Naproxen prevention of heterotopic ossification after hip arthroplasty

A prospective control study of 55 patients

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The effect of naproxen on heterotopic ossification after total hip replacement was studied in a randomized, double-blind trial. Twenty-eight patients received 250 mg naproxen thrice daily for 4 weeks postoperatively starting on the morning of the operation while 27 control patients received a placebo. Three months after the operation, 13 patients in the control group had heterotopic ossification compared with 4 patients in the group that received naproxen; and after 1 year, the figures were 15 and 4, respectively ($P < 0.01$). Three control patients had severe ossifications. We conclude that naproxen given for 4 weeks is sufficient to decrease the incidence of heterotopic ossification after cemented total hip replacement.

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In 1974, Dahl showed that there was a tendency towards less heterotopic bone formation after total hip replacement in patients treated with indomethacin. This was confirmed by Almåsbakk and Røysland (1977), Ritter and Sieber (1985), and Schmidt et al. (1988). It has also been shown that diclofenac (Wahlström et al. 1989) and ibuprofen (Elmstedt et al. 1985) can reduce the formation of heterotopic ossification.

The aim of this prospective, randomized, double-blind study was to determine the effect of naproxen on heterotopic ossification.

Patients and methods

From December 1987 to January 1989, 70 consecutive patients with primary coxarthrosis who were scheduled to have a cemented total hip replacement and who fulfilled the demands according to a predetermined protocol were included in a prospective, randomized, double-blind study. During the same period, 19 patients could not fulfill the demands of the protocol, especially due to intolerance of naproxen or a history of gastritis or gastric ulcer. Further, patients who required nonsteroid anti-inflammatory drugs (NSAIDs) for other reasons were excluded. The trial was approved by the local ethics' committee. The patients were included 14 days prior to the operation, and all the medication with NSAIDs was discontinued; the only analgetic used during this period was paracetamol. The amount of paracetamol used was not recorded.

The patients were randomized, and they received either naproxen or placebo. Naproxen was given as a suppository, 500 mg twice on the day of operation; the first dose was given together with the premedication. In the next 4 weeks, 250 mg tablets were given thrice daily. Pain was relieved with either paracetamol or narcotics, but the amount was not recorded. There were 35 patients in each group, but 15 did not fulfill the trial requirements: 7 from the naproxen group and 8 from the control group. Their exclusions were the result of wrong medication, including the receipt of other NSAIDs in 6 patients. Four patients contracted dyspepsia (1 of whom had received the placebo). Another 4 patients simply wanted to be taken off medication. One patient who had received naproxen contracted acute tubulointerstitial nephropathia (ATIN); but, according to the nephrologists, this could not be related to naproxen. This left 55 patients—28 and 27, respectively, in the naproxen and the placebo group—who were followed for 1 year after the operation. The median age was 75 (59–87) years in the naproxen group and 70 (41–83) years in the control group. Finally, the male/female ratio was 11/17 in the naproxen group and 12/15 in the control group.

All the patients were operated on under the protection of prophylactic antibiotics (dicloxacillin,

Table 1. Number of patients with heterotopic ossification after a total hip arthroplasty in relation to treatment with naproxen (N) or placebo (P) and follow-up periods

Grade	Weeks postoperatively							
	6 weeks		13 weeks		26 weeks		52 weeks	
	N	P	N	P	N	P	N	P
0	24	15	24	14	24	12	24	12
1	4	8	4	7	3	8	3	7
2	0	4	0	6	1	5	1	5
3	0	0	0	0	0	2	0	3

Table 2. Average range of hip motion after total hip arthroplasty. Number of patients in parentheses

Grade	13 weeks	52 weeks
0 + 1	189° (49)	201° (46)
2 + 3	177° (6)	184° (9)

4 mg as one dose). A posterolateral approach without trochanteric osteotomy was used, and a Müller prosthesis was inserted. As soon as the suction drain was removed, usually 2 days after the operation, full weight bearing was allowed.

Radiographic and clinical examinations were made after 6, 13, 26, and 52 weeks. Plain radiographs in the anteroposterior view were analyzed according to the four grades of calcification described by DeLee et al. (1976). Pain, range of motion, and ability to walk were recorded according to D'Aubigne and Postel (1954). For the statistical analysis, Fisher's exact test (2-tailed) and the Mann-Whitney rank sum test were used. Only results with *P*-values below 0.05 were considered significant.

Results

Six weeks after the operation, 12 out of 27 patients in the control group had heterotopic ossification. Four of these had developed Grade 2 lesions, while none had developed Grade 3 lesions. Only 4 of the 28 patients in the naproxen group had developed ossification, all Grade 1. The ossification was found to be far more prevalent in the control group throughout the year of observation (Table 1).

After 52 weeks, 1 patient in the naproxen group had a Grade 2 ossification, while none had a Grade 3 ossification. In the control group, 5 patients had a Grade 2 ossification and 3 had a Grade 3 ossification. None of the patients with a Grade 2 or Grade 3 ossification complained of pain. One patient who received the placebo and had a Grade 3 lesion had mild pain while walking. Two patients without ossifications, 1 from each group, had mild pain while walking.

