

NSAIDs AND BONE

Some orthopaedic centres do not allow the use of NSAIDs for postoperative analgesia after fractures or orthopaedic surgery because they are thought to interfere with bone healing. The purpose of this document is to examine the evidence for effects of NSAIDs on bone healing.

Searching

PubMed was searched using free text terms to detect reviews, RCTs and epidemiological reports relating to bone and fracture healing and the use of NSAIDs. We also had a look at the Cochrane Library.

Background

Bone metabolism has a complex regulatory system that includes prostaglandins, produced abundantly by osteoblasts [1]. The balance of evidence from animal experiments suggests that prostaglandins favour bone formation. NSAIDs might therefore be expected to inhibit bone formation because they inhibit prostaglandin formation. The evidence for this is by no means conclusive, and some NSAIDs in some models have been shown to inhibit bone loss.

Disagreement might be a function of type of NSAID; proprionic NSAIDs (ibuprofen, naproxen, ketoprofen) may prevent bone loss in some circumstances while acetic acid NSAIDs (indomethacin, diclofenac) may not. Dose and duration of use may also be factors. Experiments on rabbits (over 20 years ago) have shown that NSAIDs can inhibit fracture healing. Ketorolac has been implicated in failed bone fusion in spinal fusion experiments in rabbits.

Experimental work in animals seems, at best, to leave the role of NSAIDs and bone healing after fracture or operation uncertain.

NSAIDs and bone in orthodontic surgery

Flurbiprofen appeared to increase bone formation in root-form implants in two patients [2], confirmed in a randomised study of 29 patients given flurbiprofen 200 mg a day or placebo for three months [3]. Flurbiprofen was without effect in a small randomised study after periodontal surgery [4] and naproxen did not increase bone healing in another study [5].

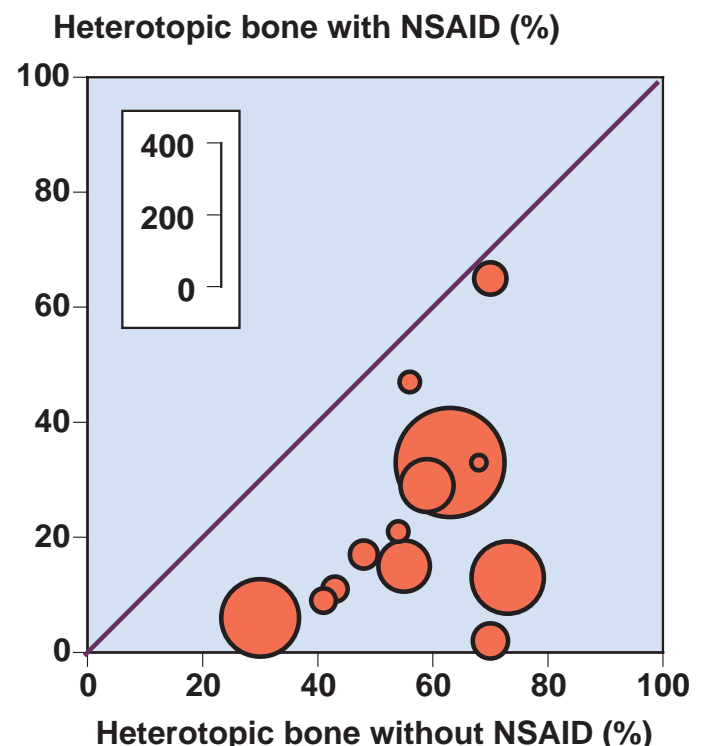
In summary there is no convincing evidence that NSAIDs have any major effects on bone in orthodontic surgery.

NSAIDs and heterotopic bone formation

A Cochrane review has examined heterotopic bone formation after hip replacement [6]. It found 12 randomised trials, predominantly relatively small studies of medium to high dose NSAID, plus one large study of low dose aspirin. In 13 studies heterotopic bone formed in 182/806 (23%) patients with medium to high dose NSAID and 430/765 (56%) patients with control (Figure 1). The relative risk was 0.38 (0.33 to 0.44) and the number needed to treat to prevent heterotopic bone formation was 3.0 (2.6 to 3.4).

Most studies recorded heterotopic bone formation at least six months after operation. Duration, dose and type of NSAID used was not given, nor was there an analysis according to degree of heterotopic bone. Serious fatal and non fatal events were small in number (nine reported), but fail-

Figure 1: Heterotopic bone formation with and without NSAID after hip replacement



ure of bone healing was not mentioned. This might repay a more thorough review of these papers.

