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Review Article

ROLE OF NSAIDS ON PERIODONTAL AND DENTAL IMPLANT THERAPY

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed group of drugs in dentistry for managing postoperative pain and discomfort. Little is known regarding their effects on the healing of periodontal and peri-implant tissues. The authors conducted a review of the literature to provide an overview of knowledge about NSAIDs and their potential effects on periodontal and implant wound healing. A Pubmed (MEDLINE) database search was conducted to identify articles evaluating the influence of administration of NSAID drugs on outcomes following periodontal treatments (nine clinical studies) and dental implant placement (four animal studies and two human clinical studies). Conflicting results were found on the effects of NSAIDs during periodontal wound healing. NSAID administration, specifically selective COX-2 inhibitors could inhibit bone formation around orthopedic implants. Within the limitations of this review, NSAIDs negatively affected Osseo integration of titanium implants. However, quality of evidence from available human clinical studies is poor and there are conflicting results from animal models. Future and better clinical studies are needed to more precisely evaluate the potential effects of NSAIDs on dental wound healing. Dental surgeons must be aware of the potential effects of NSAID use on osseous healing following common oral surgical procedures such as periodontal and implant therapy.

Key words:- Dental Implant, NSAID's, Periodontal, Pain.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used class of drugs. They have been known to inhibit and even completely abolish prostaglandin synthesis in therapeutic doses [1]. Prostaglandins (PG) such as PGE2 and PGI2 are bioactive lipid messengers produced by the action of cyclooxygenase (COX) enzymes on amino acid, arachidonic acid (AA) [2]. In 1971, it was demonstrated for the first time that NSAIDs such as aspirin, indomethacin, and salicylate inhibit the production of COX enzyme (also known as prostaglandin synthase) [3]. COX has two isoforms, the endogenous COX-1 and the inducible COX-2, which differ in their regulation of expression and tissue distribution. COX-1 activity is present at a constant level in nearly all cell types and has physiologic roles in production of PGs in the stomach, intestine, and other organs that maintain the integrity of the mucosal epithelium, renal function, and platelet aggregation [4-6]. On the other hand, COX-2 activity is normally not seen in cells, and its production is induced by stimuli such as cytokines and bacterial lipopolysaccharides, which are associated with inflammation [7].

Thus, COX-1 is considered as physiologic and COX-2 as pathologic enzymes. Inhibition of COX-1 can lead to gastric damage, ulcer formation, and hemorrhage [8]. COX-1 is also involved in production of platelet-derived thromboxanes that are responsible for platelet aggregation and vasoconstriction [9.10]. The indications for use of NSAIDs and the adverse effects caused by them can be explained based on the above background and the general overview of their actions on various organ systems of the body [11]. NSAIDs are usually used for their analgesic, anti-pyretic, and anti-inflammatory properties in various acute and chronic conditions. Since PGs are responsible for hyperalgesia and inflammatory changes, their inhibition will prevent pain and symptoms associated with inflammation [12, 13].

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NSAID Use in Dentistry

NSAIDs are commonly used in dentistry to manage postoperative pain in invasive dental procedures [14]. Various NSAIDs are the first drugs of choice in postoperative pain management [15]. In a Cochrane review it was concluded that ibuprofen was superior to acetaminophen based on pain relief and use of rescue medication data collected at 6 hours postoperatively following extraction of third molars [16-19].

Adverse Effects

Most of the adverse effects related to NSAID use are due to the non-selective inhibition of COX enzymes. These include mild effects such as dyspepsia as well as serious side effects of ulcer formation and gastric hemorrhage. The NSAID-related gastrointestinal effects can be seen at recommended doses, and these adverse effects appear to be dose-related. These drugs also also induce renal toxicity in patients whose kidney function is impaired. Studies reported that selective COX-2 NSAID use increases the risk of non-fatal myocardial infarction (MI) with no substantial effect on fatal events [20]. This also was confirmed to be the case with all other NSAIDS, including naproxen, in a recent systematic review. Rofecoxib was withdrawn from markets in 2004 because of the statistically significant increase in occurrence of MI [21,22]. This can be elaborated by the imbalance between hemostatic prostanoids, namely prostacyclin and TXA_2, which is induced by selective inhibition of COX-2-dependent prostacyclin production while maintaining the continued COX-1-dependent production of TXA_2 by platelets.

Precautions:

According to the guidelines for the prevention of NSAID-related ulcer complications published by Lanza et al (2009), patients at high risk for gastrointestinal complications include those with a history of previous ulcers or H-pylori infection and presence of multiple risk factors such as age >65 years, high-dose NSAID therapy, and concurrent use of aspirin, corticosteroids, or anticoagulants. If these patients need to be prescribed NSAIDs, this should be combined with misoprostol or high-dose proton pump inhibitors.

Effect of NSAIDs on Wound Healing

In the normal wound-healing process, a hemostatic plug is formed where poly morphonuclear neutrophils (PMNs) and platelets get entrapped and secrete inflammatory chemo-attractants. Following this, macrophages are recruited to release pro inflammatory cytokines during the early inflammatory phase, in addition to the up-regulation COX-2 at the wound site. The inhibition of COX-2 helps reduce scar-tissue formation and accelerate re-epithelialization, in turn leading to uneventful wound healing. A study by Geesala et al (2017) showed that celecoxib can lead to a dose-dependent increase in bone-marrow stem cell differentiation into keratinocyte-like cells, in vitro. The morphological analysis of the regenerated wound depicted 70% wound closure by day 7 post-surgery in the celecoxib-administered group, as compared with 50% wound closure in the control group. Hence, it is believed that NSAIDs may accelerate re-epithelialization and prevent wound opening during wound healing.

