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Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial

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Abstract

Objectives To determine the benefits and risks of a non-steroidal anti-inflammatory drug (NSAID) as prophylaxis for ectopic bone formation in patients undergoing total hip replacement (or revision) surgery.
Design Double blind randomised placebo controlled clinical trial, stratified by treatment site and surgery (primary or revision).
Setting 20 orthopaedic surgery centres in Australia and New Zealand.
Participants 902 patients undergoing elective primary or revision total hip replacement surgery.
Intervention 14 days' treatment with ibuprofen (1200 mg daily) or matching placebo started within 24 hours of surgery.
Main outcome measures Changes in self reported hip pain and physical function 6 to 12 months after surgery (Western Ontario and McMaster University Arthritis index).
Results There were no significant differences between the groups for improvements in hip pain (mean difference −0.1, 95% confidence interval −0.4 to 0.2, P=0.6) or physical function (−0.1, −0.4 to 0.2, P=0.5), despite a decreased risk of ectopic bone formation (relative risk 0.69, 0.56 to 0.83) associated with ibuprofen. There was a significantly increased risk of major bleeding complications in the ibuprofen group during the admission period (2.09, 1.00 to 4.39).
Conclusions These data do not support the use of routine prophylaxis with NSAIDs in patients undergoing total hip replacement surgery.
Trial registration NCT00145730.

Introduction

Chronic symptomatic osteoarthritis of the hip is common in those aged ≥50 and total hip replacement is a well established and highly effective treatment.[1] While surgery reduces pain and improves physical function in most people, residual symptoms are common.[2–4] One determinant of the risk of long term pain and disability after hip replacement is ectopic bone—abnormal bone that forms postoperatively in the soft tissues around the operated hip.[5] Some ectopic bone occurs in more than one third of all patients who undergo hip replacement.[6] Both the risk of occurrence and the severity, as judged from radiographic measurements, can be greatly reduced by a short course of postoperative non-steroidal anti-inflammatory drugs (NSAIDs).[7]

Routine prophylaxis with a short course of postoperative NSAIDs has been advocated for all patients undergoing total hip arthroplasty[8 9] because it is not possible preoperatively to identify patients at risk of developing ectopic bone. All recent randomised clinical trials are uniformly characterised by the lack of a placebo group. Before the widespread introduction of such a preventive strategy, more evidence is required about the balance of benefits and risks, particularly in light of recent concerns about the safety of some NSAIDs.[10] Specifically we need to determine whether improvements in radiographic abnormalities produced with NSAIDs result in worthwhile benefits for long term pain and physical function.[7] We also need to determine whether there are any safety issues.

We established the effects of a routine short course of postoperative ibuprofen[11 12] on pain and physical function 6 to 12 months after total hip replacement surgery. We also evaluated the effect of treatment on other measures of physical function, radiographic ectopic bone formation, and bleeding complications.

Methods

We carried out this double blind, randomised, placebo controlled trial in patients undergoing elective total hip replacement surgery at 20 hospitals in Australia and New Zealand between February 2002 and May 2004. All patients provided written informed consent, and an independent safety and monitoring committee reviewed the data during recruitment. Details of the study methods and implementation strategy have been published elsewhere.[13]

Participants—Patients identified within 24 hours of completed elective total hip replacement surgery (primary or revision) were eligible for inclusion, irrespective of age, reason for surgery, or procedure performed. Patients were ineligible if there was, in the opinion of the responsible physician, a definite indication for treatment with an NSAID during the 14 day study treatment period (for example, patients in whom no other analgesic agent was deemed suitable) or a definite contraindication for treatment with an NSAID (for example, previous serious adverse reaction to an NSAID, previous major gastrointestinal bleed, serious renal impairment, or known bleeding disorder). In addition, patients

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who had taken an NSAID (other than low dose aspirin) in the 48 hours before the operation were not eligible nor were patients with a postoperative spinal catheter in situ unless the catheter had been removed at least two hours before randomisation.[14]

Randomisation—Randomisation was performed centrally by using a computer based system accessible 24 hours a day via a toll-free telephone call within 24 hours after surgery. On confirmation of eligibility, researchers used a minimisation algorithm[15] to provide a unique randomisation code corresponding to a treatment pack held at the centre. We used a minimisation program to stratify treatment by study centre and type of surgery performed (primary or revision). Treatment allocation was blinded and concealed from patients and study staff until the database was locked.

