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Effect of Non-Steroidal Anti-Inflammatory Drugs on Bone Healing and Osseointegration: the Need for large Scale Human Clinical Trials

Research Article

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Abstract: This article revisits the topic whether the use of non-steroidal anti-inflammatory drugs (NSAIDs) affect bone healing and osseointegration. An understanding on this topic is crucial for clinicians to make evidence-based decisions to ensure patient safety and long-term success of implants. Based on authors' systematic search, a limited number of articles were found to merit another systematic review. The understanding on the effects of NSAIDs on bone, specifically in human subjects, and the underlying biochemical mechanism, remain limited, owing to design variations in limited published studies. Some studies may suggest NSAIDs have no adverse, if not protective effects. One can suggest that a combination of certain NSAID type, dosage, administration timing and duration may adversely affect bone. Authors would like to raise awareness and highlight the need of collective efforts and further studies with standardised quantitative measurements to help our understanding of the effects of this commonly used line of treatment.

Keywords: Non-steroidal anti-inflammatory drugs; NSAIDs; Implant; Hypoxia; Cyclooxygenase inhibitor; Osseointegration

Abbreviations: NSAIDs: Non-Steroidal Anti- Inflammatory Drugs; PG: Prostaglandin; COX: Cyclooxygenase; RANKL: Receptor Activator of Nuclear Factor-κB; NFATc1: Nuclear Factor of Activated T Cell Cytoplasmic 1; NF-κB: Nuclear Factor Kappa B; HIF: Hypoxia-Inducible Factor; BMP2: Bone Morphogenetic Protein 2

Introduction

The use of dental implants has become an integral part for the treatment of partial and complete edentulism [1]. Single stage protocol, where the implant is immediately loaded following its insertion and the installation of prosthetic tooth, is gaining popularity due to its potential in reduction of number of surgical interventions required while providing favorable clinical outcomes [2]. Optimal peri-implant bone healing during the early phases of osseointegration is crucial in providing stability and hence the long-term reliability of the treatment [3]. However, peri-implant bone healing can be affected by the quantity and quality of the bone, which is known to be affected by the patient's systemic health and certain medical conditions [4].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are regularly used globally to control chronic pain and/or inflammatory burden. In addition, both over the counter and prescription NSAIDs are extensively used as post-operative analgesics in the U.K. The effects of NSAIDs on bone remodelling and/or healing, however, are often overlooked when used as post-operative pain management. Prostaglandins (PGs) synthesised from arachidonic acid (from phospholipids bilayer in cell membrane) via cyclooxygenase (COX) activity mediate the destruction and formation of bone in the remodelling process [5]. Multiple COX isoforms (COX-1 and COX-2) exist, albeit the exact reason is an unanswered question. Depending on the type, NSAIDs can either selectively or non-selectively inhibit the activity of COX-1 and/or COX-2 and thereby influence the bone healing cascade [6].

Although there is evidence from *in vitro* and animal studies that indicate COX inhibitors, particularly, COX-2 inhibitors adversely affect bone formation [7-9], the exact role of COX enzymes and the effect of their inhibition in humans has not been ascertained. Several systematic reviews on the effect of NSAIDs on osseointegration in both orthopaedic and dental fields have been published [10-13], however, to date no consensus on this subject can be reached. The lack of information on co-factors such as smoking, alcohol consumption and other underlying conditions in many published studies exacerbate uncertainties. Through authors' own systematic literature search, several articles, which were not discussed in current published systematic reviews, have been identified. These limited findings, however, do not merit another systematic review. Therefore, authors would like to express our views and raise awareness through this opinion paper that the effect of NSAIDS on osseointegration is dependent on multiple factors and hence, carefully designed further research is needed.

Methods and Materials

Literature search

Following the initial scoping searches and formulation of the research question, in May 2020 a PRISMA (preferred reporting Items for systematic reviews and meta-analyses) workflow was used to search relevant publications in PubMed, Medline Ovid and Web of Knowledge search engines. The Search Terms used were: (anti-inflammatory agents, non-steroidal[Pharmacological Action]) OR (anti-inflammatory agents, non-steroidal [MeSH Terms]) OR ((anti-inflammatory) AND (agents) AND (non-steroidal)) OR (non-steroidal anti-inflammatory agents) OR (nsaid) OR (nsaids) OR (nsaid's) OR ((non) AND (steroidal) AND (anti) AND (inflammatory) AND (drug)) OR (non steroidalanti inflammatory drug) AND ((dental implants [MeSH Terms]) OR ((dental) AND (implants)) OR ((dental) AND (implant)) OR (dental implant) OR (dental implants)).

Inclusion and exclusion criteria

Inclusion Criteria included: osseointegration as primary/secondary outcome, randomised controlled trials, controlled clinical trials, human trials / animal trials and English language. Non-English literatures were excluded.

Results

Full-text articles of 17 studies were obtained and analysed. 9 articles were excluded as osseointegration was not defined as a primary or secondary outcome. The remaining 8 articles were assessed for this short communication.

Discussion

Two most commented human clinical trials in currently published systematic reviews are by Alissa et al. [14] and Sakka et al. [15], wherein non-selective NSAIDS ibuprofen (both 600 mg 4 times/day for 7 days post operation) were used. Neither study demonstrated statistically significant difference in bone levels in comparison to placebo or non-ibuprofen groups up to 6 months post operation. Authors further identified a human clinical trial by Bichara et al. [16], in which naproxen 500mg twice/day for 7 days was prescribed post operation and similarly, no significant difference in bone fill at defect site was reported up to 9 months post operation in naproxen and control groups. Interestingly, in a clinical trial by Jeffcoat et al. that used flubiprofen either 50 mg or 100 mg twice/day for 7 days post operation, it was reported that high dose flurbiprofen reduced ($p < 0.05$) the amount of bone loss up to 12 months post operation in comparison to low dose or placebo group [17]. Similarly, authors identified yet another clinical trial by Reddy et al. [18], in which patients who received 100 mg flubiprofen twice/day for 7 days resulted in increased bone density surrounding dental implants in comparison to control group, albeit the analyses were based on qualitative radiographs only. It is therefore not unreasonable to suspect that low dose use of flurbiprofen may result in adverse effects on bone.

