A double blind, randomized, placebo-controlled study to investigate the effectiveness of IV Acetominophen administered during functional endoscopic sinus surgery in reducing the use of opiates to treat postoperative pain

Matthew A Tyler, BA Davide Cattano, MD, PhD, Amber Luong, MD, PhD, Martin J Citardi, MD, Samer Fakhri, MD

Background and Rationale

Unrelieved postoperative pain may result not only in suffering and discomfort, but may also lead to multiple physiological and psychological consequences, which can contribute to adverse perioperative outcomes. Inadequate perioperative analgesia can potentially contribute to a higher incidence of myocardial ischemia. Additionally, the use of opioids has been associated with major side effects that can include impaired wound healing and delayed gastrointestinal (GI) motility that results in prolonged postoperative ileus. Pain and other postoperative and postanesthetic complications, directly related to surgery or to the analgesic (nausea, vomiting, headache) can potentially disturb the patient and prolong time to discharge.

Patients in ambulatory settings are especially affected if and when postoperative complications do occur. Multimodal (or, balanced) analgesia represents an increasingly popular approach to preventing postoperative pain. This approach involves administering a combination of opioid and non-opioid analgesics. Nonopioid analgesics are increasingly being used as adjuvants before, during, and after surgery to facilitate the recovery process after ambulatory surgery[1]. Early studies evaluating approaches to facilitating the recovery process have demonstrated that the use of multimodal analgesic techniques can improve early recovery as well as other clinically meaningful outcomes after ambulatory surgery[2,3].

Acetaminophen (APAP), named paracetamol outside the United States, has been available as an analgesic and antipyretic agent in the United States and the United Kingdom since the 1950s. Currently, APAP is the most commonly prescribed analgesic and antipyretic in children and is indicated for the short-term management of mild-to-moderate pain and the reduction of fever in both children and adults. In the United States, APAP has until recently only been available as oral and rectal preparations. As such, the use of this therapy in post-operative or acute care setting is hampered because of variability in analgesic effect and time of onset using these routes of administration[4,5]. Intravenous APAP is considered ~~as~~ the non-opioid analgesic of choice to treat postoperative mild and moderate pain, and has been demonstrated in several randomized trials to be both safe and effective at reducing acute post-operative pain in both children and adults[6]. Furthermore, in the treatment of severe pain, it can reduce the need for opioid-analgesics while exhibiting a relatively limited side effect profile when compared to opiods and nonsteroidal anti-inflammatory drugs[7].

Chronic rhinosinusitis (CRS) describes a group of disorders characterized by inflammation of the nasal mucosa and/or paranasal sinuses for at least 12 consecutive weeks[8,9,10].

In the United States, CRS affects approximately 30 million people, and represents 2% of the primary diagnoses in physician office visits, resulting in an estimated 200,000 sinus procedures annually[11]. Patients suffering from CRS that is refractory to medical management complain of symptoms that include fatigue, headache, nasal drainage, facial pain and pressure, and decreased sense of smell[12]. Functional endoscopic sinus surgery (FESS) represents a surgical approach to treating CRS that is unresponsive to medical management. Outcomes studies have identified FESS as efficacious at reducing the majority of symptoms related to CRS[13,14]. Despite this, pain associated with CRS remains a significant co-morbidity that often is resistant to both medical and surgical management[14]. Reducing the incidence and severity of *acute* post-operative pain is paramount to reducing the development of chronic pain that may exacerbate a patient's existing pain[15,16,17]. The use of pre- and intra- operative IV acetaminophen thus serves as a unique pain management modality in this setting, as it has the potential for reducing post-operative complications and pain, with the additional benefit of minimal intraoperative bleeding, an undesirable complication often associated with FESS[18] and with the use of NSAIDs[19,20.]

