CHAPTER 13

Injectable Nonsteroidal Anti-Inflammatory Drugs for Postoperative Pain Relief

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INTRODUCTION

Prescription narcotics and their role in the immediate postoperative period are of significant value. However, they have also taken on a life of their own. In 2015 there were 33,000 deaths due to opioid overdose in the US, with just over half of those coming from narcotic prescriptions (1). The Centers for Disease Control and Prevention (CDC) is calling it an epidemic and has been searching for viable alternatives to narcotic prescriptions for those dealing with chronic pain. In the acute phase, they defer to the Washington State Agency Medical Directors' Group (WSAMDG) for guidelines and alternatives. Currently, the recommendations from the WSAMDG are for balanced analgesia. Analogous to balanced anesthesia, balanced analgesia provides a multi-drug approach without the need to overly rely on any one medication. This approach can be achieved with the addition of nonsteroidal anti-inflammatory drugs (NSAIDs).

Any alternative or adjunct to opioids should possess similar analgesic efficacy, have fewer adverse effects, and have an alternative mechanism of action and compatibility with multiple routes of administration (2). NSAIDs are one such medication. They do not come without any side effects, but in many cases the benefits outweigh the risks. NSAIDs can decrease the amount of narcotic analgesics being used and therefore decrease the potential abuse of these medications as well as decreasing some postoperative complications such as respiratory depression and the delay in returning to activities of daily living. Currently, NSAIDs are recommended by the CDC and WSMDG as a first line analgesic for non-neuropathic pain (3). NSAIDs are not a complete replacement. There have been multiple animal studies that show an increase in nonunions attributed to NSAID use, however, these are mainly related to continued use ranging from 10-21 days. Recommendations provided herein are for the immediate postoperative period in order to accommodate the pain patients experience in the first few postoperatively when foot and ankle studies show that pain is at its highest levels (4).

MECHANISM OF ACTION

Efficacy of NSAIDs is based on their ability to reduce prostaglandin and their subsequent products. This is done by acting on the COX-1 and COX-2 enzymes. After surgical trauma, phospholipids are released, which leads to arachidonic acid production that would then pass through the cyclooxegenase pathway that is inhibited by NSAIDs.

COX-1 and COX-2 enzymes have varying effects but both do play some role in the inflammation and pain that is seen postoperatively. COX-1 in the platelets causes vasoconstriction and inhibition of aggregation. Gastric mucosa is provided gastroprotective effects from the prostaglandins. Effects of this enzyme on the endothelial cells results in vasodilation and decreased platelet aggregation. All of these actions are counteracted by NSAIDs. More relevant for the podiatric surgeon is the COX-2 enzyme, which acts at the joints. In the presence of surgical trauma COX-2 will cause an increase in pain, temperature, and inflammation. It also has more potent effects at the endothelial cells and will produce an increased vasoconstriction and platelet aggregation when compared to COX-14 (5) (Table 1).

INJECTABLE NSAIDS

Currently, there are 3 approved injectable NSAIDs that can be used in the immediate postoperative period. Ketorolac (Toradol), diclofenac (Dyloject), and ibuprofen (Caldolor). All 3 are nonselective COX inhibitors but do not affect the COX-1 and COX-2 enzymes in the same way. Ketorolac has a higher affinity for COX-1 while Caldolor has an equal affinity for the COX-1 and COX-2 enzmes. Lastly, diclofenac has a higher affinity for the COX-2 enzyme.

Table 1. COX-1 and COX-2

COX-1 Inhibition	COX-2 Inhibition	COX-1+2 Inhibition	COX-1>2 Inhibition	COX-2>1 Inhibition
Decreased platelet aggregation	Increased cardiac risk	Analgesia and anti-inflammatory	Decreased gastric protection	Decreased pain, inflammation and healing

All 3 medications can be given as an injection either intra-operatively before or during wound closure or as an injection immediately postoperatively. Dosing guides are discussed below.

