Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion

T. A. Burd, M. S. Hughes, J. O. Anglen

From the University of Missouri, Columbia, USA

Indomethacin is commonly administered for the prophylaxis of heterotopic ossification (HO) after the surgical treatment of acetabular fractures. Non-steroidal anti-inflammatory drugs such as indomethacin, have been associated with delayed healing of fractures and mechanically weaker callus. Our aim was to determine if patients with an acetabular fracture, who received indomethacin for prophylaxis against HO, were at risk of delayed healing or nonunion of any associated fractures of long bones.

We reviewed 282 patients who had had open reduction and internal fixation of an acetabular fracture. Patients at risk of HO were randomised to receive either radiation therapy (XRT) or indomethacin. Of these patients, 112 had sustained at least one concomitant fracture of a long bone; 36 needed no prophylaxis, 38 received focal radiation and 38 received indomethacin. Fifteen patients developed 16 nonunions. When comparing patients who received indomethacin with those who did not, a significant difference was noted in the rate of nonunion (26% vs 7%; p = 0.004).

Patients with concurrent fractures of the acetabulum and long bones who receive indomethacin have a significantly greater risk of nonunion of the fractures of the long bones when compared with those who receive XRT or no prophylaxis.

Received 25 October 2002; Accepted after revision 14 February 2003

Fractures of the acetabulum often result from high-energy trauma, most commonly a motor-vehicle collision. Additional musculoskeletal injuries often occur in these patients. The most common orthopaedic injury which is associated with acetabular fractures, is fracture of a long bone. One of the more frequent late complications which can occur from surgery for an acetabular fracture is heterotopic ossification (HO). Most trauma surgeons agree that some form of prophylaxis against the formation of heterotopic bone should be used perioperatively for patients who undergo posterior or extensile surgical approaches to the acetabulum, which are associated with high rates of HO. Prophylaxis usually entails either systemic indomethacin for six weeks or a single dose of local radiation to the soft tissues around the acetabulum, both of which have been shown significantly to decrease the incidence of the formation of heterotopic bone after open reduction and internal fixation (ORIF) of acetabular fractures. Both treatments involve some small risks which have been well described. These include gastrointestinal symptoms and haemorrhage with indomethacin and wound-healing problems, malignant transformation and genetic alteration with radiation. In addition, in multiple animal models and clinical studies, indomethacin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to impair healing of fractures with reduced callus and altered remodelling of the Haversian systems.

Our aim was to determine if indomethacin, when used for prophylaxis for HO after surgery for acetabular fracture, increases the risk of nonunion in patients with associated fracture of a long bone.

Patients and Methods

Between July 1992 and January 2001, 282 patients underwent ORIF for an acetabular fracture by a single surgeon (JOA). During that period, patients at risk for HO because of the use of a posterior or extensile surgical approach were given prophylaxis under an investigational protocol, which randomised them to treatment with either indomethacin or radiation. Those who were randomised to indomethacin received 25 mg three times daily for six weeks and those randomised to radiation received a single dose of 800 centigray of external beam irradiation within 72 hours of surgery. There was no verification of indomethacin compliance and no specific instructions about the use of over-the-counter nonsteroidal medication were given or monitoring of such use performed.
The initial review of the 282 patients revealed 112 (40%) with concomitant fractures of the femur, tibia, humerus, and/or forearm (radius and/or ulna). These patients formed the population of this study. All fractures of long bones were managed by the same surgeon who treated the acetabular fracture, using the same techniques, approaches and implants as any other patient in the practice, without reference to, or knowledge of the randomisation group. Approval was obtained from the Institutional Review Board to review the medical records and radiographs.

Clinical data obtained included age, smoking habits, fracture status (open or closed), and the Injury Severity Score (ISS). Three groups were identified: (i) those who received no prophylactic treatment because of the use of a low risk2 anterior surgical approach (n = 36); (ii) those who received radiation treatment (n = 38), and (iii) those who received indomethacin (n = 38) (Table I).

We defined a nonunion as any fracture which required further treatment for failed healing. The indication for further surgery was failure of clinical or radiographic healing after a minimum of three months, or obviously failed osteosynthesis. This decision was made by the treating surgeon without awareness of the method of prophylaxis administered, or that this would be the topic of a later study. Nonunion was classified as atrophic, hypertrophic or oligotrophic.28

The records and radiographs were reviewed by observers who were not involved in the care of the patients or in determining the method of prophylaxis or in the decision as to whether or not the fracture should be considered as a nonunion. Statistical analysis. This was performed using SAS Software (Cary, North Carolina) with the level of significance set at $p < 0.05$. The confidence interval (CI) and odds ratio were determined with the CI set at 95%. Chi-squared analysis was used to compare the incidence of nonunion between the groups. The final step was to perform an analysis which took into account those patients with multiple fractured long bones and, consequently, not all observations on nonunion were independent. We therefore used the Genmod procedure in SAS for the analysis. The correlation structure was modelled using the compound symmetry model.

