Indomethacin versus radiation therapy for prophylaxis against heterotopic ossification in acetabular fractures

A RANDOMISED, PROSPECTIVE STUDY

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We report a prospective, randomised, blinded clinical comparison of the use of indomethacin or radiation therapy for the prevention of heterotopic ossification (HO) in 75 adults who had open reduction and internal fixation of acetabular fractures through either a Kocher-Langenbeck, a combined ilioinguinal and Kocher-Langenbeck, or an extended iliofemoral approach. Indomethacin, 25 mg, was given three times daily for six weeks. Radiation with 800 cGy was delivered within three days of operation. Plain radiographs were reviewed and given Brooker classification scores by three independent observers who were unaware of the method of prophylaxis.

One patient died from unrelated causes and two were lost to follow-up, leaving 72, 33 in the radiation group and 39 in the indomethacin group, available for evaluation at a mean of 12 months (6 to 48). There was no significant difference in the two groups in terms of age, gender, injury severity score, estimated blood loss, delay to surgery, head injury, presence of femoral head dislocation, or operating time, and no complications due to either method of treatment. The final extent of HO was already present by six weeks in all patients who were followed up.

Three patients in the radiation group and five who received indomethacin developed HO of Brooker grade III. Two patients in the indomethacin group developed Brooker IV changes; both had failed to receive proper doses of the drug. Cochran-Armitage analysis showed no significant difference between the two treatment groups as regards the formation of HO.

Indomethacin and single-dose radiation therapy are both safe and effective for the prevention of HO after operation for acetabular fractures. Radiation therapy is, however, approximately 200 times more expensive than indomethacin therapy at our institution and has other risks.

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Heterotopic ossification (HO) is seen after many types of hip surgery, including the fixation of acetabular fractures.1-19 It is thought to involve the differentiation of pluripotent mesenchymal stem cells into osteogenic progenitor cells due to local stimuli and conditions.20-26 This begins as early as 16 hours after injury and peaks at 36 to 48 hours.9,21,25,27 Heterotopic bone has been reported to occur in up to 90% of patients treated by operation for fractures of the acetabulum who have not received prophylaxis; the effect on function may be severe in up to 50% of high-risk patients.1,3-6,9-12 A more recent report, however, concerning patients treated without prophylaxis suggests that the incidence is lower.28 HO may be seen on radiographs by three to six weeks and reaches its maximal extent by six to 12 weeks.5-7,29

The condition may adversely affect the outcome of acetabular repair and impair function.2,13,16,30 It is most common after a posterior or extensile approach1,2,7-11,19 and other risk factors are associated abdominal or chest trauma, T-type fractures, a high injury severity score,2 delay in undertaking operation,3 closed head injury,8,31 and male gender.7

A variety of treatments has been proposed to decrease the amount of heterotopic bone including the use of diphosphonates, radiation and indomethacin. Diphosphonates prevent the mineralisation of osteoid, but this begins again after withdrawal of the drug, and their use has been questioned.13,14 There have been several reports of the use of indomethacin after operation for acetabular fractures.1,5-7 Local radiation therapy has also been used after reports of successful results in hip arthroplasty.21,23,27,32-35

Both indomethacin and radiation therapy have been shown to be effective, but there have been no studies comparing the two. We have compared their use in a randomised, prospective study.
Patients and Methods

Before operation we randomised consecutively by hospital number all adult patients who required either a Kocher-Langenbeck, a combined anterior and posterior approach or an extended iliofemoral approach for the fixation of an acetabular fracture. They received either indomethacin or single-fraction low-dose irradiation for prophylaxis against HO. Informed consent was obtained from each of the 75 patients. Those with a history of allergy to indomethacin, an active peptic ulcer or who could not be transported for radiation were excluded. The age and gender distribution, injury severity score (ISS), operating time, estimated blood loss (EBL), delay before operation, presence of head injury, presence of hip dislocation, and the period of follow-up for each group are shown in Table I. The distribution of the patterns of fracture is shown in Table II.

Patients treated with indomethacin received 25 mg by mouth or rectum on the evening before operation and then 25 mg three times daily for six weeks. Those treated by radiation were transported to a separate affiliated hospital where they received a single dose of 800 cGy external-beam radiation to the soft tissues around the hip within 48 hours of operation. All operations were performed between July 1993 and July 1996 by the same orthopaedic traumatologist assisted by orthopaedic residents. In most patients a Kocher-Langenbeck approach was used. Two patients in the radiation group and six who received indomethacin had extended iliofemoral approaches; four patients who were irradiated and three who received indomethacin had both a Kocher-Langenbeck and an ilioinguinal exposure. Two patients in the radiation group had a trochanteric osteotomy. The difference between the surgical approach in the groups was not statistically significant by chi-squared testing.

