

# Indomethacin for prevention of heterotopic ossification after hip arthroplasty

## A randomized comparison between 4 and 8 days of treatment

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In a randomized, parallel group study, we evaluated the efficacy of a 4-day versus an 8-day course of indomethacin (50 mg, 3 times per day), given as prophylaxis against heterotopic ossification after

cementless total hip arthroplasty in 209 patients with arthrosis. Patients receiving the prophylaxis for 8 days had less ( $p = 0.03$ ) severe heterotopic bone formation.

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Schmidt et al. (1988) showed in a prospective 1-year study a substantial reduction of heterotopic bone formation in patients receiving indomethacin for 6 weeks, after cemented total hip replacement. Administration of indomethacin for a shorter period also inhibits bone formation experimentally (Törnkvist et al. 1985) and therefore may be effective as prophylaxis against heterotopic ossification in vivo. In this randomized comparison, we attempted to determine the shortest course of indomethacin prophylaxis effective against heterotopic bone formation.

### Patients and methods

We performed a prospective, randomized comparison of patients with primary or secondary coxarthrosis to evaluate the efficacy of a 4-day (group A) versus an 8-day (group B) course of indomethacin after cementless total hip replacement. The study was approved by the Ethics Committee at our hospital.

All procedures were primary arthroplasties in patients not previously operated on and were performed in our department from January 1992 to June 1993. Contraindications for participation in the study were active gastroduodenal ulcers or histories of ulcers or gastritis during the last 6 months. 249 patients were finally included in the randomization protocol. They were distributed in the two groups according to the final digit of their civic registration number (odd or even number). All patients were given indomethacin (Indocid®) and ranitidine (Zantac®) to minimize gastrointestinal side-effects (Metzenroth et al. 1991).

Indomethacin was administered in a dose of 50 mg 3 times per day (Table 1). No other anti-inflammatory medications were administered during the treatment with indomethacin. Postoperative pain was treated with tramadol (Tramal®) and narcotics.

The surgical technique was standardized and remained the same in all cases. We used the Bauer et al. (1986) approach and implanted a cementless prosthesis (Hofer-Imhof cup/pure titanium, Zweymüller or UNI stem/titanium alloy). All patients were given subcutaneous heparin 5000 s.c. 3 times daily, beginning on the day of surgery and continued until the third postoperative day in group A and until the seventh postoperative day in group B; at this time patients were given acenocoumarol orally for 6 weeks. Antibiotic prophylaxis was given as an intravenous 2 g cephmandol single dose just before the operation. The patients were mobilized on the third or fourth postoperative day. The amount of ossification was graded 0–III (Arcq 1973), 0–IV (Brooker et al. 1973) and 0–III (DeLee et al. 1976). Radiographs were obtained 3 months and 1 year postoperatively and evaluated for evidence of heterotopic bone formation. This follow-up period seemed sufficient, since heterotopic ossification increases in size only until the sixth postoperative month (Ritter and Sieber 1985). Patients were examined at 3 months, 6 months and at 1 year. The data were analyzed with the chi-square test, employing  $p < 0.05$  as the level of significance.

249 patients entered the study, 122 in group A and 127 in group B. 9 patients (2 in group A, 7 in group B) were excluded because of early gastrointestinal side-effects, another 20 patients (11 in group A, 9 in group

Table 1. Drug trial protocol

Group A and B	Indomethacin 100 mg supp. 1 hour after surgery Ranitidin 100 mg i.v. before surgery
Group A	Indomethacin 50 mg p.o. 3 times daily for 3 days Ranitidin 300 mg p.o. for 3 days
Group B	Indomethacin 50 mg p.o. 3 times daily for 7 days Ranitidin 300 mg p.o. for 7 days

Table 2. The amount of heterotopic bone formation according to Arcq at 1 year postoperatively. Number of patients

	0	I	II	III	Total
Group A	43	48	13	0	104
Group B	56	46	3	0	105

Table 3. The amount of heterotopic bone formation according to Brooker at 1 year postoperatively. Number of patients

	0	I	II	III	IV	Total
Group A	43	48	7	6	0	104
Group B	56	46	1	2	0	105

Table 4. Amount of heterotopic bone formation according to DeLee at 1 year postoperatively. Number of patients

	0	I	II	III	Total
Group A	43	48	9	4	104
Group B	56	46	2	1	105

Table 5. Amount of heterotopic bone formation according to Arcq after short-term (8 days) and long-term (6 weeks) indomethacin medication at 1 year postoperatively. Number of patients

	0	I	II	III	Total
Our results	56	46	3	0	105
Wurnig et al. 1992	59	35	5	1	100

Table 6. Amount of heterotopic bone formation according to DeLee after short-term (8 days) and long-term (6 weeks) indomethacin medication at 1 year postoperatively. Number of patients

