Demonstration of OTC Naproxen Sodium's (Aleve's) Anti-inflammatory Action in Dental Implant Surgery Patients

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Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line agents in managing pain following outpatient dental procedures due to their effectiveness and lack of addictive potential.[1,2] Naproxen sodium is widely used due to its rapid onset[3] and long duration of action.[4,5] While several studies have demonstrated the analgesic efficacy of naproxen sodium following third molar surgery,[4,5] the effect of naproxen sodium on postoperative levels of inflammatory cytokines has not been examined to date. Therefore, the aim of this research proposal is to evaluate the local and systemic anti-inflammatory effect of over-the-counter (OTC) doses of naproxen sodium following the placement of dental implants.[6] As a secondary endpoint this study will also compare the effectiveness of naproxen sodium and acetaminophen in delaying and reducing postoperative pain.

Background

Naproxen is a member of the propionic acid group of nonsteroidal antiinflammatory drugs and possesses analgesic, antiinflammatory and antipyretic properties.[7] The sodium salt of naproxen was developed as a more rapidly absorbed formulation of the drug,[3] where a rapid onset is particularly desirable such as treating acute pain. Prescription dosing of naproxen (Naprosyn®) and naproxen sodium (Anaprox®) is currently FDA-approved for a variety of chronic and acute inflammatory conditions including the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, polyarticular idiopathic juvenile arthritis, tendonitis and acute gout. Both formulations are also approved for the management of pain and primary dysmenorrhea.[7] When treating arthritic conditions, the maximum daily dose of prescription naproxen and naproxen sodium should not exceed 1000 mg and 1100 mg per day respectively. For bursitis, tendonitis, gout, pain and dysmenorrhea the initial daily dose can be slightly higher; 1250 mg per day for naproxen and 1375 mg per day for naproxen sodium.[7]

Naproxen sodium (Aleve®) is also marketed as 220 mg tablets, caplets and liquigels for over-the-counter (OTC) usage with a maximal daily dose not to exceed 660 mg.[8] It is indicated for temporary relief of minor aches and pains associated with arthritis, backache, headache, the common cold, muscular aches, menstrual cramps and toothache. It is also indicated for the

temporary reduction of fever. For the first dose, two tablets (440 mg) may be taken.[8] In a placebo-controlled trial of acute postsurgical pain following the removal of impacted third molar teeth, an initial 440 mg dose of naproxen sodium was highly effective, demonstrating greater peak analgesic effects and a longer duration of action than acetaminophen 1000 mg (2 Tylenol® Extra-Strength).[5] A recently published study employing the same pain model also demonstrated that naproxen sodium 440 mg possesses equivalent peak analgesic effects but a longer duration of analgesic action than ibuprofen 400 mg.[4]

Placement of dental implants is a frequently performed outpatient surgical procedure, with United States dentists currently placing implants in approximately 500,000 patients per year.[6,9] This procedure has become the gold standard for replacing missing teeth due to its high level of predictability and patient acceptance, with long-term success rates greater than 95%.[10-12] Thus, the number of patients opting for this procedure over dentures and fixed bridges continues to increase.[13] In the period between 1999 and 2000 only 0.7% of the USA population had replaced missing teeth with implants in contrast to 5.7% between 2015 and 2016. It is estimated that by 2026, if the current pace of dental implant placement continues, approximately 17% of the population will have dental implants.[13]

Dental implant surgery involves the incision of gingival tissue to expose the underlying bone, followed by the creation of a precise bony cavity where the implant will be placed using a specialized surgical drill, and lastly the screwing of the implant into bone using a specialized handpiece.[6] Thus, it is not surprising that post-surgical pain is a common sequela following dental implant surgery.[14-18] Patients often experience post-surgical pain for several days after the placement of one to three dental implants,[14,18] but at a pain intensity level that is generally less than that of dental impaction surgery. This post-surgical pain is inflammatory in nature; thus, NSAIDs have demonstrated efficacy and are the preferred analgesics in this patient population. Postoperative administration of intranasal ketorolac (SPRIX®) and oral acetaminophen 325 mg plus codeine 30 mg have both demonstrated efficacy.[14,18]

