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AMERICAN ACADEMY OF
ORTHOPAEDIC SURGEONS

Nonsteroidal Anti-Inflammatory Drugs in Orthopaedics

By Omar Abdul-Hadi, MD, Javad Parvizi, MD, Matthew S. Austin, MD, Eugene Viscusi, MD, and Thomas Einhorn, MD

An Instructional Course Lecture, American Academy of Orthopaedic Surgeons

Nonsteroidal anti-inflammatory drugs are widely used and prescribed in the United States. Between 35 and 70 million prescriptions for nonsteroidal anti-inflammatory drugs are written in the United States each year, and numerous agents are now available over the counter¹. In particular, the prescription of cyclooxygenase-2 (COX-2) inhibitors has become widespread since they were approved by the U.S. Food and Drug Administration in 1999, and in 2000 nearly 45 million prescriptions were written for celecoxib and rofecoxib². More than 17 million Americans use various nonsteroidal anti-inflammatory drugs on a daily basis. Moreover, it has been estimated that 5% to 7% of all hospital admissions are related to adverse drug reactions, with nonsteroidal anti-inflammatory drugs being the culprit in 30% of these cases³. As a result of the aging of the population, there will be an increase in the use of nonsteroidal anti-inflammatory drugs parallel to the increase in the prevalence of painful degenerative musculoskeletal conditions. Despite the rising popularity of COX-2 inhibitors, their role in ortho-

paedic surgery remains controversial. Several studies have demonstrated the inhibitory effect of COX-2 inhibitors on bone-healing, and the inhibitory effect of traditional nonsteroidal anti-inflammatory drugs is already well known⁴. The use of COX-2 inhibitors is growing in the elderly population, and there are multiple concerns regarding the adverse side effects and the theoretical basis of safety of COX-2 inhibitors in orthopaedic patients.

Role of Prostaglandins in Bone and Tendon Physiology

The skeleton is a metabolically active organ that undergoes continuous remodeling throughout life. Osteoblasts and osteoclasts, the most important contributors to bone remodeling, produce prostaglandins, which are shown to modulate the function of osteoblasts and osteoclasts in bone metabolism and healing⁵. Prostaglandins are multifunctional regulators with stimulatory and inhibitory effects on bone resorption and formation. They are autocrine and paracrine lipid mediators that act on a variety of cells including platelets as well

as endothelial, uterine, and mast cells. Prostaglandins are found in virtually all tissues and organs. Skeletal tissue is also an abundant source of prostaglandin production, so it is likely that endogenous prostaglandins play important roles in skeletal physiology and pathophysiology⁶. Changes in prostaglandin synthesis and concentration have been shown to correlate with changes in the quantity of trabecular regeneration and with acceleration of bone-healing⁷.

Prostaglandin E2 is the most abundant prostaglandin produced by osteoblasts and was first shown to increase cyclic 3',5' adenosine monophosphate (cAMP) and stimulate bone resorption in cultured fetal rat long bones more than thirty years ago⁸. Its production by osteoblasts is regulated by several cytokines, including interleukin-1 (IL-1). The action of prostaglandin E2 is mediated by rhodopsin-type receptors specific to prostaglandins. There are four subtypes of prostaglandin receptors, designated EP1, EP2, EP3, and EP4, which are encoded by different genes and expressed differently in each tissue. The intracellular signaling differs among

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the receptor subtypes; EP1 is coupled to Ca^{2+} mobilization, EP3 inhibits adenylate cyclase, and both EP2 and EP4 stimulate adenylate cyclase⁸.

Prostaglandin E2 also has bone resorptive activity and is associated with an increased number of osteoclasts. A number of studies have shown impaired osteoclast formation in cultures of cells from EP4-deficient mice, and osteoclast formation is most potently induced by EP4 agonist. Suzawa et al.⁸ reported that bone resorption was markedly stimulated by EP4 agonist and, to a lesser degree, by EP2 agonist. The three regulatory steps are binding of prostaglandin E2 to EP4 and EP2, an increase in cAMP, and induction of the osteoclast differentiation factor.

