Multi-institutional, Randomized Controlled Trial Assessing Opioid Use and Analgesic Requirements After Endoscopic Sinus Surgery

Study Protocol and Statistical Analysis Plan

NCT03783702

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Name of study: Efficacy of non-opioid analgesics in the management of pain following endoscopic sinus surgery: a multi-institutional randomized controlled trial

PI and other key investigators or key study personnel:
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Specific source of institutional funding (account number)

- N/A

List of sources from whom you are seeking funds (or have sought funding) for this project

- N/A

Specific aims and basic hypothesis including an explicit primary hypothesis or goal

1. To determine whether narcotics can be avoided entirely, or at least limited, following ESS.
2. To determine whether acetaminophen is sufficient to control pain following ESS
3. To determine whether a combination of acetaminophen and ibuprofen is sufficient pain control following ESS
4. To develop a standardized postoperative analgesic regimen for patients who undergo ESS

General background (2 page maximum including published preclinical and animal data supporting basic hypothesis, if relevant)

Despite some recent advances, the opioid epidemic remains a national public health crisis with high morbidity and mortality rates, in addition to extensive socioeconomic costs.[i] Deaths from drug overdoses tripled from 1999 to 2014 and continue to increase: In 2015, there were over 33,000 deaths in the United States directly linked to opioid overdose, roughly five times the rate seen in 1999.[ii,iii] Sharing of excess opioids with friends and family members has become the single major contributor to opioid abuse.[iv,v,vi] Among subjects who misused opioids, 41% in one study had received opioids from a family member or friend and 60% had previously obtained opioids without a prescription.[v] In another study, 20.7% of subjects admitted to giving family members and friends excess opioid medications.[vi]

In a national survey of American Academy of Otolaryngology-Head and Neck Surgery members, Svider et al found unpredictable postoperative opioid prescribing patterns.[xxi] Of the 508 surgeons who described their narcotic prescriptions following ESS, only 5% reported prescribing no narcotics, compared to 13% who prescribed 1 to 10 tablets, 32% 11 to 20 tablets, 34% 21 to 30 tablets, 12% 31 to 40 tablets, and 4% more than 40 tablets. Other studies have also shown a high rate of opioids prescribed by otolaryngologists as a whole.[xxii,xxiii,vii] Despite these numbers, Becker et al found that, on average, patients consumed only 5.1 narcotic tablets during the postoperative recovery, 90% used less than half the number of tablets prescribed, and 20% did not use any.[xxiv]

A 2017 Centers for Disease Control and Prevention (CDC) study reported high rates of opioid dependence following prescriptions provided for both acute and chronic therapy, especially among opioid-naive patients.[viii] The study found a 6% and 2.9% probability that patients who were prescribed one day of opioids would continue to use opioids one and three years later, respectively. This number increased to 13.5% at one year when the first opioid course lasted for eight or more days.

There is a growing body of evidence that non-opioid medications can sufficiently control acute pain following ESS. One study directly compared the efficacy of rofecoxib and hydrocodone-acetaminophen postoperatively and found no difference in pain scores between groups.[ix] Another study found improved pain control with pregabalin compared to acetaminophen and did not prescribe opioids to either group of patients.[x] A double-blinded RCT comparing the ability of intravenous (IV) ketorolac and fentanyl to control pain when administered in the immediate postoperative period following endoscopic sinus surgery found no

difference in pain control between the two treatment groups.[xi] Notably, despite a theoretical greater concern for epistaxis following the use of nonsteroidal anti-inflammatory drugs (NSAIDS) postoperatively, no increased incidence of hemorrhage or anemia was found in patients who were randomized to ketorolac. In fact, there are increasing calls for the use of NSAIDS as an analgesic following ESS.[xii]

Despite these findings, however, opioids are still commonly prescribed by otolaryngologists for patients who undergo ESS. More evidence and a standardized regimen are likely needed to demonstrate that non-opioid alternatives can provide sufficient pain control.

