

Intravenous Lidocaine Versus Hydromorphone for Acute Abdominal Pain. A Randomized
Trial Version date 07112018
NCT03300674

Background

Intravenous opioids are commonly used to treat acute abdominal pain in US emergency departments (ED). These medications are highly efficacious and, when used in a monitored setting such as the ED, extremely safe. Use of opioids has fallen out of favor because of a spike in opioid-related overdose deaths throughout the US. While use of opioids in the ED is unlikely to contribute to outpatient opioid deaths, minimizing the use of opioids in the ED will contribute to an opioid free culture, in which opioids are used only when absolutely necessary. A variety of different types of medications can be used in lieu of opioids. One such medication, intravenous lidocaine, has been used extensively in various arenas including the operating room, where it is an evidence-based preventive of post-operative pain, and the cardiac care unit, where it historically had been used to prevent arrhythmias. Some data suggest that it may be efficacious for acute abdominal pain as well.

Intravenous lidocaine has long been used to treat pain. In publications dating back to 1980, intravenous lidocaine has been shown to be an effective treatment for neuropathic pain (2). In the post-operative setting, intravenous lidocaine decreased pain and decreased the need for opiates (3-7). More recently, emergency medicine investigators in Iran, demonstrated that intravenous lidocaine decreased pain associated with renal colic and limb ischemia (9-11). An ED-based study in the US showed comparable efficacy between morphine and intravenous lidocaine when used for acute abdominal pain (12).

Over the years, intravenous lidocaine has been used for a variety of indications including arrhythmia prophylaxis in patients with acute coronary syndromes. Known side effects of intravenous lidocaine range from transient neurological symptoms (dizziness, paresthesias), to cardiac dysrhythmias and seizure. To date, no deaths have been attributed to its use for treating pain and the only documented significant complication was due to an unintentional overdose where a patient received ten times the normal dose (2, 3, 8). All reported side effects in pain patients have been transient and resolve by stopping the drug, decreasing the infusion rate, or by observation alone. Thus, intravenous lidocaine is an emerging medication for safe and rapid relief of pain, has no known addictive properties, and creates a potential for a pain practice paradigm shift in the United States.

We therefore propose a randomized, double blind, RCT to address the following aim:

To determine the relative efficacy and safety of IV lidocaine among patients with acute abdominal pain, when compared to IV hydromorphone, the putative standard of care

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Methods.

Study design. This will be a randomized, double blind, comparative effectiveness study conducted in two Montefiore EDs. Outcomes will be assessed through out the ED stay and by telephone 7 days later. Ethical oversight will be provided by the Montefiore Medical Center IRB. This trial will be registered online at <http://www.clinicaltrials.gov>.

Population of interest. Eligible patients are those who present to an ED for treatment of acute abdominal pain. Acute will be defined as pain for no more than seven days. At the time of enrollment, the ED treatment plan must include use of an intravenous opioid. Adults aged at least 18 years and less than 65 years will be eligible to participate. Patients will be excluded from participation if they have cardiac conduction system impairment (QTc duration > 0.5s, QRS duration > 0.12s, or PR interval duration > 0.2s), known renal (CKD >2) or liver disease (Childs-Pugh B or greater), are hemodynamically unstable, as determined by the attending physician, are pregnant or breastfeeding, or have a known allergy to either medication. Patients will also be excluded if they have used prescription or illicit opioids within the previous week, or if they have a chronic pain disorder, defined as use of any analgesic medication on more days than not during the month preceding the acute episode of pain. Patients weighing < 60kg or > 120kg will be excluded.

Study setting. This study will be conducted in the Moses and Weiler EDs.

Investigational medications. Patients will be randomized in a 1:1 ration to one of the following study arms:

- A. Lidocaine: 120mg IV
- B. Hydromorphone: 1mg IV

Each of these medications will be administered as an intravenous drip over 10 minutes. If patients report insufficient relief of pain at 30 minutes, they will be eligible for a second dose of the same medication. Thirty minutes after the investigational medication was initiated, participants will be asked, "Do you want another dose of the same medication to treat your pain?" Subjects who reply affirmatively will be administered the same medication and dose they had received thirty minutes previously. Patients who require additional medication beyond one hour will be administered medication at the discretion of the treating clinician.

