Bisphosphonate therapy for patients with osteogenesis imperfecta in different age groups: A comparative study

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Background
Bisphosphonates are currently a promising therapy and are commonly used for osteogenesis imperfecta (OI).
This study was performed to assess the outcome of bisphosphonates as a symptomatic treatment of OI.
Patients and method
A prospective observational study on 16 patients, who had been referred to the pediatric orthopedic clinic at our hospital. All patients were treated and followed up from November 2015 to November 2017. All cases were moderate forms of the disease (types I and IV).
The age at the start of treatment was 3–17 years. There were six females and 10 males. The mean age was 6.5 years.
Result
All patients showed improved pain, and activities of daily living during treatment, and this improvement sustained during the 2 years' follow-up. There was a decrease in the number of fractures per year in all patients by up to 50%. All children became pain-free during treatment; no patient needed analgesics, except in cases of fracture. No side effects were seen during the period of treatment.
Conclusion
The overall positive results and absence of adverse effects may be sufficient to recommend the use of this treatment for all children with OI who have severe and moderate forms. So early treatment with bisphosphonates may prevent and decrease skeletal deformity.

Keywords:
bisphosphonate, imperfecta, osteogenesis

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Introduction

Osteogenesis imperfecta (OI) is a congenital disease of collagen with variable phenotypes. In milder forms the fracture rate is only slightly increased and the stature is normal or slightly decreased. In severe forms, bone softness and multiple fractures lead to progressive bone deformities with extreme shortness, frequent skeletal pain, and confinement to a wheelchair. In most cases, there are mutations in COLIA1 or COLIA2 genes localized to chromosomes 17 and 7, respectively. This leads either to a reduced production of normal collagen type I, or to the synthesis of abnormal collagen type I.

The current classification into four major subgroups (types I–IV), based on clinical findings, was proposed by Sillence *et al.* in 1979 [1,2] This classification has been expanded to include a greater range of subgroups of patients (OI types V–IX)

Silence classification

Type 1:
The largest group of patients showed autosomal-dominant inheritance of osteoporosis leading to fractures and distinctly blue sclera. A large proportion of adults had presenile deafness or a family history of presenile conductive hearing loss.

Type II:
Comprised of the majority of newborns with neonatal fractures, all died before or soon after birth. These had characteristic broad, crumpled femora and beaded ribs in skeletal radiographs. Autosomal-recessive inheritance was likely for some, if not all, of these cases.

Type III:
Two-thirds of cases had fractures at birth, and showed severe progressive deformity of the limbs and spine. The density of scleral blueness appeared less than that seen in the first group of patients and approximated that seen in normal children and adults. Moreover, the blueness appeared to decrease with age.

Type IV:
This group includes fractures, with variable deformity of long bones, but normal sclera with dominant inheritance of osteoporosis.

Many types of pharmacological treatment have been tried for severe forms of OI. Sodium fluoride has been tried without any convincing benefit [3]. Growth hormone shows a beneficial effect, mostly in milder forms of OI [4]. Calcitonin had beneficial effects but with pronounced side effects [5]

Bisphosphonates are stable analogs of pyrophosphate, have a long half-life when incorporated into the bone, and have multiple effects, predominantly inhibition of osteoclast activity.

The rationale for bisphosphonate treatment in OI is that the complex function of bisphosphonate, with a predominantly inhibitory effect on osteoclasts, might lead to a net effect of increased bone mass in OI patients [6]. They have also been used to treat children with juvenile idiopathic osteoporosis and Gaucher's disease [7].

There is no cure for OI. All treatment is limited to supportive, pharmacological, and surgical treatment.

Supportive care included physiotherapy, advice about handling, and day-to-day care.

Surgical care includes corrective osteotomy and nailing for deformity. Pharmacological care including growth hormone, calcitonin, parathyroid hormone, sodium fluoride, vitamins, and now bisphosphonates have been administered in an attempt to reduce fractures and deformities in OI [6].

Oral and intravenous bisphosphonates are currently the most promising therapy and are commonly used for OI as uncontrolled clinical trials of these agents have shown improvements in bone mineral density (BMD) in people with OI [8].

Bisphosphonate types and mechanism of action

Bisphosphonates act by inactivating osteoclasts, thereby inhibiting bone resorption [6].

There are two different types of bisphosphonates (Table 1):

(1) Nitrogenous bisphosphonates disrupt osteoclast formation, survival, and cytoskeletal dynamics.

