Randomized prospective study comparing Exparel® Erector Spinae Plane Block vs Simple Bupivacaine Erector Spinae Plane Block vs Exparel® Surgeon Infiltration for postoperative analgesia following video-assisted thoracoscopic surgery

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1.0 Background

Video-assisted thoracic surgery (VATS) is being performed more frequently due to its less invasive nature, decreased postoperative pain, and shortened post-operative hospital stay. However, VATS procedure still results in significant postoperative pain and the ideal analgesic for postoperative pain control following VATS remains unclear. Many modalities for pain control have been addressed in the literature: NSAIDs, opioids, epidurals, paravertebral blocks, and surgeon infiltration (1, 2). These have been used to manage the significant pain experienced post-VATS with varying degrees of success. However, the ideal analgesic regimen for postoperative pain from VATS procedures remains to be codified and changes based on provider preference. The purpose of this study is to determine the effectiveness of Erector Spinae Plane Block (ESP) versus surgeon infiltration for postoperative analgesic control after VATS.

Erector Spinae Plane block was first described by Forero in 2016. This block has shown promise in relieving neuropathic pain and in providing analgesic coverage in laparoscopic cholecystectomy, mastectomy, and thoracic surgeries (3-7). This block can be thought of as a modified paravertebral block, and shows promise of increased safety compared to the paravertebral block. This is due to the unique anatomical approach that allows for anesthetic infiltration of the dorsal rami without the risk of needle insertion into the paravertebral space (6). The improved safety of this approach could allow this block to be used on higher risk patients, like those who present with coagulopathies.

Another common method of managing postoperative VATS pain is through surgeon infiltration of the intercostal space with local anesthetic. To perform infiltration, surgeons inject the anesthetic with direct visualization of the intercostal space, providing targeted analgesic coverage to the affected area (8). Some drawbacks to this process are the relatively short duration of action of the block, and the requirement of the surgeon to inject all affected intercostal spaces to achieve the desired dermatomal block(1, 2).

Exparel®, a liposomal formulation of bupivacaine (LB), has shown significant promise in providing extended analgesic coverage in the postoperative period. Due to its extended release format, LB can provide analgesia coverage for up to 72 hours postoperatively when compared to normal saline and has been suggested to reduce postoperative opioid use as well (9). It has provided effective analgesia in total knee arthroplasty and hip arthroplasty and has shown promise in open and laparoscopic colectomy (10-12). However, there are also studies showing that LB might not be superior to standard bupivacaine (SB) in terms of duration of analgesia (13-15). In order to compare the duration of action of both form of bupivacaine, we'll randomized the ESP group to both LB group and SB group.

Our hypothesis is that ESP block is superior to surgeon infiltration for pain scores, and LB will be superior to SB for ESP block duration of action.

2.0 Rationale and Specific Aims

The specific aim of the study is to compare the difference between the ESP block and surgeon infiltration in achieving the following:

1. Improved postoperative pain scores
2. Decreased opioid requirements
3. Improved patient satisfaction scores
4. 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 measure time to first flatus, incidence of urinary retention, incidence of respiratory depression, and time to discharge.

All patients will receive a phone survey 6 months after surgery to assess for pain and quality of life.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Pt undergoing VATS including but not limited to wedge or lobectomy at Indiana University Hospital,
- ASA 1,2,3 or 4
- Age 18 or older, male or female
- Desires regional anesthesia for postoperative pain control

Exclusion criteria:

- Any contraindication for Erector Spinae Plane block
- History of substance abuse in the past 6 months which would include heroin, marijuana or any other illegal street drugs
- Patient staying intubated after surgery
- Patient (home dose) taking more than 30mg PO morphine equivalent per day
- Known allergy or other contraindications to the study medications, which include dilaudid and bupivacaine.

- Pts. scheduled for a pleurodesis, decortication or esophagectomy at Indiana University Hospital
- BMI greater than 40.0.

