ORIGINAL ARTICLE

Effect of Intravenous Pamidronate Treatment in Children with Osteogenesis Imperfecta

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Abstract

Objective: To assess the beneficial effect of intravenous pamidronate treatment in children with osteogenesis imperfecta (OI).
Study Design: Experimental study.
Place and Duration of Study: Endocrine Unit at the National Institute of Child Health, Karachi, Pakistan, from January 2007 to December 2011.
Methodology: All children diagnosed with osteogenesis imperfecta on the basis of repeated spontaneous fractures and typical radiological findings registered during the study period, were included in this study. Pamidronate therapy were offered to those with more than 3 fractures per year or had platyspondyly. Pamidronate disodium was diluted in isotonic saline and administered by slow intravenous infusion over 3 hours in a dosage 1 mg/kg/day for 3 consecutive days 3 monthly for 2 years. Fracture rate, bone mineral density (BMD), mobility score, wellbeing and pain episodes were evaluated at baseline and 2 years after the treatment. Good response was defined as less than 2 fractures per year or mobility score improvement and poor response as more than 2 fracture per year with mobility score less than 2.
Results: Seventy two patients were included in this study. There were 40 boys and 32 girls with mean age of 3.64 ± 3.2 years. The annual fracture rate decreased overall from 5.8 ± 1.61 to 0.6 ± 0.93 ($p < 0.001$). BMD Z-score improved from -5.3 ± 1.74 to -1.7 ± 0.72 ($p < 0.001$). Mobility score was 0.94 ± 1.30 at baseline and 2.5 ± 1.02 at the end of the treatment ($p < 0.001$). Wellbeing gained from 3.63 ± 1.44 to 7.8 ± 1.18 ($p < 0.001$) and pain episode improved from 24.1 ± 8.15 to 2.7 ± 8.31 ($p < 0.001$). Good response was noted in 92% of patients and poor response in 8% patients.
Conclusion: Bisphosphonate seems to be an effective symptomatic treatment for children with osteogenesis imperfecta irrespective of severity of mutation or clinical phenotype. Cyclical bisphosphonate therapy has a positive effect on fracture rate, BMD, mobility score, wellbeing and pain episode.

Key Words: *Osteogenesis imperfecta (OI). Bisphosphonates. DEXA scan. Fracture. Mobility score. Bone mineral density.*

INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disorder largely due to mutations in the COL1A1 or COL1A2 genes encoding type-I collagen. These mutations cause either a change in the structure of the protein or in the number of collagen molecules made. Manifestations include generalized osteoporosis with multiple fractures, chronic bone pain, progressive loss of mobility and skeletal deformities that worsen over time, most notably in the children.[1] Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures. Classically, OI is divided into four types based on clinical and radiological findings, type-I being mild, type-II lethal, and type-III severe. Type-IV includes patients with a moderate to severe disease who do not fit types I or III.[2,3] Recently, other types of OI (V, VI, and VII) without identifiable collagen type-I mutations have been described.[4-6]

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Histomorphometric and biochemical studies of bone suggest that formation of abnormal bone and increased osteoclastic activity may contribute to the manifestations of OI.[7-9] In keeping with this possibility, bisphosphonates, which reduce bone turnover by inhibiting osteoclast activity, improve the outcome of children and adolescents with severe OI.[8-13] Reported benefits include gains in bone mineral density (BMD), decreases in fracture rates and improved mobility.[9,12,14-17]

Little is known about long-term safety, which is a matter of concern since bisphosphonates accumulate in bone, where they remain for many years. Experimental studies seem to support theoretical concerns that bisphosphonates may delay fracture repair by suppressing bone turnover, although several clinical studies found no increase in time to fracture healing.[18,19] Pamidronate may increase cartilage calcification by suppressing resorption and linear areas of increased bone density may develop,[8] although the clinical significance of these changes is unclear. Finally, pamidronate increases the amount of bone produced but fails to improve its quality, since the genetic collagen abnormality persists throughout life.

Osteogenesis imperfecta is a treatable paediatric disorder; there is no local data published on efficacy of

this therapy in children with OI in Pakistan. This study in hand may provide baseline data which may help to guide paediatricians and family physicians for initial evaluation and management of OI in children.

The objective of this study was to assess the beneficial effect of intravenous pamidronate treatment in children with osteogenesis imperfecta (OI).

METHODOLOGY

Children diagnosed as OI by means of clinical and radiologic evaluation, were recruited as referred to the study place between January 2007 to December 2011. Informed consent was obtained from the parents. The study protocol was approved and monitored by the local Medical Ethical Committee.

