Celecoxib versus ibuprofen in the prevention of heterotopic ossification following total hip replacement

A PROSPECTIVE RANDOMISED TRIAL

M. Saudan, P. Saudan, T. Perneger, N. Riand, A. Keller, P. Hoffmeyer
From the University Hospitals of Geneva, Geneva, Switzerland

We examined whether a selective cyclo-oxygenase-2 (COX-2) inhibitor (celecoxib) was as effective as a non-selective inhibitor (ibuprofen) for the prevention of heterotopic ossification following total hip replacement. A total of 250 patients were randomised to receive celecoxib (200 mg b/d) or ibuprofen (400 mg t.d.s) for ten days after surgery. Anteroposterior radiographs of the pelvis were examined for heterotopic ossification three months after surgery. Of the 250 patients, 240 were available for assessment. Heterotopic ossification was more common in the ibuprofen group (none 40.7% (50), Brooker class I 46.3% (57), classes II and III 13.0% (16)) than in the celecoxib group (none 59.0% (69), Brooker class I 35.9% (42), classes II and III 5.1% (6), p = 0.002). Celecoxib was more effective than ibuprofen in preventing heterotopic bone formation after total hip replacement.

Heterotopic bone formation is a common complication of total hip replacement (THR).\(^1\) In a study of 10 000 patients who underwent THR, more than half had radiological evidence of heterotopic ossification (HO), and of these 15% were symptomatic.\(^1\) Severe HO may cause protracted post-operative pain and impaired function and it may require excision. A recent meta-analysis encompassing 30 studies concluded that HO impairs movement of the hip.\(^7\) Another report noted that whereas 90% of patients without HO were satisfied with their operation, only approximately 30% with severe HO were.\(^6\) Prevention of HO is therefore important for patients undergoing elective THR.

Post-operative radiotherapy significantly reduces the incidence of HO,\(^7\) but is not widely available. Prevention with low-dose aspirin has given conflicting results,\(^8,9\) but several small trials have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) are effective.\(^2,3\) This has led to their widespread use both before operation and in the immediate post-operative period for the prevention of HO. Their inhibitory effect on the formation of HO was described in 1974 using diclofenac.\(^10,11\) Other NSAIDs, such as ibuprofen, have been found to be as effective and there is a trend towards reducing the treatment time and dosage to diminish the side-effects.\(^11,12\) Ibuprofen has been shown to be effective in a dose of 400 mg three times a day for eight days,\(^13,14\) and this has become the regimen for prophylaxis in our hospital.

The exact mechanism of action of NSAIDs on bone formation is unclear. These compounds are believed to inhibit the cyclo-oxygenase (COX) enzyme and impair the transformation of arachidonic acid into prostaglandins and thromboxanes. There are two isoforms of COX, COX-1 and COX-2, and their localisation and expression are different. COX-1 localises in most tissues and participates in the regulation of normal cellular processes, but COX-2 is expressed more selectively during inflammatory states, and localises in the brain, bone and kidney.\(^15\) Most NSAIDs are non-selective inhibitors of both COX-1 and COX-2. Because COX-1 is involved in gastric cytoprotection, non-selective inhibitors seem to induce more gastroduodenal toxicity.\(^16\) An argument can be made for the use of selective COX-2 inhibitors in elderly patients undergoing THR to avoid this. However, because of the selective expression of COX-2 in bone tissue, it is unclear whether selective inhibitors would be equally effective at preventing heterotopic bone formation.

The aim of this study was to investigate whether celecoxib, a selective COX-2 inhibitor, would be as effective as ibuprofen, a non-selective COX inhibitor, in the prevention of HO in patients undergoing THR.

Patients and Methods
A prospective randomised trial of celecoxib versus ibuprofen in the prophylaxis of HO
following THR was set up. The patients and healthcare teams were not blinded to treatment allocation, but the physicians who assessed the outcome were. The Ethics Committee of the Department of Surgery approved the study and all the patients provided written consent.

Between January 2001 and August 2002, all patients with severe osteoarthritis of the hip who were scheduled for elective THR were evaluated. Exclusion criteria included patients with moderate to severe renal impairment (serum creatinine > 2 mg/dl), a history of gastrointestinal ulcers, immediate-type hypersensitivity to NSAIDs or COX-2 inhibitors, and refusal to participate in the study.

