Protocol for a Single Center Randomized Controlled Trial of Liposomal Bupivacaine Intercostal Nerve Blockade versus Continuous Thoracic Epidural for Regional Analgesia in Patients with Multiple Rib Fractures

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BACKGROUND

Management of traumatic rib fractures continues to be a challenge for trauma surgeons. The prevalence of rib fractures amongst trauma patients ranges between 4-10%.[7,9] Associated pulmonary complications and mortality range from 16-60% and 3-16% respectively, and increases with the number of ribs fractured.[1-3,6,7,9] Specifically, the development of pneumonia, respiratory distress, and respiratory failure can be devastating, and are risk factors for increased mortality amongst this patient population.[2-5] It is presumed the development of these complications in patients suffering from rib fractures can be secondary to pain alone, which limits respiratory excursion and impairs the ability to cough, decreasing the clearance of secretions and promotes development of atelectasis.[1,4,6,7,9-11,14,16] Therefore, many clinicians seek to alleviate this pain, which has been shown to reduce morbidity and mortality associated with multiple rib fractures.

Currently, many analgesic options are available to patients suffering from rib fractures. Systemic NSAID and opioid analgesics are widely used. These medications significantly improve respiratory function and decrease rates of pulmonary complications when the number of rib fractures is low and the patient is young with few comorbidities.[10] Yet, the use of NSAIDs is limited in patients due to concerns for peptic irritation, renal injury, hepatotoxicity, hemorrhage, or coagulopathy, while opioids are used judiciously in thoracic trauma due to their sedative effects, gastrointestinal symptoms, suppression of cough, and decreased respiratory drive.[5,7,8,10]

More regional and invasive options are also available for older patients with comorbidities, individuals with multiple rib fractures, significant pain, or unstable respiratory status.[10] These include intercostal nerve blockades, catheter delivered continuous intercostal nerve blockades, and continuous epidural analgesia (CEA). However, these additional options are not without their own drawbacks, risks, contraindications, and their efficacy relative to one another is equivocal.[10]

Formulations currently used for conventional intercostal nerve blocks (CINB) are relatively safe, do not require additional equipment or specialized anesthesia personnel, do not require catheter repositioning, and provide improved analgesia immediately over the aforementioned systemic therapies.[10,11,16] However, the analgesic effect is short acting and requires multiple administrations, which multiplies the risk of secondary pneumothorax, hemothorax, and intravascular injection.[10,14] There is also a rare risk of systemic local anesthetic toxicity including hypotension, atrioventricular block, arrhythmia, and rash or infection at the needle entry site are contraindications.[10-12]

Catheter delivered continuous intercostal nerve blockade also offers an acceptable safety profile. Nevertheless, this modality is invasive, requires advanced training of personnel and additional equipment for accurate placement and adequate effect, adds extra cost, can serve as a nidus for infection, increases risk of local anesthetic toxicity due to continuous infusion, and is

contraindicated if rash or infection is present at the insertion site, or if there is a systemic infection.[5,10,15,16]

Lastly, CEA is noted by numerous authors, including the Eastern Association for the Surgery of Trauma, to be the standard of care in the setting of multiple or bilateral rib fractures.[1,7,8,10,19] Yet, CEA is invasive and its initial placement requires an anesthesiologist. Once placed, hospitalization is mandated and the associated pumps and catheter require close monitoring, often on a unit with telemetric support. These factors can delay treatment and significantly increase cost. CEA also carries risk of complications including failed catheter placement, inadequate analgesia, urinary retention, pruritis, hypotension, bradycardia, motor block, epidural hematoma, epidural abscess, dural puncture, spinal cord injury, meningitis, and respiratory failure.[1,5,7,10,15] It also has many significant contraindications common to trauma patients including hypotension, hypovolemia, heavy sedation, significant head injury, vertebral or spinal cord injury, spinal deformity, coagulopathy, prophylactic or therapeutic anticoagulation, and mechanical ventilation.[7,10,15,16] Finally, recent studies assessing CEA's superiority compared to other regional techniques have been equivocal.[2,7,9,10]

Therefore, it is the goal of these authors to introduce an additional safe option for extended local analgesia in the setting of multiple rib fractures given the inconclusive evidence supporting or refuting the current standard of care. The advent of liposomal bupivacaine makes an extended local intercostal nerve blockade of up to 72 hours a possibility.[13,15,16] With it comes a safety profile that is at least as favorable as the currently available local anesthetic drugs.[11,13,14] Theoretically, the liposomal bupivacaine formulation is designed to reduce the risk of systemic local anesthetic toxicity by providing a lipid bilayer that entraps the bupivacaine. This liposome then acts as a vehicle for delivery of the bupivacaine to the target area, which is hypothesized to limit diffusion away from the site of infiltration.[13] Thus, the utilization of liposomal bupivacaine as the local anesthetic nerve blocking agent is not expected to add any additional risk beyond that of conventional intercostal nerve blocks with bupivacaine HCl.

