Effect of aspirin on heterotopic ossification after total hip arthroplasty in men who have osteoarthrosis

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J Bone Joint Surg Am. 1991;73:924-929.

Effect of Aspirin on Heterotopic Ossification After Total Hip Arthroplasty in Men Who Have Osteoarthrosis*

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ABSTRACT: **The severity of heterotopic ossification was determined from the radiographs of eighty-three men in whom osteoarthrosis had been treated with a primary total hip arthroplasty with cement. The medical records of these patients were then reviewed, with the reviewer having no knowledge of the radiographic findings. A similar operative approach and technique had been used in all patients.**

There was no association between the amount of intraoperative loss of blood or the duration of the operation and the severity of formation of heterotopic bone.

The over-all rate of occurrence of heterotopic ossification was 72 per cent. Of the fifty-eight patients who had received aspirin throughout their course in the hospital, two (3 per cent) had severe ectopic ossification (grade III or IV[8]). In contrast, twelve (48 per cent) of the twenty-five patients who had received no aspirin or in whom aspirin had been discontinued so that anticoagulation could be begun had severe heterotopic ossification. The difference in the severity of the ossification between the two groups is significant ($p < 0.0001$).

Heterotopic ossification is a well known complication after total hip arthroplasty. If there is enough heterotopic bone in a critical location, it may seriously restrict motion and function[27,48,50].

In previous reports, the rate of occurrence of ectopic ossification after total hip arthroplasty has varied widely, with a range from 8 to 90 per cent[16,37,56,57]. Usually, symptoms are present only when the ossification is severe (grade III or IV). Wide variations also have been found in the rate of occurrence of symptomatic heterotopic ossification (range, 1 to 33 per cent)[11,39,48,54,53,57]. These discrepancies may be due to differences in the postoperative use of non-steroidal anti-inflammatory medications, since indomethacin, ibuprofen, and aspirin have been shown to inhibit the formation of ectopic bone in studies of both animals and humans[2,11,18,32,33,35,36,42,43,46,52,53,57,62,64]. To our knowledge, there has been no previous report on the specific effect of aspirin on heterotopic ossification after total hip arthroplasty.

Methods and Materials

Radiographs of the hips of eighty-three men who had osteoarthrosis were made six months or more after primary total hip arthroplasty had been done with cement. All of the procedures were performed between 1986 and 1988 by, or under the supervision of, one of the two senior authors (P. M. P. or E. A. S.). The occurrence and the severity of heterotopic ossification, according to the classification of Brooker et al.[8], were determined for each patient (Table I).

TABLE I

CLASSIFICATION OF BROOKER ET AL.[8] OF HETEROTOPIC OSSIFICATION ABOUT THE HIP

Grade I	Islands of bone within the soft tissues about the hip
Grade II	Spurs of bone from the pelvis or the proximal end of the femur, with at least one centimeter left between opposing osseous surfaces
Grade III	Spurs of bone from the pelvis or the proximal end of the femur, with the space between opposing osseous surfaces reduced to less than one centimeter
Grade IV	Apparent osseous ankylosis of the hip

Subsequently, the medical records of these patients were reviewed, with the reviewer having no knowledge of the radiographic findings. The patient's age at operation, the duration of the operative procedure, the estimated intraoperative loss of blood, and the history of any previous operation on the same or opposite hip were recorded. Bilateral procedures that had been performed during one anesthesia session were noted as well. Specific attention was given to the administration of non-steroidal anti-inflammatory drugs and of anticoagulant medications. The administration of medications was determined by examination of the physicians' order sheets and was corroborated by review

* No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. No funds were received in support of this study.

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TABLE II

AVERAGE AGE, INTRAOPERATIVE LOSS OF BLOOD, AND DURATION OF OPERATION

Grade[8]	No. of Patients	Age* (Yrs.)	Intraoperative Loss of Blood* (ml)	Duration of Operation* (Mins.)
0	23	67.8 (48-83)	338 (125-625)	110 (80-170)
1	24	69.0 (48-77)	345 (150-600)	111 (80-205)
2	22	64.3 (47-80)	286 (100-500)	107 (85-140)
3	12	63.4 (52-79)	340 (150-625)	116 (105-145)
4	2	69.0 (51, 87)	788 (275, 1300)	108 (105, 110)

* Mean, with range in parentheses.

of the medication-administration charts, which had been compiled by registered nurses.

The radiographic findings were compared with information from the medical records in order to find factors associated with the development of heterotopic ossification.