Preliminary unpublished data (1 page maximum)

None

Experimental design and data analysis, including inclusion and exclusion criteria, statistical basis for the number of subjects to be enrolled, the statistical plan for analyzing at least the primary hypothesis, matrix showing procedure plan for each study visit, data safety monitoring plan (4 pages maximum)

IRB approval will be obtained from both participating institutions. Patients will be eligible if they are 18 years or older, can legally consent, can commit to follow up with the same surgeon for at least one postoperative visit, and are scheduled to undergo ESS for sinusitis (CRSwNP, CRSsNP, or RARS). Exclusion criteria include patients with a history of chronic pain disorders, gastrointestinal ulcers or bleeding, chronic kidney disease, known decreased renal function (estimated glomerular filtration rate <60), liver cirrhosis or other hepatic impairment, prior adverse reaction to opioids or NSAIDS, alcohol or opioid use disorder, or other contraindications to any drug classes in either group. Patients taking an average of >2 analgesics (including NSAIDS, acetaminophen, opioids, tramadol, nortriptyline, amitriptyline, gabapentin, pregabalin, duloxetine, and tramadol) per week will also be excluded. Given the typical half-life of each medication, any use of acetaminophen, ibuprofen, or oxycodone within the 48 hours before surgery will lead to exclusion.

Patients will be randomized into two groups, with a stepwise regimen of analgesics assigned to each group (Figure 1 and 2).