Mechanism of Action of Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are structurally diverse compounds with common therapeutic and adverse effects. All nonsteroidal anti-inflammatory drugs, including the subclass of selective COX-2 inhibitors, are anti-inflammatory, analgesic, and antipyretic. The principal therapeutic effects of nonsteroidal anti-inflammatory drugs derive from the ability of the drugs to inhibit prostaglandin production⁹. The first enzyme in the prostaglandin synthetic pathway is prostaglandin G/H synthase, also known as cyclooxygenase or COX. This enzyme converts arachidonic acid to the unstable intermediates prostaglandin G2 and H2, leading to the production of thromboxane A2 and a variety of prostaglandins.

Within the last decade, two cyclooxygenase isoforms have been identified and are referred to as COX-1 and COX-2^{10,11}. COX-1 is also described as a "housekeeping enzyme," which regulates the normal cellular processes and is a primarily constitutive form found in most normal cells and tissues, including the stomach lining. In contrast, COX-2 is expressed at low levels unless it is induced by cytokines and inflammatory mediators and is responsible for the upregulation of the inflammatory system. COX-2 expression is inhibited by glucocorticoids, an important feature

that led to the identification of the COX-2 enzyme¹⁰. Several studies suggest that COX-2 mediates increased prostaglandin production in bone in response to tumor necrosis factor- α (TNF- α), IL-1 β , IL-6, IL-11, IL-17, and other osteotropic factors¹²⁻¹⁶, and many factors that either stimulate or inhibit bone resorption affect COX-2 expression in osteoblasts or stromal cells^{17,18}. These studies suggest that COX-2 has a role distinct from that of COX-1 in bone resorption¹⁸. A splice variant derivative of the COX-1 gene has been identified as COX-3¹⁹, but the clinical relevance of this enzyme is unknown and whether it has cyclooxygenase activity remains controversial²⁰.

Traditional nonsteroidal anti-inflammatory drugs inhibit both COX-1 and COX-2. The relatively high prevalence of gastrointestinal side effects (i.e., gastric irritation) is attributed to COX-1 inhibition, whereas the desired effect is the subsidence of inflammation that results from COX-2 inhibition.

Effect of Nonsteroidal Anti-Inflammatory Drugs on Fracture-Healing

Prostaglandin E2 induces substantial increases in bone formation, bone mass, and strength when administered systemically or locally to the skeleton²¹⁻²³. Endogenous prostaglandin E2 increases locally after fractures²⁴, and the inhibition of prostaglandin E2 production interferes with bone-healing²⁵⁻²⁷.

Li et al. demonstrated osteopenic changes and impaired fracture-healing in EP4-receptor-deficient knockout mice (mice deficient with regard to one of the four receptor subtypes for prostaglandin E2), confirming that the EP4 receptor is a positive regulator in the maintenance of bone mass and fracture-healing²⁸.

In theory, anti-inflammatory drugs that interfere with prostaglandin synthesis should delay fracture-healing. Considerable evidence has accumulated that conventional nonspecific nonsteroidal anti-inflammatory drugs, such as ibuprofen, ketorolac, and indomethacin, have an inhibitory effect on fracture-healing as well as on other forms of

postoperative bone repair²⁹⁻³⁸. COX-2-selective nonsteroidal anti-inflammatory drugs have also been reported to impair and inhibit fracture-healing in animal models, findings that are in agreement with observations of impaired fracture-healing in mice lacking a functional COX-2 gene³⁹⁻⁴¹. Krischak et al.⁴² showed that diclofenac, a nonselective nonsteroidal anti-inflammatory drug, impaired the appearance of osteoblasts in vivo during the early phase of bone-healing, confirming the hypothesis that nonselective nonsteroidal anti-inflammatory drugs can inhibit osteoblasts in the early phase of bone-healing.

