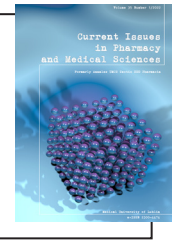
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The use of non-steroidal anti-inflammatory drugs (NSAIDs) in clinical practice for the treatment of periodontitis: a narrative review

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ABSTRACT

After dental caries, the most common multifactorial oral disease is periodontal disease. Periodontitis can result in biofilm and host dysbiosis, ultimately causing inflammation and destruction of periodontal tissues. This narrative review aimed to summarise and discuss the mechanism of action, categories and use of non-steroidal anti-inflammatory drugs (NSAIDs) in clinical practice in the treatment of periodontitis because of their analgesic, anti-inflammatory and reducing effects on platelet aggregation and thus bleeding. Also, this review illustrates the importance of studies demonstrating synergism between specialty drugs and their derivatives as valuable active substances. The eleven clinical trials conducted in small groups of adult volunteers (14-50) treated with various NSAIDs, e.g. aspirin, ibuprofen, diclofenac, ketoprofen and tenoxicam are discussed.
The results of clinical trials have shown that the use of NSAIDs together with surgical intervention in the treatment of periodontal diseases produces beneficial effects as an adjunctive treatment. It is worth noting that these studies were conducted on small cohorts of adult volunteers, with variations in the duration of treatment and doses of administered drugs. Further research on the impact of NSAIDs administration on periodontal disease may provide in-depth knowledge of patient groups with different demographics, including age, gender and comorbidities. Additional research is necessary to explore the use of NSAIDs in combination with periodontitis treatment for different patient groups.

INTRODUCTION

Periodontitis is an infectious disease of the tissues surrounding the tooth, causing progressive loss of connective tissue attachment and alveolar bone. A characteristic feature of this disease is the presence of pathological pockets, which become a reservoir niche for opportunistically pathogenic bacteria [1]. Symptoms of periodontal disease include swelling and bleeding gums, exposed tooth necks, elongation of tooth crowns, unpleasant breath, and even tooth loss [2,3]. It is caused by bacterial infection of the subgingival biofilm of teeth, caused by periodontal pathogens, in particular, a group of specific species of Gram-negative anaerobic bacteria called the "red complex". They include mostly: *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, which are found mainly in deep periodontal pockets. The bacteria penetrate periodontal tissues and secrete proteolytic enzymes, toxins and metabolic products that cause progressive damage to surrounding structures [2-7].

Host cells release biological mediators that participate in the remodeling processes of extracellular matrix components. Various host mechanisms prevent bacterial infections [1,8]. Besides physical and chemical barriers such as the skin, mucous membranes and saliva, the human immune system is involved in the defense processes [1,8]. It is now considered a multifactorial disease initiated and sustained by

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bacterial plaque [8]. In addition to the composition and size of the bacterial plaque, the determining factors are the individual characteristics of each patient: general health, as well as the genetically determined performance of the immune system and its resistance to infection [1,4-7]. The first line of the immune system consists of non-specific immune cells (phagocytes, NK cells) and the molecular effectors of the complement system, C-reactive protein [1]. The second line of the immune system is determined by specific immunity. The host immune response within the oral cavity is reduced to the production of immune mechanisms, leading to antigen elimination [5,6].

Cytokines mediate the migration of immune cells in the inflammatory environment. Cytokines regulate cellular processes, such as cell proliferation, growth, activation, inflammatory processes, immune mechanisms and repair processes [5]. Most cytokines exhibit local effects. A small group, however, also has systemic effects. These include tumor necrosis factor (TNF) and interleukin (IL-1, IL-6) [5,7]. In periodontal tissues, one of the most important cytokines inducing the body's immune response is IL-1β, which plays a key role in the development of inflammatory processes in periodontal tissues, and stimulates osteoclast formation and bone resorption [5]. Monocytes, neutrophils, fibroblasts and mast cells are mainly responsible for the synthesis of this pro-inflammatory cytokine in response to lipopolysaccharide (LPS)-induced activation.

IL-1β stimulates cells to release pro-inflammatory mediators and catabolic enzymes, such as phospholipase A2, prostaglandins (PG), acute phase protein, platelet-activating factor (PAF), as well as the pro-inflammatory cytokines IL-6 and TNF and many metalloproteinases (MMPs) [5, 7]. IL-1β is responsible for the expression of intercellular adhesion molecules such as VLA-1 and VLA-2 integrins and VCAM-1 immunoglobulin-like molecules, and increases vascular endothelial permeability [7, 9]. Another important pro-inflammatory cytokine is IL-6, produced by periodontal tissue cells in response to LPS stimulation and the pro-inflammatory cytokines IL and TNF, thereby stimulating the synthesis of acute phase proteins, inducing bone resorption similarly to IL-1β, and stimulating the synthesis of chemokines, metalloproteinases and PGE2 [10].

PGE2 is one of the most abundant PGs in periodontal tissue with pro-inflammatory properties, produced by neutrophils, macrophages periodontal ligament cells, gingival fibroblast cells, gingival tissue cells, epithelial cells, osteoblasts, cementoblasts [11-13]. It causes vasodilation of blood vessels and increased permeability, thereby facilitating leakage of immune cells and plasma into the extracellular space and local inflammation [11-13].

