Study of Ketorolac vs Opioid for Pain after Endoscopy (SKOPE):

A double-blinded randomized control trial comparing outpatient analgesic efficacy of NSAIDs and opioids in patients undergoing ureteroscopy for kidney stones

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Study of Ketorolac vs Opioid for Pain after Endoscopy (SKOPE): A double-blinded randomized control trial comparing outpatient analgesic efficacy of NSAIDs and opioids in patients undergoing ureteroscopy for kidney stones.

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INTRODUCTION, BACKGROUND AND SIGNIFICANCE

The rate at which opioid pain medication is being prescribed in the United States has increased significantly within the last two decades.[1,2] The societal cost of this trend includes an increase in rates of opioid abuse, addiction and fatal overdose. These risks have motivated exploration of appropriate patient selection as well as alternative methods of pain control in clinical settings. In this study, we aim to evaluate the efficacy and safety of an alternative (ketorolac) to opioids (oxycodone) for postoperative pain control in patients undergoing ureteroscopy (URS) for urinary stone disease.

In the era of increased healthcare costs, efforts are being made to safely decrease the amount of time that patients spend in the hospital for a given procedure. To this end, many procedures that entailed multi-day inpatient hospital stays are now treated as overnight stay, and sometimes even as outpatient procedures. In the latter scenario, a significant burden of the required pain control falls to self-administration of oral pain medication by the patient after discharge. As such, it is important for the clinician to ensure that the pain medication prescribed is: 1. effective, 2. well tolerated, and 3. of sufficient quantity to cover the expected post-operative pain period. Getting the right mix of these three factors is critical in patient satisfaction.

Currently, the American Urological Association (AUA) does not give any recommendation on the management of pain in post-URS patients. Anecdotally, in the United States, the common practice is to prescribe a short course of opioid pain medication on discharge to patients undergoing URS for urinary stone disease, while few patients receive opioids in other parts of the world. Whether this is due to decreased availability, or physician preference is unclear as the medical literature is lacking in this area. The particular opioid medication, quantity, and duration, and decision to prescribe adjunctive medication for stent pain and/or bladder spasms (eg. tamsulosin, oxybutynin, phenazopyridine etc) are usually a matter of physician preference.

There is a preponderance of data for management of pain in acute renal colic but data is lacking in the setting of post-URS pain.[3] Pathophysiologic mechanisms for pain in acute renal colic and post-URS pain likely overlap significantly. Irritation of the renal and ureteral tissues from the stone or instrumentation combined with ureteral inflammation, contraction and spasms are likely contributing factors.

There is good evidence that NSAIDs offer superior pain relief compared to opioid medications in the acute renal colic setting.[3–5] Wen et al. offer *in vitro* evidence that ketorolac decreases ureteral contractility which likely is a major contributor to pain in this setting.[6] Pathan et al. conducted a large, double blind, randomized controlled trial to compare analgesic efficacy of NSAIDs, opioid and paracetamol (acetaminophen). They found that NSAIDs produced better and more durable analgesia than opioids and had a better side effect profile.[5]

Post-URS, many patients are left with a ureteral stent to keep the ureter patent during a postoperative period of ureteral inflammation and edema. This stent unfortunately can itself be the cause of severe and bothersome symptoms, some of which are not treated effectively with opioids. Patients are given other medications (oxybutynin, phenazopyridine, tamsulosin) to help with this. There is emerging data to suggest that stent-related pain may be more effectively dealt with using NSAIDs.[7]

Clearly, there are several reasons to explore safe and effective alternatives to opioid medications in the setting of ureteroscopy. Not only are we in a period of high rates of abuse and addiction, opioids can cause constipation, nausea, vomiting, and may not be effective in managing stent related symptoms. To this end, we propose a double blind randomized controlled trial to compare pain control and safety with ketorolac (NSAID) and oxycodone (opioid) in the post-operative setting for patients undergoing ureteroscopy for treatment of urinary stones.

