

Do NSAIDs impair fracture healing? A survey of Australian Orthopaedic Surgeons

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed following musculoskeletal injuries and fractures. There is some evidence that these drugs may impair bone formation and, therefore fracture healing, although this evidence is mainly limited to low-quality human studies and animal models using supernormal dosages.^{1,2} Given the widespread use of NSAIDs for pain relief, the ease of access to these medications, and potentially plausible biological pathways for impeding bone healing,³ improved understanding of the impact of NSAIDs on fracture healing is needed.

The most recent high-quality systematic review on the association between NSAID use and fracture non-union concluded that, owing to a lack of clear evidence for impaired bone healing due to NSAID use, randomised controlled trials (RCTs) and high-quality prospective cohort studies are still needed.¹ Since this review was published in 2010, there has been no further progress within the field and the need for human studies persists.

While RCTs can provide a higher level of evidence than observational studies, they can only be undertaken where clinical equipoise exists, i.e. genuine uncertainty within the medical community as to the effect of an intervention.⁴ Equipoise would provide the ethical basis for

an RCT, enabling randomisation of NSAID provision following orthopaedic surgical intervention. A lack of equipoise would indicate that RCTs on this topic may not be feasible and that only observational studies are possible within the chosen setting.

Australian orthopaedic surgeons were surveyed about their perceptions of the relationship between NSAIDs and fracture healing in order to determine whether clinical equipoise exists within the profession.

Methods

Four hundred and eighty-three orthopaedic surgeons who were members of the Victorian, South Australian and Tasmanian branches of the Australian Orthopaedic Association (AOA) were invited to participate in the survey via an email from their branch head office. The AOA is the professional organisation for orthopaedic surgery in Australia of which most orthopaedic consultants and registrars in Australia are members. The invitation email contained an explanatory statement and a link to the online survey. All responses were anonymous, although participants were permitted to provide their contact details. Ethics approval was granted by the Monash University Human Research Ethics Committee (MUHREC).

The survey was developed by the Victorian Orthopaedic Trauma Outcomes Registry (VOTOR) Steering Committee, after a literature review on NSAIDs and fracture healing. The survey, which included five questions and took five minutes to complete, was created using the SurveyMonkey® online tool (www.surveymonkey.com). The survey questions are presented in their entirety in Table 1 and no further explanatory details were provided (e.g. the definition of an acute fracture). The survey link was emailed to participants in February 2015, a reminder sent in May 2015 and the survey closed in June 2015. Responses were collated and analysed using descriptive statistics and presented as frequencies and percentages.

Results

A total of 112 orthopaedic surgeons (23.1%) responded to the survey. Almost three-quarters of respondents prescribed or allowed prescription of NSAIDs immediately post injury, intra-operatively or peri operatively, and over half did so two and six weeks post-operatively (Table 1). Ibuprofen was the most common NSAID prescribed, followed by diclofenac and meloxicam. Over one-third of respondents (37.1%) agreed or strongly agreed that NSAIDs

are associated with delayed union but fewer (23.8%) agreed or strongly agreed that NSAIDs are associated with non-union. Almost half (44.6%) neither agreed nor disagreed that NSAIDs were associated with non-union. Almost two-thirds of respondents were willing to allow their patients to be recruited for an RCT examining the association between NSAIDs and fracture non-union.

Discussion

This study establishes a divergence of opinion within the Australian orthopaedic surgical community on the use of NSAIDs post-operatively and whether these drugs delay or prevent fracture healing. In this respect, clinical practice is reflecting the current lack of clarity within the body of research on this topic. Most of the surgeons surveyed believe that the benefits provided by NSAID use following surgery outweigh potential risks conferred by these drugs and less than one quarter believe that NSAIDs increase the risk of fracture non-union.

To the best of our knowledge there has been only one other study which has surveyed practitioners on their use of NSAIDs following orthopaedic surgery.⁵ This study, conducted with an international cohort of 61 anaesthetists found that over half would prescribe NSAIDs following surgery, in this case paediatric scoliosis surgery. Reasons cited for non-prescription amongst the surveyed sample included the risk of non-union and the risk of peri-operative bleeding, and those most opposed to prescription were based in the United States. The more favourable attitude towards NSAIDs in our study may reflect international differences or differences between professions.

