Official Title: Improving Pain Control in Paraesophageal Hernia Repair: Intravenous Lidocaine Versus Placebo

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Background and Significance:

Hiatal herniation and its associated symptoms have been recognized for many years. Paraesophageal hernias (PEH) are increasingly common with advancing age, although they may remain asymptomatic for many years. The most common symptoms include heartburn, postprandial fullness, chest pain, regurgitation, and dysphagia. However, in some cases catastrophic complications such as gastric incarceration and strangulation may occur in the absence of preceding symptoms. Many surgeons believe that the mere presence of a PEH is an indication for surgical repair due to these risks.[1-3]

Surgeons at the Carolinas Medical Center's Hernia Center treat over 60 PEH each year, and consultation numbers and patterns of regional, national, and international referrals continue to expand. With the rise of Enhanced Recovery After Surgery (ERAS) programs designed to reduce physiologic stress of surgery and minimize organ dysfunction, first developed in open colorectal surgery, our center has developed a fast track program to standardize care, lower healthcare costs, and improve outcomes for hernia patients. Successful implementation of ERAS programs targeting bariatric surgery[5], urologic procedures such as bladder resection[6], gynecologic oncology resections[7], gastric cancer resection[8], and pancreaticoduodenectomy[9] has demonstrated shortened length of stay and expedited recovery of patients.

ERAS is well suited to challenges of paraesophageal hernia patients. Similar to colorectal patients, patients undergoing PEH operations have a high risk for complications and prolonged hospital stays, with a 13% complication rate reported in large series.[10,11, 12] Pain control, wound complications, delay in bowel function, and limited ambulation are common challenges in this population, compounded by the advanced age of many patients with PEH. Patients undergoing laparoscopic PEH repair often experience shoulder pain that is likely related to the closure of the crural defect and diaphragm irritation from pneumoperitoneum, and require a significant amount of post-operative intravenous and oral narcotic pain medication to manage their symptoms.[4]

Up to this point, postoperative narcotic pain medication has been the standard approach when attempting to control postoperative pain.[13] Management of pain and bowel function is a critical aspect of patient recovery and an important factor in ERAS protocols. While they do manage pain, narcotics have negative gastrointestinal side effects, and reducing narcotic use has been shown to have a positive impact on patient recovery and length of stay. Therefore, there has been recent interest in the use of intravenous (IV) lidocaine, a non-narcotic, in abdominal surgery because of its pain modulating and anti-inflammatory effects.[14] IV lidocaine has been shown to decrease postoperative pain and facilitate faster restoration of bowel function in colorectal surgery,[2,3] but its use has yet to be studied in PEH patients. We hypothesize that the use of IV lidocaine in PEH patients will limit narcotic use and contribute to a shorter length of stay because of the increased rate in relief from post-operative nausea, achieving adequate pain control and ambulation.

Purpose of the Study:

We aim to study the impact of perioperative IV lidocaine on postoperative pain control in patients undergoing paraesophageal hernia repair. This is in the context of an established ERAS protocol. We wish to study the effect of IV Lidocaine on postoperative short and long-term outcomes, including patients' length of stay postoperative mortality, morbidity, and quality of life. We will compare this to our standard pain management.

Study Design:

Enrollment of subjects
Patients will be prospectively enrolled from Carolinas Hernia Center's outpatient clinic. All paraesophageal hernia patients, age 18 and older, undergoing PEH repair at CHS will be included. Specific, IRB-approved consent will be obtained for inclusion in surgical outcomes database (Figure 1).

Inclusion criteria
- Patients aged 18+ years of age
- American Association of Anesthesiologists (ASA) scores of I-III
- Undergoing elective laparoscopic paraesophageal hernia repair including robotic assisted laparoscopic cases.
- All paraesophageal hernia patients seen in clinic who meet inclusion criteria will be given the option to enroll.
- Cases converted to open laparotomy or hand-assisted laparoscopy will be included for intention to treat analysis.
- Patients who have complications of Clavien-Dindo class 3 or greater will be included in calculations of complication rates. However, they will not be included in calculations of postoperative morphine equivalents, as repeat intervention will confound the normal course of postoperative pain control.