Patients were randomised at the anaesthetic evaluation three months prior to surgery by opening consecutive sealed opaque envelopes which contained a computer-generated code. The randomisation was in blocks of six, eight or ten. Patients were allocated to receive either ibuprofen 400 mg three times daily or celecoxib 200 mg twice daily. Until the date of the operation, specific medication was prescribed as needed for pain control. In the celecoxib group, 80 patients received it and four were treated with an NSAID for pre-operative pain control. In the ibuprofen group, nine patients received celecoxib and 58 an NSAID pre-operatively. Ibuprofen or celecoxib were started or resumed on the first post-operative day and continued for a total of ten days. All the patients underwent THR via a direct lateral approach, with an uncemented acetabular component and a cemented femoral stem. Prophylaxis for deep venous thrombosis was implemented with low molec-
ular weight heparin (Fraxiparin) for five days after operation, and then oral anticoagulation (acenocoumarol) was given for the following six weeks.

A total of 310 patients scheduled for THR were evaluated, and of these, 250 agreed to participate in the trial. At the three-month follow-up after operation, 240 were available for radiological assessment, 123 in the ibuprofen group, and 117 in the celecoxib group (Fig. 1). Patients in the two groups were similar in age, gender, aetiology of hip disease and renal impairment (Table I). During the initial ten post-operative days, treatment was discontinued in 14 patients taking celecoxib and in 12 taking ibuprofen. An increase in plasma creatinine > 0.5 mg/dl necessitating discontinuation of the drug occurred in ten patients, four receiving ibuprofen and six on celecoxib. After the medication was stopped the serum creatinine returned to baseline levels in all patients except in one receiving ibuprofen, who died from multiple organ dysfunction. Electrolyte disorders did not occur in any patients. Gastrointestinal complications were limited to one patient in the celecoxib group, and three in the ibuprofen group. As the patients were randomised prior to the operation, most of those who needed painkillers could receive the medication which they were treated with anti-inflammatory drugs before the operation.

### Outcome measures

The primary outcome variable was the presence of HO on an anterior-posterior radiograph of the pelvis three months after operation. Radiographs were read independently by a radiologist (AK) and an orthopaedic surgeon (NR), who were unaware of the medication the patient had received. The presence of HO was assessed according to the Brooker classification.4

<table>
<thead>
<tr>
<th>Cause of joint damage (%)</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary osteoarthritis</td>
<td>46 (46)</td>
<td>46 (46)</td>
</tr>
<tr>
<td>Secondary osteoarthritis</td>
<td>15 (15)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

### Table I. Baseline and treatment characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>123</td>
<td>127</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>69 (38 to 95)</td>
<td>70 (34 to 91)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>58 (47)</td>
<td>58 (46)</td>
</tr>
<tr>
<td>Cause of joint damage (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary osteoarthritis</td>
<td>108 (88)</td>
<td>118 (93)</td>
</tr>
<tr>
<td>Secondary osteoarthritis</td>
<td>9 (7)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>5 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Treatment with NSAID* prior to the operation (%)</td>
<td>39 (32)</td>
<td>60 (47)</td>
</tr>
<tr>
<td>Treatment with selective COX-2† inhibitor prior to the operation (%)</td>
<td>80 (65)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>No treatment with NSAID or selective COX-2 inhibitor prior to the operation (%)</td>
<td>4 (3)</td>
<td>58 (46)</td>
</tr>
<tr>
<td>Serum creatinine in mg/dl, mean (range)</td>
<td>0.9 (0.7 to 1.3)</td>
<td>0.9 (0.8 to 1.2)</td>
</tr>
<tr>
<td>Operating time in minutes, mean (range)</td>
<td>127 (70 to 260)</td>
<td>130 (70 to 255)</td>
</tr>
<tr>
<td>Hip prosthesis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hybrid</td>
<td>117 (95)</td>
<td>121 (95)</td>
</tr>
<tr>
<td>Cemented</td>
<td>6 (5)</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

* NSAID, non-steroidal anti-inflammatory drug
† COX-2, cyclo-oxygenase 2

The reliability of scoring by the observers was examined before the trial by repeated reading of 30 pelvic radiographs containing HO, read twice at one-month intervals. Inter-observer analysis revealed a κ value of 0.74. In addition, the following adverse events in the post-operative period until hospital discharge were documented: 1) renal impairment, defined as an increase in plasma creatinine of ≥ 0.5 mg/dl from the baseline value; 2) electrolyte disorders, defined as serum sodium (Na) < 125 mmol/L or serum potassium (K) > 5 mmol/L; 3) gastrointestinal disturbances, including any symptoms that could be related to oesophageal, gastric or duodenal ulceration.

