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Stable bony integration with and without short-term indomethacin prophylaxis

A 5-year follow-up

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Abstract We included in a prospective study of a standardized indomethacin protocol 134 consecutive patients undergoing primary cementless endoprosthetic hip replacement between January and June 1990. Periarticular heterotopic ossification (HO) was graded according to the Arcq classification (grades 0 to III). At final follow-up, all patients were analyzed clinically and radiographically for HO and aseptic loosening. A similar group of 44 patients (mean age of 64 years, range 38–82 years) undergoing total hip replacement (THR) with the same prosthesis and technique in 1987 did not receive HO prophylaxis and served as a control group. The average age of the 134 prophylaxis patients was 66.5 years (range 32–85 years), and the average follow-up was 65 months (range 60–71 months). Thirty patients (25%) were lost to final follow-up (19 died, 10 unknown, 1 amputation). In the study group, 77% had HO grade 0, while none had HO grade III, compared with 18% HO grade 0 and 16% HO grade III in the control goup. These differences were statistically significant ($P = < 0.001$). At a minimum of 60 months follow-up, clinical and radiographic evaluation revealed no aseptic loosening in the study group: 4 cases of prosthesis subsidence during the first year did not progress. In the control group, there was a higher incidence of radiolucency around the femoral component, and one patient met all criteria for radiographic evidence of aseptic loosening. Statistical analysis revealed no significant difference between the two groups ($P = 0.104$). Based on our clinical and radiological results, indomethacin does not inhibit stable bony integration of the femoral component.

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Introduction

The development of heterotopic ossification (HO) following total hip arthroplasty may lead to a less favorable clinical outcome [1, 2, 5, 9, 13, 20, 23]. The incidence of HO following total hip replacement (THR) ranges from 8% to 90% with clinically significant lesions being reported in 1%–24% [9, 13, 26, 31].

Inhibition of HO by indomethacin has been proven in laboratory and clinical trials, and indomethacin has been used widely as a prophylactic agent for the prevention of HO. Because animal studies have shown that indomethacin reduces local bone remodeling after tauma and ingrowth into cementless, porous-coated components [19, 34] it is of clinical interest to determine whether indomethacin influences the incidence of aseptic loosening in cementless THA.

The aim of this study was to investigate the effect of a routine short-term HO prophylaxis on the clinical and radiological outcome of the cementless Zweymüller [24, 37] femoral component in comparison with a control group without indomethacin at a minimum follow-up of 5 years.

Patients and methods

In all, 134 consecutive patients, 92 women and 42 men, mean age 66,5 years (range 32-85 years) underwent cementless endoprosthetic hip replacement with a Zweymüller stem [24, 37] over a 6-month period and were administered indomethacin (100 mg/day) for 14 days in combination with ranitidine for gastric protection. The patients were followed prospectively and gave informed consent to participate in the study. A group of 44 patients, 22 men and 22 women mean age 64 years (range 38-82 years) from another prospective study of cementless THR with the same Zweymüller

stem [24, 37] served as a control group without indomethacin prophylaxis.

The Zweymüller femoral stem is a straight prosthetic stem with a finely structured surface of 3-5 µm surface roughness. The alloying element is niobium (Ti-gA1-7Nb, Protasul-100). The conically tapering stem has a rectangular cross-section. Direct anchorage of the implant in the bone is accomplished by press-fit.

In both groups, the operation was performed with the patient in the supine position. Using a transgluteal approach as described by Bauer et al. [8], with partial anterior capsular excision without a greater trochanter osteotomy. A cementless Zweymüller femoral component was implanted in combination with various acetabular components. The size of the femoral component was determined by preoperative templating and finalized intraoperatively. Machine-driven rasps prepared the medullary cavity.

Routine perioperative antibiotic prophylaxis (3 days) and low-dose heparin (3 weeks) were administered. Suction drainage was removed routinely after 48 h. Postoperatively, the patients were allowed to stand on day 1 or day 2, maintaining partial weight-bearing for 6 weeks and full weight-bearing thereafter.

