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Review Article

Analgesics Following Mandibular Third Molar Surgery

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ABSTRACT

Surgical extraction of third molars is a commonly performed clinical procedure and is usually associated with postoperative pain, swelling and trismus. Several studies have compared the drugs used to control postoperative pain after surgical removal of third molars. The adverse effects of the wisdom tooth surgery on the quality of life has been reported to show a three-fold increase in patients who experience pain, swelling and trismus alone or in combinations; compared to those who were asymptomatic. This article reviews the various analgesics used in third molar surgery and emphasizes the necessity for better pain, swelling and trismus control in patients who undergo this procedure.

Key Words: Analgesic; Impacted Third molar; Inflammation; Non-steroidal anti-inflammatory drugs; Opioids.

INTRODUCTION

The surgical removal of impacted mandibular third molars is one of the most commonly performed dento-alveolar procedures in oral and maxillofacial surgery and is associated with varying degrees of postoperative discomfort. Pain, trismus, and swelling are the most common postoperative complaints, and these influence a patient's quality of life in the days after surgery[1]. It is generally accepted that pain following third molar surgery reaches moderate to severe intensity within the first 5 hour after surgery[2,3]. .However, there are studies showing that the postoperative pain reaches its peak intensity during the first 8 hours after the surgery[4].

The removal of the impacted third molar and the resultant tissue and cellular destruction brings about the release and production of several biochemical mediators involved in the pain process, in particular, histamine, bradykinin and the prostaglandins. Histamine and bradykinin have similar functions. Both cause sensitisation of free nerve endings and similarly, both are involved in oedema formation. However, both substances have short half- lives and therefore the major role of these substances occurs in the early stages after injury. There is a wide armamentarium of analgesics available for clinicians to manage pain and other post-operative sequelae. The problem of dental pain can be tackled using peripherally acting or centrally acting drugs.

One of the most significant advances in maxillofacial surgery over the past 10 year has been in the pharmacological management of patients with acute postoperative pain.The most prevalent methods include administration of: Non-steroidal anti-inflammatory drugs(NSAIDs)[5] ,which prevent peripheral sensitization by reducing prostaglandin synthesis at the site of surgery; regional anaesthetics[6], , which block afferent nociceptive impulses prior to incision; opioids[7,8], which modulate afferent input by blocking the postsynaptic receptors and decreasing neurotransmitter release or by activating inhibitory pathways; and NMDA-receptor antagonists[9], which inhibit activation of N-methyl-Daspartate (NMDA) receptors in the human spinal cord, thus preventing the main mechanism of central sensitization.

The more prolonged periods of pain and inflammation appear to be integrally involved with the formation and function of the prostaglandins, which are a group of biologically active fatty acids derived from arachidonic acid and linoleic acid. Trauma, heat, anoxia or any stimulus which will result in deformation of the cell membrane or activation of lipolysis will elicit hydrolysis of phospholipids and triglycerides which enter the cyclooxygenase or lipooxygenase pathways to release the free fatty acid precursors of prostaglandins. It is possible therefore, that lipoxygenase products, as well as cyclooxygenase products may contribute to the development of pain and oedema in the inflammatory response.

Routes of administration: Different routes have been tried for the administration of analgesics such as topical[10], oral[11], sublingual[11,12], intramuscular[8], intravenous[13], intranasal[14,15].

Intranasal administration of medications is convenient and non-invasive. The drug may penetrate the blood–brain barrier and reach the central nervous system directly[16]. Also, because of the high vascularity of the subepithelial surface of the nasal cavity, drugs may access the venous blood of the systemic circulation, which can avoid first-pass metabolism in the liver[17].

Timing of the administration of drug: Drugs have been tried pre-operatively and post-operatively. NSAIDs, when administered pre-operatively, seem to reach effective anti-inflammatory levels in tissues before surgical trauma, and they thereby reduce formation in the postoperative phase[18]. Many anesthetists have in the past avoided preoperative administration of NSAIDs because these drugs sometimes

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require oral intake before anesthesia and operation, however with the advent of Intravenous drugs it is possible for pre-operative administration even before general anesthesia administration.

Non-steroidal anti-inflammatory drugs: There are 2 possible mechanisms for the efficacy of NSAIDs when administered prior to surgical trauma. The first may simply be a pharmacokinetic advantage. By administering the NSAIDs prior to pain onset, drug absorption would have begun and therapeutic blood level will be present at the time of pain onset. Second, the presence of a cyclooxygenase inhibitor at the surgical site may limit the production of prostaglandins and prostacyclins associated with hyperalgesia[19,20] The reduction of biosynthesis of prostaglandins by inhibition of the cyclo-oxygenase enzyme system is considered an important mechanism of action of NSAIDs. When administered preoperatively, NSAIDs have been shown to be particularly effective in combating postoperative pain and edema[20,21].