Low dose aspirin (162 mg a day) was without effect in a large (2,700 patient) trial [7]. In a detailed analysis that included NSAID use before and after operation (17% needed analgesics after the operation), there was no mention of association of NSAID use and failure of the hip replacement.

Indomethacin has a similar effect on preventing heterotopic bone formation after spinal cord injury [8].

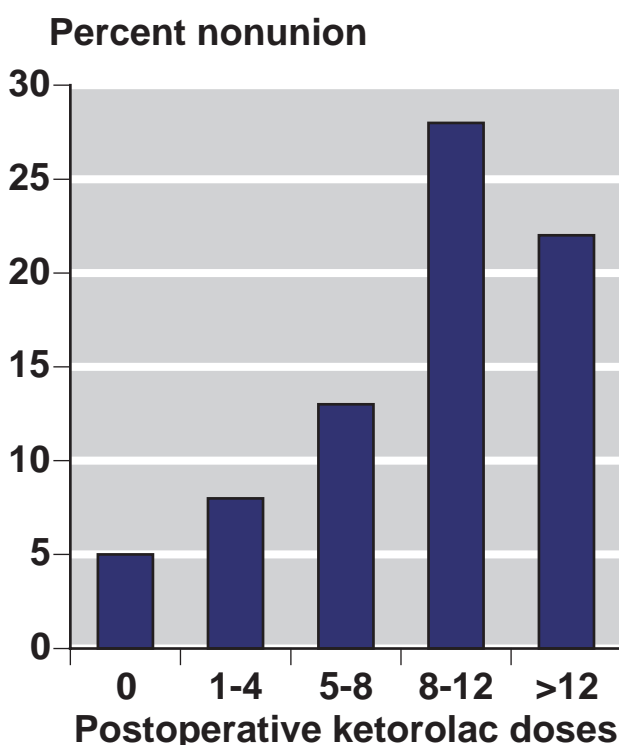
NSAIDs and spinal fusion

A retrospective review of ketorolac after spinal fusion was studied in a retrospective review of 288 cases [9] in a single centre. Patients had posterior spinal fusion between 1991 and 1992, and there was a minimum two-year follow up. Ketorolac was administered as a 60 mg intramuscular loading dose followed by 30 mg every 6 hours as needed. Seven patients given ketorolac had an additional 2-20 (mean 8) 10 mg oral doses as needed.

Ketorolac was given to 167 patients, and no NSAID to 121. Patients having ketorolac received between one and 39 doses of ketorolac after surgery (mean 10). The two groups were demographically similar.

Nonunion occurred in 5/121 (4%) of patients having no NSAID and 29/167 (17%) of those receiving ketorolac. The odds ratio was 4.9 (1.8 to 17). The same degree of increased risk was seen in all subgroups. There was a dose-dependent relationship between nonunion rates and ketorolac doses (Figure 2).

Figure 2: Nonunion rate and postoperative ketorolac doses after spinal fusion surgery



There was an apparent relationship between postoperative use of ketorolac and cigarette smoking. The nonunion rate was 2% in those who neither smoked nor had ketorolac, 7% for those who smoked but did not have ketorolac, 10% for nonsmokers having ketorolac and 25% for those who both smoked and had ketorolac.

By contrast with these results, Reuben [10] examined nonunion rates on 106 patients undergoing posterior spinal fusion with autologous crest bone grafts. All had received 50 mg rofecoxib postoperatively for five consecutive days starting on the morning of surgery. No other NSAIDs were used postoperatively.

Using the same criteria for nonunion as Glassman [9], the one-year nonunion rate was 4.7% (5 of 106 patients). This is the same rate as reported by Glassman for patients not receiving perioperative ketorolac [9].

NSAIDs and Colles fracture

A randomised double-blind study of postmenopausal women with a displaced Colles fracture examined a eight week regimen of 20 mg daily piroxicam and placebo on recovery [11]. There was no effect on bone mineral density, and no decrease in fracture healing with piroxicam.

Fracture nonunion and NSAID

A case-control study from Leeds of 32 patients with nonunion of fractured femur and 67 comparable patients whose fracture had united reported an association between nonunion and the use of NSAIDs after injury [12], and delayed healing in patients who took NSAIDs and whose fracture had united.

Several other studies of bone healing after fracture make no mention of NSAIDs:

- ◆ Nonunion among 67 ankle fusions in Houston was associated with open trauma, and with smoking, alcohol, diabetes or illegal drug use [13].
- ◆ A survey of 165 elderly patients with femoral neck fractures in Oslo noted technical issues associated with disturbed healing, but did not mention NSAIDs [14].
- ◆ A meta-analysis of the effect of reamed versus nonreamed nailing of lower leg bone fractures [15] examined a number of factors for nonunion, with higher nonunion rates being associated with studies of lower quality.
- ◆ Risk of nonunion for tibial shaft fractures in 100 consecutive patients from Gothenburg noted that high energy trauma has a relative risk of 2 and open fractures one of 8. NSAID use was not mentioned [16].

