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NSAIDS IN PERIODONTOLOGY: MOVING BEYOND ANALGESICS

Dr. Salman Khawar[1]*, Dr. Suchetha A[2], Dr. Apoorva S.M[3], Dr. Sapna N[4], Dr. Divya Bhat[5] and Dr. Latha G[6]

[1]Post Graduate Student, Department of Periodontology, D.A.P.M R.V. Dental College, Bangalore.
[2]Professor and Head of the Department, Department of Periodontology, D.A.P.M R.V Dental College, Bangalore.
[3]Reader, Department of Periodontology, D.A.P.M R.V Dental College, Bangalore.
[4]Reader, Department of Periodontology, D.A.P.M R.V Dental College, Bangalore.
[5]Senior Lecturer, Department of Periodontology, D.A.P.M R.V Dental College, Bangalore.
[6]Post Graduate Student, Department of Periodontology, D.A.P.M R.V Dental College, Bangalore.

***Corresponding Author: Dr. Salman Khawar**
Department of Periodontology, D.A.P.M R.V Dental College, 1st phase. J.P.Nagar. Bangalore-560078.

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ABSTRACT

Periodontal disease belongs to the group of inflammatory disorders that is a result of the interaction of host immunity and etiological agent. Newer approach for periodontal disease management has been emerging as more is learned about role of host response. The increasing understanding about inflammation and its resolution has opened the door to study new periodontal treatment strategies. One of the earliest pharmacological strategies described to block the inflammatory processes in periodontal tissues as well as elsewhere in the body are non steroidal anti inflammatory drugs (NSAIDs). NSAIDs act as host modulatory agent and various studies using traditional NSAIDs systemically and locally on human and animal models have shown positive results with respect to reduction in progression of periodontal disease. Hence this article aims to overview the various aspects of the feasibility of using NSAIDs in periodontics as well as an insight into the mechanism of action and adverse effects associated with it.

KEY WORDS: NSAIDs, periodontal medicine, host modulation, analgesics.

INTRODUCTION

Periodontal disease belongs to the group of inflammatory disorder, pathogenesis of which is not well defined, but it is known that interaction of host immunity and etiological agent is an important determinant for onset and progression of disease. New approaches for periodontal disease management have been emerging as more is learned about role of host response .The increasing understanding about inflammation and its resolution has opened the door to study new periodontal treatment strategies.[1]

Evidence that prostaglandins could mediate bone resorption and its role in periodontal disease progression was first reported in 1970s.It was found that prostaglandin E_2 (PGE_2) levels were significantly elevated in gingival tissues of periodontitis patient.[2] One of the earliest pharmacological strategies described to block the inflammatory processes in periodontal tissues as well as elsewhere in the body are non steroidal anti inflammatory drugs (NSAIDs).[3] NSAIDs have most commonly been used in the management of pain.[4] The rationale behind its use is to block the arachidonic acid metabolites mainly prostaglandins that are pro-inflammatory mediators responsible for bone resorption and tissue degradation.[3]

NSAIDs act as host modulatory agent and various studies using traditional NSAIDs systemically and locally on human and animal models have shown positive results with respect to reduction in progression of periodontal disease.[1] Therefore the knowledge of different effects of NSAIDs is important to understand its application in periodontal diseases. Hence an attempt is made in this review to present an overview of NSAIDs in periodontics.

History of NSAIDs

Dating back to 3000BC, literature shows the use of willow bark and leaves to treat fever and inflammation. Later in the 17th century, the active ingredient of willow bark *salicin* was identified. The mass production of salicylic acid was started by 'The Kolbe Company' in Germany in 1860. Acetylsalicyclic acid (aspirin) the more palatable form of salicyclic acid was introduced into the market by Bayer in 1899.[5] Soon after, other

drugs having similar actions to aspirin were discovered, and the group was termed the ‘‘aspirin-like drugs’’ (now also termed as the nonsteroidal anti-inflammatory drugs [NSAIDs]). Its mechanism of action was explained first by John vane in 1971.[6]

In the 1960s, prostaglandins became increasingly implicated as mediators of cardinal signs of inflammation: redness, edema, pain, heat, and loss of function. Thus, periodontal researchers began to examine the possible contribution of prostaglandins to gingival inflammation, and especially the role of prostaglandins in the resorption of alveolar bone (Klein and Raisz, 1960; Goldhaber *et al.*, 1964).[7]