Table 1 Types of bisphosphonates

Bisphosphonate	Action	Route of administration
Alendronate* (Fosamax)	Nitrogenous	Oral
Clodronate (Bonefos)	Nonnitrogenous	Oral, intravenous
Neridronate	Nitrogenous	Intravenous
Pamidronate* (Aredia)	Nitrogenous	Intravenous
Risedronate (Actonel)	Nitrogenous	Oral
Tiludronate (Skelid)	Nonnitrogenous	Oral
Zoledronate (Zometa, Reclast)	Nitrogenous	Intravenous

(2) Nonnitrogenous bisphosphonates initiate osteoclast apoptosis.

Net effect: Reduced bone resorption and an increase in bone mineral density,

Aim of the work

A comparative study to assess the effectiveness and safety of bisphosphonates in different age groups in reducing fracture rates and increasing bone density in patients with osteogenesis imperfecta.

Patients and methods

A prospective observational study on 20 patients, who had been referred to the pediatric orthopedic clinic at our hospital. All patients were treated and followed up from November 2016 to November 2018.

All the cases were moderate forms of osteogenesis imperfecta (types I and IV). Patients were divided into two groups according to their age limit. Group A included 10 patients of age between 2 and 6 years. This included six males and 4 females. Group B included 10 patients of age between 7 and 16 years. This group included eight males and two females.

The follow-up period was every 3 months for a number of fractures, long bone deformity, and pain using the FLACC Behavioral Pain Assessment Scale to access the pain score in all age groups [9].

All patients in both groups received I.V. Zoledronate (Zometa) once or twice per year according to the severity of the disease.

To compensate for a generalized decrease in serum calcium, patients were also given oral treatment with 1, 25-dihydroxycholecalciferol and calcium.

In addition to pharmacological treatment, mechanical stabilization either using orthosis or surgical

intramedullary fixation or both was used according to special indications in every case.

Dose protocol [10]

According to the protocol recommended by the European Medicines Agency

Patients aged 2 to 16 years received 0.05 mg/kg of zoledronic acid up to a maximum of 4 mg diluted in 100 ml normal saline over a 30 min IV drip.

All patients were admitted to the pediatric unit for hospitalization and discharged on the same day of infusion every 6 months in severe cases up to 2 years, every year in moderate cases up to 2 years

So, our cases received only one dose per year.

Results

Clinical results

In group A, all patients showed improved pain, and activities of daily life greatly during treatment; these were sustained for 2 years follow-up. A progressive decrease in pain was reported within 2–6 weeks of the onset of treatment in all cases. In the 8 week, all patients were pain-free. There was a decrease in the number of fractures per year in all patients by up to 80% with improved long bone deformity in all cases and no surgical correction were needed. No patient needed analgesics, except in cases of fracture

Only GIT disorders in the form of vomiting and upper abdominal pain were observed in all cases during the start of treatment and during hospitalization and all patients improved on the second day.

No side effects were reported during the period of follow-up.

In group B

All patients showed improved pain and activities of daily life; these were sustained for 2 years follow-up. A progressive decrease in pain was reported within 2–10 weeks of the onset of treatment in all cases, in the 12 weeks all patients were pain-free. There was a decrease in the number of fractures per year in all patients by up to 70%, but long-bone deformity in five cases needed surgical corrective osteotomy and intramedullary fixation. No patient needed analgesics, except in cases of fracture.

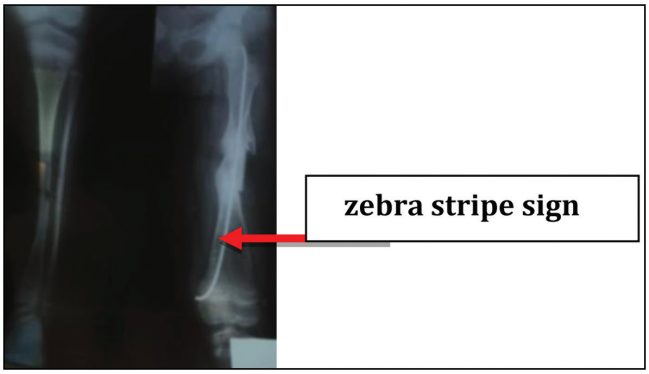
Only GIT disorders in the form of vomiting and upper abdominal pain were observed in all cases during the start of treatment during hospitalization and all patients improved on the second day.

No side effects were reported during the follow-up period.

