A systematic survey of 13 randomized trials of non-steroidal anti-inflammatory drugs for the prevention of heterotopic bone formation after major hip surgery

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ABSTRACT — We performed a systematic survey of randomized trials to determine the effects of perioperative NSAIDs on the occurrence of heterotopic bone formation, gastrointestinal side-effects and long-term clinical outcomes after major hip surgery. 13 trials involving 4,129 individuals were identified. Overall, in 12 small trials of medium-to-high-dose regimens, there was a 57% reduction (95% confidence interval 51%–63%) in the risk of heterotopic bone formation. The results of one large trial of low-dose aspirin differed markedly (2% reduction (95% CI 12% reduction to 15% increase)). The NSAID regimens studied had no definite effect on gastrointestinal complications, and data about the effects of NSAIDs on pain and function were too few, and too incompletely reported, to draw conclusions about their effects on these outcomes. Routine prophylaxis against heterotopic bone formation with NSAIDs may be a useful adjuvant therapy for patients undergoing major hip surgery, but the overall balance of risks and benefits requires assessment in a large-scale randomized trial.

Background

Several randomized trials have reported effects of NSAIDs on the risk of heterotopic bone formation after major hip surgery (Elmstedt et al. 1985, Schmidt et al. 1988, Hoikka et al. 1990, Gebuhr et al. 1991, 1996, Wahlström et al. 1991, Reis et al. 1992, Kjaersgaard-Andersen et al. 1993, Ahrengart et al. 1994, Burssens et al. 1995, Pritchett 1995, Matta and Siebenrock 1997, Neal et al. 2000). However, the individual trials have generally been too small to determine reliably the magnitude of the heterotopic bone formation protection afforded or the effects of NSAIDs on gastrointestinal side-effects, pain or function. This systematic survey, through the quantitative combination of the individual study results (meta-analysis), sought to investigate further the effects of NSAIDs. The combination of data from all studies increases the statistical power to detect and quantify treatment effects, and avoids the biases that can be introduced when estimates of treatment effects are based on results of non-representative subsets of all the relevant studies.

Methods

Study inclusion and exclusion criteria

To be eligible for this survey, a study had to fulfil all the following inclusion criteria: (1) participants scheduled for major elective or non-elective hip surgery (including hip or acetabular fracture repair); (2) random allocation to treatment; (3) treatment comparison of NSAID versus control; and (4) data on heterotopic bone formation collected at follow-up.

Search strategy

A computerized search for all studies reporting heterotopic bone formation was conducted using the electronic databases Medline, Embase, Current Contents and the Cochrane Register of Randomised Trials. A copy of the original report of each study was obtained, and screened independently for eligibility by two reviewers. In addition, the reference lists of every report were scrutinized for other possible randomized trials. For each study confirmed as eligible, efforts were made to contact the first author and the principal sponsor, to seek information about other relevant published or unpublished data.

Data collection

Standard data extraction forms were used to collect data from the published reports of the eligible trials. Data extraction was conducted independently by two reviewers and then checked for consistency. Supplementary data for patients randomized but excluded from analyses, and for outcomes of interest that were not reported, were sought directly from the investigators and study sponsors.

Treatment regimens

The agent, daily dose and duration of treatment were recorded for each study. To enable direct comparisons of the effects of different dosing regimens on outcomes, a standardized measure of NSAID treatment intensity was calculated as the daily dose prescribed divided by the maximum recommended daily dose.

Outcome measures

The primary outcome measure for the survey was heterotopic bone formation. In the original articles, heterotopic bone formation was classified on a number of different measurement scales (Arcq 1973, Brooker et al. 1973, DeLee and Charnley 1976, Rosendahl et al. 1977, Hierton et al. 1983, Hoikka et al. 1990, Matta and Siebenrock 1997), in each of which, the absence of heterotopic bone formation was graded zero and the presence of heterotopic bone formation graded between one and four. For this analysis, heterotopic bone formation was classified as present or absent. The principal secondary outcome measures were gastrointestinal side-effects, late postoperative pain and long-term impaired function.

Statistics

Analyses were conducted on published tabular data and, wherever possible, performed on an intention-to-treat basis. The relative risks and 95% confidence intervals (CI) for the effects of active versus control conditions were estimated for each study, and these estimates were combined, using a fixed effects variance weighted method (Der Simonian and Laird 1986). The analyses were all performed on dichotomous outcome measures. The study results were assessed for homogeneity using chi-squared tests and for possible effects of publication bias using a funnel plot and a regression test of funnel-plot asymmetry (Egger et al. 1997).

