

EFFECT OF INTRAVENOUS PAMIDRONATE THERAPY ON FUNCTIONAL ABILITIES AND LEVEL OF AMBULATION IN CHILDREN WITH OSTEOGENESIS IMPERFECTA

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Objective To evaluate the functional abilities and the level of ambulation during pamidronate therapy in children with moderate to severe osteogenesis imperfecta.

Study design Functional abilities, ambulation, and grip force were assessed in 59 patients (mean age, 6.1 years; range, 0.5-15.7 years; 30 girls) during 3 years of pamidronate treatment. Functional skills (mobility and self-care) were both assessed by using the Pediatric Evaluation of Disability Inventory. Ambulation level was assessed by using the modified Bleck score. For 48 patients, results after 3 years of pamidronate treatment could be matched to those of patients with similar age and disease severity who had not received pamidronate.

Results Mobility and self-care scores increased during the study period (+43% and +30%, respectively). The average ambulation score changed from 0.8 to 1.9. Maximal isometric grip force increased by 63%. Mobility and ambulation scores and grip force measures were significantly higher than in patients who had not received pamidronate. The difference in self-care scores did not reach significance.

Conclusion This study suggests that cyclical pamidronate treatment improves mobility, ambulation level, and muscle force in children with moderate to severe osteogenesis imperfecta. (*J Pediatr* 2006;148:456-60)

Osteogenesis imperfecta (OI) is a heritable bone fragility disorder characterized by decreased bone mass and variable bone deformity. The most widely used phenotypic classification distinguishes 4 major types of the disorder (OI types I-IV).¹ Type I is a mild form of bone fragility with minimal deformity and normal or near-normal final height. Type II is lethal in the perinatal period. OI type III is the most severe non-lethal form of OI. These patients have extremely short stature and limb and spine deformities caused by multiple fractures. Patients with short stature and moderate-to-severe phenotype who do not fit into one of the aforementioned categories are classified as having type IV OI. Most patients with a clinical diagnosis of OI have a mutation in 1 of the 2 genes that encode the α chains of collagen type I. We have delineated 3 additional groups of patients (classified as having OI types V, VI, and VII) who had a clinical diagnosis of OI, but who had some distinct features and were negative for collagen type I mutations.¹

Children with severe forms of OI experience frequent fractures that lead to pain, progressing deformity, and disability. These factors substantially influence the age of achieving different motor milestones, the level of ambulation, and the self-care abilities in these patients.²⁻⁴ Because a causal treatment of OI is not available, treatment strategies mainly focus on comprehensive rehabilitation programs that combine physical and occupational therapy, lower-extremity bracing, and orthopedic surgery.⁵⁻⁷ These approaches may lead to improvements in ambulation and functional abilities in children and adolescents with OI.^{6,8}

Cyclical intravenous treatment with the bisphosphonate compound pamidronate has beneficial effects in patients with OI.¹ Pamidronate therapy was reported to improve muscle force, vertebral bone mass, and size and to reduce bone pain and fracture rate. Two preliminary studies supported the assumption that intravenous treatment with pamidronate improves the level of ambulation in children with OI, but have not addressed the changes in functional abilities and muscle force.^{9,10} In this study we therefore assessed the effects of long-term intravenous pamidronate treatment on functional abilities, muscle force, and level of ambulation in children with moderate to severe forms of OI.

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BMD	Bone mineral density	PEDI	Pediatric Evaluation of Disability Inventory
OI	Osteogenesis imperfecta		

METHODS

Subjects

The study population consisted of patients with a diagnosis of OI who had received pamidronate at the Shriners Hospital for Children in Montreal, Canada, for at least 3 years. Patients were eligible for pamidronate treatment when they had long bone deformities or had sustained at least 3 fractures per year (including vertebrae) during the previous 2 years. Patients in whom OI types V, VI, and VII were diagnosed were not included in this study. Between October 1992 and October 2004, 119 patients and adolescents with a diagnosis of OI type I (n = 24), type III (n = 39), and type IV (n = 56) had received at least 3 years of intravenous pamidronate therapy.

Assessments of functional skills were not performed in children who were younger than 0.6 years (n = 20). In addition, because of several reasons, a number of patients did not undergo baseline evaluation when they first were admitted for pamidronate treatment and therefore were not eligible for further analysis (n = 36). Furthermore, 4 patients were excluded because of incomplete follow-up data. Thus, a total of 59 patients (30 girls; mean age at start of treatment, 6.1 years; range, 0.5-15.7 years; OI type I, n = 18; OI type III, n = 12; OI type IV, n = 29) were included in the study. Excluded and included patients were similar in OI type, sex distribution, age, weight, height, and lumbar spine bone mineral content at treatment start (data not shown). Collagen type I mutations were found in 50 of the 59 study patients. In 6 patients, no collagen type I mutation was detectable by sequence analysis, and 3 patients had not been tested.

