Study title: Effect of Post-operative Ibuprofen After Surgery for Chronic Rhinosinusitis

NCT number: NCT03055507

Date: October 12, 2022

RESEARCH STRATEGY

(a) Significance

Chronic rhinosinusitis (CRS) is a common condition affecting up to 10% of the population and characterized by diffuse sinonasal inflammation leading to nasal congestion, drainage, facial pain, and hyposmia or anosmia. Typical management consists of appropriate medical therapy, including antibiotics, topical and systemic steroids and saline irrigations. In persistent or recalcitrant cases, surgical treatment may be required. Functional endoscopic sinus surgery (FESS) is a commonly performed procedure for patients with CRS. The technique uses a minimally invasive approach to open the sinus cavities and allow for clearance of mucous and infection through widening of the natural ostia of the sinuses. The procedure itself is quite safe and is typically performed on an outpatient basis. FESS is becoming more and more common with current estimates of 250,000 cases performed in the United States every year.[1] Care in the immediate post-operative period varies from surgeon to surgeon, but typically includes nasal saline irrigations, antibiotics, early post-operative debridement and pain management with acetaminophen and oxycodone. Due to the theoretical risk of decreased platelet aggregation and possible increased bleeding tendency, most practitioners typically avoid the use of NSAIDs for post-operative analgesia. However, no study has been performed to assess this risk. In fact, previous studies have examined the use of preoperative ketorolac in patients undergoing FESS and found no increased risk of hemorrhage intra-operatively or post-operatively.[2] Thus, the purpose of this proposed study is to perform a pilot study to investigate key logistics for a future study to assess safety and effectiveness of ibuprofen in the post-FESS patient with the hopes of decreasing narcotic use after FESS.

The nidus for development of this study to standardize post-operative analgesia reflects the opioid epidemic in the United States and physician contribution to opioid related deaths. Opioids are now responsible for more deaths than suicide and motor vehicle accidents combined. The majority of these deaths (60%) occur in patients receiving prescriptions based on current prescribing guidelines by medical boards.[3] A recent public health report by United States Surgeon General, Dr. Vivek H. Murthy, MD, MBA, calls for immediate efforts on gathering evidence-based information on appropriate opioid prescribing practices.[4] Therefore, efforts are needed to refine the current practices of American physicians in regards to prescribing opioids. Multimodal analgesia, and demonstration of safety, is necessary to help curb the widespread, and perhaps, overuse of opioids among treated patients.

In this proposal, our goal is to perform a pilot, prospective cohort study to evaluate the use of narcotics in sinus surgery and the effect of ibuprofen in the non-packed nose following FESS. The goals will be to quantify the average number of opioid pills used after FESS and assess the impact of ibuprofen in the post-operative period on pain and epistaxis outcomes. This work will lay the foundation and allow us to design and perform a future optimal prospective, randomized study. This study will help to gain understanding of current opioid use in post-op sinus patients and assess the safety and effectiveness of post-operative ibuprofen administration on pain.

By gaining an understanding of the average number of opioids used, and the ability to decrease that need with addition of other analgesics, we can work to decrease current opioid prescribing practices and work towards curbing the current opioid epidemic plaguing the United States.

We acknowledge early in this proposal the difficulty of performing a randomized, double-blinded placebo controlled trial. Specifically, at this point the effect size on analgesia and epistaxis post-FESS is unknown, thus appropriate sample size estimate calculations cannot be performed. Therefore, we plan on performing this study as a cohort study. This pilot study will serve multiple purposes; first it will allow us to determine the adequate sample size needed to observe a significant effect. Additionally, we will be able to document patient's willingness to participate in a future randomized study thus allowing for design and execution of the optimal prospective, randomized study.

(b) Innovation

To our knowledge, there has not been a prospective study in CRS patients following endoscopic sinus surgery that examines the use over the counter NSAIDs, namely ibuprofen, in the post-operative period. One previous study has shown that perioperative IV ketorolac improves immediate post-operative pain scores and does not increase epistaxis or hemorrhage.[2] The widespread use of ibuprofen as an over-the-counter analgesic, as well as its safety and efficacy as an anti-inflammatory, necessitates further studies to assess safety and evidence-based studies in this population. The need for improved non-narcotic analgesia post-FESS is analogous to the recent paradigm shift in post-tonsillectomy pediatric patients where many national and international guidelines now discourage post-tonsillectomy narcotics and instead advocate ibuprofen and acetaminophen.[5-8]

In addition to the paucity of studies examining the use of NSAIDs in post-operative FESS patients, there are no validated scoring systems for post-operative epistaxis. This pilot study will utilize a previously used epistaxis scoring system[9], as well as a 10-cm visual analogue scale for patients to self-report their level of post-operative bleeding. This design will afford us two opportunities; first, we will be able to perform a power analysis for our future randomized control trial and second, we will be able to validate the previously used 4 point epistaxis grading scale.

