Perioperative Use of NSAIDs Might Impair Dental Implant Osseointegration

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ABSTRACT

Objective: To appraise whether adverse biological events following oral implant placement may be associated with perioperative use of non-steroidal anti-inflammatory drugs (NSAIDs). **Methods:** All patients treated in a university faculty postgraduate dental clinic between 1979 and 2012 that had experienced a failing and surgically removed dental implant (292 implants in 168 patients), were contacted to solicit additional information about their present dental and medical status and frequency of current and past use of NSAIDs. Potential associations between perioperative NSAIDs use and the occurrence of adverse biological events were explored by the use of 2x2 tables and two-tailed Fisher's exact tests. **Results:** One-hundred and four patients with initially 468 implants had experienced 238 implant failures, of which 197 were due to failing osseointegration (42%). Sixty of the participants, initially with 273 implants had used NSAIDs perioperatively and experienced 44% implant failures, versus 38% in the non-NSAID cohort. The NSAID-cohort experienced 3.2 times more cases of radiographic bone loss greater than 30% of the vertical height of their remaining implants, and 1.9 times more cases of cluster failures, defined as failure of 50% or more of the implant(s) placed. **Conclusions:** Nonwithstanding that a retrospective study design opens for potential bias, the current data indicate that dental implant osseointegration may be negatively affected by an inhibitory effect of NSAIDs on bone healing in vulnerable patients. Future and better clinical studies than the current should be designed to appraise more precisely the potential effects of NSAIDs on implant osseointegration in study populations that are not limited by stringent medical inclusion and exclusion criteria.

INTRODUCTION

The use of dental implants to support a prosthesis in a partially or fully edentate jaw has transformed the practice of dentistry. Dental implants have a good rate of success ranging from 90-95% when placed in the jaw of a patient with few or no known risk factors (Pjetursson et al. 2012; AAP 2013). Nonetheless, in some cases multiple implant failures can cluster in single individuals (Weyant & Burt 1993).

Local risk factors for unsuccessful osseointegration may include the effects of surgical trauma or unfavorable conditions like inadequate interdental space, premature prosthetic loading, or excessive overall biomechanical loading (Martin et al. 2009). As the medical literature has developed over time, the number of systemic risk factors conclusively demonstrated to be associated with the dental implants failing to osseointegrate has decreased (Bornstein et al. 2009). Although the variations of study design and/or patient selection make it difficult to assess the competing conclusions regarding the influences of local and general factors on implant failure the general consensus for now is that good and persuasive evidence is currently lacking (Salvi & Brägger 2009). It has been advised that clinical science currently cannot identify individual risk for dental implant osseointegration failure (Cochrane et al. 2009).

In this context, the research acknowledging the phenomenon of cluster failures occurring in a small subset of patients without obvious risk factors is especially troublesome. Many of the expected associations between systemic disease and osseointegration have proven difficult to demonstrate conclusively, and so this problem remains unexplained today. Moreover, a number of potential interactions between the

aforementioned risk factors makes it very difficult to explain clustered implant failures with any confidence. Clustered failures may be simply the unlikely result of a combination of several things going wrong in a single patient, or they may reflect an as yet unknown alternative single etiology (Jemt & Hager 2006).

In late 2010 a patient treated in the University of Toronto, Faculty of Dentistry, graduate prosthodontics clinic experienced persistent bleeding and rapid bone loss around three implants. Rigorous screening prior to patient treatment had failed to identify any particular local or systemic risk factor. An investigation to identify possible deviance from standard operating protocols, asepsis control or lack of patient compliance did not indicate any particular reason for the adverse outcome. While this investigation was ongoing, a second patient experienced a comparable adverse biological event. The two patient charts were scrutinized for possible causes, but nothing was uncovered except an intriguing finding that both patients had in common perioperative use of the drug Celebrex (Celecoxib). Following an internal inquiry to the graduate and staff clinicians a third patient that had been recently managed for idiopathic peri-implant bone loss was also identified as a Celebrex user (Fig 1). An initial review of the database of all implant patients treated in the clinic during 1979 to 2010 revealed that only 14 out of 1705 patients were recorded as having been taking Celebrex perioperatively. Surprisingly, nine of these 14 patients had experienced severe idiopathic bone loss subsequent to the implant surgery. Such a high prevalence of adverse biological events in a population taking a specific COX-2 inhibitor prompted the current investigation.

