

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

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.¹ Some ectopic bone occurs in more than a third of all patients who undergo hip

replacement.² The risk of occurrence and the severity can be reduced by a short course of postoperative non-steroidal anti-inflammatory drugs (NSAIDs).³ This has been recommended as routine prophylaxis for all patients undergoing hip arthroplasty.^{4 5}

We established the effects of postoperative ibuprofen on pain and physical function and radiographic ectopic bone formation 6-12 months after total hip replacement surgery and any effects 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 2004.⁶

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 a definite indication or contraindication for treatment with an NSAID, they had taken an NSAID (other than low dose aspirin) in the 48 hours before the operation, or they had a postoperative spinal catheter in situ unless the catheter had been removed at least two hours before randomisation.⁷

Randomisation was performed centrally within 24 hours after surgery (see bmj.com for full details). Treatment allocation was blinded and concealed from patients and study staff until the database was locked. Participants were randomised to receive 14 days of treatment with either ibuprofen (2×200 mg tablets three times daily) or matching placebo tablets. Treatment was scheduled to start within 24 hours after

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surgery and patients could not take other NSAIDs (with the exception of low dose aspirin) during the study period.

Data collection and follow-up

We collected data on demographic variables, baseline clinical data, anaesthetics and surgical techniques, postoperative care, and early indicators of bleeding complications. Other outcomes were recorded at a routine follow-up visit 6 to 12 months after surgery. Serious adverse events in hospital were documented as they occurred. All assessments were standardised and performed blind to randomised treatment allocation.

Our primary 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).⁸ Secondary outcomes were general health status (summary scale scores on physical and mental components⁹) of the medical outcomes study short form 36 (SF-36)¹⁰; patients' global assessment of effectiveness of treatment; use of analgesia for hip pain during the past week; mobility "out of the house"; time spent participating in physical activity during the past week; objective measures of physical performance (hip flexion,¹¹ time to walk 50 feet (about 15 metres), and timed "up and go"¹²); radiographic evidence of ectopic bone formation according to the Brooker classification¹³; and major bleeding complications during hospital admission. We also recorded red cell transfusions (or re-infusions), suction drainage volumes, and postoperative haemoglobin concentrations (measured \geq 48 hours after surgery).

Analysis

We planned to recruit 1000 patients.⁶ We used *t* tests to evaluate changes in the primary outcomes and to compare differences in other continuous outcome measures at follow-up. We compared categorical outcomes for the proportions of patients with events with χ^2 tests and evaluated the effects of randomised treatment by fitting a proportional odds model and calculating the odds ratio of an improved outcome with ibuprofen.¹⁴ 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 902 patients (452 to ibuprofen and 450 to placebo, see [bmj.com](#)). Of the 853 participants who completed the assessment of primary outcomes, 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%) assessments (in 6 and 10 participants respectively) took place \geq 14 months after surgery. Standard anteroposterior radiographs were obtained for 798 (88%) participants. There was no significant difference between the groups in follow-up rates for any of the outcome measures.

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.

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), mostly on medical advice and mainly because of suspected side effects or intolerance (11% *v* 8%, *P*=0.13) and 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).

Secondary clinical outcome measures—There were no significant differences between the groups on the secondary clinical outcomes of general health status (table), global assessments, participation in physical activity, or objective measures of physical performance. 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 not requiring analgesia for hip pain were not significantly increased among patients allocated to ibuprofen (see [bmj.com](#)).

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). 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 \geq 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

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.

180 days after the end of the study treatment (median 78 days). 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) in the ibuprofen group. 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 function 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.

Though we observed the expected beneficial effect of ibuprofen on radiographic outcomes, we found no corresponding improvement in clinical outcomes. Possibly minor or moderate ectopic bone has little effect on clinical outcomes after hip arthroplasty. 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.¹⁵ 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.¹⁶

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. We consider that routine prophylaxis with a short course of postoperative NSAIDs for all patients undergoing hip arthroplasty is not justified. While some high risk patients may derive clinical benefits that outweigh any risks, randomised trials are required to substantiate this. 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.¹⁷ 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.

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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 6-12 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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