Effects of Nonsteroidal Anti-Inflammatory Drugs on Bone Formation and Soft-Tissue Healing

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Abstract

Nonsteroidal anti-inflammatory drugs continue to be prescribed as analgesics for patients with healing fractures even though these drugs diminish bone formation, healing, and remodeling. Inhibition of bone formation can be clinically useful in preventing heterotopic ossification in selected clinical situations. In this regard, naproxen may be more efficacious than the traditional indomethacin, and short-term administration is as effective as long-term. When fracture healing or spine fusion is desired, nonsteroidal anti-inflammatory drugs should be avoided. Some nonsteroidal anti-inflammatory drugs have a positive effect on soft-tissue healing; they stimulate collagen synthesis and can increase strength in the early phases of repair during skin and ligament healing. Cyclooxygenase-2 inhibitors have an adverse effect on bone healing and may have an adverse effect on ligament healing. Therefore, further investigation is necessary to confirm that traditional nonsteroidal anti-inflammatory drugs may be preferable for the healing of collagenous tissues.

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Because of their analgesic and anti-inflammatory effects, nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications. These drugs function by blocking cyclooxygenase (COX), an enzyme involved in making prostaglandins from arachidonic acid. COX-1 is considered to be important in the production of prostaglandins during normal physiologic processes in various tissues. Inhibition of COX-1 function in the gastrointestinal tract is thought to be responsible for many of the side effects of traditional NSAIDs, including stomach and intestinal ulcers and gastrointestinal bleeding (Fig. 1). In contrast, COX-2 is thought to be an "inducible" form of COX, responsible for the inflammatory response in various tissues. Therefore the COX-2 enzyme has been the target of the coxibs, which may reduce inflammation without producing as many gastrointestinal side effects as COX-1.

Several prostaglandins, notably prostaglandin E_2, are important in the formation of new bone. Thus, NSAIDs have significant effects on new bone formation, including heterotopic bone formation after injury, new bone formation in the healing of fractures, and even the formation of bone around porous ingrowth prostheses. In contrast to these effects, many NSAIDs appear to stimulate collagen synthesis, which may have a beneficial effect on soft-tissue healing, resulting in increased strength of cartilage, skin, and tendon. Although the available data on COX-2 inhibitors are not as extensive or compelling as the information on traditional NSAIDs, COX-2 inhibitors also seem to have adverse effects on new bone formation. Celecoxib also has a negative effect on soft-tissue healing. It is extremely important that physicians take these bone and soft-tissue healing effects into account when prescribing COX-2 inhibitors.

Heterotopic Ossification

Heterotopic ossification (HO) can be a difficult problem in patients with cerebral or spinal cord injury, burn, after blunt muscle trauma (especially to the quadriceps), or following certain types of surgery, particularly around the hip (Fig. 2). Prevention of this complication in at-risk patients generally has been through the use of radiation therapy or the administration of NSAIDs. Despite a few conflicting results,[1] studies largely have shown that NSAIDs are effective in

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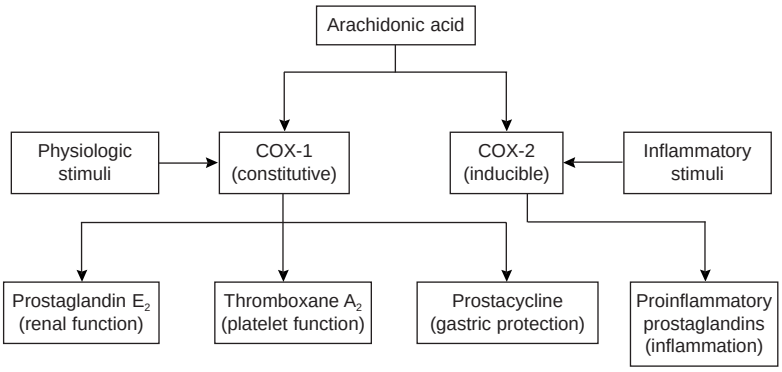

Figure 1 Arachidonic acid metabolism to prostaglandins through the COX-1 and COX-2 enzymes. Physiologic stimuli help regulate COX-1 to produce prostaglandins important in normal function, whereas inflammatory stimuli help regulate COX-2 to produce proinflammatory prostaglandins.

