Preventive effects of ibuprofen on periarticular heterotopic ossification after total hip arthroplasty

A randomized double-blind prospective study of treatment time

Per-Erik Persson[1], Bent Sodemann[1] and Olle S Nilsson[2]

We determined the efficacy and the minimum treatment time necessary for prophylaxis with nonsteroidal anti-inflammatory drugs (NSAIDs) for periarticular heterotopic ossification (HO) after total hip arthroplasty (THA). Using a double-blind placebo controlled design, 144 patients operated on with total hip arthroplasty for primary arthrosis were treated postoperatively with (1) ibuprofen for 3 weeks, (2) ibuprofen for 1 week and placebo for the next 2 weeks or (3) placebo for 3 weeks. Radiographic occurrence of periarticular heterotopic ossification and complications of the treatment were recorded for the first year.

Both ibuprofen-treated groups showed significantly less HO than the placebo-treated group. There was no difference in HO between the patients treated for 8 or 21 days postoperatively. Both 8 and 21 days of treatment with ibuprofen following THA effectively prevents clinically significant degrees of HO. No serious short-term complications of the treatment were noted.

Departments of Orthopedics, [1]Central Hospital of Kristianstad, Kristianstad, Sweden, [2]Uppsala University Hospital, SE-751 85 Uppsala, Sweden. Tel +46 18 664469. Fax -509427. Correspondence: Dr. Olle Nilsson
Submitted 97-12-28. Accepted 98-02-26

Periarticular heterotopic ossification (HO) is one of the most frequent complications of hip replacement (DeLee et al. 1976, Jowsey et al. 1977, Kjaergaard-Andersen and Schmidt 1991, Ahrengardt and Lindgren 1993) with a variation in reported incidence ranging between 8% and 90% (Rosendahl et al. 1977, Knelles et al. 1997). Widespread HO is reported to occur in between 5% and 30% of the patients, while severe HO with clinical symptoms such as pain and restricted joint motion leading to functional impairment occurs in less than 10% (Charnley 1972, Ritter and Vaughan 1977, Knelles et al. 1997). Nonsteroidal anti-inflammatory drugs (NSAIDs) administered during the first postoperative weeks are potent inhibitors of HO after total hip arthroplasty (Ritter and Gioe 1982, Ritter and Sieber 1985, Schmidt et al. 1988, Knelles et al. 1997). The shortest effective treatment time has not yet been established. The primary purpose of this investigation was to establish, by a randomized double-blind study design, if 8 days of ibuprofen treatment is sufficient to achieve a prophylactic effect on clinically significant HO after total hip arthroplasty.

Patients and methods

Experimental design

We used a prospective, randomized, double-blind, placebo-controlled design, including 144 patients operated on with primary THA for arthrosis. The group size was determined by power analysis with alpha 0.05 and beta 0.8 and on the assumption that the prevalence of HO grades I–IV, according to Brooker et al. (1973), is 80% in men and 20% in women, as determined by a previous study (Sodemann et al. 1988). Half of the patients were operated on at Karolinska Hospital, Stockholm, and the other half at the Central Hospital of Kristianstad. The patients were randomized into 3 groups that were equal in respect of sex and institution where surgery was performed. Patients with rheumatoid disease or complications of fractures were not included. Patients with contraindications to NSAIDs, such as history of liver or renal failure, allergy to salicylates or to NSAIDs or gastric ulcer/gastritis were not included.

One of 3 treatments was used:

1. Ibuprofen from the day of surgery for 3 weeks;
2. Ibuprofen for 1 week and then placebo for 2 weeks;
3. Placebo for 3 weeks.

Table 1. Reason for discontinuation of postoperative medication with ibuprofen or placebo in patients operated on with total hip arthroplasty

Treatment group	G.I. discomfort	Patient's wish to discontinue	Postoperative confusion	Total
Ibuprofen 21 d	3	4	0	7
Ibuprofen 8 d	5	2	0	7
Placebo	4	3	1	8
Total	12	9	1	22

These patients were substituted so that each treatment group included 48 patients.

