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Intercostal Liposomal Bupivacaine Injection For Rib Fractures; A Prospective Randomized Controlled Trial

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Background: Blunt chest wall injury accounts for 15% of trauma admissions. Previous studies have shown that the number of rib fractures predicts inpatient opioid requirements, raising concerns for pharmacologic consequences including hypotension, delirium, and opioid dependence. We hypothesized that intercostal injection of liposomal bupivacaine would reduce analgesia needs and improve spirometry metrics in trauma patients with rib fractures.

Methods: A prospective, double-blinded, randomized placebo-control study was conducted at a Level 1 trauma center as an FDA investigational new drug study. Enrollment criteria included patients ≥18 years admitted to the ICU with blunt chest wall trauma who could not achieve >50% goal inspiratory capacity. Patients were randomized to liposomal bupivacaine or saline injections in up to 6 intercostal spaces. Primary outcome was to examine pain scores and breakthrough pain medications for 96-hour duration. The secondary endpoint was to evaluate the effects of analgesia on pulmonary physiology.

Results: 100 patients were enrolled, 50 per cohort, with similar demographics (ISS 17.9 bupivacaine 17.6 control) and comorbidities. Enrolled patients had a mean age of 60.5 years and 47% were female. Rib fracture number, distribution, and targets for injection were similar between groups. While both groups displayed a decrease in opioid use over time, there was no change in mean daily pain scores. The bupivacaine group achieved higher incentive spirometry volumes over days 1 and 2 (1095mL, 1063mL bupivacaine vs. 900mL, 866mL control). Hospital and ICU lengths of stay were similar and there were no differences in post-injection pneumonia, use of epidural catheters or adverse events bet ween groups.

Conclusions: While intercostal liposomal bupivacaine injection is a safe method for rib fracture-related analgesia, it was not effective in reducing pain scores, opioid requirements, or hospital length of stay. Bupivacaine injection transiently improved incentive spirometry volumes, but without a reduction in the development of pneumonia.

Clinical Trial Registration: "Intercostal Liposomal Bupivacaine for the Management of Blunt Chest Wall Trauma" NCT02749968.

Level of Evidence: Level 2 ; Therapeutic/Care Management

Key words: liposomal bupivacaine, rib fracture, opioid, intercostal injection

Background

Blunt chest wall trauma remains the second most common injury observed in non-intentional injury-related death in the United States and accounts for 15% of trauma-related emergency department visits worldwide [1-4]. 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, 5]. One of the most prominent contributing factors to blunt chest wall trauma morbidity is pain from rib or sternal fractures [6-9]. The standard of care for analgesia in trauma patients with rib fractures is the use of multimodal pharmacotherapy including opioids administered via continuous infusion, intermittent intravenous (IV) push, patient-controlled IV analgesia, oral dosing, or epidural infusion [10, 11]. Although opioid agents can provide effective analgesia, they have a recognized adverse effect profile including hypotension, bradycardia, central nervous system depression, and respiratory depression [12]. Patients may not achieve adequate pain relief when doses are limited because of the risk of these effects [13]. Consequences of uncontrolled pain from rib fractures in trauma patients include exhaustion due to lack of sleep, delirium, agitation, stress response, post-traumatic stress disorder, pneumonia, and death [12, 14]. Multimodal therapeutic strategies are used in an effort to limit the need for opioids in this population, and newer, non-opioid analgesic agents may be incorporated into these strategies to achieve optimal analgesia [15].

Liposomal bupivacaine injectable suspension (Exparel®, Pacira BioSciences, Inc., Parsippany, NJ) is a novel formulation of the amide-type anesthetic approved by the Food and Drug Administration (FDA) for local infiltration into surgical sites to produce postsurgical analgesia [15]. This formulation allows for the prolonged release of bupivacaine from

multivesicular liposomes, providing anesthetic effects that can be observed for up to 96 hours [15]. Side effects of liposomal bupivacaine infiltrated locally are generally mild and this injectable suspension has been shown to improve analgesia scores and decrease opioid use when infiltrated locally at a variety of surgical and procedure sites [15-23]. By comparison, conventional bupivacaine has a duration of activity of 8 to 24 hours when administered as a single nerve block [24, 25].

