Original article

Conservative versus surgical treatment of osteogenesis imperfecta: a retrospective analysis of 29 patients

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Summary

The aim of our study was to compare the surgical and conservative treatment of patients affected by fragility fractures and deformities of long bones in osteogenesis imperfecta (OI).
Our series consisted of 29 consecutive OI patients treated at our Institute. The series comprised 14 females and 15 males of different ages. The mean age at the time of the first treatment was 8 years (median 6 years; SD ± 15; range 1 to 75). The mean follow-up was 88 months. The Sillence classification was used to classify OI. Fifteen patients were classified as Type I; five as Type III and nine as Type IV.
A total number of 245 procedures were recorded. Of these, 147 were surgical (pinning; intramedullary nailing and plating) while 98 were conservative (cast, braces and bandages). Bisphosphonate use was a major variable in the study. Clinical charts and radiographic films were analyzed for complications (delayed union, nonunion, malunion, hardware loosening). We recorded 58 complications: 13 in Type I; 28 in Type III and 17 in Type IV OI. The rate of each complication was: 15/245 nonunions (6.1%), 14/245 delayed unions (5.7%), 14/245 malunions (5.7%) and 15/245 hardware loosenings (6.1%).
We found no statistically significant differences between surgical and conservative treatments. Type III OI, which is a very crippling form of the disease, was associated with radiographically poorer results than the other types. In our analysis, the two groups were unbalanced and only five patients were treated with bisphosphonates. Nevertheless, bisphosphonate use can be considered a good adjuvant to both the conservative and surgical treatment of OI in order to reduce the rate of complications.

KEY WORDS: osteogenesis imperfecta; surgical treatment; conservative treatment; complications; bisphosphonates.

Introduction

Osteogenesis Imperfecta (OI) is a rare hereditary disorder of the connective tissue resulting in osteopenia and bone fragility. In 90% of cases, a dominant mutation in one of the two genes (COL1A1, COL1A2) encoding the α chains of type I collagen is responsible. The mutation causes a change in protein structure or in the number of collagen molecules produced (1).
Clinical expression of OI is highly variable (2, 3). In 1979, Sillence et al. (4) proposed a classification system which is still the most widely used method for classifying the disease. The original classification includes four clinical types of OI (Types I, II, III and IV). In 2000 and 2002, other authors described three additional OI variants which, unlike Types I to IV, are not characterized by mutations in the COL1A1/2 genes or by blue sclerae or dentinogenesis imperfect (5-7).
The natural history of OI is characterized by a higher susceptibility to bone fractures and a wide spectrum of skeletal manifestations, from slight abnormalities in Type I, to severe deformities in Type III. The severity increases in the following order: Type I < Type IV < Type III < Type II (8). The bones of patients suffering from this disease are typically shorter, with very thin cortices and may be bowed and flared. These patients therefore tend to undergo surgery to correct these deformities.
The surgical correction of the aforementioned deformities mainly consists of osteotomies and stabilization with intramedullary devices or plates. Unfortunately, osteosynthesis is prone to failure and complications are extremely frequent in these patients due to the very weak bone (9). The treatment of fragility fractures can either be surgical or conservative, but there is no evidence to show which is the best treatment option. Recently, several studies documented the use of bisphosphonates, a group of stable analogs of pyrophosphates which are potent inhibitors of bone turnover (10, 11), to reduce fracture rates in OI patients (12, 13).
The aim of our study was to analyze the value of surgical versus conservative treatment of long bone fragility fractures and deformity, with the occurrence of complications chosen as the end point. In addition, we analyzed the effect of bisphosphonate use on the rate of complications.

Materials and methods

A consecutive series of 29 patients (14 females and 15 males) were treated for OI at our Institute from 1980 to 2010. Patients were classified using the phenotypical characteristics proposed by Sillence (4) as shown in table 1. All 29 patients were treated for fragility fractures and correction of deformity.
Taking into account the entire series, the mean age at the time of the first treatment was eight years (median 6 years; SD ± 15;