As described earlier, periodontitis is an inflammatory disease in which the immune-inflammatory response to a disrupted biofilm is altered, leading to connective tissue destruction and bone loss. In the treatment of periodontitis, in addition to surgical intervention, both broad- and narrow-spectrum antibiotics are used, alone or in combination, or antiseptics, which are generally effective in reducing the microbial load in the blood and tissues of patients and in reducing the clinical symptoms of patients with periodontitis.

Typical antibiotic therapy includes amoxicillin with or without clavulanic acid, azithromycin, ciprofloxacin, tetracycline and doxycycline. Broader-spectrum antibiotics such as metronidazole and clindamycin are generally preferred because of their selectivity against anaerobic pathogens [7-9]. Antiseptics have many uses in periodontitis, including preoperative irrigation, postoperative care, and pocket irrigation. The most widely used antiseptics are chlorhexidine, essential oils: eucalyptol, menthol, thymol and quaternary ammonium compounds. They are supplied in the form of: mouthwashes, gels, pastes, chewing gums, lozenges and aerosols. The mechanisms of action of antiseptics are: permeabilization of the plasma membrane, precipitation of cytoplasmic proteins, disruption of the cell wall, inhibition of bacterial enzymes, extraction of endotoxins from LPS of Gram-negative bacteria and anti-inflammatory effects based on antioxidant activity. However, these are short-term benefits in terms of antibiotic resistance and its impact on the oral and gut microbiome [7-9].

It is important to remember that periodontitis is an inflammatory disease caused by microorganisms. Postaglandins (PG) are one of the mediators influencing this progress. These are formed from arachidonic acid under the influence of cyclooxygenase enzymes. Nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated therapeutic benefits in slowing the progression of periodontal disease by effectively inhibiting PG synthesis. The use of NSAIDs allows avoidance of systemic complications caused by antibiotics, and at the same, time achieve high drug concentrations in the diseased area [14].

In this narrative review, we summarize the results of clinical trials as evidence for the usefulness of NSAIDs in the treatment of periodontitis, which includes both surgical treatment and non-surgical periodontitis.

MATERIALS AND METHODS

Search strategy

This narrative review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [15]. All literature searches were conducted until March 2024, using the search tools of Embase, Cochrane Library, Web of Science, PubMed, databases, and www.clinicaltrials.gov/website with the search terms, "periodontitis" and "NSAID" or "Aspirin" or "Ketoprofen" or "Ibuprofen" or "Diclofenac" or "Naproxen" or "Flurbiprofen" and "Clinical practice in periodontitis" only publications written in English were included. Based on the titles and abstracts of the studies, the five independent researchers selected the articles. Mendeley Reference Manager Software® was used to delete duplicate articles.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (a) clinical or retrospective efficacy studies of NSAIDs in patients with periodontitis: (b) studies involving adults;

Publications were excluded if they were (a) case reports on one or two patients; (b) letters, editorials and protocols, (c) duplicate publications; (d) experimental studies on cells and animals; and (e) no detailed data.

Data extraction and analysis

The necessary data were extracted independently by five investigators, and the results were discussed with senior investigators. Among the outcomes studied, the following were included: type of drug(s) studied, number of patients and their ages, examination time, type of clinical study and results. For each article, the following data were obtained: first author, year of publication, study period, number of patients, drug dose and median follow-up time.

Quality assessment

Case series reports were rated using the case report bias assessment tool as a response of "yes", "no", or "unapplicable" or "not clear", and are presented in Table 1 [16]. The evaluation indicators are (a) inclusion and exclusion criteria; (b) clinical heterogeneity of patients (including disease severity), classification, duration and time of disease onset; (c) whether the main intervention measures (dose, method of administration, and course of treatment, etc.) are clearly described; (d) whether the method of measuring the relevant outcome measures was reasonable; (e) whether outcome measures were measured before and after the intervention; (f) whether the loss of follow-up and follow-up time was recorded; (g) whether adverse events related to clinical treatment have been documented; and (h) whether the outcome assessor was blinded. The quality of the literature was assessed independently by five members, respectively.

Table 1. Case series report quality evaluation form

Studies	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Castro Dos Santos NC *et al.* [31]	yes	yes	yes	yes	yes	yes	yes	yes
Mauro P. Santamaria *et al.* [33]	yes	yes	yes	yes	yes	yes	yes	yes
Rampally P. *et al.* [18]	yes	yes	yes	yes	yes	yes	yes	no
Sachin S. *et al.* [21]	yes	yes	not clear	not clear	unap.	yes	no	unap.
Peddengatagari S. *et al.* [42]	no	no	yes	yes	yes	yes	yes	yes
Amirhossein Farahmand *et al.* [40]	no	yes	not clear	not clear	yes	yes	yes	yes
Menon P. *et al.* [34]	yes	yes	yes	yes	yes	yes	yes	yes
Das R. *et al.* [37]	yes	yes	not clear	yes	no	yes	yes	yes
Srinivas M. *et al.* [14]	yes	no	not clear	not clear	not clear	yes	yes	yes
Özgören Ö. *et al.* [25]	yes	yes	yes	yes	yes	yes	yes	yes

