Study Title:
Intercostal Liposomal Bupivacaine for the Management of Blunt Chest Wall Trauma

Research Team:

Principal Investigator:
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1. **Length of time for research**
   a. Subject enrollment, data collection, and regulatory reporting: 18 months
   b. Statistical analysis of data: 2 months
   c. Manuscript and poster preparation, writing, and publication: 4 months

2. **Research Location(s):** University of Cincinnati Medical Center (UCMC) and UC Medical Science Building

3. **Abstract/Brief Overview:**
   Polytrauma patients with rib fractures are at risk for poor pain control resulting in adverse pulmonary outcomes, including the development of pneumonia or respiratory failure. Liposomal bupivacaine provides a novel medication and administration route that may prevent the need for rescue intubation and development of pneumonia, avoid epidural use, and improve overall patient satisfaction and pain control. This study plans to enroll adult, polytrauma patients with blunt chest wall trauma resulting in rib and/or sternal fractures to receive either liposomal bupivacaine or normal saline intercostal nerve injections in addition to current standard of care (including intravenous, oral, or epidural narcotics). Patients will be excluded if they have a known allergy to bupivacaine, respiratory failure requiring intubation within 24 hours of enrollment, have a known atrioventricular nodal blockade process, hemodynamic instability, active myocardial infarction, greater than 20 rib fractures, or if they are pregnant or actively incarcerated. The purpose of this study is to evaluate the efficacy of liposomal bupivacaine to provide analgesia via posterior intercostal nerve block following significant blunt chest trauma, minimizing adverse outcomes and length of stay and overall narcotic use. The primary outcome of this study is to compare opioid requirements between groups. Secondary outcomes include comparison of clinical outcomes and treatment failures (e.g., development of pneumonia; median patient analgesic score by verbal numerical rating scale [NRS]; median time to first breakthrough opioid dose; incentive spirometer [IS] ability; intensive care unit [ICU] length of stay [LOS]; hospital LOS; use of additional analgesia adjuncts) and to perform a cost effective analysis.

4. **Purpose of Study:**
   The primary purpose of this pilot study is to compare opioid requirements between groups receiving intercostal liposomal bupivacaine to standard of care for acute traumatic pain related to blunt chest wall trauma with resultant rib and/or sternal fractures. Pain scores will be evaluated using the NRS (Appendix). Uncontrolled analgesia following rib fractures can result in intubation, pneumonia, prolonged length of stay, and death. Achieving adequate pain control in native airway patients prevents clinical challenges. Multimodal analgesia regimens are necessary to optimize patient outcomes and prevent untoward

effects of opioid analgesia. Liposomal bupivacaine offers a novel therapy that may revolutionize pain management in patients with rib fractures. Pain control with one injection may provide analgesia for up to 96 hours through a unique mechanism of action and site of application. Overall, the combination of a nonopioid analgesic, liposomal bupivacaine, with standard of care may lead to improved analgesia with fewer adverse effects. Specific aims include to 1) compare opioid requirements (in morphine equivalents) between patients with blunt chest wall trauma and rib and/or sternal fractures receiving liposomal bupivacaine versus standard of care; 2) compare clinical outcomes and treatment failures including development of pneumonia, median patient analgesia score using verbal NRS, median time to first breakthrough opioid dose, IS ability, ICU LOS, hospital LOS, and use of additional analgesic adjuncts; 4) and to perform a cost-effectiveness analysis

5. Background:

Background and Significance

Blunt chest wall trauma remains the second most common injury observed in non-intentional injury-related death in the U.S.A. and accounts for 10% of trauma-related emergency department visits worldwide.[1-3] Current literature has identified high morbidity and mortality rates for patients suffering from blunt chest wall trauma, with mortality ranging from 4 to 20%.[2,4] The prevalence of rib fractures among blunt chest wall trauma patients requiring hospital admission is 4 to 10%.[5] One of the most prominent contributing factors to blunt chest wall trauma morbidity is pain.[6-8] The management of resultant pain serves as a core intervention in managing these patients.[8]

The standard of care for analgesia in trauma patients with rib fractures is the use of multimodal pharmacotherapy, which includes opioids administered via continuous infusion epidural routes, intermittent intravenous push, or oral dosing or provided as patient-controlled analgesia.[9,10] Although opioid agents can provide effective analgesia, they exhibit untoward effects that may be dose limiting. These adverse effects include hypotension, bradycardia, central nervous system depression, and respiratory depression.[9] Patients may not achieve adequate pain relief when doses are limited because of the risk of these effects.[11] Consequences of uncontrolled pain from rib fractures in trauma patients include exhaustion due to lack of sleep, disorientation, agitation, stress response, post-traumatic stress disorder, pneumonia, and death.[9,12] Multimodal therapeutic strategies may be used in an effort to limit the need for opioids in this population, and newer analgesic agents may be incorporated into these strategies to achieve optimal analgesia.[13]

Bupivacaine liposomal injectable suspension is a novel formulation of the amide-type anesthetic, bupivacaine, approved by the Food and Drug Administration for local infiltration into surgical sites to produce postsurgical analgesia.[13] This formulation allows for the prolonged release of bupivacaine from multivesicular liposomes, providing anesthetic effects that can be observed for up to 96 hours. Side effects of liposomal bupivacaine infiltrated locally are generally mild and include nausea, constipation, and vomiting. Pyrexia, dizziness, peripheral edema, anemia, hypotension, pruritis, and procedural pain occurred in clinical trials at lower rates.[14]