range 1 to 75). Fifteen patients were classified as Type I (six males and nine females); five as Type III (three males and two females); and nine as Type IV (six males and three females) (Table 2). In our series we only took into consideration the appendicular bony segments: the clavicle, humerus, forearm (radius and ulna) for the upper limb; the femur and leg (tibia and fibula) for the lower limb. The spine, scapula, pelvis, ribs, hands and feet were excluded from our analysis.
Fracture treatment was divided into two main categories: surgical and conservative. Surgical treatment was performed with a plate and screws, or with intramedullary nail osteosynthesis (Rush, Nancy, Grosse-Kempf, Kuntscher). No telescopic rods were implanted in this series. Conservative treatment consisted of casts, braces, splints and bandages.
Deformities were corrected using osteotomy and osteosynthesis with plate and screws, or intramedullary nails. Due to the small sizes of each group, we pooled the data on deformity correction with the surgical treatment of fractures.
Clinical charts and radiographic films were reviewed at a mean follow-up of 88 months (median 37 months; SD ± 105; range 1 to 346). The use of bisphosphonates was recorded and the patient's X ray films were checked for complications, looking specifically for delayed union, nonunion, malunion and hardware loosening. Delayed union can be defined as "when a fracture fails to unite within the established time for that fracture even if clinical or radiological signs show ongoing healing" (14), while nonunion is "when the normal biological healing process of bone has ceased, without union occurring" (15). Malunion, on the other hand, is "a healed fracture in a position that affects the mechanical function of the limb" (16). Hardware loosening is defined as "the mobilization of previously implanted metal devices used to stabilize bone fragments" (17). The effects of a single or multiple cycle of bisphosphonates was analyzed, focusing on the rate of complications; all other drugs such as estrogens, growth hormones or other antiosteoporotic drugs were excluded.

Table 1 - The table shows the OI clinical phenotypes based on the typical features proposed by Sillence. The severity increases in the following order from the top (Type I) to the bottom (Type II).

Clinical severity	Clinical type	Typical features
Non-deforming form	I	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta
Moderately deforming form	IV	Moderately short; mild to moderate scoliosis; greyish or white sclera; dentinogenesis imperfecta
Severe deformations	III	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta
Perinatal lethal form	II	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera

Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), software version 15.0 (SPSS Inc., Chicago, USA).
All continuous data were expressed in terms of the mean and the standard deviation (SD) of the mean. Grouping variables were expressed in frequency and percentage. If the Levene test for homogeneity of variances was not significant ($p<0.05$), a one way ANOVA was performed to test the differences between the means of the different groups; in all other cases, the Mann Whitney U test was used. Pearson's Chi square test, calculated with the Montecarlo Method for small samples, was performed to investigate the relationships between grouping variables. The Fisher exact test was performed to investigate the relationships between surgical and conservative treatments in the fracture group, the correlation of the complications (delayed union, nonunion, malunion, hardware loosening) and the use of bisphosphonates.
For all tests, $p<0.05$ was considered significant.

Results

We performed 245 procedures in 29 patients: 166 procedures for 110 fractures (68%) and 79 procedures for correction of deformity (32%). In the fracture series, 98 procedures (59%) were conservative and 68 (41%) were surgical. Pooling together the surgical procedures (fracture treatments and deformity correction), there were a total of 147 surgical procedures (60%) and 98 conservative procedures (40%).
The most affected bony region was the femur, with 161 procedures being recorded (65.7%); 41 procedures were carried out on the leg (16.7%); 8 on the clavicle (3.3%); 18 on the humerus (7.3%) and 17 on the forearm (7%). The lower limbs were more involved than the upper limbs (Table 3).
Out of the 245 procedures performed, we recorded 58 complications: 13 in Type I; 28 in Type III and 17 in Type IV OI (Table 2). The overall rate of complications in the conservative group was 33/98 (33.6%), while in the surgical group the rate was 25/147 (17%). No statistically significant differences were found between the two groups, although a slight tendency (p 0.13) toward better results was found in the surgical group. The mean age of patients with complications was lower (6.2 years) than the mean age of patients who did not experience complications (8.6 years) (Table 4).

Table 2 - The table shows the case series of OI patients together with the complication rate and the use of bisphosphonates.

Clinical type	Patients	Non Union	Delayed Union	Malunion	Hardware Loosening	Total Complications	Bisphosphonates
I	15 M = 6; F = 9	4	6	2	1	13	4
III	5 M = 3; F = 2	7	6	5	10	28	0
IV	9 M = 6; F =3	4	2	7	4	17	1

Table 3 - The table shows the treatments and complication rate in each appendicular bony region.

Bony regions	Treatments			Complications				
	Fractures	Deformity	Total	Delayed union	Nonunion	Malunion	Hardware loosening	Total
Clavicle	8	-	8	4	1	-	-	5
Humerus	18	-	18	-	1	1	1	3
Forearm	16	1	17	-	2	-	-	2
Femur	91	70	161	6	7	8	12	33
Leg	33	8	41	4	4	5	2	15
Total	166	79	245	14	15	14	15	58