NSAIDs and risk of new fractures

Laboratory exploration of the effect of NSAIDs on bone metabolism has demonstrated that bone resorption can be affected through prostaglandin inhibition. One implication is that NSAIDs potentially could reduce bone loss and hence

fracture risk. A huge observational study using the UK general practice research database (GPRD) [17] tells us that this hope will not be realised.

Background

A large study of aspirin and NSAID use on bone mineral density in 7,768 white women older than 65 years in the USA [18] concluded that bone mineral density was higher in users of these drugs. Risk of fracture was unaffected. The study had the benefit of being large, but aspirin and NSAID users were different from non-users. Osteoarthritis, rheumatoid arthritis, back pain and other conditions were much more common in NSAID users than nonusers. Adjustment of results for potential confounding can be difficult in circumstances where subjects and controls differ markedly. NSAID use did not affect the rate of excretion of markers of bone resorption [19], but bone mineral density at some sites was again found to be affected by proprionic acid NSAIDs in 84 older women [20]. The background evidence that NSAIDs reduce fracture risk was thin, but the apparent effects on bone density meant that some reduction in fracture risk might be expected. A very large study would be needed to show this.

Study

A large retrospective cohort study was conducted using the GPRD. It looked at fracture risk in people using NSAIDs and compared that with people who did not use NSAIDs.

NSAID users fulfilling one or more prescriptions for an NSAID from 1987 up to end 1997 were included, and divided arbitrarily into those receiving three or more prescriptions and those receiving one or two prescriptions. A control group of people never having a prescription for NSAIDs was created by matching for sex, age, and practice (where possible). Systemic corticosteroid use was an exclusion criterion for users and controls. Information on about a dozen possible confounding conditions, and about a dozen possi-

ble confounding drug treatments was collected for each case and control.

After a prescription was filled follow up was until fracture or 91 days after the last prescription. Nonvertebral fractures were assessed by ICD codes and vertebral by radiography.

Results

NSAIDs were prescribed for 501,000 patients, with 215,000 having three or more prescriptions for a median 3.4 years (regular users), and 287,000 having one or two having one or two prescriptions for a mean of 0.7 years (incidental users). There were 215,000 controls. Back pain and rheumatoid arthritis were more common in NSAID users than in controls. Incidental users were about 10 years younger than the mean age of 54 years for regular users and controls.

Nonvertebral fractures occurred more frequently in older women and the oldest men (Figure 3). For women fracture rates rose substantially after age 64.

Fracture rates with regular NSAID users were certainly not lower than controls. If anything, they were somewhat higher (Table 1) for vertebral and all nonvertebral fractures. Regular users had fracture rates no different from incidental users.

No NSAID was associated with higher or lower rates of fracture. Restricting analysis to patients with a history of arthropathy reduced the difference between regular users and controls for nonvertebral fractures, with a relative risk of 1.2 (1.1 to 1.3).

Comment

This beautiful study can tell us that there is no major effect of NSAIDs on risk of fracture. It also shows the problems with confounding. While many confounding factors could be taken into account, but others, like diet, exercise or bone

Figure 3: Nonvertebral fracture rates per 100 years for women and men not using NSAID