In 48 patients, results after 3 years of treatment could be compared with a control group of patients who were matched for OI type and age, but who had not received pamidronate before the assessments reported here. For 11 patients treated with pamidronate, no suitable control patient was available. The data in the control group were obtained between May 1992 and June 1999, whereas the corresponding examinations in the pamidronate group were performed between March 1995 and June 2000. The medical aspects of care and treatment for physiotherapy and surgical procedures did not change during the time these data were obtained.

The study was approved by the Shriners Hospital Institutional Review Board, and informed consent was obtained from parents or legal guardians.

Treatment

Pamidronate was administered intravenously on 3 consecutive days in all patients. The dose per kilogram and frequency of pamidronate varied in an age-dependent manner. Children <2.0 years of age received 0.25mg/kg on the first day of the first cycle, 0.5 mg/kg on days 2 and 3 of the first cycle, and 0.5 mg/kg daily on all 3 days of subsequent cycles. Cycles were repeated every 8 weeks. Children from 2 to 3 years of age received 0.38 mg/kg on the first day of the first cycle, 0.75 mg/kg on days 2 and 3 of the first cycle, and

0.75mg/kg daily on all 3 days of subsequent cycles. Cycles were repeated every 3 months. In children >3 years of age, treatment consisted of 0.5 mg/kg on the first day and 1 mg/kg on day 2 and 3. Subsequent cycles were administered at a dose of 1 mg/kg daily for 3 days. Cycles were repeated every 4 months. Each dose was diluted in 0.9% saline solution and administered slowly for 4 hours.

Functional skills

Occupational therapists and physiotherapists experienced in the care of children with OI assessed the children before the institution of pamidronate treatment and at each subsequent treatment cycle. Functional skills were assessed with the Pediatric Evaluation of Disability Inventory (PEDI).¹¹ The PEDI is a validated and reliable questionnaire that directly measures both capability and performance of functional activities in the self-care and mobility domain. These domains include 73 self-care and 59 mobility items, which were assessed with questionnaire and observations in each subject. The PEDI provides different summary scores that can be calculated for each content domain. In this study, the scaled score was used. This score is not adjusted for age and therefore can be used to describe the functional status of children at all ages and to document individual improvements with time.¹¹ It is based on the normative sample of 412 healthy children aged 6 months to 7.5 years, and it was developed by transforming the original logit estimates for the entire sample to a 0 to 100 distribution.¹¹ Zero represents no measurable functional ability, and 100 represents capability in all the items within the scale.

Ambulation

The level of ambulation was scored by physiotherapists according to the modified criteria of Bleck¹² with a 4-point scale as follows: non walker, score = 0; therapeutic walker with or without the use of crutches, canes, or walker, score = 1; household walker with or without the use of crutches, canes, or walker, score = 2; neighborhood or community walker with or without the use of crutches, canes, or walker, score = 3.

Grip force

Grip force was measured in subjects who were older than 4 years, unless pain or recent fracture made the measurement impossible. Maximal isometric grip force of the non-dominant hand was determined with a standard adjustable-handle Jamar dynamometer (Preston, Jackson, Michigan). The maximal value of 3 trials was noted. Grip force results were transformed to age-, height-, and weight-specific z-scores by using reference data from Rauch et al.¹³

Anthropometric variables

Height was measured by using a Harpenden stadiometer (Holtain Limited, Crymych, UK). In infants and children unable to sit or stand, height was measured in the supine

Table I. Mobility and self-care scores at start and after 3 years of pamidronate treatment in patients with OI types I, III, and IV

Variable	N	At start	Pamidronate	P Value
Mobility	59	52.3 (35.9–67.4)	75.0 (55.6–100)	<.001
OI type I	18	68.1 (55.6–100)	100 (85.2–100)	<.001
OI type III	12	37.5 (15.2–42.4)	53.5 (46.3–55.2)	<.001
OI type IV	29	48.8 (34.7–64.0)	71.6 (59.1–81.2)	<.001
Self-care	59	64.3 (47.5–93.0)	83.5 (67.6–100)	<.001
OI type I	18	87.2 (51.4–100)	100 (82.8–100)	.001
OI type III	12	55.9 (33.3–67.1)	67.6 (64.1–83.2)	<.001
OI type IV	29	59.3 (47.5–96.5)	81.4 (67.2–100)	<.001

