Prophylaxis of heterotopic ossification after total hip arthroplasty

A prospective randomized study comparing indomethacin and meloxicam

Thomas Barthel, Bernd Baumann, Ulrich Nöth and Jochen Eulert

Department of Orthopaedic Surgery, König-Ludwig-Haus, Julius Maximilians University, DE-97074 Würzburg, Germany.
t-barthel.klh@mail.uni-wuerzburg.de
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ABSTRACT – **We performed a randomized, prospective study on the prophylaxis of heterotopic ossification (HO) after total hip arthroplasty (THR), comparing indomethacin and the selective COX-2 inhibitor meloxicam. From the day after surgery, 272 patients were treated with 7.5 mg meloxicam, 15 mg meloxicam, or 2 × 50 mg indomethacin a day, for 14 days. After 6 months, radiographs of patients treated with 7.5 mg meloxicam showed that HO had occurred in one third. This treatment was therefore stopped after 26 patients have been assigned to this group. According to the intention-to-treat principle, patients given 15 mg meloxicam developed HO in 25% (20% Brooker grade I, 4% grade II and 1% grade III) and those given indomethacin in 10% (7% Brooker grade I, 1% grade II and 2% grade III), a statistically significant difference.**

Heterotopic ossification (HO) is common after total hip replacement (THR). Nonsteroidal anti-inflammatory drugs (NSAIDs), diphosphonates, calcitonin, and irradiation have been used to prevent HO formation (Thomas and Amstutz 1987, Nilsson 1992, Kolbl et al. 1997, Sell et al. 1998, Neal et al. 2000, Gunal et al. 2001). Many authors recommend indomethacin as a general prophylaxis immediately after surgery (Tozun et al. 1992, Knelles et al. 1997, Sell et al. 1998, Burd et al. 2001). Because of its common gastrointestinal side effects, the use of indomethacin is limited. Mucoprotection can reduce the side effects, but in some cases, treatment has to be stopped because of the risk of gastrointestinal bleeding. NSAIDs act via inhibition of the enzyme cyclooxygenase (COX), which is the cause of the efficacy and toxicity of NSAIDs. The discovery of two COX isoforms, the constitutive isoform COX-1 and the inducible isoform COX-2, has led to the hypothesis that selective inhibition of COX-2 can minimize the gastrointestinal side effects, without compromising the efficacy. In this prospective randomized study, we compared the efficacy of the COX-2 inhibitor meloxicam (7.5 and 15 mg a day) and indomethacin (2 × 50 mg a day).

Patients and methods

Patient selection

From 1996 to 1999, 487 patients scheduled for THR were consecutively assessed for eligibility for this study. Patients with a history of malignant diseases, gastritis, gastric or duodenal ulcer, allergic reaction to NSAIDs, and those who had developed HO after previous surgery were not included in the study. Of the 487 patients, 272 met all selection criteria. The study protocol was approved by the Julius Maximilians University Institutional Review Board. All patients provided informed consent.

Experimental groups

Patients were randomly assigned to one of the following three groups using a random-number table. In the first group, patients were treated with 7.5 mg meloxicam a day. Patients assigned to the second group received 15 mg meloxicam a day. Those in the third group were treated with 2 × 50 mg indomethacin a day. In all groups, treatment

Table 1. Characteristics of patients assigned to the three groups

	Meloxicam 7.5 mg	Meloxicam 15 mg	Indomethacin 2 x 50 mg	Total
Patients	26	123	123	272
Sex				
Male	15	43	44	102
Female	11	80	79	170
Mean age	65	63	63	63
(SD)	(8)	(12)	(12)	(11)
Stem fixation				
Cemented	16	79	83	178
Uncemented	10	44	40	94
Diagnosis				
Osteoarthrosis	19	94	86	199
AVN	3	16	19	38
Dysplasia	2	7	12	21
Fracture	1	2	1	4
Other	1	4	5	10