Results

Over 400 studies of heterotopic bone formation were identified, reviewed for eligibility and the reference lists scrutinized for possible randomized trials. 13 randomized trials were identified and included in the overview (Table). The principle reason for the exclusion of studies in this survey was non-randomized allocation of the NSAID therapy under investigation. Confirmation and supplementation of data were sought by mail from the first authors and the suppliers of study treatment in all 13 trials. Responses were received for 7 studies (Hoikka et al. 1990, Gebuhr et al. 1991, Wahlström et al. 1991, Kjaersgaard-Andersen et al. 1993, Pritchett 1995, Gebuhr et al. 1996, Neal et al. 2000), none of which changed the data provided in the published reports. There were 12 small trials of medium-to-high doses of NSAIDs and one large trial of low-dose aspirin (the Heterotopic Bone Formation Sub-study of the Pulmonary Embolism Prevention (PEP) trial).

Description of included studies and available data—surgical procedures

12 of the studies included patients scheduled for elective total hip replacement and one study included patients scheduled for acetabular fracture repair (Matta and Siebenrock 1997). There were

Characteristics of studies included in survey

Study reference	Surgery					Treatment			Patients	
	Type	Approach	Osteotomy	Cemented (%)	Antibiotic prophylaxis	Active (daily dose mg)/ Control	Duration (days)	Started preop	Male (%)	Mean age (years)
Ahrengart 1994	THR	Direct lateral	None	100	Yes	Ibuprofen (1500)/Placebo	10	Yes	47	70
Burssens 1995	THR	Charnley	None	100	No	Tenoxicam (10/5)/Placebo	42	No	100	61
Elmstedt 1985	THR	Anterolateral	–	–	No	Ibuprofen (1200)/Placebo	92	No	53	70
Gebuhr 1991	THR	–	–	100	Yes	Tenoxicam (40/20)/Placebo or morphine and placebo	5	No	40	72
Gebuhr 1996	THR	Posterolateral	None	100	Yes	Naproxen (750)/Placebo	28	Yes	40	73
Hoikka 1990	THR	Varied	–	3	No	Flurbiprofen (200)/Placebo	21	Yes	40	49
Kjaersgaard-Andersen 1993	THR	Posterolateral	–	100	Yes	Indomethacin (75)/Placebo	14	No	34	71
Matta 1997	AFR[a]	Varied	None	–	No	Indomethacin (75)/Open	42	No	74	43
Neal 2000	THR	–	Some	72	No	Aspirin (162)/Placebo	35	Yes	50	65
Pritchett 1995	THR	Anterolateral	–	–	No	Ketorolac (90)/Placebo	2	Yes	39	70
Reis 1992	THR	Transgluteal	–	49	No	Diclofenac (150)/Placebo	42	Yes	43	59
Schmidt 1988	THR	Posterolateral	None	100	Yes	Indomethacin (75)/Placebo	42	No	–	68
Wahlström 1991	THR	Posterolateral	None	100	Yes	Diclofenac (150)/Placebo	42	Yes	60	71

[a] AFR Acetabular fracture repair

no studies of patients treated for hip fracture. Data on surgical approach, frequency of trochanteric osteotomy, use of prophylactic antibiotics and use of cement were incompletely reported (Table).

Treatment regimens

The studies tested 8 different NSAID (Table). Treatment administration was blind in all but one trial, which used an open control condition. The planned duration of treatment regimens was between 2 and 92 days. In 7 studies, the first dose was scheduled to be taken preoperatively and in the remainder on the first postoperative day. 2 studies included random assignment between different doses of the active agent (Burssens et al. 1995, Gebuhr et al. 1996). 8 study reports (Elmstedt et al. 1985, Schmidt et al. 1988, Gebuhr et al. 1991, 1996, Wahlström et al. 1991, Kjaersgaard-Andersen et al. 1993, Ahrengart et al. 1994, Neal et al. 2000) indicated that NSAIDs other than the study treatment were specifically excluded from the postoperative analgesic regimen, but few reported compliance with this strategy.