Bupivacaine liposomal injectable suspension has been shown to improve analgesia scores and decrease opioid use when infiltrated locally at the surgical site in a variety of procedure types, including hemorrhoidectomy and bunionectomy.[15-17] Similar results of lower pain scores and decreased opioid use with liposomal bupivacaine compared to standards of care have been shown for patients undergoing mammoplasty, ileostomy reversal, and open colectomy.[18-21] Conventional bupivacaine, when administered as a single nerve block, has a duration of activity of 8 to 24 hours.[22] Liposomal bupivacaine, given its prolonged release, has the potential to provide anesthetic activity at the nerve site beyond 24 hours. Animal studies and phase 1 trials in healthy volunteers have shown safety with use of liposomal bupivacaine as a peripheral nerve block.[23]

Further investigation is needed to fully evaluate this route of administration. This study aims to assess the efficacy of liposomal bupivacaine when used as a regional block compared to standard of care for analgesia in trauma patients with rib fractures. This has only been done in case reports and preliminary studies to date.[24-26]

Study Justification

The potential utility of liposomal bupivacaine in trauma patients suffering from multiple rib or sternal fractures is unknown. Recent evidence has shown pharmacodynamic benefits of liposomal bupivacaine through prolonged pain relief and subsequent opioid reduction. The sustained analgesia may also reduce the likelihood of respiratory failure, development of pneumonia, increased length of stay, and patient mortality. The purpose of this study is to evaluate the efficacy of liposomal bupivacaine to provide analgesia via posterior intercostal nerve block following significant blunt chest trauma, minimizing adverse outcomes and length of stay and overall narcotic usage.

Intercostal nerve blockade has been chosen over paravertebral block, as the intent of the study is to identify a therapeutic strategy that can be employed based on standard training for emergency medicine or surgery practitioners. Both

emergency medicine and surgery practitioners are familiar with intercostal blocks for placement of tube thoracostomy. Intercostal blocks do not require additional training, as would be done in the setting of a pain medicine fellowship, and do not incur the risks of hypotension associated with epidural catheters. Additionally, intercostal and paravertebral blocks carry similar risks of pneumothorax or intercostal neurovascular bundle injury.

Study design:
This is an investigator-initiated, single-center, prospective, double-blinded, placebo-controlled trial funded by the United States Air Force. Multi-system, adult trauma patients greater than or equal to 18 years of age admitted to the University of Cincinnati Medical Center (UCMC), an urban American College of Surgeons-verified Level 1 trauma center with more than 3500 annual trauma admissions annually will be identified by the research team. Patients will be screened and those who meet all inclusion/exclusion criteria will be approached for informed consent by study personnel in their rooms. Informed consent will be obtained prior to enrollment and any study procedures are done. Patients will then receive either receive 1 mL of liposomal bupivacaine just below each affected rib or 0.9% sodium chloride peri-intercostal subcutaneous injection (as placebo control) via a 25-G needle. Goal enrollment is 200 patients with 100 patients in each group. Patients included in the study will be followed during inpatient hospitalization through discharge.

6. Research data collection/study procedures:

Intervention

Patients will be identified on admission and will be screened by inclusion/exclusion criteria. After informed consent is obtained they will be randomized into one of two possible groups:

a. Liposomal bupivacaine intercostal (group 1; interventional)
b. 0.9% sodium chloride peri-intercostal subcutaneous (group 2; placebo-control)

Patients will be placed on continuous monitoring of heart rate, EKG, and pulse oximetry. Blood pressure and respiratory rate will be measured every 5 to 10 minutes during the procedure and every at least 15 minutes for the first hour after the procedure. All patients undergoing injection will remain on heart rate, EKG, and pulse oximetry monitoring by telemetry for 96 hours following injection.

In addition, while in the ICU all study subjects will monitored with a non-invasive respiratory monitor (Expiron) to determine respiratory rate, tidal volume, minute volume and breathing pattern for up to 96 hours. This monitoring will aid in

detection of respiratory depression and add additional safety to the trial. This device measures chest expansion by thoracic impedance and is FDA approved.

Supplemental oxygen will be provided to maintain a peripheral oxygen saturation of 90% or greater.

Injections will be performed by trained trauma / critical care physicians. Training prior to initiating the study will include familiarization with the standardized procedure as described below, which will be documented in study records. Patients will be monitored by bedside nurses before, during, and after the block procedure. Standard inpatient cardiac arrest carts will be immediately available before, during, and after the block procedure.

A 20-mL vial will be obtained from IDS Pharmacy that either contains liposomal bupivacaine (266 mg in 20-mL) or 0.9% sodium chloride. Patients will be positioned either sitting up or in logroll/decubitus position. Rib fractures will be noted from previously obtained CT scan of the chest from initial trauma evaluation. The thoracic posterolateral area will be prepped and draped in sterile fashion. After aspiration to prevent intravascular injection, 1 mL of liposomal bupivacaine will be injected with a 25-G needle just below each affected rib by the intercostal neurovascular bundle in a posterior but not paravertebral position or 0.9% saline (as placebo control) will be injected with a 25-G needle in the subcutaneous space just superficial to each affected rib to minimize risk of placebo-injection complications. Optimal regional blockade will include the rib immediately above the most superior and the rib immediately below the most inferior fractured rib.