STUDY DESIGN

Methods

This study is designed as a prospective, double-blind randomized controlled trial. Two drugs will be administered in a blinded fashion and outcomes will be assessed with non-inferiority design.

Sample size

Based on previous data collected at our institution, the average pain score of patients undergoing ureteroscopy is 3.5 ± 2.5. derived from the following studies and also supported by the postoperative day 1 pain scores we have collected so far in the SKOPE trial (mean of 3.6 ± 2.0). .[8–11] Kelly showed that when using a 100mm VAS pain scale (with 0mm indicating no pain, and 100mm indicating worst pain), the minimum clinically significant difference in pain rating was 14mm for patients with moderate pain (3.0 to 7.0 on VAS).[12]

We performed a sample size calculation for the primary outcome of VAS pain rating. Using the data in the available literature for a non-inferiority limit of 1.4, significance level α=0.05, 80% power, sample size calculation yields n=40 per group.[13]

Inclusion criteria

- Patients who are diagnosed with kidney or ureteral stones confirmed on imaging (CT of the abdomen and pelvis) and who elect for definitive treatment via ureteroscopy at two sites within a tertiary care institution
- Age over 18
- Patients of either gender
- Patients of all ethnic backgrounds

- GFR >60 ml/min/1.73m^2 (MDRD equation)
- Capable of giving informed consent
- Capable and willing to fulfill the requirements of the study

Exclusion criteria

- Active or history of peptic ulcer disease, GI bleed/perforation
- History of coronary artery bypass graft surgery
- History of bleeding disorder
- GFR <60 ml/min/1.73m^2 (MDRD equation)
- History of chronic pain
- Chronic use of opioid or other pain medication (>12 weeks)
- Chronic use of NSAIDs
- Known allergy to either ketorolac or oxycodone
- Known or suspected Pregnancy
- Inability to give informed consent or unable to meet requirements of the study for any reason
- Solitary kidney
- Patients taking anticoagulants or antiplatelet medication
    - Warfarin
    - Clopidogrel
    - Dabigatran (pradaxa)
    - Xarelto (rivaroxaban)
    - Eliquis (apixaban)

RESEARCH PROCEDURES

Trial Medications

Two active treatments will be investigated:

- Ketorolac 10mg by mouth every six hours as needed for pain given for a maximum of 5 days (20 capsules dispensed)
- Oxycodone 5mg by mouth every six hours as needed for pain given for a maximum of 5 days (20 capsules dispensed)

The medicinal products will be encapsulated, packaged and labeled so as to be unidentifiable by the patient. Packaging will consist of a pill bottle labeled with the dosing and administration schedules for both drugs. Drug safety sheets for both drugs will be provided as part of the package.

Trial medication will be stored by the study pharmacy in a locked and labeled drawer for this particular study until they are dispensed to the patients. Records of allocation and dispensation will be kept by the pharmacy.

Rescue medication consisting of 3 doses of oxycodone 5mg will be dispensed along with the trial medication.

A large prospective study performed by Forrest et al. demonstrated that the rate of serious adverse outcome with ketorolac use following major surgery was as follows: allergic reaction (0.12%), acute kidney injury (0.09%), and gastrointestinal bleeding (0.04%).[14]

Common adverse drug reactions for ketorolac are abdominal pain, dyspepsia, heartburn, nausea, flatulence, dizziness, hypertension (1-10%).[15]

It is commonly recommended to limit administration of ketorolac to 5 days.

