

Selective COX-2 inhibitor versus indomethacin for the prevention of heterotopic ossification after hip replacement

A double-blind randomized trial of 100 patients with 1-year follow-up

Josef G Grohs, Maximilian Schmidt and Axel Wanivenhaus

Department of Orthopedics, Medical University of Vienna, Austria
Correspondence JGG: Josef.grohs@meduniwien.ac.at
Submitted 05-11-30. Accepted 06-07-25

Introduction Recent reports have suggested that selective COX-2 inhibition may be sufficient for the prevention of heterotopic ossification.

Methods We performed a randomized controlled study to evaluate the effect of the selective COX-2 inhibitor rofecoxib compared to that of indomethacin on the incidence and extent of heterotopic ossification in patients who had undergone hip replacement surgery. 50 patients received a daily dose of 25 mg rofecoxib and 50 patients received a daily dose of 100 mg indomethacin (25, 25, and 50 mg).

Results No ossifications were found in 48 patients. Grade-II ossifications were seen in 5/46 patients in the rofecoxib group and in 6/50 patients in the indomethacin group. Grade-III and grade-IV ossifications were seen in 3/46 patients in the rofecoxib group only. The differences were not statistically significant. The study medication had to be discontinued in 2 patients in the indomethacin group, due to dyspepsia.

Interpretation After short-term administration, the selective COX-2 inhibitor rofecoxib was effective in preventing heterotopic ossification after total hip arthroplasty.

Heterotopic ossification is a frequent complication of hip replacement. In the absence of prophylaxis, the incidence of ossification is reported to be as high as 60–75% (Schmidt et al. 1988). NSAIDs have been shown to retard fracture healing and prevent ossification (Allen et al. 1980, Keller et al. 1989).

A 6-year follow-up study revealed that indomethacin improved the functional outcome according to the Harris hip score and had no negative effect on long-term healing by way of diminished bone ingrowth after hip replacement compared to placebo (Wurnig et al. 1999). Indomethacin administered for a period of 7 days is standard treatment for the prevention of heterotopic ossification. Due to the gastrointestinal side effects of indomethacin, it is administered in combination with omeprazol.

Selective COX-2 inhibitors appear to have a better safety profile, especially with regard to gastrointestinal and platelet function (Bombardier et al. 2000), although there has been recent evidence of cardiovascular events after long-term administration. Celecoxib has been shown to have the same efficacy as indomethacin in the prevention of heterotopic ossification, but with fewer side effects (Romano et al. 2004). In a brief report, the effect of rofecoxib administered at a dose of 25 mg daily was effective to prevent heterotopic ossification after total hip replacement (Zacher et al. 2001).

In a randomized set-up, we evaluated the effect of the selective COX-2 inhibitor rofecoxib compared to that of indomethacin on the incidence and extent of heterotopic ossification in patients who had undergone hip replacement. The surgical procedures were performed in one center, thus ensuring a low degree of inter-patient variability. Owing to the high incidence of heterotopic ossification in the placebo group, we considered it unacceptable to start a new placebo-controlled trial.

Patients and methods

We performed a double-blind, randomized, two-arm, parallel-group study to determine and compare the effect of rofecoxib 25 mg given once daily vs. indomethacin (100 mg per day: 25, 25, and 50 mg), both administered for 7 days, on the primary endpoint, which was heterotopic ossification on radiographs after 12 months. The principal hypothesis was that rofecoxib would be at least as effective as indomethacin in the prevention of heterotopic ossification in patients who have undergone total hip replacement.

We used Brooker's classification of heterotopic ossification (Brooker et al. 1973) to determine the degree of ossification on conventional anteroposterior pelvic radiographs. A Brooker score of II or more was defined as a positive sign of heterotopic ossification. Radiographic assessment was performed by one radiologist who was blinded to the choice of treatment. Radiographic assessments were conducted preoperatively, and 6 weeks and 1 year after surgery.

Clinical and functional evaluation of the hip joint was performed on the basis of the Harris hip score preoperatively, and 6 weeks and 1 year after surgery. This included an assessment of joint function and the patient's subjective assessment of daily activities, as well as objective measurement of joint function.

Blood safety tests including hematology (red cell blood count, hematocrit, hemoglobin, thrombocytes) and serum chemistry (creatinine, aspartate aminotransferase, alanine aminotransferase) were performed preoperatively and 1 day, 1 week, and 1 year after surgery.

The investigation was approved by the ethics committee of the Medical University of Vienna and performed in compliance with the Helsinki Declaration of 1975, as revised in 2000.