unap. - unapplicable

Use of NSAIDs in clinical trials

NSAIDs reduce inflammation in the body, have an analgesic, antipyretic effect, and are the most commonly used drugs in this disease treatment in the world [17]. Their pharmacological action is based on blocking cyclooxygenase (COX) [18]. In general, the action of NSAIDs is to inhibit the access of arachidonic acid to the enzymatic center of COX, showing a variable ability to inhibit the activity of COX-1 (constitutive) and COX-2 (induced) [19,20]. COX 1, through the production of prostaglandins, has a protective effect on the gastric mucosa and affects blood vessels, while COX-2 produces damaged tissues, macrophages, endothelial cells and fibroblasts and is an inducible form of the enzyme, playing an important role in inflammatory processes [4,5,21,22].

The scheme of cascade of arachidonic acid metabolism under the influence of COX is presented in Figure 1. In the next step, prostaglandin PGH2 is formed under the activity of specific synthases (such as prostacyclin synthase (PGIS), thromboxane synthase (TXS), cytosolic prostaglandin E synthase (cPGES), lipocalin synthase/hematopoietic prostaglandin D synthase (L/H-PGDS), prostaglandin F synthase (PGFS)). PGH2 is subsequently transformed into the corresponding end products, i.e. prostacyclin PGI2, thromboxane A2 TXA2, PGE2, PGD2 and PGF2α (Figure 1) [23].

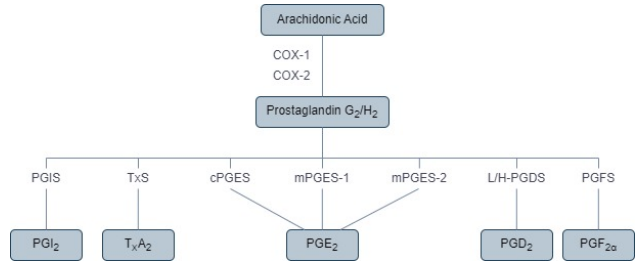


Figure 1. The cascade of arachidonic acid metabolism under the influence of COX [23].

Due to their ability to inhibit the activity of individual COX isoenzymes, NSAIDs are divided into:

- selective COX-1 – this is how acetylsalicylic acid (ASA) works in a cardiac dose of 75/150 mg;
- preferential COX-2 – showing greater affinity for COX-2 than for COX-1, e.g. nimesulide and meloxicam
- selective COX-2 (also known as coxibs) – showing 200 times or more affinity for COX-2 than COX-1, e.g. celecoxib and rofecoxib.
- non-selective COX-1 inhibitors (also known as classic NSAIDs) – exhibit a higher affinity for COX-1 compared to COX-2 e.g. ibuprofen, diclofenac, ketoprofen, naproxen, and aspirin at the classic dosage [5,22,24].

The most dangerous effect of the (over)use of such drugs and, indeed, is associated with high mortality and complications, is bleeding from the upper gastrointestinal tract. The greatest risk of its occurrence results from the use of NSAIDs, which strongly inhibit COX-1 activity. These include ketoprofen, indomethacin, acetylsalicylic acid and NSAIDs from the oxicam group. Table 2 shows selected NSAIDs used in periodontitis, along with the relative risk of upper gastrointestinal bleeding when used systemically. Elderly people suffering from stomach or duodenal ulcers or episodes of gastrointestinal bleeding are particularly vulnerable. To reduce the risk of the side effects listed in Table 3 of NSAIDs, they should be taken at meal times and with plenty of fluids. In patients with risk factors for gastrointestinal damage, it is recommended to choose NSAIDs with a low risk of gastrointestinal damage, such as selective or preferential COX-2 inhibitors and classic NSAID isomers: dexketoprofen or dexibuprofen/flurbiprofen [21,25-27].

Table 2. Non-steroidal anti-inflammatory drugs used in periodontitis, their potency, drug doses and therapeutic effects [26,27]

