Review Article

Prevention of post-operative dental pain using pre-operative medications - A review

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ABSTRACT

Pain is a complex experience consisting of a specific sensation and the reactions evoked by that sensation. Conventional analgesics either interrupt ascending nociceptive impulses or depress their interpretation within the depress their interpretation within the central nervous system or inhibit COX mediated prostaglandin synthesis ,one of the major culprit of pain and inflammation. Analgesic adjuncts have proven efficacy for managing chronic pain. They include various antidepressants and anticonvulsants that either enhance descending inhibitory pathways or modulate excitatory neural traffic that amplifies pain interpretation. These agents have marginal benefit in the management of acute pain. Relieving pain is a challenge in dental practice due to the fact that the effectiveness of the medication differs from patient to patient. The aim of this review is to list out different types of medication used to reduce or prevent post-operative discomfort of the patient and to give a clear view on medications commonly used in dental practice.

KEY WORDS: Analgesic, Extraction, Nonsteroidal anti-inflammatory drugs, Opioids, Post-operative pain, Premedication

INTRODUCTION

Pain is an unpleasant sensory and emotional feeling experienced by an individual. It is associated with the process of tissue damage that is occurring or has occurred. The nervous system detects and interprets a wide range of thermal and mechanical stimuli, as well as environmental and endogenous chemical irritants.[1] Acute and chronic pain is different clinical entities. Acute pain is associated with skeletal muscle spasm and sympathetic nervous system activation, provoked by a specific disease or injury and serves as a useful biologic indicator, and is self-limited.[2-4]

The result of the pain stimuli is the irritation of the receptors called as nociceptors.[4] Nociceptors are free nerve endings that are present in skin, muscles, periosteum, joint capsule, ligaments, cornea of the eye, and dental pulp and respond to painful stimuli. These nociceptors are stimulated by any biological, electrical, thermal, mechanical or chemical stimuli, and they transmit this information to the brain and spinal cord.[5,6] When this transmission reaches the spinal cord and then to the central areas of the brain, pain perception occurs. There are two types of fibers: A delta and C which are involved in pain transmission. The A delta fibers are large fibers and produce sharp, well-defined pain, which is typically stimulated by any external stimuli. They are myelinated. Transmission through A delta fibers is so fast that the body responds faster than the pain stimulus which provides limited possibilities for pharmacological modification of these receptors. In clinical practice, it is easy to inhibit chronic, slow pain, using analgesic drugs and difficult to block sharp, and fast pain. The smaller C fibers transmits dull burning or aching sensations. C fibers are very thin fibers and susceptible to damage because they do not have the myelin sheath. C fibers react to mechanical, thermal, and chemical stimuli. Hence, pain comes in two phases. The first phase is mediated by the fast-conducting A delta fibers and the second part due to C fibers.[5-8] C-fiber nerve endings are "sensitized" by prostaglandin and other mediators. Prostaglandin synthesis is inhibited by a nonsteroidal anti-inflammatory drug (NSAID), and inhibition of inflammation by corticosteroids reduces the fibers nerve sensitivity and increases the pain threshold. This defense mechanism is based on the cooperation between the immune and nervous systems.[4] Physiological pain has significant importance as a warning sign.[5,6]

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ROLE OF PROSTAGLANDINS

Prostaglandins are one of the main elements involved in the sensitivity of peripheral nociceptors thereby it has a key role in causing primary and secondary hyperalgesia.[9] The prostaglandins are produced by the activation of phospholipase A2, which in turn leads to the formation of arachidonic acid from membrane phospholipids in the traumatized tissue.[10,11] This arachidonic acid is converted to different subtypes of prostaglandins through cyclooxygenase (COX) dependent mechanism. The prostaglandins metabolize prostaglandin E2 (PGE2), prostaglandin F2α, prostaglandin D2, prostacyclin (PGI2), and thromboxane A2.[12-14] These prostaglandins exert their biological effects by binding to the specific G linked protein. There are nine types of prostaglandin receptors. The specific prostanoids and their receptors involved in pain are PGE2 and epinephrine (EPI) and EPI3 receptors, PGI2 and IP receptor.[14,15] The PGE2 prostanoid is important in inflammatory pain and their levels can be the related to the level of pain intensity, specifically in the extraction of impacted 3rd molars. The prostaglandin levels are insignificant in normal tissues to cause immediate pain response to tissue damage and have to be synthesized first.[16-18]