Nonsteroidal anti-inflammatory drugs also impede cell proliferation by inhibiting angiogenesis. It has been proposed that a similar mechanism occurs in the initiation of nonsteroidal anti-inflammatory drug-induced nonunions. Murnaghan et al.⁴³ investigated this hypothesis in a randomized placebo-controlled trial of the nonsteroidal anti-inflammatory drug rofecoxib in a murine femoral fracture model. Their conclusion was that rofecoxib had a significant negative effect on blood flow across the fracture gap as well as an inhibiting effect on fracture repair.

COX-2 activity is necessary for normal endochondral ossification during fracture-healing. The effects of COX-2-selective nonsteroidal anti-inflammatory drugs on fracture-healing are caused by inhibition of COX-2 activity and not by a drug side effect. This was shown by Simon et al.³⁹, who reported failure of fracture-healing in the femora of mice homozygous for a null mutation in the COX-2 gene. In that study, Simon et al. also compared the effects of indomethacin, celecoxib, and rofecoxib on fracture-healing in a rat femoral fracture model and found that treatment with COX-2-selective nonsteroidal anti-inflammatory drugs led to fracture nonunions and incomplete unions. The fracture was still clearly evident on the eight-week post-fracture radiographs of the celecoxib and rofecoxib-treated rats. No rofecoxib-treated rat was observed to have normal bridging callus radiographically, and non-

unions, incomplete unions, and unions of the fractured femora were observed in the celecoxib-treated group. Torsional strength was found to be decreased in the group treated with rofecoxib. Rofecoxib was reported to have a drastic effect on the mechanical properties of the femora. In contrast, no significant differences in the mechanical properties were found between the healing fractured femora in the celecoxib-treated rats and those in the control group. Despite that finding, the fractured femora in that group failed as a result of either nonunion (complete failure of the femur along the original fracture site) or incomplete union (new bone-bridging of the fracture site was evident, but the femur still failed primarily through the original fracture site). This was in contrast with the control group, in which most of the femora united (with failure due to a spiral fracture through the diaphysis of the femur), an indication that the fracture sites in the celecoxib group were not bridged with bone. Indomethacin also initially reduced the mechanical properties of the fracture site; however, at eight weeks, the mechanical properties were similar to those in the control group.

The histological findings were consistent with delayed fracture-bridging and remodeling in the celecoxib and rofecoxib groups. The fracture gap was still clearly evident at eight weeks in these groups, and often it was filled with fibrous tissue. This study illustrates that, with the dose of celecoxib and the treatment regimen that were used, fracture-healing was delayed and inhibited, but to a lesser extent than that found in the animals treated with the rofecoxib regimen. Indomethacin was also found to delay, but not prevent, fracture-healing.

These findings were in contrast to the results reported by Brown et al.³⁷, who compared the effects of indomethacin on fracture-healing in rats with those of celecoxib. The drugs were administered starting on the first post-operative day, and the fractures were analyzed radiographically, histologically, and biomechanically at four, eight, and

twelve weeks. At four weeks, only the indomethacin group showed delayed healing. The fractures in the celecoxib group appeared to have more fibrous tissue than those in untreated rats at four and eight weeks; however, radiographic signs of callus formation, mechanical strength, and stiffness did not differ significantly between the groups at twelve weeks. This indicated that COX-2-specific inhibitors caused less of a delay in fracture-healing when compared with that associated with non-specific nonsteroidal anti-inflammatory drugs.

COX-2-specific nonsteroidal anti-inflammatory drugs are only a third as effective as nonspecific nonsteroidal anti-inflammatory drugs in inhibiting prostaglandin-E2 levels within fracture calluses³⁸ and tissues from local sites of adjuvant-induced arthritis⁴⁴. When the effects of a COX-2 inhibitor (valdecoxib) on experimental fracture-healing were compared with those of a non-specific nonsteroidal anti-inflammatory drug (ketorolac)³⁸, ketorolac was found to lower prostaglandin-E2 levels two to three times more than valdecoxib.