Radiographs were taken at 1.5, 3, 6, 12, 24, 36 and 48 months after operation. Clinical examination included assessment of the range of movement using a goniometer with the patient supine. The radiographs included an anteroposterior view of the pelvis and iliac oblique and obturator oblique views. These films were reviewed by three independent chief residents in orthopaedics, who were blinded to the method of treatment, using the classification of Brooker et al.\textsuperscript{36} If there was doubt about the amount of HO seen on the different views from the same visit the higher of the scores was recorded. The progression of ossification was evaluated in each patient. Follow-up was about 12 months (6 to 48) in both groups.

Statistical comparison between the two groups was carried out using Student's $t$-tests (age) or Wilcoxon rank-sum tests (ISS, delay to surgery, blood loss, operative time) for quantitative variables and chi-squared tests for qualitative variables (gender, head injury, hip dislocation, fracture pattern). As multiple tests for significance were performed, a Bonferroni adjustment was used, with $p = 0.005$ required for significance. Outcome comparison between the two groups was carried out using the Cochran-Armitage test to take advantage of the ordinal nature of the Brooker classification. For the calculation of the confidence interval, the Brooker classification was modified into two categories, acceptable (grades 0 to 2) and poor (grades 3 and 4).\textsuperscript{3} Loss of movement is rare with HO of less than grade 3, but very common in grades 3 and 4. Statistical calculations were carried out for all patients included in the randomised groups so that all those who were due to receive indomethacin were still included, whether or not they had completed the full course of treatment.

### Table I. Details of the patients who received radiation treatment and those who were given indomethacin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Radiation</th>
<th>Indomethacin</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>47 (23 to 87)</td>
<td>43 (18 to 87)</td>
<td>0.31</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>29</td>
<td>0.77</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Mean ISS (range)</td>
<td>12 (9 to 25)</td>
<td>14 (9 to 27)</td>
<td>0.15</td>
</tr>
<tr>
<td>Patients with head injuries (%)</td>
<td>6 (18)</td>
<td>7 (18)</td>
<td>0.90</td>
</tr>
<tr>
<td>Patients with hip dislocations (%)</td>
<td>9 (27)</td>
<td>10 (26)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean days of delay to surgery (range)</td>
<td>5.45 (0 to 19)</td>
<td>6.1 (0 to 30)</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean EBL in ml (range)</td>
<td>1151 (325 to 3200)</td>
<td>954 (100 to 4260)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean operating time in minutes (range)</td>
<td>264 (120 to 605)</td>
<td>247 (range 88 to 545)</td>
<td>0.53</td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kocher-Langenbeck</td>
<td>26</td>
<td>32</td>
<td>0.25</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Follow-up in months (range)</td>
<td>12 (6 to 48)</td>
<td>11.7 (6 to 48)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

### Table II. Distribution of fracture patterns in the two groups

<table>
<thead>
<tr>
<th>Fracture pattern</th>
<th>Radiation</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both columns</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Posterior column</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Posterior column/wall</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Transverse</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Transverse/posterior wall</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>T-type</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>34</td>
<td>41</td>
</tr>
</tbody>
</table>
operative variables and the final outcome was carried out.

Three had DJD (2 mild, 1 severe).

high-grade HO who lost movement, one also had AVN and HO, AVN or DJD lost significant movement. Of those with tis (DJD) in seven. Only two patients without high-grade avascular necrosis (AVN) in four and post-traumatic arthritis, although in one patient it was delayed until three days after operation. Three developed grade-3 HO, but although the other claimed to have taken appropriate doses

The full protocol was not completed in five patients in the indomethacin group. In three, medication was discontinued by other physicians because they did not know the reason for it, one patient admitted non-compliance and although the other claimed to have taken appropriate doses he was thought to be unreliable. These five patients all developed HO, three of grade 2 and two of grade 4. Five patients who were believed to have taken the full course of indomethacin developed HO of grade 3. All of the patients who did not complete their course received less than two weeks of medication.

All patients randomised to radiation received the treatment, although in one patient it was delayed until three days after operation. Three developed grade-3 HO, but none had grade 4. Of those with grade 3 one received treatment on day 1, one on day 2 and one on day 3.

The range of movement in the hip improved slowly after injury. The final range was known in 67 patients, of whom 19 lost 20° or more in at least one plane. This latter group included six of the seven patients with HO of grade 3 or grade 4. Other reasons for loss of movement included avascular necrosis (AVN) in four and post-traumatic arthritis (DJD) in seven. Only two patients without high-grade HO, AVN or DJD lost significant movement. Of those with high-grade HO who lost movement, one also had AVN and three had DJD (2 mild, 1 severe).

