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Pharmacological efficacy of non steroidal anti inflammatory drugs in management of post operative dental pain: A review

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ABSTRACT

Since pain has been reported to occur in 25%–40% of patients treated for endodontics procedure, it is a major concern for dentists and their patients. Hence in dentistry, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed to treat pain and swelling. The most frequently used of these medications are ibuprofen and paracetamol. They work by inhibiting the enzyme cyclooxygenase, which then prevents the production of prostaglandins. All of these medications exhibit a comparable mode of action, which causes them to have comparable side effects. The present article reviews the knowledge currently available on NSAIDs with a focus on dental practice-related elements.

KEYWORDS

Analgesia, dental, nonsteroidal anti-inflammatory drugs, pain

INTRODUCTION

For dentists and their patients, postoperative pain following root canal therapy is a serious unfavourable complication. According to estimates, post-endodontic pain affects between 3% and 58% of people. Different degrees of discomfort can be felt by patients undergoing orthodontic tooth movement, particularly in the days immediately following the placement or adjustment of orthodontic devices.(1) Therefore, it is crucial to control post operative pain both during and after a root canal, fixed orthodontic and other dental surgical procedure. In this regard, a variety of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, cyclooxygenase-2 enzymes (COX-2 inhibitors), and drug combinations, have been used to treat post operative dental pain.(2)

NSAIDs, or nonsteroidal anti-inflammatory drugs, are frequently prescribed to treat dental pain. The NSAIDs are a diverse class of medications that fall somewhere between corticoids, which have anti-inflammatory properties, and major analgesics, such as opioids. They have analgesic, antipyretic, and anti-inflammatory properties.(3-6) A little bit more than 30% of all NSAID prescription costs were for ibuprofen.(6) NSAIDs have no impact on circulating molecules, but they do reduce inflammation, inhibit cyclooxygenase enzymes, and stop the production of new prostaglandin molecules.(2)

These medications are frequently used for self-medication, and while they are generally safe, some have significant side effects like upper gastrointestinal bleeding, gastroduodenal ulcers that can be seen under a microscope, or an increased risk of vascular accidents like acute myocardial infarction.(6)

CLASSIFICATION

There are numerous analgesics on the market right now. Opioid and non-opioid analgesics are two different categories of analgesics. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are examples of non-opioid analgesics. NSAIDs are further divided into selective cyclooxygenase (COX)-2 inhibitors and non-selective traditional non-steroidal anti-inflammatory drugs (tNSAIDs).(7)

Aspirin, diflunisal, ibuprofen, naproxen, ketoprofen, flurbiprofen, indomethacin, sulindac, etodolac, diclofenac, ketorolac, piroxicam, mefenamic acid, and nabumetone are among the tNSAIDs that are currently on the market.(7,8)

The NSAIDs exhibit distinct differences in biochemical structure and origin, but they share a similar mechanism of action, which leads to similar side effects. This circumstance is referred to as a "group effect." The differences are to be found in each drug's half-life, which helps and define the appropriate dosing intervals, and in each NSAID's relative potency, which determines how much drug substance needs to be administered in each dose. Table 1 indicates Systemic nonsteroidal antiinflammatory drugs (NSAIDs) classification. Table 2 in turn reports the most commonly used NSAIDs, specifying the commercial product and the adult and pediatric doses.(6)

Table 1: Classification of systemic nonsteroidal antiinflammatory drugs (NSAIDs)

GROUP	**DRUG SUBSTANCE**
Butylpyrazolidines	Phenylbutazone
Acetic acid derivatives	Acemetacin,Aceclofenac , Diclofenac, Indomethacin, Ketorolac
Oxicams	Meloxicam , Lornoxicam , Piroxicam , Tenoxicam
Propionic acid derivatives	Dexketoprofen , Dexibuprofen , Ibuprofen , Fluribuprofen , Ketoprofen , Naproxen
Fenamates	Mefenamic acid, Niflumic acid
Coxibs	Celecoxib , Etoricoxib , Paracoxib
Pyrazolones	Metamizol
Anilides	Paracetamol
Salicylic acid derivatives	Acetyl salicylic acid , Fosfosal

Table 2 : Most commonly used NSAIDs in dentistry

Drug substance	**Commercial product**	**Dosing form**	**Adult dose**	**Pediatric dose**
Acetylsalicylic acid	Ascad, Zorprin	Tablets	500 mg/4-6 h	--