Authors and year	Drugs	Dose of drugs and method of administration	Number of patients Non NSAID/NSAID		Age of patients	Examination time	Clinical and biochemical parameters*	Results
Supplementation with Aspirin in periodontitis								
Castro Dos Santos NC *et al*. [31]	Aspirin	Aspirin 100 mg + Omega-3 3000 mg/day, oral administration	25	50	Mean age (years) was 54.9±9.7 for CG, 55.6±8.3 for TG1, and 54.4±10.2 for TG2	6 months	• PD • CA • GR • BoP	Omega-3 fatty acid supplementation in combination with ASA after periodontal cleansing provides clinical and immunological benefits in the treatment of periodontitis in patients with type 2 diabetes
Rampally P. *et al*. [18]	Aspirin	Low dose Aspirin 75 mg or Omega-3 500 mg/day oral administration	14	14	30-65 years	3 months	• GI • PD • CAL • Hb1Ac – Glycosylated hemoglobin • Ptx	This study confirms the beneficial role of NSPT in periodontal therapy, as significant improvements were obtained for all parameters in each group from baseline to 3 months. Pro-inflammatory PTX3 was significantly lower in the Aspirin-treated group compared to the group without Aspirin
Sachin S. [21]	Aspirin	Low dose Aspirin 75 mg/150 mg, oral administration	15	15	The mean age of the study group was 54.4±6.45 and that of the control was 44.4±13.4.	Chronic use of Aspirin	• PI • BI • PD • CAL, • PPD	Aspirin 75/150 mg therapy can induce neutrophil apoptosis and improve PPD and CAL
Mauro P. Santamaria [33]	Aspirin	100 mg of Aspirin + 900 mg of omega-3 polyunsaturated fatty acids daily , oral administration	19	19	31.63±5.6	180 days	• BoP • FMPI • PD • GM • CAL	Aspirin showed an effective reduction in gingival inflammation, a reduction in pocket depth, as well as bleeding in the study sample, and an increase in CAL in the study group
Supplementation with Diclofenac in periodontitis								
Peddengatagari S. [42]	Diclofenac	Benzydamine hydrochloride 3 mmol/l undiluted 15 ml of solution for 60 seconds 2-5 times and diclofenac 50 mg twice a day.	15	15	–	3 days	• VAS • WONG BAKER FRS • MGI	A comparison of pain scores on both the VAS and WONG BAKER scales showed significant efficacy of Benzydamine as well as Diclofenac
Supplementation with Ibuprofen and its derivatives for periodontitis								
Farahmand A. [40]	Ibuprofen	Subgingival rinsing with 2% Ibuprofen	19	19	34 patients in age: 28-36	3 months	• PPD • CAL • PI • BI	The group with scaling and root planing (SRP) + ibuprofen showed more favorable results than the group with SRP + placebo ($p<0.05$)
Menon P. [34]	Ibuprofen	Ibuprofen (400 mg) or ginger powder capsules (400 mg) three times per day, oral administration	5	5	30-60 years	3 days	• VAS • MGI	VAS and MGI results between both groups were not statistically significant
Das R. [37]	Ibuprofen	Ibuprofen 600 mg or traumeel 600 mg every 8 hours for the first 24 hours then for 1 week as needed, oral administration	20	20	Range 20-60 years	7 days	• VAS • postoperative tissue response	The number of pills taken and the perception of pain was lower after traumeel supplementation compared to ibuprofen
Alshibani N. *et al*. [29]	Ibuprofen	Ibuprofen (400 mg) or ginger powder capsules (400 mg)two times per day, oral administration	22	22	Range 40-50 years	21 days	• PI • GI • CAL • PD • MBL	In group non NSAID and with NSAID, there was no statistically significant correlation between self-rated pain and age, gender or periodontal parameters PI, GI, CAL, PD and MBL
Srinivas M. *et al*. [14]	Ketoprofen	Poloxamen gel containing 1.5% Ketoprofen, local effects	10		33-55	90 days	• PI • GI • CAL • PPD	Topically administered Ketoprofen in combination with mechanical periodontal therapy (SRP) has proven beneficial in controlling clinical signs of inflammation than SRP alone
Supplementation with Tenoxicam in periodontitis								
Özgören Ö. [25]	Tenoxicam	20 mg Tenoxicam per day, oral administration	16	16	Study group 40.9±8.2 years, control group 42.3±7.3 years	10 days	• PI • GI • PD • GBTI • CAL	There was no statistically significant difference in clinical measurements after treatment between the two groups

* – Visual analogue scale (VAS), WONG BAKER face rating scale (FRS), modified gingival index (MGI), Pocket depth (PD), Clinical attachment increment (CA), Gingival recession (GR), Bleeding during probing (BoP), Supragingival biofilm accumulation (PI)30, plaque index (PI), gingival index (GI), gingival bleeding index (GBI), pocket depth (PD), clinical attachment level (CAL), Hb1Ac – Glycosylated hemoglobin, (Ptx) Pentraxin, bleeding index (BI), pocket probing depth (PPD), modified gingival index (MGI), visual analogue scale (VAS) and the Wong-Baker face rating scale (FRS), Gingival crevicular fluid (GCF), GBTI – gingival bleeding time index, BoP bleeding on probin, Full-mouth plaque index (FMPI), Gingival recession (GM), mesial in mm (MBL)

Ketoprofen as a propionate derivative in cognition with other extensions, has a significant effect on blocking the synthesis of PGE2 in the human periodontium *in vitro*. Other *in vitro* anti-inflammatory effects of ketoprofen include anti-bradykin activity and stabilization of lysosomal membranes, as well as direct inhibition of monocytes and macrophages, which are integrated cells involved in PG synthesis, thereby modifying the host response to the inflammatory process [26,27]. In patients taking aspirin regularly and additionally other NSAIDs, ketoprofen or celecoxib is preferred for the

treatment of periodontal disease. In patients with periodontitis and gastroenterological risk, selective COX-2 inhibitors or preferential COX-2 inhibitors (aceclofenac or ketoprofen with lysine) are preferred [26-28].