The use of IV acetaminophen in ENT surgery is not a novel endeavor. Indeed, studies have demonstrated the efficacy and safety of IV acetaminophen for use in tonsillectomy and FESS[21,22]. We wish to provide a more comprehensive analysis of pain management in the setting of FESS in the following ways : 1.) by administering IV acetaminophen *perioperatively* (before start of surgery, and after surgery completion; 2.) employ a pain score of 4 (whereas other studies use 3) as a cutoff for breakthrough pain; and, 3.) address novel outcomes including patient sedation and patient satisfaction, in addition to opioid analgesic use. In our institution, we have completed a preliminary pilot study exploring the use of intravenous anesthesia which included acetaminophen during bilateral endoscopic sinus surgery. Secondary outcomes measured during the study included:

1. Pain
2. Rescue analgesic use
3. Nausea/Vomiting
4. Time spent in recovery
5. Successful discharge from the PACU and the Hospital

Our pilot data has reaffirmed that the procedure is overall benign, with few associated risks and adverse events. Of note, none of the patients in our preliminary study required admission to the hospital after surgery for further observation as a result of uncontrolled pain or nausea. Based on this experience, we would like to explore the efficacy of intravenous acetaminophen (Ofirmev), a non opioid/non steroidal analgesic, in endoscopic sinus surgery.

Objectives

In this study, we wish to formally investigate the effects of IV acetaminophen (Ofirmev) administered perioperatively and during endoscopic sinus surgery on pain experienced and on

the use of opioid analgesics. Secondarily, we wish to collect data on spontaneous reports of adverse events (AEs) and overall patient satisfaction.

Specific Aims

Primary aim: Assess the efficacy of IV acetaminophen in controlling postoperative pain We hypothesize that the use of IV acetaminophen before and after FESS will reduce post operative pain by approximately fifty percent in selected patients. The incidence and intensityof pain will be assessed using a visual analog scale, or VAS, (0-100; 0 = no pain; 100 = worst pain) before (baseline) and after surgery. Each patient's baseline pain intensity will be evaluated on the day of surgery in the preoperative waiting area. Postoperative pain intensity will be measured using VAS in the postoperative anesthesia care unit different time points – 0 minutes; 15 minutes; 30 minutes; 1 hour; 2 hours; 3 hours; 4 hours postoperatively.

Secondary aims

Secondary aim 1: Investigate the effect of IV acetaminophen on the use of postoperative opioid analgesics

We hypothesize that greater pain control using IV acetaminophen will result in a decreased need for postoperative opioid analgesics. The total amount of postoperative opioid use will be recorded as follows: after the patient has arrived in the PACU (post anesthesia care unit), the incidence and intensity of pain will be assessed using a VAS (0-100) as described above . Pain relief will be achieved by incremental doses of morphine 1 mg bolus, based on a VAS score of 4 and above, to be repeated every 5 minutes if needed. The total amount of morphine utilized in PACU and time of 2nd dose of IV acetaminophen will be recorded.

Secondary aim 2: Analyze effects of IV acetaminophen on intraoperative analgesic use

Brief episodes of tachycardia and hypertension are expected in FESS procedures. These will be treated by increasing inhalational agents of 0.5% inspired fraction at a time. A supplemental dose of fentanyl in the amount of 1 mcg/kg will be available for HR and BP greater than 15-20% above baseline after no response to volatile change. The following measurements will be recorded: total amount of fentanyl utilized; the hemodynamic parameters during surgery and anesthesia; the inspired fraction of inhalational agent; and the number of step-wise increases for hemodynamic control. Differences between control and experimental groups will be analyzed for statistical significance.

Secondary aim 3: Identify potential correlation between vital signs and postoperative pain intensity

We wish to evaluate if postoperative pain intensity is associated with changes in vital signs, such as heart rate, respiratory rate, blood pressure, and temperature. Each patient's vital signs will be collected at the specified time points as outlined above, in addition to measuring pain intensity using the VAS scale. Data will be collected and analyzed to search for a statistical correlation between postoperative pain intensity and vital sign changes (e.g., increased respiratory rate correlates with greater pain intensity). In addition, differences in vital signs between groups will be analyzed for statistically significant differences.

