Review Article

The effect of non-steroidal anti-inflammatory medications on spinal fracture healing: a systematic review

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Background: The effect of non-steroidal anti-inflammatory medications (NSAIDs) on fracture healing is a topic of debate. The purpose of this study was to systematically review the effect of NSAID medications on spinal fracture healing rates.

Methods: We searched the Cochrane Library, PubMed, Medline Ovid, and SCOPUS databases from inception until April 2021, and additionally searched the NIH Clinical Trials Database. Eligible studies included those which reported on spinal fracture healing rates in patients taking NSAIDs. Two reviewers independently assessed all potential studies for eligibility and extracted data. Risk of bias was assessed with validated tools by two reviewers. The primary outcome of interest was healing rates of spinal fractures in patients taking NSAIDs. Secondary outcomes of interest included healing rates stratified by NSAID selectivity.

Results: A total of 1,715 studies were initially screened. After inclusion criteria were applied, three studies (214 patients) were included which discussed spinal fracture healing rates in patients taking NSAIDs. These studies showed acceptable reliability for inclusion. The 3 studies reported heterogeneous results, with one study reporting a 96% healing rate, and another study reporting over 90% non-union rate. The types of fracture, NSAID type, and dosage/duration of NSAID use varied widely amongst studies.

Discussion: This systematic review identified a significant paucity in the literature on the effect of NSAID medications on spinal fracture healing rates. Given the limited number of studies, as well as the heterogeneous results and methods from these studies, no consensus statement can be made on the safety profile of NSAIDs in the context of spinal fractures. Further studies are needed to better address this question.

Keywords: Spine; surgery; fracture; non-steroidal anti-inflammatory; non-steroidal anti-inflammatory medication (NSAID)

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Introduction

The use of non-steroidal anti-inflammatory medications (NSAIDs) have played a pivotal role in the management of pain in the orthopaedic realm, most notably, for arthritic related pain, pain in the perioperative period, in those with non-operative tendonitis, or following an acute injury (1-3). In light of the ongoing opioid epidemic, NSAIDs serve as a viable alternative to narcotic medications, and are being included in many multi-modal pain control regimens across various specialties (4-6).

Despite their noted benefits and prevalence, their use in the field of orthopaedic surgery has generated much controversy, due to various studies showing possible impairment of bony healing. One of the earliest studies to assess this was in 1976, when Bo *et al.* reported impaired healing of non-immobilized femoral fractures in rats who were given indomethacin (7). Furthermore, the authors noted altered mechanical properties of the healed fracture, as well as smaller and delayed callus formation in the indomethacin treated groups. This finding brought in to question the safety of NSAID use in orthopaedic patients and led to further research on the exact mechanism of NSAIDs role in bone healing biology. The concentration of Prostaglandin E2 (PGE2) may control osteoblast behavior through the relative expression of the receptor activator of nuclear factor kappa-B ligand and osteoprotegerin, which is regulated through the enzymes cyclooxygenase (COX)-1 and COX-2. It is through the inhibition of COX isozymes, which results in decreases in PGE2, that NSAIDs may delay bone healing (8).

When considering the literature on NSAID use in spine patients specifically, many recent studies have been performed, mostly in the context of spinal fusion surgeries. For example, a systematic review on in vivo, animal, and clinical studies in regards to the effect of NSAIDs on spinal fusion found that studies from the early 2000's formed a general consensus that NSAIDs increased rates of nonunion, however, all human studies published after 2005 suggested acute post-operative use (less than 48 hours) did not demonstrate this effect, highlighting the notion that dose and duration of NSAID use is an important consideration perioperatively (9). Similarly, Li *et al.* (10) performed a meta-analysis which demonstrated that pseudoarthrosis after posterior thoracolumbar fusions was related to post-operative Ketorolac use for greater than 2 days, or at doses equal or greater than 120 mg/day.