Common adverse drug reactions with oxycodone are nausea, constipation, vomiting, headache, pruritus, dizziness, somnolence (>3%), and abdominal pain, anorexia, dyspepsia, anxiety, rash (<3%).[16]

Identification and enrollment of patients (SEE CONSORT DIAGRAM BELOW)

Patients will undergo standard consultation for treatment options for urinary stones. Patients electing to undergo ureteroscopy for urinary stone disease will be identified and considered for enrollment during preoperative counseling in the urology clinic at two study sites. A log will be taken of all patients assessed for inclusion in the study to inform the CONSORT diagram. Those who satisfy the inclusion and exclusion criteria will then be approached for inclusion into the study. Background, significance, risks, benefits, alternatives will be discussed in detail and all questions will be answered before signing consent form. A copy of the research consent form with all of the above information will be given to the patients and the signed original consent form will be kept in the urology department as detailed in the Data Collection and Handling section. At the time of consent patients will also be asked if they would prefer to complete their postoperative surveys online.

Randomization and allocation

Patients will be randomized to one of two groups. Randomization allocation by blocks will be created in conjunction with Dr. Jianbo Li in Quantitative Health Sciences and Dr. John Petrich in Investigational Drug Services. Two separate randomization allocation lists will be created (one for each study site) and will be kept in a labeled, locked drawer in the study pharmacy at each study site. Once patients have consented to being included in the study, they will be assigned a sequential study number, which will be passed onto the pharmacy study contact at the appropriate site to assign randomization allocation. They will then dispense encapsulated trial medication based on that allocation.

Blinding

This is designed to be a double blinded study, in which neither the patient not the clinical team is aware of the group allocation. The medications will be packaged inside an unlabeled capsule. The medication will be dispensed to the patient with a label that describes both medications, strengths and administration schedules. In this case, both drugs are administered with the same schedule (1 capsule by mouth every six hours as needed for pain). The clinical team will be blinded to the allocation and will only receive the dispensed drug from the pharmacy contact and then bring it to the discharging nurse in the recovery room for inclusion with other discharge material.

Preoperative and perioperative procedures

- Patient will undergo standard preoperative procedures including blood work (CBC, BMP), imaging (usually chest xray), and medical clearance as required.

- The procedure itself will be performed per standard practice of the surgeon, including choice of instruments, manner of fragmentation, and postoperative management of patient with regards to follow up appointments, stent placement and removal.

Postoperative procedures

- The study pharmacy will package the appropriate drug into an unlabeled generic capsule and fill a pill bottle with appropriate instructions for both study drugs on the label.
- In the recovery room, the patient will fill out a 100mm pain visual analog scale sheet which will be kept in the study drawer in the urology department.
- The patient will then be given a packet of materials for data collection along with the pill bottle with the blinded medication with full administration instructions and safety leaflets.
- If the patient stated they would prefer to complete their surveys online then an email will be sent on postoperative day 1 with links to their surveys. Reminder emails with a link to that days survey will also be sent on days 2-5. Patients will still be sent home with physical copies of the surveys and patient identification cards in case of technical difficulties accessing the online surveys.
- The patient will fill out the data sheets for pain scale, trial, rescue and other medication usage, and adverse events on a daily basis for five days. The patient will also fill out the Ureteric Stent Symptoms Questionnaire (USSQ) on postoperative days 1 and 5.
- A phone call will be made to the patient on postoperative day 1 to assist with study related questions. Patients completing their surveys online will still be contacted via phone to assist with research related questions.
- If physical surveys completed the patient will then mail the data sheets to the urology department using a provided stamped-addressed envelope or hand in the data sheets at their postoperative appointment.
- The patient will be required to being all unused medication to the postoperative appointment, which will then be returned to the pharmacy staff.
- Postoperative visit will be scheduled for postoperative day 5 for removal of stent.

Rescue medication protocol

- Patients will be provided with three doses of rescue medication (oxycodone 5mg every six hours as needed for pain) alongside their trial medication. This can be taken at the patient's discretion for VAS pain scores >4.
- All usage of rescue medication will be recorded by the patient on the daily data sheet.
- Given that the presence of the stent itself can be a significant factor in the pain and discomfort for patients undergoing URS, we will also allow for patients to be prescribed oxybutynin and/or phenazopyridine at the discretion of the clinical team. These two medications, along with tamsulosin (given to patients routinely following URS) are very commonly used to mitigate stent pain in post-URS patients. Use of all adjunct medications will be recorded by the patient on the daily data sheet.

