Indomethacin for prevention of heterotopic ossification

A randomized controlled study in 41 hip arthroplasties

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The effect of indomethacin 25 mg 3 times daily during the first 2 postoperative weeks in preventing heterotopic bone formation after cemented total hip arthroplasty was investigated in a randomized, double-blind and placebo-controlled clinical trial on 57 patients. 16 patients were secondarily excluded, leaving 19 patients in the indomethacin group and 22 patients in the placebo group. Evaluated from the 3-month radiographs, 18/19 indomethacin patients developed either no or only the milder Grade 1 ossification. In contrast, 11/22 placebo patients developed Grade 2 or 3 ossifications. Our observations favor indomethacin profylaxis for 2 weeks in cemented arthroplasty of the hip.

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Randomized, double-blind and placebo-controlled clinical trials have shown that antiinflammatory drugs can prevent the severest degree of heterotopic bone formation after total hip arthroplasty when administered during the first 3–12 postoperative 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, Kjærsgaard-Andersen et al. 1993).

We investigated in a randomized, double-blind and placebo-controlled clinical trial whether prophylaxis with indomethacin during only the first 2 postoperative weeks prevents the severest degrees of heterotopic bone formation after hip arthroplasty.

Patients and methods

This clinical trial was designed to detect a reduction in the incidence of heterotopic bone formation after cemented total hip arthroplasty of at least 50 percent, at a 5 percent level of significance, and with a test-power of at least 90 percent. In a previous study on cemented total hip arthroplasties (Schmidt et al. 1988), 72 percent of patients without antiinflammatory medication during the first 6 postoperative weeks developed heterotopic ossifications. Using these data, it was calculated that our study should comprise 28 patients in each group.

Patients scheduled for cemented total hip arthroplasty were evaluated for admission to the study. Reasons for being primarily excluded were: known allergic reaction to nonsteroidal antiinflammatory drugs; treatment with steroids; severe disease of the liver, heart, or kidney; epilepsy; parkinsonism; conditions requiring treatment with nonsteroidal antiinflammatory drugs; and those who had already participated in the study for replacement of the opposite hip. The project was approved by the local ethical committee and the National Board of Health in Denmark.

57 patients were included in the study from May 1990 to November 1991. They all underwent cemented total hip arthroplasty with the Exeter prosthesis (Howmedica) at our department. All patients underwent surgery through a posterolateral approach. Prophylactic antibiotics were given intravenously as 1 g dicloxacillin (Diclocil, Bristol-Myers Squibb, Copenhagen, Denmark) immediately preoperatively and 2 hours postoperatively. Subcutaneous injections of low molecular heparin (Clexane, Rhône-Poulenc Rorer, Copenhagen) as 20 mg 2 hours prior to surgery, 20 mg on the evening after surgery and 40 mg daily from the day after surgery until the patients were sufficiently mobilized, which implied mainly the sixth to seventh postoperative day. The patients were mobilized with 2 elbow crutches as early postoperatively as possible, preferably on the second postoperative day, and were allowed full weight bearing. When sufficiently ambulant, the patients were discharged.

The patients were randomized to receive capsules with 25 mg indomethacin or a placebo for the first 2

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Table 1. Clinical data for 57 patients included in the trial