Few studies in the otolaryngology literature have sought to utilize over-the-counter medication to help curb the opioid use following surgery. With the increased incidence of opioid abuse in this country, the need to curb opioid prescribing practices and use is of the utmost importance. The efforts of this study will lay the foundation to help improve knowledge and understanding of non-narcotic analgesics in an effort to decrease patient use of opioids and resultant dependency or abuse.

(c) Approach

This is a prospective cohort pilot study to evaluate the use of narcotics in sinus surgery and the effect of ibuprofen on pain and epistaxis following ESS. This pilot study will provide critical baseline data for narcotic use, ibuprofen safety and ibuprofen analgesic impact to optimize the design of a future prospective, randomized study. Thus our specific aims are as follows:

Aim 1: Measure the number of narcotic pills used during the first 7 days following sinus surgery for CRS. *Hypothesis: there will be a wide range of narcotic usage among post-op patients with the mean usage being less than the amount typically prescribed post-operatively.*

The second aim seeks to evaluate the effect of ibuprofen on post-operative pain scores, as well as epistaxis rates. This information will be used to help determine the effect size for our outcome measures that will be needed for a power calculation for a future randomized trial.

Aim 2a: Determine impact of ibuprofen on post-operative sinus surgery patients' pain level. We will analyze patients with CRS that are set to undergo FESS in two cohorts (standard pain regimen and standard pain regimen plus ibuprofen) and assess postoperative pain at days 1, 3, and 7 by 10-cm visual analogue scale, amount of post-operative narcotic pain medication used, and number of days post-operatively taking narcotic medications. *Hypothesis: Addition of ibuprofen will decrease post-operative pain and decrease the number of opioid pills used.*

Aim 2b: Determine impact of ibuprofen on post-operative epistaxis following sinus surgery. In the same cohorts as above, we will measure degree of post-operative epistaxis using a 10-cm visual analogue scale, as well as a 4 point previously used epistaxis grading scale. This will allow us to both determine effect of ibuprofen on epistaxis and potentially validate a previously used epistaxis grading scale. *Hypothesis: Addition of ibuprofen will not impact post-operative epistaxis.*

Aim 3 will seek to estimate the willingness of individuals to participate in a future randomized double-blinded placebo control trial.

Aim 3: During enrollment we will ask patients to self-select the study arm they would like to join (with or without ibuprofen) and document willingness to participate in a future study given the scenario that they would be randomized to the treatment by a "coin flip". *Hypothesis: greater than 50% of patients approached will be wiling to participate and will indicate willingness to be part of a similar randomized study.*

Study Design: Prospective self-selected cohort pilot study

Study Location: Rhinology Clinic (Drs. Davis and Humphreys) at the University of Washington Medical Center

Subject approach:

All eligible patients set to undergo sinus surgery will be screened and approached in clinic at the appointment where surgery consent is completed. We will use the following criteria:

Inclusion Criteria:

- Patients with CRS scheduled to undergo functional endoscopic sinus surgery
- >18 years old
- Able to speak and comprehend written English

Exclusion criteria:

- Contraindication to NSAID use (CKD, PUD, Sampter's triad, etc.)
- Previous history of bleeding disorder
- Sinus cancer
- Cystic Fibrosis
- History of chronic pain, fibromyalgia, or opioid addiction

- Excessive bleeding during the surgery as determined by the attending surgeon

All patients with chronic rhinosinusitis who are scheduled to undergo FESS will be approached at their pre-operative clinic visit to inquire about interest in participating in the clinical study. If willing to participate, patients will be asked whether they would be interested in taking ibuprofen post-operatively, as a scheduled medication, in addition to the standard pain regimen consisting of acetaminophen and oxycodone taken as needed. If patients are interested, they will be placed in the intervention group. If they are not interested in taking ibuprofen, but willing to participate in the study, they will be placed in the control group. If interested in participating, patients will be asked whether they would like to use REDcap, a mature, HIPAA secure web application for building and managing online surveys and databases, versus paper journals to document their outcome measures. If they elect to use REDcap we will take their email address to allow for communication. If they elect to use paper journal, we will take their phone number to allow for reminder "courtesy" calls on post-operative days 1, 3, and 7.

All post-operative FESS patients are seen at two weeks after their surgery. We will collect their journal containing pain and epistaxis scores at that time. No further intervention or study will be done on these patients. In order to promote sufficient recording of daily VAS scores and other outcome measures we will provide patient remuneration with a $50 gift card.

