PREVENTION OF HETEROTOPIC OSSIFICATION WITH TENOXICAM FOLLOWING TOTAL HIP ARTHROPLASTY : A DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-FINDING STUDY

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The effect of tenoxicam 10 mg and 20 mg, administered daily for 6 weeks to prevent heterotopic bone formation after total hip arthroplasty, was evaluated in a randomized, double-blind, placebo-controlled trial involving 90 patients. After 3 months, patients who had received the active drug, including those who had received only half the recommended anti-inflammatory dosage, had significantly less heterotopic bone formation. After 6 months the difference between treatment groups and placebo became smaller but remained significant. Adverse reactions occurred in only 3 patients, reflecting no differences between the groups. The study results, including radiographic, clinical and biochemical evaluations, demonstrate that treatment with tenoxicam 20 mg daily and even with tenoxicam 10 mg daily for 6 weeks, starting immediately after total hip arthroplasty, is effective in preventing ectopic bone formation.

Keywords : heterotopic ossification ; prevention ; total hip replacement ; tenoxicam.
Mots-clés : ossifications hétérotopiques ; prévention ; arthroplastie totale de hanche ; ténoxicam.

INTRODUCTION

Heterotopic ossification (HO) is a well-known complication of total hip arthroplasty (THA). The reported incidence varies from 1% to 90%, compromising the overall outcome of the total hip replacement in up to 25% of the cases (5, 18).

Certain factors have consistently correlated with high incidence and severity of HO following THA. These include male gender with osteoarthritis of the hip, diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, hypertrophic osteoarthritis and development of HO following previous ipsilateral or contralateral hip surgery (4, 5). Surgical technique also has a role in the incidence of ectopic bone formation, as some investigators have indeed noted less HO with a posterolateral approach than with trochanterotomy (13). The only treatment for established HO consists of surgical removal, but the recurrence rate after excision remains quite high (1, 3, 21).

Various methods have been proposed for prevention of HO. The use of diphosphonates has been advocated, but the suppression effect was rather modest and did not prevent the formation of bone matrix, which became mineralized soon after discontinuing treatment (2). Although radiation therapy does not prevent ossification in all cases, bone formation is less severe. Fear of malignancy and of a detrimental effect on the healing process of trochanteric osteotomies still remains, even with the recently recommended lower dosages, single-dose irradiation techniques or partial lead shielding (15). Several nonsteroidal anti-inflammatory drugs (NSAID's) have demonstrated a prophylactic effect on heterotopic ossification after THA, mainly in retrospective studies and at full anti-inflammatory dosages (16, 5, 18).

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It is unclear however whether HO after THA can be prevented with lower dosages, which in turn are expected to decrease the risk and incidence of adverse reactions in this predominantly elderly population (4, 5, 6, 18).

As NSAID's are associated with well-known, often dose-related adverse reactions (4, 6, 8), we performed this study to evaluate the efficacy of tenoxicam at the usual anti-inflammatory dosage and at half this dosage in a double-blind, prospective placebo-controlled trial. Concomitantly both frequency and severity of adverse events were evaluated.

PATIENTS AND METHODS

A prospective, double-blind, placebo-controlled study was designed to evaluate the efficacy and safety of a 6-week treatment course of tenoxicam 10 mg daily and tenoxicam 20 mg daily in the prevention of heterotopic ossification after total hip arthroplasty.

Ninety patients, mean age 61 years (20 to 75 years), scheduled for cemented total hip arthroplasty using the Charnley technique and at risk of developing heterotopic ossification (male gender with documented radiographic diagnosis of osteoarthritis of the hip to be replaced, diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, development of heterotopic ossification following previous ipsilateral or contralateral hip surgery, or osteoarthritis of the hip with extensive proliferative osteophytes of $>$ 5 mm) were selected.

