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Effect of ibuprofen on heterotopic ossification after hip replacement

A double-blind, placebo-controlled study was made of the influence of the anti-inflammatory agent ibuprofen on heterotopic ossification after total hip replacement for arthrosis, fracture or rheumatoid arthritis. Seven drop-outs left 21 patients on medication and 22 on placebo in two comparable groups. Heterotopic ossification appeared in one third of the patients in the ibuprofen group and in three fourths in the control group 12 months after surgery. Five patients in the latter group developed true heterotopic bone, compared to one of the patients on medication. Heterotopic ossification was as common among osteoarthritic patients as among others. There was no difference in the range of motion at 12 months postoperatively between patients with and without heterotopic ossification. In the 22 patients with heterotopic ossification this was demonstrated in all but eight within 6 weeks, and in only three did it appear later than 3 months postoperatively. Five of the six patients who showed heterotopic bone with trabecular structure were male. Since inflammation is a dominant feature in the postoperative phase, the effect of ibuprofen on heterotopic ossification is probably its inhibition of the synthesis of prostaglandins. This implies that prevention is most successful if commenced before or at the time of operation.

Erik Elmstedt
T. Sam Lindholm[1]
Olle S. Nilsson
Hans Törnkvist

Department of Orthopaedics, Huddinge Hospital, S-141 86 Huddinge, Sweden and [1]Orthopaedic Hospital of Invalid Foundation, Helsingfors, Finland

Heterotopic ossification is a frequent complication of any type of total hip replacement (THR). When defined as radiographic calcifications, it has been reported in frequencies from 10 to 52 per cent (Eftekhar 1971, Nollen & Slooff 1973) and in one study as high as 90 per cent (Rosendahl et al. 1977); it seems unrelated to the clinical result. Classified as radiographic changes showing a bony structure, heterotopic ossification occurs in 5–25 per cent (Eftekhar 1971, Hierton et al. 1983) of patients after THR and, though this significantly decreases the range of motion (Jowsey et al. 1977), re-operation for heterotopic bone is seldom necessary (Nollen & Slooff 1973).

Diphosphonates (EHDP) have been reported to prevent heterotopic bone formation (Stover et al. 1975) or delay its occurrence (Bijouvet et al. 1974), while McCollister Evarts et al. (1982) showed a reduced incidence of heterotopic ossification after postoperative radiation therapy. Indomethacin has been found to prevent postoperative heterotopic ossification following THR (Ritter & Gioe 1982) and, in a previous study on a bone induction model in rats, Törnkvist et al. (1983) found a moderate inhibition of heterotopic bone formation by another nonsteroid anti-inflammatory drug, ibuprofen.

The purpose of this study was to evaluate the effect of ibuprofen on the incidence and extent of heterotopic ossification after THR.

Patients and methods

From September 1981 to June 1982, 50 consecutive patients scheduled for THR at our department participated in a double-blind, placebo-controlled study, and were given 400 mg ibuprofen or a placebo orally three times daily from the first postoperative day and for 3 months. Patients subjected to any continuous medication were excluded and the patients under study did not receive anti-inflammatory or analgesic drugs other than those forming part of the trial medication. There were seven drop-outs, leaving 21 patients in the ibuprofen group and 22 in the placebo group. Radiographs at 12 months were lost to follow-up in two patients in the latter group. Two patients never started their medication, one died shortly after operation, two had problems swallowing the capsules and in two cases the reasons for dropping out were nausea and allergy, ascribed to the medication. The mean age was 70 years in both groups and there were 11 males and 10 females in the ibuprofen group versus 12 males and 10 females

in the placebo group. The diagnoses for the patients under treatment were arthrosis in 15, rheumatoid arthritis in one and fracture in five, compared to 14 cases of arthrosis, one of rheumatoid arthritis and seven of fracture in the placebo group.

An anterolateral incision and a trochanteric osteotomy were made in all cases, except for one with a posterior approach. The following prostheses were used in the ibuprofen (placebo) group: HD II 14 (14), Charnley-Müller 5 (3), CAD 0 (2), Thompson 1 (2), Lord 0 (1) and Wagner 1 (0).

Ratings of pain, walking and range of motion as well as anteroposterior and lateral radiographs of the hip were evaluated pre-operatively, immediately postoperatively, and at 6 weeks, and 3, 6, and 12 months postoperatively. Heterotopic ossification was graded according to Rosendahl et al. (1977): no sign of periarticular calcification (0), faint shadows of minimal extent (1), scattered lumps of calcification in the periarticular tissue or small exostoses from the trochanter or acetabulum (2), widespread calcification with distinctly trabecular structure (3).