Fractures of the spine, such as vertebral compression fractures, are prevalent given the aging population, with up to 700,000 people affected each year in the United States (11,12). Despite the majority of isolated compression fractures of the lumbar spine being managed non-operatively, these fractures can cause patients significant pain and disability (11), and providers often resort to the prescription of narcotic pain medications, in addition to NSAIDs, muscle relaxers or lidocaine patches for pain management (13). Although NSAIDS may be able to provide significant relief for these patients, considering the evidence aforementioned, it may jeopardize fracture healing.

While there is current literature on the effect of NSAIDs on spinal fusion rates, there is currently, to our knowledge, no review of the literature on the use of NSAIDs in patients with acute spinal fractures. Therefore, the goal of this systematic review is to perform a comprehensive review of the literature to determine if NSAIDs effect the rate of bony healing in patients with spinal fractures, and secondarily, to determine if there is any effect of nonselective versus selective COX-2 inhibitors in regard to bony healing.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/jss-21-77) (14).

Methods

Search strategy

Using the guidelines set forth by the Cochrane Handbook of Systematic Reviews (15), and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14), a systematic review of the literature was completed. Two independent reviewers performed duplicate searches of the Cochrane Library, PubMed, Medline Ovid and Cochrane databases from inception until April 2021 (see Appendix 1, section A), for all search terms used and results. Additionally, two reviewers performed a duplicate search of the National Institute of Health (NIH) Clinical Trials Database to identify any potential ongoing relevant research (see Appendix 2, section B), for all search terms and results.

Study screening

Two study members (JP, SM) independently screened all titles, abstracts, and full texts to help determine eligibility of studies identified through the searches of the above databases. If a title/abstract was deemed potentially relevant but full-text article was not available, attempts to reach

the authors were performed when contact information was available. Additional titles found through independent searches and reference list screenings were also analyzed for study inclusion. Any disagreements at the title, abstract, or full-text review stages were resolved with discussion amongst the reviewers and senior author. A final consensus on eligibility was reached for all articles.

Assessment of study eligibility

We defined all inclusion and exclusion criteria a priori. Included studies were those (I) in English, (II) analyzing adult patients (age ≥18), (III) specifically reporting on spinal fracture healing rates in patients taking NSAIDs. Studies were excluded if they did not specifically report on fracture healing rates or did not specify if patients had fractures in the study cohort. The primary outcome of interest was the rate of spinal fracture healing in patients taking NSAIDs. Secondary outcomes of interest were any differences in spinal fracture healing rates based on the selectivity mechanism of studied NSAIDs.

Assessment of study quality

The Methodical Index for Non-Randomized Studies (MINORS) (16) was used to assess the overall quality and risk for bias in all non-randomized control studies included in this analysis. This is a validated instrument, which uses a set of 8 grading criteria for non-comparative studies, and 12 grading criteria for comparative studies. Criteria are given a grade of 2 (reported adequately), 1 (reported, but inadequate), or 0 (not reported). Non-comparative studies can therefore achieve an ideal max grade of 16 points, and comparative studies have an ideal grade of 24 points. For randomized control trials included, the Critical Appraisal Skills Programme (CASP) (17,18) checklist was used for assessment of overall study quality and bias risk. This 11-item tool gives an overall global assessment of studies, rather than a numeric graded score. If a study met the majority of this tools criteria, it was considered acceptable. All included studies were graded by two independent reviewers using the above tools, to ensure agreement on study quality and bias.

Data abstraction and statistical analyses

The basic demographic information of eligible studies was extracted, including author names, year of publication, study design, and number of study participants included. Results on overall spinal fracture healing rates in patients taking NSAIDs was recorded. When available, data on the type of NSAID, duration of NSAID use, dosage of NSAID prescribed, and method for determining fracture healing was also recorded and analyzed.