Sample Size

Due to lack of studies examining epistaxis outcomes, there is no validated outcome measure or known statistically significant effect size. This study will help us determine that effect size, as well as validate a previously used epistaxis severity scoring system. We will plan to enroll 30 patients in each arm of the study.

Measurements

Descriptive characteristics will be gathered at the initial visit.

- Demographics: age, gender, and race.
- Contact information: standard information to arrange interviews and post-operative phone calls, and dispense remuneration
- CT severity: will use the Lund-Mackay CT staging system to assess disease severity.
- Lund-Kennedy endoscopic score (0-20): endoscopic appearance will be collected and scored
- Additional predictors of CRS outcomes: nasal polyposis, asthma, aspirin sensitivity, smoking, allergies, depression.
- Functional Comorbidity Index: Previously validated in CRS as a tool for assessment of impact of comorbidities on CRS-associated quality of life

Subjective and objective details of the individual's sinus surgery:

- Operative time
- Estimated blood loss
- Extent of sinus surgery performed
- Surgical complications

Subjective and objective clinical measures will be evaluated during the post-operative period

- Patient reported opioid use: Number of opioid pills taken as noted in the daily diary
- 10-cm Visual Analogue Scale for pain and epistaxis: recorded daily in diary. Will use assessments from post-operative days 1, 3, and 7

- 0-4 point epistaxis grading scale: Previously used scoring system of 0-4 to be collected daily over the first 72 hours[9]
- Number of gauze changes on moustache dressing over the first 72 hours: Used as a subjective, clinically significant estimate of post-operative bleeding. If patient no longer required moustache dressing during this period, this will be recorded as zero (0).

Treatment Arms

This cohort study will allow patients to choose their treatment arm. If interested in taking ibuprofen post-operatively, the patient will be stratified into the experiment arm. This will consist of the standard pain regimen (acetaminophen 650 mg q4hr PRN and oxycodone 5mg q3hr PRN) with addition of ibuprofen 800 mg q8hr scheduled. If the individual is not interested in being prescribed ibuprofen, but is still willing to participate in the study, s/he will be stratified into the control arm with the standard pain regimen as described above.

Data Analysis

Data analysis will be performed using an unpaired t-test to compare our primary outcome measures of 10-cm visual analogue scales (VAS) for post-operative pain and epistaxis from post-operative days 1, 3, and 7. For all other post-operative outcome measures, we will use t-tests to compare the two treatment arms. Based on our comparison of post-operative epistaxis VAS, we will seek to perform validation of the 0-4 point epistaxis grading scale previously described by Kastl et al.[9]

Data Protection

All study participants will be protected under HIPAA policies. Individuals will be de-identified following completion of study participation. All records will be kept on an encrypted computer in password-protected documents. Written diaries will be transcribed into excel files and kept in a locked file cabinet until manuscript submission. All protected health information will be protected under HIPAA protocol and Institutional IRB.

Limitations and Potential Pitfalls:

We acknowledge a number of limitations with our proposed study: First, this is a pilot study and is not designed to evaluate a definitive outcome related to post-operative pain reduction and epistaxis with ibuprofen. The risk of severe post-operative epistaxis following ESS is extremely low and, due to the safety and low risk of ibuprofen, we will likely not observe a statistically relevant amount of epistaxis in our sample. This will be helpful for determining adequate sample size in future studies. We also acknowledge the difficulty with expecting patients to record their outcome measures daily following surgery. We hope that by providing sufficient remuneration, as well as reminder phone calls or emails on post-operative days 1, 3, and 7, we will have adequate recording to evaluate our aims. Finally, study recruitment will be a potential challenge. If, as the study progresses, it does not appear that we are meeting our expected target enrollment, we will consider opening up recruitment to additional sites of practice both within our institution and to surrounding rhinology practices.

Feasibility:

At our institution, we see a large number of patients with CRS and perform approximately 250 endoscopic sinus cases per year. Given this information, and the expectation that 75% of patients will be willing to participate in the study since they get to self-select their treatment arm, we expect this study to take 4-6 months to recruit 60 subjects (30 in each treatment arm).

Future Directions

Once this study is complete, we will have a better understanding of the sample size necessary to observe a statistically significant effect size for our proposed outcomes. Additionally, we will have a stronger understanding of individual's willingness to participate in a similarly designed RCT. At that point, we will be equipped to design and implement a well designed and appropriately powered randomized, double-blinded placebo controlled trial. We do acknowledge that the results of this study will be that of a single institution that does not pack the nose following ESS. A true randomized trial would want to look multi-institutionally with practitioners that utilize a variety of post-op regimens including nasal packing and non-packing.

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