Pamidronate therapy was offered to the children with severe OI who experienced more than 3 fractures per year including short stature, skeletal deformities and pain or with a milder form of disease with compression fracture of spine/platyspondyly.[15,20] Excluded were those aged over 15 years and those with mild OI without compression fractures of the spine. Pamidronate disodium was diluted in isotonic saline and administered by slow intravenous infusion over 3 hours in a dosage of 1 mg/kg day for 3 consecutive days every 3 monthly.[9] Pamidronate was given for 2 years from the date of inclusion in the study. All patients received physical therapy and orthopaedic intervention as needed.

Patients were evaluated 3 monthly before each pamidronate infusion and the data were recorded on standardized forms. The annual fracture rate was determined by parent's interview and radiographs.[20] Radiographs were taken 6 monthly to evaluate fracture healing. Delayed healing was defined as unhealed fracture after 6 months.[18] BMD was measured 3 monthly at the lumbar spine (L1-L4) in the anteroposterior direction by dual- energy X-ray absorptiometry (DEXA). BMD values were converted to age and gender-specific Z-scores.

Mobility was evaluated using 5- point scale according to Bleck.[21] The score division was 0 = unable to leave the bed or wheelchair or non-walker; 1= able to walk with aid but not functionally mobile, or exercise walker; 2 = able to walk in the house, with or without aid, or household walker; 3 = able to walk short distances, with or without aid, or neighbourhood walker; 4 = able to walk independently or community walker.

Pain episodes evaluated subjectively by the parents and if possible, the patients were recorded on the forms at each visit. As pain is difficult to assess, especially in small children, it chosen to ask patients or parents to record how many days per month that the children experienced pain and not to record the intensity of pain.[15] Wellbeing, based on parents and patients subjective assessment, was assessed 3 monthly before the treatment. Parents or the patients registered wellbeing using an arbitrary 10 grade scale, where 10 represents maximal wellbeing: they should choose any number between 1 and 10.[15] Two categories of treatment response were described: good response defined as less than 2 fractures per year or mobility score improvement and poor response defined as more than 2 fracture per year with mobility score less than 2.[20]

Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 17. Frequencies and percentages were computed for categorical variables like gender and responses. Mean ± Standard Deviation was computed for numerical variables like age, fractures/year, BMD score, mobility score, wellbeing scale and pain episode days/month. Student paired t-test was used to compare baseline and endpoint means of numerical variables (fractures/year, BMD score etc). $P < 0.05$ was considered as statistically significant.

RESULTS

Total patients included in the study were 72. There were 40 boys (55.6%) and 32 (44.4%) girls. Mean age was 3.64 ± 3.2 years. The age range at the start of the treatment was 1 - 13 years. The annual fracture rate decreased overall from 5.8 ± 1.61 to 0.6 ± 0.93 ($p < 0.001$). Signs of new bone formation with increased vertebral height were observed after two years of treatment. In more severe form this improvement was usually observed by X-ray. Other radiologic changes included decreased deformities of long bones. Radiographs showed discrete dense parametaphyseal lines corresponding to the time of each treatment cycle, confirming the linear growth continued. None had history of delayed fracture healing or nonunion at baseline. During the study, delayed fracture healing was noted in 5 patients, 2 in the good response group and 3 in the poor response group. Patient in the poor response group showed delayed healing in tibia, femur, humerus, radius, ribs while patient in good response group delayed healing occurred in radius and ulna. The time from fracture to nonunion ranged from 8 to 12 months.

Before the treatment, all patients had low bone mineral density. During the course of the treatment, a gradual increase in bone density was observed in all individuals from DEXA measurement in the lumbar spine. Overall, BMD Z-score improved from -5.3 ± 1.74 to -1.7 ± 0.72 ($p < 0.001$). This increase brought them closer to the age matched values after 2 years compared with the pre-treatment.

A significant mobility score improvement occurred after 2 years of the treatment. Overall mobility score improved from 0.94 ± 1.30 to 2.5 ± 1.02 ($p < 0.001$). The mobility score was 0 in 43 (59.7%) patients at baseline compared to only 4 (5.5%) patients at study completion.

Before the treatment, mobility score was 1 in 6 (8.3%) patients as compared to 2 (2.7%) at the end of treatment. Patient with mobility score of 2 and 3 were 10 (13.8%) at the start of treatment and it improved to 34 (47.2%) and 18 (25%) respectively at the end. Mobility score was 4 in 3 (4.1%) patients at baseline and 14 (19.4%) at study completion.

