Heterotopic ossification after hip arthroplasty

A randomized double-blind multicenter study of tenoxicam in 147 hips

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147 patients due to have a cemented total hip arthroplasty were randomized to 4 groups. They received either tenoxicam 20 mg or 40 mg, or placebo, for 5 days or morphine on the day of operation and placebo for 4 days. During the first 5 days 14 patients were excluded. The patients were followed for 1 year, during which another 10 patients were excluded. At follow-up, significantly fewer patients had heterotopic ossifications in the tenoxicam groups than in the placebo and morphine groups. There was no significant difference between the 2 tenoxicam-treated groups, and we therefore conclude that tenoxicam 20 mg for 5 days postoperatively can reduce heterotopic ossification after cemented total hip arthroplasty.

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Although the mode of action is uncertain, several prospective randomized studies have shown that various non-steroidal anti-inflammatory drugs can prevent or reduce heterotopic ossification after total hip arthroplasty. One question still to be solved is how short a treatment can be used; the shorter the treatment period, the higher is patient compliance. In most of the previous prospective randomized studies, the treatment period has been from 3 to 6 weeks (Elmstedt et al. 1985, Schmidt et al. 1988, Hoikka et al. 1990, Gebuhr et al. 1991, Wahlström et al. 1991, Reis et al. 1992). We have now investigated whether a treatment period of 5 days with tenoxicam, either 20 mg or 40 mg, is sufficient to reduce heterotopic ossification after cemented total hip arthroplasty. The study was originally designed to compare the two dosages of tenoxicam with morphine in the management of pain following total hip replacement (Crawford et al. 1994).

Table 1. Patient selection

Inclusion criteria
Age 18 years or more
Uncomplicated cemented total hip arthroplasty
American Society of Anesthesiology (ASA) Classes I–III
Anesthesia performed as spinal anesthesia with 2.5–4 mL bupivacain 0.5%
Written or oral-witnessed informed consent
Ability to follow the protocol
Exclusion criteria
Concomitant treatment with any other non-steroidal anti-inflammatory drug or analgesic not specified in the protocol
Oral anticoagulants
Hypersensitivity to study drugs
Treatment with anti-psychotic drugs within 3 months before the study and during the study
Concomitant intake of any other investigational drug or use of an investigational device
Pregnancy or breastfeeding
Evidence of peptic ulceration
Diagnosed asthma
Heart failure
Renal insufficiency, defined as serum creatinine level > 150 µmol/L
Previous randomization to this study

Patients and methods

From September 1992 to March 1993, 147 consecutive patients due to have a cemented total hip arthroplasty and who fulfilled the criteria for the study protocol entered this multicenter study performed in 6 centers (Table 1). The study protocol had been approved by the local ethics commitees and all patients had given signed consent before inclusion. Four types of prostheses were used: Exeter (Howmedica, Rutherford, NJ, USA), Müller (Biomet, Warsaw, IN, USA), Charnley (Depuy, Leeds, England) and Lubinus SP II (Waldemar Link

GmbH, Hamburg, Germany). Prophylactic antibiotics were given either as dicloxacillin 2 g and gentamicin 240 mg or dicloxacillin 1 g or cefuroxime 2.25–3.00 mg or ceftriaxone 2 g. The patients were randomized to 4 treatment groups:

1) tenoxicam 20 mg initially followed by placebo after 4 hours, tenoxicam 20 mg after 8 hours and placebo after 12 hours on the day of surgery, followed by tenoxicam 20 mg once daily for the next 4 days;

2) tenoxicam 40 mg initially followed by placebo after 4 hours, tenoxicam 20 mg after 8 hours and placebo after 12 hours on the day of surgery, followed by tenoxicam 40 mg once daily for the next 4 days;

3) morphine (0.1 mg/kg bodyweight) initially and after 4, 8, 12 hours on the day of surgery, followed by placebo once daily for the next 4 days;

4) placebo initially and after 4, 8, 12 hours on the day of surgery, followed by placebo once daily for the next 4 days.

The treatment started at the end of surgery and the trial drug was administered intravenously on the day of surgery. On the following 4 days the trial medication was administered perorally.

All intake of other non-steroidal anti-inflammatory drugs prior to operation was registered and medication with non-steroidal anti-inflammatory drugs was stopped at least 1 day before operation. 37 patients who had received some kind of non-steroidal anti-inflammatory drug prior to operation were evenly distributed in the 4 groups. No non-steroidal anti-inflammatory drugs were allowed during 2 weeks postoperatively. Morphine was used as an escape analgesic in the first 5 days postoperatively and morphine and paracetamol were used during the following 9 days.

59 men and 88 women with a median age of 72 (32–88) years were included. 134 had arthrosis, 10 had complications after hip fracture and 3 had rheumatoid arthritis. There were 36 patients in each of the treatment groups, 37 in the morphine group and 38 in the placebo group. The patients had anteroposterior radiographs taken postoperatively and were followed clinically and radiographically for 1 year. The degree of ossification was evaluated according to DeLee et al. (1976). Grade 0 is no ossification, grade 1 is heterotopic ossification occupying less than 50% of the distance between the femur and the pelvis, Grade 2 is ossification occupying more than 50% of the distance between the femur and the pelvis and grade 3 is bridging ossification.

All radiographs were blinded before evaluation.

During the first 5 days, 14 patients were excluded and another 10 patients were excluded during the following year (Table 2), leaving 30 patients in the tenoxicam 20 mg group, 31 in the tenoxicam 40 mg group, 32 in the morphine group and 30 patients in the placebo group to be followed.