An hour after tissue damage, the prostaglandins are synthesized rapidly to a significant level.[19] There are two types of COX enzymes, the COX-1 and COX-2. Each of these COXs expresses themselves differently from each other in terms of their site of action and function. The COX-1 enzyme is expressed in many tissues, mainly in assisting the regulation of normal cellular mechanism such as protection of gastric mucosa, platelet aggregation, and regulating the renal blood flow. Hence, COX-1 is called the constitutive COX enzyme.[20,21] The COX-2 enzyme is found in many tissues as well in brain, spinal cord, and kidney, but this enzyme is seen in pathological states such as inflammation and cancer. Hence, this enzyme is called the inducible COX enzyme.[22,23]

NSAID

Non-steroidal antiinflammatory drugs (NSAIDs) are preferred over opioids due to their effectiveness. They are recommended for mild-to-moderate pain in acute and chronic inflammatory conditions. They are used in conditions such as dysmenorrhea, gout, neck pain, back pain, headache, rheumatoid arthritis, and osteoarthritis.[23] NSAIDs consist of conventional NSAIDs and COX-2 inhibitors. Conventional NSAIDs inhibit prostaglandin production by both COX-1 and COX-2 enzyme systems. The inhibition of COX-1 leads to the development of side effects such as gastrointestinal ulceration, and it also affects renal function. While COX-2 inhibition causes analgesia, COX-2 specific medications are effective, and the side effects of conventional NSAIDs remain though reduced to 50%.[24-27] NSAIDs are available as both over-the-counter and by prescription drugs. There are both oral and topical formulations. The topical form has lesser systemic absorption; therefore, the adverse effect is lessened. However, localized adverse effect is increased instead.[28]

MECHANISM OF ACTION

NSAIDs have similar chemical structures; although there are key differences in pharmacokinetic properties, analgesic efficacy, and COX selectivity. NSAIDs are well absorbed from gastrointestinal tract. They are highly bound to plasma proteins. They are metabolized in liver and excreted by kidney. Their plasma half-life ranges between 15 min and 70 h.[27,28] There is no difference in traditional NSAIDs and coxib. They both inhibit COX but vary in their affinity. Traditional NSAIDs such as meloxicam, nimesulide, and etodolac are selective for COX-2. Ibuprofen and naproxen are generally nonselective. Other NSAIDs such as ketoprofen, flurbiprofen, and aspirin have a higher selectivity for inhibiting COX-1.[18]

PRE-OPERATIVE ACETAMINOPHEN

Pre-operative acetaminophen studies have been reported to evaluate its efficiency in managing post-operative events. In one such clinical study, 1000 mg of acetaminophen was administered 30 min before third molar surgery to 75 dental patients randomly and further postoperatively for 4–8 h interval. The data were collected based on the intensity of the pain scale for every 12 h duration. Acetaminophen could decrease pain immediately after surgery in this study. In another group of the same study, acetaminophen was given with oxycodone postoperatively if analgesia was not achieved. The study had concluded that there was no difference between the two types of administration of the drug with exception to slight delay in onset of pain between the two groups and side effects to the drug when administered preoperatively was much lesser.[29] In another clinical study, Gustafson *et al.* used pre-operative acetaminophen in a randomized crossover trial for the impacted third molar and compared the difference between pre-operative and post-operative administration. The study had concluded that pre-operative acetaminophen 1000 mg is not more analgesic than acetaminophen 1000 mg when administered immediately postoperatively. In this double-blinded study, 43 patients were randomly assigned to one of two treatment groups; acetaminophen preoperatively and placebo immediately after surgery. All patients completed an hourly questionnaire on pain onset, intensity, and side effects. The time before medicating with additional analgesics after the post-surgical treatment was measured for both groups and a

significant difference was not found. The difference in pain intensity at the time the "rescue medication" was administered was also insignificant. The two treatment groups experienced similar side effects, namely the development of drowsiness and dizziness.[30] In another double-blind, randomized study, 30 patients were selected. The first group was administered with ibuprofen 400 mg and second group was administered with acetaminophen 500 mg. This study concluded acetaminophen has better efficacy and lesser side effects than ibuprofen.[31,32]

