Attachment UUU

High Dose IV Lidocaine vs Hydromorphone for Abdominal Pain in the Emergency Department (HIDO-LIDO)

NCT = NCT04398316

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Title:	**HIgh DOse Intravenous LIDOcaine vs Hydromorphone for Acute Abdominal Pain in the Emergency Department: A Prospective, Blinded, Randomized, Comparative Efficacy Trial (HIDO-LIDO)**
Drug or Device Name(s):	Lidocaine
FDA IND/IDE	151174
Sponsor:	Elliott Chinn, DO
Protocol Date:	5/27/2020
Revision Date(s):	6/25/2020
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Protocol Synopsis

Study Title	HIgh DOse Intravenous LIDOcaine vs Hydromorphone for Acute Abdominal Pain in the Emergency Department: A Prospective, Blinded, Randomized, Comparative Efficacy Trial (HIDO-LIDO)
Funder	Department of Emergency Medicine
Clinical Phase	Phase IV
Study Rationale	The rationale for this study is to find an alternative to opioids for treating acute pain in the emergency department. In a subgroup analysis of a recently published study, intravenous lidocaine at a dose of 2 mg/kg had equivalent efficacy for acute abdominal pain compared to 1 mg of hydromorphone, thus warranting further investigation with a prospective, randomized clinical trial (14).
Study Objective(s)	**Primary** ● To determine the analgesic efficacy of intravenous lidocaine dosed at 2 mg/kg for acute abdominal pain in the emergency department, as compared to a single 1 mg dose of hydromorphone. **Secondary** ● To compare the safety of intravenous lidocaine dosed at 2 mg/kg compared to a single 1 mg dose of hydromorphone.
Test Article(s) *(If Applicable)*	Lidocaine, administered intravenously at a dose of 2 mg/kg, over 5 minutes. Hydromorphone, administered intravenously at a dose of 1 mg, over 5 minutes.
Study Design	This will be a prospective, randomized, double blinded, comparative efficacy trial.
Subject Population **Key Criteria for Inclusion and Exclusion:**	Patients aged 18-64 presenting to the emergency department with severe (defined as requiring an intravenous opiate) acute (defined as duration of 7 days or less) abdominal pain (anywhere on the abdomen or flank).
Number Of Subjects	Total Number of Subjects: 187 Total Number at Hennepin Healthcare: 187 Total Number of Sites:1
Study Duration	Each subject's participation will last one week. The entire study is expected to last twelve months.
Study Phases **Screening**	This study will have three phases. Screening and intervention will occur on the same day in the emergency department. Follow up will occur 7 days later.

Intervention Follow-Up	
Efficacy Evaluations	The primary outcome for this study will be mean pain score improvement after 90 minutes from administration of study drug.
Pharmacokinetic Evaluations	*Not applicable*
Safety Evaluations	Patient reported side effects, medications required to treat side effects, administration of naloxone, change in disposition attributed to study drug and incidence of any serious adverse events.
Statistical And Analytic Plan	Intention to treat. Statistical analysis will be primarily t-tests and chi-square tests.
Data And Safety Monitoring Plan	A DSMB will be in place.

