Randomized Prospective Study Comparison of Erector Spinae Plane Block and Intrathecal Opioid for Postoperative Analgesia after Laparoscopic Colorectal Surgery in an Enhanced Recovery Setting

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1.0 Background

Enhanced recovery after surgery (ERAS) pathways aim to standardize and integrate perioperative care. These pathways incorporating the best available evidence-based practice targeted at attenuating the surgical stress response while optimizing physiologic function, with the goal of facilitating patient recovery [1, 2]. Things which can prevent hospital discharge after surgery are pain and gut dysfunction contributing to longer patient length of stay, complications and lower satisfaction scores. The preoperative, intraoperative and postoperative fundamental elements of the enhanced recovery pathway are designed to target these issues. Many of the early efforts at ERAS pathways targeted colorectal surgery and have been highly successful at reducing patient length of stay and complications [3, 4, 5, 6].

Multimodal pain management and regional pain techniques are one of the key intraoperative components of the ERAS pathway contributing to its success not only in creating great patient analgesia, but also reducing patient opioid requirements and other complications [7]. Various regional techniques for postoperative pain control are being used in laparoscopic colorectal cases, and yet, no particular standardized technique has been elucidated to work the best for these surgical cases.

Thoracic epidurals are no longer considered the standard of care in laparoscopic colorectal cases as they have been linked to longer hospital length of stay in these types of surgical cases [8, 9, 10]. Intrathecal opioids are commonly used and remain one of the main vehicles to help control postoperative pain for these cases, but this modality can occasionally contribute to patient side effects such as nausea, itching, urinary retention and rarely respiratory depression [11, 12, 13, 14]. With the advent of peripheral nerve abdominal blocks such as the transverse abdominis plane block (TAP), the quadratus lumborum block (QL), and the erector spinae block (ESP), we have seen a shift in practice towards the use of these various blocks in laparoscopic abdominal surgery [15, 16, 17, 18, 19]. Of these abdominal blocks, the ESP block has been demonstrated to have lasting analgesic effects for more than 24 hours, and studies have shown its potential to cover both somatic and visceral pain fibers [20, 21].

The ESP block was first described by Forero in 2016 as an effective treatment method for thoracic neuropathic pain [22]. Since first described in the literature, ESP blocks have been used successfully in many surgical procedures due to its ease of application, safety, and positive outcomes regarding reduction in postoperative pain scores and analgesic requirements [23, 24, 25, 26, 27]. Even though it is not known what abdominal wall blocks work best for a particular laparoscopic surgery, an increasing number of studies on the TAP and the QL peripheral nerve blocks have shown to not be as beneficial as thought in laparoscopic colorectal surgery for postoperative pain management [28, 29, 30, 31]. The ESP block, however, has shown to provide extensive postoperative pain benefit to patients receiving laparoscopic abdominal surgery [32, 33, 34, 35]. In addition, this particular regional approach in the mid- thoracic area has been reported to have dermatomal distribution sensory loss ranging from 5-9 intercostal spaces from the point of injection, and the potential to reach nerves transmitting not only somatic pain, but also visceral pain possibly making it an optimal analgesic block for laparoscopic colorectal surgeries [36, 37].

In this study we aim to compare the ESP block combined with standard multimodal analgesia to intrathecal duramorph with standard multimodal analgesia on postoperative pain in elective laparoscopic colorectal cases within an ERAS standardized care bundle. In this unblinded prospective randomized control trial, we hypothesize that ESP block will provide a significant

reduction in patient opioid consumption when compared to intrathecal opioid analgesia in the first 24 hours in patients who undergo laparoscopic colorectal surgery in a planned ERAS protocol [38].

2.0 Rationale and Specific Aims

The two pain control modalities in this study have been used as postoperative analgesia in prior studies. The specific aim of this study is to compare the difference between these two regional pain control methods in achieving the following:

1. Decreased patient narcotics requirements
2. Improved patient postoperative pain scores and patient satisfaction scores
3. Decreased narcotic side effects (nausea, pruritis, urinary retention, respiratory depression and ileus).

The primary endpoint of this study will be cumulated oral morphine equivalent (OME) consumption (mg) during the first 24 postoperative hours.

The secondary endpoints include opioid consumption in OME and pain scores using the Visual Analog Scale at 1, 12, 24, 48 and 72 hours postoperatively, incidence of opioid side effects (nausea, pruritus, urinary retention, respiratory depression, ileus), time to patient first ambulation, time to first flatus, time to first oral liquid, time to first food intake, length of hospital stay, and patient's satisfaction scores at 24 and 48 hours.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients undergoing an elective laparoscopic colorectal procedure at Indiana University Hospital or Methodist Hospital
- ASA Class 1, 2, 3 (American Society of Anesthesiologists physical status classification system)
- Age 18 to 80 years (male or female)
- BMI < 40kg/m2
- Desires regional anesthesia for postoperative pain control

Exclusion criteria:

- Any contraindication for neuraxial analgesia or ESP block procedure
    - Contraindications for neuraxial analgesia include: Elevated intracranial pressure (except in cases of pseudo-tumor cerebri), infection at the site of injection, lack of consent from the patient, patient refusal, true allergy to any drug used in the spine, and uncorrected hypovolemia.
    - Contraindications for ESP block procedure include: Infection at the site of injection, patient refusal, true allergy to any of the drugs used in the block, and lack of patient consent.
- Any patient undergoing a laparoscopic abdominoperineal resection.