The inhibition of COX-1 in platelets by conventional NSAIDs results in modulation of platelet function leading to prolonged bleeding[22]. With NSAID therapy, dose-dependent water and sodium retention manifested by peripheral edema, elevation in blood pressure, and rarely congestive heart failure are thought to follow the inhibition of PGE2 synthesis[23]**.**

Indications

- Rheumatic disorders: e.g. ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile rheumatoid arthritis, painful syndromes of the vertebral column, nonarticular rheumatism.
- Painful post-operative inflammation and swelling (including dental and orthopedic procedures).
- Painful or inflammatory gynaecological conditions e.g. primary dysmenorrhoea.
- In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Diclofenac provides symptomatic relief but has not been shown to halt or reverse the underlying disease process. Fever alone is not an indication.

Contraindications

- Gastric or intestinal ulcer.
- Hypersensitivity.
- Patients with haemorrhagic diasthesis.
- Patients in who attacks of asthma, urticaria or active rhinitis are precipitated by acetylsalicylic acid or other agents, which inhibit prostaglandin-synthetase activity.

The side effects associated with the use of NSAIDs are numerous, but primarily they are related to gastrointestinal (GI), hematologic, and renal disorders, as well as the propensity to cause skin and mucosal reactions[24]**.**

Paracetamol: It raises pain threshold, but has weak peripheral anti-inflammatory component.Its a good and promptly acting antipyretic. It has negligible anti-inflammatory action.It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and anti-inflammatory actions is its inability to inhibit COX in the presence of peroxides which are generated at sites of inflammation, but are not present in brain. The ability of paracetamol to inhibit COX-3 (an isoenzyme so far located in dog brain) could also account for its analgesic-antipyretic action.

Adverse effects: In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally Analgesic nephropathy occurs after years of heavy ingestion of analgesics. Pathological lesions are papillary necrosis, tubular atrophy followed by renal fibrosis. Urine concentrating ability is lost and the kidneys shrink.

Paracetamol in combination with other NSAIDs have been shown to produce good pain relief in dental pain models[25].

Aspirin

Dosage: In general, for adults, doses are taken four times a day for fever or arthritis, with doses near the maximal daily dose used historically for the treatment of rheumatic fever. For the prevention of myocardial infarction in someone with documented or suspected coronary artery disease, much lower doses are taken once daily.

Pharmacological actions

- Analgesics (prevention of prostaglandin mediated sensitization of nerve endings,obtunding of peripheral pain receptors)
- Antipyeretics (reset hypothalamic thermostat thus increases heat loss)
- Antiinflamatory (suppresses pain,tenderness,swelling,vasodilatation and leucocyte infiltrations)

Mechanism of action is by irreversible inactivation of cyclooxygenase(COX) enzyme.

Adverse effects: Peptic ulcer, epigastric distress, nausea, vomiting, hypersensitivity

Propionic acid derivatives

Dosage: Ibuprofen has a dose-dependent duration of action of around four to eight hours, which is longer than suggested by its short half-life. Onset of analgesia (time to effect) is 24.5 minutes using liquigel format orally. The recommended dose varies with body mass and indication. A dose of 400 mg per dose and 1200 mg per day is considered the maximum amount for over-the-counter use,although, under medical direction, the maximum amount for adults is 800 mg per dose or 3200 mg per day based on an individual's response and tolerance.

Pharmacological action: Inhibit protein synthesis- Inhibit platelet aggregation reversibly and cause short lasting prolongation of bleeding time.

Adverse effect: Common adverse effects include: nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, headache, dizz iness, rash, salt and fluid retention, and hypertension. Infrequent adverse effects include: ulceration of esophagus, heart failure, hyperkalemia, renal impairment, confusion, and bronchospasm. Ibuprofen can exacerbate asthma, sometimes fatally.

Ziccardi et al compared the efficacy and safety of a single dose of ibuprofen 200 mg/hydrocodone 7.5 mg with acetaminophen 300 mg/codeine 30 mg, and placebo in the management of postoperative dental pain after surgical

extraction of mandibular third molar and showed that Ibuprofen with hydrocodone was found to be effective[26], however other studies have shown that Ibuprofen offered satisfactory control of pain for only 65% of patients who underwent routine dento-alveolar surgery[27]. Barden et al in a randomised placebo-controlled trial compared aspirin, ibuprofen and paracetamol and concluded that no major difference is likely[1].