To date, there has been one retrospective study evaluating the utility of liposomal bupivacaine in the treatment of rib fractures, which demonstrated fewer intubations and shorter hospital and intensive care unit (ICU) lengths of stays (LOS) compared to epidural analgesia catheters [26]. Several other case reports and preliminary nerve block studies have suggested benefit of intercostal bupivacaine use for chest wall related pain [25, 27, 28]. However, the utility of liposomal bupivacaine has not undergone comprehensive analysis in the setting of blunt chest wall trauma. In this study, we hypothesized that intercostal injection of liposomal bupivacaine would reduce analgesia needs and improve spirometry metrics in trauma patients with rib fractures.

Methods

Study Enrollment

This was an investigator-initiated, single-center, prospective, double-blinded, randomized placebo-controlled trial, approved by the University of Cincinnati Institutional Review Board (2017-0052) and registered with clinicaltrials.gov (NCT02749968). Adult polytrauma patients ≥18 years of age admitted to the University of Cincinnati Medical Center, an urban American

College of Surgeons-verified Level 1 trauma center, were screened for enrollment (**Figure 1**). Based on institutional ICU admission criteria for chest wall injury, the study inclusion criteria were age ≥18 years, 2 or more rib fractures or sternal fracture, inability to achieve >50% of predicted inspiratory capacity on incentive spirometry, and anticipated hospital LOS at least 72 hours. Those meeting inclusion criteria were approached for informed consent, which was obtained prior to enrollment and any study procedures being initiated. Exclusion criteria included age <18 years, allergy to bupivacaine, respiratory failure requiring intubation within 24 hours prior to enrollment, known or suspected atrioventricular nodal blockage requiring pacemaker insertion, hemodynamic instability on vasopressors or mean arterial pressure <55 mmHg, active myocardial ischemia, or non-ST elevation myocardial infarction, weight <50kg or >150kg, pregnant, prisoner, severe traumatic brain injury, Glasgow Coma Score <8, >20 rib fractures, or being a candidate for surgical rib fixation. Patient demographics and traumatic injury and treatment characteristics were obtained, including abbreviated injury score (AIS), hospital LOS, ICU LOS, placement of epidural analgesic catheter, adverse events (AE) related to hospitalization and procedure related AE, and hospital diagnoses.

Following informed consent, patients underwent 1:1 randomization in blocks of two to ensure equal allocation to each intervention group – either liposomal bupivacaine intercostal nerve block or 0.9% sodium chloride peri-intercostal subcutaneous injection. Randomization was performed by study personnel and was blinded to the patient and the trauma and surgical critical care provider teams. Liposomal bupivacaine for intercostal nerve blockade was chosen over paravertebral block, as the intent of the study was to identify a therapeutic strategy that can be employed based on standard training for emergency medicine or general surgery practitioners

who are familiar with intercostal blocks for placement of thoracostomy tubes. Additionally, intercostal and paravertebral blocks carry similar risks of pneumothorax or intercostal neurovascular bundle injury[29]. Liposomal bupivacaine for intercostal injection was granted status as an investigational new drug (IND) by the FDA (IND 130714) for this study, but was not permitted to be diluted to increase the injectable volume beyond the stock 20 mL in this IND status. Due to this limitation, study personnel were only permitted to inject up to 6 intercostal spaces. In addition, the FDA deemed placebo injection with 0.9% sodium chloride to be an unnecessary increased risk, so only peri-intercostal subcutaneous injection was permitted.

Injection procedure

Patients were placed on continuous monitoring of heart rate, electrocardiogram (EKG), and pulse oximetry in the surgical intensive care unit (SICU). Blood pressure and respiratory rate were measured every 5 to 10 minutes during the procedure and every 15 minutes for the first hour after the procedure. All patients undergoing injection remained on heart rate, EKG, and pulse oximetry monitoring by telemetry for 96 hours following injection. Supplemental oxygen was provided to maintain a peripheral oxygen saturation of 90% or greater.

