Heterotopic bone formation prevented by diclofenac

Prospective study of 100 hip arthroplasties

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A double-blind, placebo-controlled study was done on the influence of diclofenac, a nonsteroidal anti-inflammatory drug, on heterotopic bone formation after total hip arthroplasty. Totally, 100 operations were involved, and a follow-up was performed after 1 year. There were no cases of substantial bone formation in the treated group versus two thirds of the cases in the placebo group, and some of these had pain. Because side effects of treatment with diclofenac are few and mild, we advocate prophylactic use of this drug.

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Impaired hip function due to heterotopic bone formation (HBF) has been reported in 3–10 percent of the cases after total hip arthroplasty (THA) (Hamblen et al. 1971, Ilstrup et al. 1973, Nollen and Slooff 1973, Parkinson et al. 1982).

Prophylactic treatment with different NSAIDs has been effective in the prevention of HBF after THA (Ritter and Vaughan 1977, Elmstedt et al. 1985, Cella et al. 1988, Schmidt et al. 1988, Sodemann et al. 1988a, b, Wahlström et al. 1988). A double-blind trial on indomethacin has shown convincing preventive effects (Schmidt et al. 1988).

The present double-blind placebo-controlled study was performed to examine the effect of prophylactic treatment with diclofenac sodium (Voltaren®, Ciba-Geigy) on the occurrence of HBF, the complications resulting from the treatment, and the clinical importance of HBF after hip arthroplasty.

Patients and methods

In previous studies from the Department of Orthopedics in Linköping, oxyphenbutazone (Tanderil®, Ciba-Geigy) has almost completely prevented the occurrence of significant HBF (Wahlström et al. 1988). Assuming a 50–100 percent treatment effect and a 40 percent incidence of significant HBF, we choose 50 hips in each group in order to obtain at least a 90 percent probability of demonstrating a true treatment effect of the drug. Patients with rheumatoid arthritis, a previous gastric ulcer, continuous cortison or NSAID treatment, or intolerance to aspirin (ASA) were excluded from the study. Patients who were scheduled to undergo replacement of the hip due to arthrosis were informed and asked to participate.

Table 1. Sex and age distribution. Peroperative and postoperative blood loss. Mean *SD*

	Placebo		Diclofenac	
Female (no.)	20		18	
Male (no.)	30		28	
Age (years)	71	*6.2*	70	*6.1*
Blood loss (mL)				
peroperative	1030	*370*	1140	*600*
postoperative	1090	*480*	1120	*490*
total	2120	*650*	2260	*800*

Ninety-eight patients with 100 hips agreed to participate. Females and males were randomized separately into treatment and placebo groups. More females refused to participate in the study, which explains the male dominance. The project was approved by the local ethics committee and the Swedish National Board of Health (Socialstyrelsen).

The operations were performed from September 1985 to December 1986. In all the patients, THA was performed under spinal anesthesia through a dorsolateral approach without osteotomy of the greater trochanter using a cemented Lubinus SP II prosthesis (Waldemar Link, Hamburg, Germany).

Totally, 75 mg of diclofenac or placebo was administered intragluteally, both preoperatively and postoperatively, followed by 6 weeks of peroral treatment

Table 2. Heterotopic bone formation

Bone formed	Placebo	Diclofenac
No new bone	12	45
< 20 mm	2	1
≥ 20 mm	33	0

Table 3. Hip function at 1–2 years. Mean *SD*

	Placebo	Diclofenac
Number followed up	49	43
Harris' hip score	84 *12*	86 *9.0*
Pain (number with pain score ≤ 20)	4	0

at a dosage of 50 mg thrice daily. The identically marked ampuls and tablets were supplied by the manufacturer (Ciba-Geigy AB, Sweden). Dicloxacillin (Diclocil®, Bristol Meyers) was used as prophylaxis against infection and dextran (Macrodex®, Pharmacia, Uppsala, Sweden) against venous thrombosis. Pain treatment postoperatively included opiates and paracetamol. NSAIDs, ASA, and cortison were not given. Mobilization with full weight bearing was allowed on the first postoperative day. There were no differences in age, sex, or blood loss in the two groups (Table 1).

Four patients in the treatment group had discontinued treatment 5–28 days after the operation: 1 because of gastritis, 1 because of skin problems, 1 because of treatment with warfarin, and 1 for an unknown reason. In the placebo group, 7 patients discontinued treatment: 3 because of gastrointestinal problems, 2 because of warfarin treatment, and 2 for whom no reason was given.

Radiographic examinations, including both AP and lateral projections, were performed 1 week and 3 months after the operation. All the new calcifications were measured and documented by a radiologist (SH), with the double-blind precaution remaining in effect until after the radiographs were assessed. Calcifications were regarded as significant HBF if the widest diameter was 20 mm or more (Hierton et al. 1983). Follow-up examinations were performed 1–2 years postoperatively using the Harris hip score (Harris 1969).

The clinical follow-up after 1–2 years involved 96 patients (2 deceased, 1 with a lost protocol, 1 who could not be assessed because of other diseases).

The chi-square test and the Student's *t*-test were used for the statistical analysis.

Results

In all, 33/47 of the placebo group had substantial new bone formation, whereas no patient in the diclofenac-treated group had substantial new bone formation ($P < 0.001$). In the treated group, 2/46 patients had some bone formation, but only to a minor degree.

The Harris hip score was similar in both groups: 86 ± 9 in the treatment group and 84 ± 12 in the placebo group. The functional score was also similar, but both the total score and the functional score are influenced by the function of other joints. However, the pain score displayed some differences. There were four hips with pain in the whole group, all of which belonged to the placebo group, and all of which had formed new bone. One patient in the placebo group had serious problems with pain and loss of function, and had been reoperated on with excision of heterotopic bone.

Discussion

This study has shown that diclofenac can prevent HBF after cemented hip arthroplasties. The number of complications due to treatment was small, and no serious complication occurred. The clinical follow-up did not yield any statistically significant differences between the treated group and the placebo group; however, there were 4 patients in the placebo group with HBF, and with pain from the hip during walking. This incidence (8 percent) of clinically important HBF is similar to other studies on HBF.

Previous studies have shown a correlation between decreased range of motion (ROM) and heterotopic bone formation (Kromann-Andersen et al. 1980, Ahrengart and Lindgren 1989). Schmidt et al. (1988) found a very high incidence of HBF in the placebo group (in three fourths), but a reduced range of motion only in the most pronounced forms of HBF, and only a few cases with severe pain. In our present study, the incidence of HBF was also very high (in two thirds); and the reason for this was probably, as suggested by Schmidt et al. (1988), that no NSAID was given to the placebo group postoperatively.

The question can arise as to whether a 2 percent incidence of reoperation and an 8 percent incidence of pain during walking justify general prophylaxis with NSAIDs for hip arthroplasties? Because the complications due to the treatment are few and of minor importance, we suggest that general prophylaxis should be offered to all the patients operated on with a total hip

arthroplasty as long as there are no contraindications. Concerning uncemented prostheses, further studies must be performed to clarify the mechanism of the integration of the prosthesis to the bone surface and the interference of diclofenac in this process. In the present study, a 6-week period of treatment was used. This is a safe way to prevent bone formation, although a shorter period of treatment would probably also be effective (Sodemann et al. 1988a, b, Wahlström et al. 1988).

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