The Effect of Nonsteroidal Anti-Inflammatory Agents on Spinal Fusion

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educational objectives

As a result of reading this article, physicians should be able to:

1. Recognize possible factors that may contribute to the failure of spine arthrodesis surgeries.
2. Explain the basic physiological differences between the COX-1 and COX-2 pathways.
3. Identify the major prostaglandins involved in bone metabolism, and appreciate the basic principles regarding the roles of these prostaglandins, as well as the role of NSAIDs in this process.
4. Assess the primary outcomes of the animal studies looking at NSAID use in spinal fusion, including the effect of COX-2 selective versus non-selective NSAIDs, the timing of NSAID administration, and potential adjunctive therapies.
5. Discuss the results of the retrospective human study looking at NSAIDs and spinal fusion, including outcomes and potential compounding factors.

Spinal arthrodesis has become an increasingly common procedure in the United States, with more than 185,000 such cases performed each year. Despite the generally beneficial results of spinal arthrodesis, a significant number of cases fail to achieve the desired outcome. Often this is the result of poor patient selection or the presence of a surgical complication.

Among the various surgical complications, nonunion or pseudarthrosis is one of the most difficult to overcome. Pseudarthrosis occurs in 5% to 35% of single-level fusions and may be the source of continued spinal symptoms requiring revision surgery. The nonunion rates for multilevel procedures are even higher. Although the use of internal fixation has decreased the rate of pseudarthrosis for some procedures, this complication has not been eradicated.

Many factors are believed to contribute to pseudarthrosis, including host factors such as advanced age, chronic disease, and tobacco usage, and technical factors such as the type, quality, and quantity of bone graft used to perform the fusion. Other factors such as the mechanical stability of the fusion site and the use of postoperative medications, including corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDS), can play a role in this vexing process. While some aspects are uncontrollable, any factors contributing to pseudarthrosis can be altered to diminish the risk of fusion failure.

Continuing the use of some medications such as corticosteroids for severe asthma is necessary in the postoperative period following spinal fusion despite a potential detrimental effect on the healing of the fusion. Likewise, NSAIDS may be useful for patients with debilitating symptoms of osteoarthritis, which can limit postoperative rehabilitation and diminish the quality of life.

Nonsteroidal anti-inflammatory drugs are an effective non-narcotic analgesic and can be useful in controlling postoperative pain. In some cases, patients may experience an "arthritic flair" postoperatively when chronic NSAID therapy is withdrawn. Therefore, it is reasonable to

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consider the risk:benefit ratio with regard to NSAID therapy in selected patients following spinal fusion.

This article reviews the literature relating to the effects of NSAIDs on spinal fusion. With a better understanding of the physiologic effects of NSAIDs, surgeons will be better armed to make decisions about when NSAIDs are appropriate in the postoperative period following spinal arthrodesis.

**Basic Science**

The primary effect of NSAIDS is to inhibit the enzyme cyclo-oxygenase (COX), which is active in the process of forming prostaglandins, leukotrienes, and thromboxanes from their precursor, arachidonic acid (Figure). There are two distinct isoforms of the COX enzyme: COX-1 is ubiquitous and found in nearly every tissue in the body, notably in the stomach, small intestine, and platelets, while COX-2 is restricted to certain tissues including bones and joints.

Cyclo-oxygenase-1 is a regulatory "housekeeping" enzyme involved in homeostasis, while COX-2 is inducible, increasing more than 20-fold in macrophages, monocytes, synoviocytes, chondrocytes, and osteoblasts when stimulated by an inflammatory stimuli such as interleukin-1, tumor necrosis factor, or platelet-derived growth factor. Both COX isoenzymes are inhibited by traditional NSAIDS. However, because the musculoskeletal inflammatory effects are mostly attributable to the action of COX-2, selective inhibitors of this enzyme have been developed in an effort to avoid the negative side effects (such as gastric breakdown) linked to COX-1 inhibition.

