Short-term ibuprofen to prevent ossification after hip arthroplasty

No effects in a prospective randomized study of 47 arthrosis cases

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Heterotopic ossification after hip arthroplasty can be prevented by ibuprofen given 3 months postoperatively. To evaluate the effectiveness of 10 days of ibuprofen treatment we performed a randomized, double-blind, prospective study on 57 patients with primary arthrosis, undergoing total hip arthroplasty. 47 patients completed the study and no effect on the incidence of ossification could be detected.

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Schmidt et al. (1988) showed a substantial reduction in heterotopic ossification in patients given indomethacin for 6 weeks in a randomized prospective study. To minimize the risk of side-effects from NSAIDs it is important to determine the shortest time of drug administration that is effective as prophylaxis. Short-time administration of indomethacin also inhibits bone formation experimentally (Törnkvist et al. 1985). Knahr et al. (1988) have reported that 2 or 3 weeks of indomethacin medication counteracts the formation of heterotopic ossification after hip arthroplasty. Ibuprofen has a low incidence of side-effects in comparison to other NSAIDs (Wiholm et al. 1985), and it has proven effective in reducing heterotopic bone formation after a 3-month postoperative administration (Elmstedt et al. 1985).

In this prospective, randomized and double-blind study we evaluated the effectiveness of a 10-day course of ibuprofen for ossification prophylaxis in hip arthroplasty.

Patients and methods

Patients with primary arthrosis of the hip who were scheduled for total hip replacement were asked to participate in a double-blind, randomized and prospective study. All operations were primary interventions and were performed in our department during 1988–1989. Contraindications for participation in the study were bronchial asthma, dyspepsia or gastric ulcer problems, inflammatory bowel disease, coagulation defects or current anticoagulant therapy, liver or kidney diseases or allergy to NSAID or salicylates.We excluded all patients who required a special prosthesis, bone grafting or a different surgical approach. Moreover, patients receiving NSAID for other reasons were excluded.

27 men and 30 women with a mean age of 70 ± 7 years agreed to participate. We used a direct lateral approach, without trochanteric osteotomy (Hardinge 1982) and implanted a cemented Harris Design II prosthesis (Howmedica, Rutherford, New Jersey, U.S.A.) using CMW high-viscosity bone cement (CMW Laboratories Ltd., Marton, Blackpool, UK). Antithrombotic prophylaxis was given as an infusion of 500 mL of dextran 70 (60 mg/mL, Macrodex®, Kabi Infusion AB, Stockholm, Sweden) 3 times during the first 5 days, and cefuroxime (Zinacef®, Glaxo Läkemedel AB, Mölndal, Sweden), 1.5 g in 3 doses per day for 3 days was given intravenously to prevent infection.

We chose suppositories to minimize gastrointestinal side-effects; they contained either ibuprofen 500 mg or placebo (Boots/Astra AB, Södertälje, Sweden). The patients were given the suppositories according to the protocol, beginning on the evening before surgery. They were given twice on the day of surgery and 3 times daily for another 9 days. The patients were given crutches for 2 months. Analgesics containing salicylates or NSAID:s were not allowed postoperatively; only paracetamol or dextroproproxyphene were prescribed as pain relievers.

The amount of ossification was graded 0–IV (Brooker et al. 1973) with Class III, bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm and Class IV, apparent bone ankylosis of the hip.

Radiographs obtained 2 months and 1 year postoperatively were compared to postoperative radiographs. Since the tendency among men to develop heterotopic bone is greater than for women (DeLee et al. 1976, Søballe et al. 1988, Ahrengart and Lindgren 1993, Nollen and van Douveren 1993), we also analyzed the male patients separately. For statistical analysis the chi-square analysis and Fischer's exact test were used, $P < 0.05$ was considered significant. The study was approved by the ethics committee at the Karolinska Institute.

No deep infection or postoperative dislocation occurred. 57 patients entered the study and 10 stopped the medication because of early side-effects. 9 of the 10 excluded patients were treated with ibuprofen. 6 discontinued treatment because of gastrointestinal side-effects, abdominal pain (3), diarrhea (2), and vomiting (1). A total of 3 patients developed nausea or headache and 1 had convulsions due to epidural anesthesia. 1 placebo-treated patient discontinued treatment because of inability to retain the suppositories. Of the remaining 47 patients, 21 patients were treated with ibuprofen and 26 were given placebo. The groups did not differ in age, gender distribution, per- or postoperative bleeding, length of hospital stay or postoperative recovery.

