Review Article

Pharmacological Strategies to Control Post-operative Endodontic Pain

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ABSTRACT

Patients typically associate dental care with pain. Pain has both physiological and psychological components. Endodontic post-treatment pain continues to be a significant problem facing the dental profession. For those patients presenting with preoperative pain, it has been reported that up to 80% of this population will continue to report pain after endodontic treatment. Many studies have demonstrated that endodontic treatment is efficacious in reducing post-treatment pain. Despite the fact that the pain relief afforded by endodontic treatment is effective, it is rarely immediate and complete. Therefore, it is evident that post-treatment analgesic intervention is required in a variable percentage of endodontic cases. The purpose of this review article was to assess three main pharmacologic approaches in the control of post-treatment endodontic pain.

***Key words*:** Endodontic treatment, Pain control, Pharmacology.

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Introduction

The most common form of orofacial pain is odontalgia [1]. Patients typically associate dental care with pain. Pain has both physiological and psychological components [2]. For many patients, fear of dental pain and avoidance of dentistry are synonymous [3]. Endodontic post-treatment pain continues to be a significant problem facing the dental profession [4]. For those patients presenting with preoperative pain, it has been reported that up to 80% of this population will continue to report pain after endodontic treatment, with pain levels ranging from mild to severe [5,6]. Many studies have demonstrated that endodontic treatment either in the form of pulpotomy or pulpectomy is efficacious in reducing post-treatment pain. The pain relief afforded by endodontic treatment is effective, but rarely immediate and complete. For example, in patients who present for treatment with a diagnosis of symptomatic necrotic tooth, 47-60% may expect moderate to severe pain in the first 24 hours post-treatment [7,8]. Therefore, it is evident that post-treatment analgesic intervention is required in a variable percentage of endodontic cases. There are three pharmacologic approaches for the management of post-treatment endodontic pain: 1) drugs that block inflammatory mediators that sensitize or activate pulpal nociceptors (e.g., NSAIDs and glucocorticoids); 2) drugs that block the propagation of impulses along the peripheral nerves; and 3) drugs that block central mechanisms of pain perception and hyperalgesia [9].

1. Drugs that block inflammatory mediators that sensitize or activate pulpal nociceptors.

(a) Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have been the traditional treatment for moderate pain. They act primarily through the inhibition of cyclooxygenase (COX) enzymes 1 and 2. COX-1 is expressed throughout the body and has a role in protection of stomach mucosa, kidney function and platelet action. COX-2 is induced by various endogenous compounds such as cytokines,

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mitogens and endotoxins in inflammatory cells and is responsible for the elevated production of prostaglandins during inflammation [10]. Nakanishi et al[11] demonstrated high levels of expression of COX-2 in samples of human dental pulps with a diagnosis of irreversible pulpitis. These two proteins share a 60% homology and catalyze the conversion of arachidonic acid into prostaglandin E_2. PGE_2 is subsequently metabolized by a variety of syntheses into PGH_2, PFI_2, PGD_2, PGF_2 and thromboxane A_2 [12]. Inhibiting COX-2 blocks prostaglandin formation and ultimately prevents inflammation and sensitization of the peripheral nociceptors. However, inhibiting COX-1 attenuates its protective actions [10]. According to Bunczak-Reeh and Hargreaves [13], NSAIDs have a relatively high affinity to plasma proteins and are preferentially distributed to inflamed tissue by local vasodilatation and plasma extravasation. Numerous NSAIDs are available for the management of pain and inflammation.

Huynh [14] reported that analgesics most commonly prescribed in dentistry for acute pain relief include the non-steroidal anti-inflammatory drugs, acetaminophen and various opioid-containing analgesic combinations. Nevertheless, numerous clinical studies have confirmed that moderate to severe pain of dental origin is best managed through the use of ibuprofen or other NSAIDs and its maximum analgesic effect is at least equal to that of standard doses of acetaminophen-opioid combinations. It is important to understand that NSAIDs generally require a higher dose to achieve maximum anti-inflammatory action than that to achieve analgesic action. For example, 200 to 600 mg ibuprofen four times per day or 800 mg three times per day may be needed for an analgesic effect, but 2,400 to 3,400 mg per day may be needed for an anti-inflammatory effect. A meta-analysis of randomized clinical trials that included studies of dental pain found ibuprofen given in doses of 50 to 400 mg to be superior to placebo at all dose levels [2]. In addition, Mehlisch and colleagues [2] determined that monotherapy with ibuprofen managed dental pain better than acetaminophen. In another study, Modaresi and colleagues [15] showed that preoperative administration of ibuprofen, if not contraindicated, is a drug of choice 1 hour before local anesthesia injection as an effective method for achieving a deep anesthesia during treatment of inflamed teeth.