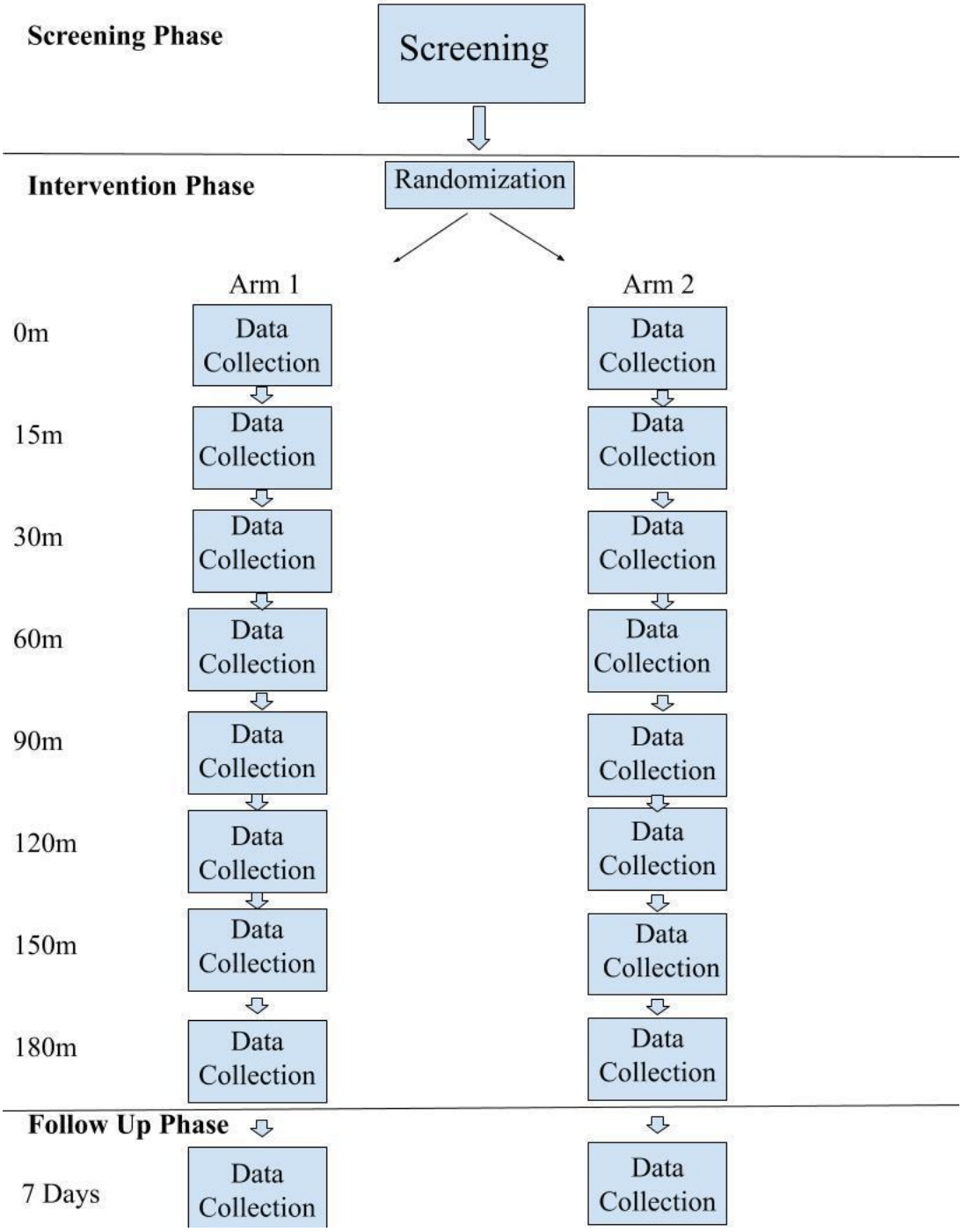
Table 1: Schedule of Study Procedures

	Screening	Minutes from initiation of infusion								7 Days
		0	15	30	60	90	120	150	180	
Informed Consent	x									
Review Inclusion and Exclusion Criteria, Including History & Physical Exam, Review of CMP, PTT and PT/INR	x									
Record Demographic Information,Medical History	x									
Record Height and Weight	x									
Pregnancy Test	x									
Screening EKG	x									
Pain Score		x	x	x	x	x	x	x	x	
Adverse events and side effects			x	x	x	x	x	x	x	x
Heart Rate		x	x	x	x	x	x	x	x	
Respiratory Rate		x	x	x	x	x	x	x	x	

TABLE 1: SCHEDULE OF STUDY PROCEDURES (CONTINUED)

	Screening	Minutes from initiation of infusion								7 Days
		0	15	30	60	90	120	150	180	
Systolic Blood Pressure		x	x	x	x	x	x	x	x	
Diastolic Blood Pressure		x	x	x	x	x	x	x	x	
Pulse Ox		x	x	x	x	x	x	x	x	
Sufficient Pain Relief			x	x	x	x	x	x	x	
Medication Preference									x	x
Adverse events Requiring Intervention			x	x	x	x	x	x	x	
Administration of Naloxone			x	x	x	x	x	x	x	
Disposition Change			x	x	x	x	x	x	x	
Presence of misdiagnosis										x

FIGURE 1: STUDY DIAGRAM



1 Background Information and Rationale

1.1 Name and Description of Investigational Product or Intervention

There are two investigational medications, lidocaine and hydromorphone.

1.2 Findings from Non-Clinical and Clinical Studies

Opiate abuse continues to be an epidemic in the United States. Between 2015 to 2016, the number of unintentional opiate overdose deaths doubled (39). While national attention to this has made slight improvements, recent data show that deaths due to opiates are four times higher than they were 20 years ago (40). The majority of those with an opiate use disorder can trace their first encounter with an opiate to a prescription opiate (38). It is intuitive that if patients require an opiate in the emergency department for their care, they are more likely to require a prescription for an opiate upon discharge. Data varies on how many of these patients will go on to develop an opiate use disorder after a prescription, but recent data showed that 1% of patients in one ED would go on to develop opiate use disorder (defined by them as 6 more more opiate prescriptions in 6 months). While that percentage may be small, one should consider that pain of any kind is the most common chief compliant of patients who present to the emergency department, with 45% of patients between 2000-2010 having pain as their chief complaint (41).

One way to combat the opioid epidemic is to use non-narcotic medications to treat acute pain. Intravenous lidocaine is a non-narcotic medication which may be a suitable candidate for this. A previously conducted clinical trial by this group tested lidocaines efficacy against hydromorphone, a commonly administered narcotic in the emergency department, for acute abdominal pain. Briefly, patients with acute abdominal pain received either 120 mg of intravenous lidocaine (approximating a 1.5 mg/kg dose) or 1 mg of hydromorphone. While lidocaine improved pain scores at 90 minutes, it did not improve them as well as hydromorphone (3.8 improvement compared to 5 on a pain scale of 1-10). However, a subgroup analysis showed that patients who received a dose of 2 mg/kg (because they weighed less) had their pain improved by 5 points, equal to that of hydromorphone. This subgroup analysis is the impetus for this clinical trial. If in fact 2 mg/kg of intravenous lidocaine can treat pain as well as hydromoprhone, the need for narcotics in the emergency department could be significantly reduced which could minimize the need for prescribing opiates from the emergency department.

1.2.1 Non-Clinical Studies

Below you will find animal data in support of the use of intravenous lidocaine. This is directly from the IND application.

Malavasi et al. (16) studied how adding intravenous lidocaine to propofol affected hemodynamics in adult goats receiving abdominal surgery. Goats were randomized to receive either a bolus of lidocaine at 2.5 mg/kg over 20 minutes followed by lidocaine infusion at 100 mcg/kg/min or placebo (saline). There were 23 goats in total, 12 in the lidocaine group and 11 in the saline group. Goats received continuous cardiac monitoring, invasive blood pressure measurements (arterial lines), and continuous end-tidal CO2 monitoring. No goats experienced any hemodynamic changes. Two episodes of bradycardia were noted in goats receiving lidocaine

and per protocol, they received atropine, however they experienced no changes in blood pressure. The authors noted that these episodes of bradycardia occurred while the goats were having their bladders manipulated, suggesting it may have been due to a vagal response rather than due to the lidocaine. Additionally, the lidocaine or saline was given in addition to 0.13 mg/kg of intramuscular xylazine, 2.2 mg/kg of intravenous ketamine, and 0.1 mg/kg of intravenous butorphanol. To summarize, goats received a comparative dose of intravenous lidocaine to the dose we are proposing without any major adverse cardiopulmonary events and only two clinically insignificant events which were unlikely to have been due to lidocaine.

Cerasoli et al. (17) studied the effects of intravenous lidocaine before induction of anesthesia with propofol on healthy dogs, assessing for quality of intubation, cough reflex and adverse effects. All dogs received intramuscular 1mcg/kg dexmedetomidine, 0.2 mg/kg intramuscular methadone, and were randomized to either 2 mg/kg of intravenous lidocaine given over 30 seconds minutes or placebo (saline). There were no major adverse events and both groups had one dog develop first degree heart block (not statistically different). Both groups had decreases in heart rate and blood pressure compared to their presurgical baseline, however no measurements were abnormal or required any intervention and there was no statistically significant difference between the two groups. To summarize, a 2 mg/kg bolus given over 30 seconds caused no significant adverse events in dogs receiving surgery.