The effect of COX-2 inhibition on fracture-healing is both dose and time-dependent⁴¹. In a study of fractured rat femora, different doses of a COX-2-specific nonsteroidal anti-inflammatory drug (celecoxib) were given at different periods before and after the fracture. Celecoxib given within the first two weeks after the fracture reduced the mechanical properties of the fracture callus and caused significantly more nonunions. In contrast, celecoxib given prior to the fracture or fourteen days after the fracture did not increase the proportion of nonunions significantly. The authors suggested that nonsteroidal anti-inflammatory drugs should be avoided by patients during fracture-healing, especially during the immediate and early inflammatory phases.

The reversibility of the inhibitory effects of the COX-2 inhibitors on fracture-healing were evaluated by Gerstenfeld et al.³⁸, who found that withdrawal of either valdecoxib or ketorolac after six days of treatment led to a twofold rebound in the levels of

prostaglandin E2 at the fracture site by fourteen days. Acetaminophen, an analgesic without anti-inflammatory activity, does not inhibit fracture-healing⁴⁵.

While animal studies have demonstrated inhibitory effects of prostaglandins on bone metabolism, there have been few investigations of the effects in humans, and there remains considerable controversy regarding the effect of nonsteroidal anti-inflammatory drugs. Many factors have been found to correlate with clinical nonunions, including a history of smoking and the type of implant used for fixation. Several studies have demonstrated a higher risk of nonunion of fractures in association with use of nonsteroidal anti-inflammatory drugs. Burd et al.⁴⁶ concluded that patients with an acetabular fracture and a concomitant fracture of a long bone who received indomethacin for prevention of heterotopic ossification were at greater risk for nonunion of the long-bone fracture than were those who did not receive indomethacin.

Giannoudis et al.³³ reported a correlation between clinical nonunions and the use of nonsteroidal anti-inflammatory drugs, especially when the drugs were taken for longer than four weeks.

In a study in the United Kingdom, Van Staa et al.⁴⁷ found no difference in the fracture risk between regular users of nonsteroidal anti-inflammatory drugs and incidental users. In a similar retrospective study, in Denmark, the effects of acetaminophen, nonsteroidal anti-inflammatory drugs, and acetylsalicylic acid (aspirin) were assessed in patients who had sustained a fracture⁴⁸. A small increase in overall fracture risk was observed in association with acetaminophen, and no increase was seen with acetylsalicylic acid. Ibuprofen was associated with an increased overall fracture risk, while celecoxib was not.

In a randomized controlled trial involving forty-two postmenopausal patients with a Colles fracture, Adolphson et al.⁴⁹ found no difference between a group treated with piroxicam (a nonsteroidal anti-inflammatory drug) and a control group with regard to either bone mineral density (as a

measure of posttraumatic osteopenia) or the rate of functional recovery.

Bhattacharyya et al.⁵⁰ found no relationship between nonunion of humeral shaft fractures and use of nonsteroidal anti-inflammatory drugs during the first sixty days after the fracture in older adults. The use of nonsteroidal anti-inflammatory drugs at sixty-one to ninety days after the humeral fracture was associated with nonunion, and this increased risk was also seen for patients exposed to opioid analgesics in the same period. This finding suggests that nonsteroidal anti-inflammatory drugs do not contribute to nonunion.