Treatment and control—Participants were randomised to receive 14 days of treatment with either ibuprofen (2×200 mg tablets three times daily) or matching placebo tablets. All study tablets were packaged in identical blister packs. Treatment was scheduled to start within 24 hours after surgery and patients could not take other NSAIDs (with the exception of low dose aspirin) during the study period. The protocol required no other changes to usual preoperative or postoperative care.

Data collection and follow-up—Demographic variables and baseline clinical data were obtained during the usual pre-admission clinic visit, typically one to two weeks before surgery. Information about the anaesthetic and surgical techniques, postoperative care, and early indicators of bleeding complications was collected during hospital admission. All other outcomes were recorded at a routine follow-up visit scheduled, depending on the operating centre, for between 6 months and 12 months after surgery. Serious adverse events in hospital were documented as they occurred and were specifically inquired about during the 14 day monitoring telephone call and at the follow-up visit. All assessments were standardised and performed blind to randomised treatment allocation.

Outcomes—Our primary study outcomes were the changes from baseline to follow-up in self reported hip pain and physical function measured by the Western Ontario and McMaster Universities arthritis index (WOMAC) questionnaire (Likert version).[16] We standardised scores to a range of 0-10, with 0 indicating no hip pain or no difficulty with daily activities and 10 indicating severe hip pain or severe difficulty with daily activities. Secondary outcomes were general health status (summary scale scores on physical and mental components[17]) of the medical outcomes study short form 36 (SF-36)[18]); patients' global assessment of effectiveness of treatment (hip status compared with before surgery; hip status today) with five response levels; frequency of use of analgesia for hip pain during the past week; ability to get "about the house" and ability to get "out of the house" with five response levels ranging from "not at all" to "no difficulty"; time spent participating in physical activity during the past week; objective measures of physical performance (hip flexion,[19] time to walk 50 feet (about 15 metres), and timed "up and go"[20]); radiographic evidence of ectopic bone formation according to the Brooker classification[21]; and major bleeding complications during hospital admission (bleeding from the wound for more than three days, evacuation of a wound haematoma, haematemesis, melaena, other serious bleeding event). Red cell transfusions (or re-infusions), suction drainage volumes, and postoperative haemoglobin concentrations (measured ≥48 hours after surgery) were also recorded.

Analysis—We planned to recruit 1000 patients to provide 90% power ($\alpha = 0.05$) to detect a difference of ≥10% between the randomised groups for each of the two primary outcomes.[13] The actual sample size of 902 achieved at the end of the recruitment period provided 87% power to detect these effects. We used *t* tests to evaluate changes in the primary outcomes of pain and physical function (WOMAC) and health related quality of life (SF-36) and to compare differences in other continuous outcome measures at follow-up. In each case we calculated the estimated difference between randomised groups, the 95% confidence interval of the difference, and the corresponding P value. We compared categorical outcomes for the proportions of patients with events with χ^2 tests to obtain a P value and calculated the relative risk and 95% confidence intervals. For ordinal outcomes we evaluated the effects of randomised treatment by fitting a proportional odds model and calculating the odds ratio (and 95% confidence intervals) of an improved outcome with ibuprofen.[15] In each case we tested the assumption of proportionality and found it was not violated. All analyses were done according to the principle of intention to treat. We carried forward baseline assessments when follow-up data were missing.

Results

We were able to randomise only 902 patients because of slow recruitment and funding limitations (452 to ibuprofen and 450 to placebo, figure). Baseline data were missing for four (0.4%) and primary outcome data were missing for 27 (6%) allocated to ibuprofen and 22 (5%) allocated to placebo (figure). Of those who completed the primary outcomes assessment, 823 (96%) assessments were conducted during an outpatient clinic visit and the remainder by telephone. The median (range) period of follow-up was 7.6 months (5-18 months) and 7.9 months (5-20 months) for the ibuprofen and placebo groups, respectively. Only 16 (2%) outcomes assessments (6 and 10 participants respectively) occurred 14 or more months after surgery. Standard anteroposterior radiographs, scheduled to be taken 6 to12 months after surgery, were obtained for 798 (88%) participants. There was no significant difference between the two allocation groups in follow-up rates for any of the outcome measures.

Baseline characteristics

The mean age of participants was 66, and 54% were men. Most had a diagnosis of osteoarthritis and were undergoing a primary hip replacement. The groups were well balanced regarding demographics, clinical history, surgical technique, and anaesthesia (table 1).

