Single Dose Oral Celecoxib (With or Without Acetaminophen) for Acute Post-operative Pain Following Impacted Third Molar Surgery.

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Protocol Title:	Single dose oral celecoxib (with or without acetaminophen) for acute post-operative pain following impacted third molar surgery.
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Population:	Approximately 100 adults (females/males) with ASA 1 and certain ASA 2 physical status classifications requiring surgical third molar extractions.
Number of Sites:	Single site in the Oral and Maxillofacial Surgery Clinic (OMS) at the University of Texas School of Dentistry at Houston (UTSD)
Study Duration:	2 years
Subject Duration:	1 week. Subject is scheduled for third molar surgery and must document pain for 3 days postoperatively. 5 to 7 days later, the subject is called to determine if he/she needs to return for a postoperative follow-up appointment.

General Information

This randomized, double-blind, placebo-controlled, prospective clinical trial is designed to compare the postoperative pain reduction of a single agent nonsteroidal anti-inflammatory drug (NSAID) and NSAID combination regimen administered preemptively. Subjects will be given a single oral dose of a cyclooxygenase-2 (COX-2) selective inhibitor (celecoxib 200mg), or celecoxib 200 mg in combination with acetaminophen (APAP 1000 mg) 30 to 60 minutes prior to the procedure. Oral surgery involving at least one impacted mandibular third molar will be performed using a combination of intravenous sedation and local anesthesia following UTSD surgical protocol. All subjects will be released with identical postoperative instructions and prescriptions for pain management. Nonopioid pain management will be prescribed as follows: 600mg ibuprofen with 500 mg APAP every 6 hours for the first 3 days, then as needed for pain. Subjects will be asked to document medication consumption, postoperative pain and complications for the following 3 days using a Qualtrics survey. An oral and maxillofacial surgery resident or faculty on call can offer emergency intervention with prescription of an opioid analgesic.

Background Information

The need for new and improved methods of pharmacological pain management without addictive properties is evident as the United States confronts a surmounting opioid epidemic. According to the CDC, more than 70,200 deaths were caused by a drug overdose in 2017. Of these deaths, about 68% involved an opioid and the total number of deaths in 2017 due to opioid overdose was 6 times higher than those seen 18 years prior. The lives of approximately 130 Americans are claimed by opioid overdose each day. (https://www.cdc.gov/drugoverdose/epidemic/index.html).

Preemptive analgesia is thought to reduce the magnitude and duration of postoperative pain by preventing the nociceptive sensitization caused by certain prostaglandins. While the topic of preemptive analgesia for dental procedures remains controversial, some studies suggest lower levels of pain in patients pre-medicated prior to surgery. In a study done by Bauer et al. 2013, preemptive ibuprofen showed no significant pain reduction following third molar surgery. However, when ibuprofen is combined with dexamethasone, superior postoperative pain management is observed.[1] A number of studies have found that ibuprofen administered before surgery shows no significant difference in postoperative pain reduction when compared with placebo or postoperative administration.[1,5] Even so, confounding evidence is seen in other studies and conclusive data for preemptive analgesia has been evasive due to differing experimental models including variations in the preemptive analgesic used, route of drug administration, local anesthesia and sedation during surgery, postoperative prescriptions, and subject selection.[8]

NSAIDs are used ubiquitously in pain management. Even so, the potential for gastrointestinal upset and bleeding occurs with nonselective COX inhibitors (eg. Ibuprofen, naproxen) due to hindrance of the gastroprotective functions of the COX-1 enzyme.[4,6] On the other hand, COX-2 selective inhibitors show no evidence of changes to platelets. As a result, COX-2 selective inhibitors may reduce patient experiences of postoperative gastrointestinal upset and perioperative bleeding. COX-2 selective inhibitors, such as celecoxib (Celebrex®), are generally overlooked due to their connection to subsequent cardiovascular and cerebrovascular events when used chronically, especially with rofecoxib (Vioxx®) which was later removed from the US market. The evidence shows some risk, though not excessive, for clot formation and sequelae in high risk individuals using COX-2 selective inhibitors for 6 months or more.[4,7] However, this study aims to exclude patients who may be at risk for these adverse events. In addition, celecoxib will be given as only a single preemptive dose for the management of acute dental pain.