Reasons for exclusion from the study were : hypersensitivity to any NSAID, documented history of peptic ulceration within the last 12 months, underlying severe cardiac, hepatic or renal disease, patients whose surgery included bone grafting, bone ingrowth prosthesis or osteotomy (excluding trochanteric osteotomy), concomitant anti-inflammatory, anti coagulant, oral anti diabetic or lithium therapy. All NSAID administration had to be stopped preoperatively.

Ninety patients were enrolled in 2 centers, respectively 60 at the University Clinic of Leuven (Pellenberg) and 30 at the St. Pierre Clinic (Ottignies). Patients were initially randomized into 3 groups to receive either placebo (P group), tenoxicam 20 mg daily (T 20 group) or tenoxicam 10 mg daily (T 10 group) for 6 weeks starting within 24 hours after surgery. Follow-up visits were planned after 6 weeks, 3 months and 6 months.

Efficacy was evaluated by analyzing radiographs made preoperatively, 6 weeks, 3 months and 6 months postoperatively using Brooker's classification system (3) : grade 0 = no heterotopic ossification ; grade I = islands of bone within soft tissues around the hip ; grade II = bone arising from the periarticular region or proximal femur with a separation of $>$ 1 cm ; grade III = bone arising from the periarticular region or proximal femur with a separation of $<$ 1 cm ; grade IV = apparent bony ankylosis. Furthermore efficacy was also evaluated from a functional point of view using an index of severity for osteoarthritis of the hip according to Lequesne (10) and an overall assessment of mobility on a 4-point scale by the investigator at the last study visit. Finally, absence of a significant increase in alkaline phosphatase was considered as a biochemical parameter of efficacy (10).

Safety was globally evaluated at the end of treatment (6 weeks) by the investigator on a 4-point scale taking into account the patient's complaints, adverse events and results of laboratory tests. Adverse events were elicited throughout the study and graded on a three-point scale (mild, moderate or severe). Relationship to the study medication was evaluated as unrelated, remote, possible or probable by the investigator. Two laboratory evaluations, one before surgery and one at termination of the treatment period (6 weeks) comprised white and red blood cell counts, hemoglobin, hematocrit, serum sodium, potassium, creatinine, blood urea nitrogen, lactate dehydrogenase, alanine and aspartate aminotransferase, alkaline phosphatase, amylase, lipase and albumin.

For statistical analysis a global comparison between the three groups and in case of significant differences, 2 by 2 comparisons using the same tests were performed. To compare efficacy on the basis of the different classifications, we used the chi-square test and for too small expected frequencies, 2 by 2 comparisons by means of chi-square or Fisher's Exact test were performed. Evolution of the severity index was analyzed with the Kruskal-Wallis test. The overall assessment was evaluated by comparisons by means of the chi-square test or Fisher's Exact test for 2 by 2 comparisons where necessary. Laboratory results were analyzed by comparing normal and abnormal values in the three groups by means of the chi-square test. When significant changes were observed, mean values expressed as percentage of the upper normal limit were compared before and after treatment.

RESULTS

There were no statistically significant differences between the 3 groups before surgery (see table I).

Table I. — Baseline demographic and medical data

A. Demography	P (N = 29)	T 10 (N = 29)	T 20 (N = 26)
Age (years)	20-75	44-70	42-75
mean ± S.D.	62 ± 11	61 ± 7	59 ± 9
Weight (kg)	56-101	57-101	61-101
mean ± S.D.	78.4 ± 10.1	78.4 ± 12.3	79.6 ± 12.3
Height (cm)	155-191	164-180	157-196
mean ± S.D.	170 ± 7.7	171 ± 4.8	170 ± 8.2
B. Medical data			
Preoperative Brooker grading			
0	6 (21%)	3 (10%)	6 (24%)
I	3 (10%)	5 (17%)	0 (0%)
II	18 (62%)	18 (62%)	18 (72%)
III	1 (3%)	2 (7%)	1 (4%)
IV	1 (3%)	1 (3%)	0 (0%)
Lequesne score before surgery	8-21	6-18	9-20
mean ± S.D.	15 ± 3	15 ± 3	15 ± 3
Risk factors			
Male gender with osteoarthritis	26 (90%)	26 (90%)	23 (88%)
Extensive proliferative osteophytes	22 (76%)	24 (83%)	24 (92%)
Number of risk factors per patient			
1	8 (28%)	8 (28%)	5 (19%)
2	18 (62%)	20 (69%)	20 (77%)
3	3 (10%)	1 (3%)	1 (4%)

