COVER PAGE:

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NCT: NCT04005859

Date of Protocol: 02/07/2018

Title of Protocol: **Pain control in colorectal surgery: liposomal bupivacaine block versus intravenous lidocaine**

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Background and Significance:

Enhanced Recovery After Surgery (ERAS) pathways are intended to reduce physiologic stress of surgery and minimize organ dysfunction. ERAS pathways often include multi-modal patient education, early diet advancement, early ambulation, and non-narcotic analgesia with goals of earlier return of bowel function, activity, and discharge from hospital. While first developed for colorectal surgery, the principles of ERAS pathways have been applied to bariatric, urologic, gynecologic oncology, gastric, and pancreatic postsurgical pathways with good success.[1–5] Effective postoperative pain control is essential to a successful ERAS pathway, as a patient with improved pain control has early oral intake, improved mobility, and potentially earlier discharge from hospital. Opiates are often included in postsurgical pain regimens, though the negative impact of patient sedation, nausea, and decreased gastric motility can impede the target outcomes of an ERAS pathway. Reducing narcotic use has been demonstrated to improve patient recovery and decrease length of stay.

In the interest of decreasing narcotic use and improving postsurgical outcomes, multiple non-narcotic analgesic interventions have been developed and implemented as integral to ERAS protocols. Preoperative administration of sodium channel blockers such as lidocaine and bupivacaine as a local anesthetic at the surgical incision, or as a transversus abdominis plane (TAP) regional nerve block, can improve postoperative pain.[6,7] Multiple studies have demonstrated that intravenous lidocaine decreases postoperative pain and facilitates faster restoration of bowel function in colorectal surgery[8–11] and its use has become commonplace at this institution as an adjunct to the current ERAS protocol. The use of intravenous lidocaine to assist in perioperative pain control is used routinely during colorectal operations at this institution. A recent meta-analysis identified fourteen randomized, controlled trials in which intravenous lidocaine was administered as an adjunct to perioperative pain control, providing a reduction in opiate pain use and pain scores after laparoscopic surgery with no adverse events associated with administration of lidocaine. This is in concordance with the timing and dosage of multiple previous studies which have safely administered this medication perioperatively, and demonstrated improved postoperative pain control.[7–13] While utilization of both TAP blocks and IV lidocaine has been shown to improve postoperative pain control, the efficacy of these

interventions is limited by the half-life of the sodium channel blocker used, with most patients benefiting primarily on the day of surgery.[13]

In response to the need for improved, long-lasting non-narcotic pain control, an extended release liposomal bupivacaine (LB) was developed for use in surgical intervention. This product suspends bupivacaine in lipid-based particle layers which are slowly absorbed by the body, releasing bupivacaine over 96 hours. The FDA has approved LB for use in hemorrhoidectomy, bunionectomy, TAP block, mammoplasty, total knee arthroplasty, and inguinal hernia repairs. Since development, the use of locally injected LB has been studied as a local injection, as a nerve block, and as a TAP block. The FDA has approved the administration of liposomal bupivacaine as a TAP block, which is considered a regional anesthetic.[14,15] As a local injection, it has been shown to improve postsurgical pain control in augmentation mammoplasty when compared to bupivacaine.[16] It has been utilized as a brachial plexus block in patients having shoulder surgery, with improved pain control over bupivacaine.[17] Patients undergoing hysterectomy had significantly decreased pain scores and opioid use after LB TAP block when compared with bupivacaine TAP block,[18] and patients undergoing open colectomy had decreased length of stay and opioid use when compared to placebo.[19]

To date, there are currently no studies directly comparing systemic IV lidocaine infusion with LB TAP block. While both have been independently demonstrated to provide improved pain control over placebo, as well as improved pain control over other local anesthesias as described above,[6,8–12,16–21] it is unclear which may provide better analgesia for colorectal surgical intervention. Currently, intravenous lidocaine is regularly used for assistance in pain control during colorectal surgery at this institution. This administered at the discretion of the attending surgeon. We hypothesize that administration of LB as a TAP block will provide longer-term and thus improved postoperative analgesia to patients undergoing minimally invasive colorectal intervention, with resulting decreased narcotic use, earlier ambulation, and earlier return of bowel function.