Torabinejad et al [16] evaluated the effectiveness of various medications on post-operative pain and found that ibuprofen (400 mg) was similar to ketoprofen (50 mg) and superior to placebo treatment. In another study, Rogers and associates [17] found that ketorolac was a potent NSAID that significantly reduced pain after endodontic surgery. They also found that ketorolac (60 mg) provided significantly more pain relief than did placebo at 12 and 24 hours after intracanal medication administration, although there was no difference at 6 and 48 hours. Penniston and Hargreaves [18] used a periapical injection of ketorolac to relieve odontalgia and suggested that intraoral injection of ketorolac is a useful adjunct in the management of endodontic pain. O'Hara et al [19] suggested that intramural injection of ketorolac may be useful for the management of endodontic pain, especially in cases where local anesthetic administration is ineffective because of inflammation or injection located at a mandibular site. In another study, Sadeghein et al [20] compared oral administration of ketorolac and acetaminophen codeine in the management of acute apical periodontitis. Their results showed that patients in the ketorolac group had significantly less pain than those who received acetaminophen codeine.

(b) COX-2 NSAIDs

Although NSAIDs are remarkably effective in the management of pain and inflammation, their use is limited by several adverse effects including gastrointestinal bleeding and ulceration, impaired renal function, and inhibition of platelet aggregation. Discovery of a second cyclooxygenase, COX-2, led to the hypothesis that NSAIDs side effects could be decreased, as the inhibition of COX-2 is more directly implicated in ameliorating inflammation while the inhibition of COX-1 is related to adverse effects in the gastrointestinal tract. This stimulated the development of selective COX-2 inhibitors that are better tolerated than non-selective NSAIDs but comparable in analgesic efficacy [21]. On the other hand, Huber [22] reported that on the basis of their perceived better safety profiles compared with analgesic agents, COX-2 inhibitors have been prescribed frequently as first-line agents to treat acute dental pain. However, recently identified adverse cardiovascular reactions associated with these drugs mandate a reappraisal of their

use in dental practice. One of the differences between the structures of two COX isoforms is the substitution of valine by isoleucine in COX-2 at amino acid 523 that lines the surface of the cyclooxygenase active site. This change permits access to a pocket near the central channel of the enzyme. Thus, the volume of the NSAID binding site in COX-2 is larger than that in COX-1 [10]. Celecoxib, the first selective COX-2 inhibitor to be approved by the FDA, accounts for nearly 25% of the anti-inflammatory drug market. Its indications include the management of rheumatoid arthritis, osteoarthritis, acute pain and primary dysmenorrhea in adults [10]. Celecoxib has demonstrated a COX-1 sparing effect in *in vitro* and *ex vivo* studies [23,24]. Khan et al [25] in an *in vivo* study examined the selectivity of celecoxib and demonstrated that administration of celecoxib, 200 mg PO, prior to the extraction of impacted third molars had no effect on thromboxane B_2 (a product of COX-1) and inhibited PGE_2 only at time points, which are consistent with induction of COX-2. However, in another study, Hubbard et al [26] used the oral surgery model and demonstrated that celecoxib was superior to placebo, comparable to 650 mg of aspirin, but generally less effective than a standard dose of naproxen. Matheson and Figgit [27] have reported that rofecoxib is more selective for COX-2 than celecoxib using *in vitro* assays. Rofecoxib seems to have greater analgesic efficacy than celecoxib based on the results of studies in the oral model surgery [10].

Brown and associates [28] compared rofecoxib 50 mg to ibuprofen 400 mg and placebo in a single dose study in the oral surgery model of acute pain using traditional analgesic end points as well as the two-stop watch method for estimating analgesic onset. They concluded that the total pain relief and sum of the pain intensity difference scores over eight hours following a single 50 mg dose of rofecoxib was superior to placebo, but not distinguishable from ibuprofen 400 mg. The median time to the onset of pain relief was indistinguishable for rofecoxib (0.7 hour) and ibuprofen (0.8 hour), but significantly fewer subjects in the rofecoxib group required additional analgesic within 24 hours of the study drug than in the placebo or ibuprofen groups. In another study, Fricke [29] compared rofecoxib inhibitors, doses of 12.5, 25 and 50 mg to naproxen 550 mg and placebo. The 25 and 50 mg doses of rofecoxib were statistically indistinguishable from naproxen for pain relief and pain intensity difference. In addition, Chen et al [30] reported that the analgesic efficacy and tolerability of single-dose COX-2 inhibitors were more effective than opioid-containing analgesics and similar to non-selective NSAIDs in post-operative pain management. Valdecoxib, a second-generation coxib, is a potent and highly selective COX-2 inhibitor [10]. According to Daniels and associates [31], orally administered valdecoxib was as rapidly acting and effective as oxycodone/acetaminophen, and it had a superior duration of analgesic effect in patients after oral surgery. They concluded that valdecoxib could be an efficacious oral safe alternative to other analgesics used to treat pain after oral surgery.