Most studies, especially those conducted on humans, do not provide a target dose of NSAIDs in combination with surgical treatment of periodontitis. For this reason, this review aimed to illustrate the importance of studies demonstrating synergism between specialized drugs as valuable active agents that may be important for the development of new drug combinations and therapeutic regimens as shown in Table 3.

Table 3. Non-steroidal anti-inflammatory drugs used in periodontitis, their potency, drug doses and therapeutic effects [25,27,31]

Division of NSAIDs according to potency and half-life	Drug example used in PD	NNT (Number Needed to Treat)	Duration of action of the drug (hours)	Doses used and route of administration	Relative risk of upper gastrointestinal bleeding following NSAIDs
"Weak" NSAIDs with a short half-life	ibuprofen	NNT 2,4 for dose 400-600 mg and 1,6 for dose 800 mg	4	Orally up to 600-2400 mg/24 h in doses administered every 6-8 h	2,0
	acetylsalicylic acid	NNT 4,4 for dose 600-650 mg	3-4	The maximum daily dose orally up to 4 g in 4-6 doses	3,1
NSAIDs with "moderate" potency and intermediate half-life	naproxen	NNT 2 for dose 440 mg	15-30	Orally up to 500-1000 mg/24 h in 2-4 delivered doses	9,1
"Powerful" NSAIDs with a short half-life	diclofenac	NNT 2,8 for dose 25 mg, 2,3 for dose 50 mg and 1,9 for dose 100 mg	4-5	Orally up to 50-200 mg/24 h in delivered doses intramuscular injection 75-150 mg/24 hours	4,2
	ketoprofen		6-8	Orally up to 300 mg/24 h in 2 doses, intravenous and intramuscular injection up to 200 mg/24 h	23,7
"Powerful" NSAIDs with a long half-life	drugs from the oxicam group – tenoxicam	NNT 2,7 for dose 20 mg	33	20 mg/24 h orally	13,7

NNT – the number of patients who need to be treated with a given drug for one patient to benefit, compared to a control group in a clinical trial

DISCUSSION

The traditional treatment of periodontitis includes cleaning the root surface to maintain the symbiosis of the host and oral microbiome [29,30]. The articles collected in this narrative review, as shown in Table 3 highlight the key role of NSAIDs as complementary pharmacotherapy in the treatment of periodontitis. The literature review aimed to examine the benefits of complementary pharmacotherapy in terms of clinical and biochemical parameters. The discussions were divided into oral and topical drug delivery in the treatment of periodontitis, as this is crucial not only in terms of the potency of the drugs but also in terms of side effects.

Oral drug administration

In a clinical study conducted by Castro Dos Santos NC *et al*. [31], after 6 months of periodontal cleaning, intra-group comparisons showed that all groups showed statistically significant differences in mean periodontitis [31]. Combination therapy involving the administration of polyunsaturated fatty acids ω-3 (PUFA ω-3) and ASA 100 mg + Omega- 3 3000 mg/day, brought clinical benefits in the treatment of periodontal diseases (also in patients with type 2 diabetes). When comparing PI reduction between groups, significant differences were detected in the NSAIDs group. For periodontitis, no significant differences were detected between groups for moderate and deep pockets. The group supplemented with ω-3 PUFA + ASA after periodontal cleaning showed an increase in CA in moderate and deep pockets and ΔPI, compared to the other groups. Moreover, the group that took ω-3 PUFA + ASA before periodontal cleaning showed a significant difference in ΔBαP compared to the control and the group supplemented with ω-3 PUFA + ASA after periodontal cleaning [31].

Another example to confirm the positive effect of ASA in periodontitis is the study of Elkhouli AM *et al*. [32]. A 6-month combination therapy carried out on 20 patients with Demineralized Freeze-Dried Bone Allograft (DFDBA) using Omega-3 acids and low-dose aspirin 75-150 mg/day showed an effective reduction in gingival inflammation, a decrease in pocket depth and an increase in adhesion levels, accompanied by a tendency to modulate the cytokine profile in the gingival crevicular fluid, compared to the control [32].

The studies done by *Mauro* P. *Santamaria et al*. [33] emphasized the synergistic effect of 100 mg of Aspirin + 900 mg of omega-3 polyunsaturated fatty acids daily in periodontitis. Aspirin showed an effective reduction in gingival inflammation, a decrease in pocket depth and an increase in CAL in the x b study group [13,33]. The inclusion of adequate amounts of ω-3 PUFA in therapy, rather than frequent increases in the dose of NSAID, may also contribute to beneficial effects in aspirin-resistant patients with periodontitis.