Celecoxib belongs to the pharmaceutical class of non-steroidal anti-inflammatory drugs (NSAIDs) and, specifically, is a relatively selective inhibitor of the enzyme cyclo-

oxygenase isoform 2 (COX-2). COX-2 inhibitors are primarily responsible for suppressing the synthesis of prostaglandins associated with inflammation and pain. In addition to the primary effects of the COX-2 enzyme on inflammation, the COX-2 enzyme is suspected to play an important role in tissue homeostasis (Ricciotti & FitzGerald 2011). This role was believed previously to be primarily a function of COX isoform 1 (COX-1), but recently this has become controversial. Non-selective formulations of NSAIDs (e.g. ibuprofen, naproxen) inhibit both COX isoform 1 and 2, and, consequently, prostaglandins that are not exclusively associated with local inflammation are also down-regulated. The effects of these prostaglandins are diverse, and involve most, if not all, tissues in the human body. The inhibitory effects of NSAIDs on COX affect many different functions, but are currently incompletely understood and may be contradictory depending on the drug, dose, and time-course of the inhibition (Thomas & Puleo 2011). Animal models that have focused on the effect of NSAIDs on hard and soft tissue healing have been shown to be largely unreliable for predicting what happens in humans (Chen & Dragoo 2013). NSAIDs also interfere with clot formation, a process that is critical for bone formation under some conditions and in particular for osseointegration of dental implants (Davies 2003). And yet, potential similarly inhibitory effects of many drugs, including NSAIDs on osseointegration of dental implants have been investigated only sparsely (Fu et al. 2012).

Obviously, the observation that the 3 patients with implant failures had used Celebrex could have been just a chance occurrence. Still, from a patient management as well as from a research perspective a methodological approach to consider the likelihood of a connection is mandated. Apparently, the potential association is hardly considered by most investigators, given that a random appraisal of publications within the field shows

that less than one in twenty clinical papers report this particular element of the surgical intervention. The current retrospective study was therefore initiated to explore whether the perioperative use of any NSAID was associated with a failures of osseointegration of dental implants. The null hypothesis was that there would be no difference in failure incidence between those exposed to perioperative NSAIDs *versus* those not exposed within the population of patients who had suffered dental implant failure.

METHODOLOGY

This retrospective study was approved by the University of Toronto Health Sciences Research Ethics Board in 2012 (#27644). All patients identified in the graduate dental clinic database who had experienced an early or late implant failure and removal were identified. During the period of 1979 to 2010, 1705 patients attending the Faculty of Dentistry graduate prosthodontic clinic received 5829 endosseous dental implants. According to the patient database, 168 (168/1705=10%) of these patients had experienced osseointegration failure of one or more implants totaling to 292 implants (292/5829=5%). The patients were contacted by letter and phone to solicit participation in the study and for follow-up interview. Once consent was obtained, the following information was acquired from the patients' charts and phone interviews: patient age; medical history; medication intake; smoking history; reason for tooth loss; type, number, and distribution of implants; surgeon; grafting; date/timing of failure; the date of prosthesis insertion and periapical/panoramic radiographs taken immediately post-operatively and all subsequent radiographs pertaining to implants associated with any adverse biological events. Clinical data entered into the patients' charts during the

surgical and restorative procedures such as signs and symptoms of peri-implant mucositis and/or osteitis, adverse restorative or technical events, etc., as well as those data entered through hygiene recall, were also collected to assist with determination of the most accurate date/time of adverse biological event, as well as the clinical presentation of other implants present in the event of coincident adverse biological events.

An implant was characterized as having an adverse biological event if mesial or distal annual bone loss was > 0.2 mm, or a peri-implant probing depth was > 5 mm, or a peri-implant probing depth was 5 mm and bleeding on probing (Salvi & Lang 2004).