Due in large part to the potential decrease in unwanted side effects from COX-1 inhibition, COX-2 selective inhibitors have rapidly become popular for musculoskeletal conditions. It is, however, important to note that none of the commercially available COX-2 inhibitors are purely selective for the COX-2 isoenzyme. In addition, the biologic activity of the COX system is more complicated than simply interpreting the effects of COX-2 inhibition as favorable and COX-1 inhibition as unfavorable.

The role of COX enzymes in bone metabolism is interesting as prostaglandins play an essential role in the processes of both bone formation and resorption. A number of factors can act on osteoblasts and osteoclasts including hormones, cytokines, prostaglandins, and mechanical factors. The major prostaglandins involved in bone metabolism are prostaglandin E1 and prostaglandin E2. Because these molecules are involved in both the formation and resorption of bone, the net bone gain or loss depends on the environment and the type of bone on which the prostaglandins act.

The effects of prostaglandins in bone were recognized in an early review by Norrbin et al who noted prostaglandins were potent mediators of bone resorption at sites of inflammation. Others have shown bone resorption at sites of inflammation can be inhibited by the administration of an NSAID. In cell cultures, prostaglandins lead to the inhibition of osteoclastic activity. Nonsteroidal anti-inflammatory drugs inhibit bone formation clinically and are used by hip surgeons to diminish heterotopic ossification.

Infants exposed to infusions of prostaglandin E1 to maintain patency of the ductus arteriosus are known to undergo accelerated periosteal long bone formation for approximately 4 weeks following treatment. Prostaglandins also have been implicated in bone formation during myositis ossificans and osteoid osteoma. Prostaglandin E1 appears to play a key role in the adaptive response of bone to stress.

In a study of weanling rats, the administration of NSAIDS resulted in increased metaphyseal bone and decreased numbers of osteoclasts. Nonsteroidal anti-inflammatory drugs have also been used to block the resorption of bone by osteoclast and prevent disuse osteopenia. However, when combined with estradiol, NSAIDS may lead to reduced cancellous bone volume. Work in animal models confirms NSAIDS have a significant
detrimental effect on the healing of fractures and osteotomies.38-48

These studies serve to underscore the complex effects of NSAIDS and prostaglandins in bone metabolism. In addition, it appears likely NSAIDS act via mechanisms in addition to cyclooxygenase inhibition. For instance, Ho et al45 found both prostaglandins and NSAIDS had similar inhibitory effects on osteoblasts in culture, suggesting the NSAIDS were acting via a prostaglandin-independent mechanism. Others have suggested NSAIDS can affect the cell cycle, thus inhibiting cell proliferation via a pathway independent of prostaglandins.17

**Spinal Fusion in the Animal Model**

The model used to study spinal fusion is important to consider when evaluating the results of animal studies. In general, the more challenging healing environment involves the posterolateral spine (intertransverse fusion) as opposed to the interbody space. The stability of the construct is also important to consider with uninstrumented fusions presenting a more difficult healing challenge. Finally, there are significant species differences in the healing of spinal fusions, with higher animals, particularly primates, representing the greatest healing challenge. To be a valid model for the challenging biologic environment in humans, an appropriate animal model should demonstrate a significant rate of pseudarthrosis when subjected to an uninstrumented intertransverse fusions.49-52

Lebwohl et al53 presented an early study using orally administered ibuprofen in a rabbit fusion model. While their data failed to reach statistical significance, a trend toward increased nonunion was observed.

Dimar et al54 used a rat model to investigate the effects of orally administered indomethacin on spinal fusion. The animals received indomethacin 1 week preoperatively and 12 weeks postoperatively. Using manual palpation, the rate of nonunion was 90% in the NSAID group compared to 55% for the control group (P<.001). Qualitative histology demonstrated significant resorption of bone graft in the indomethacin group in contrast to the control group.