Treatment with ibuprofen (Ibumetin®, Alfred Benzon AB, Helsingborg, Sweden) 400 mg 3 times daily or placebo was started on the day of surgery. On the first 2 postoperative days, the medication was given as suppositories and the remaining time with tablets. The first suppository was given before surgery.

Functional grading according to Charnley, the Harris Hip Score and range of motion of the affected joint were recorded. Per- and postoperative complications, type of anesthesia, blood loss and blood transfusions were recorded during the hospital stay. The patients were followed clinically and with conventional hip radiographs at 3 and 12 months.

The investigation was approved by the Ethics Committee at Karolinska Hospital.

Methods

The patients were operated on through a posterolateral incision. A conventional cementing technique with irrigation and pressurization was used. After insertion of the prosthesis, the wound was thoroughly irrigated with saline. Suction drainage was used for 24 hours. The patients were allowed full weight bearing from the first postoperative day. At Karolinska Hospital, the Charnley prosthesis was used, at the Central Hospital in Kristianstad, the Lubinus or Exeter prosthesis. Prophylaxis against thrombo-embolism was given with low molecular weight heparin (Fragmin®, Pharmacia, Stockholm, Sweden, 5,000 IE s.c.) from the day of surgery and 500 mL of dextrane during surgery. A single dose of cloxacillin, 2 g iv, was given before surgery. The patients were not treated with other NSAIDs, salicylates, systemic steroids, bisphosphonates or other drugs with known effects on the skeleton.

The occurrence of HO was evaluated from anteroposterior (AP) radiographs, obtained postoperatively, at 3 and 12 months after surgery. HO was rated on a 5-grade scale, according to Brooker et al. (1973) as follows: grade 0, no ossification, grade I, 1 or 2 isolated areas of ossification, each less than 1 cm in diameter, grade II, more widespread isolated areas of ossification or osteophytes of the proximal femur or acetabular rim, covering less than half of the distance between the femur and the pelvis, grade III, ossification covering more than half of the distance between the femur and the pelvis, but not bridging the entire distance, and grade IV, ossification bridging the entire distance between the femur and the pelvis. HO was graded by comparison with the postoperative radiographs taken within 1 week of surgery.

Statistical analysis of the grade of HO was performed, using log-linear transformation with ordering of the grade of HO (0–IV), in relation to the factor's gender and treatment (Goodman 1984) and using Fisher's exact test.

Results

Substitutions

When the medication was discontinued before 3 weeks, the patient was substituted using a new set of suppositories and tablets (the substitution medication had the same number as the original medication with the addition of S). The medication was discontinued in 7 patients at Karolinska Hospital and in 15 patients at the Central Hospital in Kristianstad. The reasons for exclusion were nausea and gastrointestinal discomfort (12), the patients wished to discontinue the medication (9) or postoperative confusion (1) (Table 1). There were 7 drop-outs in each of the treatment groups and 8 in the placebo-treated group. The patients who discontinued the medication due to gastrointestinal symptoms were also equally distributed between the 3 groups.

No serious complications were recorded. The amounts of per- and postoperative bleeding were similar in all groups (Table 2). The mean total blood loss was 1.7 (0.5–3.2) L in the placebo group, 2.2 (0.6–5.3) L in the group treated with ibuprofen for 8 postoperative days, and 1.8 (0.7–3.6) L in the group treated with ibuprofen for 21 postoperative days.

Table 2. Per- and postoperative bleeding (mL) and blood transfusions in patients operated on with total hip arthroplasty

Treatment group	Peroperative	Postoperative	Total	Transfusion (units)
Ibuprofen 21 d	1.200	650	1.850	3.5
Ibuprofen 8 d	1.450	750	2.200	4.6
Placebo	1.100	600	1.700	3.5

Table 3. Heterotopic ossification 3 months after total hip arthroplasty

	Grade of HO						
	0	I	II	III	IV	N	Lost to FU
1. Ibuprofen 21 d	44	3	1	0	0	48	0
2. Ibuprofen 8 d	41	5	1	1	0	48	0
3. Placebo	29	8	6	3	1	47	1

Heterotopic ossification (HO) was graded on AP radiographs using a 5-grade scale, according to Brooker. 1 patient died of a myocardial infarction 3 months after joint replacement.