Emergency situation procedures

Participants will be given a patient card, which will have the study title, investigational medication product details, participant identification number and contact details for clinical study team

members for business and after hours. If a patient has pain which is not controlled despite use of trial and rescue medications, then patient will have the option to call into the surgeon's office (during business hours) or the after-hours call number, which is usually directed to the resident on call. The patient will give the trial information on the patient card to the resident returning the call. Treatment plan at that point will be developed by the resident in conjunction with on call staff as per usual protocol. This may include medications prescribed over the phone, scheduling office visits as well as emergency room visits. .

Subject withdrawal

Participants will remain on the trial unless they choose to withdraw or they no longer meet the inclusion and exclusion criteria.

Outcome measures

The primary outcome measure will be the pain score given by patients on the 100mm continuous visual analog scale (VAS). The VAS is an easy to use instrument for evaluating pain severity. It provides reproducible results that do not differ with age, gender or cause of pain.[17,18] It is sensitive to treatment effects and data derived from it can be analyzed with standard parametric statistical techniques.[12,17,19] Each day, patients will record their maximum and average pain scores. We will compare this between the two groups in two ways: 1. overall, and 2. on a per day basis.

Secondary outcomes

- We will compare the cumulative and per day usage of analgesic medication between the two groups.
- Usage of other medications, either self-administered, or prescribed will be compared
- Requirement of rescue medication will be compared between the two groups
- Adverse events will be compared between the two groups
    - Rate of adverse drug reactions
    - Rate of unscheduled phone calls, emergency room visits, hospital admissions, and clinic visits
- Comparison of USSQ scores on postoperative days 1 and 5.

Data analysis

Data analysis with be performed using R 3.3.2 and RStudio 1.0.136. The main outcome of pain score will be analyzed using Student t test. Numerical outcomes will be analyzed using Student t test while categorical variables will be analyzed using chi square test.

Feasibility, cost and time frame

Based on query of prospectively collected stone database, we perform 320 URS for urinary stone disease. Based on a conservative 50% recruitment rate, we anticipate that we will be able to accrue 166 patients in approximately 12 months.

As this is considered an investigator-initiated study, it falls under tier 1 pricing for the Investigational Drug Service at CCF. This entails a $1500 start-up cost, $60 monthly maintenance cost, $40/patient dispensation cost, and medication cost of approximately $54.11 /100 tablets of oxycodone

5mg and $215.71/100 tablets of ketorolac 10mg. For 166 patients and a proposed 12 month schedule, total cost for this service would be approximately $13608.48.

Research coordinator support will also be required to assist with answering questions, obtaining consent and handling of data sheets. At an estimated $27/hour and estimated 414 hours, this is an estimated cost of $11178.

An additional estimated $200 will be required for printing materials related to the study, packaging, mailing costs.

Strengths

There is limited data which directly compares NSAIDs to opioid medication in the post-ureteroscopy setting as a means of pain control. A prospective randomized controlled trial would give us excellent level A evidence as to whether ketorolac is a reasonable alternative to offer to these patients. Double blinded design would decrease inherent biases of non-blinded studies. Power analysis suggests a relatively small sample size in each group which means that this would feasible to do within a reasonable time span.

Limitations

Pain scores and medication usage are self-reported, with inherent limitations of not knowing if patients are recording medication usage accurately and whether they are taking other drugs for analgesia.