Outcome data

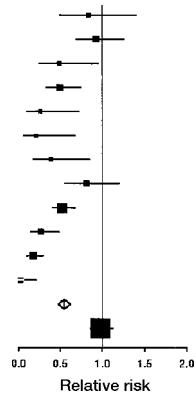
Heterotopic bone formation. Of the 4,129 participants randomized in the 13 studies, information about treatment allocation was available for 4,033 (98%) individuals, on whom all analyses are based. Of these 4,033 patients, outcome data on heterotopic bone formation were not available for 687 (17%), the majority of whom were participants in the PEP trial (Neal et al. 2000). Heterotopic bone formation assessment was reported as definitely blinded in 6 trials (Schmidt et al. 1988, Wahlström et al. 1991, Kjaersgaard-Andersen et al. 1993, Gebuhr et al. 1996, Matta and Siebenrock 1997, Neal et al. 2000), but blinding could not be confirmed for the remainder. Among the 3,346 (83%) patients for whom heterotopic bone formation data were available, 2,122 had no heterotopic bone formation and 1,224 (37%) had heterotopic bone formation equivalent to Brooker grade one or greater.

Gastrointestinal side-effects. 12 studies provided data on gastrointestinal side-effects (Elmstedt et al. 1985, Schmidt et al. 1988, Hoikka et al. 1990, Gebuhr et al. 1991, 1996, Wahlström et al. 1991, Reis et al. 1992, Kjaersgaard-Andersen et al. 1993, Ahrengart et al. 1994, Burssens et al. 1995, Pritchett 1995, Neal et al. 2000), 2 of which (Pritchett 1995, Neal et al. 2000) reported only severe side-effects. Among the 3,932 participants for whom data were available, there were 146 gastrointestinal side-effects reported: 82 were minor (e.g., nausea, dyspepsia, diarrhoea) and 64 were major (e.g., hematemesis or melena).

Pain and function. Data on pain were collected in 7 studies (Elmstedt et al. 1985, Schmidt et al. 1988, Gebuhr et al. 1991, Wahlström et al. 1991,

Figure 1. Effects of NSAIDs versus control on heterotopic bone formation. The box sizes are proportional to the square root of the number of patients with heterotopic bone formation

Study reference Individual trials	Patients with heterotopic bone formation / total patients Active	 Placebo	Treatment prevents heterotopic bone formation	Treatment causes heterotopic bone formation	Relative risk (95% confidence interval)
Ahrengart 1994	14/30	15/27			0.84 (0.50–1.40)
Burssens 1995	39/60	21/30			0.93 (0.69–1.25)
Elmstedt 1985[a]	7/21	15/22			0.49 (0.25–0.95)
Gebuhr 1991	21/72	44/75			0.50 (0.33–0.75)
Gebuhr 1996	4/35	15/35			0.27 (0.10–0.72)
Hoikka 1990	3/34	14/34			0.21 (0.07–0.68)
Kjærsgaard-A. 1993	6/29	15/28			0.39 (0.17–0.85)
Matta 1997	27/61	25/46			0.81 (0.56–1.20)
Pritchett 1995	50/152	95/151			0.52 (0.40–0.68)
Reis 1992[a]	11/74	38/69			0.27 (0.15–0.48)
Schmidt 1988[a]	13/102	72/99			0.18 (0.10–0.30)
Wahlstrom 1991	1/48	35/50			0.03 (0.00–0.21)
OVERALL (12 trials)	196/718	404/666			0.43 (0.37–0.49)
Neal 1999	312/1332	315/1317			0.98 (0.85–1.12)



[a]The total number of randomised patients allocated to each treatment arm was not available. For these trials the treatment allocation of 7, 37 and 52 patients respectively (total 96) was not stated.

Reis et al. 1992, Pritchett 1995, Neal et al. 2000), function in 7 studies (Elmstedt et al. 1985, Schmidt et al. 1988, Gebuhr et al. 1991, Wahlström et al. 1991, Reis et al. 1992, Burssens et al. 1995, Neal et al. 2000) and range of movement in 6 studies (Elmstedt et al. 1985, Schmidt et al. 1988, Gebuhr et al. 1991, Reis et al. 1992, Pritchett 1995, Matta and Siebenrock 1997). However, the effects of NSAIDs on these outcomes were incompletely reported. Data about the effects of treatment on pain were available in only 4 studies (Schmidt et al. 1988, Wahlström et al. 1991, Pritchett 1995, Neal et al. 2000), data on function in only 4 studies (Wahlström et al. 1991, Reis et al. 1992, Burssens et al. 1995, Neal et al. 2000) and data on range of movement in only 3 studies (Schmidt et al. 1988, Reis et al. 1992, Pritchett 1995).

