Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures?

This prospective multicentre study was undertaken to determine whether the timing of the post-operative administration of bisphosphonate affects fracture healing and the rate of complication following an intertrochanteric fracture. Between August 2008 and December 2009, 90 patients with an intertrochanteric fracture who underwent internal fixation were randomised to three groups according to the timing of the commencement of risedronate treatment after surgery: Group A (from one week after surgery), Group B (from one month after surgery), and Group C (from three months after surgery). The radiological time to fracture healing was assessed as the primary endpoint, and the incidence of complications, including excessive displacement or any complication requiring revision surgery, as the secondary endpoint. The mean time to fracture healing post-operatively in groups A, B and C was 10.7 weeks (SD 4.4), 12.9 weeks (SD 6.2) and 12.3 weeks (SD 7.1), respectively (p = 0.420). At 24 weeks after surgery, all fractures had united, except six that had a loss of fixation. Functional outcomes at one year after surgery according to the Koval classification (p = 0.948) and the incidence of complications (p = 0.386) were similar in the three groups. This study demonstrates that the timing of the post-operative administration of bisphosphonates does not appear to affect the rate of healing of an intertrochanteric fracture or the incidence of complications.

Treatment of patients with osteoporosis using bisphosphonates during fracture healing is controversial because the conflicting action of bisphosphonate on osteoclastic activity. Osteoclasts are important for remodelling the callus into cortical bone but bisphosphonate inhibits osteoclast-mediated bone resorption in order to prevent bone loss and improve bone strength.

Several studies have addressed the effects of bisphosphonate on fracture healing. An early study on the effects of ethane-1-hydroxy-1,1-diphosphonate was found to, dose-dependently, inhibit fracture healing in mature beagle dogs. On the other hand, it has been shown that dogs treated with alendronate during the healing period had delayed callus remodelling, but that there was no adverse effect on the fracture healing. However, despite the large number of patients who are treated with bisphosphonates, relatively few studies have reported the effects of bisphosphonate on fracture healing in humans.

The purpose of this study was to determine whether the timing of bisphosphonate administration affected fracture healing or the rate of complications in osteoporotic patients who underwent fixation of an intertrochanteric fracture.

Patients and Methods

Between August 2008 and December 2009, 124 patients with an intertrochanteric fracture from three different hospitals were entered into this prospective pilot study, the design of which was approved by the institutional review boards. Inclusion criteria were: 1) measured bone mineral density (BMD) pre-operatively confirming osteoporosis with a T-score < -2.5; 2) no bisphosphonate therapy during the two years preceding the fracture; and 3) ability to walk pre-operatively. Exclusion criteria were: 1) inability to take bisphosphonate or a contraindication to bisphosphonate treatment such as chronic renal failure; and 2) an inability to co-operate with the study because of mental illness. A total of 34 patients were excluded, leaving a study sample of 90 patients, who were randomised into three groups with different timing of the administration of bisphosphonates following fracture. Randomisation was performed using random numbers generated by a statistician who did not otherwise participate in the study. All patients received oral bisphosphonate (Risedronate, 35 mg) weekly with a daily calcium intake of 1200 mg/day and cholecalciferol at 800 IU/day. In group A this started one week...
DOES EARLY ADMINISTRATION OF BISPHOSPHONATE AFFECT FRACTURE HEALING IN PATIENTS WITH INTERTROCHANTERIC FRACTURES?

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after surgery, group B one month after surgery and group C three months after surgery. Bisphosphonate treatment was continued for a minimum of one year.

Group A had a mean age of 75.0 years (SD 10.2), group B a mean age of 75.3 years (SD 9.9) and group C a mean age of 78.1 years (SD 9.5). Based on the null hypothesis that fracture healing times would be similar in the three groups, with the equivalence limit of fracture healing time of one month that could not show clinically important difference in radiological healing of intertrochanteric fractures, a power analysis indicated that 23 patients per group would be needed to achieve an alpha error of 0.05, at a power of 0.8, two-sided tails, and equal numbers in the three groups. Assuming a 25% loss to follow-up, our groups of 30 patients each was sufficient.