PRE-OPERATIVE IBUPROFEN

Four studies have been reported with pre-operative ibuprofen. In one double-blinded, clinical study, 24 patients participated with bilateral asymptomatic impacted mandibular third molars. Each patient randomly received either 1200 mg of ibuprofen divided into three single daily doses or a placebo. Treatments were taken at specified times during the day beginning in the evening before third molar surgery. Patients were evaluated on the 1st, 3rd, and 5th post-operative days for swelling, pain, mouth-opening ability, bleeding, wound healing, hematologic findings, ibuprofen serum concentrations, and the observance of side effects. This study has reported a significant reduction in post-operative pain on the day of surgery when pre-treatment with ibuprofen had been given. A reduction in trismus was also seen when ibuprofen pretreatment was used. In a second placebo-controlled, double-blinded study, 100 patients were randomly assigned to either ibuprofen 400 mg or placebo pre-treatment and 30 min before extraction of third molars.[33] The effects of the pre-operative treatment were determined by measuring the amount of time between the completion of surgery and intake of post-operative pain relieving medication. Pain and pain relief were measured with categorical scales recorded in a patient questionnaire. Ibuprofen pre-treatment resulted in a delay of >100 min to the onset of post-operative pain when compared with the placebo premedication group. It was also shown that the severity of the initial pain was less in the group pretreated with ibuprofen. In the third study around 107 participants were randomly given either 800 mg of ibuprofen, 600 mg of acetaminophen, or placebo 30 min before removal of third molars.[34] Hourly pain intensity was noted in patients using a pain scale, which rated pain as none, slight, moderate, or severe. Those patients pretreated with ibuprofen reported significantly less pain than the acetaminophen and placebo groups at the 3 and 4 h observations. The time to the onset of pain was also greater in the ibuprofen pretreatment group as shown by the number of patients reporting pain at the first of the hourly assessments. Ibuprofen (400 mg) and codeine phosphate (30 mg) a combination of ibuprofen and codeine or placebo were randomly given 30 min preoperatively to participants in the fourth study.[35]

In another study, 155 patients were undergoing surgical removal of mandibular third molars. Similar to the other studies, the time to the onset of pain was recorded, and the pain intensity was measured on a 9-point scale for the next 5 h. Patients receiving the pre-operative dose of ibuprofen and the combination of ibuprofen and codeine had a significant increase in the amount of time between the completion of surgery and the need for post-operative analgesics relative to the other two treatment groups. The results did not indicate that the addition of codeine in combination with ibuprofen influenced the efficacy of the pretreatment strategy. The investigators in this study suggested that pretreatment with ibuprofen or ibuprofen-containing medications is of clinical value in the post-operative management of pain.[36]

PRE-OPERATIVE FLURBIPROFEN

Flurbiprofen is structurally similar to ibuprofen and is a potent analgesic.[37] A pre-operative clinical study with flurbiprofen (25 and 50 mg), aspirin (650 mg), or placebo was given 30 min preoperatively with 4 and 8 h of drug administration postoperatively. This study had 107 patients with impacted third molars surgically removed and were randomly assigned to one of the four groups above. Pain intensity was measured at the time of the first post-operative dose and then hourly for the next 8 h. Both groups of flurbiprofen resulted in significantly less pain intensity than the other groups. There were no reported differences between the side effect profiles of the groups, excessive hemorrhage, nor post-operative bleeding in any of the groups. However, information regarding the type and severity of side effects was not well recorded in the study.[38] In a crossover study, pre-operative doses of flurbiprofen (100 mg) and acetaminophen (650 mg) plus oxycodone (10 mg) were evaluated for better efficacy in the post-operative course when combined with the long-acting local anesthetic etidocaine. Analgesic doses were repeated 3 h after the completion of surgery. The pain scale was recorded for the 7 h immediately after surgery. The pain intensity between the two treatment groups was similar during the first 3 h of the study. This finding was attributed to the effectiveness of the local anesthetic. The flurbiprofen-etidocaine group has reported significantly less pain at the 4, 5, and 6 h assessments, compared with the other treatment groups. This also lowered the incidence of drowsiness, GI upset, and dizziness.[39]