Nonetheless, the most common adverse events associated with liposomal bupivacaine nerve blockades in previous phase I-III studies include nausea, pyrexia, constipation, vomiting, and pruritis. Other less commonly associated adverse events included hypesthesia, dizziness, bradycardia, and sinus tachycardia. Retrospective pooling of 6 prospective trials that utilized liposomal bupivacaine in peripheral nerve blocks suggested the liposomal formulation has a similar safety and side effect profile to bupivacaine HCl and normal saline.[13]

To our knowledge, the quality and duration of analgesia provided by liposomal bupivacaine has yet to be evaluated in a prospective controlled trial for rib fractures. However, it has been studied as an intercostal nerve blocking agent post-thoracotomy. First, in 2015, Rice et al compared patients receiving liposomal bupivacaine intercostal nerve blockades (LBINB) to case matched CEA controls post-thoracotomy. The authors found no significant difference in postoperative pain scores and complications, but do report significant reduction in the mean length of stay in the LBINB cohort.[18] Similar findings are also reported by Khalil and colleagues post-thoracotomy, with the exceptions of lower postoperative pain scores at day 1 and day 3.

Khalil et al also reports significant reductions in pulmonary complications and length of stay.[15] Limitations of the two previously mentioned studies include their retrospective methodology and potentially under powered patient cohorts.

Extrapolating from this retrospective data, we feel it is appropriate to assess LBINB against CEA prospectively to evaluate its efficacy in providing sustained analgesia during recovery from multiple rib fractures. Our Trauma Service has extensive experience with CEA, and how its many contraindications mentioned above limit our ability to provide safe, quality regional analgesia in a trauma patient. Consequently, we often find ourselves prescribing systemic opioids or applying CINBs with short acting local anesthetics. Both analgesic modalities decline in analgesic efficacy in minutes to hours and must be scheduled or readministered.[12] As a result, many patients with rib fractures endure significant pain and are under treated due to the lack of available evidence based therapies. Therefore, please consider our protocol that follows. It is our presumption based on the evidence above LBINB will providing equally efficacious, sustained analgesia, with a safety profile similar to CINB, and with fewer contraindications than CEA.

OBJECTIVES

The objective of this study is to quantify and draw inferences on the efficacy of a multiple level liposomal bupivacaine intercostal nerve blockade (LBINB) in patients with multiple traumatic rib fractures by comparing it to the current standard of care, continuous epidural analgesia (CEA).

The primary objective is to assess the quality and duration of analgesia provided by LBINB over a 96 hour period by numeric grading pain scale and/or critical-care pain observation tool when compared to CEA.

The secondary objective of this study is to assess and compare the following between the two treatment arms:

- Cumulative breakthrough analgesia in morphine equivalents
- Incentive spirometry measurements
- Reduction in pulmonary complication including atelectasis, pneumonia, respiratory failure, and ventilator days
- Length of stay
- Duration of intensive care unit (ICU) days (if applicable)
- Cost associated with the administration of CEA versus LBINB
- Overall rate of complications associated with CEA versus LBINB

METHODS AND ANALYSIS

The trial will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no

deviation from, or changes to, the protocol will take place without prior approval from the University of Illinois College of Medicine at Peoria IRB 1, Peoria, IL, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

A single center, two arm, parallel group trial will be completed. All patients 18 years of age or older suffering 3 or more rib fractures treated by University of Illinois College of Medicine at Peoria (UICOMP) attending or resident physicians at OSF St. Francis Medical Center (OSFMC) are potentially eligible for enrollment in the trial. However, patients with any of the following will not be eligible since they are contraindications to CEA, LBINB, or both:

1. Intracranial hemorrhage
2. Fever >101 degrees Fahrenheit for ≥ 1 hour(s)
3. Rash at site of catheter insertion or administration of nerve block
4. Hemodynamic instability
5. Spinal cord injury
6. Vertebral fractures
7. Allergy to bupivacaine
8. Systemic therapeutic anticoagulation required for duration of hospital admission[20]
9. Altered mental status without medical decision maker to provide consent
10. Patients without the capacity to consent or the lack of a medical decision maker to consent
11. Patients that are pregnant
12. Legally confined patients.

