No effect of low-dose aspirin for the prevention of heterotopic bone formation after total hip replacement

A randomized trial of 2,649 patients

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ABSTRACT — 2,649 patients scheduled for elective total hip replacement were recruited to the Heterotopic Bone Formation Sub-study of the Pulmonary Embolism Prevention Trial. Heterotopic bone formation was determined by radiographic examination and associated late postoperative outcomes were assessed by telephone interview. Heterotopic bone formation was observed in 627 (31%) of 2,048 radiographic examinations. There was no detectable effect of low-dose aspirin on the risks of heterotopic bone formation (RR 0.98; 95% CI 0.85–1.12), late postoperative pain (RR 1.10; 95% CI 0.91–1.35) or late postoperative impaired function (RR 1.03; 95% CI 0.94–1.12). The balance of benefits and risks of low-dose aspirin is determined by its effects on vascular events and bleeding, since it has no major effects on heterotopic bone formation or associated clinical outcomes.

Background

About one third of all patients undergoing total hip replacement will develop some heterotopic bone formation (Brooker et al. 1973, Knelles et al. 1997). Randomized trials (Neal et al. 2000) have shown a reduced risk of heterotopic bone formation in patients given medium to-high-doses of perioperative non-steroidal anti-inflammatory drugs (NSAIDs). Since reliable preoperative identification of patients at high risk of developing heterotopic bone is not possible, effective prophylaxis may only be achieved with routine prophylactic therapy (Bogoch and Wright 1994). Lower doses of NSAIDs cause fewer gastro-intestinal complications (Wilholm et al. 1985) and may be a well-tolerated and effective treatment suitable for routine administration. However, the effects of lower doses of NSAIDs on heterotopic bone formation and associated late postoperative clinical outcomes are unknown. The multicenter Pulmonary Embolism Prevention Trial provided an opportunity to assess the effects of low-dose aspirin on these outcomes. We report the principal findings of the Heterotopic Bone Formation Sub-study of the Pulmonary Embolism Prevention Trial.

Methods

Patient recruitment

The project was conducted in 21 hospitals in New Zealand that participated in the Pulmonary Embolism Prevention Trial. The design of that trial has been reported (MacMahon et al. 1994). All patients recruited to the Pulmonary Embolism Prevention Trial and scheduled for elective hip arthroplasty were included in the heterotopic bone formation sub-study. The trial was approved by the local ethics committee in each collaborating

Table 1. Baseline characteristics of study participants

	Aspirin	Placebo
Number of patients	1,332	1,317
Mean age, years	66	65
Female, %	50	51
Scheduled surgery		
Total hip replacement, %	97	95
Femoral hemi-arthroplasty and other, %	3	5
Bilateral, %	2	2
Revision, %	13	13
Regional anesthesia,%	53	55

institution and informed consent to participate was obtained from every participant.

The mean age of patients was 65 years and half were men (Table 1). Almost all the surgical procedures were total hip replacements and a little over one half were performed under regional anesthesia. A few percent of operations were bilateral and about 1 in 7 of the patients in the study was admitted for revision surgery.

