A randomized controlled trial of the effectiveness of liposomal bupivacaine (Exparel) when compared to local injection of bupivacaine after thoracoscopy

Principal Investigators
Sandeep J. Khandhar, MD
Joby Chandy, MD

Cardiac Vascular & Thoracic Surgery Associates
Fairfax Anesthesiology Associates of American Anesthesiology

Department of Surgery
Department of Anesthesiology
Inova Fairfax Hospital
3300 Gallows Road
Falls Church, VA 22042

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INTRODUCTION

Video-Assisted Thoracic Surgery (VATS) has been shown to hasten patient recovery by attenuating the physiologic stress of surgery and decreasing post-operative pain.[1] Despite this approach, incisions in the chest are proportionally more painful than in other parts of the body, and most patients require some form of narcotic pain medication.

Multiple strategies for post-operative pain control have been attempted in thoracic surgery with no obvious superiority of one versus another. Pain catheters have been increasingly used over the past decade in different surgical procedures in order to minimize incisional pain for the first 3 to 7 days after an operation.

For the past 5 years we have routinely used an axial subpleural tunneling technique that delivers local anesthetic to the intercostal space, without leakage elsewhere, creating a functional multi-level rib block. The published literature is equivocal as to the efficacy of such approaches following thoracic surgery with most recent series reporting no benefit in the use of these catheters. [2-6] Despite our own positive subjective results, objective data is lacking and therefore we conducted our own randomized trial to assess the efficacy of these catheters to standard intraoperative injection of bupivicain. This study confirms that there is no difference in patient pain, satisfaction, or narcotic use.

Exparel is a formulation of liposomal bupivacaine that is reported to allow local anesthesia for up to 72 hours post injection. It is our aim to follow our prior study with a randomized trial to compare local infiltration of liposomal bupivacaine at the conclusion of each procedure with injections of standard .25% bupivacain.

AIMS

1. To establish a safe and effective role for liposomal bupivacaine (Exparel) in thoracoscopy.
2. To provide patients with a superior and longer lasting form of pain relief.
3. To improve patient satisfaction and decrease perioperative narcotic use.

HYPOTHESIS

We hypothesize that injection of liposomal bupivacaine (Exparel) into thoracoscopic port incision sites and alongside the involved intercostal nerves will provide more durable pain relief when compared to local injection of standard bupivacaine as measured by patient pain scores and pain medication used.

STUDY DESIGN

Study Type
This is a prospective randomized controlled trial.

Setting/Location
Patients will be recruited from the Cardiac Vascular and Thoracic Surgery Associates (CVTSA) practice. Operations, injections of Exparel, and pain pump administration will occur at Inova Fairfax Medical Center (IFMC). The final patient outcome at 30 days will occur in the CVTSA offices during follow-up. Data analysis will then be performed at IFMC.

Duration of Study
Consented and randomized subjects will participate for a maximum of 30 days post-operatively (+/- 10 days). Data for the first 7 post-operative days will be recorded, beginning during the hospital stay and continuing at the patients' homes. The next and final day of subject participation is on post-operative day 30. Biological specimens will not need to be collected from the subject for the purposes of this study.

Number of Subjects
A total of 100 patients (50 per study arm) are expected to participate in this study.

Study Population Demographics
Male and female patients will be considered for this study. Any patient over the age of 18 and having an isolated thoracoscopic procedure for a therapeutic or diagnostic purpose will be screened. No study exclusions will be based on the racial or ethnic considerations. This study will not include minors or other vulnerable populations.

Recruitment
Patients who fit the inclusion and exclusion criteria will be asked to participate in the study when seen prior to their operation either in the CVTSA offices or in the pre-anesthesia unit.

