The Efficacy of NSAIDs, COX-2 Inhibitors and Gabapentin for Preemptive Analgesia

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Abstract

The objective of this literature review was to evaluate the efficacy of oral nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COX-2) and gabapentin as preemptive oral analgesics. We conducted an electronic literature search by including the Cumulative Index to Nursing and Allied Health, MEDLINE, PubMED and OVID databases. For COX-2 inhibitors and gabapentin, fourteen studies were reviewed with a date range between 2002 and 2012. Due to the lack of current research on NSAIDs, significant studies greater than 10 years old were included for review with ranging dates from 1983 to 2010. All of the reviewed studies were randomized controlled trials. Our goal was to assess postoperative pain scores and opioid consumption in patients who had received preemptive oral analgesia with one of the aforementioned drugs. The reviewed results indicated that postoperative pain scores and opioid consumption was lower in patients who had received preoperative administration of COX-2 inhibitors and gabapentin. However, postoperative administration of NSAIDs resulted in significantly greater pain relief when compared with preoperative administration. Based on these findings we would recommend the use of gabapentin and COX-2 inhibitors as preemptive analgesics, while NSAIDs administration should be implemented postoperatively.

Keywords: preemptive analgesia, postoperative analgesia, preincisional analgesia, NSAIDs, cyclooxygenase-2 inhibitors, gabapentin
The Efficacy of NSAIDs, COX-2 Inhibitors, and Gabapentin for Preemptive Analgesia

The concept of preemptive analgesia was pioneered by Crile in 1913, who based his assumptions on clinical observations that suggested analgesic interventions were more effective if administered prior to a surgical procedure (Dahl & Moiniche, 2004). Subsequent experimental evidence suggested that it may be possible to decrease or prevent the neurophysiologic and biochemical effects of noxious input to the central nervous system (CNS) rather than initiating treatment after occurrence of these events (Dahl & Moiniche, 2004). Preemptive analgesia is an antinociceptive treatment applied before tissue injury to prevent peripheral and central sensitization (Kelly, Ahmad, & Brull, 2001). By decreasing sensitization, preemptive analgesia is thought to decrease the incidence of postoperative hyperalgesia and allodynia (Ong, Lirk, Seymour, & Jenkins, 2005). This phenomenon is thought to reduce the magnitude and duration of postoperative pain by administering an analgesic treatment prior to a noxious stimulus as compared with post-stimuli analgesic administration.

Acute nociceptive signals associated with tissue damage initiate alterations in the peripheral and central pain pathways. Primary afferent neurons detect noxious stimuli from the periphery and through transduction conduct pain signals to the dorsal horn of the CNS. An inflammatory response occurs with tissue damage leading to the release of chemical mediators such as substance P, histamine, bradykinin, and prostaglandin. This leads to peripheral sensitization caused by increased conduction of nociceptive stimuli to the CNS. Central sensitization occurs as a result of amplification of nociceptive neurons in the dorsal horn of the CNS (Dahl & Moiniche, 2004).

According to the International Association for the Study of Pain (2011), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage,
or described in terms of such damage” (p. 1). Acute postoperative pain is typically caused by mechanical, chemical, and thermal nociceptive stimuli. In addition, severe acute pain is a risk factor for the development of chronic pain. Effective postoperative pain management increases patient satisfaction, improves patient outcomes, and reduces cost of care (Heck & Mitchell, 2005). Recent studies have shown that acute postoperative pain continues to be undermanaged even as surgery and anesthesia have become safer (Peng, Wijeysundera, & Li, 2007). Therefore, there has been increasing emphasis towards the improvement of secondary outcomes including postoperative pain control. A number of clinical trials have suggested that preemptive analgesia leads to a decrease in postoperative pain, less total analgesic consumption, and improved patient comfort (Ong et al., 2005). This would be clinically beneficial to health care providers that are involved in the management of acute postoperative pain, if the evidence supports the use of preemptive analgesia.