For 6 patients no data were available, due to withdrawal of consent postoperatively (2 in the T 20 group) and perioperative intercurrent illness (2 in the T 20 group, 1 in the T 10 group and 1 in the P group). Of the remaining 84 patients evaluated for efficacy and safety after 6 weeks, 3 were lost to follow-up later on (2 in the T 10 group, 1 in the P group), and 1 patient in the P group died.

During follow-up the frequency of heterotopic ossification was significantly different in the 3 groups studies, as can be seen in fig. 1 (6 w : $p = 0.4$; 3 M : $p = 0.009$; 6 M : $p = 0.084$; chi square) after grouping grade O and I, and grades II, III and IV. In the comparison of tenoxicam with placebo, significant differences were recorded at the 3-month ($p = 0.008$, chi square) and 6-month study visit ($p = 0.05$, chi square). In the comparison of each tenoxicam group individually with placebo, significantly less ossifications were found in T 20 after 6 weeks, ($p = 0.026$; chi square) and 3 months, follow-up ($p = 0.01$; chi square), while after 6 months the difference was almost significant ($p = 0.088$; chi square). In the T 10 group, a strong trend towards less ossifications was found after 3 months ($p = 0.08$, chi square) and 6 months ($p = 0.16$; chi-square).

It is worth noting that at the final study visit, 5 patients in the placebo group presented grade III ossifications, while only 2 did so in the T 10 group and only 1 in the T 20 group (table II).

The index of severity was analyzed by investigating the evolution during the trial by repeated measures analysis of variance (Manova) and comparing the values at each visit. At baseline no significant difference in index of severity was found between the 3 groups, while at 6 weeks and at the last visit, differences with placebo became significant ($p = 0.018$; Kruskal-Wallis) (see fig. 2).