Additional criteria for exclusion of patients on antithrombotic therapies can be found in the attached supplement developed by the University of Washington based on American Society of Regional Anesthesia and Pain Medicine guidelines for anticoagulation in patients receiving regional anesthesia.[20, 21] These guidelines will not supersede clinical judgement, or the judgement and recommendations of the Anesthesia department at OSF St. Francis Medical Center. Lastly, intubated and mechanically ventilated patients will not be enrolled. However, should a patient require intubation and mechanical ventilation after enrollment, the patient will remain in the trial.

Patients fulfilling the eligibility criteria will be identified by the UICOMP Trauma Surgery staff during the initial trauma evaluation. Patients will be recruited by the senior trauma surgery resident or attending. The trial and interventions will be described in a consistent and unbiased manner. Patients will be given 48 hours to consider their participation to ensure informed consent to participate in the trial. Signed and dated informed consent will be obtained by medically trained personnel. In the event any further information becomes available which may influence the patient's willingness to continue in the trial, the trial team will contact the participant. A participant may refuse enrollment or withdrawal their trial involvement at any time. Prerandomization eligibility checks will be carried out to ensure that a patient fits the

eligibility criteria and is not randomized in error. Inclusion of a patient in the trial will be flagged in their EMR, clinical notes by means of a trial sticker, and a trial flyer on the door to their room.

RANDOMIZATION

The UICOMP Department of Surgery will perform randomization. Randomization will be performed in 10 patient blocks utilizing a 1:1 allocation based on a computer-generated randomization schedule. Once generated, this schedule will be used by the UICOMP Trauma Surgery service and research team to enroll patients. Concealment of allocation will be maintained by sequential sealed envelopes. Upon enrollment in the study, the next envelope in sequence will be opened to reveal which treatment arm the patient is assigned. The rest of the trauma team will be notified, and the appropriate intervention will be initiated.

SAMPLE SIZE

We estimated the sample size based on our primary hypothesis. The primary outcome is numeric grading pain scale. We hypothesize that there is no significant difference between LBINB and CEA patients in terms of the numeric grading pain scale.

If we assume the true difference in means of pain score does not exceed 0.1, with a standard deviation of 1.0, then we need totally 38 subjects (19 per group) with 80% power and 0.05 significance level. In anticipation of a probable 15% drop-in/out and missing data in the two treatment groups, we inflate the sample size by a factor of 1.15. Therefore, the final sample size for this trial would be 44 subjects (22 per group).

If we assume the true difference in means of pain score does not exceed 0.1, with a standard deviation of 2.5, then we need totally 224 subjects (112 per group) with 80% power and 0.05 significance level. In anticipation of a probable 15% drop-in/out and missing data in the two treatment groups, we inflate the sample size by a factor of 1.15. Therefore, the final sample size for this trial is 258 subjects (129 per group).

Considering the potential for a large sample size requirement for rejection of the null hypothesis, it is our intent to enroll a minimum of 44 patients. This will allow us to roughly estimate the true difference in means of pain scores and standard deviation to predict a more accurate sample size requirement, without unnecessary utilization OSF and UICOMP resources.

BLINDING

Owing to the nature of the interventions, the patient and the UICOMP Trauma Surgery faculty will not be blinded once the patient is assigned to their respective treatment arms. This is to ensure the patient is appropriately managed in case of an adverse event or complication. Data collection also will not be blinded since the UICOMP Trauma Surgery team will be responsible for recording data during the patient's treatment. However, the trial statistician will be blinded to the treatment allocations during data analysis.

