Liposomal Bupivacaine Versus Standard Bupivacaine Hydrochloride In Colorectal Surgery

NCT # 03702621

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V2 12/30/19

1.0 Background

Each year, thousands of laparoscopic colorectal surgeries are performed for various indications including resection for colon cancer. Abdominal surgery is often complicated by post-operative pain, making pain control challenging especially with the use of opioids and postoperative ileus. Improved pain control increases patient satisfaction and may lead to improved postoperative course. Currently, our standard of practice at Indiana University Hospital is to perform Quadratus Lumborum (QL) block using liposomal bupivacaine (LB) for these patients to help with postoperative analgesia. With the current literature (mostly orthopedic surgery) suggesting that LB might not provide superior analgesia compared to standard bupivacaine hydrochloride (SB), our study aims to compare the difference in duration of analgesia between the two drugs when it's used for colorectal surgeryTo date, there are no data published on these two drugs being compared in colorectal surgery, which is significantly different from orthopedic surgery.

LB has good analgesia coverage for up to 72 hours postoperative when compared to normal saline and has been suggested to reduce postoperative opioid use as well. [6, 7] Yu et al performed a meta-analysis looking at the effectiveness of LB vs SB in total knee arthroplasty, and found that LB resulted in decreased VAS pain scores at 72 hours, but not at 24 or 48 hours. [8]. In contrast, Ma et al showed that LB provided better pain relief as assessed by VAS at 24 hours in total hip arthroplasty, but not at 48 or 72 hours.[9] When Knudson et al studied LB vs SB in colorectal surgeries, they found no difference in the use of postoperative opioid use in colorectal surgery.[10] In these studies, LB shows promise in providing superior postoperative analgesia compared to SB, but few studies directly compare them. Our study directly compares equal volumes of LB and SB in QL blocks for laparoscopic colorectal surgery.

The QL block, first described by Blanco in 2007, provides postoperative regional anesthesia targeting the T7-T12 branches of thoracolumbar nerves. There are at least four described techniques to performing the QL block, with studies still needing to be performed to compare their efficacy.[1-3] Our study will utilize the intramuscular approach to the QL block. In this technique, an ultrasound probe is used to follow the needle tip into the QL muscle. Local anesthetic is injected and its spread between the fascia and the muscle to provide the blockade of the nerves.[3]

We plan to use Exparel®, or a liposomal formulation of bupivacaine, as the analgesia for the study arm and SB for the control arm.[4-7] Because Exparel® is in liposomal form, the lipid solubility allows bupivacaine to be released over an extended period of time. It is reported to provide long-lasting analgesia for up to 72 hours and may result in decreased opioid consumption and shortened hospital stays. Exparel® use for QL block is our current standard of practice.

2.0 Rational and Specific Aims

Both of the pain control modalities in this study have been used as postoperative analgesia in prior studies.[8-15] The specific aim of this study is to compare the difference between the pain control methods in achieving the following:

1. Decreased opioid requirements
2. Improved postoperative pain scores
3. Decreased opioid side effects (Nausea, sedation, ileus, urinary retention, respiratory depression)

The primary endpoint of this study will be VAS pain score. The VAS scores will be taken with both rest and movement.

The secondary endpoint includes intravenous opioid consumption and opioid side effects (nausea, sedation, ileus, urinary retention, respiratory depression). The IV and PO opioid doses will be quantified at 1, 24, 48, and 72 hours. We will also measure postoperative nausea and sedation scores at 1, 24, 48, and 72 hours. We will also measure time to first flatus, incidence of urinary retention, incidence of respiratory depression, ambulation activity, and hospital length of stay.

3.0 Inclusion/Exclusion

Inclusion criteria:

- Patients undergoing colorectal surgery at Indiana University Hospital
- ASA class 1, 2, 3 or 4
- Age 18 or older, male or female
- Desires Regional anesthesia for postoperative pain control

Exclusion criteria:

- Any contraindication for QL block.
- History of substance abuse in the past 6 months.
- Patients on more than 30mg morphine equivalents of opioids daily.
- Any physical, mental or medical conditions which in the opinion of the investigators, may confound quantifying postoperative pain resulting from surgery.
- Known allergy or other contraindications to the study medications (Acetaminophen, Gabapentin, Bupivacaine).
- Postoperative intubation.
- Any BMI greater than 40.0.

4.0 Enrollment/Randomization

All laparoscopic colorectal surgery cases scheduled by colorectal surgeons at IU Health University Hospital will be identified. Subjects will be contacted face-to-face prior to surgery by one of the research team members. They will be informed about the study and all questions will be answered. The potential subjects will be given a copy of the informed consent form and authorization form. The subjects will then be contacted face-to-face in POCU on the day of surgery and if participation is agreed, written consent will be taken. All patients will undergo a

standardized enhanced recovery perioperative care pathway designed and agreed upon by the perioperative team of anesthesiologists and surgeons.

A total of 100 subjects will be randomized by a computer program into two groups (50 in each group):

1. LB QL block – placed by ultrasound using 266mg Exparel (20ml) and 40ml of 0.125% bupivacaine. 30ml on each side.
2. SB QL block – placed by ultrasound using 60ml of 0.25% bupivacaine. 30ml on each side.

Randomization will be performed using Research Randomizer. The primary investigator will inform the person doing the block as to what group the patients are randomized to. Both the patients and the research staff doing assessments will be blinded to the randomization.

5.0 Study procedures:

Both of the QL blocks will be done intraoperatively after induction. All procedures will be done using sterile technique with masks, hats, and sterile gloves. All procedures will be placed under the supervision of the attending anesthesiologist on the acute pain service.

