Title

Pain outcomes of non-opioid analgesia after ureteroscopy or percutaneous nephrolithotomy for nephrolithiasis: a prospective randomized controlled trial.

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Pain outcomes of non-opioid analgesia after ureteroscopy or percutaneous nephrolithotomy for nephrolithiasis: a prospective randomized controlled trial.

Purpose
To compare postoperative pain outcomes of opioid vs non-opioid analgesia in patients undergoing ureteroscopy or percutaneous nephrolithotomy for treatment of nephrolithiasis.

Principal Investigator: Dr. Kara Watts

Study Location: Montefiore Medical Center (Moses, Weiler, and Hutchinson Metro campuses)

Sponsor: none

Background/Significance
The United States is currently experiencing an epidemic of overdose deaths involving prescription opioids.[1] Along with mortality, the opioid epidemic has led to marked increases in morbidity and economic costs, as well as a rise in ED visits and substance-abuse treatment admissions. [1, 2] Perioperative pain is often managed by opioids [3-5]. Opioids bind to and modulate the effect of nociceptors in the central nervous system and peripheral tissues to cause analgesia.[6] Commonly prescribed opioids for acute pain include oxycodone, hydrocodone, and morphine. However, post surgical pain management with opioids can often lead to long-term opioid use.[7,8] This prolonged opioid use after surgical procedures has been seen both in patients who have existing opioid use and in those who are opioid-naive.[8] In addition, diversion of these opioids to others can occur when only a portion of the prescribed medication is taken; in fact, 67% of urologic patients had a surplus of opioid medication from the initial prescription in a survey of 210 patients who underwent surgery.[9] Besides dependence and addiction, opioid use can also cause unwanted side effects including respiratory depression that can lead to hypoxia and respiratory arrest, as well as nausea, vomiting, pruritus, ileus, and constipation.[6] As an alternative to opioid perioperative pain management, non-opioid analgesia has been proven to be as effective as opioid management in acute pain.[10] NSAIDs and acetaminophen are often utilized as alternatives to opioid analgesia, and have an increased efficacy when combined.[11] They both have been proven to decrease opioid requirements and have minimized opiate-induced adverse events.[12, 13] Non-opioid analgesics, including ketorolac (Toradol) and acetaminophen (Tylenol), are often used alone or in combination with opioids after major surgery.[14] Ketorolac (Toradol) is an NSAID with strong analgesic activity that works by inhibiting prostaglandin synthesis, and provides similar pain relief to that of opioids; the analgesic effect is slightly delayed but persists longer than that of opioids. It has been shown to decrease opioid requirements and has led to a decrease in opioid induced adverse

events, shorter hospital stays, and a faster return to normal gastrointestinal function than that of opioid use.[15] It does not alter gastric motility or adversely affect respiration, and it is not associated with abuse or addiction as opioids are.[15] Common side effects of ketorolac include prolonged bleeding times, GI ulceration and hemorrhage, nephropathies, and allergic reactions.[15] Acetaminophen (Tylenol) is a centrally acting analgesic that has been confirmed to be effective for acute pain, and has been shown to display opioid sparing effects.[6] A common side effect of acetaminophen is hepatotoxicity.[6] In this randomized clinical trial, we intend to investigate pain outcomes after ureteroscopy and percutaneous nephrolithotomy in patients who are treated with opioids versus a non-opioid regimen of Ketorolac and Acetaminophen. Percutaneous nephrolithotomy and ureteroscopy are minimally invasive surgical techniques to surgically remove kidney stones. This trial will seek to determine whether non-opioid therapy is noninferior to opioid therapy in the determination of pain intensity as measured by an 11-point numeric rating scale, in which 0 indicates no pain and 10 indicates the worst possible pain, one week after the surgery.

