Mitigating Post-Operative Dental Pain:

As easy as 1, 2, 4, 24

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Introduction

The majority of pain in a dental setting is the result of either infection or surgical trauma. As a result, most of the pain is predictable and as such, many of today’s providers rely on one or two standard medications to manage all of the situations they encounter. The reality of this approach is that the provider may not be treating the etiology of the pain but rather just masking its symptoms. Although dentists prescribe a relatively small amount of opioid analgesics, they play an important role in preventing misuse and diversion of these medications.1 Dentists must be cognizant of improving patient care and avoiding potential adverse outcomes by working to prescribe the appropriate medicine for the right indication to best heal the patient.

Oral healthcare professionals (OHCPs), as a part of daily clinical practice, must select and prescribe analgesics to treat orofacial pain.2 While pain has both psychological and physiological elements, an experience of poorly managed pain can lead patients to postpone or avoid dental visits, often resulting in patients who may be more difficult to manage and less compliant with prescribed treatments. Appropriately selected medications that reduce orofacial pain can improve clinical outcomes, making them an essential part of dental practice.3

The primary pathological process responsible for acute orofacial pain is tissue injury and inflammation (nociceptive pain).2,4 Tissue damage stimulates the release of inflammatory mediators (kinins, histamine, substance P, leukotrienes, and prostaglandins), which initiate and magnify the pain impulses transmitted to the central nervous system, generating the perception of pain. Of these mediators, prostaglandins are most responsible for sensitizing neurons peripherally where pain originates. They are also synthesized centrally in the higher brain centers where the pain is recognized.

Finally, in response to pain impulses, prostaglandins amplify pain sensitivity and recruit additional secondary neurons in the spinal cord in response to the primary stimulus.

While nociceptive pain can spontaneously resolve if the underlying cause is definitively treated (e.g., abscessed gingiva, inflamed pulp, or carious lesion), the standard of care also includes a pharmacological approach to pain management. Medications that target the synthesis of
inflammatory mediators such as prostaglandins are some of the most effective analgesics in our armamentarium.

**Nociceptive Orofacial Pain: Medication Selection**

In medical practice there is a commonly cited principle: match the right drug, at the right dose and the right time, for the right patient and the right procedure. The drugs of choice for postoperative dental pain include the nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. The primary mechanism of action of these analgesics is to inhibit cyclooxygenase (COX) enzymes which are responsible for the formation of prostaglandins from arachidonic acid. The other class of medications often employed in conjunction with these agents are the glucocorticoids. Glucocorticoids reduce blood levels of prostaglandins and leukotrienes, which are both involved in the pathogenesis of trismus, edema, and pain.

Since opioid-based medications target the central mu-opioid receptor and are not specifically anti-inflammatory agents, medications such as morphine, hydromorphone, and oxycodone should not be considered drugs of choice in treating dental pain secondary to inflammation. Rather, these analgesics should be reserved for a very small percentage of dental patients with severe, uncontrolled nociceptive orofacial pain, and even then they are best prescribed as combination products that contain a NSAID in addition to the narcotic moiety.

**Aspirin and Related Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)**

Aspirin and the other NSAIDs specifically impede COX activity at the site of tissue damage, thus inhibiting prostaglandin formation peripherally, along the spinal cord, and in the higher brain centers. While inhibiting this enzyme ameliorates the inflammatory triad of pain, inflammation and fever, the conversion of arachidonic acid to cytoprotective prostaglandins is also impeded.

For this reason, aspirin and other NSAIDs can cause adverse effects such as gastroduodenopathies (GI), delayed wound healing, prolonged bleeding, and an increased risk of cardiovascular (CV) events.

In 2005, the FDA began requiring manufacturers of prescription NSAIDs to include a black box warning and a medication guide with the package inserts for their products. The warning highlighted the drugs’ potential to increase the risk of CV events and potentially life-threatening GI bleeding associated with their use.

The medication guide accompanies every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks. The FDA also asked manufacturers of non-prescription, over-the-counter (OTC) NSAIDs to amend their labeling to include specific information about the potential GI and CV risks, and information to assist consumers in the safe use of these drugs. In 2016, it was concluded by meta-analysis that patients taking routine NSAIDs for ten days or less to alleviate pain are not at increased risk for adverse cardiovascular side effects.

