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NSAIDS– What to look out for?

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Abstract
Dental pain is one of the foremost reasons for patients seeking dental therapy. Some dental procedures can also lead to post-operative pain. The major part of periodontal therapy consists of relieving this pain safely and effectively to provide patient comfort. The most commonly prescribed agents for pain management include non-steroidal anti-inflammatory drugs. These are non-narcotic, non-opioid aspirin-like analgesics which do not produce physical dependence or abuse liability. However they have a wide range of effects on other organ systems which could have a negative influence. Hence it is of utmost importance to take into consideration these drug interactions before prescribing NSAIDs in daily practice.

Keywords: non-steroidal anti-inflammatory drugs (NSAIDS), systemic diseases, drug interactions, bleeding complications, cardiovascular diseases, diabetes mellitus

Introduction
Algesia (pain) is a poorly-defined, unpleasant bodily sensation, that is generally elicited by an external or internal noxious stimulus. Although it is primarily protective in nature, it can result in discomfort and suffering.
Dental pain can originate from the pulp or the periodontal structures. Pulpal pain is acute, chronic or recurrent while periodontal pain is deep somatic pain of musculoskeletal type [1].
The major reason that patients approach dentists is to control pain due to dental or periodontal disease. Also, many dental procedures can cause intra-operative as well as postoperative pain which could persist for days. Hence, the primary goal in dental practice should be to manage this pain safely and effectively.
Analgesics relieve the symptoms rather than the etiology of pain. They are used as adjuvants in treating the etiology of pain or when it is not possible to remove the stimulus causing the pain [2].
Analgesics are divided into two groups-
1. Opioid/narcotic/morphine-like analgesics
- Hydrocodone, oxycodone, codeine, tramadol
2. Nonopioid/non-narcotic/aspirin-like/antipyretic or anti-inflammatory analgesics
- NSAIDs- ibuprofen, naproxen, ketoprofen, diclofenac, ketorolac, piroxicam, meloxicam, mefenamic acid, nabumetone
- Acetaminophen

NSAIDs are non-opioid aspirin-like analgesics that have analgesic, antipyretic and anti-inflammatory actions. They are weaker analgesics than morphine. They primarily act on the peripheral pain mechanisms and do not depress the CNS [2].

NSAIDS and Prostaglandins
The mechanism of action of NSAIDs was proposed by Vane and coworkers in 1971 [2]
- Enzyme cyclooxygenase acts on arachidonic acid to produce prostaglandins, prostacyclin (PG I2) and thromboxane A2 (TXA2).
- COX-1 and COX-2 are the two isoforms of cyclooxygenase. COX-1 has physiological functions whereas COX-2 is responsible for various inflammatory changes.
- NSAIDs exhibit their action by inhibiting COX-1 and COX-2 enzymes selectively or non-selectively.

Clinical Considerations While Prescribing Nsaids
Bleeding complications associated with Aspirin
Earlier studies have reported bleeding complications associated with periodontal surgery and extractions in patients on aspirin therapy. Hence the risk of peri-operative and post-operative bleeding must be taken into consideration while deciding whether to continue or stop aspirin use before any invasive dental procedures.
Schrodi *et al*. (2002) evaluated the effect of different doses of aspirin (81mg and 325mg) on bleeding on probing and noted that there was an increase in the sites that bled on probing in those patients who were consuming 325mg aspirin. This could impair the diagnostic assessment of the periodontium [3].
Royzman *et al*. (2004) evaluated the effect that aspirin had on bleeding on probing and concluded that there was an increased tendency for bleeding on probing within the aspirin group, which could lead to incorrect diagnosis and treatment planning [4].
Traditionally it was recommended that aspirin therapy should be stopped 7–10 days before any invasive surgical procedures. However, past evidence shows that cessation of antiplatelet therapy results in gradual recovery of platelet function that has a potential risk of rebound phenomenon of thromboembolic events. After aspirin therapy is stopped, there is an increased activity of thromboxane A2 and decreased fibrinolysis.
Ferrari *et al*. (2005) suspected the occurrence of a biological platelet rebound phenomenon after aspirin therapy was interrupted, which could lead to a prothrombotic state eventually causing a thromboembolic event that could be fatal. They also mentioned that, in specific circumstances,

where it is essential to stop aspirin therapy, it should be limited to lesser than or equal to 3 days [5].