Adherence to randomised treatment

In total 875 (97%) patients started the randomised treatment, and 188 (21%) stopped prematurely (106 (24%) in the ibuprofen group and 82 (19%) in the placebo group, P = 0.06, figure). Treatment was stopped, usually on medical advice and mainly because of suspected side effects or intolerance (11% *v* 8%, P = 0.13) or other unspecified medical reasons (8% *v* 7%, P = 0.34).

Effects of randomised treatment

Pain and physical function—There was no significant differences between the groups for improvements in hip pain (mean difference −0.1, 95% confidence interval −0.4 to 0.2, P = 0.59) or physical function (−0.1, −0.4 to 0.2, P = 0.48) 6 to 12 months after surgery (table 2).

Secondary clinical outcome measures—There were no significant differences between the groups on the secondary clinical outcomes of general health status (table 2), global assessments

Table 1 Baseline characteristics and features of surgery in patients undergoing hip replacement according to postoperative treatment. Figures are numbers (percentages) of patients unless stated otherwise

	Ibuprofen (n=449)	Placebo (n=449)
Mean (SD) age (years)	66 (12)	67 (11)
Men	245 (54)	244 (54)
Diagnosis*:		
Osteoarthritis	407 (90)	424 (94)
Inflammatory arthritis	11 (2)	4 (1)
Other	53 (12)	35 (8)
Charnley grading:		
Unilateral hip	313 (70)	304 (68)
Bilateral hip	116 (26)	125 (28)
Multiple joint disease	20 (4)	20 (5)
Revision surgery	37 (8)	39 (9)
Duration >3 hours	50 (11)	55 (12)
Anaesthesia*:		
General	257 (57)	255 (57)
Spinal	279 (62)	291 (65)
Epidural	38 (8)	43 (10)
Approach:		
Anterior/anterolateral	129 (29)	137 (31)
Posterior/posterolateral	272 (60)	264 (59)
Other	50 (11)	47 (11)
Cemented components:		
Acetabular	128 (28)	122 (27)
Femoral	266 (59)	275 (62)
Trochanteric osteotomy	58 (13)	55 (12)
Bone grafting	42 (9)	52 (12)
Anticoagulant regimen*:		
Standard heparin	33 (7)	43 (10)
Low molecular weight heparin	237 (53)	241 (54)
Aspirin/antiplatelet	193 (43)	194 (43)

*Some patients had multiple diagnoses or more than one anaesthesia or anticoagulant regimen.

(table 3), participation in physical activity, or objective measures of physical performance (table 4). Furthermore, the odds of having a better outcome in terms of global assessment of effectiveness of treatment (hip status today, mobility "out of the house") or use of analgesia for hip pain were not significantly increased among patients allocated to ibuprofen (table 3).

Bleeding complications during admission—There was a significantly increased risk of major bleeding complications among those in the ibuprofen group (risk ratio 2.09, 1.00 to 4.39, P = 0.046) (table 5). There were no significant differences between groups in the proportion of patients requiring red cell transfusion (ibuprofen 37% *v* placebo 34%, P = 0.35), suction drainage volumes (415 ml *v* 424 ml, P = 0.71), or postoperative haemoglobin concentrations measured ≥48 hours after surgery (105 g/l *v* 105 g/l, P = 0.80). The latter result was materially altered when we excluded transfused (or re-infused) patients from the analyses (102 g/l *v* 100 g/l, P = 0.26).

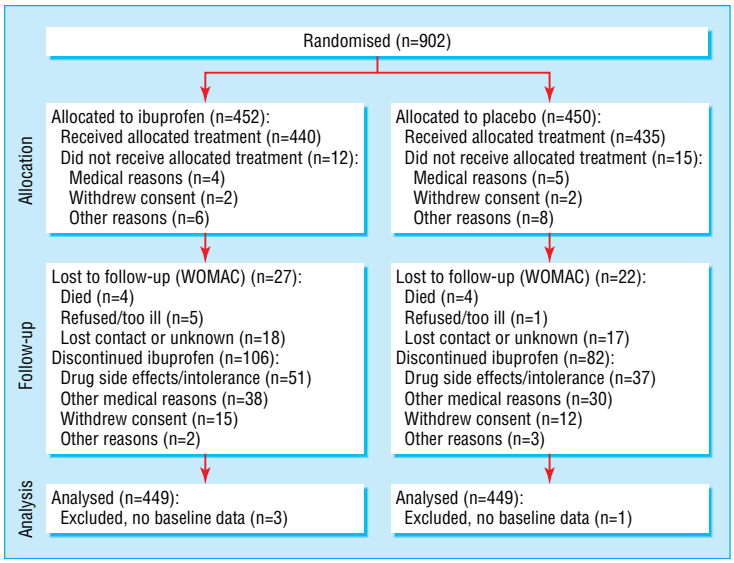
Serious adverse events during follow-up—Eight participants died. All deaths occurred between 6 days and 180 days after the end of the study treatment (median 78 days) (table 5). The difference in the numbers of serious adverse events between the allocation groups was not significant.