Radiological findings

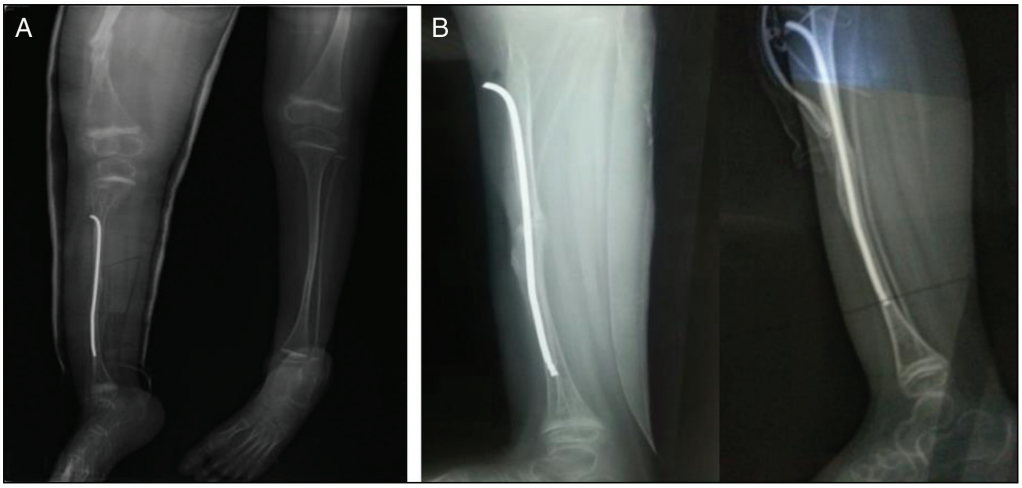
New bone formation in the form of increased cortical thickness, though serial radiographs of long bones

Figure 1



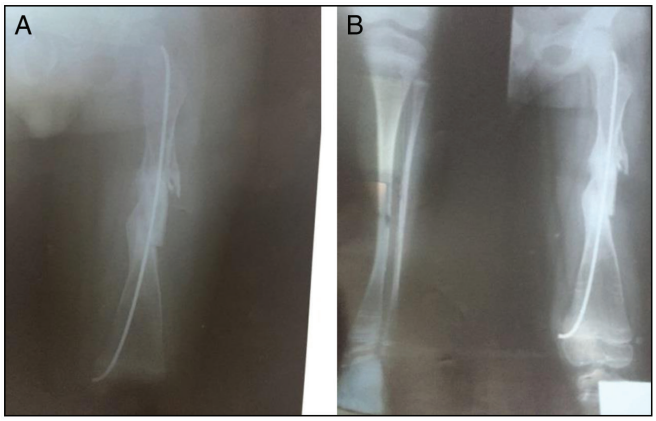
5-year male child<AQ: Radiograph of a 5-year-old male child?>.

Figure 2



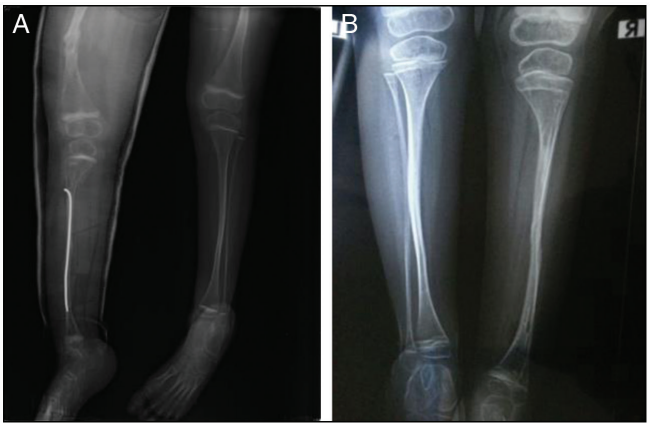
8 years male child. A: Before therapy. B: After 2 years.