To measure inter-observer agreement at various stages throughout the systematic review, Cohen's kappa (κ) coefficient, as previously described by Landis *et al.* (19), was used. The overall strength of agreement between reviewers was defined using the following: κ = 0.01–0.20 = slight agreement; κ = 0.21–0.4 = fair agreement; κ = 0.41–0.6 = moderate agreement; κ = 0.61–0.8 = substantial agreement and κ >0.8 = almost perfect.

Results

Study identification

The initial search of all databases produced 1,760 results. After the exclusion of 61 duplicates, this left 1,699 unique titles to be reviewed. Through additional independent searches and review of reference lists from relevant studies, an additional 16 studies were identified, for a total 1,715 studies ultimately considered for potential inclusion. After all stages of review, 3 articles (20-22) (214 total patients) were ultimately deemed to meet inclusion criteria and were used in the analysis (*Figure 1*). See *Table 1* for comprehensive demographics from the included studies. See *Table 2* for the comprehensive NSAID regimen for each respective study. All 3 included studies were deemed to be appropriate for inclusion based on quality and risk of bias using the MINORS and CASP checklists, with a Cohen's kappa (κ) coefficient >0.8 between reviewers.

NSAIDs and spinal fracture healing rates

All 3 studies assessed the overall rate of spinal fracture healing rates within their respective cohorts. Daniel *et al.* (20) retrospectively reviewed 29 patients (age 13–31 years, 7 children), treated at Walter Reed Medical Center for presumed traumatic spondylolysis. All patients were found to have pars defects confirmed with plain radiographs, or bone scan if plain radiographs were not diagnostic. All pars fractures were in the lumbar spine. All patients were initially managed conservatively with a 3-month trial of activity modification, bracing, NSAIDs, and narcotic medications on an as needed basis. Fracture healing was assessed at the 3-month mark by

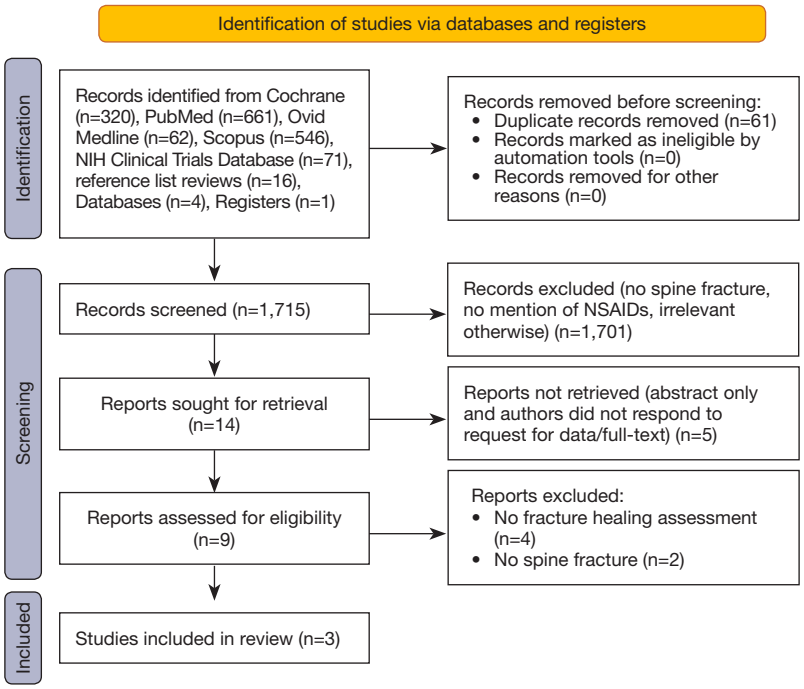

Figure 1 Flowchart of selected studies. Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page *et al.* (23).