The evidence of the role of prostaglandins in the pathogenesis of periodontal disease came from examining the levels of arachidonic acid metabolites in crevicular fluid and tissue samples of gingiva and from the synthesis of prostaglandins by gingival tissues. There were elevated level of prostaglandins found in periodontitis individuals compared to healthy.[8] By the late 1970s, periodontal researchers had begun to evaluate the effect of NSAIDs on human periodontal disease by studying patients taking NSAIDs for arthritis. It was found that people taking NSAIDs demonstrated less overall periodontal bone loss than individuals not taking the drug.[7] There has been numerous studies done since then on experimentally induced periodontitis in animal models and adult periodontitis progression using different NSAIDs.

Mechanism of Action

Vane in his book *Nature* in 1971, published his investigation about the mechanism of action of aspirin and demonstrated that aspirin reduced prostaglandin production. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) are produced from arachidonic acid by the enzyme cyclooxygenase (COX).[9] COX exists in at least two isoforms, COX-1 and COX-2. Small differences in the structure of COX-1 and COX-2 lead to their important pharmacological and biological differences.[10]

COX-1 has various physiologic functions and it produces prostacyclin upon activation, which is cytoprotective to the gastric mucosa. The inducible isoform, COX-2 is induced in a number of cells by pro-inflammatory stimuli. As COX-2 is induced by inflammatory stimuli and cytokines in migratory and other cells, it is suggested that the anti inflammatory action of NSAIDs is due to the inhibition of COX-2, whereas the adverse side-effects, such as irritation of the stomach lining and toxic effects on the kidney, are due to inhibition of COX-1(Fig: 1). Most NSAIDs nonselectively inhibits COX-1 and COX-2, but recently some selective COX-2 inhibitors have been produced.[11]

Prostaglandins are local hormones which are synthesized by virtually all tissues of mammals (Smith, 1987) and acts, at or near their sites of its synthesis. They have both autocrine and paracrine functions. The cell typically responds to a prostanoid by changing the intracellular concentration of cAMP (Sonnenburg and Smith, 1988) and Ca 2+ (Negishi et al., 1989) or both.[12]

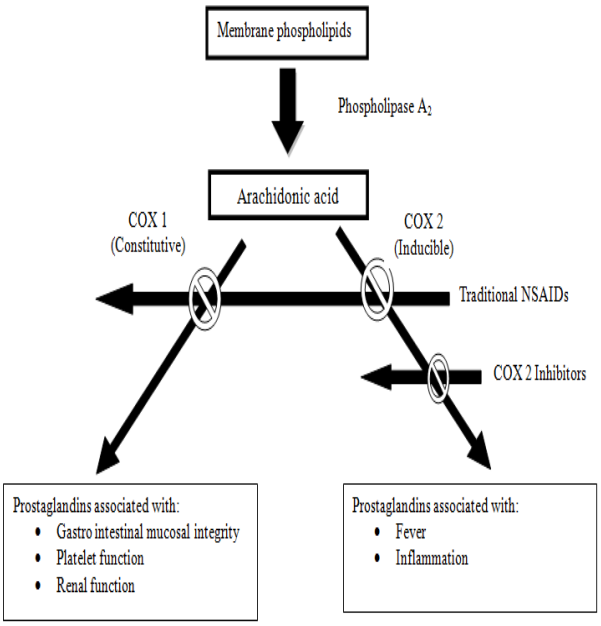

Fig 1: Mechanism of action of NSAIDs.

Enzyme can be either reversibly or irreversibly inhibited. An irreversible inhibitor is tightly bound to the enzyme either covalently or non covalently, that causes it to dissociate very slowly. In reversible inhibition, on the other hand, there is rapid dissociation of the enzyme substrate complex. Reversible inhibition can be further subdivided into competitive and non competitive. A competitive inhibitor normally resembles the substrate, and competes with the substrate for the active site of the enzyme. A non competitive inhibitor has a separate binding site to the active site; it acts by decreasing enzyme turnover rather than substrate binding.[13]

All NSAIDs variably inhibit COX-1 and COX-2 and their mechanisms of inhibition can be categorised into three types, though there are exceptions. For example, nimesulide is a weak competitive inhibitor of COX-1 but a potent time-dependent inhibitor of COX-2, whereas celecoxib shows slow competitive binding and, at higher concentrations, binds irreversibly.[14] The three categories are:

- **Category 1:** Rapid competitive reversible binding of COX-1 and COX-2 (e.g., ibuprofen, piroxicam, mefenamic acid).
- **Category 2:** Rapid, lower-affinity reversible binding followed by time-dependent, higher-affinity, slowly reversible binding of COX-1 and COX-2 (e.g., diclofenac, flurbiprofen, indomethacin).