Randomized treatment

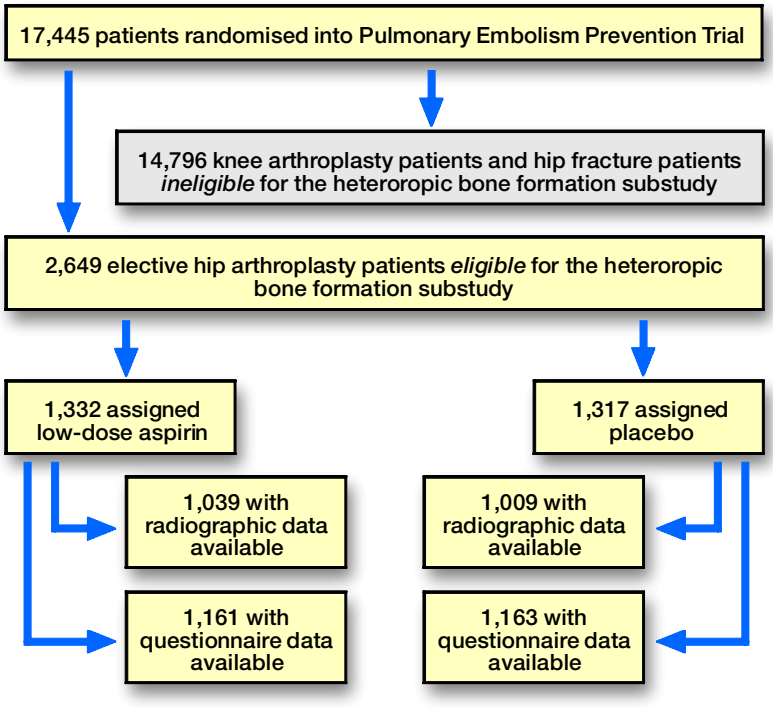
Patients were randomly assigned, double-blind, to receive daily treatment with either low-dose aspirin (162 mg/day) or matching placebo. Treatment was scheduled to begin immediately after randomization and before surgery, and to be continued daily until completion of the 35-day course. Random allocation to treatment was performed by telephone call to the Clinical Trials Research Unit randomization service located in Auckland, New Zealand. A computer program provided treatment assignment, with stratification for clinical center, age, gender, and the use of aspirin or other non-steroidal agents during the 48 hours preceding randomization.

Data collection

Patient characteristics at baseline and follow-up data from the first 35 days after randomization were routinely collected for all patients as part of the main Pulmonary Embolism Prevention Trial. Follow-up data on radiographic and late postoperative clinical outcomes were sought only from about the participants of the Heterotopic Bone Formation Sub-study. All such data were collected blinded as to the randomized treatment allocation.

Radiographic outcomes. A hip radiograph taken at least one month and as close as possible to 6 months after the date of randomization, as part of the routine postoperative follow-up, was sought for every patient. All radiographs were assessed by one study radiologist (TH). Heterotopic bone was graded using the classification system described by Brooker et al. (1973) and evidence of loosening was graded using a standard assessment system (Johnston et al. 1990). In patients who underwent bilateral surgery, the hip with worst heterotopic bone formation was reported.

To determine the repeatability of the Brooker grading, a sample of 100 radiographs was re-read



Trial profile

by the study radiologist and a second sample of 90 radiographs was read by an external radiologist. The study radiologist was blind to both the identity and timing of the radiographs submitted for re-reporting. There was reasonable correlation between the findings of initial and repeat readings of radiographs by the study radiologist (weighted Kappa correlation coefficient (Cohen 1960) 0.50 (95% confidence interval 0.30–0.70)) and between the findings of the study radiologist and the external radiologist (weighted Kappa correlation coefficient 0.50 (95%CI 0.33–0.67)).

Late postoperative clinical outcomes. One telephone interviewer sought data on late postoperative clinical outcomes from all eligible patients. Data collection was performed using 11 simple questions derived from a standard assessment system (Johnston et al. 1990) and administered via a structured questionnaire. For each question, the patient was asked to indicate the best answer from up to 4 alternatives on an ordinal scale. Patients who were not successfully contacted by telephone were mailed the questionnaire with instructions for completion.

Statistics

The principal analyses were performed according to the intention-to-treat principle and all outcomes were dichotomized. Relative risks and 95% confidence intervals were estimated for the effects of aspirin compared to placebo. There was 80% power to detect a one sixth difference in the risk of developing HBF between the randomized groups (alpha = 0.05). Chi-square tests were performed to test the significance of differences between the randomized groups. Effects of covariates were studied by stratification and by the fitting of multivariate models. Multivariate analyses, investigating the effects of the covariates age, gender, use of non-trial aspirin or other NSAIDs, use of cement, use of other antithrombotic agents, primary versus revision surgery, and time between randomization and assessment, were performed using logistic regression models for dichotomous outcomes, and proportional odds models for ordinal outcomes. The effects of missing data were studied using maximum likelihood imputation procedures (Dempster et al. 1977). Answers to the 3 questions about pain were combined by fitting mixed models, as were answers to the 5 questions about function (Littell et al. 1996). Chi-squared tests of homogeneity were performed to detect heterogeneity. Principal analyses were done using the SAS statistical package (SAS Institute 1985).

