This is the reason why authors recommend continuing pamidronate therapy during the growth period. After discontinuing pamidronate therapy, growth retardation and increased markers of bone resorption were also reported (15). In a series of 35 cases on pamidronate therapy, improvement of BMD was more evident in the first year with decreased efficacy during the 2nd and 3rd years (16). In our study, we presented the data over the first year of pamidronate therapy.

Conclusion

Pamidronate therapy in OI led to considerable recovery with increased BMD, reduced rate of fractures and pain, increased morbility and improved quality of life. Until a more effective therapy is found, pamidronate remains to be one of the most effective options for OI treatment. However, since the chronic side effects of pamidronate on bones is not clearly known, we think that optimal period, dose, and interval for bisphosphonate treatment need to be investigated by randomised controlled studies.

Ethics

Ethics Committee Approval: Uludağ University Faculty of Medicine Ethics Comittee (09 December 2014 dated and 2014-23/17 number), Informed Consent: This study retrospective.

Peer-review: Internal peer-reviewed.

Authorship Contributions

Concept: Mustafa Törehan Aslan, Design: Mustafa Törehan Aslan, Data Collection or Processing: Mustafa Törehan Aslan, Erdal Eren, Halil Sağlam, Ömer Tarım, Analysis or Interpretation: Mustafa Törehan Aslan, Literature Search: Mustafa Törehan Aslan, Ömer Tarım, Writing: Mustafa Törehan Aslan.

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