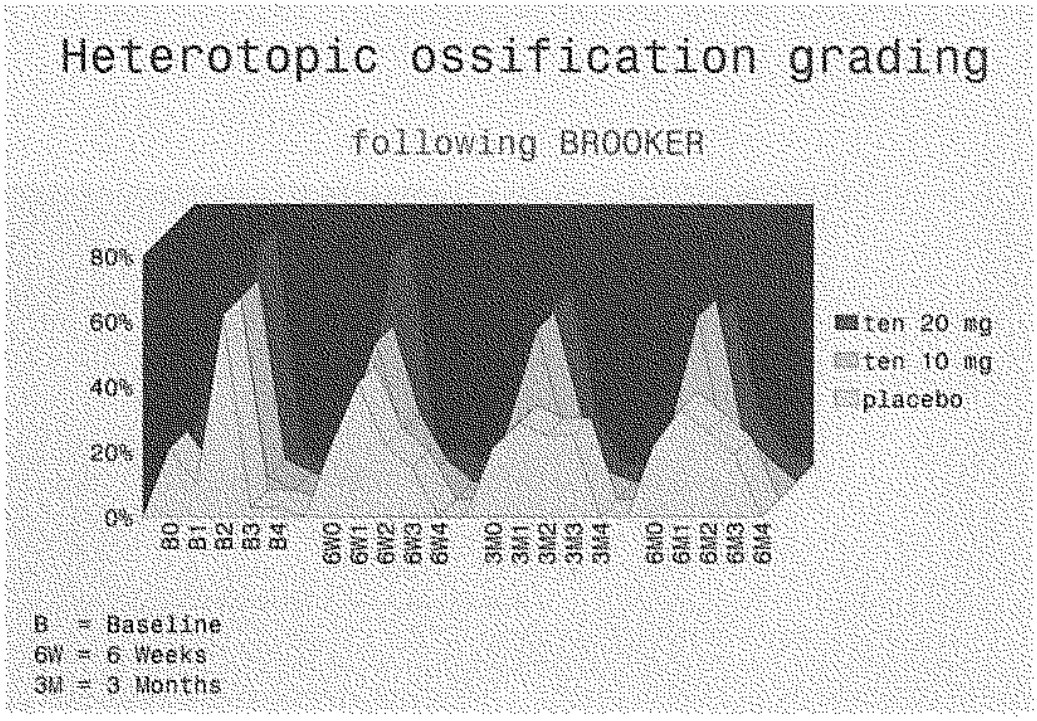


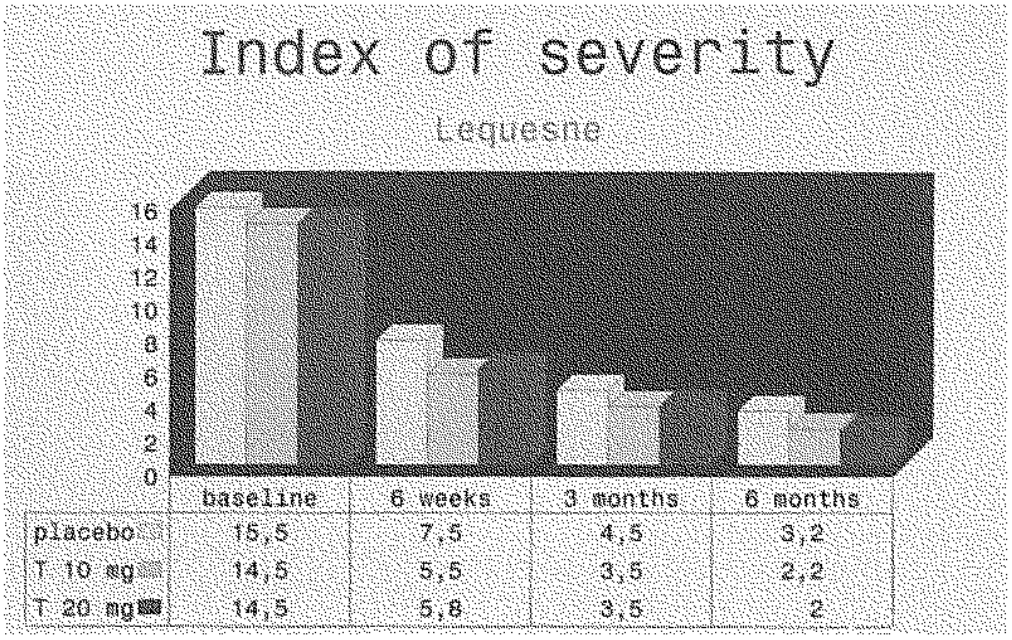
Fig. 1. — Evolution of radiographic ossification grading (Brooker).

Table II. — Degree of radiographic ossification and overall assessment of mobility 6 months after surgery

Degree of ossification 6 months after surgery	Placebo (N = 29)	T 10 (N = 29)	T 20 (N = 26)
Gradings			
0	6 (22%)	6 (22%)	8 (31%)
I	9 (33%)	15 (56%)	13 (50%)
II	7 (26%)	4 (15%)	4 (15%)
III	5 (19%)	2 (7%)	1 (4%)
IV	0 (0%)	0 (0%)	0 (0%)
Missing	2	2	0
Overall Assessment of mobility at final study visit	Placebo (N = 29)	T 10 (N = 29)	T 20 (N = 26)
Bad	1 (3%)	0 (0%)	0 (0%)
Moderate	4 (14%)	2 (7%)	1 (4%)
Good	7 (24%)	10 (34%)	6 (23%)
Very Good	17 (59%)	17 (59%)	19 (73%)

