The Effect of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) on Bone Healing around Osseointegrated Dental Implants - A Systematic Review

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ABSTRACT

BACKGROUND

NSAIDs are considered effective pain-relieving agents after dental implant placement. However, they may have related side effects. We wanted to determine as to whether these agents have a positive or negative impact on the supporting alveolar bone after dental implant placement.

METHODS

PRISMA flowchart was followed and the clinical question in PICO format was: "Do systemic NSAIDs help or impede the healing of osseointegrated implants?". The databases of Ovid, PubMed, Scopus, and Web of Science were used in this systematic literature search for clinical trials. Publications between January 1, 1990 and January 31, 2020 were searched.

RESULTS

The initial search resulted in 385 articles. Only four studies were selected for qualitative synthesis after fulfilling the eligibility criteria (three double blind randomized controlled trials (RCTs) and one retrospective cohort study) with 222 patients and 686 implants placed.

CONCLUSIONS

The results showed that the administration of NSAIDs post implant placement may not have a significant effect on the supporting bone.

KEY WORDS

Osseointegration, Bone Healing, Dental Implants, NSAIDs

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BACKGROUND

Successful dental implants are principally reliant on the well-preserved bone that support them.¹ Osseointegration define the direct contact between the ordered bone and the surface of the compatible implant material. The expected long-term function of dental implants is primarily dependent on the stable levels of the supporting alveolar bone and the preservation of the process of osseointegration.² Any change to this vital process will have a direct negative effect on the treatment outcome.³

NSAIDs are considered effective pain-relieving agents after dental implant placement utilizing from their anti-inflammatory, analgesic, and antipyretic properties.⁴ These pain-relieving drugs may have side effects on the supporting alveolar bone post dental implants placement. The enzyme of cyclooxygenase (COX) that converts arachidonic acid into prostaglandins^{5,6} becomes inactive as a result of the analgesic action of NSAIDs. COX-1 is formed in both normal and fractured bone tissues, whilst COX-2 is formed in inflamed tissues and during the primary phases of bone repair.⁷

Previous studies have shown that the rate of bone loss associated with periodontal disease can be reduced via the inhibition of prostaglandin production when flurbiprofen,⁸ naproxen⁹ or meclofenamate¹⁰ were prescribed. Also, Prostaglandin E2 (PG E2) has been found to enhance osteoblasts growth and bone formation around titanium implants¹¹. Moreover, Bone metabolism can be influenced by prostaglandins which can both enhance and impede tissue repair and osteoblasts formation¹².

It has been shown that NSAIDs can have a 'bone sparing effect'¹³ around osseointegrated dental implants. However, reports have recommended that the process of bone healing can be delayed by NSAIDs^{14,15} which can also impair bone ingrowth into orthopaedic implants.^{16,17} Furthermore, the use of NSAIDs after total hip arthroplasty is still recommended to obstruct heterotopic ossification¹⁸ that can result in functional impairment.¹⁹

The aim of this review was to identify if NSAIDs negatively or positively affect the supporting bone post dental implants placement.

METHODS

The statement of PRISMA²⁰ was used in the setup of this review. The related question based on PICO schema was: 'Do systemic NSAIDs help or impede the healing of osseointegrated implants.

Information Sources

The databases of Ovid, PubMed, Scopus, and Web of Science were electronically searched. Publications between January 1, 1990 and January 31, 2020 were considered.

Search Strategy

Mesh and keywords were combined throughout the literature search. The wide-ranging keywords were proposed to maximize the amount of related studies. Boolean operator (and, or) was used and the following keywords and terms were applied: non-steroidal anti-inflammatory drugs or agents, osseointegration, osteoblast, osteoclast, dental implants, bone healing, cyclooxygenase inhibition.

Inclusion and Exclusion Criteria

Studies were firstly screened according to the following criteria: clinical trials, observations studies, cross sectional and cohort studies peer-reviewed in English language. Non peer-reviewed publications, case reports, in vitro and animal studies were excluded.

Study Selection

Titles and abstracts were initially and independently screened by reviewers (SS) and (AAR). Another reviewer (NA) independently reviewed the studies selected in the former initial search. The full-length articles were classified according to the "Inclusion and Exclusion Criteria".

Data Items

The collected data included:

- Author – year of publication
- Sample size
- Intervention and Placebo/control group
- Method of drug administration
- Outcome measures
- Findings

Risk of Bias Assessment

The risk of bias was individually assessed during the initial screening by the reviewers (SS and AAR). Disagreements or doubts were debated with another reviewer (NA) until an agreement was reached. The Cochrane Collaboration's tool for assessing the risk of bias was used.²¹ (Table 1).

RESULTS

385 possible titles and abstracts were extracted from the databases specified in the initial search. After exclusion of the duplicate articles, abstracts were independently screened, and 39 studies were selected. 4 out of these 39 studies were suitable to be systematically reviewed after detailed assessment for eligibility (Fig. 1). The excluded 35 Studies were- animal studies (n = 20), review articles (n = 9), in vitro studies (n = 5), case reports (n = 1).

Details of the selected clinical investigations are shown in Table 2.