MacDougall et al. (18) studied the use of intravenous lidocaine on adult dogs in an outpatient setting. Dogs were randomized to receive either a bolus of intravenous lidocaine or saline at a dose of 2 mg/kg over 60 seconds following by an infusion of lidocaine at doses of either 10 mcg/kg/min, 25mcg/kg/min, 50 mcg/kg/min, 75mcg/kg/min or 100 mcg/kg/min, over 12 hours. Each dog had previously served as its own control, receiving placebo (saline) at a minimum of one week before. Several measurements were taken, including heart rate, blood pressure (automated), respiratory rate (measured visually), sedation score (on a scale of 1-4), and nociceptive threshold. These were taken at time 0, 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 12.25 hours, 12.5 hours, 13 hours, and at 24 hours after the onset of the infusion. Throughout the study, there were no significant changes to heart rate. At 4 hours, there was a paradoxical increase in blood pressure (MAP) for dogs receiving an infusion rate of 100 mcg/kg/min, this resolved at the next measurement. Decreases in respiratory rate were measured at multiple infusion rates (25, 50, 75 and 100) beginning at 2 hours and resolving by 12 hours 15 minutes after initiation of lidocaine infusion. Sedation scores ranged from 1 to 2 as early as 10 minutes after initiation of infusion at all doses. Scores were either 1, defined as "Moderate sedation, easy to handle, still spontaneously active, responds to name, but slower" or 2, defined as “Moderate-heavy sedation, less spontaneous activity, verbal encouragement needed to rise, minimal resistance to handling”.

There were two raters for each dog and the median scores were reported. Dogs receiving a rate of 10 mcg/kg/min had sedation scores of 1, those with rates of 25mcg/kg/min ranged from 0.5 to 1, those with rates at 25mcg/kg/min had scores ranging from 1 to 1.5, those receiving rates at 75mcg/kg/min had sedation scores from 0.5 to 2 and those receiving rates at 100 mcg/kg/min had scores from 0.5 to 2.

Curiously, there were multiple instances where receiving lower infusion rates had higher sedation scores. At all times throughout the study, dogs were able to walk and no dog had a seizure. Toxic doses for lidocaine in dogs are at 11.2mcg/ul. No dog had a concentration greater

than 9mcg/ul and most had levels below 7mcg/ml. To summarize, no dog suffered any significant hemodynamic events and while most dogs had some degree of sedation, none required any intervention and no dog had plasma concentrations that went over the toxic range.

1.2.2 Clinical Studies

1.2.2.1 Human Pharmacokinetics

Below you will find data in support of the broadened use of intravenous lidocaine at a dose of 2 mg/kg, specifically for patients who are taking medications that inhibit lidcaoines metabolism. This is directly from the IND application.

Lidocaine is metabolized primarily by CYP1A2 and less so by CYP3A4. Given that some patient may be taking medications that are inducers of these pathways or that affect liver function, a literature review was conducted to justify not excluding patients who are on medications that inhibit CYP1A2 and CYP3A4 or medications that slow down hepatic flow.

Lidocaine is metabolized primarily by CYP1A2 and less so by CYP3A4. Given that some patient may be taking medications that are inducers of these pathways or that affect liver function, a literature review was conducted to justify not excluding patients who are on medications that inhibit CYP1A2 and CYP3A4 or medications that slow down hepatic flow.

First, the majority of lidocaine research referenced in this application did not exclude patients taking drug that inhibit CYP1A2 and CYP3A4 or drugs that decrease hepatic flow (10, 11, 13, 14). This includes patients who received a dose of 2 mg/kg (12, 20, 21, 22). One article excluded patients taking any medication without justification why (23).

While one study excluded patients who received cimetidine (an inhibitor of CYP1A2), they included patients who took propranolol (19). The dose of lidocaine was 3 mg/kg. The worst side effects were a few cases where mean arterial blood pressure dropped below 65, requiring a dose of ephedrine, however all of those patients had received 30 mcg/kg (cumulatively) of fentanyl, 0.12 mg/kg of morphine and 2mg of lorazepam two hours before surgery, and in the morning had received their cardiac medications, either a calcium channel blocker, beta blocker, or nitrates. These patients were all having sternotomies done with subsequent cardiac bypass surgery. Opiates within the previous week would exclude someone from this study, as per the protocol, so it is reasonable to believe that patients in the proposed study would not have similar side effects (hypotension).

Second, the dose I am suggesting is actually similar to the FDA dosing for a ventricular arrhythmia. While the initial bolus is 1.5 mg/kg, additional doses at 0.5 mg/kg can be given up to three times every five minutes. Therefore, if a patient were to receive the first and second dose of lidocaine, it would be a total of 2 mg/kg over five minutes.

Third, this article specifically addresses the concern of taking a CYP1A2 medication while receiving lidocaine (24). Healthy volunteers took 6 days of fluvoxamine, a potent CYP1A2 inhibitor, then on day 6, received a 1 mg/kg intravenous bolus of lidocaine over one minute. While it did have a negative effect on metabolism, plasma level did not begin to approach a level of toxicity. Referencing Figure 1, the apparent maximum plasma concentration is 1000 ng/ml

which would be 1 mg/L. Central nervous system (CNS) and cardiovascular toxicity (CV) starts at 8 ng/L which is remarkably higher than the effect observed in the study. Furthermore, only a few patients experienced any side effects and they were all mild and transient (last paragraph of page 5). Yes, CYP1A2 and CYP3A4 will increase plasma concentrations of lidocaine, but not in a way that is clinically relevant. While they recommend decreasing doses of lidocaine in patients taking drugs that inhibit CYP1A2, they recommend that for infusions, not for one time boluses (second bullet point, page 8).

Fourth, medications that decrease hepatic blood flow (propranolol) would cause similar effects to those seen in patients with chronic liver disease (Child Pugh A). Patients did not have any serious toxicity when they were given the same bolus as the previously mentioned study (1 mg/kg over 1 minute)(24).

Fifth, another article shows that when you give erythromycin (CYP3A4 inhibitor) and fluvoxamine (CYP1A2 inhibitor), with a lidocaine infusion of 1.5 mg/kg over 60 minutes, lidocaine levels do not approach toxicity (25). The mean plasma concentration of lidocaine was 1028 ng/mL (SD 403) when both drugs were given. Again, the beginning of CNS or CV toxicity is 8000 ug/mL (or 8mg/L).