Similar data was presented in an interesting study done by Alshibani N. *et al*. [29]. The authors examined the effects of ginger and NSAIDs as adjuncts to non-surgical periodontal therapy in the treatment of periodontitis. In this study, patients with periodontitis were included. All patients underwent Non-Surgical Periodontal Therapy (NSPT). In the study groups, patients received ginger (400 mg) and NSAIDs (ibuprofen (400 mg)), respectively. Whole mouth periodontal parameters were evaluated, i.e. plaque index [PI], gingival index [GI] and probing depth [PD], asl well as clinical attachment loss [AL], and marginal bone loss at the beginning of the study and after 7, 14 and 21 days. Self-assessment of pain was assessed at the beginning of the study and after 24 hours, 3 and 7 days of follow-up. Ginger and NSAIDs were effective in reducing postoperative pain and inflammation after NSPT in patients with periodontitis. The current results showed that ginger and NSAIDs were effective in reducing postoperative pain after NSPT, with no statistically significant difference in analgesic efficacy. These results confirm the hypothesis, as statistically significant reductions in PI, GI and PD were observed in both groups. Ample evidence in the indexed literature has shown that

ginger is a powerful CAM that can be successfully used to treat inflammatory conditions such as osteoarthritis, stomatitis and mucositis. Moreover, ginger has also been shown to have analgesic effects. The exact mechanism of ginger's analgesic action remains unclear. However, preclinical research results have shown that ginger contains several compounds such as capsaicin, curcumin, gingerols, beta-carotene and caffeic acid, which have antibacterial, antiviral, antipyretic, anti-inflammatory and analgesic properties. Ginger inhibits the production of prostaglandins by inhibiting lipoxygenase (LOX) and cyclooxygenase (COX). It is worth emphasizing that NSAIDs also cause the effects described above in the publication. Additionally, ginger components such as alkylated gingerols inhibit the growth of periodontopathogenic Gram-negative bacteria, including *Porphyromonas gingivalis* and *Prevotella intermedia*. The above study results may help explain reducing gum bleeding and PD among patients and statistically significant changes in CAL and MBL [29].

Similar results were presented in the study by Menon P. [34]. Each quadrant was randomly assigned to receive ibuprofen (400 mg) or ginger powder capsules (400 mg) three times daily for 3 days. Patients were asked to record pain scores on a visual analogue scale (VAS) 8 hours after treatment and for the following two days, and gingival inflammation was assessed one week later using the modified gingival index (MGI). Although after periodontal treatment, pain scores were slightly higher in the ginger group compared to the ibuprofen group. VAS and MGI results between both groups were not statistically significant. Therefore, dried ginger powder may provide an alternative for pain management in patients for whom NSAIDs are contraindicated after periodontal surgery. However, further studies in larger samples and the effects of ginger extracts on specific inflammatory mediators are warranted [34,35].

In another interesting study conducted by Ramplally P. *et al*. [36], all patients underwent a clinical examination during which the severity of periodontal disease was measured with a Williams probe. In this work, 42 diabetic patients were selected and divided into three groups. After scaling and root planning, 14 participants received 75 mg of aspirin orally once daily for 3 months, while another 14 participants received 500 mg of omega-3 fatty acids orally twice daily for 3 months, and the control group were given empty gelatin capsules. In the periodontal treatment, significant improvement in all parameters was achieved in each group within 3 months. It was revealed, however, that the group supplementing with omega-3 acids saw greater effectiveness in the reduction of the marker of the inflammatory status plasma pentraxin (PTX3) levels compared to the group supplementing with ASA or the control group. Indices measuring both gastrointestinal status and depth of PPD, GI, PD, and CAL cone pockets 3 months after scaling and root planning confirmed the beneficial role of NSAIDs and Omega-3 in combination with NSPT in periodontal treatment [36].

The work of Sachin S. *et al*. is important in clinical practice because they present a low-dose aspirin therapy that can induce neutrophil apoptosis and improve PPD and CAL. The study group consisted of 15 patients with periodontitis, supplementing aspirin at doses of 75 mg/150 mg per day due to cardiovascular diseases. The control group consisted of 15 generally healthy periodontitis patients who did not take acetylsalicylic acid. The results indicated a decrease in PPD and CAL and a marginal increase in neutrophil apoptosis in the ASA-supplemented group, as compared to the control group [21].

A further interesting study was conducted by Das R. *et al*. [37] so to compare the analgesic and anti-inflammatory effects of ibuprofen 600 mg or traumeel 600 mg self-administered every 8 hours for the first 24 hours and then as needed for 1 week after periodontal flap surgery, along with any side effects associated with the use of the above mentioned medicines. In the presented study, 15% of all patients reported gastric irritation after taking ibuprofen. Ibuprofen is a non-selective COX-1 and COX-2 inhibitor. Inhibition of COX-1 leads to inhibition of PGI2, which has gastroprotective properties. The group that was supplemented with Traumeel in this study reported no side effects from the drug. Traumeel, instead of directly inhibiting the synthesis of prostaglandins (like Ibuprofen), has antioxidant and immunomodulatory properties, and it reduces the activity of phospholipase A2, thus modulating arachidonic acid. Therefore, the absence of stomach pain was demonstrated in the traumeel group in this study [37]. In contrast, the authors showed a better tissue response in the group receiving ibuprofen compared to traumeel.