Brennan *et al* (2007) in their review concluded that aspirin in low doses can result in an increase in bleeding on probing during periodontal examination, however, it does not have a significant effect on the amount and duration of bleeding that occurs after routine dental extractions. The cardioprotective benefits of aspirin therapy outweigh the risks of bleeding during majority of the dental procedures. Therefore, they recommended to continue low-dose aspirin therapy through routine dental extractions, unless in cases of certain circumstances where the period of discontinuation must be restricted to lesser than or equal to 3 days as discontinuation from 4 to 30 days can cause an increase in the risk for thrombotic events to occur.

Data indicates that the bleeding anticipated during oral surgical procedures in patients taking aspirin can be managed by standard local hemostatic measures like suturing, packing with gauze, resorbable gelatin sponge, oxidized cellulose, or microfibrillar collagen [6].

Medeiros *et al*. (2011) recommended that antiplatelet therapy must be discontinued 24 to 48 hours before any surgery and can be started 24–48 hours after surgery [7].

Wahl (2013) suggested that aspirin must be stopped only for 3 days. The rationale is that after 3 days of interrupting the course of aspirin therapy, an adequate amount of newer platelets will be formed which are not affected by aspirin and can bring about effective hemostasis [8].

In contrast, *Conti* recommended that when bleeding time is within the normal range, discontinuation of aspirin before invasive surgical procedures is not required [9].

R Vatsa *et al* (2018) stated that discontinuation of regular anti-coagulant medications placed patients at an increased risk of severe thromboembolic events and serious consequences. Hence they recommended that the anticoagulant regimen should not be stopped or altered prior to any dental surgical procedure [10].

Effect of NSAIDs on periodontal surgery and regeneration

Annabel Braganza (2005) evaluated intraoperative bleeding in periodontal surgery after the administration of Ibuprofen.400mg tab was given 9, 5 and 1 hr before surgery. It was observed that when ibuprofen was taken prior to periodontal surgery, there was an increase in intraoperative blood loss almost two times that of those who did not take ibuprofen. Therefore, they recommended temporarily discontinuing ibuprofen before surgery to reduce the risk of excessive bleeding during surgery, especially when osseous recontouring is involved [11].

In a similar study, Shiva Prasad BM and co-workers (2008) observed in patients with pre-administered ibuprofen who underwent periodontal surgery, there was an increase in intraoperative bleeding within the normal range. Patients described reduced pain and more comfort when they took ibuprofen preceding surgery. Hence the advantages of ibuprofen, which include being a good anti-inflammatory and analgesic agent, causing reduced alveolar bone resorption, and improved healing, overcome its adverse effect of increased bleeding during periodontal surgery which is minimal [12].

S Shetty *et al* (2014) studied the effects of ibuprofen and diclofenac sodium on bleeding during periodontal surgery and concluded that pre-operative administration of these drugs could result in prolonged bleeding time and perioperative blood loss. Hence they recommended temporary discontinuation of ibuprofen and diclofenac sodium two days prior to performing periodontal surgery for such patients [13].

Effect of NSAIDS on implants and osseointegration

Alissa *et al* (2009)- in their study stated that consumption of a short course of ibuprofen for management of post-operative pain after implant surgery may not have a major effect on the bone around the implants during the early healing phase [14].

Brent Winnett *et al* (2014)-studied the association between perioperative consumption of NSAIDs and failure of osseointegration. It was observed that most of the patients experiencing implant failure had taken NSAIDs. The data indicated that osseointegration of dental implants was negatively affected due to the inhibitory effect of NSAIDs on bone healing in vulnerable patients [15]

Etikala A *et al* (2019)- in their review concluded that NSAIDs had a negative effect on osseointegration of titanium implants [16].