Results are given as scaled scores indicating median and interquartile range (P25–P75). P values indicate the significance of the difference to baseline values.

position. Height in the remaining children was measured while standing. In cases of leg-length discrepancy, the longest leg was used in all measurements. Weight was determined with digital electronic scales for infants and mechanical scales for children (Healthometer, Bridgeview, IL, USA). Weight and height measurements were converted to age- and sex-specific z-scores with National Center of Health Statistics data.¹⁴

Bone densitometry

Bone densitometry was performed in the anterior-posterior direction at the lumbar spine (L1-L4) with a Hologic QDR 2000W or 4500 device (Hologic, Waltham, Mass). Areal bone mineral density (BMD) results were transformed to age-specific z-scores combining reference data from Salle et al and data provided by the densitometer manufacturer.¹⁵

Statistical analysis

Differences between groups were tested for significance with unpaired *t* tests or Mann-Whitney tests, as appropriate. Differences in the frequency of categorical measures between these groups were tested with the chi-square test. Paired *t* tests were used to analyze changes during treatment. All tests were 2-tailed, and throughout the study, a *P* value <.05 was considered to be significant. Differences between different types of OI at baseline and during pamidronate treatment were tested for significance with analysis of variance with Bonferroni adjustment for multiple comparisons. These calculations were performed with the SPSS software, version 11.5 for Windows (SPSS, Chicago, Ill).

RESULTS

Longitudinal analysis

Study patients had low baseline height, weight, and lumbar spine areal BMD z-scores (-3.9 ± 2.7 , -2.2 ± 1.3 , and -5.3 ± 1.6 , respectively), but experienced significant increases in all these measures (height z-score, $+0.3 \pm 0.9$, $P <.05$; weight z-score, $+0.7 \pm 1.2$, $P <.001$; areal BMD z-score, $+3.1 \pm 1.2$, $P <.001$) during the course of the 3-year study period.

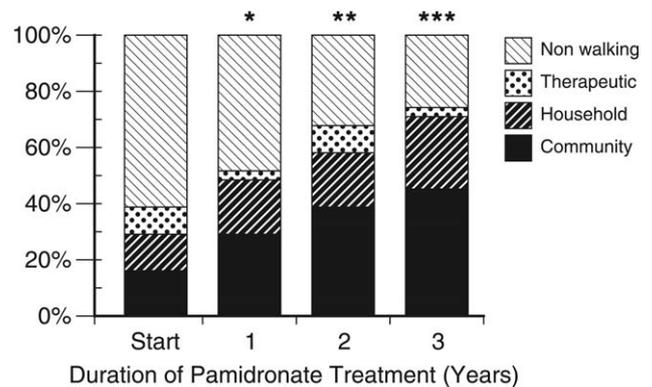


Figure 1. Level of ambulation at start and during 3 years of pamidronate treatment in children with OI types I, III, and IV. Ambulation levels were assessed with the modified Bleck score. Asterisks indicate the significance of the differences from baseline values (* $P <.05$; ** $P <.005$; *** $P <.001$).

During 3 years of pamidronate treatment, mobility and self-care scores increased significantly in the entire study group (Table I). The outcome after 3 years still reflected the severity of the disease, because results were lowest in OI type III group and close to normal in the OI type I group. The changes from baseline, however, were similar in all OI types (self-care: type I, 18.6 ± 20.5 ; type III, 21.7 ± 15.0 ; type IV, 18.5 ± 16.0 ; analysis of variance: $P = .41$; mobility: type I, 22.7 ± 18.7 ; type III, 24.6 ± 14.5 ; type IV, 21.9 ± 15.8 ; analysis of variance: $P = .59$).

Grip force increased significantly during 36 months of pamidronate treatment ($+63\%$, $P <.001$). The fastest rise was observed in the first 12 months of therapy ($+35\%$; $P <.001$ vs baseline), leading to a rapid increase in age-specific grip force z-scores (at start: -1.6 ± 1.6 ; 1 year: -1.0 ± 1.4 ; $P <.005$). Similar changes were noted when grip force z-scores were made on the basis of height (at start: $+2.0 \pm 2.0$; 1 year: 2.8 ± 1.7 ; $P <.01$) or weight (at start: 0.10 ± 1.8 ; 1 year: 0.66 ± 1.6 ; $P <.01$). After 12 months of pamidronate treatment, the ambulation score had increased from 0.84 ± 1.19 to 1.29 ± 1.35 ($P <.05$), to 1.65 ± 1.30 after 24 months ($P <.005$ vs baseline), and to 1.90 ± 1.25 after 36 months ($P <.001$ vs baseline). During the 3-year observation period, the