Hydromorphone, dosed at 1mg + 1mg, is a safe and effective strategy for management of acute pain in the ED (<https://www.ncbi.nlm.nih.gov/pubmed/21507527>). The optimal dose of IV lidocaine for acute pain is unknown. For this study, we chose a dose that was most likely to be efficacious while minimizing potential for adverse events. A Cochrane review of intravenous lidocaine for post-operative pain reported that most trials used lidocaine boluses between 1-3 mg/kg (typically 1.5 mg/kg). ED-based studies have used doses of 1.5- 2 mg/kg (8-11).

Assignment. Will be concealed. The research pharmacist will determine assignment based on a random number sequence.

Randomization. Randomization will occur in blocks of four based on a random number generator.

Blinding. Research subjects, clinicians, and research personnel will be blinded. To assess the success of blinding, which may be threatened by the occurrence of certain medication side-effects unique to particular

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arms of the trial, research subjects and research personnel will be asked, at the time of ED discharge, to guess which medications were administered.

Stratification. Subjects will be stratified by study site (Moses or Einstein) and diagnosis (presumptive diagnosis of kidney stones versus non-kidney stone presumptive diagnosis). The rationale for stratification based on presumptive diagnosis of kidney stones is two-fold: 1) kidney stones represent a large subset of abdominal pain diagnoses; 2) kidney stones may be more likely to respond to IV lidocaine than other causes of abdominal pain

Details of protocol. Patients who present to our ED with acute abdominal pain will be referred by the attending emergency physician to the research staff for enrollment. Because of the severity of pain, only those who can appropriately make an informed decision about participating will be enrolled (those who cannot will be screened and excluded). Eligibility will be ascertained by research associates and verified by the site investigator. An EKG will be performed and interpreted by the attending physician. A point-of-care urine pregnancy test will be performed. Capacity to consent to participate in this study will be assessed by the attending emergency physician and documented. Masked medication will be obtained from the pharmacy. The research associate will perform a baseline pain assessment. Prior to the administration of any medication, patients will be placed on a cardiac monitor with telemetry where they will have continuous measurement of their heart rate and oxygenation. Blood pressure will be measured every 15 minutes for the first hour. The ED nurse will administer the research medication as described above. Research associates will perform an assessment of pain and adverse events every 30 minutes. Use of off-protocol medication to treat pain or associated symptoms will be recorded. Seven days after enrollment, patients will be contacted by telephone to determine satisfaction with the medication, course of pain subsequent to the ED visit, and occurrence of any adverse events.

Measures

- 1) Pain intensity will be measured using a verbal numerical scale of which 0 represents no pain and 10 represents the worst pain imaginable
- 2) Medication preference. Preference for a specific medication is a highly patient centered outcome, in which an individual determines for herself the benefit of a particular drug versus the adverse effects experienced. We will include in this study a measure that has been used in multiple ED-based trials—"The next time you come to the ER for treatment of abdominal pain, do you want to receive the same medication again?" Patients will be asked to choose among the following responses: "Yes," "No," or "Not sure"
- 3) Side effects. We will use the following question: "Did you have any new symptoms that began only after you got the study medication?" An affirmative response will be followed by an open-ended question eliciting details.

Outcomes.

Primary efficacy outcome. The primary endpoint for this study will be improvement in improvement in 0-10 pain score between medication administration and 90 minutes later.

Secondary efficacy outcomes.

- 1) Sufficient pain relief, defined as no need for off-protocol parenteral pain medication during the ED visit. The following parenteral medications will be considered off protocol pain medication: any opioid, any non-steroidal anti-inflammatory drug
- 2) Improvement in numerical pain scores 15, 30, 90, 120, and 180 minutes after investigational medication

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administration

- 3) Patient preference for the medication they received.
- 4) Need for medication to treat associated symptoms such as anti-nausea medication or an anti-histamine

Safety endpoints

- 1) Frequency of development of any new symptom after administration of the investigational medication
- 2) Frequency of requirement of naloxone
- 3) Frequency of a change in the disposition of the patient attributable to investigational medication
- 4) Frequency of missed diagnosis, defined as an unplanned return visit to the ED resulting in hospital admission

Sample size calculation.