A	B	C	D	E	F	G	H	I	J
1	F	61	A	N	0	I	N		
2	M	75	A	Y	0	I	N		
3	F	70	A	N	0	P	N		
4	M	84	A	Y	1	I	N		
5	F	68	A	N	2	P	N		
6	F	71	A	Y	0	I	N		
7	M	74	A	Y		P	Y	1	0
8	F	63	A	Y	0	I	N		
9	F	61	A	Y	3	P	N		
10	F	67	A	Y	3	P	N		
11	F	80	A	Y	0	I	N		
12	F	84	A	Y	0	I	N		
13	M	74	A	Y	3	P	N		
14	F	65	A	Y	1	P	N		
15	M	70	A	N	3	I	Y	2	0
16	F	70	A	N	0	I	Y	3	3
17	F	72	A	Y	1	I	N		
18	F	73	A	Y	1	P	N		
19	M	57	A	N	1	P	N		
20	M	70	A	N	2	I	N		
21	F	56	A	N	0	I	Y	4	3
22	F	83	A	N	0	I	N		
23	F	65	A	Y	0	P	N		
24	F	75	F	Y		I	Y	5	0
25	M	70	A	Y	0	I	N		
26	F	57	A	Y	0	P	Y	6	2
27	F	58	A	N	2	P	N		
28	M	64	A	Y	0	P	N		
29	F	69	A	Y	1	I	N		
30	F	76	A	N	0	P	N		
31	F	68	A	Y	0	I	Y	4	5
32	M	74	A	Y	0	P	Y	7	2
33	M	78	A	Y	0	I	N		
34	F	64	F	N	0	I	Y	4	8
35	F	78	A	Y	1	I	N		
36	M	88	A	N		P	Y	8	
37	M	86	A	Y	3	P	N		
38	M	79	A	Y	0	P	N		
39	F	70	A	N	0	P	N		
40	F	49	A	Y	0	I	N		
41	F	85	I	N		I	Y	9	5
42	M	65	A	N	2	P	N		
43	M	69	A	N	3	P	N		
44	F	74	A	N	0	I	N		
45	F	53	F	Y	0	P	N		
46	F	72	A	Y	3	P	N		
47	F	84	A	N	1	P	N		
48	M	67	F	N	1	I	Y	4	2
49	M	64	P	N		I	Y	6	1
50	M	75	A	N		I	Y	6	1
51	F	70	A	Y	0	I	N		
52	M	74	A	Y	1	I	N		
53	F	60	C	N	0	I	N		
54	M	82	A	N	2	P	N		
55	M	66	A	Y	0	P	Y	10	1
56	F	79	A	Y	2	P	N		
57	F	52	L	N	2	P	Y	4	4

A Case number
B Sex
C Age
D Diagnosis
  A arthrosis
  F sequelae to fracture of the femoral neck
  I sequelae to infected hip joint
  P psoriatic arthritis
  C sequelae to Calvé-Legg-Perthes' disease
  L sequelae to congenital luxation of the hip
E Preoperative treatment with anti inflammatory drugs
  Y yes
  N no
F Heterotopic bone formation Graded from 0 to 3 (DeLee et al. 1976)
G Treatment
  P placebo
  I indomethacin
H Secondarily excluded
  Y yes
  N no
I Reason for secondary exclusion
  1 total hip arthroplasty was cancelled
  2 previous gastric ulcer
  3 informed consent withdrawn
  4 dyspepsia
  5 reaction to blood transfusion
  6 needs treatment with anti-inflammatory drug
  7 cardiac insufficiency
  8 died before the 3-month control
  9 hematemesis
  10 severe wound drainage
J Day on which the exclusion took place

postoperative weeks, both given 3 times daily, beginning on the first postoperative morning. The placebo capsules contained inactive substances, had a neutral taste, and color and form like the indomethacin capsules. The treatment was undertaken double-blind, that is, the patient, researcher and hospital staff were not acquainted with the type of capsules taken by a given patient. During the period of the study, patients were not allowed treatment with antiinflammatory drugs: postoperative pain was treated with acetaminophen or narcotics. The double-blind precaution remained in effect until all patients had been followed for three months and all radiographs had been assessed.

All patients were examined, including radiography of hips, preoperatively and 3 months postoperatively. The severity of heterotopic bone formation was graded according to DeLee et al. (1976), where Grade 0 means no formation of heterotopic bone, Grade 1 heterotopic bone occupying less than 50 percent of the distance between the femur and pelvis, Grade 2 is heterotopic bone occupying more than 50 percent but not bridging the distance between the femur and pelvis, and Grade 3 bridging heterotopic bone.