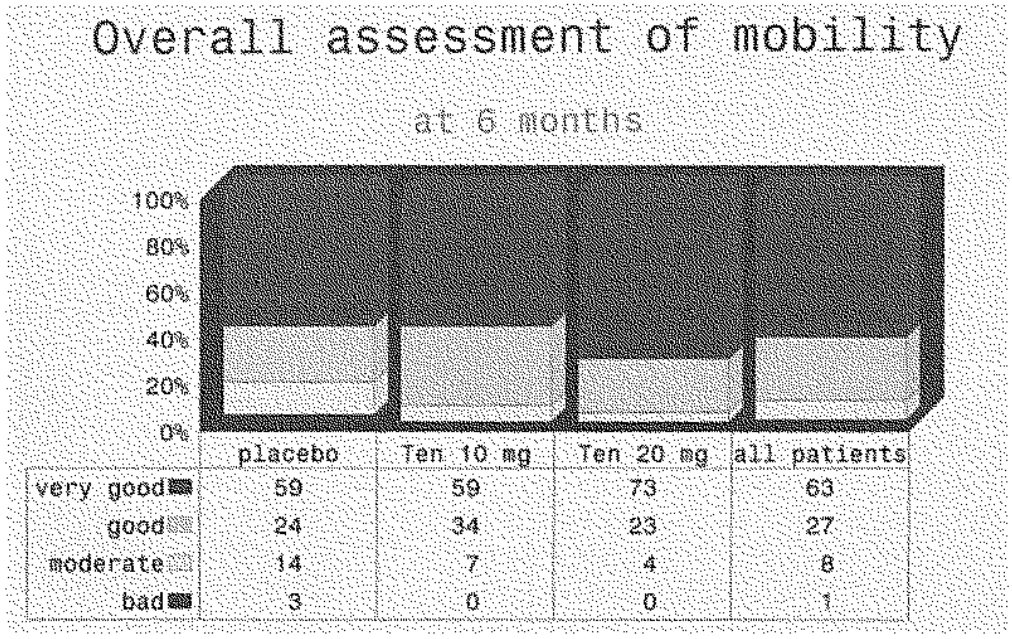
The medication effect was almost statistically significant. A final overall assessment at 6 months with a 4-point scale revealed no significant difference between groups (see table II), although for more patients mobility was evaluated as moderate in the P group, and for 1 patient the outcome was considered as poor.

Last but not least, a significant ($p = 0.013$, Anova) increase in alkaline phosphatase was observed in the placebo group after the 6-week treatment period, while no significant change was observed for T 10 or T 20 (see fig. 3).



	baseline	6 weeks	3 months	6 months
placebo	15,5	7,5	4,5	3,2
T 10 mg	14,5	5,5	3,5	2,2
T 20 mg	14,5	5,8	3,5	2

Fig. 2. — Evolution of functional mobility (Lequesne).



	placebo	Ten 10 mg	Ten 20 mg	all patients
very good	59	59	73	63
good	24	34	23	27
moderate	14	7	4	8
bad	3	0	0	1

Fig. 3. — Serum alkaline phosphatase levels before and after the 6-week treatment period.

Safety

Safety assessments by the investigator after 6 weeks' treatment showed no significant differences between the 3 groups. Adverse events occurred in 20 patients, but the frequencies in the 3 groups were not significantly different (8 in the placebo, 6 in the T 10 and 6 in the T 20 group). For 3 patients adverse events were considered to be possibly or probably related to the study medication (2 in T 10, 1 in T 20 group). There were no adverse events that were considered severe. These 3 adverse reactions were diarrhea, postprandial epigastric pain occurring during the 6-week treatment period and gastritis occurring between the 3- and 6-month follow-up visits. Laboratory evaluation showed no further statistically significant or clinically relevant changes.

DISCUSSION

The high frequency of preoperative Brooker grade II scores reflects the selection of a high-risk population. In accordance with most protocols studying NSAID's in the prevention of heterotopic ossification, we treated patients with tenoxicam for 6 weeks, although it has been suggested that a shorter treatment period may also be effective (17).