Clinical nurses, as part of the collaborative team responsible for pain assessment and management, would play a significant role in preemptive analgesic interventions. Preoperative nurses can ensure that preemptive analgesics are administered in a timely manner. Certified registered nurse anesthetists (CRNA) could initiate preoperative analgesic orders as well as ensure administration occurs prior to surgical incision. Postoperative care nurses would be responsible for evaluating the outcomes of preemptive analgesia, and if effective this may increase nursing staff productivity.

The efficacy of preemptive analgesia is controversial, and the optimal technique has not been clearly established (Moiniche, Kehlet, & Dahl, 2002). Although animal studies have been very convincing in showing a positive benefit with preemptive analgesia; human clinical trials remain inconsistent regarding its efficacy (Ong et al., 2005). This inconsistency may be due to
factors such as a lack of uniformity in defining preemptive analgesia; the variation in methodology of clinical trials; timing of the pre-stimulus versus the post-stimulus dose; and the lack of an objective standard for pain measurement (Heck & Mitchell, 2005).

Clinical trials on preemptive analgesia have evaluated different analgesics using a variety of administration routes. Multiple randomized controlled trials and systematic reviews have indicated minimal efficacy with preemptive analgesic opioids and N-methyl-D-aspartate antagonists (Kissin, 2000). A majority of clinical studies and reviews on preemptive analgesia focus individually or in combination with intravenous, intramuscular, and neuraxial modes of administration. The literature indicates a potential benefit with preemptive selective and nonselective NSAIDs, and gabapentin. This literature review will evaluate the efficacy of preemptive oral NSAIDs, COX-2 inhibitors, and gabapentin. Although the bioavailability of these drugs varies, we chose to review select oral medications as they share a similar pharmacokinetic profile.

Electronic literature searches were conducted using the Cumulative Index to Nursing and Allied Health, MEDLINE, PubMed, and OVID databases with restrictions to publications in English. A broad free text search was used with the following terms: preemptive analgesia, postoperative analgesia, and preincisional analgesia. The retrieved results were then limited to oral NSAIDs, COX-2 inhibitors, and gabapentin. Articles that were included in this literature review consist of clinical trials limited to adult patients that compared the difference in postoperative pain scores and opioid consumption between control and treatment groups when preemptive analgesic measures were initiated.
NSAIDs

NSAIDs are one of the most popular drugs used to relieve pain, fever and inflammation. In the United States more than 70 million prescriptions of NSAIDs are written annually, while over the counter purchases reach a consumption of 30 billion doses (Wiegand & Lawrence, 2010). NSAIDs are of particular interest to the practice of anesthesia because unlike opioids, they do not cause respiratory depression, nausea, sedation and urinary retention.

The concept of using NSAIDs as preemptive analgesics lies in their peripheral and central mechanism of action. NSAIDs inhibit the enzymes called cyclooxygenases leading to a decreased production of prostaglandins. Prostaglandins are primary chemicals produced by the body that carry out a variety of important chemical and biological body functions. Up to date there are a total of five primary prostanoids and 9 prostaglandin receptors present in the human body, all of which have specific functions and responses (Sundy, 2005). By inhibiting the action of cyclooxygenase 1 and 2 (COX-1 & COX-2) and preventing the production of prostaglandins, NSAIDs decrease inflammation, vasodilatation, capillary permeability, pain and fever (Sundy, 2005). A better understanding of the mechanism of action of NSAIDs sparked interest to evaluate if NSAIDs could be used for preemptive analgesia and led to several studies and literature reviews.

Our literature search conducted on NSAIDs recognized only 5 suitable studies based on the criteria identified. Out of the 5 studies, 4 analyzed the use of NSAIDS as preemptive analgesic on oral surgeries and one analyzed NSAIDs’ preemptive effectiveness in patients undergoing a mastectomy. The drugs utilized for the studies were ibuprofen and ketoprofen. Of the five identified studies only one study supported the use of ibuprofen preoperatively for postoperative pain relief when compared with the standard therapy. This study was conducted by
Dionne, Campbell, Cooper, Hall and Buckingham (1983) and included 107 dental patients undergoing removal of impacted third molars. A comparison was conducted between preoperative administration of ibuprofen, placebo, acetaminophen and acetaminophen plus codeine and the findings indicated that preoperative ibuprofen administration was superior in providing postoperative pain relief (Dionne et al, 1983).