57 patients entered the study (Table 1), but 16 patients were secondarily excluded, leaving 41 patients for the final evaluation. The male:female ratio in the indomethacin and placebo groups were 6:13 and 8:14, respectively. Mean age at surgery was 72 years (49–84) in the indomethacin group and 70 years (53–86) in the placebo group.

Among the 16 secondarily excluded patients, 10/29 in the indomethacin group and 6/28 in the placebo group, 3 patients never started the study medication. 5 patients, 4 in the indomethacin group and 1 in the pla-

Table 2. Number of hips with heterotopic bone formation

Grade	Indomethacin	Placebo	Total
0	13	7	20
1	5	4	9
2	1	5	6
3	0	6	6
Total	19	22	41

cebo group had the study medication withdrawn due to dyspepsia, and 1 patient treated with indomethacin suffered from hematemesis on the fifth postoperative day.

Data were analyzed using Fisher's test of exact probability (Swinscow 1981). *P*-values below 0.05 were considered significant.

Results

Heterotopic bone formation was observed in 15/22 placebo patients versus 6/19 indomethacin patients (Fisher's test; *P* 0.002; Table 2). In the placebo group, 3 men and 3 women developed Grade 3 ossification versus only 1 indomethacin patient.

Discussion

Although there is no clinical documentation of a negative influence of postoperative treatment with indomethacin or other antiinflammatory drugs on the outcome of total hip arthroplasty, objections have been made to such use, mainly for patients who have received noncemented prosthetic components (Hedley et al. 1989, Trancik et al. 1989, Jasty et al. 1990, Maloney et al. 1992). The suggested side-effect of antiinflammatory drugs is the inhibition of bony ingrowth. This suggestion is supported by animal studies (Keller et al. 1989, Trancik et al. 1989, Trancik 1992).

Indomethacin is the most detailed investigated drug for prevention of heterotopic bone formation after total hip arthroplasty, and it has been proposed as effective when administered for a postoperative period shorter than three weeks (Dahl 1975, Sodemann et al. 1988, McMahon et al. 1991, Kjærsgaard-Andersen and Ritter 1992). In fact, in the very first report on indomethacin as a prophylaxis against heterotopic bone formation, Dahl (1975) treated his patients for only 1 week, and found the drug to be effective. However, these studies are either retrospective or without controls, and therefore cannot inform us about the true effect of indomethacin when given for a shorter period than three weeks.

One third of our patients were secondarily excluded. There is no single explanation of this fact, but, in contrast to our previous double-blind studies using indomethacin (Schmidt et al. 1988, Kjærsgaard-Andersen et al. 1993), this series had a relatively high number of indomethacin-treated patients who suffered from dyspepsia. No prophylactic antacids or H2-blocker were prescribed to prevent this well-known side-effect, a circumstance which must be considered in future patients undergoing total hip arthroplasty where indomethacin is needed.

The incidence of heterotopic bone formation was high in our placebo group (15/22 patients). However, comparable studies, including a placebo group where no treatment with antiinflammatory drugs for 2–12 postoperative weeks had been given, show the same high incidence of the lesion (Elmstedt et al. 1985, Schmidt et al. 1988, Hoikka et al. 1990, Gebuhr et al. 1991, Wahlström et al. 1991, Reis et al. 1992, Kjærsgaard-Andersen et al. 1993). Therefore, the true incidence of heterotopic ossification after total hip arthroplasty can only be determined in patients receiving postoperative treatment without antiinflammatory drugs. Moreover, this observation indicates that heterotopic bone formation after total hip arthroplasty is a frequent event, that will develop in up to 80 percent of cases, if no postoperative antiinflammatory treatment is prescribed. This may also explain why patients with rheumatoid arthritis seldom develop heterotopic ossification after total hip arthroplasty.

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