Regional blockade will only be performed once per patient enrolled in the study and at one injection site per fractured rib. Patients will only be enrolled once per acute traumatic event and admission.

If a patient enrolled in the study should have an adverse event during the course of intercostal rib block administration and the reaction is severe or life-threatening, then the patient will be withdrawn from the study and no further injections will be administered, regardless of how many injections were originally planned.

A chest xray will be obtained as clinically indicated following the procedure if there is concern for the development of pneumothorax.

Self-reported pain will be measured using the verbal NRS, a 0-10 ordinal scale (e.g., 0 = “no pain”; 10 = “worst pain imaginable”).[27] Breakthrough opioid dosing

will be guided by a formal inpatient analgesia protocol. Pain assessments will occur every 6 hours or per standard of care for the appropriate setting (e.g., intensive care unit, trauma ward) for the first 96 hours. All opioid dosing will be converted to oral morphine equivalents for comparison purposes. Time to first breakthrough opioid dose will be recorded. Incentive spirometry will be used and assessed and recorded by respiratory therapist, with adjunct inspiratory assistance (e.g., EzPAP) applied per our institutional volume expansion protocol.

Follow-up will occur daily by study coordinators and trauma service physicians for the first 96 hours after block procedure, then daily by the trauma service physicians for 14 days or until discharge from the hospital if it occurs earlier.

Standard of care analgesia regimen on the trauma service will be provided to all patients enrolled in the study, regardless of liposomal bupivacaine or placebo injection. This regimen will be per the Trauma acute multimodality pain management protocol (Appendix).
Typical escalation of analgesics provided for these patients, as deemed medically appropriate based on age and comorbid medical conditions, includes (in order of addition to regimen):

- Acetaminophen, oral or enteral
- NSAIDs, ibuprofen or ketorolac
- Lidocaine 5% transdermal patch
- Oral or enteral tramadol
- Oral or enteral hydrocodone or oxycodone
- IV morphine or hydromorphone, intermittent dosing
- Patient controlled analgesia morphine or hydromorphone
- Long-acting narcotics, including methadone, oxycodone ER, or morphine ER
- Neuromodulating adjuncts, including gabapentin or pregabalin
- Epidural analgesia catheter placement

During this time all adverse events will be recorded. Subjects who experience serious adverse events will be followed until the event resolves. If necessary these patients will be followed up by weekly phone calls as well as at the standard of care clinic visit two weeks post-discharge.

Randomization

Following informed consent, patients will undergo 2x1 block randomization to ensure equal allocation to each intervention group. Randomization will be performed by study personnel and will be blinded as there will be placebo injections for patients randomized into group two and the same number of injections would be used regardless of intervention arm.

Data Collection:

Verbal NRS, pain assessment data, opioid use, and time to first opioid breakthrough dose will be collected as previously described. Portable spirometry will be used daily to objectively and serially assess lung function. Additional data collection points include patient sex, age, weight, body mass index, body surface area, injury severity score, chest abbreviated injury score, and ICU and hospital length of stay. Safety will be evaluated by the occurrence of *a priori* serious adverse events. Costs will be evaluated utilizing hospital and pharmacy databases.

Schedule of subject identification and data collection

Subjects will be identified based on inclusion criteria at the time of admission to the trauma service following evaluation in the emergency department. Subjects meeting inclusion criteria will be enrolled within 6 hours of admission. Vitals monitoring will occur during the intercostal nerve block procedure and continue by telemetry for the next 96 hours or until hospital discharge, whichever occurs first.

7. Specimen collection:

No serum assays are necessary for this study and will not be collected.

8. Potential Benefits:

Blunt chest wall trauma remains a common injury seen in non-intentional injury-related deaths. It accounts for nearly 10% of trauma-related emergency department visits worldwide and is associated with high morbidity and mortality. This morbidity and mortality are influenced by the pain experienced by these events which can involve rib or sternal fractures as instigating stimuli. Uncontrolled analgesia following rib fractures can result in intubation, pneumonia, prolonged length of stay, and death. Achieving adequate pain control in native airway patients prevents clinical challenges. Multimodal analgesia regimens are necessary to optimize patient outcomes and prevent untoward effects of opioid analgesia (e.g., hypotension; bradycardia; central nervous system depression; respiratory depression).

Liposomal bupivacaine offers formulation that provides prolonged yield of the anesthetic properties up to 96 hours. It has been shown to improve analgesia scores and decrease opioid requirements when used locally at surgical sites such as bunionectomies and hemorrhoidectomies (Figure 1a). It has also been shown to reduce the time to first opioid dose needed (Figure 1b). Reductions in opioid requirements have also been appreciated.