Diclofenac	Voveran, Tromax	Tablets Suppositories Injection	50 mg/8 h po 75 mg/24 h im	NOT recommended
Ibuprofen	Alfam, Brufen,	Tablets Oral suspension Suppositories	400-600 mg /6-8 h	20 mg/kg/day in 3-4 doses
Ketorolac trometamol	Ketorol, Ketroc	Tablets Solution for injection	20 mg in starting dose + 10 mg/4-6 h po 10-30 mg/4-6 h im or iv	NOT recommended under age 16 years
Piroxicam	Brexic, Doloage	Tablets Suppositories , injection	40 mg/day on first day 20 mg/day on following days	NOT recommended
Paracetamol	Albimol, aminol, Bepamol, calpol	Tablets Sachets Infusion iv, drops, Suspension Suppositories	325-650 mg/4-6 h 1 g/8 h	10 mg/kg every 4 h 15 mg/kg every 6 h
Mefenamic acid	Colispas Forte, Meftagesic –DS, Meftagesic Susp	Tablete, syrap, suspension	100mg/ 250mg/ 5ml	250-500 mg/kg in 2-3 doses
Celecoxib	Celebrex	Capsules	200 mg/12-24 h	Not evaluated in children

Ibuprofen

The NSAID class's original drug, ibuprofen, has shown analgesic activity at doses between 200 and 800 mg for periods lasting 4 to 6 hours. A 400 mg dose of ibuprofen has been found to be superior to 650 mg of aspirin, 600–1000 mg of acetaminophen, and aspirin–acetaminophen–codeine combinations with 60 mg of codeine. The NSAID class of analgesics' original member, ibuprofen, was first used in clinical settings in the US in 1974. During the first two to three days following surgery, when edoema formation linked to the inflammatory process is most noticeable, lbuprofen reduces swelling. NSAIDs may alter the neurohumoral reactions to pain, according to interactions with the release of, B-endorphin that have been shown to occur both intraoperatively during surgical stress and during post-operative pain.(1)

An NSAID and an opioid together typically have only modest analgesic effects but are more likely to cause side effects. The therapeutic effects of conventional NSAIDs may be achieved with the new generation of selective cyclo-oxygenase (COX)-2 inhibitors, but these have not been sufficiently studied for dental indications or in large numbers of subjects.(1)

Ibuprofen 200 mg or naproxen 200-225 mg individual dose are the preferred NSAIDs for the treatment of mild odontogenic pain. The combination of ibuprofen or naproxen with paracetamol is more effective than each NSAID agent alone in treating patients with chronic mild dental pain. In conditions where NSAIDs are contraindicated, 500–1000 mg of paracetamol is the recommended dosage. Due to its interference with platelet aggregation, acetyl salicylic acid is not the drug of preference for treating dental pain, and patients with heart disease receiving this drug should be treated with caution.(9)

Acetaminophen

One of the most popular analgesic antipyretic drugs, acetaminophen (also known as paracetamol), has very little anti-inflammatory activity. Although acetaminophen has a long history of use as a pain reliever, its exact mode of action is still unknown. The current theory holds that while tNSAIDs inhibit the COX activity of the COX enzyme, acetaminophen inhibits the peroxidase activity of COX at low peroxide levels. Because the peroxide level is much higher at peripheral inflammatory sites than in the brain, acetaminophen acts preferentially within the central nervous system without peripheral anti-inflammatory activity. Acetaminophen is less likely than tNSAIDs to cause gastrointestinal and cardiovascular side effects and does not prolong bleeding time due to its lack of an inhibitory effect on peripheral COX activity. Acetaminophen does not raise the risk of Reye syndrome, which harms the brain and liver in kids recovering from viral infections, unlike aspirin. There are no notable restrictions on acetaminophen use in pregnant women. Because of the side effects of tNSAIDs, such as the increased risk of gastrointestinal ulcer disease, acetaminophen is particularly suitable for patients who cannot use tNSAIDs.(7)

Aspirin

Aspirin differs from non-aspirin tNSAIDs, which are competitive reversible COX inhibitors, in that it inhibits COX irreversibly. Because of aspirin's irreversible mode of action, which prevents platelets from producing thromboxane A2 for the duration of their circulation, the antithrombotic effect of aspirin may last for 5 to 7 days. Other tNSAIDs reversibly inhibit COX, so that as their plasma concentrations fall due to metabolism and excretion, so does their antiplatelet effect. Because prostaglandins are involved in the maintenance of renal function in addition to their antithrombotic effects, dentists should exercise caution when prescribing tNSAIDs to patients with impaired renal function.(7)

