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Effectiveness and Safety of Analgesics in Oral and Maxillofacial Surgery using Cox-2 Selective Inhibitors: A Review

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ABSTRACT:-

Background: In surgical outpatients, nonsteroidal anti-inflammatory medications (NSAIDs) are the most often given analgesics. The main drawbacks of NSAIDs are renal failure, hemostatic function impairment, and gastrointestinal (GI) side effects (perforation, ulceration, and bleeding) (with long-term therapy). The COX-2 selective inhibitors (CSIs or Coxibs), a novel family of NSAIDs, were created with the intention of lowering the GI side effects of conventional NSAIDs while keeping their potent anti-inflammatory and analgesic qualities. This narrative review of the literature examines the effectiveness of CSIs as analgesics, their clinical safety, and their cost-benefit analysis in the management of pain following oral surgery.

Keywords*:* Oral Pathology, RadiolEndod Oral, Oral Surgery, Oral Medicine

INTRODUCTION: -

The delivery of optimal level of basal constitutive expression only occurs in the female reproductive system, bone, kidneys, and brain neurons where it may be up-regulated. In contrast, in most tissues, it may be inductively expressed by inflammatory cytokines and growth factors in response to tissue injury and inflammation. Effective pain control in dentistry, including oral-maxillofacial surgery, is crucial for the delivery of optimal level of basal constitutive expression (such as a surgical trauma).In animal research, the oral cavity-

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mucosa expresses COX-2 inductively within 2-4 hours of a trauma and within 1-2 hours of surgery, which causes the postoperative pain to start suddenly.

NSAIDS and COX-1 inhibition Due to the widespread expression of COX-1, gastrointestinal (GI) toxicity is the primary clinical drawback of conventional NSAIDs (especially with long-term therapy). As a result, up to 4% of patients annually and up to 20% of those taking long-term NSAIDs experience upper GI adverse events, such as perforation, ulceration, and bleeding. Additionally, up to 4% of NSAID users experience major GI side effects that necessitate hospitalization, which makes clinicians reluctant to prescribe nonselective NSAIDs to patients who are at a higher risk of experiencing such events. [7,8]

Selective COX-2 inhibitors the US Food and Drug Administration (FDA) approved a new class of NSAIDs called COX-2 selective inhibitors (CSIs or Coxibs) in 1999 with the goal of minimizing the GI side effects of NSAIDs that result from the inhibition of COX-1. The advantages of CSIs in terms of GI safety and their selective suppression of the production of inflammatory mediators may be explained by the distinct functions and localizations of the two COX isoforms. This article's goals are to examine and critically analyse evidence from well-designed studies on the clinical safety and analgesic efficacy of CSIs in the management of acute pain following oral surgery as well as to provide a cost-benefit analysis of their use in oral-maxillofacial surgery. [9]

Search Technique

On MEDLINE/PubMed, from peer-reviewed journals in medicine and dentistry, pertinent drug and clinical trials of the use of CSIs in the treatment of acute, post-oral surgery pain were found. Numerous dental publications and the bibliographies of pertinent studies were searched manually. On the FDA website, data on the tolerability of CSIs were looked up. In April 2003, the final electronic search was carried out.

Selection standards

According to the CONSORT criteria, relevant randomized, controlled clinical trials investigating the use of CSIs in the treatment of acute pain were chosen by the authors through a quality evaluation of the study's planning and execution.

Clinical Experiences with Pain Relief Following Oral Surgery

Clinical trials in which CSIs are compared to conventional NSAIDs or a placebo have provided information on the efficacy and tolerability of CSIs as analgesic drugs in the treatment of post-oral surgery pain. The majority of the research are based on the postoperative dental impaction pain model, which is a recognized, accurate, and established method for evaluating the effectiveness of novel analgesic medications in people. Celecoxib (Celebrex, Solexa, Artilog) and rofecoxib (Vioxx, Coxxil, Arofexx), both of which are currently marketed in the United States and Europe, are examples of 9-11 CSIs. Second-

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generation agents like valdecoxib (Bextra), parecoxib (Dynasta, Rayzon, Xapit), etoricoxib (Arcoxia), and lumiracoxi.