A dramatic and progressive decrease in pain and wellbeing was reported within 12 weeks of onset of treatment. Most of the patients' subjective score for wellbeing, pain and activities of daily life improved greatly during treatment. The well-being scale improved from 3.63 ± 1.44 to 7.8 ± 1.18 ($p < 0.001$). There were 66 patients who remained pain-free most of the days. Six patients reported pain everyday but with decreased intensity. The pre-treatment value for pain was 24.1 ± 8.15 and after 2 years of treatment the value was decreased to 2.7 ± 8.31.

Good response was noted in 66 (92%) patients and poor response in 6 (8%) patients. In good response group, mean mobility score, BMD Z-score, annual fracture rate, pain episodes and wellbeing scale was significantly improved ($p < 0.001$) as mentioned in Table II. In poor response group, BMD Z-score improved, fracture rate decreased but mobility score remained < 2 (Table III). No statistically significant improvement noted in pain and well-being scale even though the pain intensity decreased in poor response group.

Table I: Comparison of the 72 patients with OI before and end of treatment.

Variables	Baseline	End	p-value
Fracture / year	5.8 ± 1.61	0.6 ± 0.93	< 0.001
BMD (Z-score)	-5.3 ± 1.74	-1.7 ± 0.72	< 0.001
Mobility score	0.94 ± 1.30	2.5 ± 1.02	< 0.001
Wellbeing (10 degree scale)	3.63 ± 1.44	7.8 ± 1.18	< 0.001
Pain episode (days/month)	24.1 ± 8.15	2.7 ± 8.31	< 0.001

Figures are in mean ± SD, paired t-test was used for comparative analysis. Statistically significant p-value < 0.05.

Table II: Data in good response group (n=66).

Variables	Baseline	End	p-value
Fracture / year	5.6 ± 1.54	0.4 ± 0.61	< 0.001
BMD (Z-score)	-5.2 ± 1.80	-1.7 ± 0.70	< 0.001
Mobility score	1.03 ± 1.32	2.7 ± 0.81	< 0.001
Wellbeing (10 degree scale)	3.8 ± 1.41	8.1 ± 0.85	< 0.001
Pain episode (days/month)	23.5 ± 8.31	0.2 ± 0.53	< 0.001

Figures are in mean ± SD, paired t-test was used for comparative analysis. Statistically significant p-value <0.05.

Table III: Data in poor response group (n=6).

Variables	Baseline	End	p-value
Fracture / year	7.8 ± 0.75	3 ± 0	< 0.001
BMD (Z-score)	-6.12 ± 0.84	-1.8 ± 1.02	0.001
Mobility score	0	0.33 ± 0.52	0.175
Wellbeing (10 degree scale)	2 ± 0	5 ± 0	a----
Pain episode (days/month)	30 ± 0	30 ± 0	a----

Figures are in mean ± SD, paired t-test was used for comparative analysis. Statistically significant p-value < 0.05. The t-statistics or p-value cannot be computed because standard deviation of difference is zero.

Considering the possible adverse side effects of treatment, we only noted the fever upto 38.5°C responsive to acetaminophen after the first cycle infusion in 14 patients. During the treatment, none of our patient showed white blood cell reduction, hypocalcemia, flu-like symptoms or respiratory distress.

DISCUSSION

Bisphosphonates, a group of stable analogs of pyrophosphatase, are potent inhibitors of bone resorption and bone turnover. Bisphosphonates are currently the medical treatment most often used in children with moderate to severe OI. In Pakistan, there is no local published data on efficacy of intravenous bisphosphonates in the children. This study is an effort about the determination of beneficial effect of intra-venous pamidronate in children within the local setup at National Institute of Child Health, Karachi, a tertiary care hospital which may provide data for future studies.

Pamidronate therapy was effective in decreasing fractures and improving mobility in children with moderate to severe OI.[9,12,13] Fracture rate is difficult to assess without frequent X-rays, which is not recommended for patients with OI, as the increased fracture rate can lead to high accumulated doses of radiation overtime. Furthermore, the observed increase in mobility can increase the risk of fracture. However, most of the children or their parents reported a decrease in symptoms. In this study, all patients experienced new fractures and the annual fracture rate decrease was from 5.8 ± 1.61 to 0.6 ± 0.93 while one-third of the patients studied by Glorieux *et al*.[9] remained free of fractures while on pamidronate therapy; overall, the annual fracture rate decreased from 2.3 ± 2.2 to 0.6 ± 0.5. In another study reported by Alharbi *et al*. annual fracture rate decrease was smaller, from 2.7 ± 1.8 to 1.5 ± 1.3. One possible explanation mentioned for this discrepancy was the younger age of the patients: 60% were younger than 7 years and only 26% were pubertal, compared to 26.6% younger than 7 years and 50% pubertal in the study by Glorieux *et al*.[9] The anabolic effect of sex hormones on bone may contribute to reduce the fracture rate in older children.