Overall, there is insufficient evidence in the current literature to allow explicit conclusion on the effect of NSAIDs on osseointegration and/or implant failure. This is due to the limited literature available and discrepancies owing to variables such as dosage, dosage timing, dosage duration, choice of NSAIDs family, test species, age, sex, measurement endpoints as well as primary outcome measures. However, it may be deceptive to postulate that NSAIDS, as a class of drugs, due to their ability to inhibit COX and PGs, have adverse effects on bone and indeed, the impedance of bone healing that has been reported frequently in animal models has not always been translated to human clinical trials. Based on available literature, one can infer that different types of NSAIDs exert different effects on bone modelling, therefore further understanding of biochemical mechanisms underlying these drugs are needed.

It has been reported that flurbiprofen and its derivatives can inhibit osteoclast activation and osteoclast mediated bone resorption, through a mechanism independent of COX [19,20].This could explain, at least partially, the positive effects of flurbiprofen, when used at high dose, on bone that were seen in studies by Jeffcoat et al. [17] and Reddy et al. [18]. It should be noted that both studies prescribed flurbiprofen for a duration of 90 days, it is perhaps beneficial for patients who require long term use of NSAIDs for chronic pain relief to use flurbiprofen when an implant treatment is needed. Further studies are required to support such theory and investigate the effects of short term use of NSAIDS. It also appears that the positive effects of flurbiprofen is dose dependant [17]. Although the current literature is limited, it ispossible that other NSAIDs also have dose dependent effects on bone. For example, low dose aspirin (<100μg/ml, equivalent to approximately 100mg in human), has been shown to be beneficial for maintaining bone mass through inhibition of receptor activator of nuclear factor-κB ligand (RANKL) induced osteoclast activities via nuclear factor kappa B (NF-κB) and nuclear factor of activated T cell cytoplasmic 1 (NFATc1) pathways that are again independent of COX [21,22]. It is, therefore, possible that low dose NSAIDs should be used in combination with other biochemical factors to achieve pain relief while minimising the risk of bone loss. In addition to COX-1 and COX2, the signalling pathway of hypoxia-inducible factor (HIF), in particular HIF-1α subunit, is crucial in the regulation of osteoblast activity in bone repair [23]. While non-selective NSAID such as ibuprofen has been shown to reduce the expression of HIF in certain cell types [24,25], it has been reported that activation of HIF can attenuate the periapical inflammation, bone loss and stimulate heterotopic ossification [26,27]. Hypoxia-mimetic agents such as cobalt chloride can potentially be used in combination with NSAIDs to mitigate the possible negative effects on bone [28].

Further, while most of the animal and human studies focused on the post-operative administration of NSAIDs on bone healing, there are limited studies on the effects of pre-operative use of NSAIDs. One study by Lupepsa et al. [21] demonstrated that pre-operative use (42 days) of low dose (6.75mg/kg in rat, approximately equivalent of 75-80mg in human) non-selective NSAID aspirin resulted in an impaired bone deposition during early stage (7 days) of bone repair after implant placement [21]. Interestingly, the adverse effects were not detected after 28 days. This may partially explain the clinical trials conducted by Alissa et al. [14], Jeffcoat et al. [17] and Sakka et al. [15] did not reveal adverse effect of ibuprofen on bone, as these studies only examined patients at one time point 3 to 6 months post operation. It is possible the effect of NSAIDs on post operation bone healing occur primarily during the early stage and, it is uncertain whether any change in early-stage bone healing has a long-term effects on bone biochemically and/

or mechanically. This again highlights the need of well-designed and long-term future animal studies as well as clinical trials.

Lastly, with the advent of selective COX-2 inhibitors and their nominal advantages including lower potential for causing gastrointestinal bleeding, more clinicians may use selective COX-2 inhibitors in favour of traditional non-selective NSAIDs [29,30]. Similar to non-selective NSAIDs, the effects of COX-2 inhibitors on bone healing and osseointegration remain highly debated, owing to discrepancies in aforementioned variables in study designs. However, it is worth noting that there is an increasing number of reports that suggest the effects selective COX-2 inhibitors are detrimental to bone or facture healing [31-33]. It has been suggested that selective COX-2 inhibitors such as celecoxib inhibit bone morphogenetic protein 2 (BMP2) regulated osteoblast differentiation independent of COX activity [34], therefore, caution should be used when prescribing selective COX-2 inhibitors.

Conclusion

The limitations of our understanding on the effects of NSAIDs on bone, specifically in human subjects, are due to the wide variations in the designs of limited number of published studies. The exact effect of NSAIDs, as a class of drugs, on bone remain debatable. Although some available evidence may suggest NSAIDs have no adverse, if not protective effects on bone, one can suggest that a combination of certain type of NSAID drug, dosage, administration timing as well as duration may adversely affect bone. In addition, the question whether NSAIDs affect bone remain particularly relevant for patients on long term NSAIDs and possibly, will also be dependent on loading protocol following implant insertion. A collective effort and further studies with direct comparison of NSAIDs and control groups in well-designed studies with standardised quantitative measurement techniques are needed to help our understanding of the effects of this commonly used line of treatment.

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Competing Interests

The authors declare that they have no competing interests.

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