Concern around the adverse effects of NSAIDs was also the impetus for the development of COX-2 selective NSAIDs such as celecoxib (Celebrex, Pfizer Inc.). There are two well-described subtypes of tissue COX: COX-1 and COX-2. COX-1 is a constitutive form which promotes hemostasis (the synthesis of the prostaglandin analogue thromboxane A2 which increases platelet degranulation and adhesion), stomach mucosal integrity (where synthesis of
prostaglandins protects against acid damage), and kidney function (where prostaglandins help regulate normal renal blood flow). COX-2 is an inducible form, which promotes the synthesis of pro-inflammatory prostaglandins and plays a significant role in mediating pain, inflammation, and fever. Selectively inhibiting COX-2 mitigates the inflammatory response, while neglecting COX-1 inhibition reduces the occurrence of adverse effects seen with traditional non-selective NSAIDS.

**Acetaminophen**

Acetaminophen is found as a single-agent and in combination with other ingredients in OTC products, and is commonly combined with narcotic agents in prescription products. In general, acetaminophen is considered a safe medication, especially because it is associated with less CV, GI, renal, and bleeding adverse effects seen with the NSAIDs. Hepatic injury resulting from acetaminophen use, however, remains a serious health problem. As a result, in June of 2009, the FDA analgesic advisory committee, suggested new labeling and dosing guidelines for this ubiquitous analgesic. This language was updated on November 1, 2016 to state, “Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take: more than 4,000 mg of acetaminophen in 24 hours; with other drugs containing acetaminophen; or 3 or more alcoholic drinks every day while using this product.” The FDA also required that combination drug products not contain more than 325 milligrams of acetaminophen per tablet, capsule or other dosage unit.

**Glucocorticoids**

Produced by the adrenal gland and controlled by the hypothalamus, glucocorticoids are primarily involved with carbohydrate metabolism. The principal endogenous glucocorticoid is cortisol, although others such as hydrocortisone, dexamethasone, methylprednisolone, and prednisone are more commonly used in dentistry as immunosuppressive agents (e.g., for the treatment of erosive lichen planus and pemphigus vulgaris), anti-inflammatory agents (e.g., for the treatment of mucositis and oral ulcerations, to reduce swelling), and analgesia. The duration of glucocorticoid use in dentistry is typically short. Although glucocorticoids act similarly to NSAIDs in that they inhibit the synthesis and release of inflammatory mediators, they differ in that they affect leukocyte function and are immunosuppressive with prolonged use. Short-term use of less than seven days should not affect adrenal function and will likely avoid adverse side effects. Patients suffering from acute psychoses or with a psychotic tendency should not receive a glucocorticoid; additionally these medications should be used with caution in patients with diabetes, peptic ulcerations, and pregnant or lactating females. Although glucocorticoids are known to affect healing and bone remodeling, short courses of glucocorticoid therapy are not associated with wound disturbances or osseointegration of dental implants.

**Nociceptive Orofacial Pain**

**The Perfect Prescription, “1 – 2 – 4 – 24”**

Selecting analgesics for the management of nociceptive orofacial pain is ideally based on the patient’s medical history, the drug’s pharmacologic profile, the pain’s actual or expected intensity, the medication’s cost, the ease with which the medication can be obtained, and the
anticipated patient compliance. In other words, “the medication that works is the one the patient takes.”

Ibuprofen was the first NSAID to demonstrate analgesic superiority over aspirin.24 A 400mg dose has a greater peak analgesic effect and a longer duration of action than 600-1000mg of aspirin or acetaminophen, or 60mg of codeine, and has comparable efficacy to traditional opioid analgesic combinations.25,26 Maximum anti-inflammatory action with ibuprofen may require higher doses (e.g., 2400-3200 mg/day) than those indicated for effective analgesic action (e.g., 200-600mg four times per day; maximum 2400mg/day).27,28 With a half-life of approximately three hours, ibuprofen should ideally be administered every six hours to achieve steady-state blood levels.

Analgesia from acetaminophen in the average adult is readily measurable at a dose of 300mg and plateaus at 1000mg.29 Acetaminophen follows first-order pharmacokinetics in the body (i.e., metabolism and elimination are constant regardless dose size), and similar to ibuprofen, with a half-life of approximately three hours, it should be administered every six hours to achieve steady-state blood levels.30 The maximum effective daily dose is two 500mg tablets administered every six hours, for a total of 4000mg per day.