In summary, nonspecific nonsteroidal anti-inflammatory drugs inhibit osteoblasts in the early phases of bone-healing. COX-2 activity is necessary for normal endochondral ossification during fracture-healing. Although the newer COX-2 inhibitors are marketed as having a lower side-effect profile than traditional nonsteroidal anti-inflammatory drugs, particularly with regard to gastrointestinal effects, these drugs exert an inhibitory action on fracture repair in animal models. However, they have been found to cause less of a delay in fracture-healing than is associated with nonspecific nonsteroidal anti-inflammatory drugs. It may be prudent for patients to avoid nonsteroidal anti-inflammatory drugs following osseous injury. This is more important for fractures that are associated with a delay in healing and that are often accompanied by a reduction in blood flow to the fracture site.

Effects of Nonsteroidal Anti-Inflammatory Drugs on Spinal Fusion

Spinal fusion is a common procedure in the United States, with more than 185,000 operations performed each year⁵¹. In general, the results of spinal fusion are satisfactory, although a considerable number of patients do not obtain the desired outcome. Factors such as the composition of the bone graft, level of fusion, use of spinal instrumentation, electrical stimulation, and cigarette smoking have been shown to influence fusion rates³². The

administration of nonsteroidal anti-inflammatory drugs is also reported to negatively influence the outcome^{2,32,52,53}.

Physiologic doses of indomethacin were first reported to interfere with healing of fractures of rat femora in 1976⁵⁴. Early studies identified the pathophysiology as a net decrease in remodeling and woven-bone formation, inhibition of endosteal bone-forming cells at the fracture site, inhibition of calcification of the bone matrix, and a decrease in the inflammatory response and blood flow at the fracture site^{52,55-57}.

Dimar et al.⁵² showed that indomethacin administered subcutaneously one week before posterior spinal fusion and twelve weeks after it resulted in an increased rate of nonunion in a rat model. Riew et al.⁴ studied the time-dependent inhibitory effects of indomethacin on spinal fusion in a rabbit model and found that, when the indomethacin was begun at two weeks after the surgery, only 21% of the rabbits had fusion compared with 65% in the control group. Beginning indomethacin at two weeks also resulted in more than a twofold reduction in the fusion rate as compared with the rate when the drug was begun at four weeks. However, in another study, initiating indomethacin at four weeks after the surgery did not result in a significant difference in the fusion rate compared with that in the control group⁵⁸. Deguchi et al.⁵⁹ tried to identify the risk factors for failure in a study of eighty-three consecutive adult patients with isthmic spondylolisthesis who had undergone identical decompressive surgery combined with posterolateral spine fusion. A history of smoking or postoperative use of nonsteroidal anti-inflammatory drugs had strong negative influences on the fusion and clinical success rates. Patients who continued to smoke after surgery had a substantially higher rate of pseudarthrosis. Patients who continued to take nonsteroidal anti-inflammatory drugs for more than three months after surgery showed substantially lower fusion and success rates. Similarly, Martin et al. reported that administration of ketorolac for seven days after a posterolateral intertransverse process arthrodesis

was associated with a fivefold increase in the likelihood of pseudarthrosis developing⁵³.

Glassman et al.³² reviewed the cases of 288 patients to determine the effect of postoperative administration of nonsteroidal anti-inflammatory drugs on spinal fusion. Nonunion was detected in 4% of the patients who received no nonsteroidal anti-inflammatory drugs, in contrast to 17% of the patients who received ketorolac.

Long et al.⁶⁰ investigated the effects of COX-2 inhibitors on spinal fusions in three groups of rabbits, which were randomly assigned to receive celecoxib, indomethacin, or saline solution daily for eight weeks. The fusion rates, as determined with gross and histological inspection and radiographic evaluation, were better in the control group and the celecoxib group than they were in the indomethacin group. The authors concluded that inhibitory effects on bone-healing are likely mediated by the inhibition of COX-1, a finding that is in contrast with those of other studies³⁹.

In conclusion, there is no consensus in the literature with regard to the effects of COX-2 inhibitors on spinal fusions and fracture-healing. Nonspecific nonsteroidal anti-inflammatory drugs have a strong negative effect on spinal fusion rates. The inhibitory effects on bone-healing are likely mediated by the inhibition of COX-1. There is a paucity of clinical studies evaluating the effects of COX-2 inhibitors on spinal fusions.