Purpose of Study:

To compare the analgesic impact of intravenous perioperative lidocaine infusion with preoperative liposomal bupivacaine TAP block. This is to be integrated into the standard ERAS protocol currently utilized at Carolinas Medical Center. Primary endpoints will be postoperative pain as measured by verbal rate scale (VRS), postoperative morphine equivalents utilized per day, and over 30 days. Secondary endpoints will include date of ambulation, return of bowel function (first flatus), tolerance of goal diet, incidence of post-operative nausea and vomiting during hospital stay, length of stay (hospital and PACU), post-operative morbidity (Clavien-Dindo, related to both anesthesia and surgery), cost of hospitalization (operative, PACU, postoperative stay, and total) and quality of life on follow up.

Study Design:

Enrollment of Subjects:

Patients will be prospectively enrolled from Carolinas Medical Center Colorectal Surgery Outpatient Clinic and the Levine Cancer Institute Surgical Oncology Outpatient Clinic. Specific, IRB-approved consent will be obtained for enrollment in the study and for inclusion in the surgical outcomes database.

We will include patients 18 to 70 undergoing elective laparoscopic colon resection for benign or malignant disease. We will include laparoscopic, robotic assisted laparoscopic, and/or hand assisted cases. Cases converted to open will be included for intention to treat analysis. Creation of ostomy will not preclude enrollment.

Patients who have a history of chronic pain on chronic opioids, currently on suboxone or methadone, or with a contraindication to lidocaine administration will be excluded. Planned open interventions as well as planned concurrent non-colorectal interventions will be excluded. Patients who are under 18 or over 70, have liver or renal dysfunction, epilepsy, psychomotor retardation, BMI >40, sleep apnea, or cardiac rhythm disorders, or are pregnant will be excluded (image 1).

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.

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 primary investigators 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:

Creation of study arms:

We plan to conduct a single-center, prospective, randomized, blinded study comparing the analgesic impact of perioperative IV lidocaine infusion with post-induction, pre-incision LB TAP block. Patients will be randomized to one of two study arms using a computer-generated list. Allocation concealment will be ensured by enclosing assignments in sealed, opaque, sequentially numbered envelopes will be opened upon arrival of the patient in the operating room. Postoperative outcomes will be assessed by personnel who remain blinded to the type of intervention throughout the study.

Groups will receive administration of analgesia as follows:

1. Intravenous Lidocaine infusion (control arm, current standard of care) n= 35
    a. 100 mg/5mL intravenous bolus of lidocaine 2% PF 5mL will be initiated by anesthesia service prior to general anesthesia induction.
    b. 1.5 mg/kg/hr to begin prior to incision and continue until discontinued 1 hr postoperatively in PACU. Patients will be monitored in PACU for at least 30 minutes after discontinuation of lidocaine drip.

c. Adhesive tapes will be applied at the presumed level of TAP block puncture sites.

2. Liposomal bupivacaine TAP block (experimental arm) n= 35
    a. Block will be administered after induction of anesthesia and before incision by a specifically trained attending surgeon or surgical fellow with the colorectal service.
    b. A single vial of liposomal bupivacaine (20 mL 1.3%, 13.3mg/mL, 266 mg) will be diluted in 50cc bupivacaine to a volume of 60cc prior to administration. This will be divided into 2 doses for bilateral TAP blocks.
    c. The LB will be administered under ultrasound guidance in the transversus abdominis plain per manufacturer recommendations.
    d. Adhesive tapes will be applied at the level of the TAP block puncture sites.

Perioperative care (ERAS):

All patients involved in this study will be enrolled in the current CMC ERAS protocol, which is current standard of care at this institution. This protocol includes:

- Nutritional supplements 1 week before surgery
- Clear liquids up to 2 hours before surgery
- Early postoperative ambulation
- Clear liquid diet available immediately postoperatively
- Standard postoperative pain control per ERAS protocol with scheduled acetaminophen, gabapentin, and opiates available per request.
- Early Foley catheter removal (POD1 unless otherwise specified) and encouragement of ambulation per current ERAS protocol.

Evaluation of primary outcomes:

Patients will report pain by the verbal pain scale (VRS) every 6 hours postoperatively for the first 24 hours, then at least every 6 hours as per standard nursing protocol with vital signs and administration of pain medications. This verbal pain scale is currently recorded by nursing staff with every pain medication administered as part of standard protocol. It is available in the medical record with every pain medication administered, as well as with vital sign checks. After discharge, pain/VRS scores will be measured at 2 and 4 weeks postoperatively by patient survey. Any patient requesting more analgesia at any time will be assessed and provided with additional oral or intravenous administration of analgesia as per ERAS protocol, with goal of pain control to a level under 40mm VAS measurement. Standard postoperative analgesia includes but is not limited to scheduled acetaminophen, gabapentin, and opiates available per request.