The combination of acetaminophen and ibuprofen has previously been described and touted as an effective analgesic recipe.29,31,32 Since no marketed drug combination in the United States contains both an NSAID and acetaminophen, Dionne first proposed taking the usual analgesic dose of ibuprofen (400-600mg) every four to six hours, not to exceed 2400mg over a 24-hour period; and taking acetaminophen (650-1000mg) every six hours, not to exceed 4,000 mg in 24 hours.32 This combination of two medications; ibuprofen (600mg) plus acetaminophen (1000mg) could be administered every six hours (four times daily) for 24 hours without exceeding the maximum daily dose of either drug (“2 – 4 – 24”).

If patients are compliant with these four doses of ibuprofen and acetaminophen, additional analgesics will likely not be required. The medications can be administered every six hours either together or in a staggered fashion based on physician and patient preference. The staggered approach may be desired for patients in whom more frequent medication administration may be psychologically beneficial following dental surgery, despite no pharmacological reason or benefit in doing so. Patient compliance and adherence with the prescribed regimen is vital to success; patients should set alarms to fulfill nighttime doses during the initial 24-hour postoperative period. After the initial 24-hour timeframe, patients may opt to take the medications, either alone or in combination, on an “as needed” basis. If patients’ pain level necessitates continued routine pain medication administration after 2 days post-surgery, despite excellent compliance, follow-up and re-examination by the OHCP is encouraged.

Analgesics can also be given preoperatively to mitigate postoperative pain (preemptive analgesia).33 This strategy could employ acetaminophen and/or a NSAID, or a glucocorticoid where pain, swelling, and trismus are expected.34 Celecoxib 400 mg administered orally thirty minutes prior to the procedure may be the most attractive NSAID for preemptive analgesia as it can mitigate the inflammatory response without delaying wound healing or prolonging bleeding compared to the non-selective NSAIDs.35 Celecoxib 200 mg given every 12 hours for the initial 24-hour postoperative period could also safely replace the postoperative ibuprofen 600 mg prescription for patients maintained on anticoagulants such as warfarin, dabigatran, rivaroxaban, apixaban or edoxaban.
The final ingredient for the perfect prescription, “1 – 2 – 4 – 24” in treating nociceptive orofacial pain is adding a pre- or peri-operative dose of the glucocorticoid dexamethasone. Several studies have demonstrated that a single 4mg dose of dexamethasone can significantly reduce pain, swelling, and trismus following third molar surgery, implant surgery, and endodontic procedures.\textsuperscript{36–40} Dexamethasone is supplied as tablets, for injection, and as an elixir. If the 4mg dexamethasone tablet is used, it is recommended to administer it a day either before or at the time of surgery. Alternatively, clinicians can inject 4mg of dexamethasone submucosally (SM) peri-operatively adjacent to the surgical site in a manner consistent with an infiltration injection, as the patient will be anesthetized in this area already. Dexamethasone injectable formulations come in several concentrations but either the 4mg/mL or 10mg/mL concentration is recommended, in this case 1mL or 0.4mL, respectively, would be injected (a 1mL syringe with 29-gauge ½-inch needle can be used in both cases). While the choice of oral administration versus submucosal injection is up to the clinician, SM injection presents the advantages of not requiring patient compliance, and the opportunity to inject the medication directly into the anesthetized tissue site of injury and swelling. In addition, SM injection offers a superior duration of action of 6 days versus approximately 2.5 days for oral administration.

While the choice of oral versus submucosal injection is up to the clinician, there are several factors that make submucosal injection attractive: no patient compliance needed, the medication is deposited near the site of injury and swelling, presumably injected into anesthetized tissue, and capable of superior duration of action compared to oral administration. The duration of action of oral (PO) dexamethasone is approximately 2.5 days versus 6 days for submucosal (SM).\textsuperscript{41} OHCPs should strongly consider the “1 – 2 – 4 – 24” mnemonic as a device to remember the “perfect” analgesic formula: a single 4mg dose of dexamethasone, either pre- or peri-operatively followed by a combination of ibuprofen 600mg plus acetaminophen 1000mg administered every 6 hours for 24 hours (i.e., 1 single dose of dexamethasone, then 2 drugs for 4 doses, for 24 hours).\textsuperscript{3}

**Conclusions**

This article describes a regimen that includes either a single oral or submucosal dose of dexamethasone followed by the combination of ibuprofen and acetaminophen to help OHCPs manage acute postoperative dental pain, swelling and trismus more effectively. Prescribers should always recommend the most effective analgesic regimen balanced against potential adverse events for the anticipated length of drug therapy. Postoperative dental pain usually has a short duration, and is caused by tissue injury and inflammation; as a result, a glucocorticoid followed by NSAIDs in combination with acetaminophen should be considered the first line analgesic regimen for most patients.

**References**