Both Rofecoxib and Celecoxib

The FDA has approved celecoxib (the original Coxib) and rofecoxib for the management of inflammatory chronic pain associated with osteoarthritis, rheumatoid arthritis, and acute pain associated with primary dysmenorrhea. Adults have been the subjects of several high-quality trials for the management of moderate to severe postoperative tooth pain. [1, 2]Research has revealed that administering NSAIDs preoperatively can greatly lower the intensity and duration of postoperative pain for up to 8 hours. [5]Rofecoxib is being studied in a phase II trial of preemptive analgesia for the treatment of postoperative dental pain (extraction of impacted third molars) because it has been shown to enter the central nervous system, where it may inhibit the constitutive COX-2 enzyme. The goal of this trial is to prevent the development of central and peripheral sensitization to pain rising after a tissue injury and later manifesting as hyperalgesia. [7]

CSIs of the second generation

A single oral dose of valdecoxib (40 mg) was superior to rofecoxib (50 mg) in a study of postoperative dental pain in terms of the time it took to start reducing pain, how long it lasted, and the proportion of patients who needed rescue medication. [3, 10] In a related study, valdecoxib (40 mg) was found to have an overall analgesic efficacy comparable to that of a fixed formulation of oxycodone (10 mg)/acetaminophen (paracetamol) (1000 mg); however, valdecoxib was found to be better tolerated and to produce an analgesic duration that was noticeably longer than that of oxycodone/acetaminophen. The safety profile of valdecoxib was superior to that of conventional NSAIDs in a meta-analysis of 8 randomized, controlled studies, as evidenced by a lower incidence of adverse events. Preemptive analgesia for the management of pain following oral surgery has been demonstrated to be successful with valdecoxib, suggesting an inhibitory activity of the central nervous system's constitutive COX-2 enzyme.

The only Coxib that is accessible for intravenous or intramuscular injection is parecoxib, which is a prodrug of valdecoxib. Paracecoxib (20–40 mg) demonstrated greater analgesic efficacy to morphine (4 mg) and comparable analgesic efficacy to ketorolac (30–60 mg) in studies of acute pain following orthopedic or dental surgery. [3, 5]Paracecoxib (40 mg) has been shown to be a more effective analgesic than a placebo when given preoperatively. [3, 6]Paracecoxib may be an alternative to the few parenteral NSAIDs (such as ketorolac [Toradol]) available for the treatment of moderate to severe postoperative pain in cases of postoperative nausea and vomiting or where the oral route for administration is inaccessible (such as after oralmaxillofacial surgery).

Etoricoxib demonstrated stronger analgesic efficacy (TOPAR8) than the combination of codeine and acetaminophen in two investigations of postoperative dental pain, with analgesic

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efficacy (TOPAR8) comparable to naproxen or ibuprofen and a duration of analgesic action longer than that of comparative NSAIDs. Compared to other NSAIDs, etoricoxib has been linked to fewer upper gastrointestinal problems. [3, 8]

Limitations of CSIS and clinical safety

Although NSAIDs can reach high concentrations in inflammatory tissues, which accounts for their analgesic and anti-inflammatory effectiveness, they can also reach high concentrations in the blood, stomach wall, and kidney cortex, which causes the well-known GI, renal, and platelet side effects. [10] Because COX-2 has been discovered to be constitutive in the brain, female reproductive system, kidneys, and bone, CSIs spread uniformly throughout the body, which is concerning. Dentists, including oral-maxillofacial surgeons, should be aware of the potential effects of these medications on the hemostatic function and physiology of bone fracture and wound healing in addition to the safety profile of CSIs dealing with the upper GI tract and kidneys.