diminishing or preventing formation of HO. Although indomethacin traditionally has been used for this purpose, Vielpeau et al[2] reported that naproxen, which is generally better tolerated, may be more effective than indomethacin in preventing such bone formation around hip replacements. In a randomized prospective double-blind study, 63 patients completed treatment in one of three groups: naproxen 750 mg / day, indomethacin 75 mg / day, or placebo. Treatment was started on postoperative day 1 and continued for 6 weeks, with drug or placebo given three times a day. At 6 months, naproxen was significantly more effective than placebo ($P < 0.001$) and indomethacin ($P = 0.02$) in preventing HO (as defined by the Brooker classification[3]).

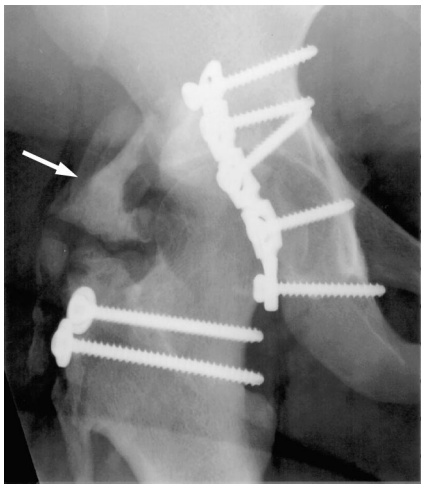

Figure 2 Anteroposterior radiograph demonstrating heterotopic ossification (arrow) in the gluteus musculature after trochanteric osteotomy for open reduction and internal fixation of an acetabular fracture.

Gebuhr et al[4] reported that 8 days of naproxen administration was effective in preventing HO after total hip arthroplasty (THA). Twenty-seven patients who underwent cemented THA (posterolateral approach without osteotomy) were given naproxen 500 mg twice a day, with the first dose administered as a preoperative suppository and continuing for 7 days postoperatively. This group was compared retrospectively with 23 control subjects who received no HO prophylaxis. At both 3 months and 1 year, the naproxen group showed a significant ($P < 0.05$) reduction in HO (Brooker classification[3]) compared with controls.

Persson et al[5] also showed that 1 week of treatment with NSAIDs is as effective as 3 weeks' in preventing HO. In a double-blind prospective study, the authors on the day of surgery randomized patients undergoing primary THA to one of three groups: ibuprofen 400 mg three times a day for 7 days, followed by placebo for 14 days; ibuprofen 400 mg three times a day for 21 days; or placebo for 21 days. One hundred forty-four patients were followed for at least 1 year, with HO outcomes determined radiographically by the Brooker classification.[3] At 1-year follow-up, a significant ($P = 0.005$) reduction in HO was seen in the patients who had received 1 week of ibuprofen compared with those who had received only placebo. No difference was seen in the rate of HO between the 1-week and 3-week ibuprofen groups ($P = 0.8$).

A retrospective study by van der Heide et al[6] included 19 patients treated with a postoperative indomethacin suppository (100 mg), followed by oral indomethacin 50 mg given three times a day for a total of 3 days. This group was compared with historical control subjects consisting of 170 patients who received no prophylaxis and 99 patients who received indomethacin for 7 days after surgery. HO outcomes were evaluated using the Brooker classification.[3] Grade 3 HO at 6 months in the 3-day indomethacin group (16%) was similar to the rate found in the no-prophylaxis control group (17%). The authors hypothesized in this study that the effectiveness of indomethacin should be at least 80% ($\alpha = 5\%$, $P = 90\%$), and their data did not meet that criteria. Therefore, they concluded that 3 days of treatment with indomethacin was not effective.

Pritchett[7] reported that only 2 days of treatment with ketorolac effectively prevented HO in THA. In a prospective double-blind study, 303 patients were randomized to ketorolac 60 mg given intraoperatively, followed by 30-mg intramuscular injections given every 8 hours for a total of 48 hours, or to saline given by the same route at the same frequency. All patients had undergone a primary THA done through an anterolateral approach by the same surgeon. HO was graded using the Brooker clas-

sification.[3] At 2 years, no patients treated with ketorolac developed severe (grade 3 or 4) HO, whereas 10 patients in the control group (6.6%) developed grade 3 and 1 patient (0.1%) developed grade 4 HO ($P < 0.005$).