### Results

A total of 190 long-bone fractures occurred in the 112 patients (mean 1.7 fractures/patient). Sixteen fractures which required additional treatment for nonunion were identified in 15 patients. The mean time at which a nonunion was diagnosed was 5.3 months (3 to 11) after injury. The patients with nonunion had 28 associated fractures of a long bone with a mean of 1.9 fractures/patient. This mean was not statistically significant from the whole group ($p = 0.656$).

**Comparison between no prophylaxis and radiation.** Patients who had an ilioinguinal approach for acetabular ORIF did not receive any form of prophylaxis.2 In this group, two of 36 (6%) developed nonunion of a fracture of a long bone compared with 3 of 38 (8%) in the radiation group. No statistical difference was seen between these two groups ($p = 0.708$), which for simplification, were then combined and compared with the patients who received indomethacin.

**Comparison between the use and non-use of indomethacin.** Patients who received indomethacin had an incidence of 29% (11 of 38 patients) of nonunion of a fracture of a long bone. This was significantly different from the incidence of 7% (5 of 74 patients) of nonunion seen in the group which did not receive indomethacin ($p = 0.004$). There were no cases of acetabular nonunion.

In terms of the total number of fractures of a long bone which were at risk of complications of healing, there were five cases of nonunion out of a total of 118 fractures (4.2%) in patients who did not receive indomethacin and eleven of 72 fractures (15.3%) in patients who did receive indomethacin. This difference is also significant ($p = 0.029$)

Comparing those patients who received indomethacin with those who did not, the odds ratio for developing a nonunion of a fracture of a long bone was 5.32 to 1. Separate comparison of the indomethacin group with the no treatment group, and with the radiation group, yielded odds ratios of 6.9 to 1 and 4.3 to 1, respectively.

**Demographic multivariate analysis.** There were no significant differences between the three groups with regard to age, use of alcohol, smoking habits and fracture status. The only significant difference was the mean ISS ($p = 0.0056$) (Table II). The patients in the indomethacin group had an ISS which was approximately four points higher than that for the other patients. The reason for this difference is unknown but the magnitude is low. Even adjusting for the ISS, there is still a significant group effect ($p = 0.042$). No significant relationship between the rate of nonunion and the five covariates listed was identified. There was no significant difference between the treatment groups in the number or distribution of fractures of a long bone, or in the distribution of fractures which were either ipsilateral or contralat-

---

**Table I.** Patients with concurrent fractures of the acetabulum and long bones

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of patients</th>
<th>Number of long-bone fractures</th>
<th>Number of nonunions</th>
<th>Patients with a nonunion (%)</th>
<th>Fractures with a nonunion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No indomethacin</td>
<td>74</td>
<td>118</td>
<td>5</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>38</td>
<td>72</td>
<td>11</td>
<td>29</td>
<td>15.3</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>190</td>
<td>16</td>
<td>13</td>
<td>8.4</td>
</tr>
</tbody>
</table>

---

© 2003 Lippincott Williams & Wilkins
There was a higher proportion of open fractures in the group which did not receive indomethacin (25 of 118, 21%) than in the group which did (10 of 72, 14%), although this difference was not statistically significant (Fisher’s exact test p = 0.25). There was a statistically significant difference in the severity of the open fractures, with the indomethacin group having fewer severe fractures. The distribution is shown in Table IV.

Table V gives details of the patients with a nonunion and the treatment required. Three of the patients (cases 2, 8 and 13) underwent total hip arthroplasty, hemiarthroplasty of the shoulder, and hemiarthroplasty of the hip, respectively, as treatment for their nonunion. The time to healing of the nonunion was therefore not recorded for these three patients. Two patients (cases 10 and 14) were lost to follow-up before healing of the nonunion.

Discussion

NSAIDs are the most commonly prescribed class of medication throughout the world.28 This group of drugs has been found to inhibit prostaglandin-mediated bone remodelling in vitro and in animal models in a dose-dependent fashion.19 Numerous reports have shown their interference with the healing of bone in both experimental and human fractures,13,15-18,22,23,25 which may be due to inhibition of cyclo-oxygenase 2 activity,29 and this may also be expected to occur with the newest anti-inflammatory drugs, the COX2 inhibitors.