Figure 3



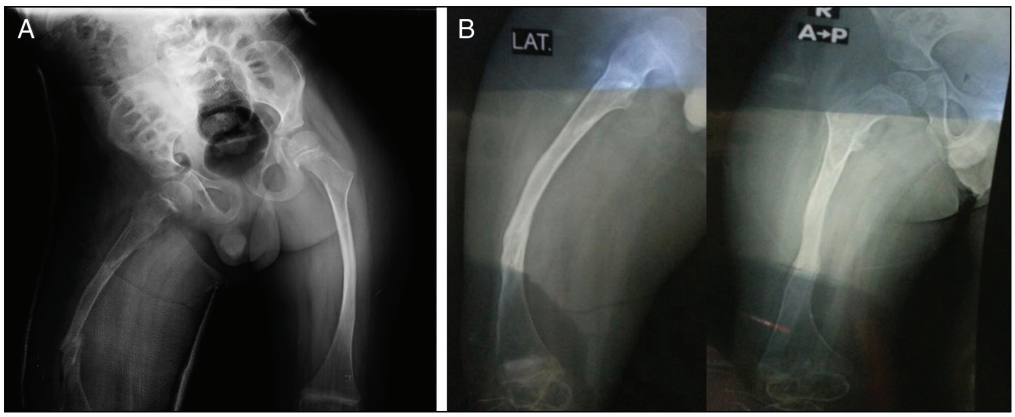
5 Year's male child. A: Before therapy. B: After a 2-year follow-up.

Figure 5



6 year's female child. A: Before therapy. B: After 2 years.

Figure 4



6 year's male child. A: Before therapy. B: After 2 years.

had been observed in all cases in both groups with no difference. Sclerotic lines (zebra stripe sign) of dense bone formed after the second dose of bisphosphonate were noted in two cases in group B Figs. 1–5.

Discussion

There are good theoretical reasons for believing that bisphosphonates could be valuable for the symptomatic treatment of OI. The overall positive results and absence of adverse effects may be sufficient to recommend the use of this treatment for all children with OI who have the more severe form and for milder forms. The effect of bisphosphonate, with a predominantly inhibitory effect on osteoclasts, leads to a net effect of increased bone mass in OI patients [8]

Results of treatment of 20 children with OI with zoledronic acid show a decrease of fracture rate by 80% in group A and 70% in group B, decrease in deformity, and pain improvement with no side effects recorded in both groups.

Bisphosphonates have a low and variable intestinal absorption and a long half-life in the bone; gastrointestinal side effects are common after oral administration, while small children may find it difficult to swallow tablets [10]. The intravenous route overcomes this problem and prevents the variable bioavailability from interfering with our interpretation of the observed effects.

The Harnik *et al*. systematic review of the effects of bisphosphonate treatment in children with osteogenesis imperfecta was conducted using the American Academy for Cerebral Palsy and Developmental Medicine Methodology for developing systematic reviews of treatment interventions [7].

In a prospective observational study by E Astrom, disodium pamidronate (APD) was given as monthly intravenous infusions to 28 children and adolescents (aged 0.6–18 years) with severe OI or a milder form of the disease, but with spinal compression fractures. All patients experienced beneficial effects and the younger patients reported a major improvement in pain and

mobility without side effects. Vertebral remodeling was also seen [11].

Carrie A Phillipi, Tracey Remington, and Robert D Steiner [intervention review] assessed the effectiveness and safety of bisphosphonates in increasing bone mineral density (BMD), reducing fractures, and improving clinical function in people with OI. Evidence suggests oral or intravenous bisphosphonates increase BMD in children and adults with OI [12].

Mona S. study with Thirty-three patients with OI and five patients with bruck syndrom, all were treated with 0.1 mg/ kg zelodronic acid intravenously every 6 months for 2 years during which they were followed up using different parameters. A clinical severity score (CSS) was applied to the patients before and 2 years after the start of therapy. This was the first Egyptian study to report a 24-month follow-up of the effect of zoledronic acid therapy in 33 Egyptian children with moderate to severe OI and is the first report in the literature illustrating the effect of treatment on five patients with Bruck syndrome [13].

Zoledronic acid proved to be safe and effective in the treatment of OI and BS. The biannual infusion protocol was convenient for patients. There was a positive correlation between disease severity and benefits of the treatment. The use of the CSS proved to be of value in the assessment of the degree of severity in OI, and with some modifications, it was a valuable tool for the assessment of response to treatment [14].

Conclusion

There is no cure for OI till now, but it is likely to be available in the near future. The overall positive results and absence of adverse effects may help the use of this treatment for all children with OI who have severe and moderate forms. So early treatment with bisphosphonates may prevent and decrease skeletal deformity.

Bisphosphonates improved the clinical status (reduce fractures and pain; improve growth and functional mobility) in this population.

Zoledronic acid has positively influenced the quality of life in pediatric patients with OI and has proved to be safe. Also, the used treatment protocol with infusion every year minimized the hospital visits to two or one per year for a few hours.

Further studies are needed to establish optimal regimens, duration of therapy, and long-term safety.

Acknowledgements

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Conflicts of interest

No conflict of interest.

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