Ectopic bone formation—There was a highly significant decrease in the risk of developing ectopic bone of any grade (0.69, 0.57 to 0.83) and in the risk of developing severe ectopic bone (Brooker grade 3 or 4) (0.44, 0.22 to 0.88) among patients in the ibuprofen group (table 6). The odds of developing a more severe grade of ectopic bone with ibuprofen was 0.55 (0.41 to 0.73). Patients with Brooker grade 3 and 4 had higher pain and disability scores than those with less severe grades of ectopic bone formation, though this trend was not significant.

Discussion

Ibuprofen routinely administered after total hip replacement surgery does not result in better long term clinical outcomes, despite significantly decreasing the risk of ectopic bone formation. Postoperative ibuprofen also increases the risk of serious bleeding complications.

We carried out this study because observational studies had reported adverse effects of ectopic bone on clinical outcomes[5] and earlier trials provided clear evidence that NSAIDs decreased the occurrence of radiographic ectopic bone.[7] We observed the anticipated beneficial effect of ibuprofen on radiographic outcomes but found no corresponding improvement in clinical outcomes. The most plausible explanation for this finding is that minor or moderate ectopic bone has little effect on clinical out-



Details of flow of participants through study

Table 2 Mean (SD) score for pain, physical function, and general health status before surgery (baseline) and at follow-up (6 to 12 months after surgery) in patients undergoing hip replacement according to postoperative treatment with change and difference in change with 95% confidence intervals

	Ibuprofen (n=449)			Placebo (n=449)			Difference in change, P value
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Pain (0-10)	5.6 (1.9)	1.4 (2.0)	4.3 (4.1 to 4.5)	5.6 (1.9)	1.2 (1.8)	4.3 (4.1 to 4.5)	–0.1 (–0.4 to 0.2), 0.6
Function (0-10)	6.0 (1.9)	1.9 (2.0)	4.1 (4.0 to 4.2)	6.0 (1.8)	1.8 (1.9)	4.2 (4.1 to 4.3)	–0.1 (–0.4 to 0.2), 0.5
SF-36 (PCS)	30.8 (8.5)	45.2 (10.8)	14.4 (13.3 to 15.5)	31.5 (8.4)	45.6 (10.2)	14.1 (13.0 to 15.2)	0.4 (–1.2 to 1.9), 0.6
SF-36 (MCS)	46.2 (12.3)	53.9 (10.2)	7.7 (6.6 to 8.8)	46.3 (12.8)	54.6 (10.6)	8.4 (7.2 to 9.6)	–0.7 (–2.3 to 0.9), 0.4

PCS=physical component summary scale score; MCS= mental component summary scale score.

comes after hip arthroplasty. This explanation is supported by the WOMAC pain and function subscales reported in table 6. While severe ectopic bone (Brooker grades 3 and 4) can impair outcome, this forms in only a small proportion of patients. Hence, although a much larger trial might detect some beneficial effect of ibuprofen on clinical outcomes, any such clinical benefit would be small in absolute terms and probably inconsequential in the context of the large improvement in clinical outcomes achieved with joint replacement surgery itself.

The study treatment was generally well tolerated, with no significant difference in rates of discontinuation between groups. There was a borderline significant increase in major bleeds among patients in the ibuprofen group, which might reflect the antiplatelet effects of cyclo-oxygenase I inhibition.[22] While there was no clear effect of study treatment on other measures of bleeding in the postoperative period, an increase in risk of bleeding is consistent with the established effects of other NSAIDs.[23]

Our results provide no evidence of clinical benefit 6 to 12 months postoperatively and raise concerns about the safety of ibuprofen for the prevention of ectopic bone formation after hip arthroplasty. There is no particular reason to believe that other conventional NSAIDs would have produced materially different results.[23 24] These findings, therefore, suggest that recommendations promoting routine prophylaxis with a short course of postoperative NSAIDs for all patients undergoing hip arthroplasty are not justified. While some patients at high risk of ectopic bone formation (such as those with a history of it) may derive clinical benefits from prophylaxis with NSAIDs that outweigh any risks, randomised trials are required to substantiate this. Our results provide further evidence that guidelines for routine clinical care in surgery, as in other specialties, must be based on clinically important outcomes rather than surrogates such as radiographic ectopic bone formation.[25] Without such evidence, the widespread use of routine prophylaxis with NSAIDs on the basis of radiographic changes may well have resulted in net harm rather than benefit.