Sixth, in the largest meta-analysis of intravenous lidocaine, 48 studies were included in their analysis and 45 had explicit exclusion criteria (3). Three did not have exclusion criteria available. The only one that did have exclusion criteria resembling what is being requested would be the article cited above that excluded patients taking cimetidine. So, 44 studies did not feel it necessary to have the exclusion criteria being requested.

Seventh, an in-depth review of the exclusion criteria in the meta-analysis for neurparthic pain (2), out of the eleven articles I could manually review (27-37), none of them had exclusion criteria matching or similar to what is being requested. Many of the doses in those studies went up to 5 mg/kg over as little as 30 minutes.

To summarize, a thorough review of the literature does not support excluding patients who, within 2 weeks or 5 half-lives of taking intravenous lidocaine, have taken either a medication that inhibits CYP1A2, inhibits CYP3A4, or decreases hepatic flow.

1.2.2.2 Clinical Studies in Adults

\ Below you will clinical human data in support of the use of intravenous lidocaine and at a dose of 2 mg/kg. This is directly from the IND application.

Lidocaine HCl is FDA approved for the treatment of ventricular arrhythmias in myocardial dysfunction and in cardiac surgery. The dose for that indication is 1.5 mg/kg, with repeat doses 0.5-0.75 mg/kg up to a total dose of 3 mg/kg over 15 minutes. Given that this indication is for the treatment of an arrhythmia, some may consider it unfair to compare the safety of that dose range for patients without a cardiac arrhythmia, since one of the most feared complications from intravenous lidocaine is an arrhythmia. To support the safety of our intended use, acute abdominal pain, we have conducted a literature of peer reviewed articles who have used lidocaine at a dose of 2 mg/kg for the treatment of pain, either in the operating room or in the emergency department.

Kasten et al. (19) investigated whether adding a 3 mg/kg dose of intravenous lidocaine with infusion of 0.05 mg/kg/min to a fentanyl infusion at 5mcg/kg/min would prevent hyperdynamic changes in patients undergoing cardiac surgery. Ten patients would ultimately receive lidocaine. This was a double blinded, randomized comparative efficacy trial. Prior to receiving either of these medications. The morning of the surgery, patients had received beta blockers, calcium channel blockers and nitrates. Forty five minutes prior to the surgery, patients received an intramuscular injection of morphine at 0.12 mg/kg and 2 mg of lorazepam. If there were increases in a patient's blood pressure or heart rate, pushes of fentanyl were given and if that was insufficient, patients received a nitroglycerin infusion and isoflurane until hemodynamics returned to baseline. Serious adverse events in those who received lidocaine occurred in three patients. Their mean arterial blood pressure dropped below 60 and per study protocol, required intravenous ephedrine to increase it. This was limited to when patients were intubated. Outside of that time period, no patients who received lidocaine had any serious adverse events.

While this article had the highest rate of serious adverse events, it had the sickest patients and there was significant polypharmacy involved. Several inclusion criteria were the patient must have been on a beta blocker, had an ejection fraction between 45-60%, and each patient had to have angiogram proven coronary artery disease. The study we are proposing would exclude patients if they had received any opiates prior to the study, primarily to eliminate a confounding variable but now also to eliminate potential hypotension. Additionally, we are excluding any patient with an EKG showing any prolonged intervals. Therefore, taking into account that we are using a lower dose and taking precautions to prevent the adverse events that occurred in this study, we believe it ultimately supports our use of it.

Kuo et al. (20) compared intravenous lidocaine at a 2 mg/kg bolus followed by an infusion at 3 mg/kg/h to thoracic epidural analgesia (TEA) with a lidocaine bolus and infusion at the same dose to a placebo group in patients receiving scheduled thoracotomies. This was a double blinded, randomized clinical trial. The amount of perioperative and postoperative opiates required was lowest in the TEA group followed by the intravenous lidocaine group and control group. There were only three instances of hemodynamically insignificant bradycardia in the lidocaine group. There was no difference between the three groups regarding the need for atropine or ephedrine for hemodynamic compromise. To summarize, intravenous lidocaine safely improved abdominal pain in patients receiving planned thoracotomies.

Saadawy et al. (21) compared intravenous magnesium sulfate (50 mg/kg) to intravenous lidocaine (2 mg/kg) to placebo, measuring post-operative analgesia requirements in patients undergoing a laparoscopic cholecystectomy. Each group also got an infusion of the same medication, with magnesium at 25 mg/kg/h and lidocaine at 2 mg/kg/h. This was a randomized, double blinded comparative efficacy trial with 40 patients in each arm. There were zero major adverse events across all groups in the study, and there were no differences between each group with recorded heart rates or mean arterial blood pressures. The lidocaine arm required the least amount of postoperative morphine and the least amount of intraoperative fentanyl and sevoflurane. To summarize, lidocaine improved abdominal pain with zero serious adverse events.

Yardeni et al. (22) compared intravenous lidocaine bolus at 2 mg/kg followed by an infusion at 2 mg/kg to placebo for patients receiving scheduled transabdominal hysterectomies. This was a prospective double blinded clinical trial and there were thirty patients in each arm.

The primary outcome was mean pain score postoperatively and lidocaine was superior to placebo up to 8 hours postoperatively, however there was no difference in opiate requirements postoperatively. There were no adverse events reported in this trial. To summarize, intravenous lidocaine bolus and infusion improved patients' post-operative pain up to 8 hours.

Yang et al. (23) compared intravenous lidocaine to thoracic epidural analgesia to placebo for patients receiving scheduled thoracotomies. This was a prospective, single blinded, comparative efficacy trial. There were 20 patients in each group. The main outcomes were time to loss of consciousness, anesthesia requirements intraoperatively (amount of propofol) to maintain normal vital signs. Essentially, these were surrogates of patient discomfort which is why it is pertinent to the study we are proposing. There were no significant adverse events in any group.

Vahidi et al. (12) compared intravenous lidocaine at 2 mg/kg bolus to morphine 0.1 mg/kg bolus in patients with critical limb ischemia in the emergency department. There were 20 patients in each arm and it was a prospective, randomized comparative efficacy trial. Primary endpoints were mean improvement in pain at 15 and 30 minutes. At both times, intravenous lidocaine had better pain improvement compared to intravenous morphine. There were zero adverse events in this study.