Figure 1. Cumulative postsurgical pain score in hemorrhoidectomy patients[15]

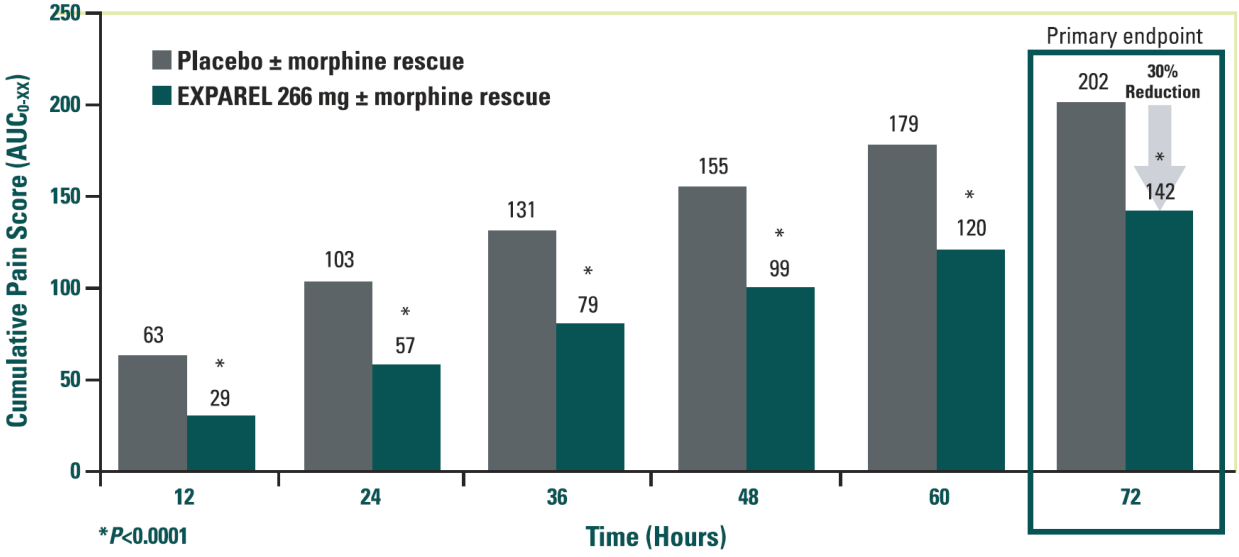
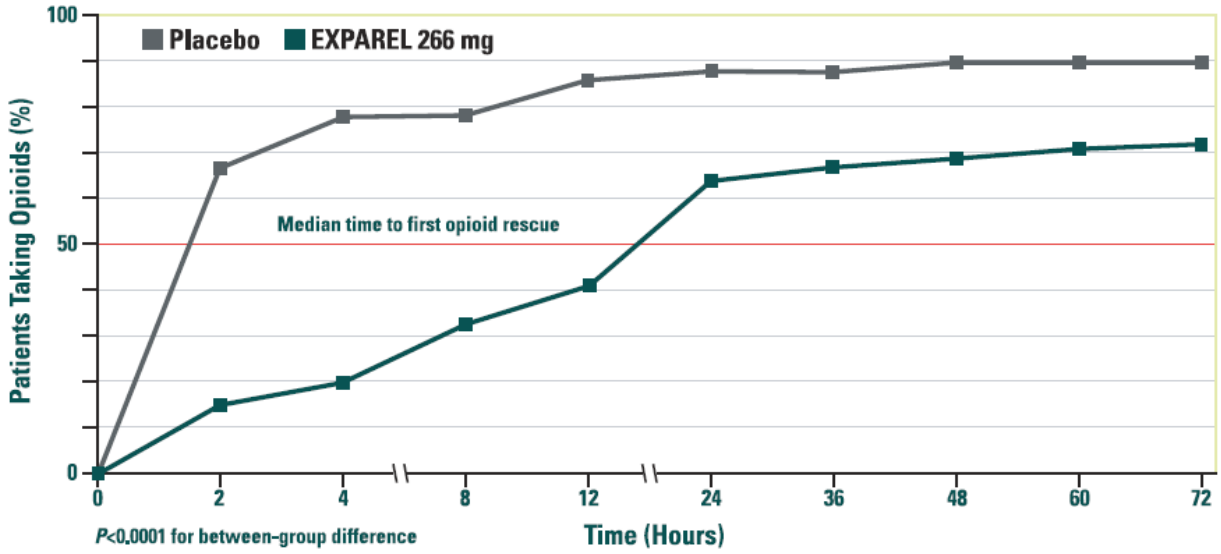


Figure 2. Cumulative portion of patients requiring opioid therapy post-hemorrhoidectomy[15]



Patients randomized into the standard analgesia plus placebo intercostal injection group will benefit from increased nursing attention to pain score assessment and treatment as well as increased respiratory therapist attention to pulmonary toilet and objective assessments of spirometry volume capacities. Patients randomized into the standard analgesia plus liposomal bupivacaine group will additionally receive the anticipated benefit of intercostal nerve blocks for improved analgesia.

In addition, all subjects will be monitored with a non-invasive respiratory monitor (Expiron) to determine respiratory rate, tidal volume, minute volume and breathing pattern. This monitoring is in addition to standard care and will aid in detection of respiratory depression and add additional safety to the trial.