Another study, where 125 mg of methylprednisolone was given preoperatively with 50 mg of flurbiprofen

for anti-inflammatory and analgesic properties. Their results reinforced the findings that corticosteroids significantly reduce post-operative edema. Routine use of corticosteroids is not recommended due to possible adrenal suppression and the risk of masking clinical signs of infection. Similarly, in another study 50 and 100 mg of flurbiprofen were compared with 1000 mg of acetaminophen and a combination of acetaminophen and oxycodone. This study was conducted in three phases; each phase involved 20 patients who had bilaterally similar impacted third molars. The crossover design allowed each patient to be his or her own comparison. In the first phase, flurbiprofen (50 mg) or acetaminophen (1000 mg) was taken 30 min before the beginning of the surgical procedure and repeated 4 h postoperatively. The second phase of the study included flurbiprofen (50 mg) taken 30 min before surgery and 4 h postoperatively or placebo preoperatively followed by a combination of acetaminophen and oxycodone taken at 4 h. Patients in the third phase received flurbiprofen (100 mg) or a combination of acetaminophen and oxycodone preoperatively and repeated the dosage at 4 h. Hourly recordings of the pain were made after 2 h from the initial dose with category scales and a visual analog scale. All phases of the study showed that pretreatment with flurbiprofen resulted in significantly less pain during the first 4 post-operative h. After the second dose at 4 h, the treatment groups became indistinguishable by their reports of pain with a slight trend toward increased analgesia with flurbiprofen.[40]

OPIOIDS

Opioids are used in the management of dental pain and malignant conditions, even though they are widely used for pain relief in cancerous conditions. However, they are only considered when NSAIDs are not effective enough or sufficient. There abuse liability and addiction tendency bring concern. Hence, their use in non-malignant conditions remains controversial.[41,42]

Mechanism of Action

Opioids act by binding to specific receptors that are scattered all around the central and peripheral nervous system called opioid receptors. The main function of opioids is analgesia accompanied by numerous side effects such as reduced peristalsis, mental clouding, respiratory depression, dysphoria, and euphoria. The higher the dosage, severe the side effects.[41,42]

TRAMADOL

Tramadol is a synthetic opioid commonly used postoperatively for pain control. In a randomized, double-blinded, and single dose clinical trials of 3453 patients who had moderate-to-severe pain and required extraction were selected. Tramadol (50–100 mg) was compared with aspirin with codeine (650 + 50 mg) and acetaminophen with propoxyphene (650 + 100 mg), respectively. Tramadol acted as analgesia rather than placebo both in post-surgical and during dental surgery. However, tramadol is more effective in post-surgical patients with fewer side effects.[43] In another double-blind placebo controlled study, 456 patients with moderate-to-severe pain within 5 h of two or more 3rd molar extraction. They were randomized to receive two identical encapsulated tablets each containing tramadol with acetaminophen (37.5 mg + 325 mg), tramadol 50 mg or placebo. Tramadol with acetaminophen showed a better response than placebo and tramadol alone.[44]

In the third study, a randomized, double-blinded and controlled clinical trials were carried out in two different centers compare the analgesic and side effect response in 200 patients who required extraction. The groups were divided as, tramadol 100 mg, tramadol 50 mg, codeine 60 mg, aspirin with codeine (650 mg + 60 mg), and placebo. Aspirin with codeine was found to be superior, followed by tramadol 100 mg, tramadol 50 mg, codeine 60 mg, and placebo. The side effects such as nausea, vomiting, and dizziness were reported.[45] In the fourth study, a double-blind, parallel group of patients with moderate to severe pain followed extraction of third molar (one or more). The patients were evenly distributed and grouped as three separate single-dose - tramadol 75 mg, acetaminophen 650 mg, and ibuprofen 400 mg or placebo. Tramadol with acetaminophen showed greater pain relief than tramadol and acetaminophen alone.[46]

CONCLUSION

Over the past decades, effectiveness , though have been used as an analgesic. Both traditional and coxibs show the effectiveness though some more than the others. Some analgesics work better in combinations. This review shows that use of pre-operative medications hels in curbing post operative pain which is a fear factor to avoid treatment by most of the patients. Although NSAIDs have known adverse effects, usage may have patient compliance when pain is considered.

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