Ketorolac in an intravenous (IV) preparation has been available in the US for significantly longer than diclofenac and Caldolor and thus is the medication on which most research is based. It does carry a black box warning, which includes increased cardiovascular risk of bleeding as well as volume depletion in patients with poor kidney function (6). Dosing for ketorolac is as follows: IM 60 x1 dose or 30 mg every 6 hours. The IV dosage is 30 mg every 6 hours. If the patient weighs <50 Kg or is older than 65 years, a half dose is given (IV dosage would be 15 mg every 6 hours), not to exceed 120 mg/day or be given for longer than 5 days (8).

The efficacy of pain relief from Toradol was seen in a landmark study in 1986 by Yee et al (7), which reported that in 241 patients IV ketorolac was as effective an analgesic as morphine. Since the initial study, there have been additional studies that both concur with and oppose this view. However, as the CDC and WSAMDG recommend, combined NSAID use is not an attempt to completely eliminate all opioid use. Rather, it is to decrease the dependency that physicians have in prescribing them for pain, which can be accomplished through balanced analgesia. Some combination of opioids and NSAIDs would provide patients with the most optimal result.

In addition to the decreased opioid requirements, postoperative bleeding has been proven to be a non-issue in the immediate postoperative period with the use of ketorolac. Patients given a dose of ketorolac at wound closure, 6 hours postoperatively, and then at 12 hours after spinal surgery were found to have a decrease in drain output after spinal surgery (9). Diclofenac was approved in 2014 by the Food and Drug Administration, and does not currently have the same amount of research and comparison studies as have been performed on ketorolac. However, there is promising evidence of the clinical significance of diclofenac. Post orthopedic surgery, diclofenac has been shown to decrease the amount of opioids needed by 40% as well as provide a sustained decrease in pain lasting more than 6 hours. Diclofenac is indicated for management of moderate to severe pain with an IV bolus of 37.5 mg infused over 15 minutes every 6 hours as needed for pain (not to exceed 150 mg per day). There is also a black box warning for diclofenac that is similar to all NSAIDs for increased cardiovascular risk and gastrointestinal bleeding.

IV ibuprofen (Caldolor) was approved for use in 2009. It is indicated for mild to moderate pain control as well as fever reduction. Dosage for mild to moderate pain is 400-800 mg infused over 30 minutes (not to exceed 4,200 mg per day). If using for fever control the dose would be simply 400 mg every 4-6 hours.

NON-UNION AND THE ROLE OF NSAIDS

There have been multiple studies in animals (11-13) showing an increase in the non-union rates when NSAIDs were used. However, a literature review of more than 300 of these articles found that NSAIDs use in these animals was well outside the acute phase of fracture healing and the medications were continued for more than 2 weeks in almost all cases (15). There are some deleterious effects from the use of NSAIDs on bone healing that are found when they are used for multiple weeks. However, modulation of the healing cascade in the acute phase of bone healing by NSAIDs is not supported (15). Specifically, with simple fractures of bone there is not clinical evidence that complications would arise from the use of NSAIDs. Patients that are kept overnight after surgery or given a one-time dose of NSAIDs after surgery would benefit from the increased pain control and long-lasting effects that a postoperative injection of NSAIDs would give (15).

Between 1993 and 2012 there was a general decrease in the amount of postoperative non-unions. This decrease was not seen between 2000 and 2004 when there was a sharp increase in the non-unions reported to hospitals throughout the US. This increase correlated with a sharp increase in the number of NSAID prescriptions given during this time. However, the specific drugs being prescribed were COX-2 selective inhibitors and one of them, Vioxx, was subsequently pulled from the market due to marked increases in thrombotic events. After a sharp decrease in the amount of COX-2 selective NSAIDs being prescribed, there was also a significant decrease in non-unions nationwide. The cause of this decrease could likely be due to the increase in quality of fixation and improved surgical techniques as much as it could be with the decrease in usage of selective inhibitors of the COX enzymes (16). Therefore, in the immediate postoperative period using the doses previously described, the podiatric patient could significantly benefit from the use of NSAIDs immediately postoperatively or at the termination of the procedure intra-operatively with the added benefits of increased patient satisfaction and decreased amounts of opioid consumption.