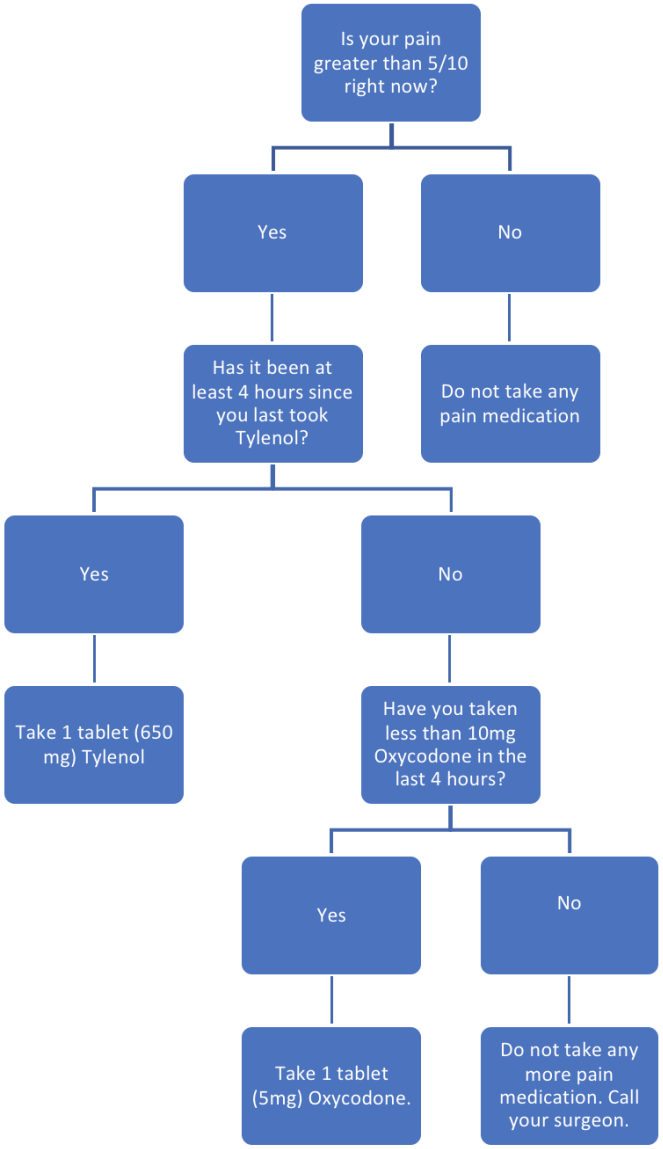

Figure 1: Control group

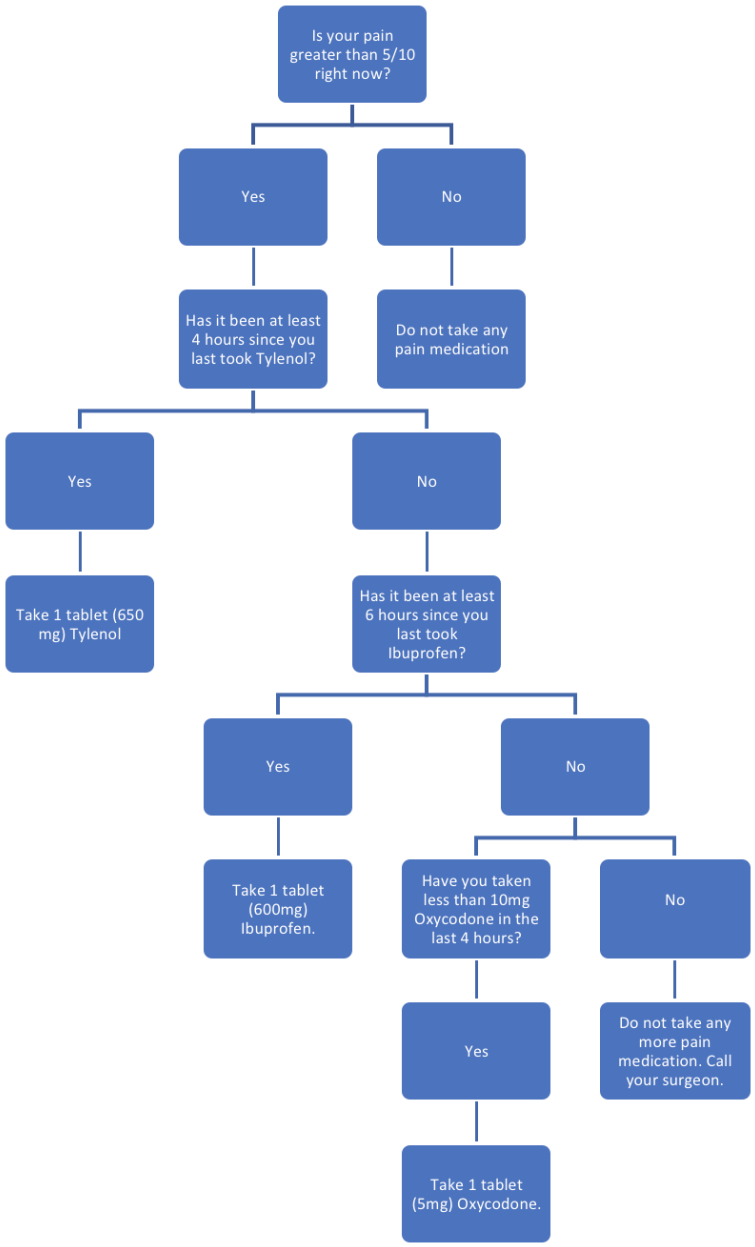

Figure 2: Intervention group

Subjects will be instructed to refer to their respective flow diagram, which will be extensively reviewed during enrollment to ensure understanding, whenever they experience pain. They will be additionally instructed to wait at least 30 to 45 minutes after taking one medication and before moving onto the next step if their pain persists so that they do not take multiple medications at once. Subjects will also be warned about maximum and hourly medication dosage limits. In the intervention group, subjects will be given a prescription of oxycodone, to be filled only if pain is not controlled by the combination of acetaminophen and ibuprofen.

All subjects will be instructed to rinse with saline at least twice per day. If subjects were using fluticasone or budesonide preoperatively, then they will be instructed to continue using these topical medications postoperatively. Given the evidence supporting postoperative oral steroids for patients with CRSwNP, and lack of parallel evidence in patients with CRSsNP or RARS, subjects with a diagnosis of CRSwNP will be prescribed 12-day prednisone taper, while those with CRSsNP or RARS will not be prescribed any postoperative oral steroids.[xiii] Subjects will be instructed to start the saline rinses and oral or topical steroids on postoperative day #1, if applicable.

Data collection at the preoperative visit will include demographics and basic characteristics, medical and surgical history, list of current medications, 12-month history of narcotic usage, and history of

contraindications to drug class from either study group. Baseline sinus/facial pain will be recorded using a 10-cm VAS ranging from "no pain" to "worst pain imaginable" and the validated 24-hour BPI Severity and Interference Scale. Comparison of preoperative disease severity will be evaluated using the 22-item Sino-nasal Outcome Test (SNOT-22), Lund-Mackay, and Lund-Kennedy scores.