Future patients can benefit from the cultivation of this knowledge to have both potential patient benefit (e.g., decreased morbidity and mortality; improved pain scores; decreased risk of pneumonia) and cost-savings (e.g., decreased medication requirement; less time in the ICU or hospital). Overall, optimal use of liposomal bupivacaine may help improve patient pain scores, pulmonary toilet and ability to use IS, and decrease the need for opioid therapy. Improved patient outcomes, expansion of scientific knowledge, and development of new blunt chest wall trauma pain protocols may result.

9. **Potential Risks, Discomforts, and inconveniences:**

Level of Risk

Consequences of poorly controlled pain associated with rib and/or sternal fractures as well as opioid use have been previously outlined above. Risks of liposomal bupivacaine include major and minor adverse events (Tables 1 and 2). Risks will be mitigated by appropriate exclusion of patients with low and high body weights as well as known cardiac history as previously described to minimize pharmacodynamic failure or excess.

Table 9.1. Adverse events occurring in >2% of patients in any treatment group[15,17,31]

	Bunionectomy[17, 20]		Hemorrhoidectomy[18, 20]	
Adverse Event	Liposomal Bupivacaine 106 mg (n=97)	Placebo (n=96)	Liposomal Bupivacaine 266 mg (n=95)	Placebo (n=94)
Any treatment-emergent adverse event	58 (59.8)	65 (67.7)	16 (16.8)	17 (18.1)
Gastrointestinal disorders	41 (42.3)	38 (39.6)	8 (8.4)	13 (13.8)
Nausea	39 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Painful defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Nervous system disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	8 (8.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Pruritus, generalized	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Abnormal laboratory investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)

Data are no. (%) of patients.

Table 9.2. Incidence of serious adverse events occurring in >1 patient in any treatment group[30]

	n (%)		
	Liposome Bupivacaine		
	≤266 mg (n = 545)	Bupivacaine HCl (n = 446)	Placebo (n = 190)
Any serious AE	6 (1.1)	24 (5.4)	2 (1.1)
Arthrofibrosis	0	3 (0.7)	0
Cellulitis	0	0	0
Congestive cardiac failure	0	0	0
Atrial fibrillation	0	2 (0.4)	0
Sedation	0	0	0
Hypoglycemia	0	2 (0.4)	0
Deep vein thrombosis	0	2 (0.4)	1 (0.5)

Cardiac and neurotoxicity that are generally seen with increased serum bupivacaine concentrations (i.e. >2000 ng/mL) should serve minimal risk as concentrations seen in previous studies using the maximum FDA-approved dose of 266 mg of liposomal bupivacaine measured maximum concentrations of 867 and <300 ng/mL each.[15, 28-29] Patients will require and be monitored by a central cardiac monitoring unit to assess for any changes in heart rate or rhythm for the first 96 hours at minimum.

There may be temporary pain or local discomfort associated with repeated intercostal injections. Additionally, there will be a small risk of a pneumothorax if the intercostal injection needle violates the parietal pleura.

Additionally, the trauma team will have discretion to hold or stop enoxaparin doses if patient is deemed to have bleeding. Patients may also have doses held due to perioperative plans. This will also allow for appropriate, safe patient care.

If a patient enrolled in the study should have an adverse event during the course of the intercostal rib block administration and the reaction is severe or life threatening, then the patient will be withdrawn from the study and no further injections will be administered, regardless of how many injections were originally planned. In addition, an adverse event based on physiologic response will include a sustained (greater than five minute) change in heart rate by > 40% from baseline or absolute heart rate greater than 160 or less than 50, change in systolic blood pressure by 40% or absolute systolic blood pressure less than 80 mmHg or greater than 180 mmHg, change in respiratory rate by 50% or absolute respiratory rate greater than 30 or less than 6, or decreasing oxygen saturation

by 10% SpO2 or less than absolute SpO2 < 85%.Any non-sinus rhythm or ST segment changes seen on the EKG monitoring strip will lead to immediate subject discontinuation.

Safety Assessments

Every adverse event, whether or not thought to be related to study drug, will be recorded and entered into the RAVE Case Report Form database.

Any medical condition present prior to study enrollment should not be reported as an adverse event, unless the medical condition worsens in severity or seriousness during the study. In this case it may be reported as an adverse event at the discretion of the Investigator.

The Investigator will review each event and assess its severity and relationship to the study treatment.

Adverse event Definitions:

Adverse Event
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Suspected Adverse Reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse Reaction
An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Serious

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-Threatening

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Table 9.3. Causality Definitions:

Causality term	**Assessment criteria***
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary

Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Table 9.4. Toxicity Grading Scale:

Local Reaction to Injectable	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Table 9.4 extracted from: Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, August 2016

Treatment of cardiovascular and neurologic adverse events

- Local anesthetic systemic toxicity
    - Treatment will be initiated as recommended as the American Society of Regional Anesthesia and Pain Medicine, according to the society's checklist (Appendix)
- Treatment will include: transfer to intensive care unit setting if not already in intensive care unit, continuous hemodynamic monitoring for at least 24 hours, appropriate airway management with assistance from respiratory therapy and a critical care consultant as needed, cardiovascular stabilization and assistance from a critical care consultant as needed, administration of Lipid Emulsion therapy, as per ASRA checklist in Appendix, Neurology consult for any observed systemic neurologic toxicity (including change in vision, mental status change, persistent headache, seizure), Cardiology consult for any arrhythmias that persist greater than 30 minutes, beyond initial appropriate medical treatment, or result in hypotension with systolic blood pressure < 80mmHg.