The patients' medical histories were scrutinized carefully for patterns related to either implant failure or NSAID usage at the time of implant surgery and thereafter or both. The time-course of the putative effect of NSAID usage concurrent with implant surgery could not be defined and usage was therefore dichotomized as yes or no. Patients were categorized as having a simple or complicated medical history; a complicated medical history was defined as one containing any local or systemic disease or medication known to interfere with the autoimmune system or bone healing directly. These diseases were deemed initially to include: osteoarthritis with medication, rheumatoid arthritis with medication, osteomalacia, immune deficiency diseases including hepatic diseases, drug use, diabetes mellitus, bleeding disorders, and radiation therapy, renal disease and thyroid disorders, with or without medication.

The timing of failure between the implant surgery and implant removal was assessed and categorized as early and late. Early failures were considered to be those that occurred prior to the restoration and loading of the implant. 'Suspected' early failures

were those that occurred within one year of restoration and loading *and* which had associated clinical notes indicating a steady progression of symptoms associated with the failed implant. Late failures were those that occurred more than one year after restoration and loading.

Amongst the patients who had experienced an implant failure, the radiographic condition of any other surviving implants placed in the same surgical session as the failed implant(s) was assessed. Radiographic bone loss greater than approximately 30% of the vertical height of the implant was considered to be clinically significant (Schnitman & Shulman 1980; Misch 1993).

For lack of a pre-existing definition, for the purposes of this study “cluster failure” was defined as the surgical removal of 50% or more of the implants, when three or more implants were placed at the same time in one surgical session. A patient who received multiple implants in separate surgical sessions and subsequently lost some of these would or would not qualify as having had a cluster failure unless the criteria described above were first fulfilled.

Potential associations between perioperative NSAID usage and the occurrence of adverse biological events were explored by the use of 2x2 tables and two-tailed Fisher's exact tests, using the patient as the statistical unit. The current limited sample size combined with heterogeneity of variables precluded meaningful the use of multivariate statistics of the data. All statistical analyses were conducted using SPSS (version 19, SPSS Inc., Chicago, USA).

RESULTS

One-hundred and twenty-two of the 168 invited patients (72%) consented to participate, and 104 of these had charts that contained sufficient information to at least determine the perioperative analgesic prescription. These 104 patients who had initially received 468 implants, experienced a loss of 197 dental implants due to failure of osseointegration (197/468=42%).

The University of Toronto Faculty of Dentistry graduate prosthodontic clinic has long employed the Brånemark standard two-stage submerged surgery, four or six months healing prior to stage two surgery, and no immediate implant placement or immediate loading. Only implants from one manufacturer, Nobel Biocare® (Göteborg, Sweden) were used until 2006. This is reflected by the types of failed implants, i.e., Brånemark Standard (35%), Mark III-TiU (19%), Mark II (14%), Mark III (9%), NobelReplace (9%), Selftap (7%) and others (Ebon, Osseospeed, Brånemark Mark IV & Mark IV-TiU, and, later, Straumann).

The patients were treated by a variety of different residents/supervising surgeons, and the prevalence of implant failures in general ranged from 1% to 7.6% amongst the 15 surgeon-supervisors who worked in the IPU between 1979 and 2011 (Table 1). These numbers appeared related to the complexity of the case and not to the expertise of either the student or supervisor: the cases ranged from straightforward limited implant therapy – most commonly undertaken by the periodontology or prosthodontics residents – to very complex cases involving, for example, severe residual ridge atrophy treated with pre-implant block autografting handled by senior oral and maxillofacial surgery residents. In the current study, two participants who received a total of six implants

underwent site augmentation prior to their implant surgery, of which three implants failed. Otherwise, there were no particular demographic predilections, implant characteristics, intraoral locations, surgical supervisors/students or any particular surgical methodologies that could be related specifically to the 197 failed implants out of the total number of implants under study (n=468).

The NSAID used at the time of implant surgery, as well as dosages was in general poorly documented in the patients' charts. Available chart entries showed that ibuprofen (e.g., Advil), was the most commonly prescribed drug, as 600mg qid for up to 14 days. Several patients reported daily intake of acetylsalicylic acid (ASA), usually 81mg. Other prescribed NSAIDS were, in decreasing order of frequency: Ketorolac (e.g., Toradol), Vioxx, Celebrex, Diflunisal (e.g., Dolobid), Meloxicam, Paracetamol/Acetaminophen (e.g., Tylenol), and Naproxen.