Chinn et al. (14) administered either lidocaine at a set dose of 120 mg intravenously or 1 mg of intravenous hydromorphone for patients suffering from acute abdominal pain in the ED. Patients were excluded if they weighed less than 60kg or more than 120kg and were eligible for a repeat dose after 30 minutes. Therefore, it was theoretical that some patients could get a dose of 4 mg/kg over 45 minutes. A subgroup analysis showed that intravenous lidocaine was equally efficacious as 1 mg of hydromorphone if patients received an intravenous dose of lidocaine at 2 mg/kg without any increase in adverse events. Zero serious adverse events occurred in this study and there was no difference in adverse events between either group.

To summarize the available data on intravenous lidocaine dosed at 2 mg/kg or higher, most studies have been done in the operating room and one has been done in the emergency department. The only study with any significant adverse events was in the first trial done by Kasten et al. These events were hemodynamically significant hypotension. However, all of these patients had critical ischemic heart disease (proven by angiography), had received a beta blocker that day, and shortly before receiving the study drugs, received morphine and lorazepam. Furthermore, neither group received intravenous lidocaine by itself, it was fentanyl with or without intravenous lidocaine. Finally, the dose they chose was 3 mg/kg, significantly higher than the dose we are proposing. The rest of the studies show, at a minimum, improved analgesia compared to placebo and at best, superior analgesia to morphine.

1.2.2.3 Clinical Studies in Children

Not applicable, only patients aged 18-64 will be recruited for this study.

1.3 Selection of Drugs and Dosages

Lidocaine (NDC 0338-0411-02) will be dosed at 2 mg/kg and given intravenously over 5 minutes. Hydromorphone (NDC 0409-1283-31) will be given at a dose of 1 mg, intravenously over 5 minutes. These are the maximum daily doses for each medication under this protocol,

however more hydromorphone can be given at the discretion of the treating provider if the patient has insufficient analgesia.

1.4 Compliance Statement

This study will be conducted in full accordance of all applicable Hennepin Healthcare Research Policies and Procedures and all applicable Federal and State laws and regulations. All episodes of noncompliance will be documented and reported according to the Prompt Reporting Guidelines, Attachment EEE, of the Hennepin Healthcare IRB Policies and Procedures.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, unless waiver of consent or other alteration is approved, and will report unanticipated problems involving risks to subjects or others and SAEs in accordance with The Hennepin Healthcare IRB Policies and Procedures and all Federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 Study Objectives

The overall objective of this study is to determine if intravenous lidocaine can have equal analgesic efficacy as hydromorphone while having an equal safety profile in patients with acute abdominal pain.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine whether intravenous lidocaine dosed at 2 mg/kg has equal analgesic efficacy as intravenous hydromorphone at 1 mg, as measured by the improvement in pain score after 90 minutes following administration of study drug.

2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Measure improvement in pain at 15 minutes, 30 minutes, 60 minutes, 120 minutes, 150 minutes and 180 minutes following administration of study drug.
- Measure frequency of sufficient pain relief, defined as no need for pain medication outside of investigational drug.
- Measure the safety of lidocaine, as determined by comparing its rate of side effects, frequency of medication administration required to treat side effects, the frequency of serious adverse events, disposition change attributed to study drug, and frequency of missed diagnosis to hydromorphone.
- To measure patient preference for the study drug they received (would they want it again).

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

Patients presenting to the emergency department with abdominal pain will be screened for eligibility. Once deemed eligible, they will be randomized to receive either intravenous lidocaine or hydromorphone. The patient, ED nurse and physician will all be blinded to the study drug. Only the research pharmacist will know the drug that the patient is receiving. Primary and secondary endpoints will be measured from the time just before the patient receives the study drug and for the next 180 minutes then once again 7 days later (please refer to Table 1 for timing and specific data being measured). The two drugs will then be compared against one another.

Much of each patient's care will be "standard of care", most likely to include intravenous access, venipuncture, labs, imaging, and potentially consultations by other services. Please refer to Figure 1 for an illustration of study interventions. Standard care can take place at anytime on Figure 1.

3.1.1 Screening Phase and Baseline Assessment

The "screening phase" will take place in triage or in a treatment area in the emergency department and will be considered to take place from when the patient arrives to the emergency department to when then patient completes their consent form, during the same visit.

Inclusion and exclusion criteria will be posted throughout the emergency department.

Any staff member can notify a physician or advanced practice provider if a patient may meet study criteria, once that has been determined, staff will notify a study research associate to ensure patient has all inclusion criteria and no exclusion criteria and then obtain informed consent.

The attending physician will ensure that each patient has capacity to participate in informed consent and will document this on the patients consent form.

3.1.2 Study Intervention

The study intervention will be the administration of either lidocaine or hydromorphone and will take place during the "intervention phase" of the study. Both drugs will be given as a drip over 5 minutes. This is for the purpose of blinding, as hydromorphone is generally given as a push dose or very slowly, and lidocaine is safest when given over a slow infusion, typically 5-15 minutes. Giving hydromorphone over 5 minutes will increase its safety as this will decrease its chances of causing respiratory depression or euphoria Lidocaine will be dosed at 2 mg/kg of patients recorded weight, hydromorphone will be dosed at 1 mg. Intravenous hydromorphone meets standard of care for severe pain in the emergency department. Intravenous lidocaine has been shown to be effective for severe pain however it would not be considered standard of care and is not FDA approved for treating pain (when administered intravenously).

3.1.3 Follow-up

The “follow up phase” will take place 7 days after administration of study drug and will be completed by a study research associate via phone call.

3.2 Allocation to Groups and Blinding

Prior to the initiation of the study, a list will be generated which will randomly assign 187 patients to either lidocaine or hydromorphone in a roughly 50/50 distribution. This list will be generated by someone not involved with the study and will be given to the research pharmacists. Patients will be randomized by the research pharmacist in accordance with the list.

Ultimately research pharmacists will give the study drug to a nurse in a bag of saline. The only identifying information on the bag will be a standardized label as follows

Header (**INVESTIGATIONAL MED**), Patient name, age, medical record number, location, tube number, order number, due time and date, drug name (INV lidocaine or hydromorphone in NaCL 0.9% 100 ml IVPB), intravenous, once, 100ml, infuse over: 5 minutes, time label printed, signature for preparer and checker, expiration, and “Caution: New Drug - Limited by Federal (or United States) law to investigational use”

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Participants will participate for 7 days, however that participation on day 1 is limited to 180 minutes after administration of study drug. Patients will then be asked to participate 7 days after administration of study drug, via a phone call, conducted by a study research associate.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will only be conducted in the Hennepin County Medical Center Emergency Department. Recruitment will stop after 187 patients have been consented.