INTERVENTIONS

Patients will receive one of the following methods of analgesia for their rib fractures:

1. Liposomal bupivacaine intercostal nerve blockade (LBINB)

Under aseptic conditions the insertion sites will be marked 3-4 cm lateral to the midline at the level of each fractured rib, and 1-2 ribs levels above and below if possible. The fingers of the non-dominant palpating hand will straddle the first insertion site at the inferior border of each rib and fix the skin to avoid unwanted skin movement. 3-5 ml of a 1.3% (13.3 mg/mL) of liposomal bupivacaine will be drawn into a syringe with a 1.5-in, 22-gauge needle. The needle will then be advanced at an angle of approximately 20° cephalad to the skin at the marked injection site. Contact with the rib will be made. While maintaining the same angle of insertion, the needle will be walked off the inferior border of the rib and the skin allowed to return to its initial position. The needle will be advanced 3 mm below the inferior margin of the rib, placing the tip in the space containing the neurovascular bundle. Following negative aspiration for blood or air, 3-5 mL of local anesthetic will be infused and the needle withdrawn. This process will be repeated to provide nerve blockade at the remaining marked levels. No more than 266 mg, or 20 ml, of the 1.3% (13.3 mg/mL) liposomal bupivacaine solution will be injected in total per the manufacturer recommended maximum dosage.

2. Continuous analgesia by epidural catheter (CEA)

If the patient is assigned to the CEA group, anesthesia will be consulted. The following is a general description of the procedure required to insert an epidural catheter. Management of CEA will be conducted in accordance with OSF St. Francis Medical Center standards, with oversight provided by the anesthesia department.

If possible, the patient will be in the sitting position. The skin will be prepped with chlorhexidine and sterilely draped. With strict aseptic technique including mask, cap, and gloves, the closest interspace to the rib fractures between T4 -T12 will be identified. 3 mL of lidocaine 1% will be infiltrated with a 25 gauge 1-1/2 inch needle. Next, a 17 gauge Touhy needle will be inserted, and the epidural space identified by loss of resistance technique. A Braun epidural catheter will then be inserted to a depth of 12cm, measured from the skin, into the epidural space.

Next, 3 mL of test solution containing lidocaine 1.5% with epinephrine, 1:200,000 will be injected with continuous EKG and SpO2 monitoring. Upon confirmation of a negative response, the catheter will be secured with a transparent dressing and tape and the returned to a supine position. Delivery of a 0.125% bupivacaine solution will then be continuously infused and titrated based on the patient's clinical status.

An alternative solution or procedure may be used for CEA if indicated based on information gathered during the patient's history and physical. This decision will be made by

the representative from anesthesiology that places the catheter. The variation will be recorded for analysis in the study.

Both study arms will receive a standardized formulary of 325mg acetaminophen PO q6h, 5mg PO TID cyclobenzaprine, and 400mg ibuprofen PO q6h will be scheduled barring any patient specific contraindications. Both arms will also receive systemic NSAID and opioid analgesia for breakthrough pain as needed. The amount and type of breakthrough analgesia provided to the patient will be based on what is safe to prescribe, indicated, and will provide the most pain relief. The amount of systemic analgesia administered will be reviewed in total and recorded in morphine equivalents.

OUTCOME ASSESSMENTS AND TIME POINTS

The primary outcome of interest is the quality of analgesia provided measured by numeric grading pain scale assessment every 24 hours.

The secondary outcomes of interest include:

- Amount of breakthrough analgesia required in morphine equivalents
- The duration of analgesia provided measure by numeric grading pain scale assessment every 24 hours
- Pulmonary function measured by incentive spirometry every 24 hours
- Supplemental oxygen requirements
- SpO_2
- Development of pulmonary complications including:
    a. Atelectasis
    b. Pneumonia
    c. Respiratory failure
- Ventilator days
- Length of stay
- Duration of intensive care unit (ICU) days
- Cost associated with the administration of CEA versus LBINB
- Overall rate of complications associated with CEA versus LBINB

If a patient agrees to enroll in the trial, all primary and secondary outcome measures available from the time of admission will be recorded after obtaining the informed consent.

DATA MANAGEMENT

Information will be obtained via admission history and physical, pre-intervention history and physical immediately after obtaining informed consent, daily examinations during morning rounds every 24 hours, discussions with the nursing staff, review of the electronic medical record per this protocol, and as clinically indicated while the patient is admitted to the hospital.

Relevant patient charts will then be reviewed by the investigative team to collect outcome variables of interest. This information will be entered into a secure spreadsheet for analysis at the end of the enrollment period.