AVN avascular necrosis

was started on the day after surgery and given for a total of 14 days. They also received mucoprotection with misoprostol 3 × 200 mg a day. Postoperative pain was treated with tramadol, paracetamol, or piritramid, which have no anti-inflammatory effects. The patients in the three groups were analyzed for sex, age, type of stem fixation, and diagnosis and showed similar baseline characteristics (Table 1). Blinded evaluation of radiographs of the first 24 patients treated with 7.5 mg meloxicam showed HO in 8/24 after 6 months. We therefore stopped assigning patients to this group. In total, 26 patients had 7.5 mg meloxicam, 123 15 mg meloxicam, and 123 2 × 50 mg indomethacin. 20 patients did not receive all the doses, but had radiographic data and qualified for the intention-to-treat analysis. 22 patients were unavailable for the follow-up examination and were excluded from the analysis. Of 272 patients assigned to the three groups, 250 were evaluated (Table 2).

Table 2. Patients evaluated in the intention-to-treat analysis

	Meloxicam 7.5 mg	Meloxicam 15 mg	Indomethacin 2 x 50 mg	Total
Patients randomized	26	123	123	272
Unavailable for follow-up				
Death	0	2	2	4
Missed assessment	2	6	10	18
Patient qualified for intention-to-treat analysis	24	115	111	250
Patients who did not receive all doses				
Gastric disorder	0	3	5	8
Non-compliance	1	1	1	3
Infection/revision surgery	0	0	2	2
Headache	0	1	2	3
Allergic reaction	0	1	2	3
Fever	0	0	1	1

Radiographic analysis

The Brooker et al. (1973) classification was used to evaluate HO. Anteroposterior and Lauenstein radiographs were taken preoperatively, immediately after surgery, and postoperatively after 3 and 12 months. Two blinded investigators assessed the radiographics for HO.

Statistics

The main analysis was done according to the intention-to-treat principle. The chi-square test was used to compare the total percentage of HO in the 3 groups. Values of $p < 0.05$ were considered significant.

Results

Of 250 patients evaluated, 48 developed HO depending on the type of treatment. According to the intention-to-treat principle, 8/24 patients treated with 7.5 mg meloxicam developed HO, 25% of those treated with 15 mg meloxicam and 10% of those with indomethacin. Severe HO (Brooker grades III and IV) occurred in 3 cases (Table 3), 2 of these (1 treated with 15 mg meloxicam and 1 with indomethacin) because they had stopped taking the medication. Statistical analysis on an intention-to-treat basis showed that indomethacin 2 × 50 mg reduces HO formation more than 15 mg meloxicam ($p = 0.03$). Statistical analysis of patients treated with 7.5 mg meloxicam was not done since we had too few cases. 2% of patients treated with meloxicam developed gastrointestinal side effects versus 4% of patients treated with indomethacin (Table 2).

Table 3. Development of HO in patients treated with meloxicam or indomethacin, number of cases

		Brooker classification (grade)					
	Total	0	I	II	III	IV	I–IV
Meloxicam 7.5 mg	24	16	7	1	0	0	8
Meloxicam 15 mg	115	86	23	5	1	0	29
Indomethacin 2 x 50 mg	111	100	8	1	2	0	11
Total	250	202	38	7	3	0	48

Discussion

No study has compared the use of preferential COX-2 inhibitors and indomethacin for the prophylaxis of HO after THA. In the present one, the incidence of HO in patients treated with indomethacin was 10%. This resembles the results reported by us and others (Sodemann et al. 1988, Kjaersgaard-Anderson et al. 1993, Knelles et al. 1997, Nilsson 1998). In contrast, 25% of patients treated with 15 mg meloxicam developed HO. The formation of HO in indomethacin treated patients was lower than in those treated with 15 mg meloxicam, suggesting that indomethacin is more effective than meloxicam in prophylaxis of HO.