In 1997, a study evaluated the effectiveness of ibuprofen-arginine as a preemptive analgesic to reduce post-mastectomy pain syndrome (Lakdja, Dixmerias, Bussieres, Funrouge, & Lobera, 1997). The study was a double blinded randomized study utilizing 30 patients who were divided into two equal groups. The first group received ibuprofen 90 minutes preoperatively, 2 hours postoperatively and every 8 hours afterwards for 32 hours. The second group received placebo during the same times. It was found that ibuprofen was not effective in decreasing postoperative pain during the first month, nor the occurrence of post-mastectomy pain syndrome.

The effectiveness of ketoprofen as a preemptive analgesic was studied by Kaczmarzyk, Wichlinski, Stypulkowska, Zaleska and Woron (2010) in patients undergoing third molar surgery. A total of 96 patients were included in the study who were then randomly divided into pretreatment, post-treatment and no treatment groups. Ketoprofen was given 60 minutes preoperatively to the pretreatment group and 60 minutes postoperatively to the post-treatment group, while a placebo was administered to the no treatment group. The results concluded that preoperative and postoperative administration of ketoprofen resulted in delayed pain development when compared with the placebo group; however, postoperative ketoprofen administration was more effective in providing pain control than preoperative administration.

In 1992, Vogel, Desjardins and Major compared the preoperative and postoperative efficacy of ibuprofen administration during periodontal surgery. The design of the study was
randomized, double blinded and included 60 patients. The results concluded that postoperative administration was superior at providing greater pain relief as well as decreased pain intensity.

Another study also looked at the best administration time for ibuprofen in providing postoperative pain relief in patient undergoing surgical removal of mandibular third molar. Eighty patients participated in this randomized, controlled study conducted by Jung et al. (2005). The participants were divided into pretreatment group, post-treatment group and no treatment group. The post-treatment group demonstrated the greatest pain relief when compared to the other two groups.

In consideration of the derived findings from the reviewed studies, the use of NSAIDs would not be a beneficial method for preemptive analgesia; however, when administered postoperative NSAIDs provided significant pain relief and decreased intensity. Given that currently NSAIDs are not generally used as a method for preemptive analgesia no change in practice is recommended.

**Cyclooxygenase-2 Inhibitors**

Activation of COX-2 by surgical trauma produces hyperalgesia and increases the sensitivity of peripheral nociceptors (Reuben, Bhopatkar, Maciolek, Wanda, & Sklar, 2002). NSAIDs inhibits both the COX-1 and COX-2 enzyme, which along with the desired effects of providing pain relief and inflammation reduction, may lead to the inhibition of normal platelet function and gastrointestinal toxicity (Boonriong, Glabglay, Nimmaanrat, & Tangtrakulwanich, 2010). The selectivity of COX-2 inhibitors accounts for the lack of gastrointestinal and platelet function side effects, thus making it an excellent choice for post operative pain management. COX-2 inhibitors commonly used include celecoxib, rofexocib, valdecoxib, etoricoxib, and lumiracoxib (Kaye, Baluch, Kaye, Ralf, & Lubarsky, 2008). Recent research shows that the use
of COX-2 inhibitors as a preemptive analgesic improves post operative pain and decreases the overall use of opioids following surgery (Celik, Gormus, Gormus, Okesli, & Solak, 2005). In this review, clinical studies supported the efficacy of using COX-2 inhibitors as a preemptive analgesic for multiple procedures including thoracotomies, arthroscopic knee surgeries, and laparoscopic cholecystectomies.