Of the 104 patients who had experienced 197 osseointegration failures, 44 patients with 78 removed implants had not used any form of perioperative NSAIDs (non-NSAID-cohort). The remaining 60 patients with the 119 failed implants had a history of perioperative use of NSAIDs (NSAID-cohort). These average age of the patients was 52 years and 51 years,respectively The patients had received from 1 to 12 implants, with variable proportions of failing implants (Table 2).The distribution of failed versus non-failed implants appeared fairly comparable in the two patient cohorts (Table 3).

The non-NSAID-cohort, representing 43% of patients and 39% of the failed implants, contained 7 patients who had experienced implant loss that met the criteria for cluster failure. The NSAID-cohort, representing 57% of the patients and 61% of the failed

implants, contained 18 patients meeting the criteria for suffering cluster failure ($p = 0.11$; Table 4).

In all the patients with a failed implant, clinically significant bone loss was often observed around the remaining implants placed during the same Stage 1 surgery as the failed implant(s). In the non-NSAID-cohort, 18 remaining implants with clinically significant bone loss at the time of the last radiograph were identified (14%). This proportion was higher in the NSAID-cohort, where 70 implants demonstrated clinically significant bone loss at the time of the last radiograph (46%). (Table 5).

The presence of a complicated medical history that included diseases known or suspected to affect bone healing or overall healing in general appeared to differ between non-NSAID and NSAID-cohorts ($p = 0.001$, Table 6). The non-NSAID-cohort included 6 patients, which included: two patients with controlled diabetes mellitus type II; two patients with a history of hepatitis, one with osteoarthrosis and one patient on warfarin anticoagulant therapy at the time of implant surgery. In the NSAID-cohort there were 26 patients with complicated medical histories at the time of implant surgery. Of those with complicated medical histories in the NSAID-cohort, seven patients had controlled diabetes mellitus type II; six patients had osteoporosis and reported taking prescription medications (three patients had used short course oral bisphosphonates (two used alendronate, and one couldn’t remember the type of oral bisphosphonate prescribed), one patient was currently taking the COX-2 inhibitor meloxicam, and one patient was using the NSAID naproxen); four patients had thyroid disease; three patients had a history of renal failure; one patient had fibromyalgia and depression and was taking several prescription medications; other conditions were asthma, hepatitis,

gout, osteoarthrosis, tuberculosis and syphilis. There were no significant differences between the two cohorts with respect to smoking, both consisting mainly of non-smokers (p = 0.29, Table 7).

The ratio of early versus late failures in the non-NSAID-cohort was 1.9 and in the NSAID-cohort 2.5. The differences in the distribution of early versus late failures between the two cohorts seemed to be fairly comparable (Table 8).

The implants in the NSAID cohort have failed predominantly failed since 1992, i.e., failures between 2011 and 2002 (n=52), 2001 and 1992 (n=54), and 1991 and 1982 (n=4). In the non-NSAID cohort, the analogous numbers are n=24, n=30 and n=24 respectively.

DISCUSSION

In any university graduate clinic the standard procedure when an implant fail to osseointegration is to careful scrutinize potential causes. Most often, particular reasons for their failures are not revealed, even though inspections cover patient demographics, local and general conditions, surgical site characteristics, clinician competency and performance, implant features, treatment planning, complexity level, temporal elements regarding loading, etc. Attempts have been made to meticulously include a large number of variables and conduct multivariate statistics, but often with low explained variance due to low sample size in combination with the multitude of variables.

The current bivariate analyses appear to indicate an association between the perioperative intake of NSAIDs and failure of osseointegration. Slightly more than half of all patients who had experienced implant failure had used NSAIDs; the proportions of failed implants of the total placed (Table 2), as well as of failed versus non-failed implants (Table 3) appeared comparable in the two patient cohorts . Yet, the NSAID cohort included 1.9 times more cases of cluster failures (Table 2 and 4), and 3.2 more cases of severe bone loss in their remaining implants (Table 5). Moreover, amongst the patients with complicated medical histories who suffered implant failure, 3.2 more had been using perioperative NSAIDs (Table 6). The observation that the failures in the non-NSAID cohort are distributed fairly equally between 1982 and 2011, while first observed in the mid-nineties in the NSAID-cohort is intriguing, albeit potential explanations will remain speculative.