(c) Corticosteroids

Corticosteroids contain 21 carbon atoms in a four-membered hydrocarbon ring system. They comprise glucocorticoids and mineral corticoids. Glucocorticoids have been used in endodontics for their potent anti-inflammatory effects [32]. The anti-inflammatory properties of glucocorticoids were first appreciated and utilized as an adjunct in endodontic therapy almost half a century ago [33]. Glucocorticoids have been used as an intracanal medication either alone or in combination with antibiotics/antihistamines, and systemically as a means to decrease pain and inflammation in endodontic patients [6]. Wolfson [33] and Blitzer [34] stated that hydrocortisone as an intracanal medication resulted in reduction and elimination of inflammatory reactions in periapical tissues. Ehrmann [35] reported that ledermix (triamcinolone dimethyl chlorotetracycline in a water soluble cream) stopped the pain associated with pericementitis. Langeland et al [36] demonstrated that Ledermix as an intracanal medication eliminated post-endodontic treatment pain within minutes to a few hours after placement. Chance et al [37] compared the effect of intracanal meticortelone (prednisolone acetate 2.5%) vs. saline on post-treatment pain in a double-blind study. The results indicated that the corticosteroid was effective significantly in reducing the incidence of pain in vital teeth when compared to saline. However, there was no difference between the two solutions in necrotic teeth. Negm [38] in a randomized double-blind study compared the effect of a corticosteroid-antibiotic combination as an intracanal medication to placebo for the treatment of post-treatment pain in vital teeth. Results showed that

the intracanal application of corticosteroid-antibiotic medication significantly reduced the mean pain score at all time periods when compared to placebo. In a randomized, prospective, double-blind, placebo-controlled study by Marshall and Walton [5] the effect of intramuscular injection of dexamethasone on post-treatment endodontic pain was compared to placebo. After endodontic instrumentation and/or obturation, 1 ml of IM injection of dexamethasone significantly reduced pain incidence and severity at four hours post-treatment. At 24 hours post-treatment, patients who received the corticosteroid showed a trend towards less pain. Krasner and Jackson [39] in a double-blind study evaluated the effect of oral dexamethasone (0.75 mg/tablet) on post-treatment endodontic pain. Their results revealed that patients receiving oral dexamethasone had significantly less pain at eight and 24 hours when compared to those receiving placebo. This result was confirmed by Glassman et al [40] in a double-blind study. Lin et al [41] evaluated the effect of Etodolac versus dexamethasone in the reduction of post-operative symptoms following surgical endodontic treatment. In conclusion, they reported that both Etodolac and dexamethasone had significant effects in reducing post-operative pain in patients who had surgical endodontic procedure compared with placebo ($P \leq 0.001$). Liesinger et al [6] in a double-blind, randomized, prospective, placebo-controlled study evaluated the effect of intraoral and intramuscular injection of four doses of dexamethasone (2 mg/ml, 4 mg/ml, 6 mg/ml and 8 mg/ml) on post-treatment endodontic pain. It was found that patients who received 0.07-0.09 mg/kg of dexamethasone IM had significantly less pain at eight hours and took significantly fewer pain medications when compared to placebo.

Gallatin et al [42] evaluated pain reduction for untreated irreversible pulpitis using an intraosseous injection of methylprednisolone. Over the seven-day observation period, subjects receiving depomedrol (methylprednisolone) reported significantly less pain compared to the placebo. Bramy et al [7] evaluated the intraosseous administration of corticosteroid for pain reduction of symptomatic necrotic teeth. They found that the steroid group had significantly less postoperative pain compared to the placebo group. After a careful review of literature, Marshall [32] concluded that the administration of systemic steroids is efficacious as an adjunct to, but not replacement for, appropriate endodontic treatment in the attenuation of endodontic post-treatment pain. He also stated that systemic steroids are highly effective in those patients who present for treatment with moderate/severe pain and a clinical diagnosis of pulpal necrosis with associated periapical radiolucency.