Tenoxicam appeared at both drug dosages to be superior to placebo in suppressing heterotopic bone formation to a clinically acceptable degree. Though the number of patients per group was rather small, statistically significant evidence or at least a strong positive trend was noted on evaluation of radiographs at the different study visits. These findings are confirmed by the clinical observations of better mobility in the tenoxicam groups which obviously is the result of less severe ossification. Finally, the most objective and reliable evidence of efficacy of T 10 and T 20 to suppress HO in this study is the absence of changes in serum alkaline phosphatase after 6 weeks' treatment (19), while the mean value in the P group increased significantly. Indeed, osteoblastic activity is known to be associated with elevated levels of serum alkaline phosphatase (11).

Though the radiological and clinical findings showed somewhat better results with tenoxicam 20 mg, half this dose also effectively inhibited heterotopic ossification, and the difference between the active drug groups never reached any level of statistical significance. The incidence of adverse reactions of NSAID's is usually dose related, but in our study we could not demonstrate any dose relationship, possibly because the number of adverse reactions was too small. Comparative clinical studies have demonstrated that tenoxicam is at least as well tolerated as other NSAID's (20).

In practice, these results might suggest the use of half the usually recommended anti-inflammatory dosage for suppression of heterotopic ossification, although the benefit in terms of adverse event reduction could not be shown in this study for tenoxicam. In contrast, shortly after surgery, one might prefer to administer higher NSAID dosages for postoperative pain management (14, 12, 7). It would be worth studying whether adequate short-term postoperative pain management with the use of NSAID administration after total hip arthroplasty could also effectively prevent heterotopic bone formation.

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SAMENVATTING

A. BURSSENS, J. THIERY, P. KOHL, A. MOLDEREZ, L. HAAZEN. Tenoxicam als preventie van heterotopische ossificatie na totale heuparthroplastiek.

De invloed van toediening van tenoxicam 10 of 20 mg per dag, als preventie tegen het optreden van heterotopische ossificaties na totale heuparthroplastiek werd bestudeerd in een gerandomiseerde, dubbel-blind, placebo gecontroleerde studie van 90 patiënten. Na drie maanden werd significant miner heterotopische ossificatie waargenomen bij patiënten behandeld met tenoxicam. Na 6 maanden was het verschil tussen de placebo- en tenoxicam groepen minder uitgesproken doch steeds significant. Bijwerkingen traden slechts op bij drie patiënten in totaal. Deze studieresultaten tonen aan, aan de hand van radiografische, klinische en biochemische evaluaties dat een behandeling met tenoxicam 20 mg per dag en zelfs met tenoxicam 10 mg per dag, gedurende 6 weken effektief is in het voorkomen van de ontwikkeling van heterotopsiche ossificaties na totale heuparthroplastiek.

RÉSUMÉ

A. BURSSENS, J. THIERY, P. KOHL, A. MOLDEREZ, L. HAAZEN. Prévention des ossifications hétérotopiques par le ténoxicam après arthroplastie totale de hanche.

L'effet du ténoxicam administré à raison de 10 mg ou 20 mg par jour pendant 6 semaines pour prévenir les ossifications hétérotopiques après arthroplastie totale de la hanche a été évalué chez 90 patients inclus dans une étude randomisée, en double-aveugle et contrôlée par placebo. Trois mois après l'opération, les deux groupes de patients traités présentaient significativement moins d'ossifications hétérotopiques que le groupe de patients ayant reçu le placebo. Six mois après l'opération, la différence entre les groupes traités et le groupe placebo était moins prononcée mais restait significative. Des effets secondaires ont été observés chez 3 patients seulement. Les résultats de cette étude comportant des évaluations radiographiques, cliniques et biochimiques démontrent qu'un traitement par le ténoxicam administré à raison de 20 mg ou même 10 mg par jour pendant les 6 semaines qui suivent une arthroplastie totale de la hanche est efficace pour prévenir l'ossification hétérotopique.