Table 2. Adherence to study treatments, and use of anticoagulants and non-trial aspirin or other NSAIDs

	Aspirin	Placebo
Adherence to study treatments		
First tablets taken preoperatively, %	92	93
Tablets continued daily until discharge, %	87	85
Discharged on tablets, %	84	82
Anticoagulants		
Heparin, %	36	39
Warfarin, %	5	4
Non-trial aspirin or other NSAID use		
Within 48 hrs preoperatively, %	26	25
Within 35 days postoperatively, %	31	29
Preoperatively or postoperatively, %	44	42

Results

Data availability

2,649 participants of the Pulmonary Embolism Prevention Trial were eligible for inclusion in the heterotopic bone formation sub-study. Baseline patient characteristics were obtained for all patients. Radiographs for the assessment of heterotopic bone formation and loosening were available for 2,048 (77%) of the participants. 142 (5%) patients had no radiograph taken postoperatively, 289 (11%) had a radiograph taken only within the first postoperative month, 122 (5%) had an untraceable radiograph and for 48 (2%), no information about radiological examinations was available. Data on late postoperative outcomes associated with heterotopic bone formation were available for 2,324 (88%) patients. These data were not collected from 96 (4%) deceased patients, and from 229 (8%) patients who could not be contacted by phone or mail.

Adherence to study treatment, and use of non-trial aspirin or other NSAIDs

Adherence to study treatments was good (Table 2). More than 9 of every 10 participants started treatment preoperatively and 8 of every 10 were

discharged on study treatment. However, use of non-trial aspirin or other NSAIDs in the perioperative period was high (Table 2). About one quarter of participants used non-trial aspirin or other NSAIDs in the 48 hours before surgery and another quarter used such treatment during the 35-day follow-up period.

Baseline characteristics, adherence to study treatments and frequency of non-trial aspirin or other NSAID use did not differ between randomized groups or between groups for which data were available and data were not available.

Table 3. Radiological findings

		Aspirin	Placebo
Number of patients with radiographic data		1,039	1,009
Time from randomization to radiologic examination			
Mean, days		270	273
Range, days		32–1367	34–1345
Cemented components			
Femoral, %		71	69
Acetabular, %		48	43
Femoral or acetabular, %		73	71
Heterotopic bone formation			
Brooker grade	0	727 (70%)	694 (69%)
	1	220 (21%)	202 (20%)
	2	60 (6%)	69 (7%)
	3	22 (2%)	32 (3%)
	4	10 (1%)	12 (1%)
Loosening			
Acetabular		6 (1%)	8 (1%)
Femoral		2 (< 1%)	2 (< 1%)

Radiographic findings

Heterotopic bone formation was found in 627 (31%) radiographs (Table 3). The range of times between randomization and the radiographic examination was wide with a mean of about 9 months. Almost three-quarters of patients had at least one cemented component. There was no detectable difference in the relative risk of heterotopic bone formation between those assigned low-dose aspirin and those assigned placebo (0.98 (95% CI 0.85–1.12, p = 0.7)). Stratification provided no evidence of different effects of treatment on the risk of heterotopic bone formation in subgroups defined by age, gender, use of cement, use of non-trial aspirin or other NSAIDs, revision versus primary surgery, concomitant use of heparin or warfarin and time between randomization and radiographic examination (p for homogeneity, all > 0.1). Multivariate analyses, analyses of ordinal outcome measures and analyses with imputation of missing data did not alter the findings.

Radiographic evidence of prosthetic loosening was observed in only 16 cases, 8 in the actively treated group and 8 in the placebo group (Table 3). In 2 cases, both the acetabular and femoral components were affected. These events were too few to estimate the effects of low-dose aspirin on the risk of loosening.

Late postoperative findings

After an average follow-up of about 22 months, persisting postoperative hip pain or a need for analgesia to control hip pain was found in 1 of every 5 patients (Table 4). 6 of every 7 patients were better able to perform activities of everyday living postoperatively, but most reported some difficulties or restriction of mobility. There was no detectable difference in the risks of impaired late postoperative outcomes between those assigned low-dose aspirin or placebo. Overall, the risk of pain in patients assigned active treatment compared to the controls was 1.10 (95% CI 0.91–1.35, p = 0.3) and the risk of impaired function was 1.03 (95% CI 0.94–1.13, p = 0.5). Multivariate analyses, analysis by ordinal outcome measures and analyses with imputation of missing data did not alter the findings.