Inclusion Criteria
All patients 18 years of age or older

- Isolated thoracoscopic procedure for therapeutic or diagnostic purposes

Exclusion Criteria

- Previous ipsilateral thoracic surgery
- Need for operative pleurectomy or pleurodesis
- Chronic use of pain medication (narcotics or NSAIDS), sedatives, or hypnotics
- Allergies to bupivacaine or other local anesthetics, narcotics, NSAIDs or acetaminophen
- Liver dysfunction (INR > 1.5, albumin < 2.8g/dl, bilirubin > 2mg/dl)
- Renal dysfunction (eGFR < 60ml/min/1.73m^2)
- History of peptic ulcerative disease
- Severe COPD requiring continuous oxygen supplementation
- Inability to consent
- Pregnancy

Study Methods and Intervention
All patients will receive a standard balanced anesthetic consisting of a mild preoperative sedative (midazolam 0.01-0.03mg/kg), induced with propofol (1-2mg/kg) or etomidate, fentanyl (1-2 mcg/kg) and rocuronium (0.6mg/kg) and maintained on a potent inhalation agent (sevoflorane 1.5%-2.5%) during procedures. Prior to emergence from anesthesia, all patients will receive ketorolac 30mg IV once, neuromuscular reversal agents, and an antiemetic (ondansetron 4mg). Patients will also be given additional narcotics (fentanyl) upon emergence, as needed, to facilitate patient comfort and extubation.

All subjects shall receive a standardized inpatient and outpatient pain regimen in accordance with ASA guidelines for acute pain management in the perioperative period. This includes a multimodal approach utilizing 3 drugs with different mechanisms of action. All patients shall receive 1,000 mg of acetaminophen orally every 6 hours, scheduled for 5 days. Other drugs will be given on an as needed basis (PRN) to maintain an analog pain score of ≤ 3, as outlined in the table below.

	Pain score > 3 ≤ 5	Pain score > 5
Immediate post-operative period (OR/PACU)	Ketorolac 30mg IV once	Dilaudid 0.5 mg IV Q10 min
Inpatient floor	Ketorolac 15mg IV Q6h or Ibuprofen 400mg PO Q6h	Dilaudid 0.5-1mg IV Q2h or Dilaudid 2-4 mg PO Q4h
Outpatient	Ibuprofen 400 mg PO Q6h	Dilaudid 2-4 mg PO Q4h

Patients in group A will receive, at the end of the surgical procedure, injections of liposomal bupivacaine (Exparel) (266 mg, 20 mL, diluted at surgeon's discretion) into the thoracoscopic port incision sites and around the intercostal nerves serving that space.

Control Group
Patients in group B will receive, at the end of the surgical procedure, injections of standard .25% bupivacaine into the thoracoscopic port incision sites and around the intercostal nerves serving that space.

Randomization
Study ID numbers will be randomly assigned to treatment groups using statistical software. Sequentially numbered opaque envelopes will be filled with the randomly selected treatment group. All the envelopes will then be sealed, placed in numerical order, and given to the PI for storage in the CVTSA office. Upon a patient's consent, the envelope with the corresponding study ID number will be opened in the OR prior to surgery to reveal to the patient's assigned study group. This will allow time for all required materials to be obtained and set up for administration. The randomization results will be recorded in the patient's study file to make sure the proper study treatment is received on the day of surgery.

The Department of Surgery research epidemiologist/biostatistician will prepare all envelopes. Due to her knowledge of the envelope contents, the research team will not take part in the randomization process that occurs after a patient consents to participate. Study personnel and the surgical team working in the CVTSA office will perform the post-consent randomization.

Patients may be excluded from the trial, at the discretion of the study investigators, if any of the follow occur:

- Need for conversion from a VATS procedure to a thoracotomy
- Patient is discharged from the hospital with a chest tube in place
- Patient fails to comply with post-operative instructions

Primary outcomes.
The primary outcome will be overall amounts of pain medications through postoperative day 7.

