NCT04008264
Study Protocol Document
4/10/19

Scientific Background:

Surgeons account for over 35% of all opioid prescriptions and patients who receive an opioid prescription after low-risk ambulatory surgery are nearly 45% more likely to become long-term opioid users compared to those who received no opioid prescription. For many patients, opioid pain medications prescribed after surgery are often their first exposure that results in an addiction. While the causes of the opioid epidemic are multifactorial, it is clear that targeted interventions must be developed to limit the overprescribing and overutilization of narcotic pain medications following surgery.

Data suggests that opioids are over prescribed by surgeons following elective upper extremity surgery. Rodgers et al. conducted a study of prescribing practices following elective outpatient upper extremity surgery and found that among 250 patients, prescribers typically provided 30 opioid pills. Overall, patients typically consumed a mean of 10 opioid pills with an average of 19 pills remaining unused per patient resulting in a total of 4,639 unused tablets for the study cohort. The study also noted differences in opioid utilization based on type of procedure with patients
undergoing bony procedures using an average of 14 pills and patients undergoing soft tissue procedures using an average of 9 pills. Moreover, in a prospective study of 1,416 patients by Kim et al., surgeons prescribed a mean total of 24 pills while patients reported consuming a mean total of 8.1 pills with a theoretical total of 21,768 pills being available for potential diversion or misuse. Similarly, the study found that opioid utilization varied by procedure type with patients undergoing soft tissue procedures consuming an average of 5.1 pills over 2.2 days, while patients who underwent fracture or joint procedures used a mean of 13.0 pills for 4.5 days and 14.5 pills for 5.0 days, respectively.

Overprovision of opioids to post-surgical patients stems in part from physician attitudes and lack of understanding. Many surgeons do not know how many pills they should prescribe to their patients and how many pills that their patients actually take. Moreover, hand surgeons were less likely to be concerned by potential adverse patient events such as opioid addiction and death compared to primary care physicians. Instead, surgeons may overprescribe narcotics to avoid undermanaging post-operative pain, minimize patient calls, and limit hospital readmissions.
The unpredictability of opioid requirements following upper extremity surgery further complicates the issue of standardizing prescriber practices. In a study by Johnson et al. of 77,573 patients undergoing elective and trauma-related hand surgery procedures, over 7,750 opioid naïve patients continued to fill opioid prescriptions between 90 and 180 days after surgery. The rate of prolonged opioid consumption following surgery has been shown to be even higher in patients who had previously taken opioids. The development of alternative modalities to curb opioid

consumption following outpatient hand surgery may potentially reduce defensive prescribing practices and give the hand surgeon greater confidence in providing a reduced number of opioid analgesics.

It is readily evident that a greater understanding of patient analgesic practices following surgery is required in order to develop targeted interventions towards reducing opioid utilization. Opioid and non-opioid analgesic usage patterns following outpatient hand surgery are poorly understood. A greater understanding of these patterns and risk factors for prolonged usage and addiction will prove invaluable in guiding practitioners in their prescribing practices. The investigation of additional non-narcotic medications to supplement existing analgesic regimens may reduce
opioid use and may establish greater consistency in opioid usage amongst patients.

The investigation of additional adjuncts in the multimodal analgesic armamentarium warrants further exploration and scopolamine may be a potential candidate to supplement established nonopioid analgesics. Scopolamine is an extremely common and effective medication used in the
perioperative period for the management of post-operative nausea and vomiting. ERAS protocols commonly utilize multi-modal analgesia and control of post-operative nausea/vomiting to reduce the consumption of opioids following surgery. Historically, scopolamine had been used in combination with opioids to produce conscious sedation by potentiating the effect of opioids. Moreover, studies have demonstrated that scopolamine via its blockade of muscarinic receptors may affect the perception of nociceptive stimuli and nociception-related memory acquisition. Therefore, scopolamine has the potential to interrupt the feedback loop that results in prolonged opioid usage and opioid use disorders. Thus, in this study we aim to demonstrate whether the usage of scopolamine in conjunction with standard of care analgesic regimens following outpatient hand surgery has the potential to reduce postoperative narcotic requirements following surgery.

Study Design:

Study objectives:

Primary and secondary study endpoints:
Aim 1: Determine whether the addition of transdermal scopolamine to a standard analgesic regimen reduces opioid utilization following outpatient hand surgery as reported by patients
Objectives: We will compare opioid usage between patients who complete logs during the pre-intervention stage of the study and the intervention stage of the study to determine the effect of including scopolamine as a medication in standard post-operative analgesic regimens following outpatient hand surgery. As this is the primary objective of our study, an a priori power analysis was conducted. Based on a two-sided two-sample independent t-test with a specified significant level of 0.05, a power of 0.8, and a moderate effect size of 0.5; 64 patients

will need to complete each portion of the study to provide an overall sample size of 128 patients.
Outcome Variables and Analysis: The absolute number of logged opioid use during the two-week study period will be compared between the pre-intervention and intervention groups using a two-sided independent samples t-test.