Table 4. Heterotopic ossification 12 months after total hip arthroplasty

	Grade of HO						
	0	I	II	III	IV	N	Lost to FU
1. Ibuprofen 21 d	38	7	1	0	0	46	2
2. Ibuprofen 8 d	38	6	2	2	0	48	0
3. Placebo	24	10	4	5	2	45	3

Heterotopic ossification (HO) was graded on AP radiographs using a 5-grade scale, according to Brooker. 5 patients were lost to follow-up; all had died 3 to 12 months after surgery from causes unrelated to the joint replacement.

Periarticular heterotopic ossification

Both ibuprofen-treated groups showed less HO than the placebo-treated group ($p = 0.001$ for the 21 days of treatment group, and $p = 0.008$ for the 8 days of treatment group). The 3-month values are given in Table 3. There was no ($p = 0.5$) difference in HO between the patients treated for 8 or 21 days postoperatively. In the group treated with ibuprofen for 21 days, there was no patient with grade III or IV HO, in the group treated for 8 days there was 1 patient with grade III, while there were 3 patients with grades III and 1 with grade IV HO in the placebo-treated group.

12 months after surgery, both ibuprofen-treated groups still showed less HO than the placebo-treated group ($p = 0.002$ for the 21-day treatment group, and $p = 0.005$ for the 8-day treatment group), but there was no difference between the 2 treatment groups ($p = 0.8$) (Table 4). In several patients, a maturation of the bone had occurred, the heterotopic bone becoming more clearly delineated. In some instances, the HO had increased in size and was classified 1 grade higher. HO was not graded lower or more than 1 grade higher in any patient.

The incidence of all grades of HO was higher in men than in women. All patients with grade IV HO were men (Table 5). 1 woman treated with ibuprofen had grade II, while none hade grades III or IV HO.

Discussion

Our aims were: (1) To determine the efficacy and the minimum treatment time necessary for prophylaxis with NSAIDs for periarticular heterotopic ossification (HO) after total hip arthroplasty (THA), (2) To determine short-term side-effects of the treatment.

The early inflammatory reaction following the surgical trauma of THA appears to be essential for the induction of HO and modification of this process by NSAIDs results in inhibition of heterotopic bone for-

Table 5. Heterotopic ossification 12 months after total hip arthroplasty

	Grade of HO						
	0	I	II	III	IV	N	Lost to FU
Men							
1. Ibuprofen 21 d	20	3	0	0	0	23	1
2. Ibuprofen 8 d	17	3	2	2	0	24	0
3. Placebo	7	7	2	3	2	21	3
Women							
1. Ibuprofen 21 d	18	4	1	0	0	23	1
2. Ibuprofen 8 d	21	3	0	0	0	24	0
3. Placebo	17	3	2	2	0	24	0

Heterotopic ossification (HO) was graded on AP radiographs using a 5-grade scale, according to Brooker.
4 men were lost to follow-up; all had died 3–12 months after surgery from causes unrelated to the joint replacement.
1 woman was lost to follow-up; she died between 3 and 12 months after surgery from causes unrelated to the joint replacement.

mation. The surgical trauma probably causes favorable conditions for bone induction by providing an appropriate set of local, paracrine, factors, such as cytokines and prostaglandins. Pluripotential mesenchymal stem cells are abundant in the soft tissues surrounding the hip joint and these cells may be transformed into osteogenic stem cells by release of an inducing agent caused by the surgical trauma. In addition, the efficacy of preoperative irradiation suggests that osteogenic precursor cells residing in the local tissues are important for new bone formation at the heterotopic site (Pellegrini and Gregoritch 1996). One or several of these key steps in the bone forming process may be affected by NSAIDs. However, NSAIDs probably act through their well known inhibitory effects on prostaglandin synthesis, thus altering the local environment by inhibiting the inflammatory response to surgery and/or the differentiation of mesenchymal cells into osteogenic tissue.