Naproxen

Ibuprofen and naproxen are both derivatives of propionic acid, but naproxen has a longer half-life. It comes in two different formulations, the sodium salt of which is more quickly absorbed than naproxen. The different formulations shouldn't be used concurrently because the naproxen anion, which they both circulate as in plasma, increases the likelihood of dose-related side effects due to the additive plasma concentration. With subsequent doses of 250 to 275 mg administered at six- to eight-hour levels, a 500–550 mg initial loading dose is used to achieve therapeutic levels more quickly. With fewer side effects, a single 550 mg dose of naproxen sodium has more analgesic activity than a 650 mg dose of aspirin.(1)

Ketoprofen

Ketoprofen shares chemical similarities with other derivatives of propionic acid that have analgesic and antipyretic properties. It inhibits prostaglandin and leukotriene synthesis, acting peripherally like other NSAIDs, but it also may have a central effect.(1)

Ketorolac

The first NSAID approved for intramuscular use in the short-term treatment of moderate to severe pain is ketorolac. It has also been used successfully in a few paediatric cases and has been given approval for intravenous administration. Ketorolac is also available as an oral medication that should be taken at a dose of 10 mg every 4 to 6 hours with a maximum daily dose of 40 mg. FDA labelling changes advised against using oral ketorolac until the injectable form has been used first. A single oral dose of 10 mg of ketorolac is more effective for treating oral surgery pain than 600 mg of acetaminophen or 600 mg plus 60 mg of codeine.(1)

Piroxicam

Piroxicam is an oxicam NSAID; it can be taken once daily and has a plasma half-life of 45 hours, with peak plasma concentration occurring 2 to 4 hours after oral administration (Insel, 1996). Piroxicam has been shown to produce analgesia that is roughly equivalent to the effects of aspirin 648 mg in single doses of 20 to 40 mg.(1)

GENERAL MECHANISM OF ACTION

NSAIDs block the activity of cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostaglandins and thromboxanes, which are chemical compounds known as eicosanoids because their precursors have 20 carbon atoms. Fundamentally, arachidonic acid is found in phospholipid-bound form in the cell membrane. Arachidonic acid is released and metabolised in response to physical, chemical, or mechanical stimuli (tissue damage, hypoxia, immune processes, etc.). Prostaglandins and thromboxanes, the resulting metabolites, have an impact on nearly all body organs and tissues. Prostaglandins typically have strong vasodilating effects in relation to inflammation, which increases vascular permeability and causes extravasation of fluids and white blood cells, all of which contribute to inflammation. Thus, cyclooxygenase synthesis inhibition clearly has an anti-inflammatory effect.(6) Anti-inflammatory therapy was the identification of two different forms (isoenzymes) of cyclooxygenase: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).(6)

COX-1, which is present in the majority of organs and tissues, is connected to general homeostasis (constitutive isoenzyme). COX-2, in contrast, is not found in tissues and only manifests in response to specific stimuli (inducible isoenzyme). Drugs known as "coxibs" or selective COX-2 inhibitors have been developed on the premise that selective COX-2 inhibition would result in the desired anti-inflammatory effects without the undesirable side effects (especially at the gastric level) associated with COX-1 inhibition.(6)

Both directly from their actions on the central nervous system and indirectly from the reduction of inflammation, NSAIDs have analgesic effects (CNS)(6)

COX-2 Inhibitors

It has been determined through research into the pathophysiology of inflammatory pain that there are at least two variations of the cyclooxygenase enzyme that are in charge of producing the byproducts of the arachidonic acid cascade. One type, known as COX-1, is in

charge of the prostaglandins' typical homeostatic actions in the GI tract, which include maintaining the integrity of the mucosa, starting platelet aggregation, and controlling blood flow to the kidneys. Initially, it was believed that the other form, COX-2, was only activated during inflammation and that it was responsible for the pain, edoema, and tissue damage connected to acute inflammation, rheumatoid arthritis, and osteoarthritis. The COX-2 enzyme is now understood to be expressed in the kidneys and brain as well, where it may have unidentified physiological functions. Based on information provided to the FDA Arthritis Advisory Committee, celecoxib and rofecoxib both seem to have a lower risk of causing gastrointestinal perforations, ulcers, and bleeding than conventional NSAIDs like ibuprofen, diclofenac, and indomethacin.(1)