During the study period, one, three, and two patients in groups A, B, and C, respectively, were lost to follow-up, and three, one, and three patients in groups A, B, and C died during the study period. The analysis was therefore conducted on 26, 26, and 25 patients in groups A, B, and C, respectively (Fig. 1). The fracture was classified according to the AO classification. The subgroups of A1.1 to A2.1 were classified as stable and A2.2 to A3.3 as unstable fractures. Pre-operatively, there were no significant differences in baseline characteristics between the groups (Table I).

Either compression screw fixation or an intramedullary nail was used for each patient (at the surgeon’s preference), and all followed the same post-operative rehabilitation programme.

At operation the fracture was anatomically reduced. Neck-shaft angle and fracture site displacement were reduced to < 5° and < 4 mm discrepancy, respectively, compared with the uninjured leg. The tip-apex distance of each lag screw was < 10 mm and the position of lag screw was central or inferior in anteroposterior (AP) view and central or posterior in the lateral radiograph.

After surgery, patients were instructed to bear weight on the third post-operative day with the aid of a walking frame, crutches, or a stick. Post-operatively the patients were assessed at four, eight, 12, 16, 20 and 24 weeks, at 12 months, and every six months thereafter. Those patients unable to attend were visited at home or contacted by telephone and asked to send recent follow-up radiographs. This affected two, three and two patients in groups A, B and C, respectively.

The primary endpoint was the time to healing of the fracture. Healing was assessed by two orthopaedic surgeons (YCH and YKL). Radiological healing was defined as bridging at the fracture site by a callus or a cortical continuity involving at least two cortices in the hip using anteroposterior (AP) and lateral views of the femur. Functional outcomes were assessed at one year post-operatively using the classification attributed to Koval et al.

The secondary endpoint was the incidence of complications, including excessive displacement, as defined by femoral medialisation of > 30%, and revision surgery. Statistical analysis. The reliability of agreement in determining radiological fracture healing was assessed using Kappa coefficients between the two reviewers (YCH and YKL) who were blinded to the treatment group. Kappa coefficients were interpreted as follows; with < 0.00 denoting poor agreement; 0.00 to 0.20 slight agreement; 0.20 to 0.40 fair agreement; 0.40 to 0.60 moderate agreement; 0.60 to 0.80 substantial agreement; and > 0.80 almost perfect agreement. For statistical analysis, one-way analysis of variance (ANOVA) was used for continuous data and Pearson’s chi-squared test for categorical data. All continuous data are expressed as means and standard deviations (SD). Statistical significance was accepted for p-values of < 0.05.

Results

The mean time to radiologically defined union was 10.7 weeks (SD 4.4), 12.9 weeks (SD 6.2) and 12.3 weeks (SD 7.1) in group A, B, and C, respectively (p = 0.420, ANOVA) (Fig. 1). All fractures in group A had healed by 20 weeks following surgery, whereas fractures without complications