NSAIDs given during the first postoperative weeks are potent inhibitors of HO after total hip arthroplasty, and are also effective in preventing the recurrence of excised HO after previous hip surgery (Ritter and Gioe 1982, Elmstedt et al. 1985, Ritter and Sieber 1985, Kjaersgaard Andersen and Smith 1986, Schmidt et al. 1988, Sodemann et al. 1988, 1990, Pritchett 1995). A number of prospective and randomized studies have confirmed the efficacy of NSAIDs in preventing significant grades of HO in both cemented and uncemented THR and in patients at risk (Gebuhr et al. 1966, Wahlström et al. 1991, Knelles et al. 1997, Wurnig et al. 1997), although one study with a rather small number of patients (47) could not confirm this effect (Ahrengardt et al. 1994). Thus, NSAIDs appear to be effective preventing HO. However, the mechanism of action of the drug and the minimum treatment time required for full efficacy has not yet been determined.

In most blinded studies—as also in ours—the tolerance to medication was good and drop-outs were not more frequent in the treatment groups than in the placebo-treated groups. Some blinded studies have shown discontinuation of the medication in as many as 20% of the patients treated with indomethacin, mainly due to gastrointestinal discomfort or central nervous effects, but similar symptoms and a similar rate of discontinuation were noted in the placebo-treated groups (Elmstedt et al. 1985, Schmidt et al. 1988, Gebuhr et al. 1996). In our study, no serious side-effects that could be attributed to the treatment were noted, except a slightly increased blood loss. The study design included the start of medication before surgery. However, if the treatment is postponed until surgery is completed, the blood loss would probably not be affected at all, since there was no difference in postoperative blood loss in the 3 groups. In most studies, the medication was initiated on the day of surgery. In one study, it was found to be ineffective when delayed for more than 5 days (Sodemann et al. 1988). These findings are in agreement with an animal study, where antiinflammatory medication inhibited osteoinduction only when given in close conjunction with the inductive procedure (Törnkvist et al. 1985, Nilsson et al. 1986). Thus, it seems important to start the treatment with NSAIDs in the early postoperative period, in order to maintain the inhibitory effect on HO. The essential period for bone induction (and inhibition of bone induction) seems to be the first couple of days following the surgical trauma—which further emphasizes the importance of trauma in the initiation of the bone formation process.

The duration of treatment with NSAIDs has been investigated in several prospective studies and it appears that treatment for more than 3 weeks does not further reduce the incidence of HO (Gebuhr et al. 1996, Knelles et al. 1997). We found that 8 days of treatment is just as effective in preventing HO as a longer period of treatment. However, there was a tendency towards higher grades of HO in some patients in the group treated with ibuprofen for 8 days, indicating that this might be the lower limit for effective prophylaxis. Even shorter treatment times have been used with good results: prophylactic treatment with tenoxicam or ketorolac for the first 5 postoperative days resulted in reduced rates of HO (Pritchett 1995, Gebuhr et al. 1996).

In conclusion, postoperative prophylaxis with NSAIDs is highly effective in preventing clinically relevant degrees of HO after THA. The treatment should start early postoperatively and continue for at least 8 days. It appears to be cost-effective and the treatment of choice in patients at risk for HO.

Acknowledgement

This study was supported by grants from the Swedish Medical Research Council No. B95-17X-06577-12A.

References

Ahrengardt L, Lindgren U. Heterotopic bone. Defining the patient at risk. Clin Orthop 1993; 293: 153-9.

Ahrengardt L, Blomgren G, Törnkvist H. Short-term ibuprofen to prevent ossification after hip arthroplasty. No effects in a prospective randomized study of 47 arthrosis cases. Acta Orthop Scand 1994; 65: 139-41.

Brooker A F, Bowerman J W, Robinson RA, Riley L H , Jr. Ectopic ossification following total hip replacement: Incidence and a method of classification. J Bone Joint Surg (Am) 1973; 55: 1629-32.

Charnley J. The long-term results of low-friction arthroplasty of the hip performed as a primary intervention. J. Bone Joint Surg (Br) 1972; 54: 61-76.

DeLee J, Ferrari A, Charnley J. Ectopic bone formation following low friction arthroplasty of the hip. Clin Orthop 1976; 121: 53-9.