Another study supporting this observation was conducted by Babaloo A. *et al*., and involved 30 patients after periodontal surgery [38]. Group 1 received Novafen capsules (containing 325 mg of acetaminophen, 200 mg of ibuprofen, and 40 mg of caffeine), and group 2 received ibuprofen (400 mg). A combination of acetaminophen, ibuprofen and caffeine resulted in better performance analgesic effects after periodontal procedures. However, the ability to control pain was similar to ibuprofen at baseline postoperative hours, with better performance 1-3 days after surgery [38,39].

Despite the data obtained from the aforementioned studies, further studies are, however, needed to determine the exact dose of NSAID in combination with plant medicines or alone in combination with SRP that should to be prescribed for the treatment of periodontitis.

Local drug administration

Researchers suggest that selective NSAIDs (COX-2 inhibitors) may reduce the bone loss associated with periodontitis. A recent study showed that the use of NSAIDs in combination with mechanical periodontal therapy improved bone maintenance during the treatment of patients with periodontal disease. Indeed, flurbiprofen and ibuprofen have been demonstrated to be readily absorbed through the gingival tissues [40]. The development of local NSAID preparations (e.g. gels, toothpastes and rinses) for daily use seems to be particularly interesting, as the above-mentioned products may attenuate the adverse effects of non-selective NSAIDs in long-term host modulation in periodontitis-susceptible individuals. Moreover, NSAIDs may influence this phase of bone loss in periodontal disease [40].

With reference to the aforementioned, a study presented by Farahmand A. [40] was conducted to evaluate the clinical

use of a combined topical ibuprofen (2%) mouthwash and a placebo mouthwash after 3 months. The study included 38 patients of both sexes, aged 28-35, who were diagnosed with mild to moderate periodontitis. Statistically, the difference in PI was significant between ibuprofen and placebo after 12 weeks. However, the PI results were significantly higher in the case of mouthwash containing ibuprofen compared with the placebo group at an interval of three months ($p<0.05$). In the compared ibuprofen group, BI and PD decreased significantly to the placebo group after 6 and 12 weeks. However, the CAL value differed significantly only after 12 weeks of ibuprofen use group, as compared to the placebo group, and the ibuprofen group showed significantly higher CAL than the placebo group. All patients tolerated the drug well, without any complications or side effects. In addition, the soft tissues healed within normal limits and without significant differences in patients subjected to the experiment. Significant improvements in pocket depth (PD), and CAL and BI readings were also observed in both groups. This analysis showed that after 3 months, a group of people supplemented with ibuprofen combined with scaling and root planning (SRP) showed significantly better results than SRP without the drug. In summary, this study demonstrated that mouthwashes containing ibuprofen can be used to support the periodontal healing process [40].

Another analysis of recent clinical studies conducted by Pappu R. *et al*. [35] showed that the group that received gel with flax seed extract and the second group using gel with flurbiprofen revealed better changes after scaling and root planning compared to the third control group that did not receive any supportive therapy. Measurements included gingival fluid (GCF) and saliva samples, plaque index, gingival index, pocket probing depth and CAL. Considering the PPD clinical parameters and CAL data analysis over the 3-month study period, both groups that used flax seed extract gel and flurbiprofen gel had comparable results. The results of the study confirmed that flaxseed extract gel could be equally associated with the effectiveness of flurbiprofen gel after 90 days. Therefore, clinical trials are paving the way for the inclusion of herbal ingredients such as linseed, omega-3 fatty acids, and ginger as targeted drugs in the treatment of chronic periodontitis, which will reduce the side effects caused by NSAIDs and enhance the effects of the therapy. Patients may be encouraged to use the above phytotherapeutic agents based on their safety, low risk, and economic benefits [35]. Omega-3 fatty acids are able to inhibit inflammation, including leukocyte chemotaxis, the production of eicosanoids from arachidonic acid, such as prostaglandins and leukotrienes, the production of pro-inflammatory cytokines and the inhibition of T-cell activity 1. Of note, omega-3 fatty acids produce eicosanoids, which are often weaker biologically than those produced from arachidonic acid, and omega-3 acids produce anti-inflammatory mediators, i.e. resolvins, protectins and maresins. The mechanisms underlying n-3 fatty acids include altering the composition of phospholipid fatty acids in the cell membrane, disrupting lipid reefs, as well as inhibiting the activation of pro-inflammatory transcription factor and nuclear factor kappa B (NfkB) and thus reducing the expression of inflammatory genes, the activation of the anti-inflammatory transcription factor activated by peroxisome proliferators, the γ receptor and binding to the G protein-coupled receptor GPR120. As it is known, NSAIDs act by inhibiting the biosynthesis of prostaglandins (PG). However, ginger contains ingredients that also inhibit PG synthesis. Studies have shown that some components of ginger can inhibit the metabolism of arachidonic acid through both cyclooxygenase (COX) and lipoxygenase (LOX) and have significantly fewer side effects than conventional NSAIDs which are contraindicated in patients with gastrointestinal ulcers, coagulation disorders and renal dysfunction [28,41].

