

## **Cover Letter**

Study of Exparel Versus Epidural for Pain Control After Thoracotomy

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## **Study Protocol**

All patients will be screened by a study coordinator and written informed consent will be obtained at the preoperative visit. Inclusion criteria will be patients age 18 years and older undergoing thoracotomy (lobectomy, segmentectomy, wedge resection or pneumonectomy). We will stratify patients by surgeon and randomly assign them to receive either standard thoracic epidural analgesia or intercostal nerve injections with liposomal bupivacaine for perioperative pain control. Operations will be performed by any of 5 board certified general thoracic surgeons at our institution. Exclusion criteria will be planned chest wall resection or abdominal incision and/or gastroesophageal surgery; current enrollment in another post-thoracotomy analgesic research protocol; pre-existing pain syndrome (such as fibromyalgia, complex regional pain syndrome or postherpetic neuralgia in a thoracic distribution); daily opioid therapy; current gabapentin or pregabalin therapy; allergy to any study medication; coagulation or infectious issues that would preclude epidural catheter placement; severe psychological disorders or inability to understand the study protocol; prisoners or other institutionalized individuals; and severe hepatic, renal or cardiovascular disorders. Women who are pregnant will not be included in this study.

## **Epidural Analgesia**

In the epidural catheter (TEC) group, a thoracic epidural catheter will be placed at the level of T6–T8 and advanced 5 cm into the epidural space and a 3 ml test dose of lidocaine 1.5% will be administered before the induction of general anesthesia. Patients will be excluded from the study if the catheter cannot be placed. A bolus dose of 0.5 mg hydromorphone plus 4.5 ml 0.125% bupivacaine will be administered before surgical incision. An epidural infusion of

0.075% bupivacaine and 10 mcg/ml hydromorphone, prepared by the hospital pharmacy, will be started intraoperatively at a rate of 5 ml/hr.

### **Intercostal Nerve Block**

In the intercostal block (ICB) group, liposomal bupivacaine 1.3% (4 ml) will be injected by the surgeon under direct vision into the proximal intercostal space at the level of the thoracotomy and one interspace above and below. In addition, liposomal bupivacaine 1.3 % (4 ml) will be injected at each of the chest tube exit sites. Thus, a total of 20 ml liposomal bupivacaine 1.3% (260 mg) will be administered.

### **General Anesthesia**

General anesthesia based on inhaled isoflurane will be administered to both groups. Intraoperative opioids, including up to 500 mcg of fentanyl and up to 1 mg of oxymorphone or up to 10 mg of morphine or up to 2 mg of hydromorphone may be given.

### **Post-operative Care**

In the post-anesthesia care unit (PACU), IV fentanyl will be given for NRS > 4 as needed, 25 mcg IV every 2 minutes up to a maximum 200 mcg. If additional analgesia was required, 15 mg of IV ketorolac will be given once for NRS > 4. An IV fentanyl patient-controlled analgesic (PCA) will be initiated for all patients ~~in the PACU~~ **on the ward**. All patients will receive acetaminophen (1000 mg orally every ~~8 hours~~ **6 hrs**) during the first 48 hours postoperatively. IV ketorolac (15 mg every 6 hours) may also be administered depending on pain severity, urine output and renal function. The epidural infusion can be temporarily stopped due to hypotension, excessive sedation, or hypoventilation, and then restarted at 4 mL/hour. If the epidural catheter is suspected to be non-functioning, the treating anesthesiologist will be allowed to test and replace the epidural catheter as necessary. The inpatient pain service will follow both groups for pain

management. Adjustments to the epidural infusion mixture and rate will be performed by the inpatient pain service depending on analgesic effect and side effect profile, according to the usual practice by standardized protocol.

For the first 48 hours following surgery, nursing staff will collect NRS pain scores every 4 hours at rest (primary outcome). Side effects such as nausea or vomiting, pruritus, sedation, dizziness, respiratory depression, and medication use will also be collected. Additional information on patient characteristics, surgical and hospital course will be collected prospectively from the medical record using a standardized data collection form by a study coordinator, who will contact the patient 3 months postoperatively to determine whether they experienced persistent pain following thoracotomy.

## **Statistical analysis**

Demographic, intraoperative, postoperative, and three-month follow-up data from the epidural and the intercostal groups will be summarized and compared between groups. Tabular summaries will be created to outline the patient and procedural characteristics. The primary outcome will be the 8 AM pain score with cough on the first postoperative day. Other pain scores recorded every 4 hours using the Numeric Rating Scale (NRS) for the first 48 hours following surgery will be analyzed as secondary outcomes. These endpoints will be compared between groups using an appropriate two-sample comparison (t-test or rank sum test). In addition, a 90% confidence interval for the difference between groups will be constructed to assess whether the lower bound is above the non-inferiority limit (-1). Secondary outcomes will include overall satisfaction with pain management, incidence of postoperative hypotension (defined as a systolic or diastolic blood pressure more than 20% below baseline), pruritus, nausea or vomiting, and postoperative sedation. Additional secondary outcomes will include postoperative complications (respiratory failure, myocardial infarction, and pneumonia), readmissions to the ICU, length of ICU stay, length of hospital stay, and in-hospital deaths. Groups will also be compared with respect to IV fentanyl PCA use and ketorolac use for 0-24 hours and 24-48 hours. Additional secondary endpoints will include pain scores and medication use at three-month follow-up. For all secondary and exploratory analyses, continuous variables will be compared between groups using the two-sample t-test (or rank sum test) and categorical variables will be compared using the chi-square test or Fisher's exact test. In all cases we will assess distributional assumptions and use transformations (e.g. log) or analysis of ranks as appropriate. The level of statistical significance for all tests was  $P < 0.05$ .

## **Power Calculation**

The number of patients required in each group was determined from a power analysis on the basis of non-inferiority hypothesis (4) for the primary endpoint which is pain with cough at 8:00 AM on postoperative day 1. For non-inferiority of the intercostal nerve block vs TEA, a maximum difference of 1 (margin of non-inferiority) on the NRS scale was considered as acceptable. On the basis of previously published data, a standard deviation of 2 was assumed for NRS distribution (3). If there is truly no difference between the standard and experimental treatment, then 138 patients (69 patients per group) are required to be 90% sure that the lower limit of a two-sided 90% confidence interval (one-sided  $\alpha=0.05$ ) will be above the non-inferiority limit of -1. Thus the proposed sample-size of  $N=140$  (70 per group) will provide adequate statistical power to detect a meaningful difference.