Results

The over-all frequency of occurrence of heterotopic ossification was 72 per cent (grade I, 29 per cent; grade II, 27 per cent; grade III, 14 per cent; and grade IV, 2 per cent). All procedures were performed through a posterolateral approach, and no trochanteric osteotomies were done. Initially, the standard postoperative protocol that is used in our institution for rehabilitation after total hip arthroplasty was employed for all patients.

No patient had had a previous operation on the involved hip, but seven patients had had an operation on the contralateral hip. We did not note the presence or degree of heterotopic ossification on the side of the previous operation. In five of these seven patients, no heterotopic bone was seen on the side of the second operation. Of the remaining two patients, grade-II ossification had developed in one and grade-III ossification, in the other.

A bilateral procedure had been done, simultaneously, in five patients. In three of the five, there was a similar degree of heterotopic ossification in each hip (either none or grade I). In the other two patients, no ectopic bone developed in one hip and grade-I bone formed in the second hip. Only the more severely involved hip of these two patients was considered for additional analysis of the data.

The age of the patient, the duration of the operation, and the amount of blood that was lost intraoperatively (Table II) were analyzed according to each grade of ossification[8], with the use of general linear models. There was no significant difference in the age of the patient or the duration of the procedure between the five groups, although a trend of decreasing age was noted with increasing heterotopic ossification (analysis of variance, $F = 2.86$, degrees of freedom = 5,77, $p = 0.02$). Compared with the other groups, the two patients who had grade-IV ossification lost significantly more blood intraoperatively (one lost 1300 milliliters) ($p < 0.005$), but there was no significant difference between any of the other groups in terms of this parameter.

Fifty-eight patients received aspirin for prophylaxis against venous thrombosis throughout the course in the hospital. Forty-three patients received 325 milligrams orally twice daily, and the remaining fifteen received 650 milligrams orally twice daily. The duration of hospitalization averaged thirteen days (range, eight to twenty-one days) for these fifty-eight patients. Severe heterotopic ossification (grade III or IV) occurred in two (3 per cent) of these patients (Table III).

TABLE III

GRADING OF HETEROTOPIC OSSIFICATION

Group	Total No. of Patients	Grade[8] 0	I	II	III	IV
All patients	83	23 (28%)	24 (29%)	22 (27%)	12 (14%)	2 (2%)
Patients who received aspirin throughout hospitalization	58	18 (31%)	19 (33%)	19 (33%)	2 (3%)	0
325 mg ×2 daily	43	15 (35%)	13 (30%)	14 (33%)	1 (2%)	0
650 mg ×2 daily	15	3 (20%)	6 (40%)	5 (33%)	1 (7%)	0
Patients who did not receive aspirin throughout hospitalization	25	5 (25%)	5 (25%)	3 (12%)	10 (40%)	2 (8%)
Warfarin given	14	3 (21%)	1 (7%)	3 (21%)	5 (36%)	2 (14%)
Aspirin discontinued	7	1 (14%)	3 (43%)	0	3 (43%)	0
Other patients	4	1 (25%)	1 (25%)	0	2 (50%)	0

In contrast, severe heterotopic ossification occurred in twelve (48 per cent) of the twenty-five patients who had received no aspirin or for whom aspirin had been discontinued before initiation of anticoagulation with heparin or warfarin. Fourteen of these twenty-five patients had been given warfarin for routine prophylaxis against venous throm-

bosis; in seven of these fourteen patients, grade-III or grade-IV ectopic bone developed. In seven others of this group of twenty-five patients, aspirin had been discontinued in the early postoperative period because anticoagulation had been instituted for the treatment of a venous thrombosis. In three of these seven patients, grade-III heterotopic bone developed. The remaining four patients in this group of twenty-five had received neither aspirin nor anticoagulant medication, and grade-III ossification developed in two of them (Table III).

None of the eighty-three patients received any non-steroidal anti-inflammatory medication other than aspirin during the period of hospitalization.

The difference in the severity of the heterotopic ossification between the patients who had received aspirin throughout the period of hospitalization and those who had not was analyzed by ridit analysis[9,24]. The group of patients who had received aspirin throughout their stay in the hospital was used as the reference group, with a mean ridit of 0.5. The mean ridit for the remaining group of twenty-five patients was 0.697. The method of chi-square analysis of Fleiss et al.[24] demonstrated that heterotopic ossification was significantly more severe in the group that had not been given aspirin (chi square = 9.53, degrees of freedom = 1, $p < 0.005$). When grades III and IV are combined into one group of patients who had severe heterotopic ossification, simple chi-square analysis is in agreement (chi square = 24.73, degrees of freedom = 1, $p < 0.0001$).