Results

At 1 year the radiographs of 15 patients in the control group showed ossification versus 14 in the ibuprofen group (Table 1), i.e., there was no reduction in the overall incidence among patients treated with ibuprofen. However, fewer patients in the ibuprofen group had substantial ossification: 9 control patients had Classes II to IV of ossification, compared to 4 in the ibuprofen group. Only one ibuprofen patient developed extensive ossification (Classes III to IV) compared to 4 among the controls. These differences were not significant, however.

Among male patients, 11 controls had ossification and 6 Classes II–IV, versus 9 and 3 males, respectively, in the ibuprofen group. Extensive ossification (Classes III–IV) occurred in 3 male control patients and in 1 taking ibuprofen. Ibuprofen thus seemed to reduce the number of patients with large amounts of ossification in the male group as well—however, without statistical significance (Table 2).

Discussion

The causes of heterotopic ossification around the hip after arthroplasty are not fully clarified. Charnley (1979) suggested that deposited bone marrow elements may cause heterotopic bone formation, but no evidence supporting this assumption has been presented. Errico et al. (1984) suggested that heterotopic ossification was related to the surgical approach, but the results of Morrey et al. (1984) and Hanslik and Radloff (1974) do not support this opinion. Schmidt et al. (1988) found that the posterior approach did not prevent heterotopic ossification. The surgical trauma and individual predisposition are crucial factors (DeLee et al. 1976, Ahrengart and Lindgren 1993). In most cases the amount of heterotopic bone is clinically insignificant and does not affect outcome. In patients with large amounts of heterotopic bone, the range of motion is impaired (Riegler and Harris 1976, Schmidt et al. 1988, Ahrengart and Lindgren 1989). Since the heterotopic bone is not resorbed, the decrease in joint motion is permanent.

Cella et al. (1988) found that one third of the patients were unable to complete indomethacin treatment because of adverse drug reactions. The frequency of side-effects varies with different NSAID drugs (Wiholm et al. 1985). Elmstedt et al. (1985) gave ibuprofen 400 mg 3 times daily for 3 months postoperatively and found that 3/4 of controls versus 1/3 of treated patients had developed ossifications 12 months postoperatively.

Our aim was to see if short-term treatment with ibuprofen would be effective against soft tissue ossification. Knahr et al. (1988) reported a retrospective study with a 2-week dosage of indomethacin which did pre-

Table 1. The amount of periarticular heterotopic bone formation at 1 year postoperatively. Number of patients

Class of ossification	0	I	II	III	IV	n
Ibuprofen	7	10	3	1	0	21
Controls	11	6	5	3	1	26

Table 2. Heterotopic ossification among male patients divided into 2 groups: those with little or no amount of bone (Classes 0 and I) and those with substantial amounts (Classes II–IV). Number of patients

Class of ossification	0/I	II–IV	n
Ibuprofen	9	3	12
Controls	7	6	13

vent ossification. Hoikka et al. (1990) found flurbiprofen was effective prophylaxis in a 3-week trial. We did not find any significant effect on ossifications by ibuprofen given as suppositories for 10 days postoperatively. However, in the ibuprofen-treated group we saw a tendency towards a reduction in the number of patients with severe ossification.

Ibuprofen suppository side-effects were the causes of withdrawal in 9 out of 10 patients. 6 discontinued the medication because of gastrointestinal side-effects. The suppositories contributed to more gastrointestinal side-effects than did the capsules containing the equivalent compound, according to the study by Elmstedt et al. (1985) in which 2 patients discontinued the medication due to adverse side-effects.

First, it is important to identify groups of patients who are liable to develop heterotopic bone after hip arthroplasty, since effective prophylactic treatment is available and the risk of joint stiffness can be reduced (Schmidt et al. 1988). Secondly, a large number of patients undergo this surgery, and we believe it is important to find the minimal effective doses of NSAID to minimize side-effects.

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