3.4 Study Population

3.4.1 Use of Vulnerable Populations and Patients Who Opt Out of Research

No vulnerable patients will be considered eligible for this study. Neonates and children do not meet the minimum age of inclusion criteria. Pregnant women and fetuses will be excluded by positive pregnancy test (urine or blood). Only patients who have capacity to consent, ultimately determined and documented by the attending physician, can participate so patients with diminished capacity to consent will be excluded. Adult prisoners will not be approached for

eligibility. Any patient who opts out of research will not be included in this study as consent is required for study participation.

3.5 Inclusion and Exclusion Criteria

3.5.1 Inclusion Criteria

1) Adults at least 18 years of age but no more than 64

2) Abdominal (abdomen or flank) pain severe enough to warrant intravenous narcotics (as determined by the clinical team), for a duration of 7 days or less

3.5.2 Exclusion Criteria

1) Pregnant or breast feeding

2) Prolonged cardiac intervals on EKG (QTc duration > 0.5s, QRS duration > 0.12s, PR interval <0.12s or > 0.2s) or any cardiac history, defined as "cardiac arrhythmias, heart blocks, congestive heart failure, or known cardiovascular disease, or deemed to have clinical signs of heart failure on physical exam". This EKG must be from the same day.

3) Renal impairment, defined as CKD > 2 (CKD 1 and 2 are acceptable), as verified by blood work in the preceding 12 months, or evidence of renal impairment by history and/or physical examination

4) Liver impairment, defined as Childs-Pugh B or greater, as verified by blood work in the preceding 12 months, or evidence of liver disease by history and/or physical exam

5) Hemodynamically unstable (as determined by attending physician)

6) Allergy to lidocaine or hydromorphone

7) Self-report of any opioid use within the previous 7 days

8) Diagnosis of chronic pain, defined as using any pain medication more days than not in the previous 30 days

9) Inability to provide informed consent

10) Not wanting to participate in research

11) History of seizures

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 Study Procedures

4.1 Screening Visit and Baseline Assessment

Please refer to Table 1 for specific timing of procedures

- Screen for meeting inclusion and exclusion criteria
- Obtaining informed consent (including attending physician certifying the patient is appropriately able to give consent
- Recording of patients demographics and medical history (age, gender, history of diabetes, high blood pressure, high cholesterol, heart disease defined as coronary artery disease or congestive heart failure, seizures), history and physical exam to exclude any clinical evidence of acute cardiac, renal or liver disease
- Pregnancy test
- EKG

4.2 Study Intervention

4.2.1 Time Zero

- Pain score (1-10)
- Patient placed on monitor
- Vital signs recorded (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, pulse oximetry, source of oxygen)
- Study drug administered by patient's nurse (mixed by research pharmacist and sent to the nurse) over 5 minutes

4.2.2 15 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no). If yes, document was medication was administered, why, and when.
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of any change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.3 30 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.4 60 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.5 90 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)

- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.6 120 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.7 150 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified at this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.2.8 180 minutes after the study drug was started (not after it finished), up to a 15 minute delay will be tolerated

- Pain score
- Vital Signs (same as above)
- Recording of any new symptoms (classified as this point as adverse events)
- Recording of sufficient pain relief (yes or no)
- Recording of any medications to treat adverse events (yes or no)
- Recording on whether or not naloxone has been administered (yes or no)
- Recording of change in disposition thought to be due to study drug (yes or no)
- Recording of any serious adverse event (yes or no)

4.3 Follow Up

Patients will be called 7 days after their visit to the emergency department by a research associate. If they cannot be contacted on that day, they will be contacted the next day (until they are reached, up to one week), and asked to answer the same questions but based off of how they felt 7 days after their visit. This will take place whether or not the patient is admitted or discharged.

4.3.1 7 days after visit to emergency department

- Any new adverse events (yes or no and if yes, list them)
- Record and report any serious adverse event that has been reported by participant
- Medication preference (If the patient were to come back for the same complaint, would they want the same drug? Yes, no or unsure)
- Missed diagnosis (if they present to another emergency department and receive a diagnosis different than what they were discharged with)

4.4 Missed Measurements

- In the event one of the numerical secondary outcomes is missed, an average of the measurements before and after will be used as a substitute. Any other data point will not be substituted and recorded as missed. These, in addition to allowing up to a 15 minute delay in measuring a variable, will not be counted as protocol deviations.

- If a patient leaves the emergency department prior to 180 minutes, they will no longer be followed for timed measurements. They will still be contacted for the follow up portion of the study.

4.5 Rescue Medication Administration

If at any point the patient expressed inadequate analgesia and the treating provider wants to administer a new pain drug, they will be eligible to do so however that will be marked as "Insufficient pain relief". The patient can continue with the study unless at any point they wish to withdraw. Rescue medication will be administered at the discretion of the treating physician or advance practice provider. Rescue medication will not be lidocaine and will never be given to a patient more than once in this study.

4.6 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator if it is later discovered that they have any exclusion criteria, as determined by chart review or "Care Everywhere". If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF and reported to the IRB.

4.6.1 Early Termination Study Visit

If a subject wishes to withdraw from the study, their entire study packet will be kept but not used for any study related analysis. The subject will be marked in REDCap as withdrawing from study but no statistical analysis will be undertaken.

5 Study Evaluations and Measurements

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

- Date of birth
- Biologic sex
- Height (inches)
- Weight (kilograms)
- Medical history (diabetes, hypertension, high cholesterol, coronary artery disease, heart failure)

5.1.2 Vital Signs

All vital signs will be recorded off the patients monitor. Blood pressure will be automated and set to record at the required intervals. The arm without the IV in it will be used for placement of the blood pressure cuff. Measurements will be taken while the patient is laying down in the supine position. If more than one blood pressure is recorded (in the event of an abnormal blood pressure), the one thought to be more accurate will be documented (as determined by the physician or advanced practice provider).

5.1.3 Laboratory Evaluations

With the exception of drawing a lidocaine level in the event of a serious adverse event, blood work is not part of the study. Any abnormal labs thought to be due to the study drug will be recorded if labs were ordered as standard of care, provided they were drawn after the study drug was administered. Pregnant patients cannot be enrolled and whichever pregnancy test is used in their standard of care workup will be used to determine eligibility for the study. Women of childbearing age presenting to the emergency department with abdominal pain nearly universally have a pregnancy test measured at ED presentation as standard of care to evaluate for pregnancy or ectopic pregnancy.