All patients without contraindications for indomethacin (history of NSAID intolerance, active gastric ulcer, or severe renal, hepatic, or cardiac insufficiency) received a general short-term HO prophylaxis according to a standard protocol: starting on the first postoperative day with 50 mg of indomethacin twice a day for 2 weeks in combination with 150 mg ranitidine twice a day for 16 days. HO risk factors, side-effects of indomethacin, and reasons for interrupting the protocol were documented. High-risk factors included patients with previous HO of the contralateral or ipsilateral hip, low risk included male gender, hypertrophic and concentric osteoarthritis, and revision THA [16].

Clinical rating using the Harris Hip Score [15] was performed at 12 months and at final follow-up (minimum of 5 years): 90–100 points was considered excellent, 80–89 good, 70–79 fair, and < 70 poor. Patients were also questioned about the presence of thigh pain.

Follow-up included standard radiographs (anteropoterior, AP, and lateral) and clinical evaluation 1 week, 3 months, 12 months and at least 60 months after surgery, to assess bony ingrowth and component fixation. The seven-zone system of Gruen, McNeice and Amstutz [14] was used for radiographic analysis of the interface around the femoral component. Subsidence was measured by the distance between the lines perpendicular to the long axis of the prosthesis at the level of the tip of the greater trochanter and the lateral shoulder of the prosthesis on subsequent radiographs. Subsidence of 2 mm was considered significant. Radiographic loosening of the femoral stem was defined as a complete radiolucency visible in all 7 zones, stem subsidence, or stem migration. HO classification was performed according to Arcq [5]. Categories in this grading system included grade 0 (normal hip, no heterotopic bone formation), grade I (islands of bone formation), grade II (HO from the pelvis and the proximal part of the femur(, grade III (apparent ankylosis).

Failure of the total hip replacement was defined as removal of the implant or definitive radiographic evidence of loosening.

For statistical analysis, the unpaired Student's *t*-test was used to compare the incidence of radiolucency and the incidence of HO in both groups. Statistical significance was defined as a *P*-value less than 0.05.

Results

Clinical results

There were no absolute contraindications such as indomethacin intolerance or active gastric ulcer at the time of surgery. In the study group, 2 patients (9%) were indicated as high HO risk and 57 patients (42.5%) had one or more HO risk factors (42 male gender, 20 hypertrophic osteoarthritis, 10 concentric osteoarthritis).

Thus, 104 patients with an average follow-up of 65 months (range 60–71 months) were available for clinical examination. Four patients who moved from our area were contacted for a telephone interview. Thirty patients (22%) were lost to final follow-up: 19 had died, 10 could not be located, and 1 had undergone an amputation of the leg. None of these 30 patients revealed clinical or radiological signs of aseptic loosening at their most recent follow-up (range 12–48 months). In the control group, the average follow-up was 68 months (range 60–77 months).

No revision had had to be performed because of aseptic loosening at the minimum 5-year follow-up.

The average Harris hip score of the study group was 91 (range 40–100) at the 1-year follow-up and 89.8 (range 40–100) at the most recent follow-up examination. The overall results were 66% excellent, 14% good, 9% fair, and 11% poor. The average Harris hip score of the control group was 69.7 points (range 32–100 points) at the most recent follow-up examination. Their overall results were 7% excellent, 18% good, 36% fair, and 39 poor.

Analyzing the study group, at final follow-up 71% (74 hips) were painfree, 18% (19 hips) complained of minimal occasional pain, 5% (5 hips) of mild pain, and 5% (5 hips) of moderate pain. One patient had severe pain. The incidence of a limp was mild in 21%, moderate in 11%, and severe in 6%. Thus, 62% of the patients had no observable limp. In addition, 71% of the patients used no aid for walking, 6% used a cane for long distances, 17% used a cane even for short distances, and 4% used two crutches.