The soft tissue and bony trauma associated with dental implant surgery upregulates inflammatory mediators both locally and systemically. Elevated levels of interleukin (IL)-6, IL-8, and macrophage inflammatory protein (MIP)-1β have been observed in gingival crevicular fluid (GCF) from the implant site and the adjacent teeth one week after surgery.[19] Prostaglandin E_2 has been measured in the GCF of teeth surrounding implant sites employing similar methodology.[20] Additionally, standard periodontal flap and bony recontouring surgery, which shares many similarities to dental implant surgery, induces an upregulation in immunoreactive prostaglandin E_2 and leukotriene B4 levels at the surgical site.[21] Dental implant surgery also increases cytokine levels in plasma, indicative of a systemic inflammatory response.[22,23] Thus, in addition to being a model to study the efficacy and tolerability of OTC analgesics, dental implant surgery also appears to be an excellent model to study the anti-inflammatory properties of NSAIDs such as naproxen sodium.

Therefore, we propose to initiate a double-blind, pilot study to evaluate the anti-inflammatory and analgesic effects of an OTC regimen of naproxen sodium versus acetaminophen in dental implant surgery patients. Notably, the vast majority of these patients are over the age of 45,[13] a patient demographic that is rarely captured in postsurgical dental pain studies. Compared to dental impaction surgery patients, implant surgery patients possess more comorbidities such as hypertension, hyperlipidemia and hyperglycemia.[24] Thus, while dental impaction patients are typically on few if any drugs, polypharmacy is more of the norm in dental implant surgery patients.[24] Performing a placebo-controlled study with OTC naproxen sodium in this population will provide the opportunity to confirm that its short-term use is generally safe and effective in these older, more medically complex patients. It will also confirm that naproxen sodium in the OTC dosage range is a good alternative to immediate-release opioid formulations, which are subject to misuse, abuse and diversion in this patient population.[1,2]

Objectives

This is a 3-day, randomized, double-blind, parallel-group, single-center study in patients following dental implant surgery. The primary objective of this study is to determine whether administration of naproxen sodium reduces levels of local and systemic inflammatory biomarkers, including PGE_2, IL-6, and tumor necrosis factor (TNF)-α, over the initial 72 hours after surgery.

The secondary objectives are 1) to determine whether administration of naproxen sodium (440 mg) compared to acetaminophen (1000 mg) immediately after surgery delays the onset of postoperative pain as determined by the time to first use of rescue medication over 12 hours, and 2) to compare the effectiveness of naproxen sodium (220 mg q8h) to acetaminophen (1000 mg q6h for three dosing intervals) in reducing postoperative pain over the first 24 hours after surgery as determined by summed pain intensity scores and use of rescue medication (tramadol 50 mg).

Further objectives of this investigation are to assess pain intensity, use of rescue medication and levels of inflammatory biomarkers at individual time points.

Study Design

This will be a pilot study in adult patients receiving one or two) dental implants. Subjects having either maxillary and mandibular implant surgery, including those requiring extraction of a tooth to place the implant or bone grafting on the day of surgery, will be included. The surgery as previously described involves the administration of local anesthesia (lidocaine plus epinephrine and/or 3% mepivacaine plain), laying a flap, creating a precise bony cavity with a specialized drill to receive the implant and "screwing in" the implant with another specialized instrument.

Patients will be excluded if they have:

- Advanced periodontal disease (>20% Clinical Attachment Loss + >20% radiographic bone loss).

- History of bisphosphonate usage
- Medical history or medical condition that makes any of the study medications (naproxen sodium, acetaminophen, tramadol, etc.) inappropriate treatment options including any scheduled or recent cardiac procedures (within 6 months)
- History of asthma, urticaria or allergic-type/ hypersensitivity reactions after taking aspirin or other NSAIDs
- History of, or active gastrointestinal perforation, ulcer or bleeding related to previous NSAID use
- Severe heart failure
- Contraindication to opioid use
- Positive urine drug screen for drugs of abuse unless on stable doses of a non-analgesic drug for a legitimate medical purpose
- Pregnancy – A urine pregnancy test will be performed immediately before the scheduled surgery on all women of child-bearing potential
- Local or systemic diseases that affects wound healing and inflammatory biomarkers (diabetes, autoimmune (rheumatoid arthritis), or inflammatory disorders – osteoarthritis is allowed).
- Smokers on this pilot study because it can affect levels of inflammatory biomarkers – a urine cotinine test will be performed immediately prior to the scheduled surgery on all subjects even if they deny smoking history
- History of systemic steroid use over 2 weeks within last 2 years.
- Poor oral hygiene on a non-compliant individual.
- Anticoagulant therapy
- Antidepressant therapy