Elmstedt E, Lindholm T S, Nilsson O S, Törnkvist H. Effect of ibuprofen on heterotopic ossification after hip replacement. Acta Orthop Scand 1985; 56: 25-7

Gebuhr P, Sletgård J, Dalsgård J, Soelberg M, Keisu K, Hänninen A, Crawford M. Heterotopic ossification after hip arthroplasty. A randomized double-blind multicenter study of tenoxicam in 147 hips. Acta Orthop Scand 1996; 67: 29-32.

Goodman L A. The analysis of cross-classified data having ordered categories. Harvard University Press 1984.

Jowsey J, Coventry M B, Robins P R. Heterotopic ossification: Theoretical considerations, possible etiologic factors and a clinical review of total hip arthroplasty patients exhibiting this phenomenon. In: Proceedings of the Hip Society. C.V. Mosby 1977: 210-21.

Kjaersgaard-Anderssen P, Schmidt S A. Indomethacin for prevention of ectopic ossification after hip arthroplasty. Acta Orthop Scand 1986; 57: 12-4.

Kjaersgaard-Anderssen P, Schmidt S A. Total hip arthroplasty. Clin Orthop 1991; 263: 78-86.

Knelles D, Barthel T, Karrer A, Kraus U, Eulert J, Kölbl O. Prevention of heterotopic ossification after total hip replacement. J Bone Joint Surg (Br) 1997; 79: 596-602

Nilsson O S, Bauer H C F, Brosjö O, Törnkvist H. Influence of indomethacin on experimental bone formation in rats. Importance of length of treatment and of age. Clin Orthop 1986; 207: 239-45

Pellegrini V D, Gregoritch S J. Preoperative radiation for prevention of heterotopic ossification following total hip arthroplasty. J Bone Joint Surg (Am) 1996; 78: 870-81.

Pritchett J W. Ketorolac prophylaxis against heterotopic ossification after hip replacement. Clin Orthop 1995; 314: 162-5.

Ritter M A, Gioe T J. The effect of indomethacin on para-articular ectopic ossification following total hip arthroplasty. Clin Orthop 1982; 167: 113-7.

Ritter M A, Sieber J N. Prophylactic indomethacin for the prevention of of heterotopic bone formation following total hip arthroplasty. Clin Orthop 1985; 196: 217-25.

Ritter M A, Vaughan R B. Ectopic ossification after total hip arthroplasty. Predisposing factors, frequency and effects on results. J Bone Joint Surg (Am) 1977; 59: 345-51.

Rosendahl S, Krogh Christoffersen J, Norgaard M. Para-articular ossification following hip replacement. Acta Orthop Scand 1977; 48: 400-4.

Schmidt S A, Kjaersgaard-Andersen P, Pedersen N W, Kristensen S S, Pedersen P, Nielsen J B. The use of indomethacin to prevent the formation of heterotopic bone after total hip replacement. J Bone Joint Surg (Am) 1988; 70: 834-8.

Sodemann B, Persson P-E, Nilsson O S. Prevention of periarticular heterotopic ossification following total hip arthroplasty. Clinical experience with indomethacin and Ibuprofen. Arch Orthop Trauma Surg 1988; 107: 329-33.

Sodemann B, Persson P-E, Nilsson O S. Nonsteroid anti-inflammatory drugs prevent the recurrence of heterotopic bone after excision. Arch Orthop Trauma Surg 1990; 109: 53-6.

Törnkvist H, Bauer H C F, Nilsson O S. Influence of indomethacin on experimental bone metabolism in rats. Clin Orthop 1985; 193:.264-70.

Wahlström O, Risto O, Djerf K, Hammerby S. Heterotopic bone formation prevented by diclofenac. Prospective study of 100 hip arthroplasties. Acta Orthop Scand 1991; 62: 419-21.

Wurnig C, Auersperg V, Boehler N, Steindl M, Kiss H, Zweymuller K, Kotz R. Short-term prophylaxis against heterotopic bone after cementless hip replacement. Clin Orthop 1997; 334: 175-83.