Analyzing the control group, at final follow-up 57% (25 hips) were painfree, 14% (6 hips) complained of minimal occasional pain, 9% (4 hips) of mild pain, and 11% (5 hips) of moderate pain. Two patients had severe pain, and 2 patients were disabled due to pain in their hip. The incidence of limp in the control group was slight in 18% of the patients and moderate in 9%. Twenty-six patients used no support for walking, 11% used a cane for long distances, and 30% used a cane all the time.

Radiographic results

Analyzing HO in the prophylaxis group, 68 patients (77%) presented with grade 0, 16 patients (18%) with grade I, 4 patients (5%) with grade II. None of the patients developed grade III (Fig. 1). In only 8 cases (4%) did HO progress 1 grade after 3 months. In none of the patients with grade I or II HO was the hip's range of motion limited. An avulsion of the greater trochanter was observed in 20 cases (23%) at the 1-week radiographic control. At final follow-up 8 of these cases developed ossification grade I, and 1 developed ossification grade II (Fig. 1 A).

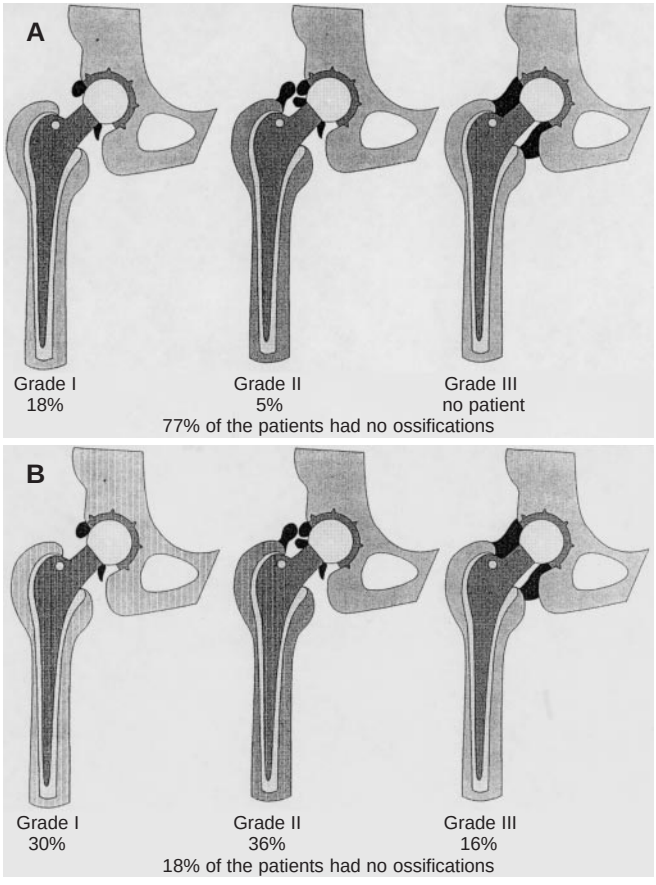

Fig. 1 Results of heterotopic ossification according to Arcq [5]: **A** Study group with indomethacin prophylaxis (n = 88), **B** control group without indomethacin prophylaxis (n = 44)

Analyzing HO in the control group, 8 patients (18%) presented with grade 0, 13 patients (30%) with grade I, 16 patients (36%) with grade II, and 7 patients (16%) with grade III (Fig. 1 B). The difference was statistically significant (P = < 0.001).

For final radiographic analysis in the study group, radiographs of 88 patients were available. On the AP view, radiolucent lines were present in various zones surrounding the femoral component. Radiolucent lines of less than1 mm were present in 14 cases (15.9%) in zone 1, in 16 cases (18.2%) in zone 7, and in 1 case in zone 2. In 5 cases (5.7%) in zone 1, 3 cases (3.4%) in zone 7, and in 1 case in zone 2, radiolucent lines of less than 2 mm were observed. In only 2 cases in zone 7 and 1 case in zone 1 did the radiolucency exceed 2 mm. No radiolucencies were observed in zones 3–6. Endosteal bone formation along the tip of the prosthesis was mild in 35.2%, moderate in 30.7%, and severe in 10.2%. In 23.9%, no additional bone formation around the tip of the prosthesis was observed. No patient had any radiographic signs of aseptic loosening (Fig. 2 A).