Study Design and Population

This will be an open label, prospective study of approximately 140 subjects undergoing either ureteroscopy or percutaneous nephrolithotomy. Depending on stone burden, location, and symptoms, patients will be counseled on the risks and benefits of both non-surgical and surgical stone management strategies including medical expulsive therapy, ureteroscopic stone extraction, ESWL, or percutaneous nephrolithotomy according to American Urological Association Guidelines. Patients who are eligible and choose to undergo ureteroscopy or percutaneous nephrolithotomy will then be asked if they would like to participate in the study and informed consent will be obtained. After consent is obtained, the electronic medical record will be checked to determine if the patient underwent a routine history and physical, as well if pre-operative imaging such as a plain abdominal film, renal/bladder sonogram, or non-contrast enhanced CT was obtained. Additionally, the chart will be reviewed to determine if there was a pre-operative urinalysis and culture. Patients will then be randomized to control (opioid analgesia) or non-opioid analgesia groups, and given this medication at discharge. Percocet (Oral, 5 mg tablet: 1 tablet every 4-6 hours, or as needed; 10 tablets prescribed) will be the medication for the opioid group, and Acetaminophen (Oral; patient directed as needed and not prescribed) and Ketorolac (Oral, 10 mg tablet: 1 tablet every 6 hours, or as needed; 20 tablets prescribed) will be the medications for the non-opioid group. The plan for randomization will be to use a random number generator to allot subjects to opioid and non-opioid groups. For all patients, we will record the age, sex, location of stone, stone burden (maximal diameter on CT scan), stone size, length of surgery, length of hospital stay, and pain medications administered after the surgery but prior to discharge. This is a non-inferiority trial in which primary outcomes are pain outcomes as measured by pain intensity levels one week after surgery when receiving non-opioid versus opioid analgesia. The patient will be asked, over telephone call, to complete a questionnaire rating their satisfaction with pain relief, current pain intensity level, worst and average pain intensity levels, and their belief of an acceptable pain intensity level since the surgical procedure; these will be measured on an 11-point ordinal scale.[16] The mean of these

values will be evaluated as the main analysis; secondary analysis will evaluate individual values. One week post-op, the patient will also be asked, via telephone call, about any adverse events experienced since the surgery, and how many medication pills they have left. As a secondary outcome, rates of constipation and rates of unused medications by the time of the phone-call one week after the surgery will be measured. Patients will be considered to complete the study after the follow up phone call, which occurs one week postoperatively.

Inclusion Criteria

1. Men and Women age>18 years old
2. Presence of renal or ureteral stones suitable for ureteroscopy or percutaneous nephrolithotomy.
3. Uncomplicated ureteroscopy or percutaneous nephrolithotomy

Exclusion Criteria

1. Pregnant/Breastfeeding/Possibly Pregnant Patients
2. Pediatric Patients
3. Sensitive or Allergic to Opioids, Ketorolac, or Acetaminophen
4. Significant Renal Disease, or Creatinine>1.5
5. Peptic Ulcer Disease
6. Chronic Pain and recovering opiate use
7. Inability to complete questionnaires.
8. Non-mobile Patients
9. Patients on methadone
10. Known Asthma
11. Bleeding Disorders

Participant Recruitment

Patients will be recruited in the course of regular care in the Urology clinic at Montefiore. Both subjects and controls will be recruited by physician referral. Patients diagnosed with ureteral or renal stones will be presented with surgical or non-surgical treatment options. If they choose ureteroscopy or percutaneous nephrolithotomy as their surgical treatment, the patient will be asked if they would like to participate in the study. Physicians will stress that participation is voluntary, that their decision will not impact the care that they receive, and that their patient privacy will always be protected. Informed consent will be obtained while the patient is in the clinic (Hutchinson clinic or pre-operative clinic) if they choose to participate.

Cost

The patient's primary insurance will cover the cost of any surgical and post-surgical care as all procedures fall within the current standard of care.