10. Data Safety monitoring plan and/or DSMB:

Patients will be screened for the adverse events described above.

Adverse events will be continuously assessed on an ongoing basis by Dr. Jason Schrager, medical monitor. Study will be stopped if:

- **Adverse events probably/likely or certainly related to study drug, regardless of severity, occur in > 10% of enrolled patients, or**
- **Serious/life-threatening adverse events, regardless of causality, occur in > 2% of enrolled patients.**

11. Data Analysis:

Primary Endpoint

1) Compare opioid requirements (in morphine equivalents) between trauma patients with rib and/or sternal fractures receiving liposomal bupivacaine versus standard of care.

Secondary Endpoints

1) Compare clinical outcomes and treatment failures including:
    a. Development of pneumonia, defined as >100,000 cfu/mL bacteria on bronchoalvelolar lavage, or clinically with leukocytosis, pulmonary infiltrate and fever
    b. Median patient analgesic score by verbal NRS
    c. Median time to first breakthrough opioid rescue dose
    d. Incentive spirometry serial volume capacity
    e. ICU LOS
    f. Hospital LOS
    g. Use of additional analgesia adjuncts
        i. Epidural catheter
        ii. Non-opioid analgesics (e.g., non-steroidal anti-inflammatory drugs; gabapentin; pregabalin; carbamazepine; ketamine; acetaminophen)
2) Perform a cost-effectiveness analysis
3) Calculate dose and exposure of lidocaine or bupivacaine over time from Lidoderm patches, intercostal nerve blocks, or epidural catheters

Statistical analyses will be performed using SAS. An intention-to-treat model will be used for data analysis. Patients randomized into the treatment arm will be included in the primary outcome analysis. Patients withdrawn from the study will have data included up to the point of withdrawal. Nominal data will be reported using frequencies of occurrence and proportions as appropriate. Continuous data will be reported using means and standard deviations or medians and

interquartile ranges as appropriate per distribution. Hypothesis testing for nominal data will be performed using the Fisher's exact test or chi square test as required based on sample size. Continuous data will be compared using student's t-test/ANOVA or rank sum/Kruskal-Wallis ANOVA for normally distributed and non-normally distributed data, respectively as appropriate. A p-value < 0.05 will designate statistical significance. Costs associated with the cost-effectiveness analysis will be pulled from hospital and pharmacy databases.

Given the pilot nature of the study, a total of 200 patients will be enrolled. Assuming a 96-hour requirement of 250-mg oral morphine equivalents (approximately 12.5-mg IV hydromorphone), we anticipate a 20% reduction to 200-mg oral morphine equivalents (approximately 10-mg IV hydromorphone) resulting in an expected difference in means of 50 mg and an anticipated standard deviation of 50 mg. To achieve an 80% power with an alpha of 0.05 for this primary outcome, the goal enrollment is 200 patients.

12. Data storage and confidentiality (include sample storage if applicable)

This project will use Medidata Rave® as its Electronic Data Capture (EDC) software, which is a robust EDC platform for capturing, managing and reporting clinical research data. This system includes a robust query management system based on the Data Quality Plan, which will identify data quality checks to be programmed into the database design. Frequent monitoring of the database throughout the study will allow for corrective action to be taken quickly if problems are identified with the data collection process. The database will be password protected and appropriately secured such that only authorized study personnel will have access to the data. Data will be maintained in a confidential manner with regular reminders of the need for confidentiality provided from the senior investigator. A single subject log will be kept by the principal investigators for matching patient study number, initials, medical record number, and admission date (attached). Once assigned to the log, patients will only be evaluated using their de-identified, study number. Data entered into the electronic database will be de-identified.

Once the study has been completed, the subject log will be destroyed and only the de-identified electronic database will be kept. Only study personnel will have access to the data.

13. Study Population

UCMC is an urban, academic American College of Surgeons-verified Level 1 trauma center that treats over 3500 trauma patients each year. Patients admitted to the UCMC trauma service are eligible for enrollment. Patients will be screened on admission or identified per the daily trauma census. Trauma team

physicians may also contact study personnel daily once a patient is identified as a potential candidate. Study personnel will screen subjects for inclusion and exclusion. If patient meets inclusion criteria, then consent will be administered by study personnel (see section 14).

Inclusion Criteria

a. Patients with an anticipated length of stay of at least 72 hours
b. Trauma patients with two or more rib or sternal fractures
c. Patients demonstrating the inability to achieve greater than 50% predicted inspiratory capacity based on ideal body weight using IS within the first 24 hours of admission (Appendix)
d. Adults age 18 and older

Exclusion Criteria

a. Patients with a known allergy to bupivacaine
b. Respiratory failure requiring intubation within 24 hours prior to enrollment
c. Patients with known or suspected atrioventricular nodal blockade process requiring cardiology evaluation and/or pacemaker placement
d. Hemodynamic instability (defined as a new intravenous vasopressor or inotrope requirement [e.g., norepinephrine; epinephrine; phenylephrine; dobutamine; milrinone] or a mean arterial pressure < 55 mmHg)
e. Signs of active myocardial ischemia or non-ST elevation MI
f. Patients with greater than 20 rib fractures (20-mL vial [266-mg dose]; 1-mL [13.3 mg] per rib)
g. Weight < 50 kg or > 150 kg
h. Pregnancy as defined by urine pregnancy test in all females of child-bearing potential
i. Incarceration
j. Inability to obtain informed consent
k. Severe traumatic brain injury, GCS <8

Patients will be followed for outcome assessment during hospitalization through discharge.

