Evaluation of a nonopioid recovery pathway after percutaneous nephrolithotomy

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Background:
Urologic surgery has played a role in the perpetuation of the opioid epidemic in the United States with the continued use of opioid medications despite evidence showing the efficacy of nonopioid protocols.[1,2] The use of opioid medications in the postoperative setting has been shown to be an important factor for chronic use, and often, outpatient surgery may be a patient's initial exposure.[3] Urologic surgery is not immune from this as recent studies have demonstrated that nearly one-in-16 opioid-naive patients develop new persistent opioid use after ureteroscopy for nephrolithiasis.[4] In addition, patients with kidney stones may have a higher risk for long-term opioid use than non-stone formers.[5,6] Recent studies have emphasized the efficacy of nonopioid protocols for outpatient urologic procedures.[7] Our own preliminary data has demonstrated that the vast majority of patients can be discharged without any opioid prescriptions after outpatient ureteroscopy with no impact on outpatient healthcare resources.[8]

What is not known, however, is whether other minimally invasive urologic procedures which historically have used opioids for postoperative pain control are also amenable to nonopioid care pathways. Percutaneous nephrolithotomy (PCNL) is a minimally invasive procedure performed by urologists for larger stone burden in the kidney. It typically is followed by an overnight stay in the hospital for observation. **Our hypothesis is that a novel nonopioid pathway after PCNL is both feasible and safe and will reduce postoperative prescriptions for opioids without impacting clinical outcomes, patient satisfaction or outpatient resources.**

Evaluation of a nonopioid recovery pathway after percutaneous nephrolithotomy has three specific aims:

Demonstrate feasibility and acceptability of the novel nonopioid protocol and describe the barriers to enrollment and reasons for drop out.
Measures: The feasibility of the protocol will be measured by dropout of enrolled patients and the acceptability of protocol will be measured by number of enrolled patients / patients approached and patient satisfaction via standardized validated questionnaire (Ureteral Stent Symptom Questionnaire).

Describe what adverse events occur to those on the nonopioid protocol as compared to the standard of care.
Measures: All adverse events occurring as an inpatient will be measured by nursing and physician reporting, and as an outpatient via patient self-reporting, electronic medical records of emergency department visits, requests for opioid prescription refills and telephone calls to clinic.

Begin to reduce overall opioid prescription writing for patients undergoing PCNL at the Miriam Hospital.
Measures: The electronic medical records will be queried for prescriptions written at discharge. The Rhode Island Opioid Prescription Monitoring Program (PMP) will be queried for a 30-day period following surgery to evaluate for opioid prescriptions written by other providers.

Our long-term goal is to determine if this nonopioid recovery pathway for PCNL is more effective for postoperative pain control than the standard of care (routine opioid prescription) and this study will provide the pilot feasibility data to enable a randomized controlled trial (RCT) to be performed.

We have previously demonstrated that outpatient ureteroscopy and stent placement without postoperative opioid prescriptions is possible in the vast majority of patients.[8] The success of this is dependent upon a multimodal

approach to the patient's experience of undergoing endoscopic kidney stone surgery (ureteroscopy) and focuses on the preoperative, perioperative, and postoperative stages of intervention.[9]

Preoperatively, all patients were counseled and postoperative expectations were discussed: Counseling strategies were codified in a script for surgeons and advanced practice providers to discuss before surgery to describe the procedure, the need for a ureteral stent, symptoms associated with stents, and most importantly, that the vast majority of patients tolerated surgery without opioids. This preoperative counseling approach has been shown to improve patient satisfaction, clinical outcomes, and significantly decrease patient anxiety.[9,10] Intraoperatively, the intent to discharge patients without opioids was communicated to the anesthesia team as well as the postoperative care nurses, highlighting the importance of cooperation and communication among the stakeholders involved in the care of these patients. Postoperatively, a standardized discharge order set was utilized so that all patients received adjunct medications in addition to a prescription for NSAIDs if no contraindications existed.

Our most recent findings demonstrate that approximately 90% of patients (271 / 300) selected for the nonopioid care pathway were able to be successfully discharged without opioids over a 26-month period.[11] Additionally, the avoidance of postoperative opioid prescriptions did not result in increased postoperative adverse events or use of outpatient resources for pain management. This protocol was released as an open-source toolkit at the American Urological Association annual meeting in San Francisco in May, 2018. It is currently in use in academic and private practice settings nationally.[12]

Research strategy:
Evaluation of a nonopioid recovery pathway after percutaneous nephrolithotomy will apply the knowledge and experience gained with development of the previous outpatient opioid reduction protocol to percutaneous nephrolithotomy (PCNL), a minimally invasive procedure performed by urologists for nephrolithiasis too large or difficult to treat endoscopically. While previous efforts have targeted outpatient urologic procedures for opioid reduction, procedures like PCNL are opportunities for opioid reduction as well. These procedures with < 24-hour observation often may be the highest yield for intervention as the barrier to receiving opioid pain medication may be lower while they are admitted to the floor. The observation period also prioritizes prompt pain control and timely discharge, which may also lower the threshold for opioid pain medication administration.