Both indomethacin and radiation therapy administered perioperatively have been shown to be effective in reducing the formation of heterotopic bone after surgery for an acetabular fracture.7,10,12 Stannard and Alonso8 surveyed 14 senior trauma surgeons in order to identify the best method of prevention of HO and found mixed results, thus reflecting the lack of consensus on prophylaxis. Most (50%) believed that indomethacin was the best treatment in posterior and extensile approaches to the acetabulum. Numerous studies have verified that indomethacin is effective in preventing HO after extensile approaches to repair acetabular fractures.4,10,30,31 In a recently published, prospective, randomised study of 166 patients,12 we showed equivalent results for the efficacy of indomethacin and radiation therapy in prophylaxis for HO after ORIF of acetabular fractures. Indomethacin was found to be well tolerated, approximately 200 times less expensive and as effective as radiation. Our study appeared to favour indomethacin, pro-
### Table V: Details of patients with a nonunion and required further treatments

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>ISS</th>
<th>Prophylaxis for HO*</th>
<th>Smoking habit (PPD)</th>
<th>Number of long-bone fractures</th>
<th>Nonunion location</th>
<th>AO/OTA fracture class</th>
<th>Open (grade†)</th>
<th>Side of acetabular fracture</th>
<th>Type of nonunion</th>
<th>Treatment of nonunion‡</th>
<th>Time from injury to diagnosis of nonunion (mths)</th>
<th>Nonunion healing time (mths)</th>
<th>Follow-up (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>10</td>
<td>I</td>
<td>I</td>
<td>2</td>
<td>L-femur</td>
<td>32-C3.2</td>
<td>C</td>
<td>R</td>
<td>Atrophic</td>
<td>XN, ICBG</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>18</td>
<td>I</td>
<td>N</td>
<td>1</td>
<td>L-ulna</td>
<td>21-B1.1</td>
<td>C</td>
<td>L</td>
<td>Oligo</td>
<td>XP</td>
<td>3</td>
<td>UNK</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>22</td>
<td>I</td>
<td>N</td>
<td>2</td>
<td>L-femur</td>
<td>32-C1.3† 31-B2.1</td>
<td>C</td>
<td>R</td>
<td>Oligo</td>
<td>THA</td>
<td>3</td>
<td>N/A</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>10</td>
<td>I</td>
<td>N</td>
<td>3</td>
<td>L-ulna</td>
<td>22-A1.2</td>
<td>1</td>
<td>L</td>
<td>Oligo, oligo</td>
<td>ORIF, ICBG, IBS</td>
<td>8</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>9</td>
<td>I</td>
<td>N</td>
<td>2</td>
<td>L-femur, R-femur</td>
<td>L-32C3.2; R-32B2.2</td>
<td>C</td>
<td>L</td>
<td>Oligo, oligo</td>
<td>ORIF, BS &amp; L, XN, BS</td>
<td>4.4</td>
<td>6.6</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>27</td>
<td>I</td>
<td>I</td>
<td>3</td>
<td>R-tibia</td>
<td>42-C3.1</td>
<td>3B</td>
<td>R</td>
<td>Atrophic</td>
<td>XN, IBS, ICBG, BS</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>18</td>
<td>I</td>
<td>N</td>
<td>1</td>
<td>R-humerus</td>
<td>11-A3.2</td>
<td>C</td>
<td>R</td>
<td>Atrophic</td>
<td>HWR, ICBG, Hemi</td>
<td>11</td>
<td>N/A</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>9</td>
<td>I</td>
<td>I</td>
<td>4</td>
<td>L-tibia</td>
<td>41-C2.3</td>
<td>C</td>
<td>L</td>
<td>Oligo</td>
<td>ORIF, BS</td>
<td>3</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>9</td>
<td>I</td>
<td>N</td>
<td>2</td>
<td>L-tibia</td>
<td>43-C3.3</td>
<td>C</td>
<td>L</td>
<td>Hyper</td>
<td>ORIF, ICBG, IBS</td>
<td>6</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>10</td>
<td>I</td>
<td>N</td>
<td>1</td>
<td>R-tibia</td>
<td>43-C3.3</td>
<td>C</td>
<td>L</td>
<td>Atrophic</td>
<td>XN, ICBG, IBS</td>
<td>3</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>9</td>
<td>Rad</td>
<td>I</td>
<td>2</td>
<td>L-femur</td>
<td>31-B2.1+32-C2.1</td>
<td>C</td>
<td>R</td>
<td>Atrophic</td>
<td>ORIF, OS, IBS</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>9</td>
<td>Rad</td>
<td>N</td>
<td>1</td>
<td>L-femur</td>
<td>31-A+32-A3.2</td>
<td>C</td>
<td>L</td>
<td>Oligo</td>
<td>HWR, ICBG, ORIF, Hemi</td>
<td>4</td>
<td>N/A</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>10</td>
<td>Rad</td>
<td>N</td>
<td>1</td>
<td>R-femur</td>
<td>31-A3.2</td>
<td>C</td>
<td>R</td>
<td>Atrophic</td>
<td>HWR, ORIF, ICBG, IBS</td>
<td>4</td>
<td>UNK</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>14</td>
<td>No TX</td>
<td>N</td>
<td>3</td>
<td>R-femur</td>
<td>31-A2.3+shaft ext</td>
<td>C</td>
<td>L</td>
<td>Oligo</td>
<td>OS, ORIF, IBS</td>
<td>6</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>10</td>
<td>No TX</td>
<td>N</td>
<td>1</td>
<td>L-humerus</td>
<td>L-32C3.2</td>
<td>C</td>
<td>L</td>
<td>Atrophic</td>
<td>HWR, ORIF, ICBG, IBS</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