Functional outcomes were not assessed because the observers in charge of clinical follow-up were not blinded to the treatments.

### Statistical methods

For the equivalence study, we considered that a difference of SD 0.25 between means (continuous scoring) would be compatible with equivalence of the two groups. To achieve a power of 70%, (one-sided test, α = 0.05) 150 patients were required in each group.

The characteristics of the two patient groups were compared at baseline. Outcomes were compared on an intention-to-treat basis. A chi-squared test was used to assess a linear trend for the ordinal ossification score. Because of the small numbers of observations, Brooker classes II and III were pooled in the final analysis. Statistical modelling was carried out using multinomial logistic regression, where no calibration was taken as the reference level. In the unadjusted model, treatment as randomised was the only predictor. However, in the adjusted model, patient gender, age, duration of operation (in minutes), and whether the patient was treated with anti-inflammatory drugs before the operation were taken as additional predictors. All statistical tests were two-tailed. A p-value of < 0.05 was considered significant.
Discussion

In this study a ten-day prophylaxis with celecoxib in the post-operative period was found to reduce the risk of Brooker class I HO by 50% and the risk of classes II and III HO by 75% compared with ibuprofen, based respectively on the difference in adjusted odds ratio for the appearance of Brooker classes I and classes II and III combined. The incidence of gastrointestinal and renal problems did not differ between the two groups, but our trial was not powered to detect such differences.

Prescription of coxibs in the post-operative period seems to be safe. Their lack of interaction with platelet aggregation suggests that no increase in blood loss was demonstrated in patients undergoing total knee replacement. Coxibs such as rofecoxib have been implicated in an increased long-term cardiovascular risk compared with classic NSAIDs. An increased incidence of cardiovascular events associated with the use of rofecoxib or celecoxib became apparent only after 12 to 18 months of continuous treatment. However, even with the short-term use of these drugs in patients prone to cardiovascular disorders, caution should be exercised.

What could be the likely explanation for the difference in efficacy between celecoxib and ibuprofen in preventing HO? Animal studies suggest that COX-2 receptors are involved in the formation of enchondral bone following a fracture. The inflammation induced by a fracture produces prostaglandins through COX-2 activation, which is necessary for healing. In mice, activation of COX-2 regulates mesenchymal cell differentiation and osteoblastogenesis; fracture healing was delayed in a knockout mouse model selectively deleting the COX-2 gene. It has also been shown that inhibition of COX-2 with rofecoxib suppresses bone formation in New Zealand White rabbits. Therefore, it is likely that COX-2 selective inhibitors may inhibit not only fracture healing but also heterotopic bone formation.

There is very little information available on the use of coxibs in patients at risk for the development of HO. Although a recent study suggested that meloxicam was no better than indometacin in preventing HO, meloxicam is not a pure COX-2 inhibitor. Indometacin administered post-operatively at a dose of 25 mg three times daily for ten days in patients with an uncemented THR significantly deterred the formation of HO while having no deleterious effect on fixation of the implant at 24 post-operative months. However, inhibition of bone formation by coxibs could impair the long-term fixation of an uncemented THR to bone.

We acknowledge that there are some limitations in our study. We were unable to blind the patients and the surgeons to their specific treatment group. Therefore, our assessment of HO was only radiological. However, the classification of HO was made by physicians who were not involved in patient care and were blinded to the treatment.

Radiological assessment at three months may be too preliminary, as some HO may mature up to 12 months post-operatively. However, 96% of HO appears on radiographs within six weeks of surgery. The sample size did not permit a determination of whether celecoxib was superior to ibuprofen in terms of side effects. Patients with chronic renal failure or those with a past history of gastrointestinal ulcers were excluded from this study, and our conclusions need to be validated in these high-risk populations.

Our findings suggest that celecoxib is more effective than ibuprofen in preventing HO following THR. These results, as well as previous reports demonstrating reduced gastro-
intestinal side effects, suggest that following THR, a short period of prophylaxis with selective COX-2 inhibitors may be the preferred treatment for the prevention of HO. Longer follow-up is necessary to ascertain whether celecoxib impairs the long-term fixation of an uncemented THR to bone.

We thank Dr Richard Stern for his critical review of the manuscript.

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