Delayed fracture healing is a well-known feature of OI. Here, nonunion was defined as absence of fracture healing after 6 months, in accordance with previous data.[18] It was reported in about 19% of patients in a study.[22] However, nonunion of spontaneous fractures occurred in as many as 5 (6.94%) of our patients. None of our patients had a history of nonunion before pamidronate therapy, suggesting a possible role for pamidronate in delayed fracture healing. It may indicate greater inhibition of bone resorption by pamidronate, which may have contributed to delay healing. Munns *et al*.[19] reported that delayed fracture healing associated with older age, proximity to pamidronate cycles and

osteotomy. Neither the duration of pamidronate therapy nor the timing of the cycles relative to the fractures influenced the occurrence of non-union.[19] They suggested that improved mobility increased the risk for delayed healing during pamidronate treatment. However, two-third patients with nonunion experienced little or no improvement in their mobility scores. These results suggest a need for minimizing delayed healing by assaying bone markers before and after pamidronate infusions.[22,23]

The mean BMD Z-score increased significantly by 3.6 over a mean follow-up of 2 years. Similarly, Glorieux *et al*.[9] reported a mean BMD Z-score increase of 1.9 over 2.1 years in 30 patients given pamidronate while Plotkin *et al*. reported a significant decrease in lumbar DEXA values over a one year period in their historical control group of 6 patients with a mean age of 10.7 months at the start of observation.[24] Data from earlier studies indicate that the BMD Z-score is unlikely to normalize with age in patients with OI who do not receive bisphosphonate therapy. Thus, the BMD increase seen in this study can be ascribed to pamidronate therapy.

Most of our patients experienced statistically significant mobility score improvements. However, these mobility gains may be ascribable not only to pamidronate therapy, most notably via a decrease in fractures, but also to physical therapy and orthopaedic interventions.[9,12]

Pain is sometimes difficult to estimate in the more severe forms of OI. As these children have had fissures, compressions, and fractures since the neonatal period, they are used to a certain amount of skeletal pain, regarding this as normal, so tend to complain only when they suffer larger fractures. It is clear that the intensity of pain is an essential part of the feeling of well-being. However, it is evident that a total absence of pain does not result in maximal well-being in all cases. It was, therefore, chosen to present both pain and well-being variables. The reduction in pain that occurs early in treatment permits more effective physiotherapy, which also positively affects mobility and might also affect fracture rate.[21] Early body weight bearing with the aid of plastic orthoses, mobility devices, and intramedullary rodding provides stress to the lower limb bones and is of the utmost importance to avoid additional osteoporosis caused by immobilisation.[21,25] Mechanical use of the skeleton in standing and walking also stimulates new bone formation.[25] These positively interacting factors lead to an overall beneficial effect on the patients.

In this study, 6 (8%) patients failed to experience a decrease in pain episode, although their mobility scores remained low and their BMD Z-scores and fracture rates showed significant improvements similar to those seen in other patients. The reasons behind the poor response to pamidronate in our patients are unclear. The baseline values of the study parameters in our patients were not different from those in the good response group. Thus, no factors predicting the response to pamidronate therapy were identified. In keeping with earlier data,[9,15] the bone resorption marker urinary deoxypyridinoline decreased during pamidronate infusions so bone markers may be useful for predicting the response to pamidronate treatment.

Although bisphosphonate treatment is a symptomatic not curative treatment that does not alter the genetic defect underlying OI, it is an adjunct to physiotherapy, rehabilitation and orthopaedic care that must be continued carefully.

This study is baseline data for future studies. Further long-term studies are required to assess the effects of bisphosphonates on bone modelling and re-modelling capacity in children with OI. Data from this study would facilitate the establishment of an optimal dosage, as well as treatment frequency and duration of bisphosphonate therapy in osteogenesis imperfecta during childhood.

CONCLUSION

Bisphosphonate seems to be an effective symptomatic treatment for children with osteogenesis imperfecta irrespective of severity of mutation or clinical phenotype. Cyclical bisphosphonate therapy has a positive effect on fracture rate, BMD, mobility score, wellbeing and pain episode.

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