Long-term administration may add to the complication rate without extending the benefit. Surgeons considering the use of NSAIDs in preventing HO after THA should consider the possible adverse effect this regimen may have on bone ingrowth if an ingrowth prosthesis is to be used.[8,9]

Bone Ingrowth

The effects of NSAIDs on biologic fixation in porous ingrowth implants have been evaluated in several animal studies. Indomethacin, aspirin, and ibuprofen all diminished the amount of bone ingrowth in a dose-related fashion in porous implants in rabbits followed for up to 8 weeks.[8] Keller et al[9] also found a decrease in bone ingrowth at 8 weeks in rabbits treated with indomethacin. A canine study quantifying ingrowth and strength of fixation as influenced by indomethacin showed a transient decrease in attachment strength in the first few weeks, but this was no longer evident between 6 weeks and 24 weeks.[10]

Wurnig et al[11] retrospectively studied a series of patients implanted with cementless stems and treated with and without indomethacin prophylaxis for HO. Eighty patients who underwent primary cementless THA done through a transgluteal approach were given indomethacin 50 mg twice a day for 6 weeks starting on postoperative day 1. This group was compared with 82 historical controls who received no HO prophylaxis. After 6 years, no difference was seen between the two groups in prosthetic subsidence or radiolucent lines. In fact, in this study, the indomethacin group had significantly higher results on the Harris hip score. The same results were found in animal studies. Thus, although NSAIDs diminish early bone ingrowth, it may well be that, even in their presence, bone ingrowth eventually occurs and therefore that the use of NSAIDs to control HO is a reasonable choice. However, the data on this issue are limited.

Bone Healing

Preclinical animal data regarding the effects of NSAIDs on fracture healing are abundant. Although a few studies have not found statistically significant effects, the majority have demonstrated slower healing, more nonunions, and weaker union in animals treated with NSAIDs.[12-15] This effect seems to be dose-dependent.[12,15] Even aspirin at a sufficiently high dosage has been found to impede healing.[12] Low-dose aspirin treatment did not have a statistically significant effect[12] but, because there was a trend, one cannot be sure that "baby aspirin" (81-mg tablets) thromboprophylaxis does not have a negative effect. Ho et al[15] found that, at 6 weeks, ketorolac decreased the strength of grafted rabbit ulnar defects similar to the effect of methylprednisolone. Høgevold et al[14] reported a significant ($P > 0.05$) decrease in the strength of healing fractures with indomethacin compared with methylprednisolone during short-term treatment.

A retrospective study by Giannoudis et al[16] compared 32 patients who developed nonunion of the femoral diaphysis with 67 comparable control patients whose fractures had united. The authors found no significant effect for factors such as type of implant, mode of locking, reaming, fracture distraction, or smoking—factors to which nonunions often have been attributed. However, they did find a statistically significant ($P = 0.000001$) association between nonunion and the use of NSAIDs after injury. Sixty-three percent of the patients who developed nonunions admitted to taking NSAIDs versus 13% in the control group. Of the patients who took NSAIDs, average duration of treatment was 21 weeks in the nonunion group and 1 week in the control group. The authors also noted that the fractures in the patients who took NSAIDs healed much more slowly than did the injuries in the patients who had not taken NSAIDs (average time to radiographic union, 7.5 months and 5.5 months, respectively).

Spinal Fusion

Using a rat spine fusion model, Dimar et al[17] reported that the posterior fusion rate dropped from 45% in the placebo group (27 / 60 segmental levels) to 10% in the indomethacin-treated group (4 / 42). Martin et al[18] reported that ketorolac had a significantly ($P = 0.037$) adverse influence on rabbit spine fusion rates, which was overcome by adding bone morphogenic protein (rhBMP2) to the graft used for the fusion.

