Document Cover Page

Official Title of the Study: A randomized clinical trial of single dose liposomal bupivacaine delivered via VATS intercostal nerve block vs continuous bupivacaine infusion delivered via indwelling subscapular analgesic catheter in patients undergoing surgical stabilization of rib fractures

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Project Title: A randomized clinical trial of single dose liposomal bupivacaine delivered via VATS intercostal nerve block vs continuous bupivacaine infusion delivered via indwelling subscapular analgesic catheter in patients undergoing surgical stabilization of rib fractures
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I. Hypotheses and Specific Aims:

The hypothesis of this clinical trial is that among patients undergoing surgical stabilization of rib fractures (SSRF), liposomal bupivacaine delivered via VATS intercostal nerve block provides comparable analgesia to the pain catheter, as measured by both pulmonary function and narcotic use.

II. Background and Significance:

Rib fractures represent a common injury pattern with high associated morbidity and mortality (1). Effective pain control in both the acute and long term periods remains a challenge (2). Surgical stabilization of rib fractures (SSRF) is now a recommended treatment for patients with severe chest wall injuries (3-5). In addition to stabilization of the chest wall, SSRF offers a unique opportunity to deliver directed, loco-regional anesthesia. Loco-regional anesthesia is a recognized, essential component of multi-modal anesthesia for patients with rib fractures in order to both decrease pain and minimize the use of opioids and their associated side effects (6, 7).

Delivery options for loco-regional anesthesia to patients with rib fractures share in common the intention of anesthetizing the intercostal nerves. Moving from the spinal cord distally, modalities include thoracic epidural catheters, paravertebral blocks or catheters, and rib blocks. Although rib blocks may be accomplished via a variety of techniques, the two most common intra-operative techniques are video-assisted thoracoscopic surgery (VATS) intercostal nerve blocks **[Figure 1**] and indwelling, subscapular catheters (**Figure 2**).

In general, neuraxial modalities such as thoracic epidural and para-vertebral injections/catheters are subject to a wide array of limitations, including patient coagulopathy (Internal Normalized Ratio > 1.5), co-existing spine fractures, peri-insertion and removal holding of venous thromboembolism pharmacoprophylaxis, and provider availability. For these reasons, our current practice is to insert a subscapular “pain catheter” at the conclusion of the SSRF operation (**Figure 2**); this catheter provides a continuous infusion of 0.25% bupivacaine and may be left in place for several days.

Although favorable results using the pain catheter have been published in patients with rib fractures who have not undergone SSRF (8), we have noticed several limitations to this treatment modality. First, position is highly variable; and, because the catheter is not truly in the space of the intercostal nerves (**Figure 3**), drug delivery is likely irregular. This variability may be particularly relevant in obese patients; and the median body mass index of patient who underwent SSRF at Denver Health is 29 kg/m^2. Beyond catheter placement, we have also experienced issues with leakage of drug from the skin entry site of the catheter. Moreover, catheters frequently become dislodged or inadvertently removed during patient transport. Further, the indwelling foreign body likely introduces some risk of infection. Finally, the presence of the catheter is distressing to many patients.

Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Inc., Parsippany, NJ, www.pacira.com) provides sustained analgesia for up to 72 hours following a single injection of the drug delivery system. The safety and efficacy of liposomal bupivacaine has been evaluated

in over 1,300 subjects and 21 clinical trials (refs from pamphlet). Although many of these trials have included thoracic surgery patients (9-11), no trial has evaluated the efficacy and safety of liposomal bupivacaine administered to patients with rib fractures undergoing SSRF. Potential benefits as compared to current practice include directed injection into the intercostal nerve space using a VATS approach, as well as obviation of the need for an indwelling catheter. The hypothesis of the current clinical trial is that, among patients undergoing SSRF, liposomal bupivacaine delivered via VATS intercostal nerve block provides comparable analgesia to the pain catheter, as measured by both pulmonary function and narcotic use.

III. Preliminary Studies/Progress Report:

Although SSRF is now a recognized treatment for patients with severe chest wall injuries, the method of loco-regional anesthesia is less standardized. Currently thoracic epidural and para-vertebral catheters are a both common methods for delivering loco-regional anesthesia. Thoracic epidural catheters offer the benefit of bilateral analgesia and have been shown to reduce the length of mechanical ventilation (3). Unfortunately they are contra-indicated in the setting of spine fractures and mild coagulopathy, and may require the addition of a consultative service to manage. Paravertebral pain catheters have equivalent pain control to epidural catheters, but can be used in patients with spine fractures and can be placed surgically or by emergency teams using anatomic landmarks or ultrasound guidance (3). Denver health has found that these catheters are not without issues for our patients. Some issues that we have personally experienced include drug leakage, dislodgement, and irregular drug delivery. Other pain loco-regional analgesic modalities such as intrapleural pain catheters, transcutaneous patches, transcutaneous electrical nerve stimulation, and acupuncture have limited evidence to support their use (3). While still a relatively new technique for loco-regional anesthesia, liposomal bupivacaine has shown favorable results in patients undergoing thoracoscopies and thoracotomies, resulting in shorter hospital length of stay (11) and statistically significant additional analgesics (10). The ease of delivery of liposomal bupivacaine and the ability to avoid bothersome catheters may make it the optimal method for loco-regional anesthesia in patients undergoing SSRF.

IV. Research Methods

A. Outcome Measure(s):

Individuals undergoing SSRF will be randomized to two treatment arms. Primary outcomes will be pulmonary function and narcotic requirement by each subject.