All patients will provide informed consent prior to any study-related procedure. Baseline blood, urine, and GCF samples will be collected prior to implant surgery (T=baseline) for

assessment of COX pathway activity *ex vivo* and *in vivo*, plasma cytokine (IL-6, TNF-α) levels, and GCF PGE_2 and cytokine levels. Baseline COX-1 and COX-2 activity will be assessed *ex vivo* using whole blood assays as previously described.[25,26] Urine will be collected to measure COX activity *in vivo* by quantification of urinary prostanoid metabolites by liquid chromatography/mass spectrometry as previously described.[27] GCF samples will be collected by inserting a paper filter strip (Periopaper, Proflow, Amitville NY) into the gingival crevice of the teeth surrounding the implant site at three sites (distal, facial and lingual/palatal).[20] For two non-adjacent implants, one surgical site will be chosen for GCF collection.

Surgery will then be performed according to the standard of care in the PENN Dental Medicine Periodontics Clinic with lidocaine plus 1:100,000 and/or 1:50,000 epinephrine, and/or 3% mepivacaine plain. Nitrous oxide sedation will be allowed. Prohibited medication during or following surgery will be the use of glucocorticoids or the long-acting local anesthetic bupivacaine plus 1:200,000 epinephrine.

After completion of the surgery, additional blood, urine, and GCF samples will be collected (T=0). GCF will be collected from teeth surrounding the implant site at three sites (distal, facial and lingual/palatal), but not the implant site itself to avoid contamination with blood post-surgery. To more closely resemble published guidelines for the control of dental postsurgical pain,[1] the blinded administration of naproxen sodium 440 (n=15) or acetaminophen 1000 mg (n=15) will take place immediately after the completion of the surgical procedure, before the onset of postoperative pain in most cases. Because of potential screen failures due to positive uring drug screens, positive urine pregnancy tests and recent intake of confounding medications, we may to consent and enroll up to 35 subjects. Blinding will be performed by the University of Pennsylvania Investigational Drug Services employing an over-encapsulation technique. Study analgesic (naproxen sodium 440 mg or acetaminophen 1000 mg) will be ingested by patients with at least 8 ounces of water. Patients will be queried every 20 minutes throughout the 6-hour observation period after study medication ingestion for their pain intensity on a validated 10-point numeric scale.[28] Additional blood, urine and GCF samples will be

collected at 1, 2, 4, and 6 hours post study drug administration. Blood, urine and GCF collection will always occur after pain intensity assessments. If postoperative pain reaches at least a level of 4 on the numerical pain scale before 6 hours patients will be allowed to take the supplemental medication tramadol 50 mg.

Following the 6-hour sample collection time point, research patients will receive their second dose of study medication. Those in the naproxen sodium group will receive 2 placebo capsules and those in the acetaminophen group will receive two 500 mg acetaminophen capsules under blinded conditions. Patients will then receive post-operative instructions and discharged home.

At 12 hours post-surgery (while the patient is at home) patients in the naproxen sodium group will receive one active naproxen sodium 220 mg capsule and one placebo capsule and those in the acetaminophen group will receive two 500 mg acetaminophen capsules. Rescue tramadol 50 mg will be available (a maximum of one every 6 hours) for both groups if pain becomes intolerable.

Upon awakening on Day 2 patients in the naproxen sodium group will ingest one active naproxen sodium 220 mg capsule and one placebo capsule, while those in the acetaminophen group will consume two 500 mg acetaminophen capsules. At 6 hours those in the naproxen sodium group will receive two placebo capsules, followed by one active naproxen sodium 220 mg capsule and one placebo capsule at 8 hours, two placebo capsules at 12 hours and one naproxen sodium capsule at 16 hours. Those in the acetaminophen group will receive two acetaminophen 500 mg capsules at 6 hours, 2 placebo capsules at 8 hours two acetaminophen capsules at 12 hours and 2 placebo capsules at 16 hours. The same doing strategy will occur on Day 3 as Day 2. A global assessment of both study medications (poor, fair, good, very good or excellent will occur at the follow-up visit on Day 3. Rescue tramadol 50 mg will be available for insufficient pain relief but no more than one every 6 hours. The following table illustrates the dosing schedules:

	Naproxen Sodium Group	Acetaminophen Group
Day One:		
Immediately post-surgery	220 mg x 2	500 mg x 2
6 hours post-surgery	Placebo x 2	500 mg x 2
12 hours post-surgery	220 mg x 1 plus placebo x 1	500 mg x 2
Day Two		
On Awakening	220 mg x 1 plus placebo x 1	500 mg x 2
6 hours post dose one	Placebo x 2	500 mg x 2
8 hours post dose one	220 mg x 1 plus placebo x 1	Placebo x 2
12 hours post dose one	Placebo x 2	500 mg x 2
16 hours post dose one	220 mg x 1 plus placebo x 1	Placebo x 2
Day Three		
On Awakening	220 mg x 1 plus placebo x 1	500 mg x 2
6 hours post dose one	Placebo x 2	500 mg x 2
8 hours post dose one	220 mg x 1 plus placebo x 1	Placebo x 2
12 hours post dose one	Placebo x 2	500 mg x 2
16 hours post dose one	220 mg x 1 plus placebo x 1	Placebo x 2

Research patients will return to the study site at 24 and 72 hours for single urine, blood and GCF collections, pill counts, and verification of pain diary entries.

Schedule of Activities

	Pre Op (T=baseline)	**Surgery**	**Post Op (T=0)**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**	**48h**	**72h**
Urine pregnancy test, drug and cotinine screens	X											

Blood for COX-1 and COX-2 activity and plasma cytokines	X		X[2]	X	X	X	X			X		X
Urine for measurement of PG metabolites	X		X[2]	X	X	X	X			X		X
GCF for PGE_2 and cytokine levels	X		X[2]	X	X	X	X			X		X
Pain Intensity[3]			X	X	X	X	X	X	X	X	X	X
Global Assessment of Study Medication												X

[1] First dose immediately after post op sample. Dosing continued of fixed schedule for 48 hours, prn thereafter

[2] Biological samples will be collected immediately prior to dosing

[3] Pain intensity will also be measured every 20 minutes during the 6 hours inpatient observation period at the time immediately prior to the intake of any tramadol and at the time of study medication dosing during the inpatient and outpatient period.

Assays

COX-1 and COX-2 inhibition will be determined using *ex vivo* and *in vivo* indices of enzymatic activity. The *ex vivo* COX-1 activity assay is based on the capacity of platelets to form thromboxane (Tx) A_2.[26] PGE_2 formation in heparinized blood stimulated with lipopolysaccharide (LPS) correlates with the activity of induced COX-2 in monocytes.[25] Prostanoids will be quantified by liquid chromatography/mass spectrometry (LC/MS/MS) as previously described.[25,26] Systemic production of PGE_2, PGI_2, PGD_2, and TxA_2 will be determined by quantifying urinary concentrations of: 7-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid (PGEM), 2,3-dinor 6-keto-$PGF_{1\alpha}$ (PGIM), 11,15-dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid (tetranor PGDM), and 2,3-dinor TxB_2 (TxM), respectively. These

will be measured by LC/MS/MS as previously described.[29,30] Results will be normalized by comparison to urinary creatinine.

Paper strips containing GCF will be pooled at each individual patient time point and placed into a labeled Eppendorf microcentrifuge tube in ice and stored at -20°C until assayed. Samples will be eluted from the paper strips by the addition of 215 µl of sterile phosphate buffered saline (PBS) containing 0.1% bovine serum albumin to each tube and then incubated overnight at 4ºC. PGE_2 concentrations will be quantified by LC/MS/MS. Cytokine levels (IL-6, TNF-α, etc) in plasma and GCF will be quantified by ELISA or a commercially available multiplex bead assay kit (human cytokine group I kit, Bioplex™ Cytokine Assay, Bio-Rad Laboratories Inc) following manufacturer instructions.[19]

Sample Size and Data Analysis

We plan to enroll up to 35 patients in this pilot study in order to obtain 30 who have dosed with study drug. This sample size is based on our recently published study in patients undergoing third molar extraction (N=29), in which we demonstrated that ibuprofen 400 mg significantly reduced pain intensity and COX activity compared to placebo.[28]