The double-blind clinical study done by Srinivas M. *et al*. [14] included 10 periodontitis PDs. In the study, two similar preparations were prepared for the patients: the first preparation for local drug administration in the form of a gel was a placebo, the second preparation was a gel containing 1.5% ketoprofen. All parameters were assessed at baseline, 30 days and 90 days, respectively. In this study, the overall oral hygiene status showed significant improvement. Although a very significant overall increase in CAL and reduction in PPD was observed, differences between groups were not found to be statistically significant. The clinical increase in CAL was highest in the group that took ketoprofen in addition to SRP but the work showed no statistically significant differences between the groups that took the local drug and those that did not supplement ketoprofen [14]. It is worth noting that these studies should be repeated on larger groups, along with equal dosages to confirm/deny the synergism of ketoprofen and SRP in periodontitis as compared with SRP alone in adults.

In the context of the narrative review, it should be noted that the study conducted by Peddengatagari S. [42] was the only one that reported the effectiveness of a mouthwash containing benzydamine hydrochloride compared to diclofenac tablets in the treatment of postoperative pain after periodontal procedures. Benzydamine hydrochloride is the NSAID most commonly used in the treatment of stomatitis. It has physical, chemical and pharmacological properties that differ from aspirin-like NSAIDs. Benzydamine acts specifically on local mechanisms of inflammation, granuloma and exudate. In this study, 30 patients with chronic periodontitis scheduled for periodontal surgery were randomly assigned to receive benzydamine hydrochloride (MW) or diclofenac (TB) tablets after surgery. Patients in the MW group were instructed to rinse with undiluted 15 ml of the solution for 60 seconds 2-5 times a day for three days. The TB group was asked to take a 50 mg diclofenac tablet twice daily for three days. To measure patients' pain perception, a 10-point visual analogue scale (VAS) and the Wong-Baker Facial Rating Scale (FRS) were recorded. MGI was assessed at baseline and on day seven. Intra-group comparison of pain scores on the first and second day on the VAS and WONG-BAKER scales showed greater effectiveness in the group using benzydamine mouthwash than in the group using oral diclofenac, suggesting greater effectiveness of the mouthwash than tablets. It is important to emphasize, however, that both groups experienced pain relief at the beginning of the study, on days one and two, suggesting that both products were effective [42].

In addition, a similar situation was observed in the work of Coll Y. *et al*. [43]. This observational study compared the analgesic efficacy of topical ibuprofen paste (Odontocide) with systemic ibuprofen 400 mg capsules. Accordingly, 90 patients who had qualified for endodontic treatment were divided into 3 groups: 1 group received ibuprofen topically, 2 group was prescribed ibuprofen for systemic use and 3 group did not receive ibuprofen (control). Pain scores were measured at established time points within the first 48 hours after endodontic instrumentation. In previous work, systemic ibuprofen has been shown to provide statistically significantly better pain relief compared to topical ibuprofen paste applied to root canals, but only within the first 24 hours after root canal preparation. However, after 24 hours, group 2, who had received systemic ibuprofen, had a lower mean pain score compared to group 1, but this was not statistically significant. Systemic ibuprofen was consistently more effective at relieving pain than the control group [43].

In summary, ibuprofen is the safest NSAID used in PD, but its effect is short-lived, so the dose must be repeated frequently. However, tenoxicam or naproxen in a single dose works for up to 30 hours, although the risk of side effects in the gastrointestinal tract and beyond is much higher. Therefore, the use of local NSAIDs may prolong the duration of drug action in PD and reduce the risk of side effects [17,20,25].

LIMITATIONS AND CONCLUSIONS

This manuscript reviews the literature on the use of NSAIDs for the treatment of periodontitis in clinical practice. Several studies were identified in the literature, of which only eleven could be used to quantitatively evaluate the primary and secondary outcomes of periodontal treatment. Taking into account the complexity of these studies and the effects of drugs, the results revealed that the combined use of NSAIDs with surgical treatment in periodontitis brings beneficial effects as an adjunct therapy in the cleansing of the root surface.

Based on the above information, we suggest that combining surgical treatment of periodontal disease with NSAIDs may represent a breakthrough in the treatment of acute and chronic oral diseases. A current problem in medical science is the lack of evidence that NSAIDs should be used in different patient groups in terms of council, gender and age. However, there is still uncertainty about the effects of NSAID use in clinical trials, in many cases due to study limitations. Firstly, the analyses were performed on a very small number of patients. Secondly, the studies differed in the duration of drug use and were not consistent in the control dose of NSAIDs. Thirdly, many NSAID derivatives, including selective COX-2, also known as coxibs, are missing from the reviewed studies. Coxibs have a much greater affinity for COX-2 than COX-1 (e.g. celecoxib and rofecoxib), and hold strong anti-inflammatory and analgesic properties, but do not affect platelets, unlike the popular ASA, and thus could reduce bleeding during the procedure.

Further research is thus necessary to demonstrate the synergism of the action of NSAIDs with SRP, hence enabling the use of lower doses of drugs, shortening the duration of periodontitis treatment and reducing the number of side effects after NSAIDs administration, and thus enhancing the effectiveness of treatment and providing safer therapy for the patient. Due to the side effects of aspirin administration, it would also be crucial to determine the most appropriate target dose of omega-3 fatty acids in combination with NSAIDs.

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