No difference between two doses of diclofenac in prophylaxis of heterotopic ossifications after total hip arthroplasty

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Background In a monocentric, randomized, placebo-controlled double-blind study, we investigated the efficacy of two doses of diclofenac-cholestyramine for the prevention of heterotopic ossification (HO).

Patients The study comprised 245 patients undergoing total hip arthroplasty (THA).

Results With 150 mg cholestyramine-bound diclofenac (2 × 1 capsule Voltaren® resinate) daily during a postoperative period of 14 days, 19% of patients showed slight HO (Brooker grade 1), and no patient had more severe ossifications (grades 2–4). In the group receiving 75 mg daily (1 × 1 capsule), 17% of patients showed grade 1 HO and 4% grade 2 HO. No patient had grades 3–4 HO. No differences in clinical results were seen between the two groups 6 months after THA.

Interpretation Since the rate of adverse gastrointestinal events was lower (23% versus 38%, $p = 0.02$) in the group receiving the lower dose, we recommend it.

The rate of postoperative heterotopic ossification (HO) in patients not receiving prophylaxis after total hip arthroplasty (THA) has been reported to be between 15% (DeLee et al. 1976) and 88% (Fingeroth and Ahmed 1995). Severe lesions can lead to pain, restricted movement or even complete stiffening of the joint (Hanslik and Radloff 1974, Holz et al. 1977, Ritter and Vaughan 1977, Ahrengart and Lindgren 1989).

The main problem in treatment with nonsteroidal antiinflammatory drugs is the occurrence of gastrointestinal side effects, which may necessitate the withdrawal of medication in some patients. A major focus of our study, therefore, was to determine whether one can reduce the daily dose of diclofenac to lower the incidence of side effects, without affecting its efficacy as regards prophylaxis against heterotopic ossification.

Patients and methods

Patients

245 patients were recruited who underwent either primary or revision total hip arthroplasty between January 1998 and March 1999 in the Orthopedic University Clinic of Tübingen (Table 1). Exclusion criteria were: known allergies and incompatibilities with diclofenac, unhealed gastric ulcers, known gastrointestinal sensitivity to NSAIDs, and unwillingness of the patient or the surgeon to participate. In all patients, we used Bauer's lateral transgluteal approach.

Study procedure

The study medication was cholestyramine-bound diclofenac (Voltaren® resinate capsules, 1 capsule containing 140 mg diclofenac-cholestyramine, corresponding to 75 mg diclofenac sodium). Two groups of patients were compared, who were randomized to receive 1 capsule of active substance in the morning and 1 placebo capsule in the evening or 1 capsule of active substance each in the morning and evening from the 1st to the 14th day after the operation. For this purpose, the study medica-

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tion was double-blind, packed in numbered cases which were filled according to a random generator. All patients also routinely received the proton pump inhibitor lansoprazole 15 mg once every morning throughout the period of study medication to prevent postoperative peptic ulcers.

The double-blind study was approved by the Ethics Committee of the University of Tübingen and done in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. During the 14-day postoperative treatment, the patients were given additional NSAIDs. Paracetamol or opioid analgesics (e.g., tramadol) were used as analgesic rescue medication. All adverse events (AEs) and adverse drug reactions (ADRs = AEs with a possible causal association with the study medication) were recorded and rated for their severity and their causal association with the study medication on the basis of a standardized trial protocol, as recomended by the GCP. In addition, all comedication was recorded. On the last day of receiving the study medication, the patients were asked to rate its tolerability—i.e., very good, good, moderate and poor.

6 months after the operation, the patients underwent a radiographic follow-up for the development of heterotopic ossifications. The ossifications detected were rated using Brooker et al.'s (1973) classification. This was done blinded.

The patients were examined immediately before the operation and at the 6-month follow-up. Hip-joint mobility was determined as a measure of the overall function (OF) of individual mobility criteria, as defined by Reis et al. (1992): OF = A+C+D+F+G+I-B-E-H, where A/B/C correspond to the angles of flexion/neutral position/extension, D/E/F the angles of adduction/neutral position/abduction, and G/H/I the angles of medial rotation/neutral position/lateral rotation in degrees, according to the neutral-zero method. Pain and walking ability were rated on the Merle d'Aubigné scale (score 0 = persistent severe pain, walking not possible; score 12 = no pain, unrestricted walking ability).