Effects of Nonsteroidal Anti-Inflammatory Drugs on Osseointegration and Aseptic Loosening

Approximately 200,000 total hip arthroplasties are performed annually in the United States. Patients who have these operations require multimodal pain management, in which nonsteroidal anti-inflammatory drugs play a pivotal role. Also, nonsteroidal anti-inflammatory drugs have a role in the prevention of heterotopic bone formation after total hip arthroplasty. Therefore, the effect of these drugs on the

outcome of total hip arthroplasty is an important issue that necessitates meticulous consideration.

Press-fit total hip arthroplasty implants, which are designed to achieve biologic fixation by means of bone ingrowth into a porous-coated surface, are being used with increasing frequency. There are two main issues with regard to the role of nonsteroidal anti-inflammatory drugs in the osseointegration of press-fit hip implants: first, whether the drugs decrease bone ingrowth and thus affect the integration of bone into the prostheses, and second, whether they help to prevent aseptic loosening, a major cause of failure of total hip arthroplasty.

Bone Ingrowth

Trancik et al.⁶¹ found a substantial decrease in bone growth into porous-coated cobalt-chromium implants in rabbits treated with indomethacin, ibuprofen, or high-dose aspirin when they were compared with controls. The inhibitory effects of indomethacin and aspirin were dose-related, with higher doses having a greater inhibitory effect. Keller et al.⁶² found a similar inhibitory effect with indomethacin. They reported that bone ingrowth into a porous cylindrical implant system did not increase between two and eight weeks after implantation in rabbits treated with indomethacin; in contrast, a placebo control group exhibited a substantial increase in bone ingrowth in the same time period.

Cook et al.⁶³ reported that perioperative administration of indomethacin did not affect bone-implant-interface attachment strength of porous-coated implants except during the first three postoperative weeks. In an attempt to distinguish between the effects of COX-1 and COX-2, Goodman et al.⁴⁰ investigated the effects of naproxen and rofecoxib in vivo by using a harvest chamber. Both naproxen and rofecoxib were found to significantly decrease bone ingrowth. In addition, both decreased the number of CD51-positive osteoclast-like cells per section compared with that seen in the control group. Rofecoxib also decreased the area

of osteoblasts per section area compared with that in the controls, although this difference did not reach significance. The conclusion was that bone formation was suppressed by oral administration of a nonsteroidal anti-inflammatory drug that contains a COX-2 inhibitor.

Aseptic Loosening

The potential role of nonsteroidal anti-inflammatory drugs in the prevention of aseptic loosening has been investigated in humans. The premise is that COX-2 expression contributes to activation of the macrophages responsible for the pseudomembrane surrounding loose implants and that inhibiting COX-2 activity can result in a decrease in the prevalence of aseptic loosening.

Hukkanen et al.⁶⁴ examined the bone-implant interface membranes of patients with aseptic loosening following total hip replacement in an attempt to determine whether there was an increase in inducible nitric oxide synthase (iNOS) and COX-2 expression in macrophages in these pseudomembranes, contributing to periprosthetic bone resorption. Prostaglandin E2, an indicator of COX-2 activity, was measured with enzyme immunoassay, and COX-2 was evaluated with quantitative peroxidase immunocytochemistry. They found that iNOS and COX-2 proteins and the corresponding enzyme activities were present in the interface tissues surrounding loose implants. There was a colocalization of CD68+ macrophages with iNOS, nitrotyrosine, and COX-2, suggesting that both the iNOS and the COX-2 pathways may be directly involved in aseptic loosening.

