COVER PAGE:

Official Title: A Randomized Trial Comparing the Combination of Intravenous Lidocaine and Ketorolac to Either Analgesics Alone for ED Patients with Acute Renal Colic

NCT #: 02902770

Date of Document: September 24, 2018

Protocol Template

1. Study Purpose and Rationale

Include pertinent background description with references that are related to the need to do this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

The literature regarding analgesic modalities, their combinations and routes of administrations for patients with pain related to renal colic is expanding. Non-steroidal anti-inflammatory drugs (NSAID's) ketorolac and opioids (morphine) constitutes the mainstay of treatment of renal colic either alone or in combinations. Despite their synergism and analgesic superiority when administered together, both classes of these medications possess a set of unfavorable side effects that limit their use. Emerging data of the use of IV lidocaine for patients with renal colic demonstrated good analgesic efficacy and safety profile. However, none of the trials directly compared lidocaine to ketorolac or the combination of both as viable options in patients unable to tolerate or to have serious contraindications to opioids.

2. Study Design and Statistical Procedures

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations based on the number of participants to be entered into the study.

All data will be recorded on data sheets separate from clinical data and entered into Microsoft Excel. The Microsoft Excel spreadsheet will be exported to SPSS 19.0 for statistical analyses. Data will be analyzed by intention to treat and will include frequency distributions, and repeated measures ANOVA to assess a difference in pain scores, and vital signs. The chi-square test will assess the presence or absence of side effects between the three groups. A p-value of < 0.05 will be used to denote statistical significance.

3. Study Procedures

Describe the procedures in sufficient detail so that a reviewer who is not familiar with them can comprehend what is to be done and can evaluate any risks. Differentiate between procedures that are already being performed for diagnostic or treatment purposes from those that are being done for research, i.e., clearly identify those procedures that would be occurring whether or not the individual was participating in this research.

We designed a double-blinded, randomized, clinical trial to evaluate analgesic efficacy, safety and feasibility of non-opioid analgesic –IV Lidocaine and IV Ketorolac and combination of both in patients with renal colic. Our hypothesis and proposed study will try to determine if a combination of IV lidocaine and IV ketorolac is superior to either drug alone and if this non-opioid analgesic combination is effective for controlling pain of renal colic origin. The trial will compare pain scores at 15 min and 30 min between and within the three treatment groups of the study: IV ketorolac 30mg push with 10 minute normal saline drip placebo, 1.5mg/kg IV lidocaine drip (given over 10 minutes) with normal saline push placebo, or IV ketorolac push with IV lidocaine drip.

Once patient is enrolled, the on duty ED pharmacist will prepare any one of the three treatment groups based on a predetermined randomization list generated via SPSS 19.0.17 The study investigators will record pain scores, vital signs, and side effects at baseline, 15, 30 and 60 minutes post-medication administration. If the still patient reports pain of five or greater and requests additional pain relief then morphine at 0.1mg/kg will be given as the rescue analgesic. Blinding of medication from the patient, research team, and staff will be strictly maintained by the pharmacist investigators.

4. Study Drugs or Devices

If the study involves a drug, device, or biologic, describe how the drug or device works and past experience.

1. Lidocaine works by reducing pain signal transmission along the afferent pain pathway thus, altering the muscular tone of the ureter that leads to passage of the stone.

2. Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that belongs to a group of non-opioid analgesics which primarily inhibit (reversibly) the activity of both COX-1 (constitutive) and COX-2 (inducible) enzymes and block the synthesis of prostaglandins and thromboxanes that leads to ureteral dilation

5. Study Instruments (e.g., Questionnaires, Interview Outlines, Focus Group Guides)
Describe any study instruments that will be used, and identify which are standardized instruments.

Not applicable.

6. Study Subjects
Give detailed inclusion and exclusion criteria and number of participants to be enrolled based on the statistical description and any other considerations. This information should relate to the background information provided above. If this is a clinical trial, this should include a description of the disease and the goals of therapy.

Patients who will be included in the study are adults aged between 18 and 55 years, clinical diagnosis of acute renal colic, and pain rating of ≥5 out of 10 on the numerical rating scale. Exclusion criteria includes documented or suspected pregnancy, breastfeeding, contraindication to nonsteroidal anti-inflammatory drugs or lidocaine, known renal dysfunction, received analgesics within 4 hours before presentation, history of bleeding diathesis, history of peptic ulcer disease, current use of warfarin, HR <50 or >150, history of cardiac arrhythmias, peritonitis or presence of any peritoneal sign, altered mental status, weight >100 kg. We aim to enroll 300 total participants, 100 patients into each study arm.

Nephrolithiasis specifically refers to calculi in the kidneys, but renal calculi and ureteral calculi (ureterolithiasis) are often discussed in conjunction. The majority of renal calculi contain calcium. The pain generated by renal colic is primarily caused by dilation, stretching, and spasm because of the acute ureteral obstruction. The standard of care in the Emergency Department for severe acute renal colic pain control is ketorolac as a single agent or in combination with opioids (morphine). Opioid use is associated with severe nausea and vomiting, sedation and even respiratory depression. Thus, our goal of this project is to evaluate feasibility and analgesic efficacy of medications such as lidocaine. We are evaluating whether the combination of IV lidocaine and IV ketorolac is superior to either drug alone.