*HO, heterotopic ossification; I, indomethacin; Rad, radiation; No TX, no treatment
†Gustilo and Anderson classification
‡BS, external bone simulator; Hemi, hemiarthroplasty; HWR, hardware removal; IBS, implantable bone stimulator; ICBG, autogenous bone grafting; ORIF, open reduction and internal fixation; OS, osteotomy; THA, total hip arthroplasty; XN, exchange nailing; XP, exchange plating

Abbreviations: AO/OTA, Arbeitgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; ISS, injury severity score; Oligo, oligotrophic; n/a, not available; PPD, packs per day; R/L, right/left; UNK, unknown
vided that there were no contraindications from gastrointestinal or renal comorbidities. We did not assess the potentially deleterious effects that this potent NSAID may have on healing of bone when taken for prolonged periods, which was the purpose of our re-evaluation of these patients.

There are limitations to our study. The analysis was performed retrospectively, although the study data were collected prospectively as part of a randomised investigation. Nonunion was determined at the time of clinical follow-up and not retrospectively. At that time, the senior author (JOA) was unaware of the patients’ treatment group or that the issue would subsequently be the topic of a study. We did not collect details about the initial treatment of the fractures of a long bone, a feature which could affect rates of nonunion, but they were all treated by a single surgeon who used consistent methods and philosophies. We did not control for, or collect information about, the use of NSAIDs for control of pain or other purposes.

The definition of a nonunion can be controversial and arbitrary. We chose to include only those fractures which, in the judgement of the senior author, required surgical treatment for complications of healing. This determination was made before it became a topic of a study. It constitutes an easily identified event in the medical records and is a definition which has a significant impact on a patient’s care.

Although the groups were randomised, there is the possibility that they differed in some way. The patients who received indomethacin had a slightly higher ISS and a less severe spectrum of open fractures than those who did not, neither of which would account for the increase in the rate of nonunion which was observed. We found no significant differences between the groups in age, smoking, alcohol use, associated number or location of fractures, or the rate of open fracture.

An intriguing possible future solution to this problem was recently reported by Martin, Boden and Titus, who used recombinant human bone morphogenetic protein-2 (rhBMP-2) to compensate for the detrimental effects of ketorolac on the formation of bone in a rabbit spine fusion model. Further research may indicate that if indomethacin is necessary for prophylaxis for HO after ORIF for acetabular fracture in patients with additional fractures of a long bone, fracture site rescue with rhBMP-2 may lessen the risk of nonunion.

While our study included only patients with an acetabular fracture with associated fractures who were also treated with indomethacin for six weeks, we believe, based on the literature, that the results can be generalised to other patients with fractures who may use other NSAIDs for other reasons. Unfortunately, the newer COX2 inhibitors would seem to suffer from the same drawback. We recommend the avoidance of NSAIDs for analgesia or anti-inflammatory purposes during healing of the fracture.

HO can be a significant complication after extensile and posterior approaches to the acetabulum. Most surgeons believe that radiation therapy and/or the use of indomethacin is an important prophylactic measure against HO. Our earlier study showed indomethacin to be safe, as effective, and dramatically cheaper than radiation therapy. However, the data from this current study strongly suggest that in patients with acetabular fractures and concomitant fractures of a long bone, those who receive indomethacin for heterotopic ossification are at greater risk for nonunion of a fracture of a long bone. In this situation, the surgeon may wish to use radiation.

We wish to thank Dr Richard Madsen, Professor of Biostatistics, and James L. Cook, PhD, DVM, for their contributions to the statistical analysis of this project. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