General linear models and logistic regression analysis[38] were used to examine the effect of covariates, including administration of aspirin, age of the patient, loss of blood, operative time, previous operative treatment, and a unilateral or bilateral procedure, on the subsequent development of heterotopic bone. The over-all general linear model is significant ($F = 6.35$, degrees of freedom = 6,76, $p = 0.0008$). There was a weak, non-linear relationship between a bilateral procedure, a previous operation on the hip, and a milder degree of heterotopic ossification. An attempt was made to corroborate this relationship by logistic regression. (In the analysis, the group that had grade-IV ossification was too small to be considered.) Administration of aspirin ($p = 0.007$), a bilateral procedure ($p = 0.04$), and a previous operation on the hip ($p = 0.03$) predicted a subsequent lower grade[8] of ossification. Administration of aspirin was the strongest predictor.

Discussion

Severe heterotopic ossification after total hip arthroplasty may be heralded in the first few weeks after the operation by the development of local tenderness, erythema, and inflammation at the operative site[4,13,23,26]. Ectopic bone becomes visible radiographically one to two weeks later[57]. These developments are accompanied by a rise in the level of serum alkaline phosphatase[36,44,47]. During the next several months, the heterotopic bone undergoes considerable remodeling to become a mature structure containing cortical and trabecular bone and bone marrow[46,50]. Six months to one year after the operation, the rate of remodeling decreases, and the tissue tends to stabilize[50]. When sequential bone scans suggest that the ectopic bone is mature, excision may be warranted, but the heterotopic bone frequently recurs, especially in the absence of adjuvant treatment[2,10,20,50].

For unknown reasons, heterotopic bone forms more often after an operation or traumatic injury at certain sites such as the hip, the thigh, and the elbow. One report[44] suggested that an elevated preoperative level of serum alkaline phosphatase indicates a somewhat increased risk for ectopic ossification, but this has been disputed by others[35]. It has been reported that, after total hip arthroplasty, patients in whom ectopic bone had formed after a previous procedure are at great risk for subsequent formation[16,48,53,54]. Bilateral osteophytic osteoarthrosis, ankylosing spondylitis, and diffuse idiopathic skeletal hyperostosis have also been considered by some to increase the risk of heterotopic ossification after total hip arthroplasty[5,6,14,16,21,25,31,48,53,61].

The operative approach[30,45], the amount of blood lost intraoperatively, and the duration of the operative procedure have also been associated with the development of heterotopic bone[29,58]. The last two factors did not appear to have a significant effect in this study, and we did not assess the effect of operative approaches, since all of the approaches in our series were posterolateral. Men have frequently been found to have a higher rate of occurrence of heterotopic ossification than women[16,29,30,32,40,58]. Also, ectopic bone is more common in patients who have osteoarthrosis than in those who have rheumatoid arthritis[14,16,29,30,34], possibly because of the increased use of non-steroidal anti-inflammatory drugs by rheumatoid patients. In the present study, only men who had osteoarthrosis were included because we believed that they were at higher risk for heterotopic ossification.

The cause of formation of heterotopic bone has not been completely elucidated[66]. Chalmers et al.[12] identified three prerequisites: (1) the presence of an inducing agent (such as operative trauma), (2) an osteogenic precursor cell, and (3) an environment that is conducive to osteogenesis. Evidence suggests that the bone-forming cells originate from osteogenic stromal elements[50]. Osteoinductive substances are probably released as a result of the operative insult, and they may cause a localized proliferation of these mesenchymal cells[30]. These cells are thought to differentiate later into osteoblast-like cells[33]. An osteoid matrix is formed and then mineralized.

The inhibitory action of non-steroidal anti-inflammatory drugs on heterotopic ossification is probably related to the inhibition of the activity of prostaglandin synthetase by these drugs[17,22,67]. The resulting decrease in local concentrations of osteoactive prostaglandins (especially prostaglandin E_2) may be a key to the inhibition of formation of heterotopic bone[35]. In studies of animals, non-steroidal anti-inflammatory drugs have been shown to delay the healing of bone after local trauma[1,19,55,62]. Allen et al.[1] revealed a dose-related delay in fracture-healing in rats that had been fed an aspirin-rich diet. Dekel and Francis[15] reported that

aspirin reduced radiographic evidence of destruction of bone and formation of new bone in rabbits that had experimental osteomyelitis. Non-steroidal medicines, including aspirin, have also been reported to reduce the destruction of bone that is associated with malignant tumors[49].

Törnkvist et al.[62], who induced formation of heterotopic bone in rats by implantation of demineralized bone matrix, showed that when indomethacin was administered at the time of implantation, the formation of ectopic bone was reduced in a dose-dependent fashion. Subsequently, Nilsson et al.[46] reported that a six-day course of indomethacin decreased the formation of new bone as much as a six-week course. If indomethacin was not given until one week after implantation, it did not affect formation of bone.