Admittedly, utilizing a retrospective chart analysis study model should be considered as a potential weakness of this investigation. However, identifying the role of NSAIDs in causing dental implant failure by the use of human clinical research is challenging given that perioperative NSAIDs may inhibit inflammatory bone metabolism in vulnerable populations while having no measurable clinical effect in healthy patient populations. Robust estimates of the effects of NSAIDs on dental implant outcomes in patients, with or without comorbid conditions can best be obtained by undertaking an adequately powered RCT that includes participants requiring regular intake of an NSAID, and followed over a relevant period of time, e.g., 5 years. Clearly, such study is unrealistic for ethical and logistic reasons. Alternative evidence must therefore be sought to clarify the potential relationship between NSAID use and effects on dental implant osseointegration. An observational approach, such as a retrospective study, is not

optimal from a study validity perspective, but may still provide indicators of possible cause-effect relationships if such exist.

Implants do not fail without cause, but unfortunately in many cases the causes are unknown. There is no reason to believe that implant failure is a random phenomenon, yet historical and modern literature addressing putative factors affecting implant success and survival frequently ignore unexplained failure as if it is a random phenomenon. Alternatively, it has been considered that one particular systemic illness or another might explain the incidence of implant failure, particularly cluster failure, but as more research has been done, these specific hypothetical relationships have become increasingly difficult to accept. Indeed, as a consequence of this, increasing numbers of patients with ‘complicated’ medical histories are being accepted for treatment – and being treated successfully – with dental implants. Nonetheless, implants do not always survive, and they certainly do not always achieve clinical success. The persistence of early failure, cluster failure, and clinically important early peri-implant bone loss epitomizes the unknown nature of the underlying etiology of peri-implant disease. It seems unlikely that all implant failures are caused solely by the lack of adequate peri-implant bone or poor surgical technique, yet currently there are no other evidence-based explanations if systemic disease cannot be implicated.

Different areas of medicine and particularly orthopedics and rheumatology have identified NSAIDs as a potential cause of altered bone healing. In dentistry, research has considered the use of NSAIDs in a favorable context in periodontology and as a problematic element in orthodontics. A common theme in the these papers is their identification of a lack of clear understanding of the various ways these drugs these

drugs affect bone metabolism (Kalyvas & Tarenidou 2008; Fracon et al. 2008). In a periodontal context, statistically significant reduction in the progression of periodontal disease was observed in beagle dogs (Williams et al. 1988, 1989, 1999). The same research group also investigated the effect of flurbiprofen on chronic inflammation, periodontal disease, and peri-implant bone levels in humans, with similarly positive results (Jeffcoat et al. 1993, 1995). However, although NSAIDs seem to delay inflammatory bone remodeling, the use of flurbiprofen for the purpose of reducing bone resorption after periodontal surgical procedures due to periodontitis is not common. Within orthodontics, it is known that NSAID use causes impairment of the tooth movement process (Walker & Buring 2001, Arias & Marquez-Orozco 2006), possibly by inhibiting osteoclast activity (Bartzela et al. 2009; Retamoso et al. 2011). The limited dental literature that is available regarding the topic supports the concern that the concurrent use of NSAIDs may clinically inhibit bone metabolism in response to orthodontic force application.

Our apprehension about the potential catabolic effect of the perioperative use of NSAIDs in implant surgery contrast conclusions made recently by an investigator group who have published findings from randomized clinical trials aimed at assessing the influence of ibuprofen on bone healing around dental implants (Alissa et al. 2009; Sakka & Hanouneh 2013). The authors reported no differences in peri-implant bone levels between patients after 6-months. Interestingly, the latter trial reported a large variance in the experimental study arm, i.e., the NSAID-group, to the extent that a non-parametric rather than a parametric test for statistical significance was used, albeit the mean values were comparable in the two study arms; the authors did not elaborate on the statistics (Sakka & Hanouheh 2013). Another important detail of the two trials was

that all subjects with any pre-existing systemic diseases were excluded from study participation. This strategy of only including only “healthy” study participants in controlled clinical trials carries some advantages, but may decrease the external validity of a controlled study (Britton et al. 1999).