Study Design:
We propose a pragmatic pilot study which will prospectively compare a cohort of 15 patients undergoing PCNL prior to implementation of the novel nonopioid pathway to 15 patients undergoing the same procedure utilizing the novel nonopioid pathway. A historical cohort of patients was analyzed to determine the study population size needed to achieve our goals. Sixty-four patients underwent PCNL at The Miriam Hospital in 2018 and approximately 80% of patients were discharged home with a prescription for opioid pain medication (20% opioid-free discharge rate). Current standard of care following PCNL remains the routine prescription of opioid medications for pain control. Since PCNL is a more invasive procedure than ureteroscopy and is a non-natural orifice surgery, we expect to reduce opioid prescriptions from 80% to 50% (50% opioid-free discharge rate). To power a study with a beta of 0.8 and an alpha of 0.05 requires only a small sample size of 13 patients with this large reduction. In order to account for patient drop out and protocol non-adherence, we plan to enroll 30 patients in our pilot study.

The subject population will be adult patients referred to The Miriam Hospital Kidney Stone Center (Lifespan – Providence, RI) and Brown Urology (Brown Physicians, Inc. – Providence, RI) for complex kidney stone disease and scheduled for percutaneous nephrolithotomy (PCNL) during the active study enrollment period who meet inclusion criteria. As the prevalence of nephrolithiasis in the United states is seen more in men (1.4:1 male

vs female),[13] we anticipate our patient population to include more men than women. The risk difference between men and women, however, has been narrowing and we would expect that given our anticipated study population size of 30 patients, approximately 12-15 patients will be women. Nephrolithiasis affects all races and given the diverse population of the greater Providence, RI region, we anticipate a significant portion of our study population to be of non-white race. Every effort will be made to offer participation to eligible women and minorities.

Inclusion and Exclusion Criteria:
Patients ≥18 years old undergoing primary percutaneous nephrolithotomy at the Miriam Hospital (Lifespan Network, Providence, RI) will be eligible for enrollment. Patients will be excluded if undergoing concurrent non-PCNL procedure, second-look PCNL (subsequent PCNL after primary PCNL), or present with Chronic Kidney Disease Stage ≥3 or eGFR < 50 mL/min/1.73m^2 at time of surgery. Patients with allergy to NSAIDs or have history of NSAID related GI bleeding or ulcers will be excluded.

Inclusion of Women and Minorities:
As the prevalence of nephrolithiasis in the United States is seen more in men (1.4:1 male vs female), we anticipate our patient population to include more men than women. The risk difference between men and women, however, have been narrowing and we would expect that given our anticipated study population size of 25 patients, approximately 10 patients will be women. Nephrolithiasis affects all races and given the diverse population of the greater Providence, RI region, we anticipate a significant portion of our study population to be of non-white race. Every effort will be made to offer participation to eligible women and minorities.

Inclusion of Children
Patients under the age of 18 will not be eligible for participation in the study. The study is aimed at understanding adult nephrolithiasis and the feasibility of nonopioid postoperative pain control after percutaneous nephrolithotomy, and nephrolithiasis of childhood is a distinct clinical entity not addressed by this study.

Vulnerable Subjects:
Special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, or institutionalized individuals will not be eligible for participation in the study.

Recruitment and retention plan:
Patients referred to The Miriam Hospital Kidney Stone Center / Brown Urology for complex kidney stone disease and scheduled for percutaneous nephrolithotomy (PCNL) during the active study enrollment period who meet inclusion criteria will be offered participation in the study. Our center performs approximately 75 PCNLs yearly and we anticipate enrolling 25 patients, which will be adequate to demonstrate the safety and feasibility of the protocol (see Statistical Design and Power).

Urology housestaff and an attending urologist are on call 24 hours a day. Patients will be encouraged to reach out via telephone for questions concerning the study or continued participation. At the postoperative follow up visit (scheduled for 7-10 days after surgery), the research assistant will administer the Ureteral Stent Symptom Score (USSQ), a validated questionnaire regarding postoperative pain control. This will also function to establish continued participation in the study. Patients will complete their participation in the study 30 days after surgery.

Study Timeline:
Two months after notice of award, eligible patients scheduled for percutaneous nephrolithotomy (PCNL) will be offered participation in the study. The study will accrue patients through for one year or until the enrollment goal (25 patients) has been met. Statistical analysis will be performed following accrual and initial findings will

be summarized and reported per protocol to COBRE Opioids and Overdose as well as ClinicalTrials.gov approximately 24 months after notice of award.