5.1.4 Other Evaluations, Measures

EKG's will be performed on all patients the day of their presentation to the emergency department and prior to them being allowed to participate in the study as an EKG with an abnormal interval would exclude them from the study.

5.2 Safety Evaluation

Subject safety will be monitored by serious adverse events, reported adverse events, vital signs, physical examinations, laboratory data (obtained through standard care), and medications required to treat any adverse events thought to be due to the study drug. In the event of any serious adverse event, a lidocaine level will be drawn on the patient.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is mean improvement in pain score, defined as the difference between pain score at the beginning of the study drug infusion (time zero) and 90 minutes after the study drug was administered (time zero). The mean pain improvement will be compared between each study drug using a two tailed t-test with an alpha level of 0.05 and confidence interval.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- The mean pain improvement at time 15, 30, 60, 120, 150 and 180 minutes (using same test as primary end point).

- Difference in proportion of patients with adverse events, who experience serious adverse events, require medication to treat adverse events, report insufficient pain relief, require naloxone, have a change in disposition, and a missed diagnosis will be evaluated using a Chi-Square test with an alpha level of 0.05.
- Proportion of patients who prefer to receive the same drug at a future visit will be compared as proportions using a Chi-Square test with an alpha level of 0.05.

8.1 Statistical Methods

6.2.1 Baseline Data

Baseline and demographic characteristics and medical history will be summarized by standard descriptive summaries. Mean and standard deviation will be recorded for age. Percentages will be recorded for categorical variables.

6.2.2 Efficacy Analysis

The primary outcome will be assessed using a two-tailed t-test using an alpha level of 0.05. A 95% confidence interval will be recorded for each mean. The same test will be used for all numerical pain outcomes. All other tests will use a chi-square test with an alpha level of 0.05 and confidence interval of 95%.

6.2.3 Pharmacokinetic Analysis

No pharmacokinetic analysis will take place.

6.2.4 Safety Analysis

All subjects entered into the study will be included in the safety analysis, with the exception of those who wish to withdraw from the study. The frequencies of AEs by type will be summarized. Serious adverse events will be described in detail. Incidence of all safety outcomes will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.3 Sample Size and Power

Our sample size was calculated using an alpha level of 0.05, beta level of 80%, standard deviation (SD) of 3 (previous research showed a SD of 3.1 for IV lidocaine and 2.9 for hydromorphone), and a minimal importance clinical difference in pain score of 1.3. This resulted in 85 patients per arm. Anticipating a loss of 10% of patients per arm, our final sample size was 187.

6.4 Interim Analysis

The decision to stop the study for efficacy or safety will be primarily determined by the Data Safety Monitoring Board (DSMB). After 94 patients have been enrolled, they will complete an interim analysis.

The stopping boundary for efficacy will be met if the P-value using a t-test for the difference between groups in the primary outcome is 0.001 or less. Using this conservative

Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The stopping boundary for safety will be met if the P-value using a chi-square test for the difference between groups in the serious adverse event outcome is 0.025 or less.

7 Study Medication (drug, DEVICE, or OTher Study INTERVENTION)

7.1 Description

Study drugs will include lidocaine and hydromorphone.

7.1.1 Packaging

Study drugs will be prepared by the research pharmacist who will place each drug in a non-descriptive 100cc bag of saline. Both medications are clear and if placed side by side in a bag of saline, would be indistinguishable as the research staff will be blinded to medication assignment.

7.1.2 Labeling

Each study drug will be labeled with the standardized label below:

Header (**INVESTIGATIONAL MED**), Patient name, age, medical record number, location, tube number, order number, due time and date, drug name (INV lidocaine or hydromorphone in NaCL 0.9% 100 ml IVPB), intravenous, once, 100ml, infuse over: 5 minutes, time label printed, signature for preparer and checker, expiration, and “Caution: New Drug - Limited by Federal (or United States) law to investigational use

7.1.3 Dosing

Lidocaine will be dosed at 2 mg/kg. The patients recorded weight will be used. Hydromorphone will be dosed at 1 mg. Both drugs will be given over 5 minutes through an infusion pump.

The IV lidocaine solution that we are using for the Lidocaine component is premixed in 5% Dextrose. The appropriate amount based on milligrams will be removed from the Lidocaine and Dextrose 5% bag and added to a bag of 100 ml 0.9% Sodium Chloride. Prior to adding the lidocaine solution to the Sodium Chloride 100 ml bag, the volume equivalent to the amount to be added will be removed from the saline bag. The NDC for the 0.9% Sodium Chloride 100 ml is 0338-0049-18.

The expiration for prepared lidocaine and hydromorphone bags are 24 hours but will be given as quickly as possible after they are mixed, most likely in less than 30 minutes.

7.1.4 Treatment Compliance and Adherence

Not applicable.

7.1.5 Drug Accountability

A list of which drug each participant received will be maintained by the research pharmacist. It will only be made available to the DSMB by request and to the prinicpal investigator after 187 patients have been recruited and their data has been recorded.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study and SAEs will be reported to the IRB in accordance with IRB Attachment EEE: Prompt Reporting Guidelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized and submitted to the IRB at the time of continuing review. Abnormal blood work will only be reported as an adverse event if it was drawn after the patient received the study medication and is a departure from baseline lab work.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject receiving a test article and which the occurrence does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the test article, whether or not related to the product.

All AEs (including SAEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in a persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms: certain, probable/likely, possible, unlikely/unrelated, or unassessable.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all internal (occurring in subjects enrolled at this site) unanticipated problems involving risks to subjects or others, and Serious Adverse Events that are related to the research activity. Reports will be submitted to the IRB in accordance with the timeline below.

Category of Prompt Report	Initial Notification
Internal (occurring in subjects enrolled at this site), related (or more likely related than unrelated) SAE	5 days
Internal, unrelated SAE	30 days
Unanticipated Problems Involving Risks to Subjects or Others	5 days

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

The Principal Investigator is also the Sponsor but will report all events to Hennepin Healthcare Research Institute which is functioning as a Sponsor.

8.7 Medical Emergencies

Participants will be in the emergency department while receiving their study drug and will have comprehensive resources immediately available to treat any medical emergencies potentially related to the study drug. This can include oxygen, cardiac drugs, defibrillators, naloxone, equipment to put the patient on a ventilator, etc.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization or Other Assignment

The research pharmacist will be in charge of randomizing patients to either study drug. They will maintain the unblinded subject list.