	0	I	II	III	Total
Our results	56	46	1	2	105
Schmidt et al. 1988	89	13	0	0	102

B) were withdrawn due to other side-effects (nausea, headache) or incorrect study protocol. 7 patients (3 in group A, 4 in group B) died of causes unrelated to surgery or treatment. 2 patients in each group were lost to follow-up. The remaining 209 patients (104 in group A, 105 in group B) received the indomethacin medication, according to the study protocol. The groups were similar in age, gender distribution, post-operative bleeding, length of hospital stay and post-operative recovery time. As men are more at risk of developing heterotopic ossification than women (DeLee et al. 1976, Kromann-Andersen et al. 1980, Hierton et al. 1983, Morrey et al. 1984, Søballe et al. 1988), we looked at the gender distribution in our 2 groups and found no difference, group A 40/104 men, group B 42/105 men ( $p = 0.96$ ). No deep infection or postoperative dislocation occurred in either group.

## Results

At 1 year, 61 patients in group A ( $59 \pm 9.5\%$ , mean  $\pm$  95% CI) and 49 patients in group B ( $47 \pm 9.6\%$ , mean  $\pm$  95% CI) showed radiographic evidence of heterotopic ossification. These differences were not statistically significant ( $p = 0.09$ ).

However, fewer patients in group B had severe ossification (Tables 2-4). Regardless of the classification system used, the difference was always statistically significant ( $p < 0.05$ ). No patient from either group developed extensive Arcq grade III, Brooker grade IV or DeLee grade III ossification. Only 1 man had to be revised (group A) because of a permanent decrease in joint motion.

## Discussion

The cause of heterotopic ossification after total hip replacement is not clear. Surgical trauma and individual predisposition are the chief factors (DeLee et al. 1976, Ahrengart and Lindgren 1993). Several authors suggested the surgical approach as a cause of heterotopic ossification, but it does not seem to be a crucial factor (Hanslik and Radloff 1974, Morrey et al. 1984, Schmidt et al. 1988). The incidence which varies from 5% to 90% (Nollen and Sloof 1973, DeLee et al. 1976, Kromann-Andersen et al. 1980, Errico et al. 1984, Hamblen 1984, Eyb and Zweymüller 1985, Cella et al. 1988) seems to be higher after cementless than cemented hip arthroplasty (Maloney et al. 1991). To determine the amount of heterotopic ossification, several classification systems are employed (Arcq 1973, Brooker et al. 1973, DeLee et al. 1976). Wurnig

et al. (1992) showed that the severity of heterotopic ossification, according to the Arcq grading system, correlates closely with clinical findings—for instance, hip motion. We used the Brooker and DeLee classification systems as well, to determine whether the same results would be achieved.

Since Dahl suggested in 1975 that oral indomethacin may be effective as a prophylactic measure against heterotopic ossification, several supporting retrospective and prospective reports have been published (Ritter and Gioe 1982, Ritter and Sieber 1985, Kjærsgaard-Andersen and Schmidt 1986, Nilsson et al. 1986, Schmidt et al. 1988, McMahon et al. 1991, Kjærsgaard-Andersen and Ritter 1992).

Optimal duration and dosage of indomethacin prophylaxis are still unknown. Most authors recommend treatment for at least 3 weeks. Our aim was to see whether short-term treatment with indomethacin would also be effective. Compared with results of prospective trials using indomethacin treatment for several weeks (e.g., Schmidt et al. 1988, Wurnig et al. 1992), no obvious difference in the effectiveness of our 8-day course of indomethacin was found (Tables 5 and 6). Treatment with indomethacin was discontinued due to gastrointestinal side-effects in only 9 cases. No patients in either group showed clinical signs of gastric ulceration. Our findings indicate the effectiveness of short-term treatment with indomethacin (Kjærsgaard-Andersen et al. 1993) in the prophylaxis of heterotopic ossification after cementless hip arthroplasty and that the incidence of side-effects is acceptable.

Although several randomized studies have shown that various NSAIDs can prevent or reduce heterotopic ossification after total hip arthroplasty (Elmstedt et al. 1985, Schmidt et al. 1988, Hoikka et al. 1990, Gebuhr et al. 1991, Wahlström et al. 1991, Reis et al. 1992), the question still to be solved is how short-term treatment can be used. In most of the previous studies the treatment period was 3–6 weeks, only 2 randomized studies reported shorter treatment periods; 1 with a 10-day treatment period with ibuprofen, in which there was no significant reduction in the ibuprofen-treated group, and 1 with a 5-day treatment period with tenoxicam, where the reduction in heterotopic ossification was found to be statistically significant (Ahrengart et al. 1994, Gebuhr et al. 1996).

Our study clearly demonstrates that the incidence of heterotopic bone formation after total hip arthroplasty was not statistically different after 4-day and 8-day treatment. The incidence of substantial heterotopic bone formation was statistically significantly less ( $p = 0.03$ ) after the 8-day treatment. Therefore we

recommend an 8-day prophylaxis to prevent heterotopic bone formation after total hip arthroplasty.

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