Effects of NSAIDs on Periodontal Disease

Conflicting results were found on the effects of NSAIDs, because NSAIDs can affect the alveolar bone by either stimulating or inhibiting bone formation or preventing the progression of alveolar bone loss in periodontitis patients. Jeffcoat and coworkers conducted a series of studies on human subjects to evaluate the potential of NSAIDs in altering the progression of alveolar bone loss in subjects with periodontitis.

The findings from a study on 2-year pre-treatment with flurbiprofen (Ocufen®,Allergan, Inc) as adjunct to nonsurgical periodontal therapy in human subjects with chronic periodontitis show that this drug can inhibit alveolar bone loss as measured radiographically at 12 and 16 months from baseline; however, at 2-year timepoint the rate of bone loss was similar to the placebo group. Later, the same research group tested the effects of naproxen as an adjunctive to scaling and root planing on reducing periodontal disease activity in 15 patients with rapidly progressive periodontitis. The test group received 500 mg naproxen twice per day for 3 months. Significantly less bone loss as well as significant increase in the proportion of teeth demonstrating bone gain was reported in the naproxen-treated group. In a randomized controlled study, when sites with high risk for bone loss in periodontitis patients were treated with topical NSAID rinse containing ketorolac or 50 mg twice per day flurbiprofen capsule in conjunction with 3-month prophylaxis cleanings, it was observed that ketorolac rinse preserved more alveolar bone than systemic flurbiprofen at the dose regimens utilized.

Looking at the animal models, in a study on beagle dogs to investigate the changes in the concentrations of COX products present in crevicular fluid in naturally progressing periodontitis and the effects of various NSAIDs on these metabolite levels and disease progression, three different formulations of systemic ibuprofen, systemic naproxen, or topical flurbiprofen were administered to these animals. During the 6-month treatment phase, the authors reported that rate of bone loss in untreated animals increased by 38% and there was a significant depression in levels of both PGE2 and TXB_2 in crevicular fluids in all NSAID-treated groups. The authors then suggested that products of the cyclooxygenase pathway might be responsible for bone

loss occurring in periodontal disease, and controlling this regulatory step can prevent bone destruction.

In an experimental study conducted on Wistar rats, it was observed that COX inhibition prevented alveolar bone loss in an experimental periodontal disease model. However, the drug needed to be continuously administered to maintain these effects. In another study conducted to determine the impact of meloxicam (Mobic) on bone loss in ligature-induced periodontitis in a rat model and its post-treatment effect after administration withdrawal, results suggest that meloxicam may reduce bone loss associated with experimental periodontitis, but no remaining effect can be expected after its withdrawal. Some reports, however, also suggest NSAIDs may produce opposite results. In a randomized controlled study to determine the effect of a 1-week course of postsurgical naproxen on the osseous healing in intrabony defects following treatment with polylactide bioabsorbable membrane, it was reported that administration of postsurgical naproxen failed to produce osseous healing that was statistically superior to that obtained with polylactide bioabsorbable membranes alone as measured at re-entry surgery. Findings from some in-vivo studies support the above results. There is evidence that meloxicam, which is a selective COX-2 inhibitor, reduced bone healing in critical size calvarial defects in rats after continuous administration during healing phase. Hence, conflicting data were noted with regards to how NSAIDs affect periodontal wound healing; early studies often suggested that NSAIDS can prevent periodontal bone loss and even promote bone formation or repair, although the results were not sustained after 2 years.

Effect of NSAIDs on Osseo integration Following Implant Placement

The findings from medical literature suggest that systemic NSAID administration during the healing period following placement of implants impairs bone healing. But findings from experimental periodontitis models and human periodontitis are indicating that NSAIDs can either slow the rate of alveolar bone loss or produce no effect at all. In view of these findings, it is a matter of great interest to know the effects of systemic administration of NSAIDs on bone healing and osseointegration following placement of dental implants[23].

***In vivo* Studies**

Most of the in vivo studies (discussed below) using animal models support the findings that NSAIDs have an inhibitory effect on bone healing and osseointegration around titanium implants. A study conducted to investigate the effects of meloxicam on titanium implants placed in rat tibia concluded that after continuous administration meloxicam may negatively influence bone healing in the cortical and cancellous bone around titanium implants inserted in rats. Meloxicam also reduced the contact area between the implant and bone, area of bone formation, and bone density as compared to controls. However, in a recently published study conducted to investigate the short- and long-term effects of a 7-day regimen of parecoxib (Dynastat) and diclofenac sodium on osseointegration of dental implants in calvarial bone of rabbits, it was concluded that appropriate doses of diclofenac sodium and parecoxib did not adversely affect osseointegration of dental implants and bone healing in calvaria. One limitation of this study was that parecoxib was administered intravenously to the study animals[24].

Findings from studies on knockout mice also provide valuable insights into the effects of NSAIDs on healing following implant placement. When titanium implants were placed in femurs of wild type as well as COX-2 knockout mice, it was observed that new bone formation was minimal in COX-2 knockout mice and osteocalcin expression was induced in bone surrounding implants only in the control group. In another study on wild-type rats, diclofenac sodium seemed to delay peri-implant bone healing and decrease bone-to-implant contact as compared to meloxicam and no drug.

CONCLUSION

With NSAIDs being the most commonly prescribed group of drugs in dentistry, it is of great interest to dental surgeons to be aware of the potential effects of their use on osseous healing following periodontal and implant therapy. In this review, the authors have highlighted the evidence available regarding these effects from experimental studies in laboratory animals and human clinical studies. However, the effect of NSAIDs on the osseointegration of titanium implants is not well understood. The conflicting results from animal models can be attributed to the species studied, the methodologies used, and the pharmacokinetics of the drugs that can be affected by local or systemic compensatory factors. Further studies are needed to assess the effect of NSAIDs for short periods simulating the postoperative use.

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