9.1.2 Blinding

The research pharmacist will randomly select which patient will receive which medication prior to enrollment. No one else will know which medication the patient received during the study. Each bag of medication will only have the subject number on it, an HCMC ID sticker identifying the patient, and the clinical trial name (HIDO-LIDO).

9.1.3 Unblinding

The DSMB can request unblinded data at any time if required to analyze a serious adverse event or during the interim analysis. The principal investigator can only receive unblinded data after all subjects have been recruited and their data has been completely recorded. In the unlikely event of a medical emergency, the treating providers can request which medication the patient received from the research pharmacist.

9.2 Data Collection and Management

1. Confidentiality: Each subject will have a dedicated study packet. Each page in the study packet will have the participant's subject number on it. Only the first page of the packet will have the patients PHI on it, all other pages will have no PHI on them. All forms will be locked in the research office. Data will then be transferred from hand written data to electronic data in REDCap.

2. Security: Once a week, the REDCap file will be downloaded onto a HCMC password protected laptop.

3. Anonymization, de-identification, or destruction: Only data from REDCap will be used for statistical analysis. When files are to be downloaded for importing into statistical software, only de-identified data will be downloaded. All study packets will be locked in the research office and will only be made available to the IRB, DSMB, or the FDA if necessary. All subject data will be kept for the legally required amount of time, after that it will be destroyed. Each packet will have a "destroy by this date" label on the front of it.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Principal Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards to protect participant privacy include locking up each study packet and storing all digital data on REDCap which is password protected.

No identifiable data will be used for a future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and

any recipient researchers (including others at Hennepin Healthcare) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

A monitor plan will be put in place throughout the study to verify study compliance with regulations (ensuring all consent forms are complete along with other monitoring requirements). An independent DSMB will also be utilized. No member of the DSMB will be an author on the study. The DSMB procedure is described in detail in the IND application.

9.4.2 Risk Assessment

Hydromorphone has been well studied and there are no specific risks for using it in this clinical trial that are unique to the risks encountered in routine clinical care.

Lidocaine is FDA approved for ventricular arrhythmias at an initial dose of 1.5 mg/kg (IV push) and up to three repeat doses of 0.5 mg/kg at intervals of 5 minutes after the initial bolus. We are using a dose of 2 mg/kg over 5 minutes and for the indication of abdominal pain. While the initial dose is marginally higher, it will be given over 5 minutes which will improve the safety profile compared to giving it as an IV push. Additionally, the cumulative dose will be less than the maximum dose available for an FDA approved use.

Side effects from lidocaine will be prevented by eliminating subjects most likely to experience them. This is part of the exclusion criteria. Lidocaine is metabolized by the liver and cleared from the body by the kidneys, so any patient with significant renal or hepatic impairment will be excluded. Lidocaine can also affect the heart, so any patient with an abnormal EKG (defined as any interval abnormality) will be excluded. Geriatric patients can be more sensitive to intravenous lidocaine, so patients aged 65 and older will be excluded.

Patients will be on a cardiac monitor throughout the study (unless taken away for imaging but usually this would happen after at least 30 minutes from the patient receiving the study drug), thus allowing the treatment team to quickly identify any arrhythmia from lidocaine. If the patient is off of a cardiac monitor, they will continue to be closely supervised. If a patient is eligible for discharge prior to 180 minutes of cardiac monitoring, they will be asked to re remain in the department until 180 minutes but will not be placed on a hold if they decide to leave. They will not be excluded from the study if they elect to leave before 180 minutes of monitoring.

Finally, lidocaine toxicity has a typical course, generally starting with perioral anesthesia then moving on to feeling light headed or having mildly slurred speech with increased toxicity. These potential side effects will be explained to the patient so if they experience them, the infusion can be stopped and once the symptoms clear, started again but over a period of 10 minutes, not 5 minutes.

9.4.3 Potential Benefits of Trial Participation

Participants will have no direct benefit from participating in the study. While treatment for their pain is part of the study, they do not have to participate in research to have that and this will be made clear to them when they are approached to participate in the study.

9.4.4 Risk-Benefit Assessment

As stated above, there are minimal risks for participating in this study. While patients will not directly benefit from participating in this study, future patients can benefit if lidocaine has equal analgesic efficacy as hydromorphone. Essentially, it would minimize the need for narcotics to treat acute abdominal pain in the emergency department.

9.5 Recruitment Strategy

Subjects will all be recruited from the HCMC emergency department. Anyone involved in the patients care can refer them to either a physician or advanced practice provider for meeting the primary inclusion criteria of acute abdominal pain severe enough to require an intravenous opiate. Once that has been met, a research associate can formally screen them for the rest of the inclusion and exclusion criteria. Research associates can also scan the track board of patients in the emergency department to see if patients may be a good candidate for the study.

9.6 Informed Consent/Assent and HIPAA Authorization

Written informed consent will be obtained only by personnel certified to do so. This will include research associates, physicians or advanced care providers who have the required IRB approval to obtain consent for this study. Additionally, the attending physician must see the patient and determine if they have capacity to sign the consent form. This requirement is in place because the patients being recruited in this study have severe pain which may impair their ability to participate in the informed consent process.

9.6.1 Waiver of Consent

Not applicable.

9.6.2 Waiver of Assent

Not applicable.

9.6.3 Waiver of HIPAA Authorization

Not applicable.

9.7 Payment to Subjects/Families

Not applicable.

9.7.1 Reimbursement for travel, parking, and meals

Not applicable.

9.7.2 Payments to parent for time and inconvenience (i.e. compensation)

Not applicable.

9.7.3 Payments to subject for time, effort, and inconvenience (i.e. compensation)

Not applicable.

9.7.4 Gifts

Not applicable.

10 References

14. Chinn E, Friedman BW, Naeem F, Irizarry E, Afrifa F, Zias E, Jones MP, Pearlman S, Chertoff A, Wollowitz A, Gallagher EJ. Randomized Trial of Intravenous Lidocaine Versus Hydromorphone for Acute Abdominal Pain in the Emergency Department. Ann Emerg Med. 2019 Aug;74(2):233-240. doi: 10.1016/j.annemergmed.2019.01.021. Epub 2019 Feb 26. PubMed ID: 30819520

11 Appendix