Informed Consent

A written informed consent will be obtained (full text submitted to the institutional review board). Patients will be counseled that we are investigating pain outcomes based on the type of

analgesia utilized after undergoing ureteroscopy or percutaneous nephrolithotomy. Patients will be given all the available information regarding the risks and benefits of the type of analgesia, and they will be given the choice as to whether they would like to be enrolled in the study. Informed consent will be obtained by study personnel. All consent will be obtained in the Urology clinic (Hutchinson clinic or preoperative clinic) at the patient's regularly scheduled appointment once a patient chooses to undergo ureteroscopy or percutaneous nephrolithotomy.

Risk/Benefit

The risks associated with participation in the study include the known risk factors of ureteroscopy and percutaneous nephrolithotomy, as well as that of opioid, Ketorolac, and Acetaminophen use. The known risk factors for ureteroscopy and percutaneous nephrolithotomy include infection, bleeding, ureteral damage or perforation, or injury to other organs. Common adverse events of opioids include confusion, vomiting, nausea, constipation, respiratory distress, urinary retention, and physical dependence. Possible risks of Ketorolac include peptic ulcers, gastrointestinal bleeding, cardiovascular thrombotic events, myocardial infarction, and volume depletion. A possible risks of acetaminophen is liver damage. Possible benefits to inclusion in the study include less opioid-induced side effects such as nausea, vomiting, constipation, and respiratory distress with similar pain relief. Broader benefits of the study include identifying whether non-opioid analgesia is as effective in treating postoperative pain as that of opioid analgesia. Perioperative outcomes may allow future patients to be spared side effects and the possibility of physical dependence that comes with opioid use. Additionally, the greater use of non-opioids post-operatively can be a modulating factor in reducing the current widespread opioid epidemic.

Data Analysis

Statistical Analysis

Analysis will be based on the null hypothesis that there is no difference among opioid and nonopioid analgesia use in patients in regards to pain outcomes and adverse events. The alternate hypothesis is that there is a difference in regards to these 2 outcomes. This trial seeks to determine if non-opioid analgesia is non-inferior to opioid analgesia after ureteroscopy or percutaneous nephrolithotomy. Data will be analyzed using the Mann-Whitney U-Test. Patients will be analyzed via intention-to-treat analysis.

Data Monitoring

We will be following a Data Safety Monitoring Plan, with oversight by a Data Safety Monitoring Board (DSMB). The monitoring group will consist of three independent physicians in the Montefiore Urology department: Dr. Evan Kovac, Dr. Alexander Sankin and Dr. Beth Drzewiecki. The PI will give reports to the monitoring committee every six months for the duration of the trial on matters concerning enrollment and loss to follow up. This report will also include an analysis of protocol deviations, violations and adverse events.

Minutes of each DSMB meeting, along with recommendations, will be sent the PI. The investigator will also report to the DSMB immediately if there are any serious adverse events related to the study.

We do not anticipate the trial will last long enough for many new scientific developments to occur in the interim, but the research assistant will monitor the literature (via pubmed) on nonopioid analgesia for postoperative pain.

Determination of Sample Size

The primary outcome in this study will be pain intensity as measured by the numeric rating scale at the postoperative visit. Other reported randomized trials measuring similar outcomes utilized a non-inferiority margin of 1.3. [17] Assuming a power of 80% with a 95% confidence interval, as well as a standard deviation of 2.6, each arm must contain 51 patients (total of 102) as calculated using PASS Software. Assuming a 36% attrition rate, we will recruit 140 patients (70 for the opioid group, 70 for the non-opioid group).

Data Quality Control and Database Management

All data will be kept on a secured, password-protected server that only the PI and research assistants will have access to. All data will be entered by the PI or research assistant. Data will be submitted in a de-identified manner (without name, MRN, zip code, or date of birth) to the DSMB to ensure quality of data entry on a monthly basis. Data collected for analysis will contain only de-identified patient information. The identifier log will only be able to be accessed by members of the study team. Once all patient data is collected and the study is over for three years, all patient identifiers will be removed from the database.

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