



**RANDOMIZED, DOUBLE-BLIND, PLACEBO-
CONTROLLED TRIAL COMPARING OPIOID-SPARING
AND OPIOID-CONTAINING ANALGESIA REGIMENS
FOLLOWING TRANS-SPHENOIDAL SURGERY FOR
PITUITARY TUMORS**

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Study Title

Randomized, Double-Blind, Placebo-Controlled Trial Comparing Opioid-Sparing and Opioid-Containing Analgesia Regimens Following Trans-sphenoidal Surgery for Pituitary Tumors

Study Hypothesis

An opioid-sparing postoperative analgesia regimen provides superior postoperative pain control, limits opioid-related adverse events, and improves inpatient hospital charges compared to a standard opioid-containing postoperative analgesia regimen.

Objectives

Primary Objective

- 1) Compare postoperative pain control regimens using an opioid-sparing analgesia approach and a standard opioid-containing approach in patients that have undergone endonasal, trans-sphenoidal (ENTS) surgery.

Secondary Objectives

- 1) Determine if the institution of an opioid-sparing analgesia regimen decreases the use of rescue narcotics in postoperative patients.
- 2) Determine if the institution of an opioid-sparing analgesia regimen decreases opioid-related adverse events
- 3) Determine if the institution of an opioid-sparing analgesia regimen decreases hospital length of stay, pharmacy charges, and overall hospital charges.

Background

Post-operative pain control is a common concern patients have when they consider undergoing a surgical procedure. Although effective for treating acute pain, opioid analgesics are also associated with dose-dependent adverse effects, including constipation, nausea and vomiting, altered mental status, and respiratory depression, all of which have been shown to increase patient length of stay (1). The use of non-opioid analgesics with different mechanisms of actions for acute pain control via a multi-modal approach is efficacious in reducing opioid consumption, decreasing the incidence of adverse effects, improving patient satisfaction and recovery time, and decreasing hospital costs (2,3,5).

Certain minimally invasive procedures may afford many patients the opportunity to achieve adequate post-operative pain control with minimal to no requirement of opioid analgesics, thereby sparing the patient known adverse effects that can increase length of stay and costs(3). The ENTS approach for resection of pituitary tumors is the standard surgical procedure for these lesions, and is associated with pain that is more easily managed post-operatively, making it an ideal procedure for an opioid-sparing post-operative pain regimen(4). Anecdotally, we have noted in our post-operative pituitary patient population that we are frequently able to adequately manage post-operative pain with scheduled non-opioid analgesics, often without requiring breakthrough opioid doses. Another safe and effective non-opioid analgesic that is widely used in multi-modal pain management for moderate pain is IV Caldolor (ibuprofen) (6.7.8). After literature review, we were unable to find a study that had attempted to use an opioid-sparing analgesic regimen for post-operative pain control following ENTS approach for resection of pituitary tumors.

Study Design

A randomized, double-blind, placebo-controlled, intervention trial involving 100 treated patients undergoing ENTS resection of pituitary lesion. Patients will be randomized into two groups; 50 treated patients in the opioid-sparing arm and 50 treated patients in the standard post-operative medication arm.

Selection and Enrollment of Subjects

Inclusion criteria

- 1) Adult patient undergoing ENTS surgery for resection of pituitary tumor
- 2) Adults ≥ 18 and ≤ 80 years of age
- 3) English speaking and literate or able to understand the use of a pain scale
- 4) BMI >19 and $<40 \text{ kg/m}^2$
- 5) Free of any physical, mental, or medical condition which, in the opinion of the investigator, made study participation inadvisable

Exclusion criteria

- 1) Renal failure (acute or chronic) or creatinine ≥ 2.0
- 2) Allergy or intolerance to acetaminophen, ibuprofen, or opioids
- 3) Pre-operative opioid tolerance, dependence, or abuse
- 4) Anaphylaxis to opioids
- 5) History of peptic ulcer disease or recent GI bleed requiring surgery
- 6) Cirrhosis, hepatitis, liver transplant, or liver function studies out of normal range (AST/ALT/bilirubin $\geq 3x$ upper limit of normal range)

- 7) Any subject who is unwilling or unable to sign informed consent for the study
- 8) Pregnancy
- 9) Incarcerated patients
- 10) Patients with chronic pain or significant medical disease whereby involvement in the study may, in the investigator's opinion, impact the patient's welfare
- 11) Patients with a history of TIA (transient ischemic attack) or stroke or myocardial infarction or a patient with risks factors for the above (such as hypertension, diabetes, hyperlipidemia, or smoking) that in the judgment of the PI places the patient at significantly elevated risk of adverse event after surgery.

