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 Silence 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, 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 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.

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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). The mean follow-up was 88 months.

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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 antiostoporotic drugs were excluded.

### 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 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).

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

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

<table>
<thead>
<tr>
<th>Clinical type</th>
<th>Patients</th>
<th>Non Union</th>
<th>Delayed Union</th>
<th>Malunion</th>
<th>Hardware loosening</th>
<th>Total Complications</th>
<th>Bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>M = 6; F = 9</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>M = 3; F = 2</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>M = 6; F = 3</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

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

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

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 OI. 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 (9.1%) after conservative treatment (Table 5).

No statistically significant differences were found in terms of the complication rate between the plate and screw versus intramedullary osteosynthesis. We recorded 6/147 (4.1%) after surgical treatment and 8/98 (8.1%) after conservative treatment (Table 5).

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).

The surgical treatment of OI treats skeletal fractures, by correcting the deformity in order to improve self-sufficiency. 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.

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 fractures, 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.

References