Patients

100 patients admitted for primary total hip replacement were randomized to receive either rofecoxib or indomethacin (50 patients in each group). For randomization, a computer-generated sequence was used. Concealment of the outcome of randomization was achieved by the use of identical tablets with either rofecoxib or indomethacin.

Table 1. Baseline data (median and range)

	Rofecoxib	Indomethacin
Age (years)	60 (18–83)	60 (21–82)
Men:women	17:33	20:30
Hemoglobin (g/dL)	10.7 (8.0–15.2)	11.5 (9.2–15.4)
Thrombocytes (G/L)	205 (103–367)	214 (125–405)
Creatinine (mg/dL)	0.8 (0.5–1.4)	0.8 (0.5–2.6)
ASAT (U/L)	16 (6–37)	12 (6–57)
ALAT (U/L)	11 (4–43)	12 (5–36)

ASAT: aspartate aminotransferase;
ALAT: alanine aminotransferase.

Eligibility criteria were age 19 to 85 years, weight less than 120 kg, and written informed consent. Exclusion criteria were the administration or scheduled administration of acetylsalicylic acid or thrombocyte aggregation blocking agents (e.g. clopidogrel) in the week prior to surgery and within 5 weeks after surgery, and additional COX inhibitors during the first 5 weeks after surgery. Any patients with gastrointestinal ulcers during the preceding 3 months, heart failure (NYHA III), hepatic cirrhosis, renal failure (serum creatinine > 2.5), and women of child-bearing age without a negative pregnancy test were also excluded. Patients were recruited over a period of 15 months.

Hip replacement was performed in the routine manner by an anterolateral approach with cementless implantation of the Zweymueller endoprosthesis (Alloclassic, Winterthur, Switzerland).

All patients received enoxaparin 40 mg and omeprazol 40 mg daily for 5 weeks after surgery.

Statistics

We used the two-tailed Fisher's exact test for statistical analysis. The sample size was determined by power analysis (alpha 0.05, power 0.7) using data from earlier studies.

Results

There were no differences in baseline data (Table 1).

In the rofecoxib group, grade-I heterotopic ossifications were found in 16/46 patients, grade-II in 5/46, grade-III in 2/46, and grade-IV in 1/46

Table 2. Heterotopic ossifications 6 weeks and 1 year after surgery, graded according to Brooker's classification^a

Brooker score	6 weeks		1 year	
	Rofecoxib	Indomethacin	Rofecoxib	Indomethacin
0	36	33	22	24
I	10	15	16	20
II	3	1	5	6
III	1	0	2	0
IV	0	0	1	0

^a The differences were not statistically significant using Fisher's exact test ($p = 0.4$).

patients. In the indomethacin group, grade-I ossifications were found in 20/50 patients and grade-II in 6/50; no grade-III or grade-IV ossifications were observed in this group. Heterotopic ossifications equal to or greater than Brooker's grade II were registered in 8/46 of the rofecoxib group and 6/50 of the indomethacin group (Table 2). The numbers of patients with ossifications of less than grade II were compared to those with ossifications of grade II or more. The p -value in Fisher's exact test was 0.4. 3 patients in the rofecoxib group had intraoperative fractures of the major trochanter and did not develop any ossifications.

In 1 patient in the rofecoxib group, the study drug was discontinued after reoperation because of a periprosthetic fracture; the patient developed a grade-III heterotopic ossification. In 2 patients in the indomethacin group, the study drug had to be discontinued due to dyspepsia; the patients developed grade-I heterotopic ossifications. 4 patients in the rofecoxib group failed to attend the 1-year follow-up examination. The drop-outs were not replaced. Analysis was by intention-to-treat.

In the rofecoxib group the relative risk for an ossification equal to or greater than grade II was 1.5 (95% CI: 0.5–4.2).

1 patient in the indomethacin group had cerebral ischemia 3 days after the last dose.

Preoperatively, the median Harris hip score was 50 (17–75) in the rofecoxib group and 49 (15–79) in the indomethacin group. At the 1-year follow-up investigation, the median Harris hip score was 100 (63–100) in the rofecoxib group and 96 (46–100) in the indomethacin group. There was no correla-

tion between the Harris hip score and the grade of ossification (correlation coefficient = 0.02).

Neither group showed unusual changes in blood count, or in blood levels in kidney and liver function tests conducted postoperatively. There were no differences registered between the treatment groups. No bleeding, or septic or aseptic loosening was observed in either group.

Discussion

The efficacy of indomethacin in reducing ectopic bone formation after total hip replacement has been described in several studies (Brooker et al. 1973, Wurnig et al. 1999). Radiation therapy is an expensive alternative for prevention of heterotopic ossification. In our department it is used only in patients with contraindications to COX inhibitors, such as those with severe renal failure.