- Any physical, mental or medical conditions which, in the opinion of the investigators, may confound quantifying postoperative pain resulting from surgery.
- Known true allergy to the study medications (morphine, bupivacaine, decadron, Tylenol, Celebrex)
- Takes over 30 mg of oral morphine equivalents daily
- Any history of substance abuse in the past 6 months
- End stage liver disease, end stage renal disease
- Body weight of < 50 kg

4.0 Enrollment/Randomization

All laparoscopic colorectal cases scheduled by colorectal surgeons at IU Health University or Methodist Hospital will be identified using medical records. The subjects will be contacted face-to-face prior to surgery. 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 Pre-Operative Care Unit on the day of surgery and if participation is agreed, written consent will be taken.

A total of subjects (n=126) will be randomized by a computer program into two groups (63 per group):

1. Intrathecal preservative free morphine (duramorph) 200 mcg with 7.5mg of hyperbaric bupivacaine for patient 18-75 years of age and duramorph 150 mcg with 7.5mg of hyperbaric bupivacaine for patients 75- 80 years of age – placed by a spinal needle (n=63)
2. Bilateral ESP block at thoracic vertebrae level 10 (T10) – placed under ultrasound using 30 ml of 0.25% bupivacaine and 4 mg of Decadron (n=63)

Randomization will be performed using Research Randomizer. The primary investigator will inform the person doing the regional techniques as to what group the patients are randomized to. Neither the patients and the research staff doing assessments will be blinded to the randomization.

5.0 Study Procedures

Both the ESP blocks and the intrathecal procedure will be done prior to anesthesia induction. All procedures will be done using sterile technique with masks, hats, and sterile gloves. All ESP blocks will be placed by the anesthesiologist or the resident directly under the supervision of the attending anesthesiologist on the acute pain service as will the intrathecal duramorph placement. Standardized postoperative multi- modal analgesia will be administered to all study patients according to the institutional ERAS protocol.

All patients will receive 1 gm of Tylenol and 200mg of Celebrex preoperatively. Patient will be randomized into one of two arms, those receiving the ESP block and those receiving the intrathecal duramorph.

The ESP block will be placed bilaterally prior to anesthesia induction. After skin sterilization, an ultrasound probe will be placed on the 10^{th} thoracic vertebrae (T10) after counting down from the spine of the seventh cervical vertebrae. Dependent on the patient's body habitus, a high frequency linear or curvilinear ultrasound transducer probe will be used. The probe will be placed 2-3 cm

lateral to the T10 spinous process using a sagittal approach. After identification of the transverse process (TP) and the erector spinae muscle, a 21gauge Stimuplex® needle will be advanced using an in-plane technique until the needle is between TP and the erector spinae muscle [39]. The correct location of the needle tip will be confirmed initially by hydro-dissection with a small amount of sterile saline. After the appropriate needle tip positioning between the TP and the erector spinae muscle is confirmed, 30 ml of 0.25% bupivacaine mixed with 4 mg of Decadron will be administered at the site. This procedure will be repeated following the same steps on the other side of the patient's back. A total dose of local anesthetic bupivacaine 150mg in a volume of 60 ml will be used to complete the procedural block.

Patients assigned to the (intrathecal) IT group will receive 150 mcg of duramorph with 7.5 mg of hyperbaric bupivacaine injection in the operating room before induction of general anesthesia, with the patient under conscious sedation in the sitting or lateral decubitus position. 24-G Pencan® pencil-point spinal needle (B. Braun Medical) or a 22- or 25-G Whitacre spinal needle (Medline Industries) will be inserted in the L3 – 4 or L4 – 5 spinal space via the midline approach. Alternatively, the paramedian approach can be used if the midline approach is unfavorable. Entry into the intrathecal space will be confirmed by the presence of free-flowing cerebrospinal fluid.

All patients will receive standardized endotracheal general anesthesia with Propofol or Etomidate for induction and paralytic per choice of the anesthesiologist. As part of the ERAS protocol, all patients will receive a ketamine bolus of 0.35 mg /kg IBW and then a ketamine infusion (average of 0.15-0.25 mg/kg/hr IBW) which is our current standard of practice. Medications for nausea prevention will also be given. Intraoperative opioids will be given as needed at the discretion of the anesthesiologist.

All patients will be scheduled on PO acetaminophen and Celebrex per ERAS protocol until discharge. PO oxycodone as needed will be started once patients are tolerating diet. PRN IV hydromorphone, morphine or fentanyl will be added for breakthrough pain.

Patients in the intrathecal group will be monitored according to the institutional guidelines outlined in a standardized intrathecal for analgesia order set. All patients will be monitored with continuous pulse oximetry, end tidal CO2 monitoring, and nursing assessments.