Indomethacin is a non-selective NSAID, while meloxicam is a preferential COX-2 inhibitor with a lower risk gastrointestinal side effects, which are commonly encountered with indomethacin (Hawkey et al. 1998, Chan et al. 1999). The inhibition of COX-1 and COX-2 by meloxicam is known to be dose-dependent. Doses of 7.5 mg meloxicam primarily inhibit COX-2, while in higher doses, COX-1 inhibition increase (Pairet et al. 1998). The data obtained from these in vitro investigations, and the high incidence found in patients treated with meloxicam in this study suggest that both COX isoforms and not only COX-2 are important in the mechanism leading to formation of HO after THR. This is supported by the fact that indomethacin is known to be a potent COX-1 and COX-2 inhibitor (Chan et al. 1999). Gastrointestinal side effects were rare probably because of misoprostol mucoprotection. Without mucoprotection, the incidence of these side effects with indomethacin rises to 22% (Wurnig et al. 1992). In our study, only 2% of the patients treated with meloxicam and 4% treated with indomethacin developed such side effects.

The preferential COX-2 inhibitor meloxicam has fewer gastrointestinal side effects, but is not as effective as indomethacin for the prophylaxis of HO after THR. We therefore recommend indomethacin as a general prophylaxis in a dose of 2 × 50 mg for 2 weeks after surgery, together with a mucoprotective drug.

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Brooker A F, Bowerman J W, Robinson R A, 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.

Burd T A, Lowry K J, Anglen J O. Indomethacin compared with localized irradiation for the prevention of heterotopic ossification following surgical treatment of acetabular fractures. J Bone Joint Surg (Am) 2001; 83: 1783-8.

Chan C C, Boyce S, Brideau C, et al. Rofecoxib [Vioxx, MK-0966; 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone)]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. J Pharmacol Exp Ther 1999; 290: 551-60.

Gunal I, Hazer B, Seber S, et al. Prevention of heterotopic ossification after total hip replacement: a prospective comparison of indomethacin and salmon calcitonin in 60 patients. Acta Orthop Scand 2001; 72: 467-9.

Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA study group. Meloxicam large-scale international study: safety assessment. Br J Rheumatol 1998; 37: 937-45.

Kjaersgaard-Andersen P, Nafei A, Teichert, et al. Indomethacin for prevention of heterotopic ossification. A randomised controlled study in 41 hip arthroplasties. Acta Orthop Scand 1993; 64: 639-42

Knelles D, Barthel T, Karrer A, et al. Prevention of heterotopic ossification after total hip replacement. A prospective, randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. J Bone Joint Surg (Br) 1997; 79: 596-602.

Kolbl O, Knelles D, Barthel T, et al. Randomised trial comparing early postoperative irradiation vs. the use of non-steroidal anti-inflammatory drugs for prevention of heterotopic ossification following prosthetic total hip replacement. Int J Radiat Oncol Biol Phys 1997; 39: 961-6.

Neal B C, Rodgers A, Clark T, et al. A systematic survey of 13 randomised trials of non-steroidal anti-inflammatory drugs for the prevention of heterotopic bone formation after major hip surgery. Acta Orthop Scand 2000; 71: 122-8.

Nilsson O S. Non-steroidal anti-inflammatory drugs for prevention of heterotopic ossification after total hip arthroplasty. Semin Arthroplasty 1992; 3: 172-7.

Nilsson O S. Heterotopic ossification. Acta Orthop Scand 1998; 69: 103-6.

Pairet M, van Ryn J, Schierok H, et al. Differential inhibition of cyclooxygenases-1 and -2 by meloxicam and its 4'-isomer. Inflamm Res 1998; 47: 270-6.

Sell S, Willms R, Jany R, et al. The suppression of heterotopic ossifications: radiation versus NSAID therapy - a prospective study. J Arthroplasty 1998; 13: 854-9.

Sodemann B, Persson P E, Nilsson O S. Prevention of heterotopic ossification by non-steroid anti-inflammatory drugs after total hip arthroplasty. Clin Orthop 1988; 237: 158-63.

Thomas B J, Amstutz H C. Prevention of heterotopic bone formation: clinical experience with diphosphonates. Hip 1987: 59-69.

Tozun R, Pinar H, Yesiller E, Hamzaoglu A. Indomethacin for prevention of heterotopic ossification after total hip arthroplasty. J Arthroplasty 1992; 7: 57-61.

Wurnig C, Eyb R, Auersperg V. Indomethacin for prevention of ectopic ossification in cementless hip arthroplasties. A prospective 1-year study of 100 cases. Acta Orthop Scand 1992; 63: 628-30.