The rate of each complication was: 15/245 (6.1%) nonunions, 14/245 (5.7%) delayed unions, 14/245 (5.7%) malunions and 15/245 (6.1%) hardware loosenings.
We found seven nonunions in the femurs, four in the legs, one in the clavicle, one in the humerus and two in the forearms (Table 3). Four nonunions were recorded in Type I; seven in Type III and four in Type IV OI. Seven of these (4.7%) occurred after surgical treatment while eight (8.2%) occurred after conservative treatment (Table 5). No statistically significant differences were found between surgical and conservative treatments.
With regards to delayed union, six were recorded in the femurs, four in the legs and four in the clavicles (Table 3). Six delayed unions were recorded in Type I, six in Type III and two in Type IV OI. We recorded 6/147 (4.1%) after surgical treatment and 8/98 (8.1%) after conservative treatment (Table 5).
Malunion was observed in eight femurs, five legs and one humerus (Table 3). Two occurred in Type I, five in Type III and seven in Type IV OI. Of these, 5/147 occurred after surgical treatment (3.4%) and 9/98 (9.18%) occurred after conservative treatment (Table 5).
Hardware loosening occurred in twelve femurs, two legs and one humerus (Table 3). One loosening was recorded in Type I, ten in Type III and four in Type IV. The Type III phenotype was associated with a higher rate of hardware loosening ($p = 0.03$) compared to the other Types. We recorded 7/147 (4.8%) loosenings after surgical treatment and 8/98 (9.2%) after conservative treatment of a new fracture in the same limb (Table 5).
No statistically significant differences were found in terms of the complication rate between the plate and screw versus intramedullary osteosynthesis. We recorded 4/18 (18.2%) complications in the plate group and 23/112 (20.5%) in the intramedullary nail group.
The use of bisphosphonates significantly reduced the rate of complications. There were 57/223 (25.6%) complications in the group who did not receive bisphosphonates, but only 1/22 (4.5%) in the group receiving bisphosphonates ($p = 0.032$). The complication in the latter group was a stiff elbow which occurred as a consequence of cast immobilization, unrelated therefore to bisphosphonate use.

Table 4 - The table shows that patients with complications were significantly younger than those who did not have complications (Mann Whitney $p = 0.04$).

	N.	Mean age	Std. Deviation
No Complications	187	8.6	9.0
Complications	58	6.2	5.2
Total	245	8.0	8.3

Table 5 - The table shows each complication in the surgical and conservative groups.

Complications	Surgical	Conservative	Total
Non union	7	8	15
Delayed union	6	8	14
Malunion	5	9	14
Hardware loosening	7	8	15
Total	25	33	58

Discussion

OI is a rare genetic syndrome but has a negative psychological and economic impact on patients. In the literature there is still debate about the best type of treatment for these patients. While complications are rare after surgical or conservative treatment of fractures in non-affected patients, OI patients are prone to developing complications (18). To our knowledge, this is the first paper reporting the complications arising from the surgical and conservative treatment of OI patients at long-term.
The aim of our study was to analyze the results of conservative and surgical treatment, focusing on the most common complications of this rare syndrome and also to evaluate whether bisphosphonates, which are antiresorptive drugs used for the treatment of osteoporosis, are effective in reducing the rate of complications.
The surgical treatment of OI treats skeletal fractures, by correcting the deformity in order to improve self-sufficiency.
In our series, the rate of nonunion and delayed union was slightly lower in the group treated surgically compared with the group treated conservatively, but the difference was not statistically significant. No differences were found in terms of malunion and hardware loosening between surgical and conservative treatments.
The rate of hardware loosening was higher in Type III OI, confirming that this phenotype is the most severe form of OI among children who survive the neonatal period.
Bisphosphonates were found to have a protective effect against complications. In our analysis, only a stiff elbow was reported in the group of patients receiving bisphosphonates. This is mainly related to the long period of cast immobilization.
However, there are some limitations in our study relating to the use of bisphosphonates. The two groups were unbalanced in number and only 5 patients were treated with cycles of bisphosphonates. In addition, our study was non-randomized and was not placebo-controlled.
Complications are very frequent in OI patients. In our series, we found more complications in the lower limbs compared to the upper limbs, in accordance with the findings reported by Engelbert R.H. et al. (19). In addition, we found that the incidence of new fractures and the complication rate decreased after puberty because of the natural history of the disease, in agreement with the literature (20).

Several authors (21-23), have reported good clinical results on the treatment of OI with bisphosphonates. Such treatment is mainly indicated in children aged 3 years and the drug can be administered for up to two years. In addition, calcium and vitamin D supplements should always be provided (24, 25). Bisphosphonate treatment can therefore be considered a good adjuvant not only for the prevention of further fracture, but also as a therapy to reduce the incidence of complications in young and adult OI patients.
In this series, the rate of complications related to surgical or conservative treatment did not differ, hence we suggest planning the appropriate treatment in accordance with the needs of each individual affected by OI. The use of newly-developed intramedullary devices in association with bisphosphonate treatment appears to be the better approach, particularly in patients affected by Type III OI.

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