Selective COX-2 inhibitors: The tNSAIDs that cause NSAID-induced gastropathy, nephropathy, and prolonged bleeding time inhibit COX-1. To prevent the negative gastrointestinal and bleeding-related effects brought on by COX-1 inhibition, selective COX-2 inhibitors were created. Numerous COX-2 inhibitors, also known as coxibs, have been developed; however, some medications, including rofecoxib, have been taken off the market due to such cardiovascular side effects. Celecoxib, etoricoxib, and polmacoxib are now accessible in Korea. COX-2 inhibitors are said to have similar anti-inflammatory, analgesic, and antipyretic effects to tNSAIDs.(7)

ANALGESIC POTENCY AND EFFICACY

The majority of studies in which an NSAID is given orally after the onset of pain show that activity begin within 30 minutes and peaks 2 to 3 hours after drug administration.(1)

There are numerous publications in the literature that compare the relative effectiveness of one or more NSAIDs when applied to a particular disease process, either alone or in combination with other medications. Numerous articles also examine the analgesic effectiveness of NSAIDs in the treatment of swelling and pain resulting from the extraction of third molars. No classification of the analgesic-anti-inflammatory efficacy of the various NSAIDs has been established that is comparable to that created for corticoids. The NSAIDs, however, have a "ceiling effect" that prevents additional dose increments from producing a stronger analgesic effect after the maximum advised dose has been administered. As a result, the various NSAIDs have equivalent effectiveness when taken as a whole daily.(6)

There were no statistically significant differences in the mean pain reduction among the different options, despite the fact that the combination of paracetamol and diclofenac was the first to achieve significant pain relief and induced the greatest reduction in pain (as measured by a visual analogue scale, or VAS).(6)

In both oral surgery and general surgery, the preoperative administration of NSAIDs seems to be more effective for the control of pain than the postoperative administration. The central and peripheral nervous systems' reactions to the harmful stimuli would be lessened by the decrease in prostaglandin production, according to biological theory. This decreased sensitivity to pain may lessen central and peripheral sensitization phenomena and, as a result, the patient's reaction to subsequent painful stimuli.(6)

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SIDE EFFECTS

Since not all of the effects described are negative, it is preferable to use the term "side effects" rather than "adverse effects," as will be explained below. The various NSAIDs all generally work in a similar manner, and as a result, their side effects are also comparable. The most frequent use of NSAIDs is associated with arthrosis-arthritis, usually in elderly patients who are on long-term treatment plans.(6)

Gastrointestinal alterations

All NSAIDs, to some extent or another, are linked to gastrointestinal changes. Up to 50% of patients who regularly use these medications report experiencing nausea or dyspepsia, and 40% of those who take NSAIDs for three months experience endoscopically visible ulcerations, even though the majority of these lesions do not manifest clinically. There is no link between dyspepsia symptoms and serious side effects like gastrointestinal bleeding or intestinal perforation. According to estimates, chronic treatments have a 15% and 5% incidence of gastric or duodenal ulceration, respectively.(6)

Ibuprofen was found to have the lowest risk of gastrointestinal toxicity in a meta-analysis by Henry et al. that assessed the risk of serious gastrointestinal complications (hospital admission due to bleeding or perforation) associated with 12 widely used NSAIDs. In contrast, some NSAIDs' relative risks (RR) compared to ibuprofen (RR=1) rose as high as 3.8 (piroxicam) and 4.2. (ketoprofen). Diclofenac ranked second in this study for least harmful drugs. In this study, acetylsalicylic acid (aspirin), indomethacin, naproxen, sulindac, and ranked intermediate. A similar increase in gastrointestinal toxicity to that of naproxen or indomethacin is linked to the use of higher ibuprofen doses.(10)

Cardiovascular complications

Acute myocardial infarction is listed in the Summary of Product Characteristics as a rare (0.01%) side effect of rofecoxib, but clinical use of the medication was linked to an increase in the number of vascular incidents, including acute myocardial infarction and stroke. As a result, in September 2004 the marketing company pulled the drug off the shelves.(6)

Antiplatelet action

The conventional NSAIDs' non-selective inhibition of cyclooxygenase results in a decrease in the production of thromboxane A2, which in turn prevents platelet aggregation, a crucial step in hemostasia. This is especially important for a specialty like dentistry that involves surgical procedures. Because the platelets are unable to produce cyclooxygenase, aspirin causes an irreversible toxic effect that lasts for the entirety of the platelet's life (7–10 days) while the effects of the other NSAIDs are reversible.(6)

When contemplating surgery, it is advisable to suppress NSAID medication according to the protocol recommended by the United States Food and Drug Administration (FDA):

- 4-5 days before the intervention in the case of aspirin
- 3-4 days before in the case of NSAIDs administered once a day
- 2-3 days before in the case of those administered 2-3 times a day
- 1-2 days before in the case of those administered 4-6 times a day