Exclusion

- Patients with end stage renal disease
- Patients with allergies to lidocaine and other amide local anesthetics.
- Patients with contraindications to sodium channel blockers.
- Patients with psychomotor retardation
- Patients with body mass index >40 mg/kg^2.
- Patients receiving opioid pain medication in the previous week or taking daily medication for chronic pain
- Patients with a seizure disorder
- Patients with cardiac intraventricular conduction delays, congestive heart failure, first and second-degree heart conduction blocks.
- Patients undergoing planned concomitant procedures other than PEH repair
- Patients that are classified as ASA 4 or 5 during pre-operative anesthesia visit (if needed) will be excluded. Documentation from the pre-op visit will be reviewed by the research team prior to the surgery date.
- Exclusion from all or portions will be at the discretion of the attending surgeon and anesthesiologist.

Data Collection:

Research fellows, data analysts, and clinical research team will be responsible for tracking subject enrollment and compliance with protocol. Patient outcomes and quality of life will be entered under a deidentified patient key in the surgical outcomes database which is prospectively maintained.

The patient key containing PHI will be stored in a password accessed digital file on a limited access folder on a secure network. Access to this folder is only available to principal investigator and associated staff. Password access to this file will be granted only to sub-investigators. Computer access to this network is in an office space limited to employees during the working hours and requires fob access granted by security during after-hours.

Data of interest will be recorded on a deidentified spreadsheet with no linking patient information. The spreadsheet will be kept on a limited access folder on a secure network. Following data collection period, all variables and data will be deidentified including during any subsequent data analysis or publication.

Research Design:
We will conduct a two-arm prospective randomized study, IV Lidocaine versus placebo, to study the reduction of narcotics, return to bowel function and length of stay. Both arms will receive standard multimodal pain control in the operative and postoperative period.

There will be two arms:

1. IV Lidocaine
2. Placebo

Patients randomized to the IV lidocaine group will be administered IV lidocaine as follows:

- **IV lidocaine will be administered:**
    - 100 mg/5ml Lidocaine Bolus Intravenously (lidocaine 2% PF 5ml) injection prior to general anesthesia induction
    - 1.5 mg/kg/hr to begin prior to incision, run throughout the operation and continue in PACU until 1 hour postoperatively OR until one 2gm/250mL D5W bag has been infused, whichever occurs first.
    - Dosing will be directed by the anesthesia team as they will be unblinded during this process. They may make changes to the rate during the surgery based on hemodynamic monitoring. A dosing sheet will be completed at the end of the procedure.
- **Dosage amount of IV lidocaine/ dosage timing of when lidocaine will be administered**
    - 100 mg Lidocaine bolus on induction, then an infusion of 1.5 mg/kg/hr to begin prior to incision, run throughout the operation and continues into PACU for 1 hour OR until one 2gm/250mL D5W bag has been infused, whichever occurs first. The Patient will be monitored by nursing staff with the aid of continuous cardiac monitoring in the PACU for at least 30 minutes after the discontinuation of the lidocaine drip.
    - Patients randomized to the placebo group will receive D5W solution (as this is the carrier for lidocaine) at the same volume and rate as the IV lidocaine.

Endpoint

Subject participation will last approximately 6 months for this study.

Lidocaine will be used as a perioperative adjunct. At the conclusion of the study, chart review will be performed to evaluate if Lidocaine infusion limited narcotic need, or effected Visual Analog Scale (VAS) values. VAS is the standard nursing method of documenting pain using pain scores. The nurses ask the patient to rate pain from 0 (no pain) to 10 (excruciating pain). LOS is a secondary endpoint of the study, as subjects in the lidocaine arm are hypothesized to have improved pain control and require lower narcotic dosing, potentially leading to earlier discharge.

Risk to Subjects

Consequence associated with participating in the study is the need for additional or other pain medications, and possibly developing an allergy to anesthetic medication. We do not expect IV lidocaine to eliminate the need for narcotics to control pain after PEH repair surgery, therefore all patients will be routinely assessed for pain, regardless of participation in this study. Each patient's pain will be adequately controlled by routine assessment of pain level and treated until controlled. Lidocaine will be used only as a perioperative adjunct.

The side effects of lidocaine are directly related to the serum lidocaine level. Side effects are rare at serum levels within the 2-6 mcg/mL range. Side effects are more pronounced in patients with liver dysfunction, pulmonary diseases where the predominant problem is carbon dioxide retention, and congestive heart failure, who are therefore excluded from the study. We will comply with manufacturer and FDA warnings regarding the maximum dosage of lidocaine.[15,16] Multiple precautions via pharmacy, anesthesia, and OR staff will be taken to prevent administration of both drugs to a single patient.

