

## ORIGINAL ARTICLE

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## Prevention of periarticular heterotopic ossification after endoprosthetic hip joint replacement by means of Diclofenac

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**Abstract** This prospective study involves 644 patients who received ossification prophylaxis by means of the drug diclofenac after implantation (87.5%) or revision (12.5%) of a total hip endoprosthesis between August 1992 and June 1994. One hundred patients (15.5%) stopped the treatment because of side-effects of the drug, and medication was stopped when gastrointestinal troubles occurred. The follow-up examination after 6 months revealed ossification of HO degree 1 according to Brooker in 13.8% of cases, of degree 2 in 4.8%, and of degree 3 in 1.4% of cases. Severe HO of degree 4 was not observed at all, and 80% of the patients exhibited no ossification what ever. Thus, in comparison to our own studies and to the literature, diclofenac must be regarded as an extremely effective drug for the prevention of ossification.

### Introduction

Next to loosening of the prosthesis, heterotopic ossification (HO) represents one of the main problems of hip joint replacement. The extent and the incidence of this reaction are stated very differently in the literature, with rates of ossification between 5% and 90% [10, 26]. As ossification of a greater degree can lead to impairment of function in the operated extremity, prophylactic measures must be considered. Postoperative radiation has up to now proved to be just as efficient as prophylaxis with non-steroidal, anti-inflammatory drugs [3, 15, 16, 27]. Indomethacin is most frequently used in the latter case.

After a prospective, randomized, double-blind study carried out at the Orthopaedic University Clinic in Tübingen had shown that postoperative oral prophylaxis with diclofenac was significantly effective, this effectivity was

checked in a common prospective study involving as large a number of patients as possible.

### Patients and methods

In the period of time between May 1992 and June 1994, all patients undergoing total hip endoprosthesis or a revision of the same were given a daily dose of  $3 \times 50$  mg diclofenac orally from the 1st postoperative day for 3 weeks. Patients with known contra-indications for medication with non-steroid anti-inflammatory drugs were excluded from the study, as were patients who were undergoing permanent medication with anti-phlogistic drugs because of other illnesses. The clinical and radiological follow-up examinations were carried out after 3 months and again at least 6 months after the operation. The patient was not only examined, but pre- and post-operative radiographs in a standardized technique were also compared in order to assess ossification. This was carried out according to the classification of Brooker et al. [4] and is shown in Table 1.

### Results

Originally, 644 patients were included in the study. One hundred patients (15.5%) were excluded because the drug did not suit them. Medication was stopped when complaints arose. Gastrointestinal difficulties constituted the main reason. Serious complications such as ulcers or gastrointestinal haemorrhages were not observed. After the medication was stopped, no patient had any problems due to diclofenac, and no further diagnostic procedures were necessary.

Thus, 544 patients remained in the study. Women were in the majority,  $n = 335$  (61.6%), the number of male pa-

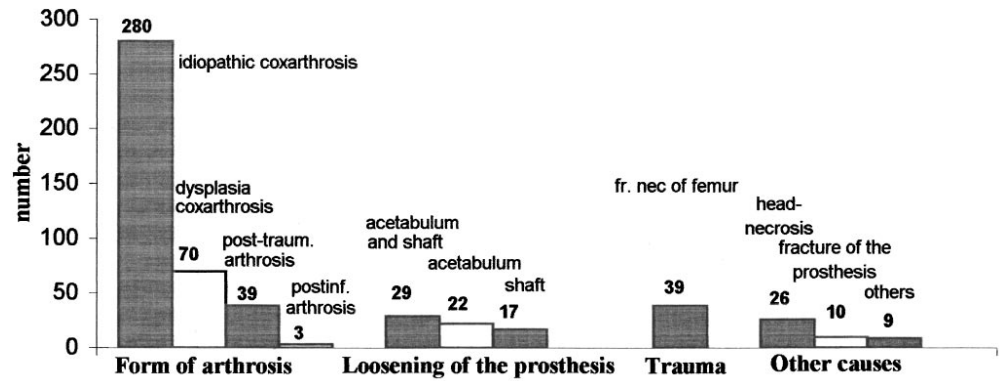
**Table 1** Classification of the degree of ossification according to Brooker et al. [4]

- 1 Little, diffuse ossification
- 2 Stronger ossification with origin in the pelvis or femur, distance to other side > 1 cm
- 3 Distance to other side < 1 cm
- 4 Connective ossification

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**Fig. 1** Distribution of indications for operation