Pulmonary function will be measured using the Standardized Assessment of Respiratory Function (SCARF) score, measured at 10 am daily. This scale has 4 components, and one point award for each of the following:

1) Numeric Pain score >4 (on the 10 point pain scale)
2) Incentive spirometry <50% predicted
3) Poor cough
4) Respiratory rate ≥ 20

Daily Narcotic use will be measured using equi-analgesic doses as shown in the table below.

Narcotic	Dose	Unit	Route
Hydromorphone	1.5	Mg	IV
Hydromorphone	7.5	Mg	PO
Fentanyl	100	Mcg	IV
Morphine	10	Mg	IV
Morphine	30	Mg	PO
Oxycodone (Percocet)	20	Mg	PO
Hydrocodone (Vicodin)	30	Mg	PO

B. Description of Population to be Enrolled:

Adults undergoing surgical stabilization for rib fractures are eligible for this clinical trial. Any individuals that are pregnant, incarcerated, less than 18 years old, or have a known allergy or hypersensitivity to bupivacaine will not be eligible for enrollment.

C. Study Design and Research Methods

This is a non-inferiority, randomized clinical trial that compares two different delivery options for loco-regional anesthesia for patients undergoing surgical stabilization of rib fractures. Randomization will be accomplished using a standard function in Microsoft Excel that randomly chooses either the number 0 or 1.

Prior to patient's SSRF procedure they will be localized to one of two study arms:

1) Pain Catheter: placed in the subscapular space at the time of surgery and results in a continuous infusion of 12ml/hr of 0.25 bupivacaine and is left in place for a maximum of 120 hours.
2) Single injection liposomal bupivacaine: a mixture of 20mL liposomal bupivacaine, 20 mL 0.25% bupivacaine, and 10mL sterile saline (50mL total) that is delivered into the intercostal space during VATS using a 22 gauge needle directed at ribs 3 through 8. (178mm????)

The SSRF procedure will be standardized for all patients to include: 1) flexible bronchoscopy, 2) E-Z Blocker bronchial blocker (figure 5), and 3) VATS evacuation/irrigation of the pleural space.

Postoperatively, standard multimodal analgesia will be used in all patients (barring any contra-indications) to include: 1) Acetominophen 650 mg PO q6H, 2) Ibuprophen 800 mg PO q6h, and 3) Gabapentin 300 mg PO TID

Subjects will be followed for 28 days or until discharged from the hospital, whichever comes first. Crossover from one study arm to the other will not be permitted. Patients in whom pain is not well controlled postoperatively will be given additional analgesics other than bupivacaine.

Occasionally patients with rib fractures receive a pain catheter placed prior to surgery using anatomic landmarks. For these patients the presence of a pre-existing pain catheter will be noted in the data collection sheet. Patient's with a pre-existing pain catheter will have it removed at the time of SSRF. Depending on randomization status, the patient will receive either a new pain catheter placed intra-operatively and under direct vision, or liposomal bupivacaine administered via VATS intercostal nerve block.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

On October 28th 2011, the Food and Drug Administration approved liposomal bupivacaine for the following indication: "administration into the surgical site to produce postsurgical analgesia".

This study will be conducted and reported in accordance with the recommendations of the Consolidated Standards of Reporting Trials Statement (14) and registered with the U.S. National Institutes of Health (clinicaltrials.gov). An independent study monitor (Catherine Dionne, Pharm D) will submit written reports to COMIRB every six months. Adverse events will be recorded and reported to both the data safety monitor and COMIRB.

E. Potential Scientific Problems:

This is a randomized, clinical trial, however, due to the nature of the two treatment arms this study is not blinded. Clinical providers, patients, and the research coordinator collecting data will know which treatment arm the patient is assigned to. This study is subject to the Hawthorne Effect in which the patients may modify their behavior while being observed. Specifically, patients may exaggerate or downplay their pain level while being enrolled. Reported pain, especially on the 10-point pain scale is also highly subjective and will be a limitation in this study. The SCARF

score also incorporates other variables, such as respiratory rate and incentive spirometry volumes which are less subject measures. These will help mitigate the subjectivity of self-reported pain scores.

F. Data Analysis Plan:

Inferiority of liposomal bupivacaine as compared to pain catheter will be defined as median daily SCARF score one point higher. Standard deviation of the SCARF score among patients with rib fractures in Denver Health surgical intensive care unit is 1.1. Using beta = 0.80 and alpha = .05, this returns a total sample size of 34 subjects. Twenty-four SSRF procedures are performed annually at Denver Health, thus we conclude that the trail is feasible and may be completed in 1.5 years.

A standard data collection tool will be used (see Data Collection Tool). All statistical analysis will be conducted using SAS version 9.4 (SAS Inc., Carey, NC). Statistical significance will be defined as $p < .05$. The distribution of continuous variable will be accessed for normality using the Kolmogorov-Smirnov test. Normally distributed continuous variables will be compared using the student's t-test. Non-normally distributed variables will be compared using the Wilcoxon Rank test. Categorical variables will be compared using chi-squared test, unless expected cell counts were <10, in which case Fischer's exact test will be used.

G. Summarize Knowledge to be Gained:

Rib fractures are common and associated with both acute and chronic pain. This trial will compare two loco-regional treatment modalities currently in use at Denver health to determine the optimal method to decrease post-operative pain and minimize opioid use. Denver Health is a leader in trauma care, including rib fractures. Our team has been produced multiple peer reviewed studies detailing current recommendations for treatment of rib fractures. We will continue to explore novel approaches for trauma patients suffering from rib fracture pain control to further improve patient outcomes and patient satisfaction.

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