All patients will receive 1 gm acetaminophen and 600 mg gabapentin preoperatively. Patients above 70 years old will receive 300mg gabapentin. Patient will be randomized to one of the two arms. Patients will be blinded to which arms they are assigned to. All research personnel involved in ordering post-operative opioids and doing post-operative assessments will be blinded as well. The proceduralist will be informed as to which arms patients are assigned to prior to the procedure, hence only the proceduralist will be aware of the randomization.

For the QL block, Shamrock sign consistent of the quadratus lumborum muscle, psoas major muscle, erector spinae muscles and the L4 transverse process will be identified. Under ultrasound guidance with an in-plane technique, the needle will be advanced into the fascial plane between the quadratus lumborum and psoas major muscles. For the LB group, 0.125% bupivacaine 20ml plus Exparel®10ml will then be injected into the fascial plane on each side. For the SB group. 30ml 0.25% bupivacaine will be injected on each side. Saline will be used for hydro-dissection until the QL block target is confirmed on ultrasound.

As part of the ERAS protocol, all patients will receive ketamine and lidocaine drip during surgery, which is our current standard of practice.

All patients will be scheduled on PO acetaminophen and PO gabapentin daily postoperatively per ERAS protocol. PO oxycodone PRN will be started once patients tolerate diet. PRN IV dilaudid may be given for severe breakthrough pain.

Opioid usage at 1, 24, 48 and 72 hours after the block will be recorded by a member of the research team. Pain scores at rest and on movement (knee flexion) will be measured by the investigator using Visual Analog Scale (VAS). Nausea will be measured using a categorical

scoring system (none=0; mild=1; moderate=2; severe=3). Sedation scores will also be assessed by a member of the study team using a sedation scale (awake and alert=0; quietly awake=1; asleep but easily roused=2; deep sleep=3). All these parameters will be measured at 1, 24, 48 and 72 hours after the QL block and patients will be encouraged to ambulate on postoperative day 1 under supervision. Their ambulation activity will be recorded.

Data management will include quality assurance and quality control measures. All collected data will be monitored by a data and safety monitoring group independent from the research team. Data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety and procedures designed to protect the privacy of subjects will be monitored at least annually.

6.0 Reporting of Adverse Events

Patients will be monitored by the primary team during the postoperative period, and any adverse events or unanticipated problems such as local anesthetic toxicity or any injury to the bowel or kidney as a result of the block will be reported to the acute pain service and research team. All adverse events or unanticipated problems that meet the criteria for prompt reporting will be reported to the IRB within 5 business days.

7.0 Study withdrawal/DC

The patient can withdraw from the study at any time by contacting the research team or acute pain anesthesia resident. In such an event, patient may still have access to all the IV and oral pain medications. Anesthesia acute pain team will continue to follow the patient for 24 hours. After 24 hours, the anesthesia acute pain team will sign off and all further pain management will be done by the primary team.

8.0 Statistical consideration

Primary outcome: VAS score at 24 and 48 hours

Primary Research Hypothesis: Liposomal bupivacaine will provide lower postoperative pain scores compared to standard bupivacaine in QL blocks for laparoscopic colorectal surgery as measured by VAS scores at 24,48, and 72 hours under an enhanced recovery perioperative care pathway.

Secondary outcomes: Narcotic usage after 1, 24, 48 and 72 hours. Pain scores using VAS at rest and on knee flexion at 1, 24, 48 and 72 hours. Nausea scores at 1, 24, 48 and 72 hours. Sedation scores at 1, 24, 48 and 72 hours. If the patient is discharged within 72 hours, every effort will be made to obtain data points, but we will not consider these data points deviations since our 72-hour data point will not change the integrity of the study.

Secondary Research Hypotheses: LB QL block will show improved patient satisfaction scores

and decreased nausea and sedation scores compared to SB QL block.

Statistical analysis will be performed using a standard statistical program (SAS or SPSS). All data will be summarized (means, standard deviations, standard errors, and ranges for continuous variables; frequencies and percentages for categorical variables) by group. Demographic data will be compared between the two groups using ANOVA or chi-square tests as appropriate. The primary outcome, VAS at 24 and 48 hours, will be compared between the groups using repeated measures ANOVA; the model will include fixed effects for group, time, and the group by time interaction and random effects to allow correlations between the two times and different variances for the two times. Pain and satisfaction scores and opioid usage over time will be analyzed using repeated measures ANOVA. Nausea and sedation scores will be compared between groups at each time point using Mantel-Haenszel chi-square tests for ordered categorical data. Distributions of the continuous variables will be examined, and a transformation of the data (e.g. natural logarithm) or nonparametric tests will be used as necessary. A 5% significance level will be used for all comparisons.

Based on prior studies, the coefficient of variation for the VAS score at 24 and 48 hours is estimated to be 0.70. With a sample size of 30 per group the study will be able to detect a 60% decrease in VAS score between any two groups, assuming two-sided tests each conducted at a 5% significance level. We assume a dropout rate of up to 40%, hence we'll enroll up to 50 patients per group for this study.

9.0 Privacy

All study papers containing patient identifiers will be kept in each subjects confidential study file accessible to only the research team. All records will be kept in a locked room in a locked cabinet that only authorized staff enters. Collected data from each enrolled participant will be recorded on Redcap, which is a secure web-based data collection tool. Three years after completion of the study, all electronic information and paperwork containing patient identifiers will be deleted or shredded.

10.0 Follow-up/record retention

The study will start in the middle of 2018 and will end when a sample size of 100 subjects is achieved. The estimated time frame to enroll 100 study subjects is 24 months. After 100 subjects have been enrolled, the study will be stopped and the data collected will be analyzed using statistical methods.

Three years after completion of the study, all study papers with patient identifiers will be shredded and only data without any patient identifiers will be retained by the research team for an indefinite time.

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