Zhang et al.¹⁸ provided further evidence of COX-2 involvement in osteolysis. To investigate the role of COX-2 in wear-debris-induced osteolysis, titanium wear-debris particles were implanted in a calvarial model to induce an inflammatory response similar to osteolysis. In this study, celecoxib reduced inflammation and its associated bone resorption at doses that did not inhibit COX-1 activity. Furthermore, COX-2-lacking mice had substantially less bone resorption in response to the particles than did COX-1-lacking mice.

This study also provided direct evidence of an important role of COX-2 that is distinct from that of COX-1 and suggested that selective COX-2 inhibition could have a therapeutic role for patients with inflammation-induced bone diseases.

More recently, Bukata et al.⁶⁵ investigated the importance of the COX-2 enzyme in vitro. Periprosthetic membranes from major osteolytic areas were obtained during revision operations. Histochemical analysis showed an abundance of COX-2 and minimal amounts of COX-1 along the membrane borders. Bukata et al. also studied the relationship of prostaglandin-E2 production with COX-1 and COX-2 in a transgenic mouse model. The levels of prostaglandin E2 produced in the COX-1-lacking fibroblasts were substantially increased in response to titanium particles. In contrast, prostaglandin-E2 levels in the COX-2-lacking cultures did not significantly increase above background levels under any conditions tested, indicating that a functional COX-2 gene is required for prostaglandin-E2 production by fibroblasts and that particle-induced prostaglandin-E2 production is mediated by this enzyme. Consistent with the prostaglandin-E2 data, there were no increases in IL-6 production in any of the COX-2-lacking cultures, indicating a dependency of IL-6 production on prostaglandin-E2 levels. When exogenous prostaglandin E2 was added to the COX-2-lacking cultures, there was a remarkable increase in the IL-6 levels compared with the levels in the cultures lacking exogenous prostaglandin E2. This finding suggested that IL-6 production is dependent on prostaglandin-E2 levels at least in one pathway.

In conclusion, there is evidence that COX-2 inhibition causes suppression of bone ingrowth if the drug is administered in the early postoperative period. In cases of aseptic loosening, particle-induced prostaglandin-E2 production is mediated by the COX-2 enzyme. Therefore, COX-2 inhibition plays a role in decreasing the prevalence of aseptic loosening of cementless implants.

Soft-Tissue Healing

There is controversy regarding the effect of nonsteroidal anti-inflammatory drugs on soft-tissue healing⁶⁶. These drugs are reported to not only reduce pain and swelling but also lead to earlier motion, which promotes early ligament healing. The use of COX-2 inhibitors may be beneficial when thickening of a healing tendon can cause problems—e.g., in the hand⁶⁷. In cases of direct tissue trauma, tissue damage results from traumatically induced inflammatory reactions, with tissue hypoxia being the most likely trigger. In these cases, there is a transient upregulation of COX-2 expression. COX-2 has also been reported to be upregulated in surgery-associated paraspinal muscle injury, but levels were not found to reach their peak before three days⁶⁸.

The effects of COX-2 inhibitors on soft-tissue healing have been investigated in several basic-science studies, with contradictory results. Several reports have illustrated the detrimental effects of COX-2 inhibitors on ligament healing⁶⁹, whereas others have indicated a possible beneficial effect on ligament healing⁷⁰ and still others have revealed no relationship between ligament healing and use of nonsteroidal anti-inflammatory drugs^{71,72}.

Elder et al.⁶⁹ reported that the healed ligaments of rats that had received a COX-2 inhibitor had a 32% lower load to failure, measured fourteen days after injury, than did a control group.

Bogatov et al.⁷¹ found that treatment with a pure COX-1 inhibitor, SC-560, had no significant effect on the tensile strength of the site of healing of acute injuries of rat medial collateral ligaments. However, there was an increase in the strength of the uninjured collateral ligaments. This suggests that COX-1 inhibitors do not improve the strength of ligament-healing sites but do improve the strength of the contralateral uninjured ligament. Thus, a pure COX-1 inhibitor probably does not have a positive influence on ligament healing but might provide benefits in terms of prevention of ligament injury.