Discussion

In this study, almost 1 in 3 patients developed some heterotopic bone and 1 in 10 moderate-to-severe heterotopic bone (Brooker grades 2, 3 or 4). Low-dose aspirin had no detectable effect on the risk of heterotopic bone formation after hip arthroplasty despite good statistical power. This

Table 4. Late postoperative pain and function

	Aspirin	Placebo
Number of patients with data from questionnaire	1,161	1,163
Time from randomization to interview		
Mean, days	679	679
Range, days	139–1631	214–1768
Replies to questionnaire		
Pain		
Still has pain in hip	217 (19%)	185 (16%)
Hip pain no better than preoperatively	37 (3%)	47 (4%)
Need for regular painkillers for hip	203 (17%)	182 (16%)
Activities of daily living		
Unable to do everyday tasks better	159 (14%)	148 (13%)
Difficulty with shoes and socks	612 (53%)	597 (51%)
Needs support to climb stairs	722 (62%)	722 (62%)
Difficulty rising from an armchair	943 (81%)	941 (81%)
Unable to walk unsupported for 30 minutes	345 (30%)	349 (30%)
Other		
Gave up work because of surgery	29 (2%)	22 (2%)
Moved house because of surgery	28 (2%)	16 (1%)
Not very satisfied with surgery	84 (7%)	79 (7%)

finding differs from the results of other randomized trials of NSAIDs which have together shown an approximate halving of the risk of heterotopic bone formation with NSAID therapy (Neal et al. 2000). The difference between the findings of the Heterotopic Bone Formation Sub-study of the Pulmonary Embolism Prevention Trial and those of the previous studies are unlikely to have arisen by chance and most probably reflect differences in the treatment regimens study.

The dose of aspirin used in the Pulmonary Embolism Prevention Trial (162 mg/day) was selected for investigation of the effects on thrombotic and hemorrhagic outcomes not for effects on heterotopic bone formation. A higher dose of aspirin might have had effects on the risk of heterotopic bone formation, although it is also possible that aspirin is a less effective prophylactic agent than other NSAIDs. Another recent study suggested that aspirin in a much higher dose (2,250 mg/day) reduced heterotopic bone formation, but its efficacy appeared to be less than half that of indomethacin or radiation therapy (Knelles et al. 1997).

A modest effect of low-dose aspirin may have been underestimated or missed by the heterotopic bone formation sub-study of the Pulmonary Embolism Prevention Trial. Although adherence to study treatments was good, the use of non-trial aspirin and other NSAIDs in the perioperative period (drop-in) was high (42%). This level of drop-in would be expected to result in an underestimate of the true effects of treatment by about one third, even though drop-in was equally distributed between active and placebo groups (Rodgers and MacMahon 1995). However, analyses stratified by use of non-trial aspirin and other NSAIDs provided no evidence to support dilution of a marked treatment effect by drop-in. Errors in the classification of heterotopic bone formation may also have resulted in underestimation of the true effects of low-dose aspirin (Rodgers and MacMahon 1995). However, the correlation between initial and repeat measurements makes it unlikely that misclassification would have resulted in a failure to detect any important effect of treatment.

Most patients in the study appeared to obtain benefit from surgery but persisting late postoperative pain and impaired function were common among trial participants. In accord with the absence of any effect of low-dose aspirin on heterotopic bone formation, there was no evidence of any effects of low-dose aspirin on the risk of the associated late postoperative outcomes of pain and impaired function. It therefore still remains uncertain whether effective prophylaxis against heterotopic bone formation would have clinically important effects on pain and function after hip surgery.

In conclusion, low-dose aspirin did not provide effective prophylaxis against the risks of heterotopic bone formation, late postoperative pain or long-term impaired function. The balance of benefits and risks of low-dose aspirin is therefore determined largely by its effects on vascular events and bleeding.

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