- **Category 3:** Rapid reversible binding followed by covalent modification of COX-1 and COX-2 (e.g., aspirin).

Classification of NSAIDs

NSAIDs can be classified depending upon various characteristics that includes COX selectivity, and chemical and pharmacological properties. All NSAIDs are relatively lipid soluble and weak acids. However; there are some clinically relevant differences in their pharmacokinetic properties.[15] One can chemically categorise the following four major groups of NSAIDs on the basis of their inhibitory activity on COX-1 and COX-2 which is as follows:-

A. Nonselective COX inhibitors (traditional NSAIDs)

	Class	Drug
1	*Salicylates*:	Aspirin, Sodium salicylate, diflunisal.
2	*Propionic acid derivatives*	Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3	*Fenamate*	Mephenamic acid.
4	*Enolic acid derivatives*	Tenoxicam, Piroxicam
5	*Acetic acid derivatives*	Indomethacin, Ketorolac , Nabumetone
6	*Pyrazolone derivatives*	Oxyphenbutazone, Phenylbutazone

B. Preferential COX-2 inhibitors

Diclofenac, Nimesulide, Aceclofenac, Meloxicam, Etodolac.

C. Selective COX-2 inhibitors

Etoricoxib, Parecoxib, Celecoxib.

D. Analgesic-antipyretics with poor anti-inflammatory action.

1	*Para aminophenol derivative*:	Paracetamol
2	*Pyrazolone derivatives*	Metamizol, Propiphenazone
3	*Benzoxazocine derivative*	Nefopam.

This classification of NSAIDs follows chemical categories that are not satisfactory because it does not allow one to predict important properties of the various drugs, both between and within the individual categories. By including the newly developed NSAIDs, which belong to further chemical classes, the nomenclature would be even more complex.[16]

NSAIDs as Host Modulating Agent in Periodontics

Within the context of immunology host response specifically refers to the response against parasites. Therefore, host response in the periodontium is the defence mechanisms in periodontal tissues against bacterial infections.[17] The concept of *host modulation* was first introduced to dentistry by Williams in 1990 and Golub et al. in 1992 and later on expanded by many researchers. The rationale behind host modulation is to help the host in defending against infectious agents by changing the course of inflammatory system and supplementing the natural host defence mechanisms. The agents that aids in host modulation are called *host modulatory agents.*

Host modulatory agents, which is a vital part of perioceutic that restores the balance between proinflamatory mediators and destructive enzymes, as well as between anti-inflammatory mediators and enzyme inhibitors. Host modulation is indicated for patients who are unable to effectively reduce risks such as patient's genetics, smokers who are unable to quit the habit, patients who are unable to maintain adequate oral hygiene, failure to reduce stress, poorly controlled diabetics, and the inability or unwillingness of the physician to alter medications of the patient.[18]

One of the earliest pharmacological strategies described to block the inflammatory processes in periodontal tissues as well as elsewhere in the body is Non steroidal anti-inflammatory drugs (NSAIDs). The basic rationale behind the use of non steroidal anti-inflammatory drugs is to block the arachidonic acid metabolites that are proinflamatory mediators concerned with bone resorptive and tissue degrading processes.[17]

Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins, including prostaglandin E_2, that is produced by an array of resident and infiltrating cell types in the periodontium (neutrophils, macrophages, fibroblasts and epithelial cells) in response to bacterial toxins. It is also the key inflammatory mediator in periodontal disease as it up regulates osteoclastic bone resorption. Various studies have found elevated levels of prostaglandins in the GCF of chronic periodontitis patients. Hence; NSAIDs aids in reducing the inflammation and inhibits bone resorption.[19]