**Table 2** Change in the degree of ossification (6 months post-operatively and later)

	<i>n</i>
From degree 0 to degree 1	13
From degree 1 to degree 2	6
From degree 2 to degree 3	1

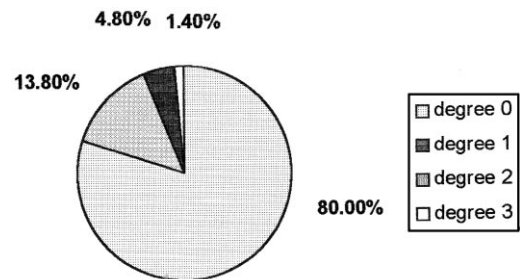
tients being  $n = 209$  (38.4%). Twenty-two patients were between 21 and 40 years old, 149 between 41 and 60, 319 between 62 and 80, 54 patients were older than 80 years. Thus, 74% was older than 60 years, while 26% belonged to the younger group. Idiopathic coxarthrosis was the most frequent indication for a primary implantation ( $n = 280$ , 51.5%). A revision of the prosthesis was undertaken in 68 patients (12.5%). The operation was performed on 39 patients because of a fracture of the neck of the femur. The group 'others' included 7 patients with chronic polyarthritis and 2 with Morbus Bechterew (Fig. 1).

As far as the operation technique was concerned, a cementless acetabulum and shaft implant predominated and was given to 370 patients (68%). Some 87 patients received a cemented shaft (16%). The technique of a completely cemented endoprosthesis was rarer, as were combinations of a cemented acetabulum and a cementless shaft (16%).

A follow-up examination of all 544 patients was available. After 6 months and later, there was a further examination of 497 patients (91.4%). In 86% of the patients, the last examination was carried out after more than 12 months.

In the follow-up examination after 3 months, radiographs showed no ossification in 83.6% of cases. Slight grades of HO degree 1 and 2 were observed in 14.5% of cases. The rate of clinically significant HO (degree 3) was 1.1%. Ossification of the 4th degree was not observed at all. Further examinations after 6 months and more showed changes which were very slight and of no clinical importance. Ossification increased by one degree in 20 patients (3.7%). The single changes can be seen in Table 2.

Thus, at final follow-up 397 patients (80%) exhibited no HO, 93 patients had either degree 1 or 2 (18.6%). Ossification of degree 3 was observed in 7 patients (1.4%), all belonging to the revision group. Degree 4 was not observed at all. Figure 2 summarizes the postoperative rates of ossification in the follow-up examination after more than 6 months. HO of degree 2 and 3 was seen three times more



**Fig. 2** Rate of ossification after diclofenac prophylaxis

**Table 3** Ossification in high-risk patients

	Pre-operative contralateral	Postoperative ipsilateral
Degree 1	4	3
Degree 2	13	0
Degree 3	6	0
Degree 4	0	0

often after revision arthroplasty than after a primary operation. Patients with posttraumatic arthrosis or with a fractured neck of femur did not evidence a higher risk for post-operative ossification. Among the patients excluded because of side-effects from the drug, the incidence of HO of degree 3 was four times higher, and of HO of degrees 1 and 2 two times higher, than in the group taking medication.

A total of 32 patients exhibited ossification on account of the previous implantation of a prosthesis on the contralateral side. These high-risk patients were again at risk for a renewed occurrence of ossification. Nineteen patients with contralateral ossification of degrees 2 and 3 exhibited no heterotopic ossification ipsilaterally after prophylaxis by means of diclofenac. The single results of these patients are shown in Table 3.

No correlation was observed between the occurrence of HO and the kind of implant (cemented/cementless).

## Discussion

The cause and the mechanisms of pathogenesis for the occurrence of heterotopic ossification are still unclear. The

most important causal factor is considered to be the operation trauma itself. The operation approach, the implantation technique and the operation time all influence the occurrence of HO [1, 26, 29]. Furthermore, it is assumed that pluripotent mesenchymal cells are transformed into osteoblast progenitor cells, a process which mostly takes place in tissue with a high concentration of fibroblasts [11, 20]. It is also thought that tiny particles of bone which are set free during the operation, during osteotomy of the femur and by filing, for example, form a nucleus of crystallisation for HO [14].

Certain risk factors for the extent of HO have been proposed by different authors: male sex, repeated operation on the hip joint, necrosis of the femoral head, ankylosing spondylitis, fracture of the femoral neck and coxarthrosis with massive osteophytes [1, 2, 7, 8, 19, 21].