Effects of treatment on heterotopic bone formation

In the 12 small trials that studied medium-to-high doses of NSAIDs, there was a 57% reduction (95% CI 51%–63%) in the risk of heterotopic bone formation among patients assigned active treatment (Figure 1). Among these 12 trials, there were differences in the size of the observed effects of NSAIDs on heterotopic bone formation (p homogeneity = 2×10^{-10}) which ranged between reductions of 7% and 97%. The results of the PEP trial (2% reduction (95%CI 15% reduction to 12% increase)) were also different from those of the other 12 trials (p homogeneity = 7×10^{-25}). Sensitivity analyses based on characteristics of trial methodology (blinding and duration of follow-up), characteristics of the patients (age, gender and inclusion diagnosis), experimental intervention (NSAID, control condition and treatment intensity), operative technique (cement, approach and trochanteric osteotomy) and use of concomitant treatments (heparin and antibiotics) were not helpful in explaining the differences in the effects of treatment on heterotopic bone formation between the studies.

A funnel-plot analysis of the 12 studies of medium-to-high doses of NSAIDs was performed (Figure 2). The regression approach to funnel-plot asymmetry (Egger et al. 1997) yielded an intercept of –0.01 and p = 0.9, providing reassurance that the findings of the survey were unlikely to have been significantly influenced by publication bias.

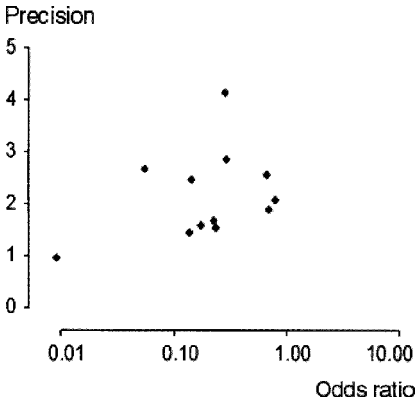


Figure 2. Funnel plot of the 12 trials of medium-to-high dose non-steroidal anti-inflammatory drugs for the prevention of heterotopic bone formation

Effects of treatment on gastrointestinal side-effects

There was no clear effect of NSAIDs on the incidence of gastrointestinal side-effects (Figure 3). In all studies combined, there was a 22% increase (95%CI 13% reduction to 71% increase) in the risk of gastrointestinal side-effects among patients assigned to NSAIDs (p = 0.3). There were no clear differences between the results of the individual studies (p homogeneity = 0.1). The effect of NSAIDs on severe gastrointestinal side-effects (all but 4 of which were observed in the PEP trial) was not significantly different from the effects observed on minor gastrointestinal side-effects (p homogeneity = 0.06).

Effects of treatment on pain and function

Data about the effects of treatment on clinical outcomes were incompletely and inconsistently reported. 3 studies (Schmidt et al. 1988, Wahlström et al. 1991, Pritchett 1995) reported that there were fewer patients with pain in the actively treated group than the placebo group, but provided no data or statistics to describe the reliability of these findings. One study reported a beneficial effect of treatment on an index of mobility (Burssens et al. 1995), another an improvement in hip scores (Reis et al. 1992) and a third no effect on hip scores (Wahlström et al. 1991). The beneficial effect of treatment on the range of movement at the hip observed in one study reached standard levels of significance (Reis et al. 1992), but in two others (Wahlström et al. 1991, Pritchett 1995) no effect of treatment on similar outcomes was observed. The large trial of low-dose aspirin found no effect

Figure 3. Effects of NSAIDs versus control on gastrointestinal side-effects. The box sizes are proportional to the square root of the number of patients with gastrointestinal side-effects

Study reference Individual trials	Patients with gastrointestinal side-effects / total patients Active	 Placebo	Treatment prevents gastrointestinal side-effects	Treatment causes gastrointestinal side-effects	Relative risk (95% confidence interval)
Ahrengart 1994	9/30	1/27			8.10 (1.10–59.8)
Burssens 1995	3/60	0/30			3.56 (0.19–66.7)
Elmstedt 1985[a]	2/21	0/22			5.23 (0.27–102)
Gebuhr 1991	2/72	3/75			0.69 (0.12–4.04)
Gebuhr 1996	3/35	1/35			3.00 (0.33–27.5)
Hoikka 1990	6/34	4/34			1.50 (0.46–4.84)
Kjærsgaard-A. 1993	5/29	1/28			4.83 (0.60–38.8)
Pritchett 1995[b]	1/152	1/151			0.99 (0.06–15.7)
Reis 1992[a]	10/74	3/69			3.11 (0.89–10.8)
Schmidt 1988[a]	12/102	15/99			0.78 (0.38–1.57)
Wahlstrom 1991	1/48	3/509			0.35 (0.04–3.22)
Neal 1999	27/1332	33/1317			0.81 (0.49–1.34)
Minor	51/505	31/469			1.54 (1.01–2.35)
Severe	30/1989	34/1937			0.88 (0.54–1.41)
OVERALL	81/1989	65/1937			1.22 (0.87–1.71)

