L. Vastel · L. Kerboull · O. Dejean · J-P Courpied
M. Kerboull

Prevention of heterotopic ossification in hip arthroplasty

The influence of the duration of treatment

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Abstract A retrospective study has been carried out to assess the effectiveness of indomethacin in preventing heterotopic ossification after total hip arthroplasty, and the effect of using it for different periods of time. One hundred and sixty-eight hips operated on in 1983 were not given indomethacin and acted as a control. One hundred and fifty hips operated on in 1988 were given indomethacin and divided into 3 groups: 42 received indomethacin for 5 days, 49 for 11 days and 59 for 45 days. The results indicate that ossification is significantly reduced in those patients receiving indomethacin for 5 and 11 days, but there was no additional reduction when it was given for 45 days. Treatment should begin on the night of operation and continued for 11 days while the patient remains in hospital.

Résumé La révision de 318 patients opérés pour arthroplastie totale à l'hôpital Cochin a permis aux auteurs d'évaluer l'efficacité de l'indométacine pour la prévention de la survenue d'ossifications, et de comparer les résultats obtenus en fonction de la durée de traitement. La réduction de l'incidence des ossifications obtenue avec l'indométacine est très significative, passant de 61,3% dans le groupe non traité à 26% pour l'ensemble des patients traités, encore plus nette pour les ossifications de haut grade (21,8% dans le groupe non traité contre 4,6% dans le groupe traité). Un seul patient développant des ossifications de degré 3 sur les 150 patients traités. L'analyse des résultats en fonction de la durée de traitement met en évidence une réduction significativement des ossifications pour des traitements de 5 jours (40,5% d'ossifications), une réduction significativement meilleure pour des traitements de 11 jours (20,4% d'ossifications), sans réduction d'incidence supplémentaire pour des traitements plus long. Ces résultats démontrent que la durée optimale de traitement pour une prévention efficace des ossifications

péri-prothétiques est de l'ordre de 11 jours, soit en pratique une administration limitée à la durée d'hospitalisation, et débutée le soir ou le lendemain de l'intervention.

Introduction

Heterotopic ossification is a well known complication of total hip arthroplasty. Although only responsible for slight pain, apart from during the maturation phase [12, 36, 38], it has been shown to alter the mobility of the hip once the ossification has spread [9, 22, 27], which justifies the need for effective preventive measures.

Ever since Dahl [8] observed that there was a low incidence of ossification in his patients treated with indomethacin for analgesic purposes, the effectiveness of this non-steroidal anti-inflammatory prophylaxis has been proven in numerous studies [1, 4, 10, 14, 15, 16, 17, 18, 19, 25, 26, 28, 29, 31, 32, 32, 35, 42].

However, the minimum period of administration required for the desired effect remains unknown. Apart from rare exceptions [11], published studies refer to protocols of treatment for periods of 3 weeks or more. None of these have shown statistically any proof of the effectiveness of indomethacin treatment for periods shorter than 15 days.

In vitro [40] and animal experiments [5, 39] have shown that the events responsible for the development of ossification take place during the first few days following the operation.

Since indomethacin can have side effects, particularly digestive, we considered it important to determine whether a period of administration, shorter or the same as the time the patient is in hospital, would prevent ectopic bone formation.

Material and method

The study was carried out on a total of 312 patients with 318 total hip replacements. Four groups have been defined in two consecutive series of arthroplasties.

L. Vastel (✉) · L. Kerboull · O. Dejean · J.-P. Courpied
M. Kerboull
Hôpital Cochin, Service de Chirurgie Orthopédique,
27 rue du Faubourg Saint-Jacques, F-75674 Paris Cedex 14,
France

Table 1 Preoperative joint degeneration in both series

	Non-treated group	Treated group	Total
(+) Supero-lateral narrowing	8	10	18
(++) Global narrowing	27	38	65
(+++ Moderate bone degeneration	56	54	110
(++++ Important bone degeneration	77	48	125

One hundred and sixtyeight hips operated on during 1983 (164 patients) form the control group who were not given indomethacin.

One hundred and fifty hips operated on during 1988 (148 patients) received preventive indomethacin treatment for periods of 5 days, 11 days or 45 days. Each surgeon chose one of the 3 protocols which allowed us to study 3 groups of hips defined by the duration of treatment:

Group A – 42 patients treated for 5 days (± 2).