7. Recruitment
Describe in detail how participants will be recruited including type (e.g., newspaper advertisements, posters) and location (e.g., MMC, private practices, clinics). Attach a copy of each written advertisement, and the script for each recruitment media or method that is verbal (e.g., video, telephone script).

Participants will be recruited at the Maimonides Medical Center Emergency Department. These participants are patients in the ED that are evaluated by emergency physicians and require pain management for acute renal colic. The research assistant and research fellow will screen for such patients and obtain consent from the patient when suitable.

8. Informed Consent Process
Describe how consent will be obtained, including by whom (i.e., list one or more titles, roles, or names), when, and by what method (e.g., use of consent form requiring signature, verbally in-person, verbally by telephone). Be sure to describe means of communicating if non-English speaking, illiterate, or other vulnerable persons will be included among study subjects. Also if necessary, describe any visual aids or devices that may be used to help explain a complicated procedure or process.

After being evaluated by the treating ED physician and determined to meet eligibility criteria, each patient will be approached by a member of the research team (other than the pharmacists or research manager) for acquisition of written informed consent and HIPAA authorization. In situations where English is not the participant's primary language a staff interpreter or licensed phone interpreter will be used.

9. Confidentiality of Study Data

Describe how this will be maintained (if it is to be maintained) locally, and during transmission to another site, if applicable. Include a clear description of how data will be stored, specifically indicating whether data will contain direct or indirect identifiers. Describe protections related to accessing the study data, whether in an electronic or paper form.

Please note that "deidentified" means that identifiers have been removed and no one (research team or others) can identify from whom the data or sample was collected. "Coded" means that the data/specimens are labeled with a code number, and there is a link between the respondent/donor and the data/specimen, i.e., someone can identify from whom the data/sample was collected if they have the link to the code. For any coded data/samples, indicate who, if anyone on the research team has access to the identifiable data.

Identifiable information will be stored in a secure manner (e.g., locked file cabinet, password protected database) accessible only to research study investigators. All research files will be locked while they are unsupervised.

10. Privacy Protections

Describe how subject privacy will be protected, and the limits to protection. Privacy protection may be summarized as safeguarding an individual's expectation that the information they offer will be held in confidence. Protections should cover (e.g.,) screening activities, HIPAA provisions, forums such as focus groups where private information may be shared, and recordings of research activities, as applicable. Limitations such as compelled disclosure and mandatory reporting should also be described.

A HIPAA Research Authorization will be obtained when the participant is enrolled in the study, after eligibility is determined. The protected health information (PHI) described within this request is limited to the minimum necessary to accomplish the intended purpose. The PHI is to be used for the sole purpose of this research project and will not be disclosed to any other person or entity without prior authorization.

11. Potential Risks

Describe risks including data on risks that have been encountered in past studies. That is, if the occurrence of a certain adverse event was 20%, include those data in this description.

Lidocaine administration is associated with nausea/vomiting, dizziness, periorbital/perioral numbness, tinnitus, slurred speech. These side effects are transient and rapidly reversible. In severe cases, seizures and cardiac arrhythmias might occur; therefore the patient will be placed on the monitor and will be closely and continuously monitored for these side effects. In addition, we will have an antidote (lipid emulsion) readily available that will be given in case of developing severe side effects.

12. Data and Safety Monitoring

Describe how data and safety will be monitored locally to identify unanticipated problems (i.e., events, outcomes, or occurrences that are unexpected, at least possibly related to the research, and suggest an increase in risk of harm to subjects or others).

The data will reside in a password protected computer file and in a locked filing cabinet. All research data will be kept for 10 years after publication and then destroyed according to hospital policy. The research manager will oversee and monitor all data collection in case of unanticipated problems.

13. Potential Benefits

This description should also be based on accrued data from related studies that have been completed. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit, describe benefits to society.

As mentioned above, the goal is relief of acute renal colic pain in the most effective way possible. Our hypothesis that the combination of IV lidocaine and IV ketorolac will result in superior analgesia in comparison to each agent alone and is to be considered as feasible non-opioid analgesics modality for treating patients with renal colic.

14. Alternatives

If this is a clinical trial involving therapy, describe alternative therapies providing data to support their efficacy or lack of efficacy. An important alternative is also not to participate in this research.

The alternative to the proposed therapy of intravenous ketorolac and /or lidocaine is opioid analgesia that includes morphine and /or fentanyl..

15. Research at External Sites

If MMC investigators will be conducting research at one or more non-MMC site(s), additional information is required. This includes, but is not limited to, plans for authorization and/or IRB approval at each site, explanation of funding and organizational relationships, description of procedures at each site, and plans for data and safety monitoring.

Not applicable.