[a] The total number of randomised patients allocated to each treatment arm was not available. For these trials the treatment allocation of 7, 37 and 52 patients respectively (total 96) was not stated.
[b] Only severe gastro-intestinal side effects reported.

of treatment on pain or function (Neal et al. 2000). No formal surveys of the data about the effects of treatment on clinical outcomes were possible.

Discussion

This survey shows that perioperative regimens involving medium-to-high doses of NSAIDs significantly reduce the risk of developing heterotopic bone formation after hip surgery. The most likely size of the effect is between a one third and a two thirds reduction in the risk of heterotopic bone formation. Given that heterotopic bone formation occurs in about one third of all persons undergoing hip arthroplasty (Knelles et al. 1997), NSAIDs may prevent one or two cases of severe heterotopic bone formation and 10–20 cases of mild-to-moderate heterotopic bone formation among every 100 patients treated.

There was strong evidence of differences in the size of the treatment effects observed in the 13 trials. Statistical tests of homogeneity found that the results of the Heterotopic Bone Formation Substudy of the Pulmonary Embolism Prevention Trial differed most clearly from the others. Sensitivity analyses failed to find the reasons for the differences between the trials, but the statistical power of such analyses was limited by the use of tabular group data and the incomplete reporting of the study characteristics of interest. However, it is likely that the low dose of NSAID used in the PEP trial was one cause of the differences observed. A recently completed study also suggests that aspirin may provide less effective prophylaxis than other NSAIDs (Knelles et al. 1997).

The results of this survey provided no clear evidence of an effect of the NSAID regimens tested, on the risk of gastrointestinal complications. The 95% confidence intervals were, however, wide, and compatible with both a two thirds increase and a one fifth decrease in the risk of gastrointestinal side-effects. There were no apparent differences between individual studies in the effects on gastrointestinal outcomes, but once again the statistical power to detect differences between studies was low. Other studies have shown clear differences in the gastrointestinal side-effect profiles of different NSAID regimens (Wilholm et al. 1985). Data on the effects of NSAIDs on other side-effects such as non-gastrointestinal bleeding and prosthetic loosening were not systematically reported and cannot be determined from this survey. Similarly, data on the late postoperative outcomes of pain, impaired function and range of movement were infrequently collected and even less frequently reported. Few of the data collected on these outcomes were actually available and no formal surveys of the findings were possible.

The effects of NSAIDs on heterotopic bone formation may have important implications for clinical practice. Based on previous estimates (Hori et al. 1978, Griffiths et al. 1984, Vincent and Wijne 1986, Konski and Pellegrini 1990), it is likely that worldwide more than 800,000 total hip replacements are performed each year. At least one third of total hip replacements are liable to complication by heterotopic bone formation, and in about one fifth of cases the heterotopic bone formation may be severe (Brooker et al. 1973). Since perioperative NSAIDs appear to produce between a one third and a two thirds reduction in the risk of heterotopic bone formation, among every 100,000 total hip replacements performed, such agents may prevent 10,000–20,000 cases of heterotopic bone formation (2,000–4,000 severe). Since the reliable preoperative identification of patients at high risk of developing heterotopic bone is not possible (Kromann-Andersen et al. 1980), such effects can be achieved only with a strategy of routine heterotopic bone formation prophylaxis (Bogoch and Wright 1994).

However, while medium-to-high doses of perioperative NSAIDs can clearly produce a substantial reduction in the incidence of radiographic heterotopic bone formation, there remains some uncertainty about short-term side-effects and much uncertainty about effects on long-term clinical outcomes. While the net effects of routine heterotopic bone formation prophylaxis with NSAIDs are likely to be beneficial, routine prophylaxis requires formal assessment in a randomized trial designed to determine the balance of benefits and risks for all outcomes.

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