Secondary outcomes
Secondary outcomes include summed visual analog pain scores, patient satisfaction, analog pain scores at post-operative day 30, incidence of paresthesias, hospital length of stay (days), return to baseline activity, return to work, and overall hospital cost calculated as a factor value.

Consent
Patients shall be consented by one of the study investigators or approved clinical staff either in the outpatient office setting or in the pre-anesthesia unit. Patients will be enrolled for up to 1 year from the date that IRB approval is received.

Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study.
The surgical team and/or study personnel shall perform in-hospital data collection. The assessment will include visual analog pain scores upon admission and discharge from the post-anesthesia care unit (PACU). Complaints such as paresthesias (numbness) shall also be recorded. Intra-operative narcotic utilization shall be clearly recorded in the anesthesia records and collected retrospectively. Any amount of pain medicine administered will be collected from the charted medications tab in the electronic medical records after subjects' discharge. Date of birth (DOB), past surgical history (PSH), past medical history (PMH), psychiatric history, and any use of steroid medication will also be collected from the patient's medical records to test for confounding effects.

Outpatient data collection will depend on patients or family members by way of a standardized data collection sheet. The timing of visual analog pain score recording should be whenever a pain medication is taken but at least three times a day (morning, afternoon, night). Each administered medication should also be recorded on a real time basis. Detailed instructions will be given to the patient and/or caregiver to ensure proper data collection.

All patients shall have a post-operative visit at 1 week (+ 4 business days) for retrieval of these data sheets. At 30-days post-operatively (+/- 1 week), patients will receive a telephone call from a member of the study research personnel for one final assessment of the visual analog pain score and complaints of paresthesias.

All data from the study will be collected and maintained by database managers at Mednax Medical Group. Upon completion of data collection, this data will be released to the IFMC DOS epidemiologist/biostatistician for data analysis.

Patients who, for whichever reason, need other surgical procedures within 30 days of enrollment shall be removed from the trial. Patients are allowed to voluntarily withdraw from the trial at any time.

STATISTCAL EVALUATION

Our pre-study sample size estimate assumes equivocal measurement (50% difference) of use of postoperative pain medications between the group receiving the liposomal bupivacaine, Exparel, and the group receiving standard bupivacaine injections. We found that a two-arm study of 50 patients per group is needed, assuming α-level=0.05 and power=80%. We plan to perform an interim analysis midway through randomization for assessment of statistical validation of our predictions.

Statistical analyses will be performed using SAS v.9.3. Demographics, comorbidities, and past medical history will be described for both study groups, and compared using X^2 tests and Fisher's exact tests (for categorical variables) and Student's t-tests or Wilcoxon rank-sum tests (for continuous variables). Due to the randomization process, study groups are expected to be similar with respect to these factors.

The primary outcome, overall amounts of pain medication administered through postoperative day 7, will be compared between the study groups using analysis of covariance (ANCOVA) controlling for potential covariates of interest. Secondary outcomes, such as hospital length of stay, incidence of parasthesias, will also be compared among study groups using Student's t-tests and Wilcoxon rank-sum tests.

Statistical significance will be assessed at $\alpha = 0.05$. Power calculations were performed, assuming a 50% difference in the amount of overall pain medication for group A. A power of 80% will be achieved by including 50 patients in each study arm, for a total of 100 subjects.

LIMITATIONS

There are inherent limitations with using patient reported subjective pain scores to evaluate the effectiveness of a treatment, which is why we will be measuring overall use of pain medication as well. We suspect that use of pain medications will be small in both arms.

Then incidence of paresthesia is extremely small and this study will not be powered enough to study it.

TIMELINE

IRB approval	1-2 months
Enrollment	8-9 months
Data analaysis	1-2 months
Submission for publication	1-2 months

BUDGET

Cost of Exparel, .25% bupivacain	$30,000 (approx. $300 per pt x 100). Should be covered by patient's insurance
Research Assistant (for data collection/analysis and patient follow up)	$15000 (0.25 FTE)

REFERENCES

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