Table I. Baseline characteristics of the three study groups

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (yrs)</td>
<td>75.0 (10.2)</td>
<td>75.3 (9.9)</td>
<td>78.1 (9.5)</td>
<td>0.450</td>
</tr>
<tr>
<td>Male:female</td>
<td>7:19</td>
<td>10:16</td>
<td>10:15</td>
<td>0.536‡</td>
</tr>
<tr>
<td>Mean (SD) ASA grade</td>
<td>2.6 (0.5)</td>
<td>2.3 (0.5)</td>
<td>2.4 (0.5)</td>
<td>0.438</td>
</tr>
<tr>
<td>Mean (SD) BMI (kg/m²)</td>
<td>20.8 (2.0)</td>
<td>20.1 (1.3)</td>
<td>21.5 (2.5)</td>
<td>0.359</td>
</tr>
<tr>
<td>Mean (SD) BMD (g/cm²)</td>
<td>3.2 (0.6)</td>
<td>2.8 (0.9)</td>
<td>3.3 (0.8)</td>
<td>0.157</td>
</tr>
<tr>
<td>Spine</td>
<td>3.2 (1.0)</td>
<td>3.3 (1.0)</td>
<td>3.6 (1.1)</td>
<td>0.238</td>
</tr>
<tr>
<td>Fracture type (n)</td>
<td>19</td>
<td>16</td>
<td>20</td>
<td>0.336‡</td>
</tr>
<tr>
<td>Stable (AO A1.1 to A2.1)</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>0.836‡</td>
</tr>
<tr>
<td>Unstable (AO A2.2 to A3.3)</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>0.836‡</td>
</tr>
<tr>
<td>Implant type (n)</td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>0.836‡</td>
</tr>
<tr>
<td>CHS</td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>0.836‡</td>
</tr>
<tr>
<td>ASA, American Society of Anesthesiologists; BMI, body mass index; BMD, bone mineral density; IM, intramedullary; CHS, compression hip screw</td>
<td></td>
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<td></td>
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<tr>
<td>† analysis of variance (ANOVA), unless otherwise stated</td>
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<td></td>
</tr>
<tr>
<td>‡ Pearson’s chi-squared test</td>
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</table>
in groups B and C had healed at 24 weeks. Fractures in group A showed a tendency to heal sooner but this was not statistically significant compared with the other two groups (Table II). A total of six patients had a loss of fixation and underwent revision using a bipolar hemiarthroplasty but there was no statistical difference for his complication between groups.

The intra- and interobserver reliabilities for the assessment of union were 0.78 and 0.75, respectively, indicating good reliability.

The functional outcomes at one year after surgery according to the Koval classification (p = 0.948) and incidences of complications (p = 0.386) were similar in the three groups (Table II).

**Discussion**

Although bisphosphonate therapy reduces the risks of secondary fracture and mortality after hip fracture, the optimal timing of bisphosphonate administration following a hip fracture in elderly osteoporotic patients remains unclear. This prospective, randomised pilot study found the timing of bisphosphonate therapy after hip fracture in elderly patients did not affect fracture healing or the incidence of complications.

Animal studies on fracture healing and bisphosphonate treatment after surgery have shown increased callus formation and delayed callus remodelling with bisphosphonates, but no influence on the bending strength of fractured bone or fracture healing. Adolphson et al examined prospectively BMD in the fracture callus of 32 postmenopausal women with a fracture of the distal radius. At two months after fracture the patients treated with bisphosphonates had a 20% higher mean BMD at the fracture site compared with placebo controls, but this difference decreased with time, and there was no difference between the two groups in terms of pain or function. Rozental et al compared 43 patients with a fracture of the distal radius who were taking bisphosphonate with
153 controls, and reported that time to union in the bisphosphonate group was 55 days compared with 49 days in the control group. Eriksen et al. analyzed data obtained during the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial to determine whether the timing of the first intervention (that the authors did not specify) during the first critical year following hip fracture to prevent accelerated bone loss and reduce the risk of subsequent fractures in this period. In the present study, we did not observe any delay in time to union or any increase in the incidence of complications in group A.

This study has limitations. In order to evaluate the influence of bisphosphonate administration on fracture healing, it would have been better to compare just two groups; one with bisphosphonate treatment and one in which bisphosphonate was withheld until the fracture had healed. Another limitation of this multicentre study is that the implants used were dependent on surgeon’s preference. Only patients who had not received bisphosphonate preoperatively were included in this study, and thus, our results cannot be applied to patients who are receiving bisphosphonates at the time of fracture. Finally, the sample size – although calculated with the radiological healing time as a primary endpoint – is not large enough to evaluate the clinical outcomes of fracture healing such as pain relief, return of mobility and peri-operative complication rates between the three groups.

In conclusion, this study shows that the timing of bisphosphonate therapy after hip fracture surgery, in elderly osteoporotic patients, did not affect radiologically determined fracture healing or the incidence of complications.

References