Table 1 Demographics of included studies

Author	Year	Study design	N	Age, years	Fracture type	Fracture levels	Quality tool	Quality assessment score
Van Dam *et al.*	1995	Retrospective review	29	13–31	Traumatic pars	L2-L5	MINORS	12/16
Tanaka *et al.*	2017	Randomized control	107	62–88	Osteoporotic	T5-L4	CASP	Acceptable
Zhang *et al.*	2017	Prospective cohort	78	Mean age 69.5	Osteoporotic	T7-L3	MINORS	15/24

MINORS, Methodical Index for Non-Randomized Studies; CASP, Critical Appraisal Skills Programme.

Table 2 NSAID regimen of included studies

Author	NSAID (dosage)	COX inhibition	Duration of use	Study proportion taking
Van Dam *et al.*	Not provided	Not provided	3 months	29/29
Tanaka *et al.*	Etoldolac 200 mg BID	Non-selective	6 months	54/107
Zhang *et al.*	Naproxen 250 mg qid	Non-selective	12 weeks	12/78
	Indomethacin 25 mg qid	Non-selective	12 weeks	14/78
	Flurbiprofen 50 mg TID/qid	Non-selective	12 weeks	11/78
	Piroxicam 20 mg OD	Selective COX2	4 weeks	13/78
	Celecoxib 200 mg BID	Selective COX2	12 weeks	12/78
	Rofecoxib 25 mg OD	Selective COX2	12 weeks	15/78

NSAID, non-steroidal anti-inflammatory; COX, cyclooxygenase.

Table 3 Non-union rates of selective *vs.* non-selective COX inhibitors

Author	Non-selective COX inhibitor	Non-union rate	Selective COX2 inhibitor	Non-union rate
Zhang *et al.*	Naproxen	6/12 (50%)	Piroxicam	5/13 (38.5%)
	Indomethacin	3/14 (21.4%)	Celecoxib	2/12 (16.7%)
	Flurbiprofen	5/11 (45.5%)	Rofecoxib	1/15 (6.7%)

NSAID, non-steroidal anti-inflammatory; COX, cyclooxygenase.

patient reports of pain, as well as repeat radiographs. In the instances where patients were pain free but didn't demonstrate clear fracture healing on radiographs, a bone scan was obtained. The authors reported that based on these criteria, only 2 of the 29 patients (6.8%) had healed their fractures, the remaining patients were offered a direct pars repair. Of note, the type of NSAID, dosage, duration, and compliance were not reported on. Additionally, results were not stratified by patient age, so it is unclear which 2 patients went on to heal.

Tanaka *et al.* (21) performed a randomized parallel controlled trial of 107 female patients (age 62–88 years) with acute osteoporotic vertebral fractures, and assessed fracture healing rates in those receiving intramuscular Elcatonin (calcitonin derivative) *vs.* the NSAID Etoldolac, a non-specific COX inhibitor, for a 6-month period. Those in the NSAID group additionally received an active form of vitamin D3, Alfacalcidol 0.5 µg daily. All included patients had acute thoracic or lumbar osteoporotic vertebral fractures confirmed on both radiographic imaging, as well as magnetic resonance imaging (MRI). Fracture healing was assessed with repeat MRI imaging. The authors reported that 52/54 (96.3%) patients in the NSAID group healed their fractures, and 51/53 (96.2%) of the calcitonin derivative group demonstrated fracture healing.

Zhang *et al.* (22) performed a prospective cohort study of 78 patients (mean age 69.5 years) with acute osteoporotic vertebral fractures in the thoracic or lumbar spine diagnosed with dual energy X-ray absorptiometry (DEXA) scans. Patients were divided into 6 groups, with each group being prescribed a different selective or non-selective NSAID for 12 weeks. The non-selective COX inhibitors included were as follows; Naproxen, Indomethacin, and Flurbiprofen. The selective COX2 inhibitors included Piroxicam, Celecoxib, and Rofecoxib. Fracture healing was assessed with repeat DEXA scans. The authors reported a non-union in 22/78 (28.2%) of their cohort.