Analyzing the control group, radiolucent lines of less than 1 mm were present in 6 cases (13.6%) in zone 1, in 2 cases (4.5%) in zone 7, and in 1 case each in zones 2–5. In 9 cases (20.5%) in zone 1, in 9 cases (20.5%) in zone 7, in 3 cases (6.8%) in zone 6, in 2 cases (4.5%) in zone 3, and in 1 case each in zones 2 and 4, radiolucent lines of less than 2 mm were observed. In 2 cases each in zones 7 and 1 and in 1 case in zone 2, the radiolucency exceeded 2 mm. Endosteal bone formation along the tip of the prosthesis was mild in 35.2%, moderate in 30.7%, and severe in 10.2%. In 23.9%, no additional bone formation around

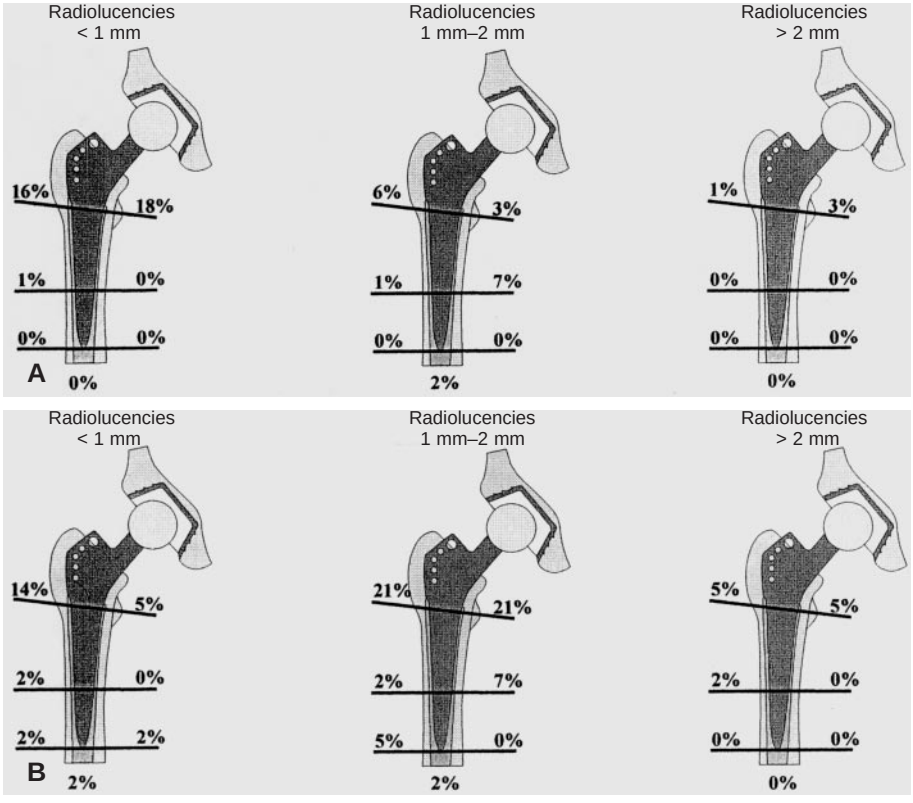

Fig. 2 Radiographic zones of the femoral component according to Gruen et al. [14]: **A** Study group with indomethacin prophylaxis (n = 88), **B** control group without indomethacin prophylaxis (n = 44)

the tip of the prosthesis was observed. One patient with radiolucent lines of less than 2 mm in all Gruen zones was classified as having aseptic loosening (Fig. 2 B).

Thus, in the control group without indomethacin prophylaxis there was a higher incidence of radiolucent lines around the femoral component, and one patient had a defined aseptic loosening based on the radiographic appearance. Statistical analysis revealed no significant difference between the two groups ($P = 0.104$).