Protocol:

Informed consent will be obtained at the time of consent for surgery in the outpatient urologic clinic setting. Either the principal investigator or the trained research assistant (TBA) will conduct the consenting process. Consent will be in written form. A description of the study will be described by the physician or research assistant and will be provided in written form. Patients deemed able to consent for the surgery will have capacity to consent to participation in the study. Patients not able to consent to surgery will not be eligible for the study. The consent process will inform a volunteer about the study, indicate the participation is voluntary and he/she has the right to stop at any time. Risks will be enumerated in the informed consent form and described verbally during the consent process.

After written consent and enrollment, patients will undergo preoperative counseling regarding pain after PCNL in the preoperative holding area prior to surgery. The patient will then undergo percutaneous nephrolithotomy. No procedural changes will be made for study participants. The procedure will follow standard of care for PCNL. The nonopioid pathway will be discussed with the anesthesia team intraoperatively. Postoperatively, patients will be admitted to the post-anesthesia care unit (PACU) and standard of care adjunctive and analgesic medications will be administered. The patient will be admitted to the floor following surgery and postoperative specialized nonopioid PCNL pathway orders will be communicated to nursing staff via electronic medical record. The patient's pain will be treated with multimodal nonopioid analgesic agents such as cold packs, repositioning, ambulation, acetaminophen, tamsulosin, phenazopyridine, ketorolac, and oxybutynin on an as necessary basis (medications contraindicated due to allergy or intolerance will not be administered). Opioid medications **will not be withheld** for patients with severe (8-10 score on the numerical rating scale) pain. The patient's pain will be recorded by nursing staff every 4 hours as in standard of care. On postoperative day one (POD#1), the patient will be assessed for discharge as in standard of care. They will be asked about their perceived need for a prescription for opioids. If requested, the patient will be given a prescription for a limited quantity of opioids (five [5] tabs of 5mg oxycodone to be taken every 8hours only as necessary for severe 8-10 pain). Nursing staff will complete specialized nonopioid PCNL pathway instructions and patients will be given written instructions regarding medications and activity. Patients will be seen in 7-10 days for stent removal in the office per standard of care, and will complete the Ureteral Stent Symptom Questionnaire (USSQ), a validated quality of life survey for pain after kidney stone surgery.

Specific multimodal interventions of the pathway:

- Preoperative counseling script regarding pain after PCNL surgery
- Post-Anesthesia Care Unit (PACU) nursing instructions and standard recovery medications
- Perioperative pain protocol EMR orderset including medication instructions
- Tailored PCNL discharge instructions for patients and nursing staff
- Standardized discharge medication prescriptions

Primary study outcome:

- Feasibility of the protocol (number of enrolled patients / patients approached),
- Adherence to and acceptability of the protocol (dropout of enrolled patients and patient satisfaction)

- Adverse events (AEs) while inpatient and following discharge
- Discharge following PCNL without prescription for opioid medications

Secondary study outcomes:

- Postoperative inpatient opioid utilization (morphine mEq / kg / day)
- Opioid prescriptions written at time of discharge (morphine mEq / kg / day)
- Ureteral Stent Symptom Questionnaire (USSQ)[14] scores at postoperative visit
- Non-opioid medications given for pain
- Length of stay (hours)
- Calls to clinic for pain / discomfort within 30 days
- Requests for refills or opioid prescriptions within 30 days
- Presentations to ED for pain within 30 days

Data Analysis:

The protocol will be assessed for feasibility of implementation and safety through analysis of acceptability (number of enrolled patients / patients approached), Adherence to and acceptability of the protocol (dropout of enrolled patients and patient satisfaction via a validated questionnaire (USSQ) and adverse events (AEs) while inpatient and following discharge. Statistical analysis of the pre- and post- intervention groups will be performed to assess for significant overall reduction in opioid prescriptions. Analysis of the patient characteristics and primary / secondary outcomes of the patients will be used to assess potential reasons for opioid necessity following PCNL. A Redcap database designed with assistance from the Data and Research Methods core will be maintained in accordance with the institutional data safety plan.

Statistical Analysis Plan:

This is a pragmatic pilot study which will prospectively compare a cohort of 15 patients undergoing PCNL prior to implementation of the novel nonopioid pathway to 15 patients undergoing the same procedure utilizing the novel nonopioid pathway. A historical cohort of patients was analyzed to determine the study population size needed to achieve our goals. Sixty-four patients underwent PCNL at The Miriam Hospital in 2018 and approximately 80% of patients were discharged home with a prescription for opioid pain medication (20% opioid-free discharge rate). Current standard of care following PCNL remains the routine prescription of opioid medications for pain control. Since PCNL is a more invasive procedure than ureteroscopy and is a non-natural orifice surgery, we expect to reduce opioid prescriptions from 80% to 50% (50% opioid-free discharge rate). To power a study with a beta of 0.8 and an alpha of 0.05 requires only a small sample size of 13 patients with this large reduction. In order to account for patient drop out and protocol non-adherence, we plan to enroll 30 patients in our pilot study.