The prevention and management of periodontal disease in highly susceptible subjects such as aggressive or refractory periodontitis, diabetics, smokers and IL-1 genotype positive will require either extreme plaque control or a combination of plaque control in conjunction with host modulating agents such as NSAIDs.[18] However, the non steroidal anti-inflammatory drugs have some considerable disadvantages that prevents their use as an adjunctive treatment for periodontal disease. For periodontal benefits to become apparent, Daily administration for extended periods of time (years rather than months) is necessary. Apart from that NSAIDs are associated with significant side effects, including gastrointestinal problems, Haemorrhage, renal and hepatic impairment. Also, once patients cease taking non steroidal anti-inflammatory drugs, a return or even acceleration of the rate of bone loss is seen, that is known as a "rebound effect".[20]

Various NSAIDs like flurbiprofen are easily absorbed through the oral mucosa and has shown significant reduction in periodontal parameters.[24] Therefore, the development of topical NSAIDs formulations with an appropriate carrier (i.e. gel, toothpaste, rinse) an optimal concentration having minimal systemic adverse effects seems to be of particular interest. When compared to systemic administration, topical route would help to improve patient's compliance in long-term NSAIDs administration.[18]

NSAIDs as analgesic

Post operative pain is one of the complications of periodontal surgery. According to some studies, mild pain after periodontal surgery is experienced by 70% of the individuals, 40 % shows mild to moderate pain and only 4.6% experience severe pain. Hence it is very important to manage these patients effectively so that treatment is pain free. Vogel et al concluded that Ibuprofen, if given immediately before or immediately after periodontal surgery significantly delays the onset of pain.[21] Hungund et al found that presurgical dose of ketorolac significantly reduces the initial pain intensity postoperatively.[22] Gallardo et al preferred meclofenamates as an alternative to the mild analgesics such as aspirin or acetaminophen after the comparative study.[24] Tucker et al told that it is beneficial to use Etodolac for postoperative periodontal surgery discomfort in situations where severe pain is expected over an extended period.[23] There is also a good evidence for the efficacy of topical NSAIDs in acute and chronic musculoskeletal pain. The exact formulation of a topical medication is often determined by the speed of drug absorption required.

NSAIDs as Anti inflammatory agent

Inflammation results due to the participation of a number of chemotactic, vasoactive and proliferative factors at different stages, and there are many targets for anti-inflammatory action. The most important mechanism of anti-inflammatory action of NSAIDs is considered to be inhibition of COX-2 mediated enhanced PG synthesis at the site of injury. But PGs are only one of the mediators of inflammation, and inhibition of COX does not inhibit the production of other mediators like LTs, PAF, cytokines, etc. Certain NSAIDs may act by additional mechanisms like inhibition of free radicals, stabilisation of lysosomal membrane, and kinin antagonism that enhances its action as an anti inflammatory agent.[26]

Adverse Effects of NSAIDs

NSAIDs appear to induce toxic reactions in almost all of the major organ systems in man, albeit to varying severity and frequency. Generally, the adverse effects are dose-related, though some are idiosyncratic, and largely (but not solely) attributable to inhibition of prostaglandin synthesis (Rainsford, 1988).[27] The unwanted effects of NSAIDs are summarised in Table-1.

Table 1: Adverse Effects of NSAIDs.

Adverse Effects of NSAIDs
Gastrointestinal Ulceration Perforation Haemorrhage
Renal Acute renal failure Hypertension Cardiac failure
Hypersensitivity Rashes Bronchospasm
Haematological Neutropenia Thrombocytopenia Haemolytic anaemia Red cell aplasia
Neurological Headache Tinnitus Dizziness Blurred vision
Personality changes Irritability nervousness drowsiness depression hyper reactivity

Studies related to NSAIDs

Author	*Study aim*	*Method*	*Result*
Animal studies			
Marilyn et al 1982	To evaluate if prostaglandin plays role in periodontal bone loss.	Indomethacin was used to inhibit prostaglandin in squirrel jaw.	Indomethacin treatment abolished the significant losses of alveolar bone height and bone mass seen in non-Indomethacin-treated (NIT) animals.[28]
Jeffcoat et al 1985	To evaluate the effect of flurbiprofen on the progression of naturally occurring periodontal disease	The effects of non-surgical and surgical periodontal therapy were compared over a 12-month period when each	Daily administration of flurbiprofen significantly decreased the rate of alveolar bone loss in both