Specific am 4: Examine the effect of IV acetaminophen on post-operative quality of recovery

In this study, we will analyze the post-operative quality of recovery by researching three different factors: 1.) the number of spontaneous reported adverse events; 2.) the level of post-operative sedation; and, 3.) the patient's overall reported satisfaction with hospital experience.

We will monitor and record any adverse events including, but not limited to, dizziness, nausea, vomiting, tachycardia, bradycardia, arrhythmia, hypertension, hypotension, allergic reaction, in addition to any other complaint from the patient.

Sedation will be assessed using a 4-point scale, with 3 = sleeping, not arousable; 2 = sleeping, arousable; 1 = awake but drowsy; 0 = fully awake. Each assessment will be conducted every 10 minutes for the first hour, and then every 30 minutes until time of discharge.

A questionnaire evaluating pre-discharge quality and efficacy of pain management will be given to the patient before discharge. A telephone interview and questionnaire will be administered within 48 hours but ideally 24-30 hrs from discharge to assess for pain control, utilization of analgesics, and patient satisfaction. The follow-up questionnaire will be tailored to discriminate overall experience but differentiating immediate postoperative pain control versus control of pain at home.Hypothesis

The use of IV acetaminophen (Ofirmev) is both safe and efficacious in reducing post-operative pain; we hypothesize that its use will reduce post-operative pain by 50% when compared to control group using the VAS analog pain scoring system.

Study Design

Study design type: Double blind, prospective randomized controlled study at a single institution

Study population: Patients undergoing medically indicated functional endoscopic sinus surgery for management of chronic rhinosinusitis (with or without polyps).

Inclusion criteria:

1) Patients undergoing surgical management for CRS (with or without polyps)
2) Operating time must be at least 2 hours in duration.
3) Number of sinuses involved must be 3 or greater

Exclusion criteria:

1) History of hypersensitivity to acetaminophen
2) End stage renal disease
3) End stage liver disease
4) History of chronic pain, or use of opioid medication in the previous two weeks
5) Severe depression or anxiety
6) Use of gabapentin or any other pain modulator
7) History of acute sinusitis or mucocele
8) History of seizures
9) Known or suspected history of alcohol or drug abuse
10) Known or suspected history of morphine intolerance

Study groups: A total of 60 patients will be enrolled in the study. 30 patients will be randomized to the control group, and 30 will be randomized to the experimental treatment group.

Experimental group: The experimental group will receive a preoperative dose of 1000mg IV acetaminophen over 15 minutes. This will occur at least 15 minutes before the start of surgery and no earlier than 1 hour before the start of surgery. Another 1000mg dose of IV acetaminophen will be administered 4 hours after the first dose. Patients will be discharged with instruction to continue APAP 500 mg PO every 6-8 hours. A rescue analgesic containing oxycodone will also be provided (with APAP concentrations of 325 mg per Hospital and FDA recommendations). Patients will be instructed verbally and by a written note, not to exceed a total 4grams of acetaminophen per day, total dose includes both IV and PO intake. A safety explanation pamphlet will be provided to the patient and accompanying family members or significant others, with the written instructions about the 4 grams limits of APAP per day.

Control group: The control group will receive 100 mL of 0.9% normal saline in place of IV acetaminophen in the same manner as the experimental group; the investigator/physician in question will be blinded to the agent that is being administered. Patients will be discharged with instruction to continue APAP 500 mg PO every 6-8 hours. A rescue analgesic containing oxycodone will also be provided (with APAP concentrations of 325 mg per Hospital and FDA recommendations). Patients will be instructed verbally and by a written note, not to exceed a total 4 grams of acetaminophen per day, total dose includes both IV and PO intake. A safety explanation pamphlet will be provided to the patient and accompanying family members or significant others, with the written instructions about the 4 grams limits of APAP per day.

Protocol*:* Patients scheduled for FESS that meet inclusion and exclusion criteria will be approached in the ENT clinic at the time that the patient is being scheduled for surgery. The typical procedure lasts an average of 3 hours and the average recovery time (phase and phase 2 PACU combined) is 3-4 hours before discharge. Patients and family members or significant others will be notified about the study and the consent will be reviewed. If the patient wishes to proceed with enrollment, a consent form will be signed. At that time, a preoperative

assessment questionnaire will be completed which documents the patients baseline vitals, global pain based on a visual analog scale (VAS), list of medications, and validated Brief Pain Inventory questionnaire (see attached).