14. Consenting process and plan

Patients will be identified as previously described and permission to consent per the trauma team attending will be obtained prior to administration of consent. Study personnel will administer consent in the patient's room. Patients who meet inclusion and exclusion criteria will be eligible for consent. Informed consent will be obtained prior to randomization into treatment arms. Patients unable to give consent will have LAR or next of kin consented. LAR must show proof of health care POA or court document. A copy of the documents will be kept with the

consent form. Next of kin is a person who may act as LAR without a document granted by court. Next of kin will be determined by team social workers' note. The order in which the next of kin may act as LAR is: spouse, parent, adult son or daughter, adult brother or sister. If next of kin available at the time of consent cannot agree, the person cannot participate in the research. Investigators will be available seven days a week and will continue correspondence with subjects throughout the study for up to 7 days or until hospital discharge, whichever comes first.

Subjects can withdraw from the study at any time per their desire or may be withdrawn at the discretion of the trauma team. Subjects will be withdrawn as appropriate based on any adverse event that may occur as described above in Section 9. Any subject who withdraws will be placed on standard of care.

15. Compensation:

Patients will not receive any compensation for research involvement.

16. Subject costs:

There are no additional costs to subjects.

In case of injury or illness related to the study, the University of Cincinnati Medical Center will provide emergency medical care at no cost to the subject. The University of Cincinnati will review each case and determine on a case by case basis whether to reimburse any out of pocket expenses.

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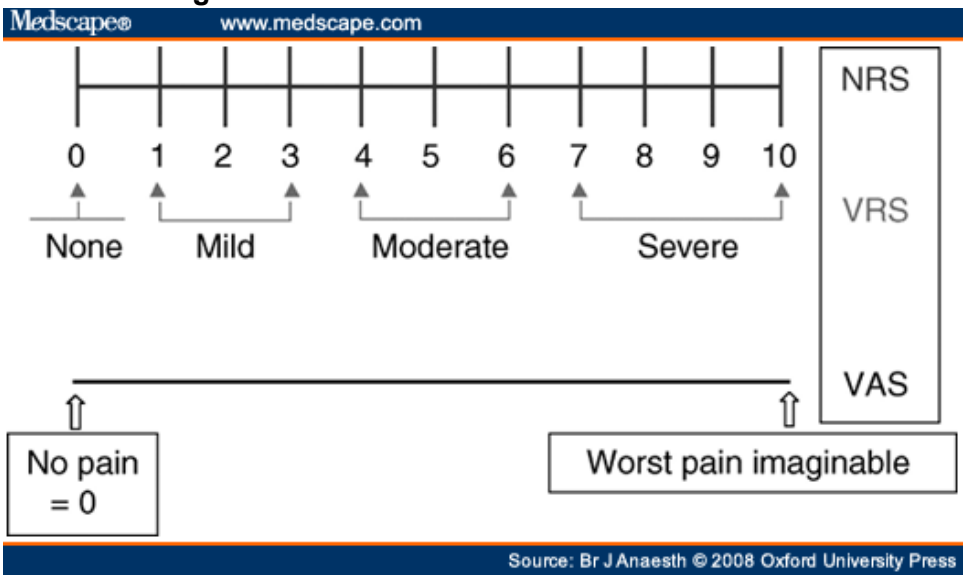
APPDENDIX

Numeric rating scale



Predictive Nomogram–Inspiratory Capacity* (mL)**

FEMALE

AGE IN YEARS	HEIGHT IN INCHES								
	58"	60"	62"	64"	66"	68"	70"	72"	74"
20	1900	2100	2300	2500	2700	2900	3100	3300	3500
25	1850	2050	2250	2450	2650	2850	3050	3250	3450
30	1800	2000	2200	2400	2600	2800	3000	3200	3400
35	1750	1950	2150	2350	2550	2750	2950	3150	3350
40	1700	1900	2100	2300	2500	2700	2900	3100	3300
45	1650	1850	2050	2250	2450	2650	2850	3050	3250
50	1600	1800	2000	2200	2400	2600	2800	3000	3200
55	1550	1750	1950	2150	2350	2550	2750	2950	3150
60	1500	1700	1900	2100	2300	2500	2700	2900	3100
65	1450	1650	1850	2050	2250	2450	2650	2850	3050
70	1400	1600	1800	2000	2200	2400	2600	2800	3000
75	1350	1550	1750	1950	2150	2350	2550	2750	2950
80	1300	1500	1700	1900	2100	2300	2500	2700	2900