For statistical analysis, the Chi-square method was applied.

Results

Heterotopic ossification defined as Grade 1–3 appeared in three fourths of controls and in one third in the ibuprofen group, and six patients had true heterotopic ossification (Grade 3 Table 1). Heterotopic ossification appeared within 6 weeks in all but eight patients and in only three was it demonstrated later than 3 months postoperatively.

Heterotopic ossification (Grade 1–3) was significantly more frequent among controls at 6 weeks and at 3, 6, and 12 months postoperatively ($p < 0.05$). Five patients on placebo had true heterotopic ossification (Grade 3) at 12 months compared to one of the patients on medication. Of these six patients, five were male and three suffered from hip fracture and another three from arthrosis. Heterotopic ossification was equally as common among those patients with arthrosis as among those without. There was no difference in the range of motion at 12 months postoperatively between patients with and without heterotopic ossification (Grade 1–3).

Table 1. Heterotopic ossification (H.O.) among controls and patients treated with ibuprofen 1.2 g daily during 3 months after THR. Number of controls within parentheses.

H.O. Grade	Weeks postoperatively				
	0	6	12	26	52
0	21 (22)	17 (12)	16 (8)	14 (7)	14 (5)
1	– –	4 (7)	3 (6)	5 (4)	3 (4)
2	– –	– (3)	2 (7)	2 (7)	3 (6)
3	– –	– –	– (1)	– (4)	1 (5)

Discussion

Several explanations have been offered for the occurrence of heterotopic bone formation after THR. Surgical technique is considered to be of great importance by most authors (Rosendahl et al. 1977). Bone chips and marrow from the site of operation or incautious treatment of the acetabular rim have been suggested to promote heterotopic bone formation (Boitzy & Zimmerman 1969). Conditions such as ankylosing spondylitis, fracture-dislocations and osteoarthrosis in males are regarded as predisposing to heterotopic bone formation (Ritter & Vaughan 1977). In this study, heterotopic ossification was as common among those patients with osteoarthrosis as among those without. Five of the six patients with true heterotopic ossification (Grade 3) were male, however.

The origin of heterotopic bone formation remains obscure. The bone-forming cells probably originate from inappropriate differentiation of fibroblasts, which normally develop into muscle or connective tissue. Trauma provides a source of uncommitted fibroblast-type cells, which may become differentiated into bone-matrix-forming cells. The bone that is formed is highly organized and contains secondary haversian systems as evidence of bone remodelling (Jowsey et al. 1977). The process of heterotopic bone formation progresses rapidly. As early as 3 or 4 weeks after the trauma, the calcific shadow may be discerned on radiographs, and biopsy at this time may be misinterpreted as osteosarcoma owing to the high cellular activity. Among 22 patients with heterotopic bone formation in this study, all but eight were affected within 6 weeks and only three later than 3 months after THR. Unlike Jowsey et al. (1977), we found no correlation between the extent of heterotopic ossification and range of motion.

The results of this study indicate that ibuprofen reduces the incidence of heterotopic bone formation after THR. Another anti-inflammatory agent, indomethacin, has also been shown to have a restrictive influence on heterotopic ossification (Ritter & Gioe 1982). Anti-inflammatory drugs exert their effect through inhibition of the synthesis of prostaglandins and related substances that promote the initiation of inflammation. The presence of prostaglandins is probably of importance for bone formation, raised levels of prostaglandins have been found in surrounding muscle of tibial fracture from rabbits *in vitro* (Dekel et al. 1981). It is therefore not surprising that indomethacin delays fracture healing in various experimental models (Allen et al. 1980). Since inflammation is a dominant feature in and around the postoperative wound, treatment with anti-inflammatory drugs may inhibit the formation of heterotopic ossification after THR. In this study we did not find any delayed union of the trochanteric osteotomies which might have been expected, due to the treatment of ibuprofen (Törnkvist et al. 1984). On the other hand, as soon as the administration of an anti-inflammatory drug ceases, experimental fractures usually heal (Allen et al. 1980), which might explain the lack of delayed union of the osteotomies in the present study.

Experimental models of bone induction indicate that it is essential to impede the system of bone formation as soon as possible: during the early phase of mitosis of precursor cells rather than during the phase of cytodifferentiation (Craven & Urist 1971). In this study, medication was started on the first postoperative day. It is likely that prevention of heterotopic bone formation, by radiation or drugs, is most effective if commenced before or at the time of operation.

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