Effect of NSAIDS on post–endodontic pain

Mokhtari F *et al* (2016) showed that prophylactic administration of 400 mg ibuprofen in a single-dose 1 hr prior to endodontic therapy provides effective reduction of post-operative pain lasting for up to 8 h [17].

Elzaki Wail *et al* (2016) evaluated the efficiency of paracetamol alone and in combination with 3 different NSAIDS for controlling post-endodontic pain. Ibuprofen-paracetamol combination had the maximum pain reduction, followed combined diclofenac K-paracetamol, then mephanamic acid-paracetamol, followed by paracetamol alone [18].

Effect of NSAIDs on orthodontic tooth movement-

Villa P.A *et al* (2005)- concluded from their study that administration on nabumetone did not hinder orthodontic tooth movement and was effective in relieving the pain associated with orthodontic forces [19].

Knop L A *et al* (2012)- Analysed the remodeling of bone during orthodontic movement under NSAID treatment of male Wistar rats. It was seen that, in 3 and 7 days, NSAID and SAID groups showed lesser blood vessels, howship lacunae, and osteoclast-like cells when compared to the control group while on the 7th and 14th days, there was a decreased amount of mature collagen in the SAID group. This indicated that potassium diclofenac and dexamethasone can cause inhibition of bone resorption during the initial phase of orthodontic movement [20].

Karthi M and co-workers (2012), in their review, stated that acetaminophen and celecoxib should be preferred over other NSAIDs for relieving orthodontic pain since they do not interfere with orthodontic tooth movement [21].

Multiple animal studies have shown that NSAIDs can delay the process of tooth movement. Until long-term human data are obtained, acetaminophen is considered as an appropriate alternative to NSAIDs for managing orthodontic-associated pain.

Drug Interactions

Anticoagulants

NSAIDs can result in an increased anticoagulant activity which is due to a delayed metabolism of S-warfarin. Hence

NSAIDs should be avoided in patients who are on warfarin therapy. On the contrary, one of the metabolites of acetaminophen (N-acetyl-para-benzoquinone-imine) can interfere with certain enzymes in the vitamin K cycle, that can eventually reduce the synthesis of clotting factors thereby leading to excessive anticoagulation. Acetaminophen when prescribed with anticoagulants even for a short duration can increase the international normalized ratio (INR), thereby leading to an increased risk of bleeding [22].

Anti-hypertensive therapy

A significant interaction takes place between antihypertensive drugs and NSAIDs. Anti-hypertensives acting on renal prostaglandins (eg. Furosemide or other diuretics and ACE-inhibitors) show decreased efficacy when administered along with NSAIDs due to the inhibition of renal prostaglandins. This results in an increase in blood pressure, fluid retention and risk of acute renal injury. Hence it is necessary to avoid chronic use of NSAIDS and when used patient's blood pressure should be closely monitored [22].

Oral Hypoglycemics

Higher doses of aspirin can potentiate the hypoglycemic effect of sulphonylurea drugs. Both phenylbutazone and azapropazone impede the metabolism of oral hypoglycemic agents potentiating their hypoglycemic effects. This drug interaction is not seen with other NSAIDs and is very selective for these two agents [23].

Phenytoin

Phenytoin metabolism is inhibited by phenylbutazone that could lead to clinical toxicity. Salicylates can displace phenytoin from plasma proteins thereby increasing its concentration and thus enhancing its clearance. Serum folate that is essential for phenytoin clearance will thus be depleted. This can result in phenytoin intoxication which can be reversed with supplemental folate [23].

Interaction of NSAID in Patients with Systemic Conditions

Effect of NSAIDS on patients with cardiovascular diseases

Ray *et al*. (2009)- Observed patients admitted for acute MI, coronary revascularization procedures, or unstable angina. Compared with those not using any NSAIDs, patients who had taken naproxen did not show any increased risk of coronary heart disease or serious cardiovascular disease.[24]

Fosbøl *et al*. (2009) - Studied healthy persons and showed that selective COX-2 inhibitors and diclofenac was associated with increased cardiovascular risk in a dose-dependent manner. Hence they stated that NSAIDS should be used cautiously and high doses of the drug must be avoided [24].