Statistics

The results regarding the frequency of AEs, ADRs and the withdrawal of treatment owing to intolerability were tested for significance, using the chi-squared test. The differences in clinical scores, frequency and severity of HO, and in the rating of tolerability were tested for significance, using Mann-Whitney's rank sum test. Differences in overall function (OF) of the hip receiving the prosthesis were tested, using the Student's t-test. Differences were considered not to be significant if the probability of error was $p > 0.05$.

Table 1. Patients in the two treatment groups: demographic data, primary diagnoses, type of implanted prosthesis

	Total	Prophylaxis with diclofenac	
		75 mg/day	150 mg/day
Number of patients	245	121	124
Women/men	135/110	67/54	68/56
Age (yr) [a]	63 (11)	63 (11)	63 (11)
Height (cm) [a]	168 (8.5)	168 (9.1)	168 (7.9)
Weight (kg) [a]	78 (13)	76 (14)	75 (12)
Coxarthrosis			
idiopathic	167	87	80
dysplastic	32	14	18
Rheumatoid arthritis	16	8	8
Necrosis of head of femur	13	5	8
Loosening of prosthesis	11	4	7
Others	6	3	3
Press-fit cup	233	116	117
Cemented cup	6	2	4
No cup	6	3	3
Cementless shaft	151	76	75
Cemented shaft	90	44	46
No shaft	4	1	3

[a] Mean value (SD)

Results

The two groups of patients were similar as regards sex distribution, age, height, weight and distribution of the primary diagnoses (Table 1). At follow-up, 238 patients were evaluated, which corresponded to a follow-up rate of 97%. Among these patients, 21% of those in the group which received 75 mg diclofenac a day had mild HO (17% Brooker grade 1 and 3.7% Brooker grade 2). The patients who received 150 mg diclofenac a day had only slightly better results, with an incidence of 19% for HO (all mild cases of ossification corresponding to Brooker grade 1), but the difference

Table 2. Patients reporting adverse events (AEs) and adverse drug reactions (ADRs) probably related to the study medication are shown in the two treatment groups (including patients who withdrew from prophylaxis prematurely). Values are number of patients (percentage)

	Total	Prophylaxis with diclofenac 75 mg/day	150 mg/day	P-value
Number of patients	245	121	124	
Patients without AEs	144 (59)	78 (65)	66 (53)	
Patients with AEs and relationship to the study drug				
not related	1 (0.4)	0 (0.0)	1 (0.8)	
unlikely related	30 (12)	14 (12)	16 (13)	
possibly related	49 (20)	22 (18)	27 (22)	
probably related	19 (7.8)	6 (5.0)	13 (11)	
very probably related	2 (0.8)	1 (0.8)	1 (0.8)	0.09 [c]
Patients with ADRs [a]	21 (8.6)	7 (5.8)	14 (11)	[d]
Patients with gastrointestinal ADRs [b]	16 (6.5)	5 (4.1)	11 (8.9)	[d]
Nausea, vomiting	13	4	9	[d]
Flatulence	1	0	1	[d]
Abdominal pain	4	1	3	[d]
Diarrhea	3	2	1	[d]
Hot flashes	2	0	2	[d]
Edema (dorsal aspect of hands)	1	0	1	[d]
Rash	1	1	0	[d]
Agitation	1	1	0	[d]
Patients with gastrointestinal AEs of				
mild intensity	29 (12)	10 (8.3)	19 (15)	
moderate intensity	38 (16)	17 (14)	21 (17)	
severe intensity	8 (3.3)	1 (0.8)	7 (5.6)	0.04 [c]

[a] Patients in whom one or more ADRs occurred
[b] Patients in whom nausea/vomiting, flatulence, abdominal pain and/or diarrhea occurred
[c] Mann-Whitney
[d] p > 0.2 in all comparisons, Mann-Whitney

was not statistically significant (p = 0.8). Severe HO corresponding to Brooker grades 3 and 4 was not found in either group.