All electronic patient-identifiable information will be held on a secure, password protected database accessible only to essential personnel. Paper forms with patient identifiable information will be held in secure, locked filing cabinets within the Department of Surgery at OSF Saint Francis Hospital in Peoria, IL. Participants will be identified by name and medical record number throughout the data collection process. All personal identifying information will then be stripped from the raw data upon transition to the data analysis phase. No personal identifying information will be published. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained upon completion of the study in accordance with the law and the University of Illinois College of Medicine at Peoria IRB 1, Peoria, IL, or otherwise destroyed to ensure no risk to patient privacy.

STATISTICAL ANALYSIS

The ITT principle will be applied our analysis. We will use different methods to compute the missing data, such as last observation carried forward, mean replacement, and maximum likelihood estimation.

For the primary outcome, we will use two-sample equivalence test for the univariate analysis. We will also use general linear model adjusting for appropriate covariates for multivariate analysis.

For other variables, we will conduct univariate analysis using Pearson's chi-square or Fisher's exact tests on categorical variables, and t test or equivalent non-parametric methods on continuous variables depending on the distributions. In addition, we will use general linear model or generalized linear model for multivariate analysis, adjusting for appropriate covariates.

Since we collect data at different time points, we will use generalized estimating equation(GEE) models to assess the correlated outcome variables when comparing the group differences over time.

The two-tailed p values will be calculated for all tests, and $p< 0.05$ is considered the statistical significant test. SAS 9.4 (SAS Institute Inc., Cary, NC) will be used for all data management and analysis.

TRIAL ORGANIZATION, REGULATION, AND OVERSIGHT

The trial will be coordinated by the Principal Investigator and Director of Trauma/Critical Care, Dr. Chadrick Evans, and the Trial Manager, Dr. Melisa Medina. All issues pertaining to the management of the trial will be continuously monitored by these individuals, including

unanticipated problems in research involving research subjects or others (UPIRSOs) and unanticipated adverse events (AEs).

These trial leaders are also responsible for data safety monitoring. Statistical analysis will be performed every 6 months. The trial leaders will present this analysis, which will include both outcomes and safety data, to the Trauma Morbidity and Mortality Boards conducted by the UICOMP Department of Surgery and the OSF St. Francis Medical Center Drug Analysis Work Group (OSF SFMC DAWG). The statistical model for data analysis developed with the UICOMP Division of Research Services in the section titled "Statistical Analysis" will be applied to the presented data if applicable. Research will be immediately suspended if sufficient data has been collected to determine a clear and significant benefit or risk to the patient from either the CEA or LBINB pain protocols. In the absence of significant data displaying risk/benefit, and mean differences in pain scores and standard deviations outside of the parameters required to accept or reject the null hypothesis based on our power analysis, the trial leaders will request continuation of the study through the Department of Surgery and the OSF SFMC DAWG. Yearly status reports will be submitted to Peoria IRB 1 as required by section 6 of the University of Illinois College of Medicine at Peoria IRB 1, Peoria, IL "Policies and Procedures," or more frequently as determined by Peoria IRB 1.

At no time will participation in this trial compromise the quality of care provided to the patient, elevate the patient to a level of care beyond that required based on the patient's clinical condition, or extend a patient's hospital stay beyond what is clinically required. Patients suffering multiple injuries will be assessed, and their injuries addressed, in the appropriate order based on severity. The enrollment and consent process for this trial will never interfere with this evaluation and management. Also, once enrolled, ALL patients will have the option to receive CEA (the current standard of care) for their rib fractures, barring contraindications, regardless of randomization. Patients will also receive systemic analgesia for severe, breakthrough pain. Participating patients may withdrawal from participation in the study at any time. However, data collected up to the time of their withdrawal will be included in analysis, and the patient will be informed of this during the consent process.

ETHICS AND DISSEMINATION

All UPIRSOs and AEs will be reported in accordance with section 9 of the University of Illinois College of Medicine at Peoria IRB 1, Peoria, IL "Policies and Procedures."

Participants in the study are not covered by indemnity for negligent and non-negligent harm through UICOMP. UICOMP does not have, or provide, insurance to cover for non-negligent harm associated with the protocol. The liability of the manufacturer of medicinal products being administered is strictly limited to those claims arising from faulty manufacturing of the product.

The results of the trial will be disseminated via scholarly article in peer reviewed academic journals, presentation at local, regional, national, and international conference, and on

http://www.ClinicalTrials.gov, as required by U.S. Law. All published results will be stripped of personal identifying information to ensure privacy rights of the participants are fully protected.

FUNDING AND SPONSORSHIP

This study will not be funded.

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