After 1 year, 2 out of 9 patients with a Grade 2 or 3 ossification could only walk with the aid of a crutch, and then for less than 1 hour. Three of the patients with Grades 2 and 3 lesions were able to walk normally. Of the 46 patients with a Grade 0 or 1 ossification, 37 had a normal walking ability, whereas in the 9 patients who had a reduced walking ability, 4 could only walk for less for than 1 hour, and then only with support of a crutch, but in 2 of them a nonoperated on contralateral hip was the cause of their disability. The total number of patients with an unencumbered walking status was higher among patients with a Grade 0 or 1 ossification than among patients with a Grade 2 or 3 ossification.

There was no difference in the total average range of motion between patients with Grades 0 and 1 ossification and those who had Grades 2 and 3 ossification (Table 2).

Discussion

The incidence of heterotopic ossification after total hip replacement has been reported to vary from 0.6 to 90 percent (Freeman et al. 1973, Nollen and Slooff 1973, Rosendahl et al. 1977). Only patients with the most severe lesions have clinical symptoms, most often a reduced range of motion (Ritter and Vaughan 1977, Schmidt et al. 1988). Several clinical investigations have shown indomethacin to have an inhibitory effect on heterotopic ossification (Almåsbakk and Røysland 1977, Ritter and Sieber 1985, Schmidt et al. 1988). Ibuprofen and diclofenac have been found to have the same effect (Elmstedt et al. 1985, Wahlström et al. 1989). The number of prospective randomized studies concerning the effect of NSAIDs on heterotopic ossification are but few. Our present prospective study has shown that naproxen also has an inhibitory effect on heterotopic ossification, and this could indicate that all the NSAIDs have an inhibitory effect on heterotopic ossification.

In most of the previously reported studies, there is either a lack of information concerning the use of NSAIDs in the weeks prior to the operation or

whether any patients in the control group have received NSAIDs postoperatively for other reasons. The use of NSAIDs can of course confound the results. In the present study, all medication with NSAIDs was stopped 2 weeks before the operation, and this was continued for 4 weeks postoperatively. During this period, the patients received paracetamol, which, in fact, can also have an anti-inflammatory effect (Skjelbred and Løkken 1979). Because of the analgetic effect of naproxen, the need of paracetamol in the naproxen group has probably been less than in the control group, and therefore the anti-inflammatory effect of paracetamol has been greater in the control group. This can have made the difference in ossification less pronounced between the two groups. Törnkvist et al. (1985) stated that to inhibit experimental new bone formation indomethacin must be present before or at the time of implantation of demineralized bone matrix. Elmstedt et al. (1985) found that the prevention of heterotopic bone formation is most effective if commenced before or at the time of the operation.

The effect of NSAIDs is thought to be due to their inhibition of the synthesis of prostaglandins and related substances that promote the initiation of inflammation, and because inflammation is present early in the course, it seems reasonably to start the medication before the inflammation makes its debut. Elmstedt et al. (1985) gave ibuprofen for 3 months, whereas Schmidt et al. (1988) gave indomethacin for 6 weeks, and Wahlström et al. (1989) gave ibuprofen for 6 weeks. In the present study, we prescribed naproxen for only 4 weeks. Future studies will show whether or not even shorter periods of medication will suffice, and, in fact, Sudman et al. (1979) showed that indomethacin given for only 1 week could inhibit fracture healing.

As in most other reports (Jowsey et al. 1977, Rosendahl et al. 1977, Kromann-Andersen et al. 1980, Schmidt et al. 1988), we found that the total range of motion was reduced, although not appreciably, in patients with Grades 2 and 3 ossification. Severe ossification is seldom associated with severe pain (DeLee et al. 1976, Jowsey et al. 1977, Kromann-Andersen et al. 1980, Schmidt et al. 1988), and we could not correlate pain with the degree of ossification. On the other hand, the patients with Grades 2 and 3 ossification had a considerably reduced walking ability.

Among the 19 patients who developed ossifications, 16 were affected within 3 months (84 percent). Elmstedt et al. (1985) found that 86 percent of the patients had developed ossification before 3 months. Progression to Grade 3 ossification occurred after 3 months, which also accords with the findings of Elmstedt et al. (1985). This implies that medication after the fourth week has no effect on ossification.

Many risk factors have been elucidated in recent years. Most authors agree that males are affected more then females, and patients with primary osteoarthrosis, high body weight, high age, heterotopic ossification after previous ipsilateral or contralateral hip surgery or previous surgery on the ipsilateral hip are predisposed to heterotopic ossification (Hierton et al. 1983, Lindholm et al. 1986, Pedersen et al. 1989). The operative tissue trauma seems to be an important factor in evoking heterotopic ossification (Hierton et al. 1983).

None of our patients has had to be reoperated on because of heterotopic ossification; but in the study of Jowsey et al. (1977), 11 out of 3,204 hips were reoperated on because of ossification; and Schmidt et al. (1988) reported that 1 out of 99 patients who received a placebo was reoperated on. Lindholm et al. (1986) had to reoperate on 4 out of 623 patients. This gives a reoperation incidence between 0.4 and 1 percent.

Four weeks of medication with naproxen costs approximately 185 DKK per patient, whereas 10 days of hospitalization in conjunction with a reoperation costs about 30,000 DKK. The cost of postoperative medication with NSAIDs therefore seems to be low when compared with the cost of a reoperation, especially if only the predisposed patients are treated.

We recommend that prophylactic naproxen should be given in connection with a cemented total hip replacement starting preoperatively and continuing for 4 weeks.

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