Non-selective vs. selective COX2 inhibitors

Zhang *et al.* (22) was the only study to specifically compare spinal fracture healing rates in those taking non-specific COX inhibitors *vs.* those taking selective COX2 inhibitors. The comprehensive results of their non-union rates can be seen in *Table 3*. Of additional note, the authors also assessed delayed union rates while stratifying by selective *vs.* non-selective NSAIDS. When looking at the non-selective COX inhibitors, they reported delayed unions in 7/12 (58.3%) of those taking Naproxen, 4/14 (28.6%) of those taking Indomethacin, and 4/11 (36.4%) of those taking Flurbiprofen. In the selective COX2 inhibitor groups, delayed union was reported in 3/13 (23.1%) of those taking Piroxicam, 1/12 (8.3%) of those taking Celecoxib, and in 2/15 (13.3%) of those taking Rofecoxib.

Discussion

The present systematic review identified 3 studies which attempted to assess the rates of spinal fracture healing in patients taking NSAIDs. Overall, the methods and results of these studies were extremely heterogeneous, which makes forming an educated or informed consensus statement on the safety profile of NSAIDs in this patient population not possible. On one end of the spectrum, Daniel *et al.* (20) reported that almost none of their study population went on to heal their pars fractures, with only 6.8% of participants demonstrating ultimate fracture healing. The results of this study must be considered within the context of its limitations. First, the type of NSAID, dose, and compliance were not reported on. Second, participants ranged in age from 13 to 31 years, with 7 being identified as children. The ages of which patients went on to heal *vs.* those that did not, is not reported on, which also limits the generalizability of results. Lastly, pars fractures are a unique spinal fracture, and bony union is not necessarily the ultimate goal, as many can go on to fibrous unions, and the ability to detect

this on XR or bone scan as used in this study, may not be the best method for assessing this. Ultimately, this study was still included because it provides some insight into this controversial issue but must be interpreted within the context of its limitations.

On the opposite end of the spectrum, Tanaka *et al.* (21) reported that 96.3% of its study population taking Etoldolac for 6 months healed their osteoporotic vertebral fractures. The major strengths of this study include the randomized controlled nature of the trial, as well as the fact that MRI was used to diagnose fractures and fracture healing. One limitation of this study is that blinding is not discussed, and whether this introduced any bias into the results is a consideration. Additionally, only females age 55 or over were considered for inclusion, which limits the overall generalizability of their findings. Ultimately, this represented the strongest study design of all included papers in this review, and additionally analyzed the largest number of patients.

Lastly, Zhang *et al.* (22) reported results in the middle of the spectrum, while comparing non-union rates in non-selective *vs.* selective COX2 inhibitors, making their study design unique to the other include studies in this review. Interestingly, they reported the lowest overall non-union rates amongst the selective COX2 inhibitors Celecoxib and Rofecoxib, at 16.7% and 6.7%, respectively. When looking at the non-selective COX inhibitors Naproxen and Flurbiprofen, non-union rates were 50.0% and 45.5%, respectively. Limitations of this study include the fact that study personnel blinding is not discussed, how patients were chosen to take which NSAID is not described, the baseline characteristics of patients in each group was not analyzed, and DEXA scan, rather than advanced imaging, was used to diagnose non-union. These factors must all be considered when determining the weight of the results from this study.

Similar to the results of this systematic review, prior studies on the effects of NSAIDs on bone healing in animal and human models is heterogeneous. Altman *et al.* (24), assessed fracture healing rates and strength in rats with induced femur fractures. Rats were given either Ibuprofen, Indomethacin or no NSAID. The authors found that the rats which received Ibuprofen for either 4 or 12 weeks had lower strength of healed fractures on mechanical testing as compared to the control group. The rats which received Indomethacin for 10 or 12 weeks additionally showed this decreased fracture strength, although Indomethacin for only 4 weeks did not cause any strength differences. The authors also noted delayed fracture healing in rats which received Ibuprofen or Indomethacin for either 4 or 12 weeks. Mullis *et al.* (25) examined fracture healing properties in 296 mice with induced tibia fractures. The mice received Ketorolac, Ibuprofen, Indomethacin, Rofecoxib or placebo for 12 weeks. While some differences in ultimate energy absorbed at fracture site was seen at 4 weeks in mice receiving Ketorolac, they ultimately found no significant differences in healing, stiffness, or load to failure amongst groups.