An additional risk to is the release of information from the patient's health records. The research physician/institution will protect records so that patient name, address, and phone number will be kept private. HIPAA compliance in clinical and pathologic data handling will ensure protection of patients' rights to privacy. Data access will be restricted to those involved in data collection or analysis. Study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available.

Disposition of Results

We will evaluate patient demographics, preoperative lab values, intraoperative and perioperative variables, as well as postoperative outcomes and pain reported by VAS. Postoperative data to be reviewed will also include total opioid analgesia administered, time from surgery to a clear liquid diet, time from surgery to a post-fundoplication diet, time to return of bowel function, length of stay, pain/VAS scores at 6 hours postoperatively, pain/VAS scores on each post-operative day until discharge, pain/VAS scores at 2 and 4 weeks, and pain/VAS scores at 6 months, infectious complications (urinary tract infections as well as surgical site infections, deep organ space infections,

pneumonia), and non-infectious complications (stroke, myocardial infarction, respiratory failure, post-op bleeding, unplanned return to the OR, acute renal failure, death, etc.). When results of the study are published, the subject's identity will remain confidential.

Endpoints:

- Postoperative consumption of morphine equivalents (documented in EMR and obtained through chart review)
- VAS Pain scores 6-hour post op then daily at noon until discharge, 2-week, 6-week, and 6-month phone appt. Nursing VAS documentation would be reviewed post operatively via chart review.
- Length of Stay (chart review)
- Return of bowel function (chart review)
- Day to toleration of diet (chart review)

Power and Sample Size

Based on retrospective data from our institution in the same surgical population, a power analysis was performed using postoperative pain and length of stay as the primary outcome variables. We will need 21 patients per group to show a clinically significant reduction in pain and total morphine equivalents with 80% power and type I error rate of 5%. Anticipating study withdrawals (3-4 per group), we will enroll 50 patients in total.

Data Analysis

Data will be analyzed using standard statistical methods; all patient-identifying information will be removed prior to analysis. Descriptive statistics including means and standard deviations, medians and interquartile range, or counts and percentages, will be used to describe the study population on all variables. For continuous variables comparisons will be made between groups using t-tests and Wilcoxon Rank Sum test. For categorical variables, Chi-Square test and Kruskal-Wallis tests will be used for comparisons between groups. Multivariate regression will be performed as needed to control for potential confounding factors such as age, gender and type of procedure. A p-value of <0.05 will be used for all significance determinations. The SAS® system version 9.4 (Cary, NC) or similar program will be used to complete all statistical analyses.