Sandhu, Paiboonworachat, and Ko-iam (2011) research was a double-blinded randomized controlled trial involving laparoscopic cholecystectomy patients. A sample size of 120 patients were enrolled with half receiving 120 mg etoricoxib plus diazepam and the other half receiving placebo plus diazepam prior to surgery. The postoperative VAS scores in the etoricoxib group were significantly decreased overall with an additional reduction in oral analgesic usage postoperatively (Sandhu, Paiboonworachat, & Ko-iam, 2011). In a similar study by Horattas, Evans, Sloan-Stakleff, Lee, and Snoke (2004), 116 patients undergoing laparoscopic cholecystectomies received 50 mg of rofecoxib or a placebo preoperatively. This study also found a significant decrease in narcotic usage as well as an increase in activity level postoperatively (Horattas, Evans, Sloan-Stakleff, Lee, & Snoke, 2004).

While the effects of preemptive COX-2 inhibitors on laparoscopic procedures is evident, the results for orthopedic procedures are not as convincing. Research conducted by Duellman, Gaffign, Milbrant, and Allan (2009) involved patients undergoing total joint arthroplasty. The sample consisted of 69 patients who received a post operative patient controlled analgesia (PCA) pump and 58 patients who received 200 mg of celecoxib preoperatively and then every 12 hours postoperatively during their hospitalization. The PCA group required significantly more morphine (17.7 mg vs. 7.2 mg average dose), had a longer length of hospital stay (3.7 vs. 2.73 days on average), as well as a decrease in participation of postoperative rehabilitation (Duellman,
Gaffigan, Milbrandt, & Allan, 2009) when compared to the group who received the PCA and celecoxib. A study by Boonriong, Tangtrakulwanich, Glabglay, and Nimmaanrat (2010) found mixed results for patients undergoing an anterior cruciate ligament reconstruction. The sample of 102 patients were divided into three groups with the first receiving etoricoxib 120 mg preoperatively, the second receiving 400 mg preoperatively, and the third group receiving a placebo. While the etoricoxib group had significant less pain intensity postoperatively, the celecoxib group showed no significant difference from the placebo group (Boonriong, Tangtrakulwanich, Glabglay, & Nimmaanrat 2010).

The last procedure that studied the efficacy of preemptive COX-2 inhibitors use was for patients undergoing a thoracotomy. Celik, Gormus, Gormus, Okesli, and Solak (2005) conducted a double-blind, placebo-controlled, prospective study with 60 patients giving half 50 mg of rofecoxib preoperatively while the other half received a placebo. The researchers found that patients who received rofecoxib preoperatively had a significant decrease in opioid requirements compared to the placebo group (Celik, Gormus, Gormus, Okesli, & Solak, 2005). Clearly evidence shows that regardless of the surgical procedure, COX-2 inhibitors given preoperatively have positive effects on postoperative pain scores, opioid use, and length of hospital stay.

**Gabapentin**

Historically, the mainstay for postoperative pain management has been opioid, although side effects including nausea, vomiting, pruritis and respiratory depression may limit their use. Additionally, NSAIDs are commonly used as adjuncts to reduce pain postoperatively in minor surgery, but their use may be limited in patients with bleeding diathesis, renal or gastrointestinal problems (Chiu, Leung, Lau, & Burd, 2012). Therefore, recent studies have explored alternative
approaches to pain control. Gabapentin, a structural analog of gamma aminobutyric acid, is an antiepileptic drug for partial seizures whose role in pain management has been limited to neuropathic pain, diabetic neuropathy, post-herpetic neuralgia, and reflex sympathetic dystrophy (Parikh, Dash, & Upasani, 2010). Recently, an increasing number of studies have suggested that gabapentin, when used preemptively, has a beneficial effect on both pain scores and postoperative opioid consumption (Srivasta et al., 2010).

In clinical studies gabapentin has exhibited a reduction in hypersensitivity induced by inflammation and injury. In addition, it has demonstrated an inhibitory effect on not only the development but also on preexisting secondary allodynia and hyperalgesia resulting from central sensitization, while having no effect on pain transmission in normal skin (Pandey et al., 2004). These effects, which are comparable to those observed with Remifentanil, are of considerable importance because though pathological pain is reduced, other protective nociceptive mechanisms remain intact (Pandey et al., 2004). Additionally, it has been shown that the combination of gabapentin with other antinociceptive drugs produce a synergistic action (Srivastava et al., 2010).