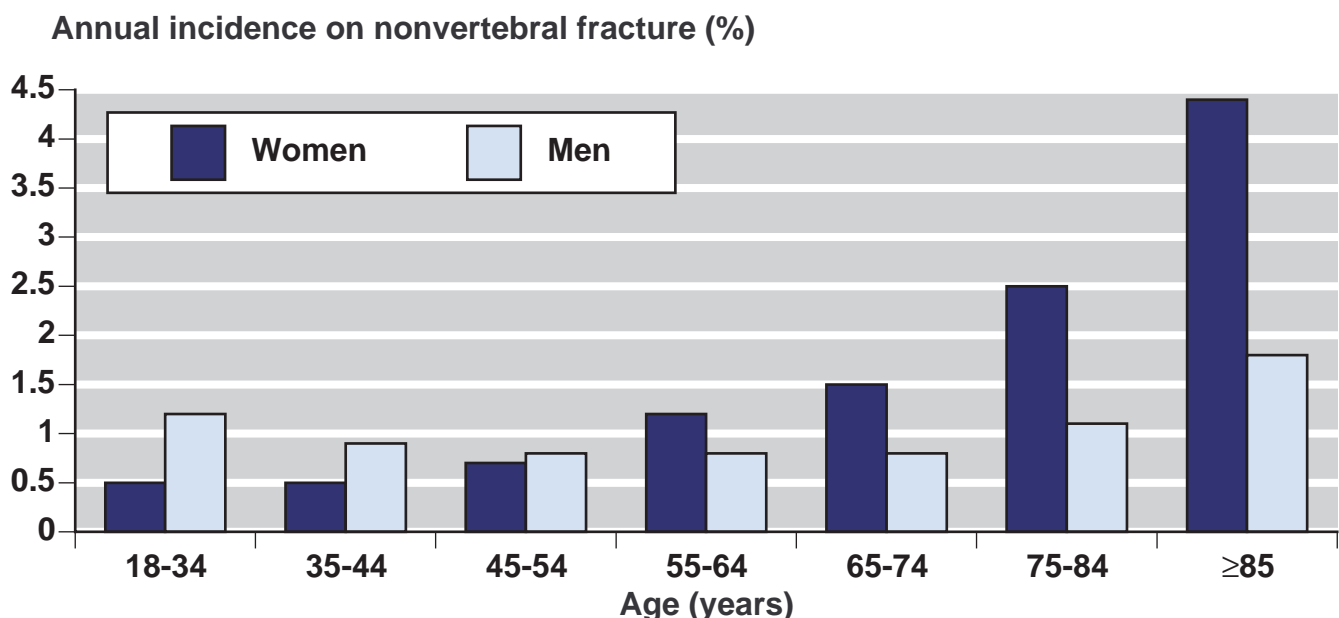


Table 1: Fracture type, rates and relative risk for regular NSAID users versus controls (about 215,000 each group)

Fracture type	Regular NSAID user		Control		Relative risk (95%CI)
	Number of fractures	Rate per 100 years	Number of fractures	Rate per 100 years	
Vertebral	808	0.1	192	0.03	2.9 (2.5 to 3.4)
All nonvertebral	10505	1.5	5793	1	1.5 (1.4 to 1.5)
Forearm	2516	0.3	1556	0.3	1.3 (1.2 to 1.4)
Hip	973	0.1	686	0.1	1.1 (0.98 to 1.2)

density could not. To properly take account of confounding factors you have to know what they are, and how much to adjust for them.

Summary

So far this is the sum of the evidence that appears to be available.

The animal experiments are interesting, but may not be relevant to clinical situations. For instance, the RCT on NSAIDs in Colles fracture [10] was performed by researchers who had shown an inhibitory effect of NSAIDs on fracture healing in rats, but no effect was seen in man.

We have three possible bits of evidence.

The first is in spinal fusion surgery [9, 10]. The problems with the original retrospective survey [9] include the choice of drug. Ketorolac, especially at the high doses given intramuscularly, is hardly representative of NSAIDs as a class. Intramuscular ketorolac at 30 mg is equivalent to 10 mg orally in analgesic effect [21], but gives a bigger body load of drug. It is particularly effective at producing gastrointestinal bleeding. Then there is the problem that patients needing ketorolac needed more postoperative analgesic, but we do not know whether that itself was a marker for some other pathology. And the synergistic effect with smoking is a puzzle, though this has been examined in a retrospective analysis of 357 patients after spinal fusion [22] (but some of the patients may have been in the earlier analysis [9]). But retrospective analysis of 106 patients given 50 mg of rofecoxib for five days has no increased rate of non-union using similar nonunion criteria [10].

The second bit of evidence is a case-control study from Leeds suggesting that NSAIDs inhibit healing of fractured femur [12]. The study had only 32 patients with unhealed femur, and small retrospective case-control studies have their problems. No other investigation into failure of fractures to heal mentioned NSAIDs.

So there's not much in the way of top quality evidence for failure to heal. None from randomised controlled trials, and what randomised trials there are show no effect, and no evidence from large good quality observational studies. This latter is important, because it is a dog that doesn't bark in the night. Given the millions of orthopaedic operations per-

formed and bone fractures every year, plus the frequent use of NSAIDs for postoperative analgesia, and available from pharmacists without prescription, is it credible that a major effect of NSAIDs on bone healing could be missed?

This is borne out to some extent by our third bit of evidence, the huge observational study on fracture rates in 500,000 patients taking NSAIDs and 215,000 controls [17]. The conclusion was that NSAIDs had minimal effects on fracture risk, especially given the large number of possible confounders considered, and some major ones that could not be considered.

So far the evidence that NSAIDs play any major role affecting bone, apart from their important effects on heterotopic bone formation [6], does not stack up.

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