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Data Safety Plan:
A minimum of PHI (protected health information) that might identify patient participation will be collected for data analysis purposes. HIPAA identifiers that will be collected include medical record number (MRN) and date of surgery. All HIPAA identifiers will be coded and a de-identified separate database will be held electronically in a secure password protected workstation.

Potential Risks:
Besides the risks of the surgical procedure itself which apply to participants and nonparticipants equally, potential risks of the study include inadequate treatment of pain postoperatively. Patients will be queried prior to discharge on their comfort level regarding discharge without opioid pain medications, and opioids will not be withheld if requested or if the physician feels the patient will not be successfully discharged without opioid prescription. If pain is not controlled after discharge, urology housestaff and an attending urologist are available 24 hours a day for telephone consultation and pain medication refill requests.

This risk is not unique to study participants. Following surgery, there is always a risk of inadequate treatment of pain postoperatively, even with those prescribed opioids. The benefits of avoiding opioids have been well described and potentially outweigh the risks of undertreatment of pain. Additionally, patients exposed to opioids are at risk for opioid induced hyperalgesia. Opioid exposure has been linked to chronic opioid use in patients undergoing ureteroscopy as well, and opioid avoidance can mitigate that risk. Other potential risks including the risks to privacy and/or confidentiality due to data breach will be mitigated with the data safety plan above.

Informed Consent and Assent:
Informed consent will be obtained at the time of consent for surgery in the outpatient urologic clinic setting. Either the principal investigator or the trained research assistant (TBA) will conduct the consenting process. Consent will be in written form. A description of the study will be described by the physician or research assistant and will be provided in written form. Patients deemed able to consent for the surgery will have capacity to consent to participation in the study. Patients not able to consent to surgery will not be eligible for the study. The consent process informs a volunteer about the study, indicates the participation is voluntary and he/she has the right to stop at any time. Risks are enumerated in the informed consent form and described verbally during the consent process.

Potential Benefits of the Proposed Research to Research Participants and Others:
There is a growing body of literature describing the benefits of opioid avoidance after surgery and the use of adjunct or multimodal nonopioid analgesic agents. Patients participating in the study will benefit from increased surveillance of the adequacy of pain control postoperatively while admitted, and increased availability of staff to address concerns while at home. The risk of opioid hyperalgesia and the potential for opioid tolerance or dependence will be mitigated if participants are not exposed to opioids. The families or cohabitants of the patient will benefit from the lack of opioid medications at home that may be subject to possible diversion or accidental ingestion. In light of these potential benefits, the risks of inadequate pain control are reasonable in relation to the anticipated benefits to research participants.

In light of the opioid epidemic, research that advances our understanding of nonopioid therapies for acute pain after surgery are paramount. This study proposes to evaluate a novel nonopioid pathway for pain control after PCNL, and aims to reduce the opioids administered and prescribed after a common urologic procedure. The

knowledge that will be gained will better inform our practices as urologists and physicians and will allow us to better understand patient characteristics that increase the likelihood of needing opioids after surgery. As such, the risks described above are reasonable in relation to the importance of the knowledge that we will gain from this study.

Definition, Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UPs):

Due to the small prospective cohort size, monitoring for AEs, SAEs and Ups will be conducted on a weekly basis by the PD/PI and the compliance officer. The Office for Human Research Protections (OHRP) reporting requirements will be followed. Any unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with the OHRP policy or the requirements or determinations of the IRB; and any suspension or termination of IRB approval will be reported per protocol by either Dr. Sobel or Christopher Tucci, the designated compliance officer. Adverse Events and Serious Adverse Events will be documented in a secure electronic file and a report will be made to the Institutional Review Board (IRB), the Center for Opioids and Overdose, and the NIH promptly (within 5 days for SAEs and within 14 days for AEs). Reports will include actions The Miriam Hospital and the PD/PI is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.).

Dissemination Plan:

The principal investigator will ensure that the clinical trial is registered with ClinicalTrials.gov as outlined in the policy (NOT-OD-16-149). Summary results information will be submitted per policy to ClinicalTrials.gov following conclusion of the trial and completion of data analysis. Informed consent documents will include a specific statement regarding the posting of clinical trial information at ClinicalTrials.gov. The Miriam Hospital (Lifespan – Providence, RI) has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

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