Differences in the mechanisms of COX enzyme isoforms (COX-1 and COX-2) warrant further investigation of the efficacy of preemptive analgesia considering the COX selectivity of various NSAIDs. The COX-1 role in gastroprotective mechanisms suggests that NSAIDs with lesser COX-1 selectivity offer a safer, more tolerable alternative to nonselective NSAIDs for acute dental pain management.[6] The role of the COX-2 isoenzyme in pain and inflammation is observed after a painful stimulus elicits its synthesis of prostaglandins (PG).[2,4] By reducing or inhibiting the sensitization of nociceptors by the prostaglandins produced by COX-2, such as PG E2, preemptive COX-2 selective inhibition offers a potentially better postoperative experience for patients being managed for acute dental pain. The expected result is a decrease in postoperative dental pain while leaving the gastroprotective function of COX-1 intact.

Objectives

The goal of this clinical trial is to explore the preemptive effect of COX-2 selective inhibitors in combination with APAP on acute dental pain after surgical removal of impacted third molars. With evidence of the efficacy of COX-2 selective inhibitors in acute dental pain management, dentists can potentially offer various nonopioid pain management therapies to address the opioid epidemic while preserving the gastrointestinal housekeeping roles of COX-1.

Subjects will be given preemptive analgesics prior to undergoing impacted third molar extractions using a combination of intravenous sedation and local anesthesia. A survey will be given to the subjects for postoperative pain evaluation. Pain assessment with a visual analogue scale (VAS) at

predetermined times after surgery (3, 8, 12, 18, 24, 36, 48, and 72 hours) will be used as the primary outcome measure. Secondary outcome measures will include a verbal descriptive scale to supplement the VAS pain assessment and a record of any emergency analgesic consumption. Presence of infection and delayed healing will also be documented at the postoperative follow up call/appointment.

Study Design

This is a randomized, double-blind, placebo-controlled, prospective clinical trial comparing the preemptive effects of celecoxib vs. celecoxib/APAP on postoperative dental pain following impacted third molar surgery.

Per UTSD protocol, subjects will undergo assessment, radiographic imaging, and treatment planning. If all inclusion criteria are met, subjects will be scheduled for third molar surgery and asked to document his/her postoperative experience for 3 days with a Qualtrics survey online or printed. Patients will also document postoperative medication consumption using a medication diary. A follow up phone call 3-5 days after surgery will focus on questions pertaining to pain, infection, and other postoperative complications. If deemed necessary by this phone call, subjects are to present to UTSD (OMS Clinic) for a follow up 5 to 7 days after surgery for inspection of surgical site if deemed necessary during the follow up phone call. Any signs of delayed healing and postoperative infection will be documented and treated.

The survey for postoperative pain evaluation includes pain assessment with a visual analogue scale (VAS), which will be used as the primary outcome measure. Secondary outcome measures will include a verbal descriptive scale to supplement the VAS pain assessment and a record of any emergency analgesic consumption. These records are to be documented by the patient on the questionnaire at predetermined times following surgery (3, 12, 18, 24, 36, 48, and 72 hours).

Study Population

Approximately 100 adults presenting to UTSD with an ASA 1 and certain ASA 2 physical status classifications for impacted third molar extractions are to be included in the study. Both females and males between the ages of 18 and 45 with at least one mandibular third molar planned for extraction will be eligible to participate. Patients with third molars showing signs of severe pericoronitis will be excluded. Additionally, patients with known drug allergies to any NSAIDs, aspirin, acetaminophen, or sulfa drugs will be excluded. Also, patients with cardiovascular or hepatic diseases will be excluded. Non-compliance with pre- and post-operative medication regimens will result in exclusion.

Study Procedures

Day of Surgery: Patients will present to the UTSD OMS clinic for extraction of third molars. After signing informed consent forms, they will be randomly administered a preemptive regimen by a research team member to take 30 to 60 minutes prior to scheduled procedure. Randomization will be achieved by use of a random number generator. The PI and other members of the research team will not be blinded. The administration of preemptive medications will be dispensed prior to the start of daily operations. The research member tasked with dispensing will not be involved with the administration of medications to patients on the day of surgery. Subjects will be given either a single

oral dose of celecoxib 200mg with a placebo (Group 1) or celecoxib 200 mg in combination with acetaminophen 1000 mg (Group 2).