These studies indicate that the stimulus for the induction of heterotopic ossification is present for only a short time and, therefore, heterotopic ossification may be inhibited by a short course of treatment. The studies also suggest that non-steroidal anti-inflammatory drugs diminish the formation of ectopic bone by modifying the inflammatory response that is characteristic of the initial phase of formation. This morphogenetic stage is associated with mesenchymal proliferation before cytodifferentiation. However, Törnkvist et al. found that indomethacin did not inhibit the proliferation of mesenchymal limb-bud cells of chickens or inhibit the formation of cartilage and mineralized tissue in an *in vitro* study[63].

It thus appears that, in the inflammatory period immediately after an operation, anti-inflammatory drugs, through their inhibition of prostaglandin synthetase, alter the local environment at the site of operative trauma. This change in environment tends to inhibit the proliferation and maturation of pleuripotential osteogenic precursors and limits the development of heterotopic bone.

In previous clinical studies, indomethacin[2,11,32-34,42,52,53,57] and ibuprofen[18,64] have been shown to decrease the severity of heterotopic ossification after total hip arthroplasty. Aspirin has been reported to inhibit the development of heterotopic bone after head injury[43], and its inhibitory action was implied in two studies involving total hip arthroplasty[33,37].

Our series was retrospective, with the possibility of bias in the selection of patients. Although a prospective study with random assignment of patients is preferable, our results clearly indicate that aspirin significantly decreases the severity of heterotopic ossification after total hip arthroplasty in men who have osteoarthrosis.

Indomethacin has been used most commonly to reduce the formation of ectopic bone, but aspirin may have a similar effect, and it is associated with fewer gastrointestinal side-effects and is tolerated better by patients. Cella et al.[11] reported that 37 per cent of patients who were candidates for prophylaxis against heterotopic ossification could not complete a six-week course of indomethacin. No patient in our study was forced to discontinue the use of aspirin because of intolerance to the drug.

Our patients were asked to discontinue use of all non-steroidal anti-inflammatory agents for at least one week before admission to the hospital. When aspirin was used, it was begun on the day of the operation. The patients were monitored for the administration of aspirin only during their hospitalization, but many were instructed to continue taking the drug for six weeks after the operation. At least twenty-eight patients were given both written and oral instructions about this, and many of the others were given oral instructions. We cannot assess the compliance of the patients in terms of their taking aspirin or other non-steroidal anti-inflammatory agents after discharge from the hospital, but experimental evidence has suggested that a short course may be as effective as a long one. Indeed, McMahon et al.[42] recently reported successful inhibition of heterotopic ossification with the use of indomethacin for ten days.

Knahr et al. examined the effects of different methods of prophylaxis against thrombosis on the development of heterotopic bone after total hip arthroplasty[37]. They found a significantly lower rate of heterotopic ossification in patients who had been given 1000 milligrams of aspirin and 400 milligrams of oxyphenbutazone daily for ten to fourteen days compared with the rate in patients who had received low-dose heparin or dextran 40. A group that had been given low-dose heparin together with indomethacin had an intermediate rate of formation of heterotopic bone, but gastrointestinal side effects were common. Ritter and Vaughan[54] noted no difference in heterotopic ossification between groups that had been treated with warfarin or low-dose heparin. It is likely that neither group had received anti-inflammatory drugs.

In order to reduce the risk of excessive bleeding, non-steroidal anti-inflammatory drugs are withheld from our patients when warfarin or heparin is administered. However, we have found that these patients have a higher rate of severe heterotopic ossification. Therefore, in patients who are already at high risk for severe heterotopic ossification, one might consider alternatives to the use of warfarin or heparin for prophylaxis against thrombosis, such as aspirin or sequential compression boots. If the risk of deep venous thrombosis is high or if thrombosis occurs early in the postoperative period and warfarin or heparin is given to a patient who is also at high risk for heterotopic ossification, low-dose radiation can be used to retard the formation of ectopic bone[3,7,14,28,30,41,48].

It should be emphasized that all patients in this study had a total hip arthroplasty with cement. Studies in animals have shown that anti-inflammatory drugs inhibit fracture-healing[1,55] and haversian remodeling[59,60]. In addition, it has been shown that indomethacin, ibuprofen, and high-dose aspirin reduce the ingrowth of bone into porous-coated implants in rabbits[65]. The use of indomethacin was recently reported to have no apparent effect on the clinical results of total hip arthroplasties that were done without cement[33,42], but other authors have advised caution in the use of these drugs in the presence of a porous implant[57,65].

NOTE: The authors thank Margaret G. E. Peterson, Ph.D., for statistical analysis of the data.

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