Kaczmarzyk et al in a prospective double blind randomised double blinded clinical trial examined whether ketoprofen administered 60 min before surgical extraction of the lower wisdom teeth provides effective postsurgical analgesia compared with ketoprofen administered 60 min after surgery or placebo and it was found that Ketoprofen administered after third molar surgery provides more effective pain control than ketoprofen administered before the surgery or placebo[28]

Aryl-acetic acid derivatives

Dosage: Diclofenac Potassium: 50 mg orally 3 times a day. In some patients an initial dose of 100 mg of diclofenac potassium, followed by 50 mg doses, will provide better relief. After the first day, the total daily dose should generally not exceed 150 mg.

Pharmacological Actions: Antiplatelet actions are short-lasting- Neutrophil chemotaxis and superoxide production at the inflammatory site.

Diclofenac sodium is a phenylacetic acid derivative belonging to the carboxylic acid class of NSAIDs. It has been used successfully in the treatment of postoperative pain after oral surgery[29]. The anti-inflammatory property of diclofenac in lower third molar surgery was compared with methylprednisolone by Lopez et al who suggested that less inflammation was observed in Methylprednisolone group although there was no severe difference way in the reduction of trismus[30]. In another study intramuscular diclofenac sodium produced significant pain relief compared to tenoxicam[18].

Bailey et al compared the analgesic efficacy and patient acceptability of soluble aspirin and Diclofenac dispersible in patients with postoperative pain after removal of impacted third molars and showed Diclofenac dispersible is superior to soluble aspirin in terms of pain relief and extent of mouth-opening achieved after extraction of impacted third molars[31]. It was shown by Chang et al that a single dose of rofecoxib 50 mg provided greater overall analgesic efficacy over 24 hours than with 3 doses of enteric-coated diclofenac sodium 50 mg [32]. In a single-blind, randomized study the analgesic efficacy and tolerability of a single dose of 100 mg Diclofenac potassium , 100 mg Diclofenac sodium softgel, and placebo for postoperative pain after third molar extraction were compared and concluded that softgel produced better pain relief. This could be attributed to the reason that the softgel gets rapidly absorbed and may positively affect the time of onset and duration of inflammatory[10].

A prospective, randomized study comparing the effects of dexamethasone 8 mg IM and Diclofenac potassium 50 mg par oral (PO), dexamethasone 8 mg IM and acetaminophen 1000 mg PO, and monotherapy with Diclofenac K 50 mg PO on postoperative pain, swelling, and trismus after surgical removal of third molars concluded concomitant treatment with dexamethasone and Diclofenac K provided significant relief[33]. Lima et al evaluated the analgesic efficacy of pre-operative and post-operative administration of aceclofenac in the control of pain after surgical extraction of impacted mandibular third molars and concluded that, Aceclofenac was more efficient in controlling pain when administered before the surgery[34].

Ketorolac: Ketorolac is a potent analgesic with modest anti-inflammatory activity.

Adverse Effects: Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus.

In a randomized, double-blind, placebo-controlled study it was found that ketorolac and tramadol were equally effective in relieving post-operative pain following third molar surgery and pre-operative administration of ketorolac was better than its post-operative administration[35]. Grant et al evaluated the efficacy and safety of intranasal (IN) ketorolac in patients who had third molar extraction surgery with bony impactions and showed a single IN ketorolac 31.5 mg dose was well tolerated and provided rapid and effective pain relief in oral surgery patients for a period up to 8 hours[14]. Sublingual ketorolac has also been found to be effective for post-operative pain, trismus and swelling management in lower third molar surgery[12].

Oxicam derivatives: Piroxicam is a Short-term analgesic and long-term anti-inflammatory.

Dosage: 20mg orally once a day or 10mg orally twice a day.

Adverse effects: Anorexia, heart burn, nausea

Pain, trismus and swelling following mandibular third molar surgery can be controlled by piroxicam administered orally or sublingually and there has been no significant difference between the two routes of administration of piroxciam[11]. Sublingual piroxicam has been equally effective to sublingual ketorolac in management of pain, swelling and trismus following lower third molar surgery[12].