Slight HO of degrees 1 and 2 according to Brooker et al. [4] is of no clinical importance, whilst HO of degrees 3 and 4 results in impairment of the function of the operated hip joint. Therefore, the aim of all prophylactic measures should be the prevention of HO of a higher degree. The prophylactic effectivity of postoperative radiation had already been shown in 1981, and currently a reduction in the frequency of radiation is being tested [3, 6, 15, 24, 33]. Beside the general risk of radiation, the high degree of organisation is a disadvantage, because the patients must be transported immediately after the operation for radiation treatment. In addition, direct negative effects such as a disturbance of the wound healing process have been described [17]. In the case of cementless implantation of a prosthesis, a negative influence on the so-called bone ingrowth into the surface of the implant is also being discussed as a possible problem [20, 31, 32].

Non-steroidal anti-inflammatory drugs show the greatest effectivity in the prevention of HO [7, 16, 27]. The effect would seem to be dependent on the inhibition of prostaglandin synthesis, but the exact mechanisms are not yet known. Up until now indomethacin has been predominantly used, but acetylsalicylic acid also exhibited a significant prophylactic effect [18].

A prospective, randomized study by Reis et al. [25] proved the significant effectivity of diclofenac. The present study was undertaken because of the relatively small number of patients in that study.

In a prospective study undertaken by the Berufsgenossenschaftlichen Unfallklinik in Tübingen, a follow-up examination after 5 years showed that of 250 patients who had undergone a cementless prosthesis implantation without prophylaxis, 49.8% had HO rates of the 1st and 2nd degrees. Clinically relevant severe ossification of the 3rd degree was found in 3.9% of the cases, HO of the 4th degree in 5 patients (2%). This comparative study of patients who had been given 3 × 50 mg of diclofenac from the 1st postoperative day showed that this measure was highly effective. Similarly, low rates of ossification were found only after postoperative radiation [3, 15]. The results with and without prophylaxis are shown again in Fig. 3. A positive side-effect was the significantly lower

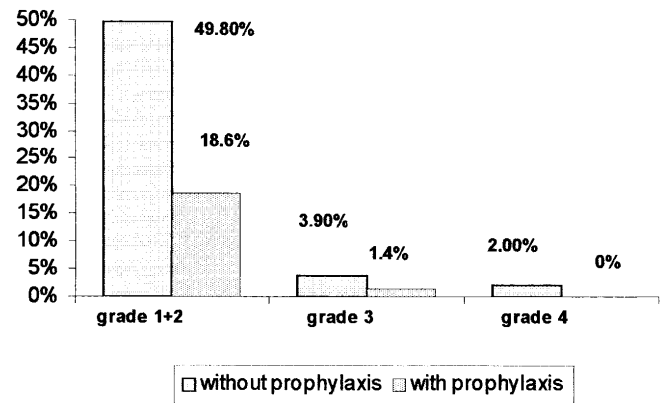


Fig. 3 Comparison of HO with and without prophylaxis

use of analgetic drugs in the postoperative phase. Serious side-effects such as gastrointestinal haemorrhage or ulcers were not observed. It must be noted that no ulcer prophylaxis was given. If patients complained, the medication was stopped, and this explains the relatively high proportion of 15.5% of patients who stopped treatment. In the case of prophylactic treatment with indomethacin, more serious complications are reported, and the exclusion rates in several studies were between 20% and 33% [5]. Because of the better compatibility, we would prefer diclofenac to indomethacin. The question of frequent loosening of implants requires an ensuing long-term study.

In order to decrease further the side-effects described, the question of the necessary dosage and duration of diclofenac treatment must be pursued. Up to now a medication of 6 weeks' duration has usually been recommended [9, 13, 14]. The study of Sodeman et al. [30] and the one presented here prove that a prophylaxis of 3 weeks' duration is highly effective. On the basis of knowledge concerning the pathogenesis of HO, it can be assumed that a shorter treatment of 7–10 days, for example, should be sufficient. Recently published studies showed that a medication with non-steroidal drugs such as tenoxicam and naproxen for 5 and 7 days, respectively can be effective [11, 12].

Finally, we conclude that prophylaxis by means of diclofenac using the abovementioned dosage is highly effective with less serious side-effects in comparison with indomethacin, whereas in future an accompanying medication, for example, misoprostol, will be able to reduce the rate of exclusion. The effect of a shorter duration of medication should be examined in an ensuing study.

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