On the morning of their surgery, the patient will be randomized into either the control or experimental group. The medication will be picked up from the Memorial Hermann Hospital pharmacy where it has been packaged such that the investigators are blinded to the medication vs. saline. The process of randomization will be coordinated by the pharmacy.

Patients will receive midazolam for preoperative anxiety (1 mg for body weight up to 60 kg, 2 mg for body weight greater than 60 kg), a standard intravenous induction (propofol 2 mg/kg, lidocaine 1% 0.5 mg/kg and rocuronium 0.5 mg/kg) and maintained by inhalational anesthesia (sevoflurane based, no nitrous oxide) with supplementation of a standard induction dose of 2 mcg/kg of fentanyl. A supplemental dose of fentanyl in the amount of 1 mcg/kg will be available for HR and BP greater than 15-20% above baseline after no response to volatile change. Sevoflurane will be maintained at 1 MAC (minimal alveolar concentration) based on the age of the patient (ventilator calculated MAC) under semiclosed circuit conditions (1-2 L oxygen/air mixture/minute of fresh gas flow).

Adverse Events

Definition and reporting of Serious Adverse Events. A serious adverse event (SAE) is a subtype of adverse event. An SAE is any adverse event occurring at any dose of the medication when the subject outcome is:

- death
- life-threatening (i.e., Subject was at substantial risk of dying at the time of the AE)
- inpatient hospitalization or prolongation of existing hospitalization
- disability or permanent damage
- congenital anomaly/birth defect in the offspring of a subject who received study medication

Note: Other serious (important) medical events that do not fit the above outcomes, but which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes, are also considered to be SAEs. Examples of such events allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The investigators are obligated by regulation to report SAEs and information pertaining to the safety of a drug under clinical investigation to local and other drug safety regulatory authorities.

Cadence Pharmaceuticals must be notified within 24 hours of an Investigator's/Sponsor initial discovery of an adverse event meets the protocol definition of an SAE. The procedure for reporting serious adverse events are as follows:

- Call the Cadence Pharmacovigilance Call center at 1-877-647-2239
- Provide as much identifiable Subject and SAE information as possible to the Call Center staff. Even if incomplete information is initially known about the SAE, the initial report should be made as the case continues to be investigated.

- Enter the SAE information into the Subjects CRF and Source Note.
- Provide supplemental SAE information and/or documentation upon request of Call Center staff.
- If deemed necessary for the medical management of the subject, obtain the treatment assignment for the subject from the study pharmacist.

Serious adverse events will be monitored up to 2 days following the last Study Medication dosing and followed to resolution or stabilization.
Additionally, the Investigator should notify Cadence of any SAE which occurs after the 2-day time period, if the SAE is believed to be certainly, probably or possibly related to study medication.
The Investigator or designee must comply with applicable local regulatory authority and IRB/IEC requirements concerning the reporting of SAEs and any safety-related documentation (e.g.., safety letters, revised IB) that may be received from Cadence. Additionally, Investigators should keep all safety-related documentation in site files.

Statistical Methods

Our power analysis was conducted using the following hypotheses:

1.) At the time of arrival in PACU recovery, the incidence of postoperative pain in the control group will be 70%; the incidence of postoperative pain will be less than 35% in the experimental group.

We determined that at least 25 patients in each group should be enrolled to achieve a power of 80%, allowing for an α error of 0.05 and a β error of 0.2.

All numerical results will be expressed as mean ± SD; categorical results will be expressed as a percentage. Differences between groups will be assessed using the Student's *t* test for the normal and the Mann-Whitney *U* test for nonnormal distributed data. A Chi-squared test will be used to compare the difference of categorical variables between groups. A p-value less than 0.05 will be considered as significant. All statistical analysis will be performed using GraphPad Prism(GraphPad Software, Inc., La Jolla, CA, USA).

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