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Effects on blood pressure

Arterial hypertension is another side effect of NSAIDs (AHT). The use of other NSAIDs was linked to relative risks of 1.78 and 1.60, respectively, while the use of paracetamol over 500 mg/day was found to be associated with an increased risk of AHT (RR=1.93 in women between 51 and 77 years of age and 1.99 in women between 34 and 43 years of age). Although earlier studies had suggested a connection between aspirin use and arterial hypertension, the study in question found no evidence to support this.(6)

Kidney toxicity

Acute renal toxicity caused by an NSAID in people with normal kidney function is essentially nonexistent. Prostaglandin synthesis is increased in the kidneys of patients with reduced renal perfusion (due to hypotension, cirrhosis, congestive heart failure, use of diuretics, or blood loss), in order to increase the filtration rate and ensure an adequate renal flow. However, renal hypoperfusion, nephrotic syndrome, or interstitial nephritis can result from NSAIDs' inhibition of prostaglandin synthesis. For indomethacin and phenylbutazone, the risk is high; for naproxen, ibuprofen, diclofenac, piroxicam, and aspirin; and for paracetamol, the risk is minimal.(6)

Use of NSAIDS in Pregnancy

A significant portion of the blood flow from the pulmonary arteries is diverted to the descending aorta by the ductus arteriosus. The duct typically functionally seals off right away after delivery. Although it is advisable to prescribe the medication after consulting with an obstetrician, paracetamol is safest drug during pregnancy (6)

USE OF NSAID IN DENTISTRY

Use for chronic temporomandibular pain

Since more definitive treatments are expected to eventually correct the underlying pathophysiologic process, pharmacologic intervention is typically regarded as adjunctive to definitive treatment in the management of chronic orofacial pain. Many alleged dental and surgical treatments for temporomandibular disorders (TMD) are now acknowledged to have fallen short of rigorous scientific testing. Due to this, some types of chronic orofacial pain are now treated primarily with drugs. When pain is not adequately controlled after trying unsuccessful treatments, such as surgical interventions, or when there are no other options for treatment, palliative management of intractable pain may also be considered as an indication for pharmacologic management. (1)

Effects on Edema

Other symptoms of inflammation brought on by tissue damage are also present in the acute post-operative sequelae of dental procedures, with edoema standing out. The ability of synthetic analogues of endogenous corticosteroids to suppress the immune system, which raises the risk of infection, restrains their use post-operatively even though they are widely used to control the effects of both acute and chronic inflammation. Since NSAIDs have a more favourable side-effect profile than glucocorticoids and a more selective mechanism of action, it is possible that these medications will be able to reduce inflammation without the side effects associated with corticosteroid use.(1)

NSAIDS as adjuncts to periodontal therapy

The use of non-surgical pharmacotherapy as an adjunctive treatment for periodontal disease has attracted a lot of attention over the past ten years. Numerous studies have looked

at the use of antibiotics as a supplement to conventional periodontal therapy to lower the number of potential periodontal pathogens. Additionally, the host response to periodontal disease has been altered by the use of NSAIDs. The link between prostaglandins and gingivitis and alveolar bone loss is widely accepted.(1)

Recommendations for the use of NSAIDS in dentistry

NSAIDs, along with aspirin, acetaminophen, and codeine, are some of the most commonly prescribed medication classes for dental pain. Due to the inflammatory aetiology of the majority of dental pain and the NSAIDs' prominent anti-inflammatory effects, they are typically more effective than these standard medications in most studies. For ambulatory patients, who typically experience a higher incidence of side effects after ingesting an opioid, a single dose of 400 to 600 mg of ibuprofen is usually more effective and has fewer side effects than combinations of aspirin or acetaminophen plus an opioid, typically codeine or oxycodone. Ibuprofen and flurbiprofen also have a modest anti-inflammatory effect after surgery, adding to the therapeutic benefits while avoiding the risks associated with steroid use. Ibuprofen is the medication of choice for dental pain in patients who do not have contraindications to its use because of these factors and the vast clinical experience gained over the previous 25 years.(1)

Conclusion

Given their apparent lack of efficacy and the possibility of serious gastrointestinal and renal toxicity and tolerance with repeated dosing, the use of NSAIDs for chronic orofacial pain should be reassessed. Ibuprofen and other NSAIDs will probably still be used for this patient population because there aren't any good alternatives. However, if symptoms of gastrointestinal or renal toxicity are noticed, their use should be restricted to a brief trial and stopped.

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