Meloxicam is a preferential COX-2 inhibitor. The analgesic and anti-inflammatory response of meloxicam was evaluated based on a dose dependent phenomenon after surgical extraction of lower third molars. The study concluded that pain, trismus and swelling after lower third molar removal not requiring osteotomy can be successfully controlled by a dose regimen of 7.5 mg meloxicam once daily. For more aggressive extractions 15 mg meloxicam is advisable[36]. It was shown in a study that patients who received meloxicam pre-operatively had less pain intensity than those receiving tramadol pre-operatively[37].

Tenoxicam, a NSAID, is a thienothiazine derivative belonging to the oxicam group. Pharmacokinetic studies have shown that it is rapidly absorbed after oral administration,with a bioavailability of more than 99% and a plasma half-life of 72 hr[38].

Nimesulides: Nimesulides are preferential COX-2 inhibitors.

Dosage: The usual dose is 100mg twice a day.

Children: 5mg/kg of body weight in 2 or 3 divided doses.

Adverse effects: Gastrointestinal- Abdominal discomfort, heartburn, abdominal cramps, nausea, vomiting and diarrhea.
Central Nervous System - Headache, dizziness and drowsiness.
Genitourinary - Blood in urine, decrease in urination and kidney failure.
In a double blind randomized study, the analgesic effectiveness and tolerability of oral treatment with once-daily nimesulide was compared with ibuprofen q6h over 24 hours in patients with postoperative pain associated with surgical extraction of an impacted third molar and the results suggested that the analgesic effect of nimesulide had a faster onset (<15 minutes) and was stronger than that of ibuprofen[39]. The efficacy of nimesulide and meloxicam in the control of pain, swelling and trismus, following the extraction of impacted inferior third molars was compared. In conclusion, pain control was similar in both treatment groups but nimesulide was more effective than melonoxicam in the control of swelling and trismus following the extraction of impacted lower third molars[40].
Selective Cox-2 inhibitors Selective COX-2 inhibitors have the property of inhibiting COX-2 without affecting COX-1 function.
Concerns regarding selective COX-2 inhibitors

- These drugs do not have a wide range, as they do not control inflammation mediated by COX-1
- COX-2 inhibtion can be injurious to gastric mucosa as they play a protective role by producing gastroprotective Prostaglandins
- COX-2 inhibtion causes salt and water retention precipitating Congestive Heart Failure

The analgesic efficacy of preoperative rofecoxib, ibuprofen, and placebo in the control of postoperative pain after third molar surgery was compared in a clinical randomized, double-blind study and concluded that preoperative intake of rofecoxib provides a significantly better analgesic benefit than ibuprofen[41]. Daniels et al compared the efficacy of rofecoxib and valdecoxib in the treatment of acute postoperative dental pain. Rofecoxib had comparable analgesic efficacy to valdecoxib[42]. The analgesic efficacy and tolerability profile of rofecoxib with those of the centrally acting, nonsalicylate, opiate/nonopiate analgesic combination oxycodone/ acetaminophen in patients with pain after dental surgery was studied and rofecoxib was found to be associated with a significantly lower incidence of nausea and vomiting compared with oxycodone/acetaminophen[43].
Moore et al in a randomized prospective clinical trial compared the analgesic efficacy and the reduction in trismus of preoperative rofecoxib, intraoperative dexamethasone, and both rofecoxib and dexamethasone following third molar extraction surgery and showed that the combination of preoperative rofecoxib and intraoperative dexamethasone was most effective in minimizing pain and trismus following third molar surgery[19]. A systematic review of oral analgesics for third molar surgey showed that Ibuprofen, diclofenac and COX-2 inhibitors (valdecoxib and rofecoxib) offered distinct advantages over drugs such as aspirin, paracetamol and dihydrocodeine. Furthermore, the superior efficacy of these compounds was also supported by a reduced risk of unwanted effects[44].
The pre-operative administration of injectable Cyclooxygenase-2-Specific Inhibitor Parecoxib Sodium was found to be effective, safe, and well tolerated, providing significantly more analgesia[45].
Oxaprozin: Oxaprozin is a long-acting non-steroidal anti-inflammatory drug. Its available as 600mg tablets and maximum recommended dose is 1800mg/day.
Kara et al studied the efficacy of oxaprozin in terms of their effects on edema, pain, and trismus after surgery for impacted mandibular third molars and showed that administration of either oxaprozin during the postoperative period is effective in reducing pain but questionable benefit for the management of trismus and edema[46].
Lysine Clonixinate: Lysine Clonixinate is an analgesic that inhibits prostaglandin synthesis. Lysine Clonixinate showed a life span of 3 hours, and it is recognized as a non-steroid anti-inflammatory with the shortest life span when compared to other drugs of its category[47,48].
The efficacy of Lysine Clonixinate, Dipyrone and Paracetamol in controlling the postoperative pain in the surgery of inferior impacted third molars was assessed and it was founs both lysine Clonixinate and dipyrone were effective in pain control[49].
Tramadol: Tramadol Hydrochloride is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects
Dosage: Most people are recommended to start with a low dosage of tramadol, such as 25 mg (half a tablet) once daily in the morning. The usual dose is 50 to 100 mg every four to six hours as needed for pain, up to a maximum of 400 mg total per day.
Pharmacological actions