Group B – 49 patients treated for 11 days (± 3).

Group C – 59 patients treated for 45 days.

Only hips that had not been operated on previously were included. There were 303 arthritic hips (263 with primary coxarthrosis, 15 coxarthrosis with dysplasia, 19 congenital dislocations, 6 with the sequelae of epiphysitis), 13 with aseptic osteonecrosis and 2 with sequelae of coxarthrosis. These diagnoses were distributed evenly among both series.

Patients who had taken aspirin-based analgesics, anti-inflammatory drugs or who had a chronic inflammatory disorder were not included. There were 158 right hips and 160 left hips, equally distributed among the four groups with 144 men and 174 women. The treated groups included a higher proportion of men (54% compared with 37.5% in the untreated group). The average age was 65 years; 63 years in the treated groups and 66 years in the untreated patients.

All operations were carried out through a lateral transtrochanteric approach. The technique was not modified throughout the 2 years of study and consisted of a capsulectomy and trochanteric reinsertion with 3 or 4 metal wires.

The prosthesis used was the Charnley-Kerboull type with a polyethylene acetabulum and steel femoral component with a head diameter of 22.2 mm. Antithrombotic prevention was used with a protocol consisting of an initial dose of low molecular weight heparin followed by a coumarin derivative after removal of the suction drainage on the third day after operation.

Indomethacin prophylaxis was begun on the night of operation; one suppository of 100 mg of indomethacin was given each day for 3 days and then an oral dose of 75 mg per day, given as 25 mg 3 times a day, or as a single 75 mg dose.

Anteroposterior radiographs of the hips were taken when the patient left the hospital, at 3 months and at one year, in order to monitor the possible appearance of ossification. The classification used [23] was derived from Brooker [3] and has 4 stages from 0 to 3.

We have verified the validity of the comparisons between the different groups for each case by assessing the past history of the patients, their general status before the operation, the functional scoring system of Merle D'Aubigné and Postel [23]; the walking time in minutes, the degree of degeneration of the joint, and the amount of osteophyte formation before operation. The general condition of the patient was classified as very good, good, average or poor.

The degree of degeneration of the joint was assessed in 4 stages (Table 1) and the amount of preoperative osteophyte formation in 4 specific stages (Table 2).

The data obtained was stored in a computer (File Maker*, Claris*, Excel 3-3*, Microsoft*) and analysed using the statistical epidemiology survey method developed by the Faculty of Medicine of the University of Toulouse.

We have compared the different groups for age, sex ratio, initial diagnosis, functional score, walking time before operation, general condition, the most frequent pre-existing conditions, the degree of articular degeneration and the amount of osteophyte formation before operation.

Within the untreated group, we compared the ossification rates of the various surgeons which allowed for the choice of different duration of treatment and the constitution of the treated groups (A, B and C). The effectiveness of indomethacin was evaluated by comparing the frequency of ossification in both series and the incidence of ossification within the four samples namely the untreated group and the three groups defined by the duration of indomethacin treatment.

Results

None of the patients were lost to follow up during the study period and none died. Within the control group, there was no differences between the incidence of ossification for the various surgeons involved in groups A, B and C.

No significant difference was observed between the two series for parameters such as the side of hip operated on, the general status of the patient and the preoperative functional score. Groups A, B and C do not diverge significantly from the average values of the treated series.

The amount of osteophyte formation was evenly distributed among the groups.

Joint degeneration did not show any significant difference in the 2 series, nor between the different groups of patients (Table 1).

The average walking time was 22 min and identical for all groups, except for 3 patients whose walking before the operation was unlimited.