Deguchi et al[19] retrospectively studied 83 consecutive patients with isthmic spondylolisthesis who underwent posterolateral spine fusion with autogenous bone graft. Twenty-eight patients continued to take NSAIDs >3 months after surgery. At an average follow-up of 3.8 years, only 44% of these patients had achieved fusion compared with 98% of control subjects ($P = 0.001$). Glassman et al[20] reported similar results. In a retrospective study, 288 patients underwent instrumented spinal fusion from L4 to the sacrum. Five nonunions (4%) were reported in the 121 patients who did not receive postoperative ketorolac compared with 29 nonunions (17%) in the 167 patients who did receive postoperative ketorolac ($P < 0.001$). Ketorolac was given in a 60-mg loading dose after surgery, followed by 30 mg every 6 to 8 hours

as needed. The odds ratio for developing a nonunion when exposed to ketorolac was 5, compared with 2.8 for smokers. The mean number of doses of ketorolac in the postoperative period was only 10, indicating that the threshold for this effect is quite low.[20]

Soft-Tissue Healing

The effects of NSAIDs on soft-tissue healing are not so clear-cut as those on bone healing. Tissue culture studies show decreased collagen synthesis with naproxen and indomethacin but increased synthesis with aceclofenac.[21] In 1977, Vogel[22] reported that administration of acetylsalicylic acid, indomethacin, or phenylbutazone in rats increased collagen deposition as well as the strength of physeal cartilage, skin, and tendon and of granulomas induced by implantation of glass rods. Studies of ligament healing in animal models have shown no effect from using ibuprofen[23] but positive effects with piroxicam.[24] However, piroxicam did not provide any notable benefit in healing experimental muscle strains.[25] Despite its ability to stimulate collagen synthesis, piroxicam has been found to diminish intraperitoneal adhesion reformation in rats.[26] If synovial adhesions are similarly inhibited, piroxicam may be beneficial in the prevention of arthrofibrosis or tenosynovial adhesions.

Numerous clinical studies have evaluated the effects of NSAIDs in acute and chronic soft-tissue injuries. The outcomes evaluated in many of these studies include swelling, patient perception of pain, and opinions of therapists; such outcomes are more likely to be influenced by the analgesic properties of NSAIDs than their effect on soft-tissue healing. More than 50 studies report the use of NSAIDs in sports-related injuries. Eight prospective randomized placebo-controlled double-blind studies have concluded that NSAIDs are beneficial after various sprains and strains, but three studies found no effect.[27] Two studies[28,29] specifically evaluated the treatment of ankle sprains with ibuprofen. McLatchie et al[28] reported that patients treated with ibuprofen (2,400 mg / day) after grade 1 or 2 ankle inversion injuries had less tenderness 7 days after injury and were able to achieve a higher level of training than those who received placebo. Fredberg et al[29] found that the same dose of ibuprofen (2,400 mg / day) had no effect on ankle swelling or analgesia in patients immobilized after acute ankle sprains.

COX-2 Inhibitors

Because it is an inducible form of cyclooxygenase, COX-2 presumably would be induced after injury and therefore would be important in the body's response to injury. Forwood[30] documented in rats that deposition of new bone in response to mechanical loading, which can be partially inhibited by indomethacin, was completely blocked by a COX-2 inhibitor. More recently, rofecoxib has been shown to significantly ($P < 0.05$) inhibit fracture healing in rats.[31] Celecoxib was evaluated in the same study[31] and found to have minimal effect on bone healing; however, the celecoxib dosage regimen was low.

With regard to soft tissue, a study of injured ligaments in the rat has shown a 32% lower load to failure in a group treated with celecoxib.[32] Interestingly, aggressive fibromatosis (desmoid tumor) has been shown to express COX-2. Tissue cultured from aggressive fibromatosis specimens can be inhibited by indomethacin and a COX-2 blocker.[33]

Summary

Generally, NSAIDs, including COX-2 inhibitors, diminish bone formation and therefore should be used as needed to decrease bone formation when desired but avoided when bone formation is the preferred outcome. NSAIDs appear to be beneficial for soft-tissue healing, but results are inconclusive. A COX-2 inhibitor has shown a negative effect on ligament healing in the single study published to date. More studies are needed to determine the effect COX-2 inhibitors might have on tendon or ligament healing in sports-related injuries.

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