Prior to planned procedures for each day, the medication regimens (Group 1: celecoxib with placebo and Group 2: celecoxib with acetaminophen) will be dispensed into disposable cups labeled with a unique identification number for investigators to track which regimen is given to each of the patients. This identification number will link the regimen in the disposable cup to the Group 1 or Group 2 regimens. This number will be documented at time of drug administration and later used to identify the preemptive medication taken by each patient. The surgical procedure is not to be completed by any member of the research team. Intravenous sedation and local anesthetic agents will be documented with details about time of administration and dosage. Intravenous agents that may be used include midazolam, fentanyl, ketamine, and propofol. A titrated moderate sedation approach will be used with midazolam and fentanyl. No fixed dose can be predetermined due to differences in patient response to sedative medications. Ketamine and propofol may be used for deeper sedation as needed. General adult dosing guidelines for sedation medications will be as follows:

Midazolam (Versed): 0.02- 0.1 mg/kg initially, may repeat with 25% of initial dose after 3- 5 minutes. Not to exceed 2.5 mg per dose (1.5 mg for elderly). Not to exceed 5 mg cumulative dose (3.5 mg for elderly).

Fentanyl: 1-2 mcg/kg with slow IV push (over 1-2 minutes), may repeat dose after 30 minutes.

Ketamine: 1-2 mg/kg.

Propofol: 0.5- 1 mg/kg loading dose, may repeat by 0.5 mg/kg increments every 3- 5 minutes.

Local and topical anesthetics will be used at the discretion of the dental surgeon. Commonly used anesthetic agents are 2% Lidocaine with 1:100,000 epinephrine, 4% Articaine with 1:100,000 epinephrine, and 0.5% Bupivacaine 1:200,000 epinephrine. Topical anesthetic used is 20% Benzocaine gel. Surgical procedure should not exceed 2.5 hours.

Postoperative pain assessment: Subjects will be given postoperative instructions, prescriptions, medication diary, and a survey for documentation of pain 3 days after surgery.

Postoperative follow-up: Subjects will be called 5-7 days after procedure and asked to present to UTSD OMS clinic if necessary. Evidence of infection or delayed wound healing will be documented and treated.

Data and Safety Monitoring

Postoperative swelling, pain, bleeding and potential infection are risks associated with any dental extraction. Additionally, patients may experience trismus or suffer from dry socket after the procedure. The OMS clinic, or an on-call OMS resident after hours, will address any issues concerning postoperative care that is not manageable with the instructions and analgesic regimen given to study subjects. Emergency intervention might include other nonopioid and/or opioid analgesic pharmacotherapy, addition of corticosteroids or antibiotic prescriptions, or surgical therapy as determined by the OMS resident. Intolerable pain should be noted by the patient and the resultant emergency intervention should be documented on the questionnaire.

It is possible that patients may experience allergies or other adverse drug reactions to ibuprofen, acetaminophen, and celecoxib during postoperative pain management. If such an event occurs, patient will be advised to discontinue the medications, seek immediate emergency medical attention in severe reactions, and document the adverse reaction. Time of event, description of event, and the patient response to the event should be documented on the patient survey.

Statistics

For each of eight increments over 72 hours, we will measure multiple response variables indicative of pain for the both the NSAID and NSAID/APAP combination groups. As this study involves multiple measures of the same individual, we will use generalized linear mixed effects model to assess the effect of pain killers on pain as a fixed factor and (time|individual) as a random effect. In addition, we will derive one index measure for the difference between the peak in pain minus the minimum pain to allow us to use a more simplified statistical model without a random effect, for which we will analyze the data using a generalized linear model with appropriate error structure.

Ethics

IRB approval will be sought from UTHealth Committee for the Protection of Human Subjects (CPHS) prior to any study procedures.

Only subjects completing informed consent forms will be allowed to participate. A Spanish version of the consent document will be submitted after the English version has been approved.

Data handling and record keeping

New patient records including radiographs will be reviewed by OMS faculty (Harry Gilbert, DDS; Principal Investigator) and prospective participants will be selected by criteria mentioned previously. Subjects meeting the criteria will be invited to participate in the study before surgery. Patient name, DOB, telephone number, EHR number, and date of procedure will be accessed by team members of the study. Records for this study will be stored in a locked file cabinet within a locked office space, accessible only to study team members. A folder for each participant will contain PHI, panoramic radiographs, signed consent forms, surgical details, and survey data retrieved during this study.

Publication Plan

Abstract submission, poster or platform presentation, and publication in a peer-reviewed journal.

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