	in beagle dogs.	modality was combined with either systemic flurbiprofen administration or placebo.	surgically and non-surgically treated animal groups.[29]
Azoubell et al 2008	To compare the effect of etoricoxib, a selective cox-2 inhibitor, and Indomethacin, a non-selective Cox inhibitor, on experimental periodontitis	Animals were treated daily with oral doses of 3 or 9 mg/kg etoricoxib and 5 mg/kg Indomethacin after inducing periodontitis.	Treatment with etoricoxib showed reduces inflammation and cementum and bone resorption, with fewer gastrointestinal side effects compared to indomethacin.[30]
Xin et al 2014	To investigate the short- and long-term effects of parecoxib and diclofenac sodium on osseointegration of dental implants in rabbit calvaria.	The rabbit were divided into 3 groups -the parecoxib grp, diclofenac grp, and no NSAIDs grp; and implants were placed in carvaria of rabbit.	Diclofenac sodium and parecoxib did not affect osseointegration of dental implants and bone healing in calvaria, neither in short or long term.[31]
Human studies			
Vogel et al 1984	To investigate the effects of systemic sulindac, a NSAID used in rheumatoid arthritis therapy on experimental gingivitis.	The effects of sulindac were compared to those of fluocinonide, a topical steroidal anti-inflammatory	The topical steroid significantly inhibited gingival inflammation while the systemically administered sulindac had no apparent effect.[32]
Heasman et al1993	To evaluate the effect of systemic flurbiprofen administration in combination with tooth brushing on resolution of experimental gingivitis.	After 21 days of oral hygiene abstinence, subjects were prescribed 100 mg flurbiprofen daily or placebo for 7 days in conjunction with tooth brushing.	The flurbiprofen group demonstrated greater resolution of gingival inflammation.[33]
Williams et al 1989	To examine the effect of the NSAID, flurbiprofen, on slowing the radiographic loss of alveolar bone.	Patients with radiographic evidence of alveolar bone loss were recruited for study half of the patients were administered flurbiprofen, 50 mg. b.i.d., while half were administered a placebo	Flurbiprofen, as an inhibitor of cyclooxygenase, can inhibit human alveolar bone loss as measured radiographically.[34]
Preshaw et al 1998	To study the effects of topical ketorolac tromethamine mouth rinse (0.1%) on gingival crevicular fluid (GCF) Prostaglandin E2 (PGE2) concentrations in moderately advanced chronic adult Periodontitis.	PGE2 were assessed in GCF post mouth rinse at baseline and 42 days.	Mean PGE2 level was reduced following mouth rinse but the level came to normal in 12 hours.[35]
James et al 2004	To compare the combination of ibuprofen 400 mg with 5 mg of hydroxycodone to ibuprofen 400 mg used alone in the management of pain following periodontal surgery.	12 patients underwent periodontal surgery in two quadrants 2 weeks apart and given different combination of drugs at predetermined time and visual analog scale were used to determine the patient comfort.	The combination of analgesic preparation ibuprofen with hydrocodone resulted in better pain control compared to ibuprofen used alone.[36]
Srinivas et al 2011	To assess the effects of ketoprofen, on patients with chronic periodontitis.	Poloxamen gel containing 1.5% ketoprofen was used as a local drug delivery along with SRP and compared with SRP alone and various periodontal parameters were recorded.	The results of this study indicate that the combined effect of locally delivered ketoprofen with SRP was more effective in controlling periodontal disease than SRP alone.[37]

Winnett et al 2016	To evaluate whether adverse biological events following oral implant placement could be linked to perioperative use of non-steroidal anti-inflammatory drugs (NSAIDs).	All patients between 1979 and 2012 that had experienced a failing dental implant were contacted to ask for additional information about their present dental and medical status and frequency of current and past use of NSAIDs.	The result indicate that dental implant osseointegration may be negatively affected by an inhibitory effect of NSAIDs on bone healing in vulnerable patients.[38]

CONCLUSION

The past decade has provided enough evidence that NSAIDs are potent drugs in combating pain and inflammatory involvement of periodontium. We now have lot of research examining the effect of NSAIDs on slowing periodontal disease progression in animal models and in humans. Although the data clearly indicate that NSAIDs, either taken systemically or applied topically, can diminish the periodontal disease process but there is much work to be done to clarify the role of NSAIDs in periodontal therapy. We need to evaluate the beneficial effects of NSAIDs on slowing periodontal disease progression outweighing potentially harmful side effects. As it is becoming easier to selectively influence the inflammatory cascade, it is anticipated that NSAIDs will become more site-specific and reduce unwanted reactions.

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