The most frequent previous disorders were separated into three categories: digestive, vascular and cardiac. No

Table 2 The extent of osteophyte formation system in this study

Size of the osteophytes		Localisation
+	Osteophyte <1 cm	Zone 1: Femoral osteophyte
++	Osteophyte from 1 to 2 cm	Zone 2: Peri-acetabular osteophyte
+++	Osteophyte >2 cm	Zone 3: Intra-acetabular osteophyte
Stage:		
0	No osteophytes.	
1	Osteophytes in one or two areas, not >1+.	
2	Osteophytes in 2+ in one zone, or as 1+ in the 3 zones.	
3	Osteophytes of 3+ in one zone or in all 3 zones of which at least one is as 2+	

Table 3 Percentages of ossification related to duration of treatment

	Non treated Group	Group A (5 days)	Group B (11 days)	Group C (45 days)
Ossifications=0	65 (39%)	25 (60%)	39 (80%)	47 (80%)
Ossifications >0	103 (61%)	17 (40%)	10 (20%)	12 (20%)

Fig. 1 Incidence of ossifications in both series

differences in distribution were found in the two series as the incidence of the considered antecedents did not allow for statistical comparison between the treated groups.

Two significant differences were found when the groups were analysed. There was greater proportion of men in the series of treated patients as compared to the untreated group (54% to 38%) without, however any significant difference between the treated groups. The average age was lower in the treated groups (64 years compared with 66 years for the untreated group), without any significant difference between the treated groups.

Effectiveness of prevention with indomethacin (Fig. 1)

The reduction of the incidence of ectopic bone formation was significant; the incidence was 61% for the untreated group against 26% for the series of treated patients (chi-square test=44.923 with degrees of freedom=3, $P<0.001$).

For stage 2 and 3 ossification, the difference is even greater: 22% for the control group and 4.6% for the series of treated patients. Only one of the 150 treated patients developed stage 3 ossification.

Frequency of ossification related to the duration of treatment (Table 3)

We have compared the degree of ossification in Group A and the untreated group; the difference is significant (chi-square=5.955, $df=1$, $P<0.05$). Treatment for 5 days in this series has thus induced a significant reduction in the occurrence of ossification. We then compared the occurrence of ossification between groups A and B and the difference was significant (chi-square=4.365, $df=1$, $P<0.05$). Treatment for 11 days also significantly prevented ossification.

We finally compared groups B and C and the differences are no longer significant. In this study, treatment for 45 days does not significantly prevent ossification better than treatment for 11 days.

Discussion

Throughout the study the protocol for total hip replacement has not been modified, and as far as indomethacin treatment is concerned, both series are exactly similar. The main characteristics of the different groups of patients were distributed identically among the 4 study groups.

The two series had two particular differences in that the treated groups contained more men and had a lower average age than the untreated group, but the differences were not significant.

The results of the comparisons between the treated groups depending on the duration of indomethacin treatment was valid. Hence the differences that are only found between treated and untreated patients could only influence the evaluation of the global effectiveness of indomethacin.

The incidence of ossification is significantly higher in men than in women [6, 9, 13, 23, 27, 34, 41], and age does not have any effect [9, 20, 21, 24, 27, 30]. However, Sodemann concludes that there is a higher incidence of ossification in younger patients [33]. Our treated series was younger and included more men. The influence of these factors could therefore only have reduced the apparent effectiveness of indomethacin in this study. The only patient who developed stage 3 ossification was elderly woman who was operated on because of rapidly degenerating coxarthrosis and was prescribed 45 days of treatment.

The results should carefully be taken into consideration because this is a retrospective study. However, the recording of the different duration of treatment according to the surgeons, but constant for each of them has allowed us to form four homogeneous groups of patients.

Within the control group, no significant difference was found between the surgeons for the occurrence of ossification. A prospective study would have lead to the occurrence of avoidable ossification in the light of present knowledge.

While studying the differentiation of fibroblasts into osteoblasts in the soft tissues, Tonna measured maximal mitotic activity 32 hours after operation [42]. The necessary mediation of the inflammatory prostaglandins explains the effectiveness of certain anti-inflammatory agents in preventing ossification because they inhibit the synthesis of some prostaglandins [5]. This hypothesis is confirmed by the clinical observations carried out during numerous studies with preventive irradiation [2, 7, 37] and the administration of anti-inflammatory agents, such as indomethacin or ibuprofen [10, 31]. The initiation of preventive treatment after the third or fourth postoperative day does not produce any significant reduction in the incidence of ossification.

Our study shows that prevention of heterotopic ossification following total hip arthroplasties can rely on the administration of indomethacin begun on the night of the operation and followed up while the patient is in hospital (about 11 days). Prevention can be carried out in hospital and under medical supervision.

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