Olsen *et al*. (2012)- observed that NSAIDS were associated with an increased coronary risk irrespective of the time passed after myocardial infarction and hence they should be used cautiously in patients after MI [26].

Floor-Schreudering. A *et al* (2015)- in their study showed that there was negligible changes in mean blood pressure after initiating NSAID therapy in patients who were taking RAS inhibitors, beta-blockers or diuretics. However, few patients showed an increase of 10 mmHg in their SBP within two weeks of treatment. Patients who consumed etoricoxib and high doses of NSAID showed an enhanced risk for a rise in SBP. NSAIDs must be used cautiously in patients on antihypertensives with monitoring of blood pressure before and during the course of NSAID therapy [27]. Existing data suggests that the use of NSAIDs exhibits a major cardiovascular risk and therefore, high doses of the drug should be avoided. The safest drug in terms of cardiovascular side effects is naproxen.

Effect of NSAIDs on patients with Diabetes Mellitus

Sone *et al* (2001) and J Li *et al* (2017) in their respective studies stated that some NSAIDs like ibuprofen can cause hypoglycemia in diabetic patients who are taking sulphonylurea drugs. The risk of NSAID-induced hypoglycemia must be considered during the administration of glucose-lowering compounds [28, 29].

Effect of NSAIDs on patients with Renal disorders

Samuel Brown *et al* (2014) in their review stated various nephrotoxic effects associated with NSAIDs due to the inhibition of renal prostaglandin that causes a reduction in GFR and renal vasoconstriction. They can lead to nephritis, nephrotic syndrome, glomerulonephropathy, and other conditions. They also enhance sodium reabsorption from the distal convoluted tubules and secrete antidiuretic hormone that results in hypertension, hyponatremia, and edema. Hence, NSAIDS must be limited to specific situations like acute pain and should be used only for a short-term (3 to 7 days).

NSAIDs that have a half-life which is longer than 12 hours like Meloxicam or naproxen must be avoided as they can result in a decreased renal blood flow thereby causing a significant reduction in GFR and acute renal failure, in addition to severe hyperkalemia.

Patients who are more prone to NSAID-induced kidney disease should have their serum creatinine monitored every two to four weeks after initiation of therapy because of the possibility of renal insufficiency that can occur in the early phase of therapy.

Acetaminophen metabolism takes place in the liver and hence in CKD, dose adjustment is not required. Therefore it is safe to be used in patients with advanced CKD [30].

Baker M *et al* (2020) in their review proposed a few recommendations for the using NSAIDs in patients suffering from chronic kidney disease (CKD). Patients with stages 1 and 2 CKD who are stable and do not have predisposing risk factors, can be monitored like those without kidney disorders. For stage 3 CKD with minimal predisposing risk factors, short-term NSAID therapy for up to 5 days is tolerable and it has a low risk of nephrotoxicity. Routine monitoring and follow-up every 2 to 3 weeks is adequate to watch out for adverse effects. Due to the adverse outcomes of long-acting agents, short-acting NSAIDs are preferable. In stage 4 CKD patients who are stable, low doses of NSAIDs with short half-life should be used for lesser than or equal to 5 days and close monitoring is required. In patients with stage 5 CKD NSAIDs are contraindicated and must be absolutely avoided due to the high risk of fatal renal complications [31].

Conclusion

As dentists, we come across a wide range of patients, like those suffering from various systemic disorders or those

who are undergoing different drug therapies. It is essential that patients reporting to the dental clinic be relieved of any pain or discomfort caused due to dental problems or that are a consequence of dental procedures. NSAIDs play an integral role in this field. However, their mechanism of action and interactions with other drugs or systemic conditions must be taken into consideration to prevent any untoward consequences.

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