4.0 Enrollment/Randomization

All VATS cases scheduled by thoracic surgeons at IU Health University Hospital will be identified. The subjects will be contacted initially face-to-face by either Dr. Ceppa or Dr. Birdas in their clinics prior to their scheduled surgery date. They will be given a copy of the consent and authorization form explaining this study. The subjects will again be contacted face to face in POCU on the day of surgery and the study will be explained in detail and all questions will be answered. If participation is agreed, written consent will be taken and a signed copy of both the authorization and consent will be given to the participant.
A total of 120 subjects will be randomized by the computer program Research Randomizer into three groups (40 per group): The primary investigator will inform the anesthesiologist who will be doing the block as to what group the patients are randomized to. The research staff completing the patients assessments will be the only person blinded to the randomization.

1. Ultrasound guided LB Erector Spinae Plane Block with 20ml of Exparel® and 10ml 0.25% bupivacaine
2. Ultrasound guided SB Erector Spinae Plane Block with 30ml 0.5% bupivacaine
3. Surgeon Infiltration under video guidance with 20ml of Exparel® and 10ml of 0.25% bupivacaine

5.0 Study Procedures

All the erector spinae plane blocks will be placed preoperatively after sedation, before intubation and prior to surgery. 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 or the attending anesthesiologist in the VATS room.

To perform the ESP block, an ultrasound probe is used to visualize the ES musculature about 3 cm laterally from the T5 spinous process. In a cephalad-to-caudad direction advance the needle and inject the anesthetic in the interfacial plane deep to the ES muscles. Confirm positioning by visualization of needle tip and elevation of ES muscles off the transverse process with anesthetic injection. Surgeon infiltration is performed intraoperatively under direct thoracoscopic guidance. The intercostal space will be visualized and injected with LB. Typically, T4 through T8 are infiltrated with 2-3mL of the anesthetic mixture.

All patients will receive 1gm of acetaminophen and 600mg of gabapentin preoperatively. Patients above 70yo will receive 300mg of gabapentin. General anesthesia will be induced in the operating room and the patient will be placed in the lateral position for the VATS procedure. All patients will

receive intraoperative lidocaine and ketamine which is used to decrease opioid use after surgery and is being used as part of ERAS protocol. The patients will be intubated with dual lumen endotracheal tubes and placed on one-lung ventilation for the procedure. All patients will receive intravenous patient-controlled analgesia (PCA hydromorphone) post-operatively for breakthrough pain. They will also be scheduled on PO acetaminophen. PO oxycodone PRN will be started on POD 1 once patients tolerate diet.

Opioid usage at 1,24,48,72 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 epidural or PVB. Patients will be encouraged to ambulate on postoperative day 1 under supervision.

All patients will receive a phone call 6 months after surgery for assessment for chronic post-surgical pain. Patients will be assessed by a member of the research team over the phone. They will be assessed on their pain score and narcotic usage by using the Brief Pain Inventory. Study participation will conclude after the 6 month follow questionnaire has been completed.

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 which is after surgery, through hours, 24, 48, and 72. We will also follow up in 6 months with a telephone call to complete a questionnaire which will conclude all study participation. Any adverse events or unanticipated problems that are reported to the acute pain anesthesia resident who is not listed on the study will contact the Principal investigator or one of the study personnel and all events will be addressed immediately. 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/Discontinuation

The patient can withdraw from the study at any time by contacting the research team or acute pain anesthesia resident.

8.0 Statistical Considerations

Primary outcome: VAS score at 24 and 48 hours
Primary Research Hypothesis: ESP will provide lower pain scores compared to surgeon infiltration and ESP with LB will provide longer pain control than ESP with SB.

Secondary outcomes: Opioid usage after 1, 24, 48 and 72 hours. Pain scores using VAS at rest and on movement at 1, 24, 48 and 72 hours. Patient satisfaction scores at 24 and 48 hours. Nausea

scores at 1, 24, 48 and 72 hours. Sedation scores at 1, 24, 48 and 72 hours. Time to first bowel movement, incidence of urinary retention, and incidence of respiratory depression will be recorded as well.

Secondary Research Hypotheses: ESP blocks will show improved pain control, improved patient satisfaction scores, and decreased nausea and sedation scores compared to surgeon infiltration. 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 three 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 40 per group, the study will have 91% power 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.

9.0 Privacy/Confidentiality Issues

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 and Record Retention

The study will start in late 2018 and will end when a sample size of 120 subjects is achieved. The estimated time frame to enroll 120 study subjects is 24 months. After 120 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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