Based on previous work, we anticipate a mean improvement in 0-10 pain score of 4.9 and a standard deviation of 2.8. Using a between-group difference of 1.3 as a minimum clinically significant difference, an $\alpha = 0.05$ and a $\beta = 0.20$, we determined the need for 73 patients in each group. We will enroll 105% of this N in anticipation of protocol violations and missing data, thus leaving us with a sample size of 154 patients. With 73 patients in each arm, the sample size is sufficiently robust that the ttest can be used even if the data are not normally distributed (central limit theorem).

Analysis.

Baseline characteristics will be reported as mean (SD), median (IQR), or n/N (%), as appropriate. The primary outcome, improvement in 0-10 pain score between baseline and one hour will be reported as mean (95%CI) for each group. The between-group difference in mean improvement in 0-10 pain score will be calculated with 95%CI. If this 95%CI does not cross zero, the results will be considered statistically significantly different. All dichotomous values will be reported as proportions with 95%CI. For formal statistical testing, we will use the ttest.

We will use an intention to treat analysis. Once an investigational medication is initiated, the patient will be included in the analysis, regardless of whether or not the patient completed the medication infusion and regardless of whether or not the patient requests off-protocol analgesic medication.

Data collection and processing. Data acquisition will be performed using REDCap (Research Electronic Data Capture), a secure, web-based application designed specifically to support data capture for research studies. The REDCap project (<http://project-redcap.org/>) is an international project, with more than 70 institutional partners from CTSA and GCRC funded institutions. Paper consent documents will be maintained in locked research cabinets.

Data monitoring committee and interim analysis. This committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist and include Dr. Esses, MD, the director of the Moses ED. The committee will meet every month with the PI to 1) monitor adverse events and develop strategies to minimize these; and, 2) monitor recruitment and enrollment. Because our goal is to report the results with sufficient precision to influence clinical practice, we will not perform an interim efficacy analysis.

Registration. The study will be registered at <http://www.clinicaltrials.gov>.

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Consent. Informed consent will be obtained after the patient has been evaluated in the ED, while they are having acute pain. Unfortunately, there is no other feasible way to obtain consent because severe acute abdominal pain is not predictable. As part of this consent process, we will be sure that patients understand they do not have to participate in the study to obtain analgesics. Also, we will offer to help patients call a family member or friend to discuss the study with them if they wish. Finally, we will have the patient's attending physician confirm that the patient has the capacity to consent to participate in the study at the time they are asked to provide consent. Both research associates and health care providers will participate in the consent process. Both will document their participation with a note in Epic and by signing the consent document.

Pyxis procedures. The healthcare provider will place an order in Epic for the study medication. The order will trigger a specific pocket in Pyxis to open. The research associate and the clinical nurse will then complete the RA/RN checklist (Appendix).

Description of orientation and education that providers receive about this study and about research procedures. This study in particular and research procedures in general are introduced during faculty meetings and reinforced with emails and Powerpoints. The PI then meets with providers in brief one-on-one sessions to describe these. Finally, the investigators and research associates discuss these during the in-shift briefs.

Risks/Benefits

Hydromorphone is commonly used in US EDs for treatment of acute abdominal pain. Intravenous lidocaine is an emerging medication for acute severe pain with some data to support its use. Regardless of results, this study will likely have a national impact. Study subjects will benefit by receiving a medication that is likely to improve their pain. In addition to breach of confidentiality, which is unlikely, and inconvenience to the subject, which will undoubtedly occur, it is likely that subjects will experience adverse medication effects. For the most part, these are nuisance events. All the medications can cause drowsiness, which may be functionally impairing. Opioids such as hydromorphone can cause respiratory depression and hypotension. Lidocaine can very rarely cause hemodynamically significant cardiac arrhythmias or seizures.

Data Storage & Confidentiality

Data will be stored and maintained in REDCap. Data analysis will occur on password-protected computers. Consent documents will be maintained in locked research cabinets. Only study personnel will have access to the data and consent documents.

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