The primary efficacy endpoint for the anti-inflammatory effects of naproxen sodium will be a comparison of cytokine levels in plasma and GCF between the naproxen sodium and acetaminophen groups. Secondary measures will include *ex vivo* COX activity in the blood and measures of prostaglandin metabolites in the urine. The primary efficacy measure for analgesic effects will be comparison between the two treatment groups for the 24 -hour area under the pain intensity curve. Individual pain intensity scores averaged at each time point will also be compared between groups. As an exploratory measure, the time to rescue medication after the first dose of naproxen sodium (naproxen sodium 440 mg) and the first two doses acetaminophen 1000 mg q 6hr) will also be analyzed, which will be censored at 12 hours. The percentage of patients requiring any rescue medication and the total amount rescue medication consumed (tramadol mg) will also be calculated and compared between groups.

For each of the overall blood assay levels, a Repeated Measures ANOVA will be used to compare the entire mean profile of naproxen sodium to acetaminophen. And, for each individual time period comparison, an ANOVA will be used to compare the two treatments and displayed using time-action curves with means and SEMs. Pain intensity scores will also be analyzed with ANOVA at each time period and Repeated Measures for the entire time dependent mean profile comparison.

The efficacy variable 'time to rescue medication' will be analyzed with survival analysis, a log-rank test, and Kaplan-Meier survival curves. All tests will be two-sided and $p< 0.05$ will be considered statistically significant.

Anticipated Results

We anticipate that patients receiving naproxen sodium 660 mg/day will display a significantly higher 24-hour SPID score compared to patients receiving acetaminophen 3000 mg/day. In addition, we expect both systemic (urine) and local (GCF) levels of prostaglandins to be reduced by naproxen sodium compared to acetaminophen, consistent with its mechanism of action as a greater peripheral COX inhibitor. Moreover, we postulate that naproxen sodium's anti-inflammatory effect, will result in decreased levels of cytokines both locally (GCF) and systemically (plasma). Equally as important, we expect naproxen sodium to be well tolerated in this patient population. Around the clock naproxen sodium 220 mg tablets dosed for the first 48 hours should provide adequate pain relief with less than 25% of subjects requiring supplemental tramadol 50 mg, although the current study is probably not adequately powered to demonstrate statistical superiority in this parameter compared to dosed acetaminophen 500 mg X 2 tablets

Organization and Leadership

This project will be performed by an interdisciplinary team with complementary areas of expertise. **Drs Hersh and Theken** will lead the project. **Dr. Hersh** will oversee the dental surgery component and regulatory aspects of the study. Surgery will be performed by four of his

colleagues in the PENN School of Dental Medicine, **Drs Jonathan Korostoff**, **Joseph Fiorellini**, **Yu-Cheng Chang and Thomas Yoo**. The study will be coordinated by **Ms. Stacey Secreto-Dankanich**, CCRC, EMT, who has coordinated more than 30 analgesic and local anesthetic clinical trials with Dr. Hersh and most recently has coordinated two ibuprofen inflammatory biomarker 3rd molar postsurgical pain studies. Postsurgical observation of patients and sample collection will initially occur in the Periodontal Clinic within the PENN School of Dental Medicine on the first floor of the Schattner Building. For later sampling and pain evaluations the patients will be moved to the Clinical Trial Unit on the third floor of the Schattner building. **Dr. Theken** will be responsible for the processing and analysis of NSAID biomarkers and also building and monitoring a REDCap database. **Matt Hutcheson MS** who was the biostatician on 8 FDA clinical trials where Dr Hersh was PI including 2 studies on CTY-5339A topical anesthetic spray, 2 studies on Kovanaze®, and 4 studies with Articaine®. will be responsible for clinical trial biostatistics. **Dr Mitchell** is a neurobiologist whose laboratory we will use (and have used in the past) to process urine, blood and GCF samples.

Future Efforts

This study should establish the assay sensitivity of a dental implant surgery pain model to evaluate analgesics in the OTC dosing range. In the future, this model can be used to study other biomarkers which may impact on individual patient variability to the analgesic effects of naproxen sodium including oral and GI microbiome, presurgical measures of anxiety and postsurgical pain expectations, naproxen pharmacokinetics and presurgical genomic measures.

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