There is still a need for RCTs investigating the effect of NSAIDs on fracture healing and the results of this survey provide an ethical basis for doing so. Having only received responses from one-quarter of orthopaedic surgeons from South-Eastern states of Australia, the results may not be representative of all Australian orthopaedic surgeons, and because the survey was anonymous, we cannot make assumptions regarding the profile of respondents. Nonetheless, the results are surprising, given traditionally held beliefs, and lend support to the commencement of RCTs testing the influence of NSAIDs on fracture healing.

To avoid repeating the design flaws of previous studies, a number of factors must be incorporated into future study designs and be amenable to appropriate analysis: participant age, sex, ethnicity, nutritional status, bone quality, endocrine disorders, muscle mass, smoking status, fracture location and pattern, infection, exposure to radiation and medication

use, including steroids, chemotherapy and NSAIDs. It is suggested that participants with chronic NSAID use be excluded. In designing the pharmacological intervention, there is a need for clear detail on the NSAID type, dose, length of exposure and route of administration. Prescription compliance monitoring is necessary and a multi-arm study may be required, to account for different dosing regimes. Furthermore, valid and objective measures of delayed healing are essential, with pre-determined follow-up periods.

It is hoped that the results of a well-designed trial, taking these multiple influences into account, will help clinicians make better-informed decisions as to the use of NSAIDs with fracture patients. In doing so, patients who are in need of the effective analgesia provided by NSAIDs will not be unnecessarily denied access, and patients at risk of delayed fracture healing will be shielded from unnecessary harm.

References

1. Dodwell ER, Latorre JG, Parisini E, Zwettler E, Chandra D, Mulpuri K, et al. NSAID exposure and risk of nonunion: a meta-analysis of case-control and cohort studies. *Calcif Tissue Int.* 2010;**87**:193-202.
2. Taylor IC, Lindblad AJ, Kolber MR. Fracture healing and NSAIDs. *Can Fam Physician.* 2014;**60**:817.
3. Wheeler P, Batt ME. Do non-steroidal anti-inflammatory drugs adversely affect stress fracture healing? A short review. *Br J Sports Med.* 2005;**39**:65-9.
4. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med.* 1987;**317**:141-5.
5. Hayes J, Pehora C, Bissonnette B. The use of NSAIDs in pediatric scoliosis surgery - a survey of physicians' prescribing practice. *Paediatr Anaesth.* 2009;**19**:756-63.

Table 1. Survey responses from Australian orthopaedic surgeons regarding NSAID use and fracture healing (n=112)

Survey questions	Responses n (%)
1. For patients with acute fractures, do you prescribe or allow your anaesthetist to	

prescribe (any) NSAIDs for analgesia:

a) Immediately post-injury / intra-operatively or immediately peri-operatively?	Yes	83 (74.1)
	No	29 (25.9)
b) Post operatively > 2 weeks?†	Yes	57 (53.3)
	No	50 (46.7)
c) Post operatively > 6 weeks?‡	Yes	54 (52.4)
	No	49 (47.6)

2. If you answered "Yes" to any of the responses in Question 1, which NSAIDs are you comfortable using (Please tick all that apply): (n=94)

Ketorolac	50 (53.2)
Indomethacin	42 (44.7)
Naproxen	57 (60.6)
Diclofenac	69 (73.4)
Meloxicam	64 (68.1)
Celecoxib	62 (66.0)
Ibuprofen	77 (81.9)

3. Please rate your level of agreement to the following statement - NSAIDs are associated with fracture delayed union.

Strongly agree	4.5 (5)
Agree	36 (32.1)
Neither agree or disagree	43 (38.4)
Disagree	24 (21.4)
Strongly disagree	4 (3.6)

4. Please rate your level of agreement to the following statement - NSAIDs are associated with fracture non-union.

Strongly agree	4.5 (5)
Agree	21 (18.8)
Neither agree or disagree	50 (44.6)
Disagree	33 (29.5)
Strongly disagree	3 (2.7)

5. Would you be willing to have your patients recruited into a Randomised Control Trial (RCT) examining the association between NSAIDs and fracture non-union?

Yes 71 (63.4)

No 42 (37.5)

† Data missing for n=5 respondents

‡ Data missing for n=9 respondents

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