Statistical comparison of the preoperative and intraoperative variables and the final outcome was carried out using the Spearman rank-correlation coefficient with a Bonferroni adjustment. There was slight evidence for a relationship between outcome and delay to operation ($p = 0.0146$) and operating time ($p = 0.0044$) but, using a proportional odds model which accounted for these variables, there was no evidence of a significant group effect. There was no significant difference in outcomes for the categorical variables of gender, head injury, dislocation, fracture type and surgical approach. There was no relationship between case order and HO.

## Results

There was no difference between the two groups in any demographic or preoperative variable examined (Table I), but there was a significant difference ($p = 0.003$) in the distribution of the pattern of fracture (Table II). There were more isolated fractures of the posterior wall in the indomethacin group, and more associated transverse and posterior-wall fractures in those who were irradiated. We cannot explain this, but there was no bias in selection.

Table III shows the results in terms of the Brooker classification. There were three patients with grades 3 and 4 (9%) in the radiation group and seven (18%) in those taking indomethacin. There was no significant difference in the distribution of grades between the two groups ($p = 0.089$). The 95% confidence interval for this comparison is $-0.0782$ to $+0.2145$. For this approximate sample size and outcome effect, $p = 0.05$ with a power of 80% would require an outcome difference of 27% between the two groups.

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## Discussion

Radiation appears to prevent differentiation of pluripotential mesenchymal cells into osteogenic progenitors. The timing of administration is important since the success rate decreases from 98% to 33% after the fourth postoperative day. While the potential risks of irradiation include malignancy, impaired healing, infertility, and genetic alteration, these have not been reported with modern dosage levels. Bosse et al treated 17 patients with 1000 cGy of radiation after operation and achieved a significantly lower incidence of formation of heterotopic bone compared with a group of historical controls. Other authors have likewise showed significant reductions using various doses and we have reported the use of a single low dose with good results. No problems with healing of the fracture or wounds or other complications were encountered.

Indomethacin and other non-steroidal anti-inflammatory drugs seem to prevent HO in patients at risk but the mechanism is uncertain. Potential complications of indomethacin include decreased fracture healing, gastrointestinal irritation and/or ulceration, decreased platelet aggregation, and renal toxicity. Their use after arthroplasty of the hip is well known, and similar significant reductions in severe HO with low complication rates have been reported after indomethacin in patients with fractures of the acetabulum.

Moed and Letournel advocated the use of low-dose irradiation and indomethacin in combination to prevent severe HO. The two treatments seem to have different mechanisms of action and their combination may therefore be more effective than using either alone; in their study of 54 fractures so treated, none formed high-grade HO.

The disadvantages of irradiation include difficulty in transferring multiply injured patients and the cost, which at our institution is approximately $2400.00 compared with $12.00 for a six-week course of indomethacin. Management with indomethacin depends on patient compliance which may be as low as 50% in long-term medication regimens. Three of our patients had their indomethacin stopped by other physicians after they had left our care; all developed HO and one required reoperation. None of our patients discontinued the drug because of gastrointestinal symptoms.
We found radiotherapy and indomethacin to be similarly effective. Our study included relatively small numbers of patients, lacked stratification by fracture type and/or surgical approach, and produced a relatively wide confidence interval for the outcome comparison. Despite randomisation, there was a difference in the distribution of fracture patterns in our two groups. Although one previous study identified the T-type fracture as a significant risk factor for the formation of HO, we do not believe that the difference in the distribution of fracture pattern significantly altered the risk between the two groups. We could demonstrate no relationship between the pattern of fracture and the final grade of HO. It seems likely that the extended iliofemoral approach, rarely used in our series, carries an increased risk of ectopic bone formation. Further subdivision of the groups by surgical approach or type of fracture would weaken the analysis, and these questions must be addressed in larger prospective series. Our 95% confidence interval is fairly wide, including the possibilities of up to a 20% worse outcome for the indomethacin treatment group, or up to an 8% worse outcome for the radiation group. Although we are not able to say with certainty that there is no difference in efficacy between these two treatments, there does not appear to be a large difference. The choice of treatment must also take into account the underlying medical problems, potential risks, expected compliance and cost, as well as the known efficacy.

We have found both methods of treatment to be safe and effective. Compliance was a problem in some patients taking indomethacin but, provided that there are no contraindications to its use, we prefer this method of prophylaxis since it is much less expensive. In patients judged to be at highest risk combination therapy may be considered. The authors thank Dr J. Mark Blue and Dr Michael Corcoran for their assistance in the radiological evaluation. 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


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