Opioid consumption at 1, 12, 24, 48, 72 hours will be recorded by a member of the research team from the time of arrival to the Post Anesthesia Care Unit. Pain scores will be measured using Visual Analog Scale ranging from 0 (no pain) to 10 (severe pain) [40] at 1, 12, 24, 48, 72 hours. Incidence of nausea will be measured using a categorical scoring system (none=0; mild=1; moderate=2; severe=3). Incidence of urinary retention will be determined by foley catheter placement or straight catheterization. Incidence of pruritis will determined by nalbuphine or Benadryl use. Incidence of respiratory depression will be determined by Narcan requirement. These secondary endpoints will be measured at 1 and 24 hours after arrival to the Post Anesthesia Care Unit. Incidence of ileus will also be recorded if it occurs throughout the patient's stay. Patients will be encouraged to ambulate on postoperative day 0 under supervision. Time to ambulation will be recorded along with time to flatus, time to first liquid and time to first food intake. The patient's satisfactions score will be determined at 24 and 48 hours and will be defined as follows: very unsatisfied =0 unsatisfied =1, neutral =2, satisfied =3, very satisfied= 4.
The length of stay will be measured by the number of days the patient is in the hospital until discharge from the hospital.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Patients will be monitored by the primary team during the postoperative period, and any adverse events or unanticipated problem such as lower extremity weakness, spinal headache, injection site infections, nerve damage, and hematoma formation or pneumothorax will be recorded and reported to the acute pain anesthesia resident and research team. All adverse events will be promptly reported to the IRB committee using an appropriate reporting form.

7.0 Data Safety Monitoring

This study will be monitored by members of the study team annually. Data quality, subject recruitment, outcomes and adverse event data, assessment of scientific reports and therapeutic development, results of related studies that impact subject safety, and privacy procedures will be monitored.

8.0 Study Withdrawal/Discontinuation

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. 24 hours after patient's withdrawal, anesthesia acute pain team will sign off and all further pain management will be done by the primary team.

9.0 Statistical Considerations

Primary outcome: Cumulated oral morphine equivalent (OME) consumption (mg) during the first 24 postoperative hours.

Primary Research Hypothesis: ESP block will provide a significant reduction in patient opioid consumption when compared to intrathecal opioid analgesia in the first 24 hours.

Secondary outcomes: Narcotic usage at 1, 12, 24, 48, and 72 hours. Pain scores using VAS at 1, 12, 24, 48 hours, 72 hours. Nausea, pruritis, urinary retention, respiratory depression at 1, 24 hours. Incidence of ileus. Time to ambulation, time to flatus, time to first liquid and time to first food intake. Length of stay. Patient satisfaction score at 24 and 48 hours.

Secondary Research Hypotheses: ESP block will show improved pain control and a lower incidence of nausea, urinary retention, pruritis, respiratory depression, and ileus compared to intrathecal opioid. Time to patient oral intake, ambulation and length of stay will be shorter. Patient satisfaction scores will also improve.

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 using either t-test or Wilcoxon rank sum test as appropriate for continuous variables

and chi-square or Fisher's exact test as appropriate for categorical variables. Either median, 25th percentiles, and 75th percentiles or % counts will also be reported for each group.

The primary endpoint of cumulated oral morphine equivalent (OME) consumption (mg) during the first 24 postoperative hours will be compared between the two groups using the Wilcoxon Rank-Sum Test. Secondary endpoints of pain scores and opioid consumption at 1, 12, 24, 48, and 72 hours postoperatively will each be analyzed using a using a Mixed effect Model Repeat Measurement (MMRM). These models will include a fixed effect for group, time, and group by time interaction along with a random intercept effect. Differences between the two groups at each time point for each of these three endpoints will be computed via LSMEANS. A Šidák correction will be employed to adjust these resulting p-values for multiple comparisons across time points.

For other secondary endpoints the analyses will be as follows. The ordinal endpoints of nausea, and satisfaction scores will all be compared between the two groups using the Wilcoxon Rank-Sum Test at each time point. Incidences of urinary retention, ileus, pruritis, and respiratory depression will be compared between the two groups using the chi-square or Fisher's exact test as appropriate. Finally, the differences between the two groups for the time to event outcomes, including time to ambulation, time to flatus, time to first liquid, time to first food intake and length of stay will each be compared using the Wilcoxon Rank-Sum Test.

Group sample sizes were determined from a statistical power analysis. Based on previous studies, we've estimated a coefficient of variation of 1.1 for the primary outcome. From this estimate this study will have a power of 80% to detect a 40% decrease in cumulated opioid usage during the first 24 hours between the two groups with a sample size of 63 per group (50 assuming a 20% dropout rate), assuming a two-sided test conducted at a 5% significance level.

10.0 Privacy/Confidentiality Issues

All study papers containing patient identifiers will be kept in each subject's 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. At the end of the study, all electronic information and paperwork containing patient identifiers will be deleted or shredded.

11.0 Follow-up and Record Retention

The study will start in September or October of 2021 and will end when a sample size of 126 subjects are achieved. The estimated time frame to enroll 126 study subjects is 30 months. After 126 subjects have been enrolled, the study will be stopped and the data collected will be analyzed using statistical methods.

At the end 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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