One explanation for the sometimes contradictory findings in the medical and dental literature surrounding alleged effects of NSAIDs is likely the unresolved dose and time-course of NSAID therapy necessary to yield clinically important impediments (or improvements, for that matter) in bone healing in humans (Thomas & Puleo 2011). There have been a wide variety of different surgical/periodontal trauma models in different tissues with different NSAIDs in different doses for different durations in the experimental or observational study designs employed, and the results are understandably heterogeneous (Geusens et al. 2013).

In terms of the effects of NSAIDs on peri-implant bone healing, there is no reason to presume that the process of osseointegration is meaningfully different from fracture healing. Recent research focuses more and more on the intracellular signaling necessary for the complex cascade of osteogenic metabolism using the paradigms of fracture healing (Terheyden et al. 2012). Bone metabolism is altered by the NSAID-mediated inhibition of prostaglandin synthesis (Geusens et al. 2013), and NSAIDs have demonstrated effects on traumatic bone metabolism both *in vitro* and *in vivo* as shown in multiple areas of medicine (Li et al. 2011; Thomas & Puleo 2011; Abdul-Hadi et al. 2009; Vuolteenaho et al. 2008; Simon & O’Connor 2007).

Compromised bone healing may be the result of a single severe dysfunction or the summation of several less severe insults to the overall maintenance or repair of

homeostasis (e.g. NSAID use and one or more systemic illnesses). These findings suggest that the perioperative use of NSAIDs is a complicating factor that interacts with peri-implant bone healing in vulnerable patients; the absence of specificity of effect does not seem to outweigh the specificity of association. One example is dental implant treatment of patients with rheumatoid arthritis, where guidelines internationally are inconsistent with regard to potential risk (Bornstein 2009). While one experienced investigator team has observed no implant failures amongst such patients (Alsaadi et al. 2007), another has reported more marginal bone resorption and bleeding due to the underlying disease (Krenmair et al. 2010). The observations made in the current study infer that also the amount and type of NSAIDs that many of these patients take on a regular basis may have an impact on outcomes, along with potential sideeffects of other anti-inflammatory and immunosuppressive medication used by many of these patients.

It is the express purpose of the therapeutic use of NSAIDs to specifically inhibit the production of prostaglandins long known to play a critical role in inflammation, pain and ultimately, repair. There is abundant evidence that NSAIDs inhibit the normal course of bone healing and a dose-response relationship between NSAIDs and the degree of impairment of bone healing as well as the degree of COX inhibition achieved by a particular NSAID with regard to its ability to impair the healing of bone (Pountos et al. 2012). These relationships have been demonstrated repeatedly, but not universally. Variations in drug, timing, and duration have led to conflicting results (Geusens et al. 2013), but for reasons that are not definitively understood. In humans, the complexity of the absorption-metabolism-excretion cycle of pharmacotherapy in the presence of various systemic diseases – or other medications for the treatment of these diseases – makes determining this relationship even more difficult. A precise understanding of

bone remodeling and the interaction of common medications with this process is necessary if we are to prevent the development of complex pathological conditions in vulnerable patients in the future (Conte-Neto et al. 2012).

It cannot be overemphasized that the associations demonstrated in this study are not intended to be used to confirm causality. Nonetheless, the authors believe that the data are so clear as to suggest that a relationship between the use of NSAIDs and failure of dental implants cannot be ruled out. This hypothesis is supported by a significant amount of physiological and pharmacological evidence supporting the notion that NSAIDs interfere with the healing of bone from either fracture or surgical treatment (e.g. joint prostheses) as introduced earlier. Clearly then, further study – preferably prospective – is needed to determine whether the observed data are the consequence of a variety of factors impairing the patients' bone healing where the perioperative presence of NSAIDs then overwhelmed the patient's pre-existing limited bone healing capacity, or whether the observed data are the direct effects of inhibition of prostaglandin synthesis on reparative osteogenesis and dental implant osseointegration.

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Figure. Rapid bone loss development within a few months following implant placement in three low-risk considered patients with low expectation of an adverse outcome. No obvious cause for bone loss was identified. One common denominator for the three patients was a perioperative use of Celebrex.