Postoperatively, subjects will be asked to complete a daily medication log and pain assessment (VAS and BPI) during the first five postoperative days. Total and daily medication dosages will be compared across treatment groups for each medication used. Bleeding will be assessed using a 10-item VAS, with subjects being asked to describe their bleeding on a continuum between "No bleeding" to "Continuous bleeding." Subjects will also be asked to record the frequency and duration of daily epistaxis episodes. Potential adverse reactions to the medication regimen will be evaluated using a patient-reported checklist of 21 standard medication-related symptoms.[xiv] Sino-nasal specific data, including the SNOT-22 and Lund-Kennedy scores, will be collected at the postoperative visit, which will occur five to ten days after surgery.

The primary outcome of this study will be the postoperative VAS scores. The VAS is a continuous, patient-reported outcome measure determined using a horizontal 100-mm scale ranging from "no pain" with a score of 0 to "worst imaginable pain," corresponding to a score of 100. Given the simplicity, ease of use, reliability, and validity of the VAS, it is an ideal tool to measure postoperative pain.[xv] In a noteworthy study, Todd et al showed that a change in 13-mm on a VAS is the minimal clinically important difference (MCID) for acute pain severity.[xvi] Multiple other studies have since confirmed this finding.[xvii] It has also been noted that grouping patients by VAS score (<31, 31 to 70, and 71 to 100) can provide greater clinical clarity when evaluating postoperative pain.[xviii]

The power calculation was based on the VAS for pain. Using the MCID of 13-mm for acute pain, a standard deviation of 23.2 from the Tyler et al study, a significance level of 0.05, and power of 0.8, the minimum recommended sample size is 50 per arm.[xix] In other words, with a total sample size of 100, there is an 80% chance of obtaining a statistically significant difference between the two treatment groups at a 5% significance level. Taking into account dropout rates, this study will aim to enroll a total of 120 participants, with 60 in each arm.

Statistical analysis will be performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). The prevalence of baseline characteristics, comorbidities, and prior sinus surgery will be compared across treatment groups using Pearson Chi square (χ^2) testing, t-tests, and 1-way analysis of variance (ANOVA), where appropriate. The absolute value of scores for the patient-reported outcome measures will be compared across treatment groups using the two-sample t test. The quantitative change in scores from baseline to the first postoperative visit will be compared across treatment cohorts using paired t tests or Wilcoxon rank-sum (Mann -Whitney U) tests, where appropriate. Logistic regression will be used to evaluate the association between the baseline characteristics and outcomes. A standard alpha level 0.05 will be used to determine significance for all calculations.

Significance (1 paragraph or less)

Given the ongoing national opioid epidemic, an increased interest has developed in optimizing opioid prescribing practices of physicians, including otolaryngologists. Endoscopic sinus surgery (ESS) is one of the most commonly performed surgeries by otolaryngologists with over 250,000 ESS's performed annually in the U.S.[xx] Multiple studies have shown that, compared to the amount patients actually consume, otolaryngologists prescribe a high quantity of opioids to patients recovering from ESS).[xxi-xxiv] It has been shown that these excess opioid medications contribute to prolonged use or abuse by the patient, family members, or friends.[xxiv] The purpose of this study is to better understand the pain management requirements of patients who undergo ESS for recurrent acute rhinosinusitis (RARS) or chronic rhinosinusitis (CRS). This prospective, single-blinded, randomized controlled trial will aim to determine the degree to which pain following ESS can be adequately controlled by non-opioid medications. It will also determine whether post-ESS narcotic use can be avoided entirely, or at least significantly limited. Patients will be randomized into two groups, each of which will receive a stepwise analgesic regimen consisting of acetaminophen and oxycodone or

acetaminophen and ibuprofen. Pain will be assessed daily using visual analog scales (VAS) and the Brief Pain Inventory (BPI). The results of this study will help to develop a standardized approach to pain management in the post-ESS setting and help to elucidate the role of non-opioid pain medications. The ultimate goal would be to positively affect opioid prescribing patterns among surgeons who perform ESS in order to significantly reduce the quantity of opioids prescribed to patients while continuing to adequately manage patients' pain.

Key references

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