Total opioid analgesia administered postoperatively will be recorded as morphine equivalents and stratified per postoperative day, per hospitalization and at 2 and 4 weeks postoperatively. In hospital, PCA and PRN opioids will be reviewed and recorded daily. This information is available in the patient medical record, as all analgesic medications are recorded at distribution by nursing staff. After discharge, patients will bring opioid prescription bottles to follow up appointments for accurate recording of usage, in addition to self-reported opioid dosing.

Evaluation of secondary outcomes:

Secondary outcomes will be recorded and evaluated, including date of ambulation, return of bowel function (first flatus), tolerance of goal diet, incidence of post-operative nausea and vomiting during hospital stay, length of stay (hospital and PACU), post-operative morbidity (Clavien-Dindo, related to both anesthesia and surgery), cost of hospitalization (operative, PACU, postoperative stay, and total) and quality of life on follow up.

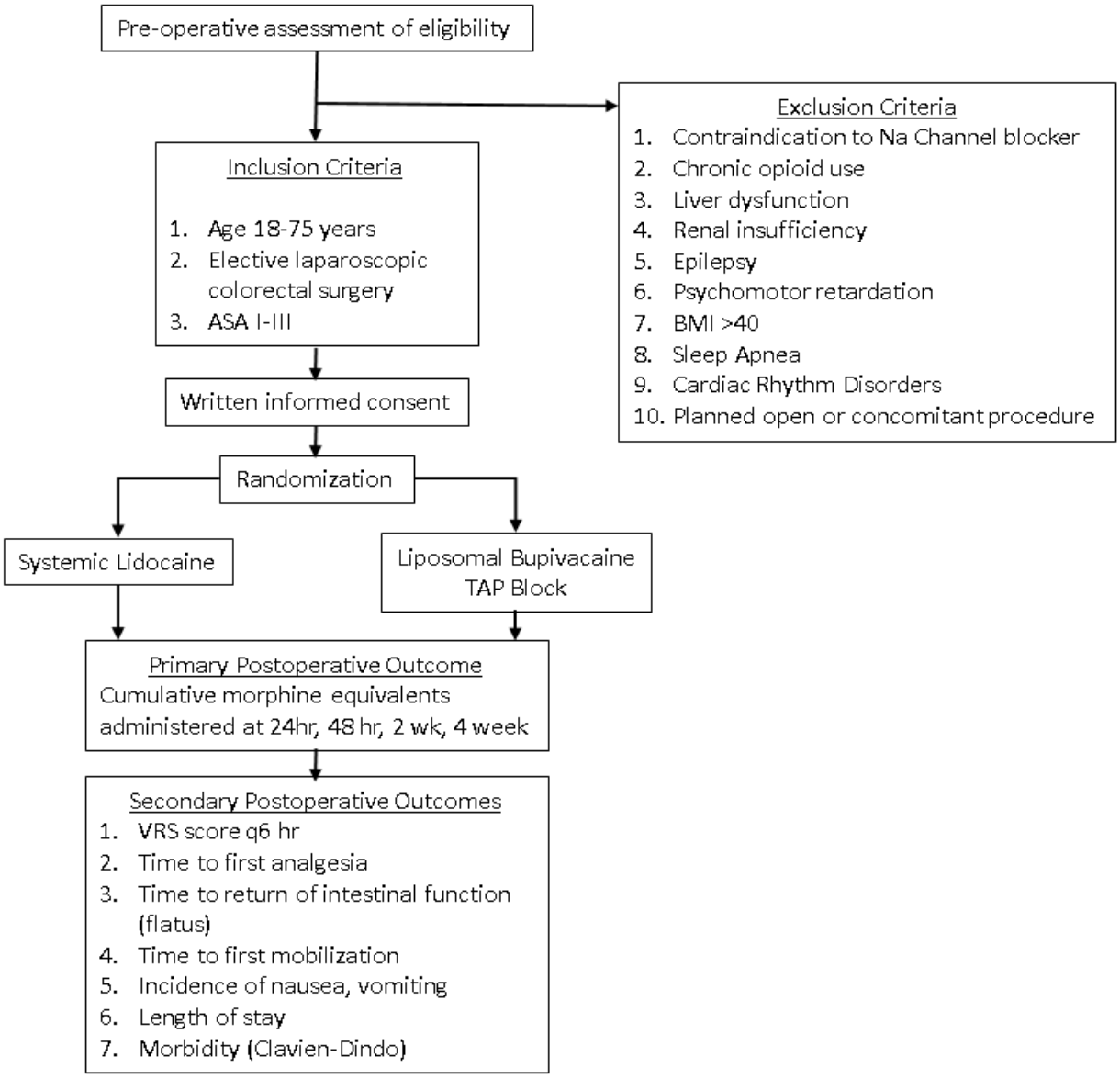
Evaluation of adverse outcomes:

Postoperative outcomes will be recorded and categorized per Clavien-Dindo classification of surgical outcomes. Outcomes of grade III or greater will be considered major complications, and these patients will be removed from further evaluation of pain control. These complications will be included in total outcomes.

Endpoint

Intravenous lidocaine or TAP Block will be used as a perioperative adjunct, then at the conclusion of the study chart review will be performed to evaluate if either intervention provided superior pain control as demonstrated by narcotic need, VAS pain scale values, return of bowel function, time to diet, or length of stay (LOS).

Image 1: Trial study design



Power and Sample Size:

Based on differences detected in prior studies, a power analysis was performed using postoperative pain and length of stay as the primary outcome variables. We will need 20 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 (3-5 per group), and complications requiring further intervention (3-5 per group), we will enroll 35 patients per group, 70 patients in total.

Data Analysis:

Data will be analyzed using standard statistical methods utilizing the SAS program version 9.3 (SAS, Cary, NC, USA). Descriptive statistics including means and standard deviations, or counts and percentages, will be used to describe the study population on all

variables. Patients will be grouped based on study arm. Demographic and baseline measures will be compared for differences between groups. For continuous variables, comparisons will be made between groups using t-tests and Wilcoxon-Mann-Whitney tests. For categorical variables, Chi-square and Fisher's exact tests will be used to make comparisons between groups. For the primary analysis, morphine equivalents, pain scores, weight (kg), length of operation (min.), estimated blood loss (cc), total cost ($), and length of postoperative stay (days) will be compared between groups using the same tests as outlined above; additional analyses will compare prevalence of peri-operative complications between groups. Multivariate regression will be used to control for potential confounding variables such as age, gender, or others as identified. The level of significance will be set at $p < 0.05$ for all comparisons.

Risks and Benefits:

Both analgesic interventions (IV lidocaine and LB TAP block) have been demonstrated to be superior to opioid-only analgesia for postoperative pain control in multiple studies. IV lidocaine is routinely used for augmentation of perioperative pain control in colorectal and other surgical procedures at this institution.[7–13] The administration of a long acting LB has the potential to improve pain control for a longer period postoperatively.[6,16–19] Improved postoperative pain control can improve patient outcomes on multiple levels, including earlier diet, earlier ambulation, and earlier return of bowel function.

Adverse outcomes to administration of liposomal bupivacaine include the potential cardiac side effects of administration of sodium channel blockers such as lidocaine and bupivacaine. The side effects of these medications are directly related to the serum level. For lidocaine, 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 this study. We will comply with manufacturer and FDA warnings regarding the maximum dosage of bupivacaine and/or lidocaine.[14,22,23] Multiple precautions via pharmacy, anesthesia, and OR staff will be taken to prevent administration of both drugs to a single patient. Other adverse events include accessing confidential PHI, which we hope to prevent using the data security plan detailed previously.

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. The Co-investigators will document adverse events as follows:

1. Any adverse events potentially related to the intervention (IV lidocaine or liposomal bupivacaine TAP block) will be reported to the safety monitor, the primary 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 or bupivacaine 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
d. Events associated with injection of liposomal bupivacaine into the abdominal wall for the TAP Block as listed in the consent form.
    i. Abdominal wall swelling or bleeding in excess of appropriate post-surgical changes
    ii. Abdominal wall bleeding requiring transfusion or intervention

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 primary investigator and the safety monitor every 6 months for review. Upon review by the primary 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 primary 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 primary investigator, or the IRB committee.
    b. An intervention is deemed significantly superior, rendering further utilization of the alternate intervention unethical.

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