We did not observe any increased wound bleeding complication in the study group from using indomethacin [17].

Discussion

Indomethacin has been thoroughly investigated regarding its effectiveness in the prevention of HO after THA. Radiation therapy [6, 7, 10, 25, 28] has been proven to successfully prevent the development of HO; however, even a single dose of radiation therapy bears the risk of development of a sarcoma [4, 11]. Transplantation of free fat has also been described for the prevention of HO, but due to the small number of patients, no conclusive results are available [29]. Our results of a 2-week course of indomethacin postoperatively are comparable to indomethacin prophylaxis for 6 weeks or single-dose radiotherapy [6, 16, 21, 28, 30, 32, 36]. More recent reports showed that a 7-day postoperative course of indomethacin produced identical results for the prevention of HO, although the rate of side-effects was not significantly reduced [36].

Short-term indomethacin prophylaxis is easily administered, inexpensive, and effective. Limiting treatment to only patients at risk for HO will still result in a considerable number of patients developing HO. A risk of delayed bony ingrowth for uncemented THA and nonunions of trochanteric osteotomies have been reported after indomethacin prophylaxis [18] and local radiation [6, 7, 10, 25, 28, 33, 35]. Allen et al. [3] studied the effect of clinical indomethacin doses on fracture healing in rats and found a delay in the fracture repair process. However, there was only a delay of bone repair since the fractures in rats treated with indomethacin did go on to complete union. Trancik et al. [34] performed an animal study and administered various therapeutic doses of indomethacin, aspirin, and ibuprofen to New Zealand White rabbits after porous-coated chrome cobalt implantation. Rabbits were treated with indomethacin 1 mg/kg/day, 2 mg/kg/day, and 3 mg/kg/day (which corresponds to 75, 150 and 225 mg/kg/day, respectively, in a 75-kg man). There was no statistically significant difference of bone occupying the ingrowth pores at 2 weeks after implantation between the 1-mg or 2-mg groups and the control group. At 4 and 8 weeks in the 1-mg and the 2-mg groups and at 2, 4, and 8 weeks in the 3-mg group, there was a statistically significant decrease in bone ingrowth compared with the control group and the 1-mg and 2-mg groups for 2 weeks. The conclusion of this animal study is that administration of 75 mg or 150 gm indomethacin for a period of 2 weeks does not interfere with the ingrowth into the cementless component.

The analysis of our study group with HO prophylaxis of 50 mg of indomethacin twice a day for 2 weeks in combination with gastric protection using 150 mg ranitidine twice a day for 16 days demonstrated similar results, and suggested that the feared gastrointestinal side-effects could be prevented by the administration of ranitidine 150 mg [17].

In order to prove whether or not indomethacin interferes with stable bony integration, we had to compare our study group to a control group without indomethacin. Since administration of indomethacin has been performed at our institution since 1984, we were unable to present our own control group. To perform this comparative study, we used the data from another institution using the same prosthesis, the same surgical technique, and the same approach.

Overall, the incidence of HO in the control group was significantly higher ($P < 0.001$) than in the study group. Surprisingly, the incidence of radiolucent lines was higher in the control group than in our study group. Most important was that in the study group there was not a single case of grade III HO vs 7 cases in the control group.

The limitation of this study is that its control group was examined retrospectively, and no prospective, controlled, double-blind study was performed. Also, There is no study in the literature of this design. However, with more than 2000 THAs already performed at our institution, it would not be feasible to initiate a prospective, double-blind study from an ethical standpoint given the results of indomethacin therapy.

Indomethacin administration of 50 mg twice a day for 2 weeks is an effective, inexpensive, and easily administered HO prophylaxis as an alternative to single-dose radiotherapy. A minimum follow up of 60 months clinical and radiographic evaluation demonstrated no signs of aseptic loosening in these patients. Comparing our clinical and radiological results with indomethacin to a control group, there is no risk of diminished stable bony integration of the femoral component. Based on these results, we recommend short-term indomethacin prophylaxis in uncemented endoprosthetic THA.

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