NSAIDs are a valuable option for immediate postoperative pain control with a decrease in pain seen up to 2 days postoperatively (17). As with any medication, they are not without risk, however, in a suitable patient they are an excellent choice for pain control and are recommended

as a first line analgesic by the CDC. Possible increased risk of bleeding and non-union has little human evidence when used in the acute setting. This fact along with an increase in narcotic dependency has led to the search for viable alternatives. Specifically, in the postoperative setting NSAIDs are an excellent option and should be utilized regularly for patients who are able to take them as part of a balanced analgesic approach to surgery.

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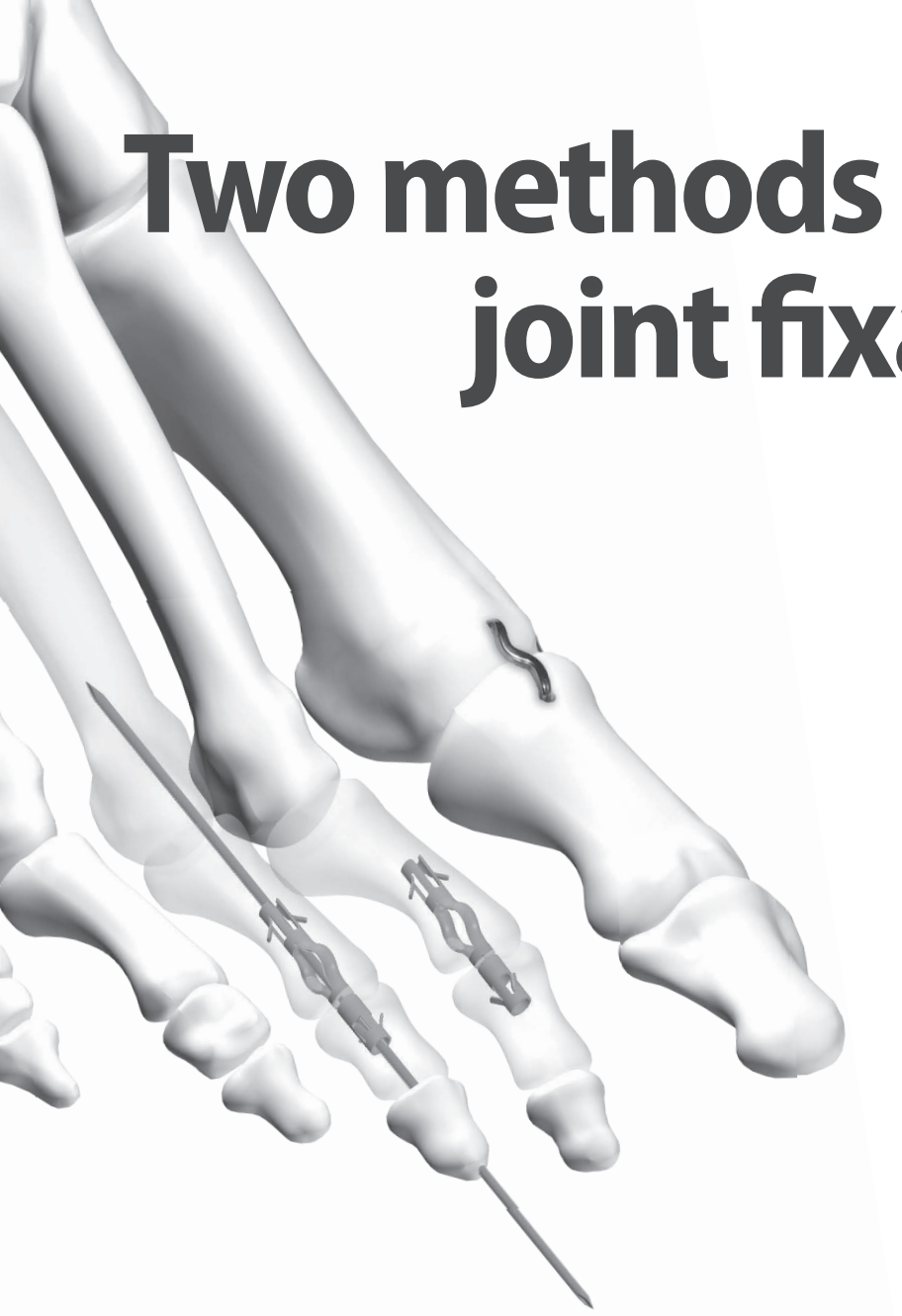

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