NSAIDs' gastrointestinal adverse effects can include bleeding and perforation, which can be fatal, as well as nausea, dyspepsia, gastroduodenal ulcers, and other conditions. More than 39,000 patients with chronic pain (osteoarthritis and rheumatoid arthritis) in four large studies of CSIs, the VIGOR trial (Vioxx), the CLASS trial (Celecoxib), the ADVANTAGE trial (Vioxx and Naproxen), and the SUCCESS trial (Celecoxib), examined the GI safety profile of rofecoxib and celecoxib in various patient populations with an age. [14]

Since both COX-isoforms are constitutively expressed in the human kidney, CSIs have a renal safety similar to that of traditional NSAIDs. In the renal cortex, COX-2 enzyme increases in response to a high salt diet and water deprivation, therefore a high degree of COX-2 inhibition can alter renal blood flow, urine formation, and salt and water homeostasis, thus leading to hypertension. [2] Data from the FDA's Adverse Event Reporting System (AERS) database indicate that the renal tolerability of CSIs in patients with normal or impaired renal function is similar to that of traditional NSAIDs, even after short-term therapy. [3,4] Patients at risk for severe renal adverse events with CSIs are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly.

Until new platelets are formed, aspirin has an irreversible inhibitory effect on platelet activity. Traditional NSAIDs increase the risk of perioperative bleeding by reversibly inhibiting platelet aggregation and lengthening the bleeding period (by reducing platelet synthesis of thromboxane). Platelet aggregation is not affected by rofecoxib or valdecoxib, and rofecoxib does not change aspirin's antiplatelet action. [6-8]These results imply that CSIs may be administered in perioperative situations and to patients taking concurrent low-dose aspirin for the prevention of cardiovascular events more safely than standard NSAIDs.

In experimental animal models, nonselective NSAIDs like indomethacin appear to slow but not halt fracture repair. [5] Both rofecoxib and celecoxib inhibited normal fracture healing

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and caused the development of incomplete unions in an experimental animal study looking into the function of COX-2 inhibitors in bone fracture healing. This finding suggests that COX-2 activity is necessary for a normal endochondral ossification during fracture healing. While the amount of celecoxib used (280 mg/70 kg) was within the range of the daily dose range for humans, the total amount of rofecoxib used to treat the rats (200 mg/70 kg) was around four times the maximum daily dose of 50 mg that is advised to control acute pain in humans (200 mg twice a day).

Celecoxib is metabolized by the cytochrome P450 enzyme system, while rofecoxib is reduced by cytosolic enzymes, just like nonselective NSAIDs.

Rofecoxib would be less likely to interact with other medications than celecoxib since it does not affect the metabolism of medications metabolized by the P450 isozymes. [15] Rofecoxib can be administered safely to aspirin-allergic individuals due to its absence of cross-reactivity in aspirin-sensitive patients. Numerous combinations between CSIs and oral anticoagulants have been reported to enhance the risk of bleeding. [15]

Ratio of cost/benefit

The clinical advantage of these medications is essentially based on their lack of major GI side-effects, as numerous clinical trials have shown that CSIs have analgesic efficacy comparable to that of standard NSAIDs. The use of CSIs may result in cost savings, even if the prices of the currently available CSIs, rofecoxib and celecoxib, are significantly higher than those of generic and over-the-counter NSAIDs. In fact, CSIs should reduce indirect expenses of diagnostic and therapeutic procedures needed to manage potential GI impairment (coming from long-term NSAID medication) because they have less GI problems than NSAIDs. In comparison to naproxen-treated VIGOR study participants, rofecoxib-treated patients required less upper GI diagnostic procedures (biopsies or endoscopies), comedications (antacids, histamine 2-receptor antagonists, proton pump inhibitors, sucralfate, or prostaglandins), and hospitalizations. [10] These findings imply that CSIs are a cost-effective therapy option for people who are more likely to experience major gastrointestinal adverse events linked to NSAIDs. They also suggest that they may help patients using long-term analgesic and anti-inflammatory medicines live better lives. [6]

Despite this, it is unclear that the short-term use of CSIs will produce considerably greater patient tolerance and a cost-savings benefit than that seen with conventional NSAIDs for the treatment of acute post-oral surgery pain.