Table II. Clinical outcome measures of children and adolescents with OI who had received 3 years of pamidronate treatment and of untreated patients

Variable	Pamidronate (n = 48)	Untreated (n = 48)	P Value
OI type (I/III/IV)	16/10/22	16/10/22	
Age (years)	7.6 (3.2)	7.6 (3.5)	
Sex (male/female)	24/24	21/27	.89†
Height (z-score)	-3.3 (2.3)	-4.1 (2.9)	.17
Weight (z-score)	-1.4 (1.6)	-2.4 (1.3)	.006
Areal BMD (z-score)	-2.2 (1.0)	-5.1 (1.3)	<.001
Level of ambulation (score)	2.1 (1.2)	1.0 (1.2)	.001
Mobility*	76.3 (55.8–100)	58.3 (44.5–79)	.002
Self-care*	81.4 (66.8–100)	73.7 (58.8–100)	.23
Grip force (N)	101.7 (64.9)	74.3 (61.5)	.04

Results are given as mean ± SD.

P values indicate the level of significance between the groups.

*Median and upper and interquartile range (P25–P75) are given and a non-parametric test (Mann-Whitney test) was used.

†Chi-square test was used.

number of non-walkers decreased from 61% to 25%, and the number of community walkers increased from 16% to 45% (Figure 1).

Cross-sectional comparison of treated and untreated patients

For 48 patients, results after 3 years of pamidronate treatment could be matched to those of patients with similar age and OI type who had not received pamidronate (Table II). Mean weight and areal BMD z-scores were significantly higher in patients who underwent treatment. The ambulation score was significantly greater in patients who had received pamidronate (Table II). The percentage of community walkers was 50% in the pamidronate group, compared with 18% in untreated patients, and the percentage of non-walking patients was 18%, compared with 50% (Figure 2). In the pamidronate group, grip force and mobility scores were 37% and 18% higher, respectively. Self-care scores also were numerically higher, but the difference compared with patients in the untreated group did not reach significance.

DISCUSSION

This study suggests that long-term cyclical pamidronate treatment improves gross motor function, muscle force, and level of ambulation but not self-care in children with moderate to severe OI. The findings of our longitudinal analysis confirm results of smaller observational studies.^{9,10} Improvements in functional abilities can also be achieved in children with OI who do not receive bisphosphonate therapy.⁸ It was therefore important to compare the study patients to an untreated cohort. This comparison confirmed a significantly better performance in mobility, ambulation, and grip force in children who had received a 3-year course of pamidronate treatment. The mechanism through which pamidronate

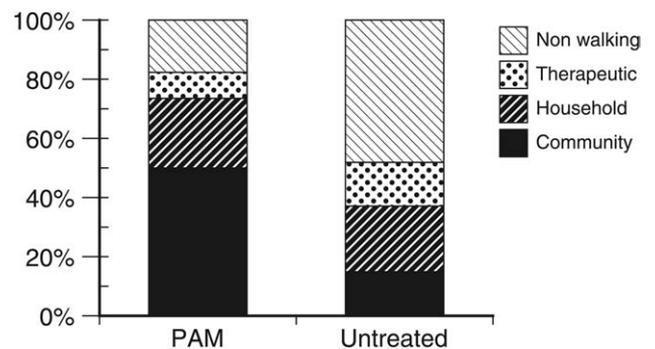


Figure 2. Level of ambulation in patients who had received 3 years of pamidronate treatment (PAM) and in untreated patients. Ambulation levels were assessed with the modified Bleck score. Significant differences were found in the 2 groups ($P < .005$).

treatment improves functional outcome is not entirely clear, but it is plausible that pain relief, increased muscle force, and increased bone mass (and thereby bone strength) all contribute.

Our findings are in contrast to the results of 2 recent placebo-controlled studies on oral olpadronate and alendronate,^{16,17} in which no beneficial effect on mobility outcome could be demonstrated. It is possible that this comparison with historic control subjects overestimated the effect of pamidronate, but it is also conceivable that the treatment effects of intravenous pamidronate are superior to those of oral bisphosphonates. Moreover, the number of patients may have been too small in 1 of the earlier studies,¹⁷ and the observation period in both of these studies may have been too short^{16,17} to demonstrate clearly treatment effects on function. Whatever the interpretation of these discrepant outcomes may be, adequately powered studies are needed to address the question whether the intravenous drug leads to a better functional outcome than oral administration.¹⁸

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