Study enrollment procedures

- 1) Screening procedure: The outpatient clinic records of patients scheduled to undergo transsphenoidal surgery will be screened to determine if patients meet study criteria.
- 2) Tracking procedure: Inpatients will be followed by the study team for 48 hours or until discharge, whichever is first, after surgery. Patient data will be collected with a data collection sheet (Addendum B).
- 3) Informed consent procedure: The Investigator or a designee is responsible for obtaining informed consent from each patient and for obtaining the appropriate signatures and dates prior to the performance of any protocol procedures and prior to the randomizing subjects. The informed consent document will be used to help explain the risks and benefits in simple terms to the patient (Addendum C).
- 4) Randomization: Eligible patients who provide consent will be randomized to opioid-sparing or standard pain medication regimen.

Study Interventions

Pre-operative education and consent visit

All patients will attend a pre-operative education, consent, and pre-testing visit one or two days prior to the scheduled surgical date. Prior to this session, the patient's history from initial consult will be reviewed to screen for eligibility for the study; eligible patients will be contacted. If consent is obtained, the patient will be randomized to either the opioid-sparing arm or the standard arm (Addendum A).

Randomization

Patients will be randomized in a 1:1 ratio with blinded treatment assignment. The patients will be randomized using a computer generated list of random numbers from www.random.org. A list of 120 numbers will be randomized. Twenty extra numbers will be randomized to account for patients that randomize but do not undergo treatment. The randomized list will be placed with an ordered list of numbers from 1 to 120. Odd numbers will be assigned to the treatment group and even numbers to the control group. For example, the first randomized number of 61 would be assigned to the treatment group; a second number of 4 would be assigned to the control group. Enrollment will continue until at least 50 patients in each group have received treatment.

Opioid-sparing group

Intravenous Caldolor (800mg every 8 hours) will be initiated during surgery and oral acetaminophen 1000 mg every 6 hours will be initiated post-operatively and continued until discharge or 48 hours, whichever comes first. Breakthrough pain will be treated with rescue narcotics (intravenous morphine 2-4mg every 2 hours and oral oxycodone 5-15mg every 4 hours immediately post-operatively through discharge). Hydromorphone (IV 0.5-2mg every 2 hours and oral 2-4mg every 4 hours) will be used in patients with morphine or oxycodone allergy or intolerance. The dosing assignments in the study group are based on previous clinical studies of IV Caldolor (6).

Standard treatment group

Intravenous Caldolor PLACEBO will be initiated during surgery and oral acetaminophen 1000 mg every 6 hours will be initiated post-operatively and continued until discharge or 48 hours, whichever comes first. Breakthrough pain will be treated with rescue narcotics (intravenous morphine 2-4mg every 2 hours and oral oxycodone 5-15mg every 4 hours immediately post-operatively through discharge). Hydromorphone (IV 0.5-2mg every 2 hours and oral 2-4mg every 4 hours) will be used in patients with morphine or oxycodone allergy or intolerance.

Primary endpoints:

- 1) Comparison of pain scores between groups: Visual Analog Scale for Pain score at 4hr interval x 48 hours or until discharge, whichever comes first, per hospital policy (Addendum C).

Secondary endpoints:

- 1) Breakthrough narcotic requirement: The use of rescue narcotic in both groups will be recorded and compared using a standard equianalgesic oral morphine equivalent (OME) calculation (9).
- 2) Anti-emetic requirement: The total number of doses and type of any anti-emetic required post-operatively in both groups will be compared.
- 3) Constipation: The number of patients that do not have a bowel movement during hospitalization will be compared in both groups. Both groups will be treated with a standard bowel care protocol (Addendum D).
- 4) Opioid-related adverse events: The number of patients with opioid-associated adverse events, such as respiratory depression or sedation, will be documented; POSS sedation scale will be monitored.
- 5) Hospital economics: Total hospital charges, pharmacy charges, and length of stay will be compared.
- 6) Other adverse events: Epistaxis, potentially related to intravenous ibuprofen, will be compared.

Unblinding

Unblinding will occur in the case of adverse or hypersensitivity reaction to the study medications for the purposes of treatment and allergy documentation, or when the Principal Investigator and/or the Co-investigators feel that blinding is impacting patient care or patient safety.

The codes for each patient will be stored with the Research Pharmacy and the Clinical Research nurse and documented on the study drug form.

If it is necessary to break the blind, it will be documented, including reason for breaking the code, and the researchers will notify the IRB.

Data Analysis:

Frequencies will be reported for ordinal and categorical variables. Descriptive analyses such as minimum, maximum, mean, median, and standard deviations will be used for continuous variables. Demographic variables such as age, gender, and ethnicity will be reported. Independent samples t-tests will be used to compare mean VAS scores between the opioid-sparing and standard groups.

50 treated patients in each group are required to detect a 2 point difference on the 11 point (0-10) VAS with a standard deviation of 3.2 for the placebo group and 3.5 for the treatment group with alpha set at .05 and 90% power.

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