CONCLUSIONS:-

The ideal CSI would exhibit efficacy on par with or better than the best NSAID, be less gastrotoxic than the safest conventional NSAID, have no impact on hemostatic function, and have minimal or no adverse effects on the cardiovascular system or the kidneys. There is solid proof that the prescription CSIs celecoxib and rofecoxib exhibit analgesic efficacy

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comparable to that of conventional NSAIDs (such as ibuprofen or naproxen) when used to treat acute, post-oral surgery pain. According to the Australian COX-2-Specific Inhibitor Prescribing Group, which recently sought to develop evidence-based clinical practice guidelines, these new medications are preferable in patients who are at an increased risk of experiencing serious upper GI complications (with long-term medications), in patients who take aspirin for cardiovascular comorbid conditions, and in patients who are allergic to aspirin. Furthermore, because CSIs do not interfere with platelet aggregation, they may be administered more safely than NSAIDs in perioperative conditions.

To sum up, there are certain significant benefits and drawbacks to take into account before recommending a CSI to patients having oral-maxillofacial surgery: (1) In the short-term treatment of acute, postoperative dental pain, CSIs are equivalent to traditional NSAIDs (such as ibuprofen or naproxen); (2) CSIs exhibit a longer duration of analgesic effect than aspirin, acetaminophen, and ibuprofen; (3) CSIs are linked to a lower incidence of upper-GI complications, especially bleeding; and (4) CSIs do not inhibit platelet.

REFERENCE:-

1. Fu JY, Masferrer JL, Seibert K, Raz A, Needleman P. The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes. J BiolChem 1990;265:16737-
2. Pairet M, Engelhardt G. Distinct isoforms (COX-1, COX-2) of cyclooxygenase, possible physiologic and therapeutic implications. FundamClinPharmacol 1996;10:1-17.
3. Simon AM, Manigrasso MB, O'Connor JP. Cyclooxygenase-2 function is essential for bone fracture healing. J Bone Miner Res 2002;17:963-76.
4. Komhoff M, Grone HJ, Klein T, Seyberth HW, Nusing RM. Localization of cyclooxygenase-1 and -2 in adult and fetal human kidney: implication for renal function. Am J Physiol 1997; 272(4 Pt 2):F460-8.
5. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ. Interleukin-1beta-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410(6827):471-5
6. Desjardins PJ, Grossman EH, Kuss ME, Talwalker S, Dhadda S, Baum D, et al. The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. AnesthAnalg 2001;93(3):721-7.
7. Riendeau D, Percival MD, Brideau C, Charleson S, Dube D, Ethier D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J PharmacolExpTher 2001;296(2):558-66.
8. Cochrane DJ, Jarvis B, Keating GM. Etoricoxib. Drugs 2002; 62(18):2637-51.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

9. Stichtenoth DO, Frolich JC. The second generation of COX-2 inhibitors: what advantages do the newest offer? Drugs 2003; 63(1):33-45.

10. Brune K, Neubert A. Pharmacokinetic and pharmacodynamic aspects of the ideal COX-2 inhibitor: a pharmacologist's perspective. ClinExpRheumatol 2001;19(6 Suppl 25):S51-7.

11. Scheiman JM. Outcomes studies of the gastrointestinal safety of cyclooxygenase-2 inhibitors. Cleve Clin J Med 2002;69(Suppl 1):SI40-6.

12. Harris RC Jr. Cyclooxygenase-2 inhibition and renal physiology. Am J Cardiol 2002 Mar 21;89(6A):10D-7D.

13. US Food and Drug Administration. Celebrex capsules (celecoxib) NDA 20-998/S-009 Medical Officer Review

14. US Food and Drug Administration. NDA 21-042, s007, Vioxx gastrointestinal safety-Medical Officer Review. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/ 3677b2-03-med.doc. Accessed June 2002.

15. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. Am J Med 1999;106(Suppl 5B):25S-36S