In 41% of patients, AEs occurred which were not related to the operation. In 29% of patients, the AEs were classified as “at least possibly related to the study medication”. The percentage of patients with AEs and the causal association of these events with the study medication are shown separately in the two treatment groups in the first part of Table 2. Significantly fewer gastrointestinal AEs were found in the group treated with 75 mg diclofenac daily (23% versus 38%, p = 0.02). In the second part of Table 2, only the adverse drug reactions (ADRs) for which there was a probable or highly probable causal association with the study medication are shown to filter out the frequent symptoms after major surgery. The incidence of treatment withdrawal in the group treated with 75 mg diclofenac was 7.4%, and in the group with the higher dose it was 11% (p = 0.5). As regards the differences in severity of the gastrointestinal AEs (third part of Table 2), better tolerability (p = 0.05) was found in the group receiving the lower daily dose. 93% of the patients treated with 75 mg daily described the tolerability as good or very good as compared to 88% of patients receiving the higher dose (p = 0.2).

In the evaluation of joint mobility as well as pain and walking ability on the Merle d’Aubigné scale, we found no significant differences between the clinical results (p > 0.2) in the two groups before (75 mg vs. 150 mg: 120° (SD 41°) vs. 124° (39°), 5.54 (2.12) vs. 5.42 (2.2) or 6 months after the operation (193° (38°) vs. 189° (34°), 11 (1.1) vs. 11 (1.2)).

Discussion

Clinically relevant heterotopic ossifications after

implantation of a total hip endoprosthesis occur in more than 20% of patients who do not receive prophylaxis (Wahlström et al. 1991, Fingeroth and Ahmed 1995). Good reductions of HO have been achieved in some studies using NSAIDs. Knelles et al. (1997) reported relatively severe HO (Brooker grades 3–4) in only 1% of patients receiving 50 mg indomethacin daily for 2 weeks. Jockheck et al. (1998) found an incidence of 1.4% severe HO (Brooker grades 3–4) with a regimen of 3 × 50 mg diclofenac sodium for 3 weeks. Good prophylaxis must therefore achieve results comparable with these figures. Prophylactic administration of 3 × 50 mg diclofenac sodium daily for 1 week seems to be less effective as regards Brooker grade 3-4 HO (Sell and Schleh 1999), as does 3 × 500 mg ibuprofen for 10 days (Ahrengart et al. 1994). These treatments have been associated with an incidence of grades 3–4 HO of 3–4%.

Even if comparisons between different studies are difficult, we obtained good results as compared with other studies (Jockheck et al. 1998, Sell and Schleh 1999). Comparable efficacy despite the lower frequency of taking the drug may be explained by the combination of diclofenac with the ion-exchange resin cholestyramine, which produces a longer-lasting absorption and consequently a prolonged effect (Brune 1995). It can also be assumed that effective concentrations of active substance are present in the target tissue for a longer period (Fowler et al. 1986, Todd and Sorkin 1988).

Yeomans et al. (1998) showed that, with the prophylactic administration of proton pump inhibitors, the frequency of gastrointestinal (GI) side effects is markedly reduced during a 1- to 4-week regimen of NSAID treatment. We also gave prophylactic treatment with a proton pump inhibitor, which may explain the relatively small number of patients in our study who withdrew from treatment because of GI side effects as compared with other studies involving diclofenac. However, the administration of cholestyramine-bound diclofenac is also tolerated better than other formulations of diclofenac. In the SPALA study (The SPALA Project Team 1992), 10% of patients reported gastrointestinal disorders (n = 3,839 patients) while taking diclofenac-cholestyramine versus 14% with diclofenac sodium (n = 14,477) (Müller-Faßbender 1998).

Our findings show that, in patients receiving THA, a regimen of 75 mg diclofenac once daily for 14 days (1 capsule of diclofenac-cholestyramine a day) provides good prophylactic efficacy against HO, with a lower incidence of side effects than a regimen of twice this daily dose. The clinical result after THA implantation also showed no significant difference from that observed in the treatment group receiving a daily dose of 150 mg diclofenac. Prophylaxis with 75 mg diclofenac a day (1 capsule diclofenac-cholestyramine a day) is therefore recommended.

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