MALE

AGE IN YEARS	HEIGHT IN INCHES										
	58"	60"	62"	64"	66"	68"	70"	72"	74"	76"	78"
20	2000	2200	2400	2600	2800	3000	3200	3400	3600	3800	4000
25	1950	2150	2350	2550	2750	2950	3150	3350	3550	3750	3950
30	1900	2100	2300	2500	2700	2900	3100	3300	3500	3700	3900
35	1800	2000	2200	2400	2600	2800	3000	3200	3400	3600	3800
40	1750	1950	2150	2350	2550	2750	2950	3150	3350	3550	3750
45	1700	1900	2100	2300	2500	2700	2900	3100	3300	3500	3700
50	1650	1850	2050	2250	2450	2650	2850	3050	3250	3450	3650
55	1550	1750	1950	2150	2350	2550	2750	2950	3150	3350	3550
60	1500	1700	1900	2100	2300	2500	2700	2900	3100	3300	3500
65	1400	1600	1800	2000	2200	2400	2600	2800	3000	3200	3400
70	1350	1550	1750	1950	2150	2350	2550	2750	2950	3150	3350
75	1300	1500	1700	1900	2100	2300	2500	2700	2900	3100	3300
80	1250	1450	1650	1850	2050	2250	2450	2650	2850	2050	3250

* Formula used in the above Nomogram published in The American Review of Respiratory Diseases official journal of American Thoracic Society, September 1979, Vol. 120, Number 3 by G. Polgar and V. Promadhat

** Milliliters — Inspiratory capacity measured in milliliters rounded off to the nearest 50 ml.

AMERICAN SOCIETY OF
REGIONAL ANESTHESIA AND PAIN MEDICINE

Checklist for Treatment of Local Anesthetic Systemic Toxicity

The Pharmacologic Treatment of Local Anesthetic Systemic Toxicity (LAST) is Different from Other Cardiac Arrest Scenarios

- ❑ **Get Help**
- ❑ **Initial Focus**
  - ❑ **Airway management:** ventilate with 100% oxygen
  - ❑ **Seizure suppression:** benzodiazepines are preferred; **AVOID propofol** in patients having signs of cardiovascular instability
  - ❑ **Alert** the nearest facility having **cardiopulmonary bypass** capability
- ❑ **Management of Cardiac Arrhythmias**
  - ❑ **Basic and Advanced Cardiac Life Support (ACLS)** will require adjustment of medications and perhaps prolonged effort
  - ❑ **AVOID vasopressin, calcium channel blockers, beta blockers, or local anesthetic**
  - ❑ **REDUCE epinephrine dose to <1 mcg/kg**
- ❑ **Lipid Emulsion (20%) Therapy** (values in parenthesis are for 70kg patient)
  - ❑ **Bolus 1.5 mL/kg** (lean body mass) intravenously over 1 minute (~100mL)
  - ❑ **Continuous infusion 0.25 mL/kg/min** (~18 mL/min; adjust by roller clamp)
  - ❑ Repeat bolus once or twice for persistent cardiovascular collapse
  - ❑ Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
  - ❑ **Continue infusion** for at least10 minutes after attaining circulatory stability
  - ❑ Recommended upper limit: Approximately 10 mL/kg lipid emulsion over the first 30 minutes
- ❑ **Post LAST events at** www.lipidrescue.org and report use of lipid to www.lipidregistry.org

OBJECTIVE

Provide a multidisciplinary trauma service protocol for acute pain management in non-intubated, alert and oriented patients (GCS 15) with transition through inpatient and outpatient settings.

Medication and Injury-Specific Guidelines
Rib fractures (≥ 2 ribs):

1. Lidocaine 5% transdermal patch
    a. Apply 1-2 patches to affected area
    b. Apply for 12 hours and remove for 12 hours
    c. Do not apply to open cuts or abrasions
    d. Use caution if applied for > 7 days
2. Epidural
    a. Consider AIPS consult
3. IV Acetaminophen
    a. Restricted to patients who are NPO with no feeding access
    b. Patients must be ≥ 65 years old with ≥ 2 rib fractures
    c. Patients can only receive IV acetaminophen for 24 hours or until PO/FT status confirmed, whichever comes first
    d. All other IV acetaminophen use is subject to a non-formulary request per current UC Health policies and procedures

    Non-steroidal anti-inflammatory drug (NSAIDs)
4. Allowable in orthopedic fractures EXCEPT:
    a. Tibia shaft fracture
    b. Humerus shaft fracture
    c. Spine fractures/surgeries
    d. Any non-union or fusion surgeries

    Nerve Injury / Burn Injury / Neuropathic Pain
5. Gabapentin
    a. Start at 300 mg q8h
        i. Elderly (age ≥ 65 years), low-weight (≤ 50 kg), or renal dysfunction (CrCl ≤ 30 mL/min) will require dose reduction to daily administration
    b. Up titrate q72h as needed based on patient response
    c. Caution in patients with altered mental status

    History of Narcotic / Heroin Abuse / High Pain Scores or Tolerance
6. Initiate patient home medications as able
    a. If on formulary, initiate home dose

    b. If non-formulary, consult pharmacy for appropriate conversion
7. Early Methadone initiation should be initiated for early pain control in patients with high pain scores or opioid tolerance
    a. Initiate the lowest effective dose and up/down titrate as able
    b. Up titrate q48-72h as needed based on patient response
    c. Contraindicated in patients with history of QTc prolongation > 500 seconds, elderly patients, or those on concomitant NMDA receptor antagonists