Indomethacin acts by inhibiting COX-1 and COX-2, which are needed for the production of prostaglandins. The role of prostaglandins E and F in fracture healing and bone metabolism has been described in detail (Dekel et al. 1981). This activity is probably the reason why prostaglandins prevent ectopic bone formation after hip surgery.

Recent reports have shown that selective COX-2 inhibition may be sufficient for the prevention of heterotopic ossification. However, some authors have emphasized the need for further evidence of this (Fijn et al. 2003).

We found that rofecoxib, a selective COX-2 inhibitor, was effective in preventing clinically important degrees of heterotopic ossification after total hip replacement. There was a tendency for more severe ossification (grades III and IV) in the group with rofecoxib 25 mg daily, but the dosage may not be equipotent to indomethacin 100 mg daily. Rofecoxib 25 mg given daily for 1 week appears to be less effective than celecoxib 200 mg administered twice daily for 2 weeks (Romano et al. 2004). Nevertheless, there was no correlation between the grade of ossification and the functional outcome. Since rofecoxib had no gastrointestinal side effects, it did not have to be discontinued in any patient. In other investigations, rofecoxib in doses of up to 50 mg was found to be advantageous in postoperative control of pain due

to COX-2 inhibition without any decrease in platelet aggregation (Reuben et al. 2002, Ruvanendran et al. 2003). Even so, there is recent evidence of cardiovascular complications after viox treatment (Gislason et al. 2006).

Our findings confirm that heterotopic ossification can be prevented by short-term administration of a selective COX-2 inhibitor, especially in patients with potential gastrointestinal problems.

Contributions of authors

AW: initiated the study. MS and JG: included the patients and collected data. JG: interpreted the data and prepared the manuscript.

Merck Sharp & Dome supported the study with a grant and supplied coded drug blisters. We appreciate the discussions held during the planning of the study, but the company took no part in data collection, interpretation of data, or writing of the manuscript.

Allen H L, Wase A, Bear W T. Indomethacin and Aspirin: effect of nonsteroidal anti-inflammatory agents on the rate of fracture repair in the rat. *Acta Orthop Scand* 1980; 51: 595-600.

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz M B, Hawkey C J, Hochberg M C, Kvien T K, Schnitzer T J. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520-8.

Brooker A F, Bowerman J W, Robinson R A, Riley H Jr. Ectopic ossification following total hip replacement. Incidence and a method of classification. *J Bone Joint Surg (Am)* 1973; 55: 1629-32.

Dekel S, Lenthall G, Francis M J. Release of prostaglandins from bone and muscle after tibial fracture: an experimental study in rabbits. *J Bone Joint Surg (Br)* 1981; 63: 185-9.

Fijn R, Koorevaar R T, Brouwers J R. Prevention of heterotopic ossification after total hip replacement with NSAIDs. *Pharm World Sci* 2003; 25: 138-45.

Gislason G H, Jacobsen S, Rasmussen J N, Rasmussen S, Buch P, Friberg J, Schramm T K, Abildstrom S Z, Kober L, Madsen M, Torp-Pedersen C. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006; 113: 2906-13.

Keller J C, Trancik T M, Young F A, St Mary E. Effects of Indomethacin on bone ingrowth. *J Orthop Res* 1989; 7: 28-34.

Reuben S S, Bhopatkar S, Maciolek H, Joshi W, Sklar J. The preemptive Analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. *Anesth Analg* 2002; 94: 55-9.

Romano C L, Duci D, Romano D, Mazza M, Meani E. Celecoxib versus Indomethacin in the prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty* 2004; 19: 14-8.

Ruvanendran A, Kroin J S, Tuman K J, Lubenov T R, Elmofly D, Moric M, Rosenberg A. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement. *JAMA* 2003; 290: 2411-8.

Schmidt S A, Kjaersgaard-Andersen P, Pedersen N W, Kristensen S S, Pedersen P, Nielsen J B. The use of Indomethacin to prevent the formation of heterotopic bone after total hip replacement. *J Bone Joint Surg (Am)* 1988; 70: 834-8.

Wurnig C, Schwameis E, Bitzan P, Kainberger F. Six-years results of a cementless stem with prophylaxis against heterotopic bone. *Clin Orthop* 1999; (361): 150-8.

Zacher J, Walther E, Gursche A. Prevention of periarticular ossification (PAO) after total hip replacement (THR) with Rofecoxib 25mg. *Annals of the Rheumatic Diseases (Suppl 1)*: 2001; 60: 79.