Adverse events and reporting

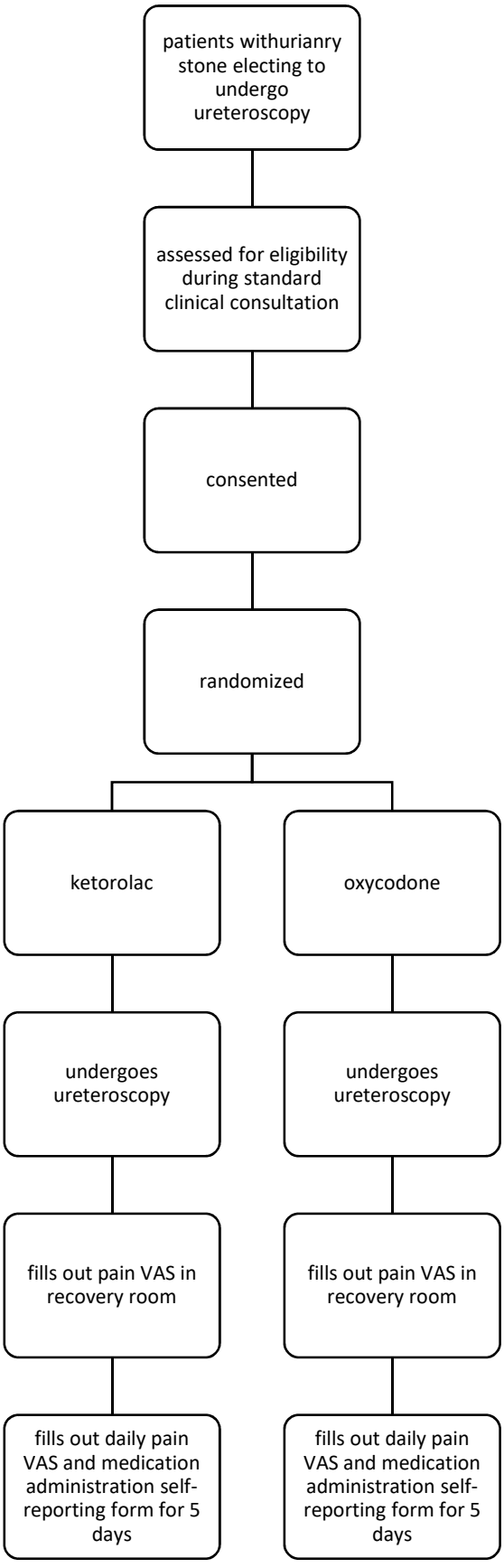
1. Collection of adverse events will be done by a combination of patient self-report on data sheets and data gathering from electronic medical record to search for evidence of phone calls, emergency room visits, hospital admissions, clinic visit notes.
2. Reporting to IRB - The principal investigator or other member of the research team will report any adverse events to the IRB within 7 days of awareness. Participant safety will be protected by standard of care for the surgical procedure which includes standard postoperative follow up visit usually within 8 weeks of the procedure.

CONSENT

Patients who select ureteroscopy for treatment of their renal calculi will be recruited to the study by Drs. Monga, Noble or Sivalingam , study team members or research coordinators during their initial clinic visit. These staff surgeons will first determine if they are interested in participating in research, and upon agreement, the study coordinator will introduce the study details and initiate the consent interview at the time of the clinic visit in a private clinic room.

The consent form will be thoroughly discussed, including the research procedures, risks, benefits and alternatives. Voluntary agreement to participate in the study and signing of the consent will be conducted in the presence of the study coordinator either at the time of the initial clinic visit or at the pre-operative clinic appointment. As an option, the patient may be given the consent form to review for a few days at home, with plans to contact the study coordinator with questions. During this time, the study coordinator will conduct a follow-up phone call to ensure the patient has received adequate

counseling on the study. Initiation of the consent process at the time of their first clinic visit will be noted in their electronic medical record. The patient will receive a signed copy of consent form and the original signed consent form will be kept in a study folder kept in a locked cabinet in the urology department.


patients withurianry stone electing to undergo ureteroscopy
assessed for eligibility during standard clinical consultation
consented
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undergoes ureteroscopy
fills out pain VAS in recovery room
fills out pain VAS in recovery room
fills out daily pain VAS and medication administration self-reporting form for 5 days
fills out daily pain VAS and medication administration self-reporting form for 5 days

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