The lack of consensus in this area led Hanson et al.⁷⁰ to undertake a more

comprehensive study to resolve the issue. They compared the effects of piroxicam, naproxen, rofecoxib, butorphanol, and acetaminophen on the healing of rat medial collateral ligaments with the findings in a control group. The only drug that improved ligament healing was piroxicam, which led to a 27% greater load to failure compared with that in the control group. This study showed that opioid analgesics, acetaminophen, and COX-2 inhibitors do not appear to categorically affect ligament healing and that piroxicam's effects cannot be attributed to all nonsteroidal anti-inflammatory drugs.

Ferry et al.⁷² investigated the effects of ibuprofen, acetaminophen, naproxen, piroxicam, celecoxib, and valdecoxib on the healing of rat patellar tendons. The tendons in the acetaminophen and ibuprofen groups were significantly stronger than those in the celecoxib group; however, they were not significantly different from those in the control group. This study suggests that none of the tested nonsteroidal anti-inflammatory drugs, including piroxicam, had a beneficial effect on ligament healing.

The effects of nonsteroidal anti-inflammatory drugs in the setting of soft-tissue trauma and their role in angiogenesis were investigated by Gierer et al.⁷³. Closed soft-tissue trauma to the hindlimb was induced in anesthetized rats, to which either parecoxib or an equal volume of saline solution was administered. Regardless of whether the parecoxib was administered before or after the injury, the microcirculatory flow was completely restored within the injured muscle. In contrast, skeletal muscle in the saline-solution-treated animals revealed persistent perfusion failure, with tissue hypoxia, and enhanced endothelial interaction of both leukocytes and platelets at eighteen hours after the trauma. The authors concluded that treatment with parecoxib before as well as soon after a skeletal muscle soft-tissue injury may be effective in restoring disturbed microcirculation. Moreover, a reduced inflammatory cell response could help to prevent leukocyte or platelet-dependent secondary tissue injury.

Cohen et al.⁷⁴ studied the effect of nonsteroidal anti-inflammatory drugs on tendon healing to bone by administering celecoxib or indomethacin for fourteen days to 180 rats that had undergone acute rotator cuff repair. Both the celecoxib and the indomethacin group had significantly lower failure loads compared with those in the control groups at two, four, and eight weeks. The controls demonstrated progressively increasing collagen organization during the course of the study, whereas the groups treated with the nonsteroidal anti-inflammatory drugs did not. There were no significant differences between these two drugs with regard to their negative effect on healing of the rotator cuff tendon, which implies that the inhibition of the healing process is linked to the COX-2 enzyme.

In summary, despite the common use of nonsteroidal anti-inflammatory drugs in the treatment of closed soft-tissue injuries, our understanding of the effect of these medications on soft-tissue healing is incomplete. COX-2-selective inhibitors exhibiting a low side-effect profile may be of superior therapeutic value in protecting the microcirculation and preserving skeletal muscle from secondary inflammatory tissue damage following closed soft-tissue injury. In addition, COX-2 inhibitors may play a role in the postoperative management following ligament reconstructions and repairs by reducing pain and swelling and allowing an earlier return of motion.

Overview

Many orthopaedists rely on narcotic analgesia for pain control after fractures and operative procedures in their patients because traditional nonsteroidal anti-inflammatory drugs have been shown to delay fracture-healing and possibly impair tendon repair. This effect is thought to be smaller with COX-2-specific inhibitors.

The COX-2 enzyme plays an important role in bone and soft-tissue healing, and the inhibition of this enzyme can interfere with recovery. However, there is a considerable

amount of evidence from several clinical studies that COX-2 inhibition is not detrimental to healing and recovery. We believe that additional controlled clinical studies with appropriate randomization are essential to address concerns in this field and to discern the roles of COX-1 and COX-2 enzymes in the healing of musculoskeletal tissues.

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