Boden et al51 used a rabbit intertransverse model to study fusion. This is an attractive model with a nonunion rate for autograft fusion similar to humans. Using this model, Martin et al52 found the postoperative administration of ketorolac (infused via a subcutaneous pump) increased the nonunion rate from 25% to 65% (P=.037). They also reported the use of bone morphogenetic protein-2 for spinal fusion overcame the inhibitory effects of ketorolac and yielded a fusion rate of 100%.

Long et al55 were the first to compare a COX-2 inhibitor to a nonselective NSAID in a spinal fusion model. Using the same rabbit fusion model as Boden et al, the authors compared the effects of 8 weeks of orally administered indomethacin and celecoxib (a COX-2 selective drug). This study confirmed the deleterious effects of the nonselective NSAID, which reduced the fusion rate from 64% in the control animals to 18% in the indomethacin-treated animals (P=.002). The COX-2 treated animals demonstrated a 45% fusion rate, which was not statistically different from the control group (P=.224), but may show a trend toward poorer healing that could have been seen with larger numbers of animals.

Riew et al56 reported on a study designed to evaluate the time course following fusion when NSAIDS exerted their detrimental effects. With a hypothesis that NSAIDS must act during the initial inflammatory phase to prevent early osteogenesis, the authors examined the effects of indomethacin when initiated at 2 and 4 weeks post fusion surgery.

In rabbits given indomethacin 2 weeks postoperatively, the rate of successful fusion was 21%. When the indomethacin was delayed until 4 weeks, the rate of successful fusion increased to 48%. The control group received saline starting at the 2-week time point and achieved a fusion rate of 65%. Statistically significant differences were noted when comparing the 2-week indomethacin group with the control group (P<.002) and when comparing the 2- and 4-week indomethacin groups (P=.05).56 These data seem to confirm an

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| **Selective COX-2 Inhibitors** |
| Diaryl-substituted furanones |
| Rofecoxib |
| Diaryl-substituted pyrazoles |
| Celecoxib |
| Indoleacetic acids |
| Etdolac |
| Sulfanilamides |
| Nimesulide |

Abbreviation: COX=cyclo-oxygenase.
initial inhibitory effect that may diminish with time.

**Spinal Fusion in Humans**

Glassman et al. studied the effects of NSAIDS in humans. They reported on a retrospective series of 288 patients undergoing posterolateral intertransverse fusions with a minimum of 2 years of follow-up. One hundred twenty-one patients received no NSAIDS postoperatively, while 167 received ketorolac in the early postoperative period for pain control. Nonunions were defined as failure of fusion noted on the basis of surgical exploration, broken hardware, or tomograms. The nonunion rate was 4% in the group without NSAIDS and 17% in the ketorolac group. This difference was statistically significant (P<.001) and suggests an approximately five times greater likelihood of developing pseudoarthrosis following the administration of ketorolac. An additive effect was noted for smokers who received ketorolac, with a 25% rate of nonunion. More doses of ketorolac appeared to increase the risk of nonunion, up to the range of 9 to 12 doses per patient.

**Summary**

A large body of information suggests NSAIDS have a negative impact on the healing of bone. Although each clinical healing scenario presents a slightly different level of challenge, the healing of a posterolateral spinal fusion is one of the most difficult challenges in bony healing. Clinically, this results in a relatively high rate of nonunions using traditional fusion techniques.

Spinal fusion models have confirmed NSAIDS have a definite inhibitory effect on healing of the fusion. It appears likely NSAID use following a spinal fusion procedure will increase the rate of pseudoarthrosis. The literature suggests that avoidance of NSAIDS in the postoperative period may avoid nonunion. Additionally, we propose that chronic NSAID usage should be addressed in a similar manner to cigarette smoking. While neither are absolute contraindications to elective spinal fusion, patients should be counseled to discontinue the use of NSAIDS in the peri- and postoperative period to maximize their chance for a successful fusion.

**References**


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