While the exact mechanism of action of gabapentin is not clearly understood, it appears there may be multiple mechanisms. It has been proven that gabapentin does not act via opioid mechanisms, instead it binds to alpha-2-delta subunits of voltage-gated calcium channels, located presynaptically in the doral root ganglia (Menda et al., 2010). Subsequently, this reduces the release of excitatory neurotransmitters involved in pain pathways from sensory neurons including glutamate, noradrenaline, and substance P (Chiu et al., 2012; Menda et al., 2010). Additional proposed mechanisms of pain reduction from gabapentin include an increase in the concentration and rate of synthesis of GABA in the brain, modulation of glutamate receptors,
inhibition of voltage activated sodium channels, and an increase serotonin concentrations (Menda et al., 2010; Montazeri, Kashefi, & Honarmand, 2007). Therefore, it is thought that preoperative dosing of gabapentin exerts its analgesic effects by preemptively decreasing the spinal cord excitation caused by surgical trauma (Moore et al., 2011).

In order to determine if preoperative gabapentin was effective in reducing postoperative pain and whether it showed evidence of opioid sparing effects eight recent studies were evaluated between 2004 and 2012. Each study reviewed a different type of surgery, as well as multiple gabapentin dosages and timing. The variety of surgeries comprised in this review include thyroidectomy, tongue reconstruction with anterolateral thigh flap, cardiac, lower extremity orthopedic, cesarean section, lumbar discectomy, abdominal and minilap open cholecystectomy. Of the eight studies, seven were randomized, placebo controlled studies (Al-Mujadi et al., 2006; Menda et al., 2010; Montazeri, Kashefi, & Honarmand, 2007; Moore et al., 2011; Pandey et al., 2004; Parikh, Dash, & Upasani, 2010; Srivastava et al., 2010), where as one was considered a non randomized retrospective cohort study (Chiu et al., 2012).

In all eight studies, patients in the gabapentin group received it as a single preoperative dose ranging between 300 and 1200 mg. To facilitate analysis of the eight studies three subgroups were created based on dosages: (1) group that received 300 mg preoperatively; (2) group that received 600 mg preoperatively; and (3) group that received 1200 mg preoperatively. In each study, pain intensity using VAS scores, analgesic consumption and rescue analgesia requirement were analyzed. In addition to postoperative pain scores and opioid consumption, all studies recorded and analyzed the occurrence of side effects possibly related to gabapentin administration. The most commonly reported adverse effects were nausea, vomiting, sedation,
dizziness, respiratory depression, and pruritis. Due to the nature of the literature review side effects were not discussed.

**Gabapentin 300 mg Preoperatively**

Two studies using a dose of 300 mg of Gabapentin preoperatively were included in our analysis. In both studies patients in the treatment group had significantly lower VAS scores at all time intervals measured in the first 24 hours. Although the two studies utilized different opioids for postoperative pain control, Fentanyl (Montazeri, Kashefi, & Honarmand, 2007) versus Morphine (Pandey et al., 2004), both treatment groups required less drug consumption in the first 24 hours postoperatively. The study conducted by Montazeri, Kashefi and Honarmand reported the total 24 hour morphine consumption to be on average 15.43 mg in the gabapentin group versus 17.94 mg in the control group. The research also showed a significant difference between the two groups in the first time of patient demand for morphine administration after surgery (31.57 minutes in gabapentin group versus 26.71 minutes in the placebo group) (Montazeri, Kashefi, & Honarmand, 2007). Similarly, Pandey et al. (2004) reported in their study that total Fentanyl consumption after surgery in the first 24 hours on average was significantly less in the gabapentin group (233.5 mg) versus the control group (359.6 mg). Furthermore, Montazeri, Kashefi, and Honarmand concluded that there was no difference in recovery duration between the two groups.