2. Drugs that block the propagation of impulses along peripheral nerves: long–acting local anesthetics

(a) Bupivacaine

Bupivacaine is available as a 0.5% solution with 1: 200,000 epinephrine. The patient's requirement for postoperative opioid analgesics is considerably lessened when bupivacaine is administered for pain control. For postoperative pain control following a short procedure, the bupivacaine may be administered at the start of the procedure; for post-operative pain control in a lengthy procedure, it might be reasonable to administer bupivacaine at the conclusion of the procedure, immediately before the patient's discharge from the office [43]. For many patients receiving bupivacaine, the onset of anesthesia will be similar to that observed with other amide anesthetics (two to four minutes); however, in some patients the onset of anesthesia will be delayed for six to 10 minutes, a finding understandable in view of its pK_a of 8.1. The duration of action of bupivacaine in block techniques is approximately eight hours. If this occurs, it may be advisable, at subsequent appointments, to initiate procedural pain control with a more rapid-acting amide (e.g., mepivacaine, lidocaine or prilocaine), which provides clinically acceptable pain control within a few minutes and permits the procedure to commence more promptly [43].

(b) Etidocaine

Etidocaine is a long-acting local anesthetic, chemically related to lidocaine. Its clinical indications are identical to those of bupivacaine. The primary differences in clinical activity between the two are their onset of anesthetic action and duration for infiltration anesthesia. Etidocaine (with a pK_a of 7.7) has an onset of action of about three minutes, whereas bupivacaine (with a pK_a of 8.1) starts the action in six to 10 minutes. In addition, the duration of clinical action of etidocaine is extremely dependent on the type of administered injection [43].

3. Drugs that block central mechanisms of pain perception and hyperalgesia

Opioids are potent analgesics that are often used in dentistry in combination with acetaminophen, aspirin or ibuprofen. This analgesic blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within neuronal membranes of synapses. These bindings result in a decreased synaptic chemical transmission throughout the central nervous system, thereby inhibiting the flow of pain sensation into the higher centers. Mu and kappa receptors are the two subtypes of the opiate receptors that narcotics bind to and cause analgesia. The narcotics are not anti-inflammatory in nature and do not inhibit cyclooxygenase or block the production of inflammatory factors such as prostaglandins [44]. Codeine, hydroquinone, oxycodone and meperidine are the most commonly used narcotic analgesics. Codeine is an opioid analgesic, which occurs naturally as a component of the Poppy plant along with morphine and can be recovered as such from the opium extract of the plant [44]. Codeine is often considered the prototype opioid for orally available combination drugs. Most studies have found that a 60 mg dose of codeine produces significantly more analgesia than placebo, although it often produces less analgesia than either aspirin 650 mg or acetaminophen 600 mg [38]. Tramadol is a synthetic, centrally acting analgesic that is thought to relieve pain through synergistic monoaminergic and μ-opioid mechanisms of action [45]. It is widely used for the treatment of acute and chronic pain, but has low abuse potential [46], and unlike pure opioids, clinically relevant effects on respiratory or cardiovascular parameters are rare at recommended doses for postoperative pain [47]. A meta-analysis of data from 3,453 patients in 18 placebo-controlled trials established the safety and dose-dependent efficacy of tramadol in the treatment of moderate-to-severe dental or postsurgical pain [48]. In patients with dental pain, tramadol, 100 mg, provided at least equivalent analgesia compared with an opioid combination (e.g., codeine/aspirin 60/650 mg or propoxyphene/acetaminophen [APAP] 100/650 mg). A single dose of tramadol, 100 mg, was clearly more effective than tramadol 50 mg or tramadol 75 mg in this patient population, but increasing the dose to 150 mg provided no additional analgesia. Dose-related adverse events with Tramadol treatment included vomiting, nausea, dizziness and somnolence [49].

Combination analgesia therapy for post-operative pain

Analgesic monotherapy has shown equivocal success in treating dental pain. The goal of combining analgesics with different mechanisms of action is to use lower doses of the component drugs, thereby improving analgesia without increasing adverse effects [2].