Study	Generation of Random Sequence	Concealment of Allocation	Blinding Function (Subjects and Assessors)	Blinding of Outcome Assessment	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Jeffcoat et al.	-	-	-	+	+	+
Alissa et al.	+	+	+	?	+	+
Sakka et al.	-	-	-	+	+	+
Winnet et al.	N / a	-	-	-	?	+

Table 1. Quality and Bias Assessment

(+) = low risk, (-) = high risk, (?) = unclear, n/a = not available

Author – Year of Publication	Sample Size	Intervention and Placebo / Control Group	Method of Drug Administration	Outcome Measures	Findings
Jeffcoat et al. -1995-	29 subjects	Flurbiprofen: one-third received 50 mg and one-third received 100 mg Placebo: one-third received a placebo	Flurbiprofen, 50 mg/ 100 mg B.I.D for 3 months after placement	Radiographic bone loss and changes during the healing period and after dental implant therapy.	Patients who received 100 mg of flurbiprofen had approximately half the bone loss as the other patients between the third and sixth month
Alissa et al. -2009-	61 Subjects	Ibuprofen: (n = 31), 67 Implants placed Placebo: (n = 30), 65 Implants placed	Ibuprofen, 600 mg, 4 times a day. for 7 days	Radiographic bone level (3 and 6 months follow up appointments)	Marginal bone around dental implants was not significantly affected
Sakka et al. -2013-	28 subjects	Ibuprofen: (n = 14), 31 Implants inserted Placebo: (n = 14), 26 Implants inserted	Ibuprofen, 600 mg, 4 times a day. for 7 days	Radiographic bone level (3 and 6 months follow up appointments)	Marginal bone around dental implants was not significantly affected
Winnett et al. -2014-	104 subjects	NSAIDs treatment group (n = 60), 119 implants failed. Non-NSAIDs cohort (n = 44), 78 implants failed.	Ibuprofen was mainly given, 600 mg four times a day.	Radiographic bone loss	More implants failed in NSAID cohort compared to non-NSAID cohort.

Table 2. Description of the Selected Clinical Investigations

Figure 1. PRISMA Flow Diagram of the Screening Procedure

DISCUSSION

Positive or negative effects on bone can be applied by the basic pathophysiology of NSAIDs. These groups of agents inhibit the conversion of arachidonic acid AA to prostaglandins which themselves have been involved in bone resorption^{22,23} and bone formation.^{24,25}

Prostaglandins effectively intermediate the process of inflammation.²⁶ It is well known that, during the inflammatory process, level of prostaglandins is elevated in inflamed tissues including gingival tissues.²⁷ Furthermore, a raised level of prostaglandins is often linked with a localized activity of bone resorption.^{28,29} On the other hand, a bone sparing effect can be achieved as observed in several reports in Dental Implantology^{13,30} and periodontology.^{10,31} However, the

indication for this is questionable because prostaglandins produced by osteoblasts under physiologic or pathologic conditions have dual roles during the process of bone remodeling.³² Moreover, it was recognized that bone formation in the mandible was stimulated by low levels of prostaglandin E2³³. Therefore, it could be argued that NSAIDs could inhibit bone healing around implants due to their inhibitory action on prostaglandin formation, as indicated in orthopedic literature.^{16,17} However, the former results were achieved in animal models using doses that differ from those given to humans. Therefore, contradictory conclusions might be created here, particularly if applied to osseointegration and bone biology in humans.

Jeffcoat et al., concluded in their clinical trial that Flurbiprofen appears to be effective in preserving the jaw bone around dental implants. For three months, approximately one-third of the patients received 50 milligrams of flurbiprofen two times a day, one-third took 100 mg of flurbiprofen two times a day, and one-third received a placebo. During the healing period after the implant was placed, bone height and bone mass were similar among patients in all treatment groups. Between the third and sixth month, all patients lost bone mass as the implants were exposed and dental prostheses were made. Patients who received 100 mg of flurbiprofen had approximately half the bone loss as the other patients. Bone mass stabilized in patients in all treatment groups between the sixth and 12th month after implant placement¹³. Furthermore, Kehoe et al³⁴ found that PG E2 production was dramatically decreased at the site of the periodontal ligament space when a 30 mg/kg dose of ibuprofen was given two times a day to detect its effect on orthodontic tooth movement. They concluded that a reduction in bone resorption as measured by tooth movement might be achieved by the administration of ibuprofen.

Alissa et al., measured the bone level around dental implants following a course of 600 mg of ibuprofen, given four times a day for 7 days post implant placement. The results of their clinical trial showed that the marginal bone around dental implants in both the intervention and the control group was not significantly affected.³⁵ The same methodology of drug administration was followed in the clinical trial conducted by Sakka et al.³⁶ Their results were in agreement with those of Alissa et al.³⁵ In fact, all the implants in the Jeffcoat et al., study¹³ were exposed and allowed to function after 3 months. However, the doses administered in their study were chronically used in contrast to in Alissa et al., and Sakka et al., studies^{35,36} that prescribed doses for postoperative pain relief. Nevertheless, generalization of the findings related to Alissa et al³⁵ and Sakka et al³⁶ studies should be treated with caution since their sample size was relatively small.

Winnett et al., have suggested in their retrospective study that the perioperative administration of NSAIDs (mainly ibuprofen 600 mg given four times a day) was linked with adverse biological events post dental implant insertion.³⁷ Their results showed that failing to achieve osseointegration has led to a total loss of 197 implants (119 implants failed in NSAIDs treatment group; 78 implants failed in the non-NSAIDs cohort). They believed that the results of their retrospective study are referring to a possible relationship between dental implants failure and the administration of NSAIDs. Their

suggestion is strongly reinforced by the biological evidence of NSAIDs interference with the healing process of fractured bone¹⁵ or surgery.^{38,39}

CONCLUSIONS

It is hard to evidently conclude that the administration of NSAIDs post dental implant surgery may have a significant effect on the supporting bone. Further clinical trials with larger sample size are highly required to satisfactorily answer the question of whether systemic nonsteroidal anti-inflammatory drugs (NSAIDs) have an impact on the supporting bone post dental implant insertion.

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