Hassan *et al.* (26) assessed bony union in 232 human patients after foot and ankle surgery who received different post-operative pain protocols, including 2-week of NSAIDs in some patients. They found no difference in the rate of non-unions within their cohort and concluded that short term use of oral Ketorolac and Ibuprofen was not detrimental to bony healing.

Specifically, in regard to bone healing in the spine, several studies have examined the effects of NSAIDs, most commonly after fusion surgeries. Dimar *et al.* evaluated the effect of Indomethacin for 12 weeks on rats after undergoing 3 level posterior spinal fusion. They reported a significantly decreased rate of fusion in the Indomethacin group as compared to controls (27). Park *et al.* (28) assessed union rates after posterior lumbar fusion in 88 patients, who received either Ketorolac + Fentanyl IV for 3 days post-operatively *vs.* only Fentanyl. The authors reported a non-union in 5/30 (16.7%) of those who received Ketorolac, as compared to 2/58 (3.4%) in the Fentanyl only group, and this was significantly different.

Strengths and limitations

The present study is the first to our knowledge, to systematically review the current literature that exists on spinal fracture healing rates in patients taking NSAIDs. The major limitation of this review is the quality of included studies. While all studies were ultimately deemed acceptable based on quality assessment tools, they each had their own limitations, which must be considered and taken into context when interpreting their results. Additionally, due to the wide variability of NSAID type, dosages, duration of use, and methods for assessing fracture healing amongst the included studies, no succinct meta-analysis can be performed. Lastly, given that only three relevant studies were identified in the literature, it is difficult to form an educated consensus on this issue with the limited available current data. One strength of this study is the wide variety of NSAID type, fracture types, and patient demographics included, as this provides a broad spectrum of data points

that physicians can use to help in their decision-making process when considering these medications. Lastly, the major strength of this study is that it identified a large void in the literature that can help direct future research.

Conclusions

Spinal fractures are common throughout the world, and are often associated with pain and disability, especially in the osteoporotic population. While NSAIDs are commonly prescribed by physicians for pain, the literature still has not come to a definitive conclusion on their safety profile when considering patients with healing fractures. The aim of this systematic review was to provide a succinct summary of the available evidence on spinal fracture healing rates in patients taking NSAID medications. The paucity of literature that exists on this topic, in addition to the limitations and quality of the available current evidence, makes it difficult to make any consensus statement or guidelines for physicians considering using NSAIDs in this patient population. Ultimately, this review highlights the need for further investigation and high-quality studies designed to better assess this relationship and provide further guidance for patients and physicians.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/jss-21-77

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jss-21-77). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix

Section A: Search terms used for PubMed, Cochrane, OVID Medline, SCOPUS

(spine OR spinal OR vertebral OR back OR cervical OR thoracic OR lumbar) AND (fracture OR trauma) AND (NSAID OR "non-steroidal anti-inflammatory" OR toradol OR motrin OR celebrex OR ibuprofen OR ketorolac OR celecoxib OR advil) in all possible combinations. Filters: Human, English language.

PubMed produced 661 results, Cochrane produced 320 results, OVID Medline produced 62 results and SCOPUS produced 546 results on 4/13/2021.

Section B: Search terms used in NIH Clinical Trials Database

a. (Spine fracture + NSAID), no filters, all studies: 2 results on 10/1/21;
b. (Spine fracture), no filters, all studies: 155 results on 10/1/21;
c. (NSAID + fracture), no filters, all studies: 14 results on 10/1/21.

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