Aim 2: Determine patient compliance with usage of multi-modal analgesic medications and the feasibility of supplementing with an additional agent
Objectives: During the pre-intervention stage of the trial, we will encourage patients to utilize non-opioid analgesics over opioids and have patients keep a log of their NSAID and acetaminophen usage. This aim will partially establish whether patients are being adequately counseled regarding multi-modal pain control as patients with high opioid consumption should also have high rates of use of their non-opioid analgesics. It will also establish whether it is feasible to expect patients to comply with the introduction of novel medications into analgesic regimens. It will establish baseline rates of non-narcotic pain medication use overall and stratified by procedure. It may also further support the existing evidence that non-opioid pain medications reduce opioid requirements while providing more significant pain relief than opioids alone.
Outcome Variables and Analysis: Data analyzed will include percentage of individual non-opioid pain medications used (prescriptions will be provided so patient could take medication around the clock), patient pain scores, and percentage of opioids used. Percentages of non-opioid pain medications and opioid pain medications will be compared on a patient-by-patient basis by utilizing a paired t-test. The association between patient perceived pain levels and percentage of each medication used will be determined with multiple linear regression.

Aim 3: Assess patient and operative factors that contribute to prolonged or greater than expected opioid usage.
Objectives: The factors contributing to prolonged patient use of opioids and need for repeated refills are poorly understood. An analysis of factors contributing to prolonged opioid use and a determination of baseline opioid use rates would allow hand surgeons to have a better understanding of factors that may place a patient at risk or to identify when patients are exceeding the typical requirements for opioids. Identification of these patients may allow for increased counseling, referral to a pain specialist, or increased surveillance. Details of the operative procedure and typical narcotic requirements will guide providers in prescribing more limited opioid prescriptions appropriate to an individual procedure with few to no refills authorized.
Outcome Variables and Analysis: Patients will be separated into groups based on whether they used over 80% of their opioid prescription or if they requested a refill of their opioid prescription within the two week study period. A univariate analysis of patient demographic factors and operative details will identify factors that are potentially associated with higher rates of opioid consumption following surgery. Chi square tests will be performed for categorical variables and student's t-tests will be used for continuous variables. Binary logistic regression will then be performed using variables identified in the univariate screen in order to identify independent factors contributing to a higher number of opioids used after surgery.

Study design and methods:

This is a descriptive, observational study in which there will be a 3 month pre-intervention phase where participants will be placed on a standard post-operative analgesic regimen consisting of an opioid, a NSAID, and acetaminophen. Patients will record their narcotic and non-opioid analgesic usage patterns in the two weeks following outpatient hand surgery.

During the observational phase, patients will be given a prescription for an additional 3 day supply of scopolamine (total of 6 days of use), and patients will record the same data as prior to the intervention. The patients who incorporate scopolamine into their post operative analgesia regimen will be eligible for inclusion in the study.

Provide a description of the following study timelines:
Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries): 150
Duration of an individual subject's active participation: 3 weeks
Duration anticipated to enroll all subjects: 9 months
Estimated date for the investigator to complete this study (complete primary analyses): 7/1/2020

Eligibility criteria:

List the inclusion criteria:
Patients between the ages of 18-55 undergoing outpatient hand and wrist surgery via sedation and a regional block will be eligible for participation. Procedures eligible for inclusion will be limited to those involving the wrist and the hand in order to mitigate the effect of anatomic variability on pain and subsequent utilization.

List the exclusion criteria:
Patients undergoing procedures under local, regional anesthesia alone, sedation alone, and general endotracheal anesthesia will be excluded to attempt to isolate procedures of similar complexity and presumed pain level.

Patients will be selected for enrollment in the study based on their need for hand surgery, and their decision to undergo sedation with the regional block.

Additional exclusion criteria are based off of FDA prescribing information for transdermal scopolamine and include patients with a history of acute angle closure or open angle glaucoma; history of drug hypersensitivity to scopolamine, other belladonna alkaloids; or any other ingredient or component in the formulation or delivery system; history of previous

gastrointestinal or urinary bladder obstruction; history of seizures or psychosis; patients with hepatic or renal impairment; patients under the age of 18 or over the age of 55; and patients who are currently pregnant or nursing.

Patients currently using prescription opioids for other chronic medical conditions or who are actively using heroin will be excluded from the study.
Children or any gender, racial or ethnic subgroups will be explicitly excluded from participation.

Statistical considerations:

Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):
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