NSAIDs combinations

There are two general methods of combining an NSAID with an opioid in treating cases of moderate to severe pain. The first method achieves the analgesic advantages of both an NSAID and an opioid by prescribing an alternating regimen consisting of an NSAID followed by an acetaminophen and opioid combination [50]. For example, the emergency pain patient could take ibuprofen 400 mg (or an NSAID of choice) at the office. Then, the patient could take an acetaminophen and opioid combination two hours later. The patient would then take each treatment every four hours, taking each drug on an alternating two-hour schedule. In most cases, these treatments need not to be continued beyond 24 hours [51]. The second method for combining an NSAID with an opioid in treating rare cases of moderate to severe pain achieves the analgesic advantages of both an NSAID and an opioid by administering a single combination drug consisting of an NSAID and opioid combination [52]. For example, oxycodone/ibuprofen 5/400 mg (Combunox) is an oral fixed-dose combination tablet with analgesic, anti-inflammatory and antipyretic properties. It is approved in the US for the short term (up to seven days) management of acute, moderate-to-severe pain and is the first and only fixed-dose combination containing ibuprofen and oxycodone [53]. According to Dionne [53], ibuprofen 400 mg and oxycodone 10 mg provided a faster onset of relief of dental pain than did ibuprofen 400 mg alone. Ziccardi et al [54] found that the combination of ibuprofen 400 mg and hydrocodone 15 mg was superior to the combination of acetaminophen 600 mg and codeine 60 mg in providing analgesia after third-molar extraction, as demonstrated by superior total analgesic effect, duration of analgesia and global evaluation.

Tramadol has been shown to be effective in managing dental pain when combined with a peripherally acting NSAID. Doroschak et al [55] demonstrated that combining tramadol 100 mg with flurbiprofen 100 mg significantly reduced pain vs. placebo at 6 hours and 24 hours following pulpectomy; compared to placebo, neither tramadol nor flurbiprofen significantly relieved pain in 6 and 24 hours when used as monotherapy.

Pre-emptive analgesia

The concept of preventing the development of central sensitization was first explored as a clinical strategy through a retrospective review of medical records. McQuay [56] reported the amount of time to the first request for a postoperative analgesic in patients immediately following a variety of surgical procedures performed under general anesthesia. The preoperative administration of a local anesthetic delayed the postoperative request for a postoperative analgesic in patients immediately following a variety of surgical procedures performed under general anesthesia. The preoperative administration of a local anesthetic and an opioid delayed the postoperative request for medication by approximately six and three hours respectively. The combination of a local anesthetic and an opioid resulted in an even greater delay suggestive of an additive effect. Tverskoy et al [57] provided evidence that the administration of a local anesthetic before the surgical incision resulted in substantially less pain for up to 72 hours post-surgically, particularly when pain intensity was elicited after a standardized movement. Gordon et al [58] demonstrated that preoperative administration of bupivacaine (a long-acting local anesthetic) in patients undergoing removal of impacted third molars under general anesthesia resulted in less pain and analgesic consumption at 48 hours than a parallel group of subjects administered saline placebo injections. Although less pain was experienced in the bupivacaine group long after the local anesthetic had dissipated, it was not clear whether this was a result of less nociceptive input during surgery, less postoperative pain or the additive effects of both.

Preventive analgesia

Most studies in which an NSAID is administered orally after the onset of pain demonstrated an onset of activity within 30 minutes and peak analgesic activity in two to three hours after drug administration. The administration of an NSAID before pain onset (preventive) will suppress the release of inflammatory mediators, particularly prostaglandins, which contribute to the sensitization of peripheral nociceptors [59]. According to Dionne [60] the combination of NSAID pretreatment before pain onset and a long-acting local anesthetic markedly prevents pain during the initial six to seven hours after oral surgery.

Preventive analgesia or pre-emptive analgesia

It appears that optimal clinical benefits can be achieved by administering drugs such as local anesthetics and NSAIDs before the onset of postoperative pain. Administering these drugs before a surgical or an endodontic procedure may be of benefit for longer procedures or for minimizing peripheral sensitization, which is a result of the cascade of inflammatory mediators that are released by tissue injury and fuel the subsequent inflammatory process [60].

Conclusion

Patients typically associate dental care with pain. For many patients, fear of dental pain and avoidance of dentistry are synonymous. Endodontic post-treatment pain continues to be a significant problem facing the dental profession. Therefore, it is evident that post-treatment analgesic intervention is required in a variable percentage of endodontic cases. In conclusion, NSAIDs are effective for inflammatory pain, but they carry potentially serious gastrointestinal, cardiac and renal toxicities. Acetaminophen is effective and safe for mild pain, but often is inadequate for more severe pain. Systemic steroids are highly effective in those patients who present for treatment of moderate/severe pain with a clinical diagnosis of pulpal necrosis along with the associated periapical radiolucency. Opioids typically are effective for more severe pain, although they can have limited efficacy as monotherapy. Combination analgesic therapy can increase the efficacy of dental pain management, reduce the side effects and decrease the recovery time.

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