Table 2. Exclusion criteria. No. of patients

	Tenoxicam		Control	
Exclusion criteria	20 mg	40 mg	Mo [a]	Pl [b]
Early (within 5 days)				
Nausea		1	2	1
Protocol violation	2	1		
Coronary infarction	1		1	
Dislocation		1		
Bronchial asthma				1
Agitation			1	
Pain				1
Hematemesis		1		
Total	3	4	4	3
Late (6 days–1 year)				
Unrelated death			2	1
Deep infection	1			
Hemiprosthesis	1			
Refused to participate	1	1	2	1
Total	3	1	4	2

[a] Morphine
[b] Placebo

For the statistical analysis, Fischer's exact test (2-tailed) was used. The relative risk of ossification with 95% confidence limits was calculated. The Kruskal-Wallis one-way analysis of variance was used for treatment comparisons. Multiple comparison procedures were performed when the Kruskal-Wallis test revealed significance between the treatment groups (0.05 was chosen as the significance level).

Results

After 1 year there were 21/61 patients with ossification among the tenoxicam-treated groups versus 44/62 in the placebo/morphine groups (p 0.0001) (Table 3). Each of the treatment groups had signifi-

Table 3. Heterotopic ossification

Degree	0	1	2	3	Total
Tenoxicam 20 mg + 40 mg	40	15	6	0	61
Placebo + Morphine	18	17	19	8	62
Total	58	32	25	8	123

P 0.0001 between groups

cantly fewer ossifications than the placebo/morphine group ($p < 0.05$). There was no difference between the 2 tenoxicam groups or between the placebo and the morphine group. In the tenoxicam 40 mg group the relative risk of ossification was 0.64 (0.42–0.97) and in the tenoxicam 20 mg group the relative risk was 0.33 (0.17–0.64). Severe grade 3 ossification was only found in the placebo/morphine groups (5 in placebo group, 3 in the morphine group). Among male patients there were 6/27 with ossification in the tenoxicam-treated groups and 11/24 in the placebo/morphine groups (p 0.04). In patients with non-steroidal anti-inflammatory drug consumption within 6 months prior to operation, there were 20/37 patients with ossification versus 45/86 among the patients with no non-steroidal anti-inflammatory drug consumption (p 1.0).

The relative risk of ossification in patients treated with non-steroidal anti-inflammatory drugs preoperatively was 1.09 (0.76–1.57).

Discussion

The incidence of heterotopic ossification after total hip arthroplasty is reported to be 1–90% (Freeman et al. 1973, Rosendahl et al. 1977). In most of the prospective randomized trials the incidence of heterotopic ossification in the placebo groups has been 60–80%. The cause of heterotopic ossification is still not clarified and the mode of action of non-steroidal anti-inflammatory drugs is also uncertain, but is thought to be mediated through an inhibition of the synthesis of prostaglandins.

In previously reported randomized prospective studies the period of treatment has been between 3 and 6 weeks. Two randomized studies have reported shorter treatment periods, one with a 2 weeks' treatment period with indomethacin, where the reduction in heterotopic ossification was found to be significant and one with a 10-day treatment period with ibuprofen, in which there was no significant reduction in the ibuprofen-treated group (Kjærsgaard-Andersen et al. 1993, Ahrengart et al. 1994).

This is the first prospective randomized study showing that a non-steroidal anti-inflammatory drug given for as short a period as 5 days can reduce heterotopic ossification after cemented total hip arthroplasty. The advantages of a short course of treatment are higher patient compliance, greatly reduced frequency and severity of gastrointestinal complications following intake of non-steroidal anti-inflammatory drugs, reduced cost and greater convenience (Bogoch and Wright 1994).

In the present study there was no difference between the placebo group and the morphine group. Nevertheless, there were more ossifications in the placebo group than in the morphine group and 5 of the severe grade 3 ossifications were in the placebo group, versus 3 in the morphine group. There were no grade 3 ossifications in the treatment groups. If ossification is caused by pain (-mediators?), the ossifications in the morphine group will probably diminish, as morphine alone is a more potent analgesic. Grade 3 ossification is the type of ossification that most often leads to reoperation (Lindholm et al. 1986, Schmidt et al. 1988).

The results of several previously published studies concerning heterotopic ossification after total hip arthroplasty have been questioned because no information has been given about the use of non-steroidal anti-inflammatory drugs preoperatively. In our study and in the study by Kjærsgaard-Andersen et al. (1993), it was found that the use of non-steroidal anti-inflammatory drugs preoperatively did not influence the incidence of heterotopic ossification.

The number of side-effects of tenoxicam was low—only 1 patient in the tenoxicam 40 mg group had severe side-effects caused by tenoxicam in the form of gastrointestinal bleeding.

Tenoxicam is one of the non-steroidal anti-inflammatory drugs with the lowest frequency of gastrointestinal side-effects in comparison with other non-steroidal anti-inflammatory drugs (Tanaka et al. 1981). There was no significant difference in the amount of ossification between the two treatment groups, although the relative risk of ossification was higher in the tenoxicam 40 mg group.

As this is a randomized double-blind study, the influence of differences in surgical approach, number of surgeons at the different centers, duration of surgery, estimated blood loss, prophylactic medication to prevent deep vein thrombosis and patients at high risk of developing heterotopic ossification (i.e., contralateral heterotopic bone, male gender, etc.) can be neglected.

1 patient in the tenoxicam 40 mg group developed hematemesis and as there is no statistical difference between the two tenoxicam groups, it is concluded that 20 mg tenoxicam given postoperatively for 5 days reduces heterotopic ossification after cemented total hip arthroplasty.

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