Table 3 Numbers (percentages) of patients with global assessments 6 to 12 months after hip replacement according to postoperative treatment

Global assessments	Ibuprofen (n=424)	Placebo (n=424)	Odds ratio* (95% CI)
Hip status today: excellent/very good	347 (82)	332 (78)	1.1 (0.9 to 1.5)
At least daily analgesics for hip pain	112 (26)	103 (24)	1.1 (0.8 to 1.4)
No problems walking "out of the house"	341 (80)	342 (81)	1.0 (0.7 to 1.4)

*Estimated constant per category changed, therefore not explicitly related to numbers (%) in 2nd and 3rd columns.

Table 4 Mean (SD) measures of physical activity and physical performance, 6 to 12 months after hip replacement according to postoperative treatment

	Ibuprofen	Placebo	Mean difference (95% CI)
Physical activity (minutes/week)			
No of patients with data	419	423	—
Walk outdoors >10 minutes	243 (290)	215 (276)	27.4 (–10.3 to 65.0)
Vigorous activity	143 (245)	125 (231)	16.6 (–14.8 to 50.3)
Vigorous exercise	41 (118)	34 (101)	6.8 (–8.2 to 21.9)
Moderate exercise	68 (157)	71 (141)	–3.5 (–23.9 to 16.9)
Physical performance measures			
No of patients with data	387	393	—
Hip flexion (degrees)	92.7 (18.4)	93.9 (17.4)	–1.2 (–3.7 to 1.3)
Up and go (seconds)	9.9 (7.6)	9.7 (7.4)	0.2 (–0.6 to 1.0)
Time to walk 50 feet* (seconds)	14.2 (7.5)	14.5 (7.7)	–0.3 (–1.4 to 0.8)

*About 15 metres.

Table 5 Adverse events during admission and follow-up after hip replacement according to postoperative treatment

	Ibuprofen	Placebo
Patients with bleeding events (admission period)*		
No (%) of patients with bleeding event	21 (5)	10 (2)
Bleeding from wound >3 days	11	8
Evacuation wound haematoma	3	2
Haematemesis	1	2
Melaena	4	1
Other bleeding event†	4	1
Serious adverse events (in 6 to 12 month follow-up)		
No (%) of patients with serious adverse event	67 (15)	63 (14)
Death	4	4
Life threatening event	5	2
Permanent/substantial disability	7	8
Admission to hospital/prolonged admission	20	11
Medically important	31	38

*Some patients with more than one bleeding event
†Haemorrhage (2), haematuria, bleeding haemorrhoids.

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Table 6 Ectopic bone formation and associated clinical outcomes (WOMAC pain and function), 6 to 12 months after hip replacement surgery according to postoperative treatment. Figures are numbers (percentages) of patients with mean (SD) pain and function

Brooker grade	Ibuprofen (n=391)	Placebo (n=407)	Pain (0-10) (n=798)	Function (0-10) (n=798)
0 (none)	274 (70)	230 (57)	0.97 (1.47)	1.56 (1.57)
1 (mild)	78 (20)	108 (27)	0.99 (1.49)	1.43 (1.57)
2 (moderate)	28 (7)	43 (11)	0.97 (1.57)	1.87 (1.79)
3 (severe)	9 (2)	22 (5)	1.25 (1.85)	2.23 (1.95)
4 (bony ankylosis)	2 (0.5)	4 (1)		

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What is already known on this topic

Ectopic bone, or abnormal bone that forms in local soft tissues, is common after hip replacement surgery

A short course of postoperative NSAIDs greatly reduces the risk of this abnormal radiographic outcome

As it is not possible to identify patients at risk, routine prophylaxis has been recommended

What this study adds

Despite a significantly reduced rate of ectopic bone formation among patients who took NSAIDs postoperatively, there were no significant clinical benefits 6 to 12 months after surgery

Postoperative NSAIDs are also associated with an increased risk of bleeding events among these patients, and routine prophylaxis is not recommended

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