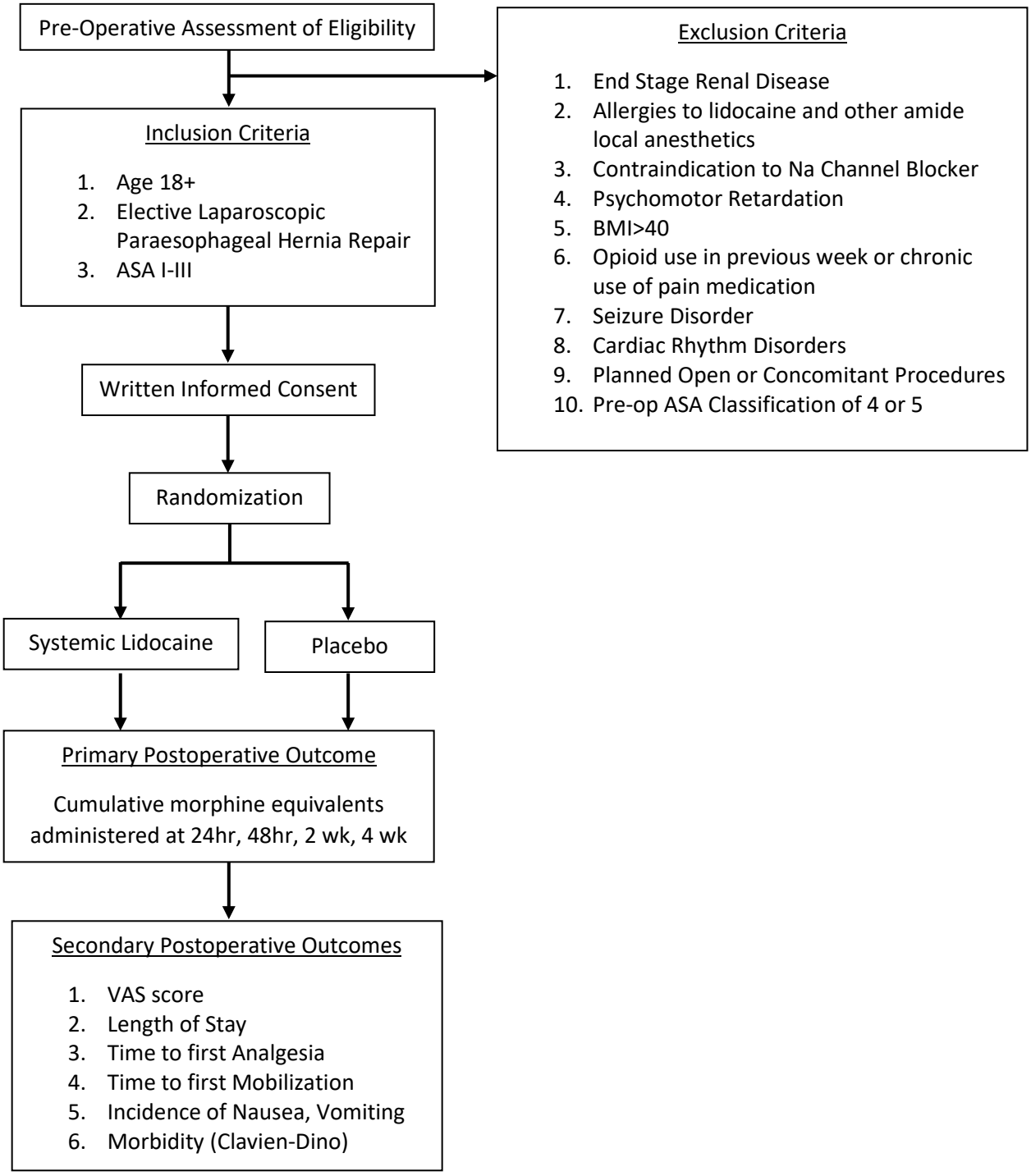
Safety Monitoring:

The safety monitor will provide a professional opinion and review of any adverse events potentially related to the intervention. The co-investigators and research staff will regularly review and document the operative and postoperative course of patients enrolled in the study. The patient will be seen daily by the surgical team monitoring their care and wellbeing. The patient will also be seen or reviewed daily by an attending surgeon or resident involved in the study while they are in hospital. Residents will be instructed in the details of the protocol by the research attending. The research staff will document adverse events as follows:

1. Any adverse events potentially related to the intervention (IV lidocaine) will be reported to the safety monitor, the principal investigator, and the IRB within 48 hours of discovery.
   Events potentially associated with the intervention include but are not limited to:

   a. Allergic reaction to administered medication as demonstrated by rash, puritis, airway compromise, or hives.
   b. Withdrawal from the study due to adverse reaction to medication.
   c. Events potentially associated with lidocaine toxicity as listed in the consent form and the FDA labels.[14,23,24]
      i. Not severe: perioral numbness
      ii. Mild to Moderate: severe dizziness, decreased hearing, tremors, changes in blood pressure and heart rate
      iii. Severe: drowsiness, confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias, and cardiac arrest
2. All adverse events not potentially related to the intervention will be recorded and reviewed per Clavien-Dindo complication classifications. A list of adverse events will be emailed to the principal investigator and the safety monitor every 6 months for review. Upon review by the principal investigator and safety monitor, any adverse events potentially associated with the interventions performed (as listed above) will be submitted to the IRB within 48 hours of discovery.
3. Any patient who is withdrawn from the study for any reason will be reported to the principal investigator and safety monitor every six months for review. Reasons for withdrawal include but are not limited to patient preference, physician judgment, anesthesiologist judgment, adverse event not related to intervention, adverse event related to intervention.
4. The study will be stopped if
   a. Either intervention is deemed unsafe by the safety monitor, the principal investigator, or the IRB committee.
   b. An intervention is deemed significantly superior, rendering further utilization of the alternate intervention unethical.
5. A monitor, auditor, IRB and/or other regulatory authorities will have access to study-related medical records.

Figure 1. Protocol Flow Chart Including Patient Inclusion/Exclusion Criteria



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