- Inhibits reuptake of Na and 5-HT and activates monoaminergic spinal inhibition of pain.
- Analgesic
- Preanaesthetic medication
- Balanced anaesthesia and surgical anaesthesia
- Relief of anxiety and apprehension

The possible mechanism by which this drug brings about pain relief as effective as NSAIDs is an interesting factor which warrants discussion. Opening of potassium channels located in the primary afferent nerve endings produces anti-nociception and represents an important step in the peripheral anti-nociceptive effect of several NSAIDs. Activation of the NO-cyclic guanosine monophosphate (GMP) pathway could also induce anti-nociception through the opening of potassium channels.
Tramadol Hydrochloride is contraindicated in:

- Individuals with known hypersensitivity to Tramadol Hydrochloride or any excipients
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs
- Patients who are taking MAO inhibitors or who have taken them within the last 14 days
- known hypersensitivity to opioids
- Patients with uncontrolled epilepsy or epilepsy not adequately controlled by treatment.

Jung et al compared the onset of analgesia and other measures of analgesic efficacy of a combination of Tramadol Hydrochloride and acetaminophen and other strong combination analgesics for the management of acute pain. The study concluded that the combination of Tramadol Hydrochloride and acetaminophen provided rapid and effective analgesia for acute postoperative dental pain[50].

Studies have reported that intra-muscular (IM) administration of tramadol pre-emptively offered better pain relief than post-operative administration via the same route[8]. It has also been shown that intra-venous (IV) tramadol provides better pain relief than oral tramadol. But administration of tramadol via the IM or IV routes could result in side effects like depression and sedation[13]. In a study of the effects of Tramadol Hydrochloride on dentoalveolar surgical pain by Collins et al, 39% of patients on high doses of Tramadol Hydrochloride (100 mg 4 times a day orally), 12% on moderate doses (50 mg 4 times a day), and 6% on low dose (50 mg 2 times a day) withdrew from the study owing to nausea, vomiting, dizziness, or drowsiness[51].

Ketamine: Ketamine is an anesthetic agent which acts on the central nervous system and produces dissociative anesthesia. It has been found to produce profound analgesia.

Local anesthetic combined with sub-anesthetic ketamine for the relief or prevention of postoperative pain, swelling, and trismus after the surgical extraction of third molars was studied and it showed that this combination produced good local anesthesia while affording a comfortable procedure for the surgeon and patient and providing good postoperative analgesia with less swelling and significantly less trismus[52]. The clinical efficacy of midazolam plus low-dose ketamine conscious intravenous sedation on relief from or prevention of postoperative pain, swelling, and trismus after the surgical extraction of third molars was analysed.and concluded that intravenous low-dose ketamine may be safe and effective in reducing postoperative pain[53].

Narcotics: Narcotic agents are at some hospitals the standard for relief of postoperative pain, but these drugs are often inappropriate for use in day-case hospitals since, they can cause respiratory depression, nausea.

Dexmedetomidine is an alpha 2-adrenoreceptor agonist, which provides sedation, analgesia, and anxiolysis in clinical practice[54]. Activation of central alpha 2-adrenoreceptors in the locus ceruleus2 is responsible for both analgesic and sedative effects[55]. In a study by Cheung et al it was found that intranasal Dexmedetomidine produced improved postoperative analgesia for unilateral third molar surgery under local anaesthesia and there was no increase in complications or delay in psychomotor recovery[15].

CONCLUSION

The pain and discomfort associated with third molar surgery is as a result of inflammatory sequelae and therefore, non-steroidal anti-inflammatory drugs remain the first choice of analgesics. For whom non-steroidal anti-inflammatory drugs are contraindicated, synthetic opioids such as tramadol has been found as effective alternative. These drugs produce significant pain relief and improve the quality of patient's life in the immediate post-operative period.

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