**Gabapentin 600 mg Preoperatively**

Four studies using a dose of 600 mg of gabapentin preoperatively were included in this analysis. In all four studies the pain scores in the treatment groups were significantly lower than the control groups for the first 24 hours postoperatively at both rest and with movement or
coughing (Menda et al., 2010; Moore et al., 2011; Parikh, Dash, & Upasani, 2010; Srivastava et al., 2010). Srivastava et al. (2010) also assessed pain scores beyond 24 hours up to 48 hours and showed that pain scores at 48 hours were comparable in both treatment and control groups. For rescue analgesia two studies used Morphine (Menda et al., 2010; Moore et al., 2011), one used Diclofenac (Parikh, Dash, & Upasani, 2010) and Tramadol was used in the other (Srivastava et al., 2010). In three of the studies the total drug consumption for postoperative pain and need for rescue analgesia was lower in the gabapentin groups (Menda et al., 2010; Parikh, Dash, & Upasani, 2010; Srivastava et al., 2010). In fact Menda et al. (2010) showed that the total morphine consumption in the first 24 hours postoperatively was 57% lower in the gabapentin group versus the control group. The fourth study by Moore et al. (2011) did not show a difference in postoperative opioid consumption but did find that patient pain and satisfaction scores to be higher in the gabapentin group at both six and 12 hours (Moore et al., 2011).

**Gabapentin 1200 mg Preoperatively**

Two studies using a dose of 1200 mg of gabapentin preoperatively were included in our analysis. Both studies showed postoperative pain assessment scores to be lower in the gabapentin group versus the control group in the first 24 hours (Al-Mujadi et al., 2006; Chiu et al., 2012). For postoperative analgesia both studies utilized Morphine and indicated that the consumption of Morphine in the gabapentin groups were both significantly lower when compared to the control groups (Al-Mujadi et al., 2006; Chiu et al., 2012).

We consider this review to be evidence of the efficacy of preemptive gabapentin for control of acute postoperative pain. The potential benefit would be better postoperative pain control in a multitude of surgeries.
Discussion and Implications

In our review of the literature we consider preemptive analgesia beneficial with the administration of oral COX-2 inhibitors and gabapentin and recommend their administration for select surgical procedures. However, based on our review of NSAIDs, there appears to be no clinical benefit to their use as a preemptive analgesic. We suggest that nurses incorporate the use of preemptive COX-2 inhibitors and gabapentin into their practice. To facilitate this into practice, nursing administration and clinical nurse educators can establish preoperative protocols to guide clinical nursing staff on its implementation.

Specific barriers must be considered when facilitating such a change in perioperative practice. Patient and or surgeon refusal may be of particular concern due to the potential adverse effects of the of gabapentin or COX-2 inhibitors, although recent studies have shown favorable safety profiles for both drugs. The side effects of Gabapentin include but are not limited to nausea, vomiting, sedation, pruritus, constipation, urinary retention, and dizziness (Srivastava et al., 2010). Additionally, potential prothrombotic effects of COX-2 inhibition and delayed wound healing must be considered (Cicconetti, Bartoli, Ripari, & Ripari, 2004). Contraindications to administration of either of these drugs must also be considered for every patient, as well as the drug to drug interactions that can occur.

Once the practice has been changed, the most reliable way to assess the benefits of the change is to assess the pain scores of the patients 24 hours postoperatively. Since pain scores are already assessed in the inpatient setting, this would be an excellent approach to evaluate the effectiveness of preemptive analgesia without increasing cost. Methods to assess the pain scores would be dependent on the hospitals chosen policy for pain assessment and most commonly include a VAS score or a functional pain assessment. To assess the overall efficacy of the
change, a quarterly pain audit of the patients who receive those agents preoperatively should be completed.

The use of preoperative use of gabapentin and Cox-2 inhibitors has demonstrated to be a valid method for reduction of postoperative pain in a diverse type of surgeries. Further studies should be conducted to improve incorporation of these drugs into practice. Future research can focus on the role of timing administration, long term pain reduction and cost effectiveness. In addition, future studies can look at the effectiveness of co-administration of these drugs as preemptive analgesics for specific surgeries.
References


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