Injections were performed by trained trauma / acute care surgeons who were aware of the randomization given the difference in injection depth and technique but were not directly involved in the patient's daily care or decision-making about analgesia needs. There were a total of 6 trauma/ acute care surgeons who performed the procedures. Training prior to initiating the study included familiarization with the standardized procedure as described below. Patients were also monitored by SICU bedside nurses before, during, and after the injection procedure.

Standard inpatient cardiac arrest carts were immediately available before, during, and after the block procedure.

A 20 mL vial, within its original manufacturer provided packaging, was obtained from Investigational Drug Service Pharmacy of the University of Cincinnati Medical Center, containing either liposomal bupivacaine (266 mg in 20 mL) or 0.9% sodium chloride. Patients were positioned either sitting up or in logroll/decubitus position as tolerated and permitted by spine clearance status. Rib fractures were noted from previously obtained CT scans of the chest from initial trauma evaluation. The thoracic posterolateral area was prepped and draped in sterile fashion. After aspiration to prevent intravascular injection, 3 mL of liposomal bupivacaine was injected with a 25-G needle just below each affected rib by the intercostal neurovascular bundle in a posterior but not paravertebral position; or 1 mL 0.9% saline as placebo control was injected with a 25-G needle in the subcutaneous space just superficial to each affected rib to minimize risk of placebo injection complications. Up to 6 intercostal spaces were injected in total, allowing for use of up to 18 of the 20 mL in the supplied vial. Ultrasound was used at the administering providers discretion to localize the intended intercostal space, and was only used in 5 patients.

Primary Endpoint-assessment of inpatient pain and MME use

The primary endpoint was oral morphine milligram equivalents (MME) per day over the first 96 hours following intercostal injection and self-reported pain assessment. The standard of care analgesia regimen for the trauma service was provided to all patients enrolled in the study, regardless study randomization. This regimen could have included acetaminophen, oral or enteral; non-steroidal anti-inflammatory drugs including 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; neuromodulating adjuncts, including gabapentin or pregabalin; epidural analgesia catheter placement; or IV continuous infusions of fentanyl, hydromorphone, or morphine. All opioid dosing was converted to MME for comparison purposes[30]. Time to first breakthrough opioid dose after injection was also recorded and compared. A planned subgroup analysis comparing MME over time based on number of rib fractures was performed.

We also evaluated daily self-reported pain scores between groups the first 96 hours following intercostal injection. Pain scores were measured using the verbal numeric rating scale (NRS), a 0-10 ordinal scale (e.g., 0 = "no pain"; 10 = "worst pain imaginable") [31]. Pain assessments occurred per standard of care for the appropriate setting (e.g., SICU, trauma ward) for the first 96 hours.

Secondary Endpoint-respiratory physiology

Incentive spirometry volumes were assessed and recorded by respiratory therapists, with adjunct inspiratory assistance (e.g., EzPAP®) applied per our institutional volume expansion protocol. Additional safety measures were employed in order to detect potential respiratory depression or distress during study period. While in the SICU, all study subjects were additionally monitored with a non-invasive thoracic impedance respiratory monitor (ExSpiron™, Respiratory Motion, Inc., Watertown, MA) to determine respiratory rate, tidal volume, minute ventilation and breathing pattern for up to 96 hours.

Statistics

All analyses were conducted by a dedicated biostatistician using SAS 9.4 (SAS Institute, Cary, NC). Assuming a 96-hour requirement of 250-mg MME (approximately 12.5-mg IV hydromorphone), we anticipated a 20% reduction to 200-mg oral morphine equivalents (approximately 10 mg IV hydromorphone) resulting in an expected difference in means of 50 MME 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 was 200 patients. Interim analyses were performed after 50 patients further providing evidence to support the 200 patient goal for enrollment. Due to changes in analgesia protocols away from epidural catheters to erector spinae plane catheters and a change in exclusion criteria to include those who were candidates for surgical stabilization of rib fractures, as well as the COVID-19 pandemic, enrollment was stopped at 100 patients (**Figure 1**). Based upon the final study population of 100 patients, a 45% change in baseline MME would provide a statistical power of 86%. The initial data was reviewed for safety per FDA IND guidelines after 50 patients were enrolled.

Data was reported as mean ± standard deviation (SD) as well as median with interquartile range (IQR) for each outcome to account for several outliers. Group comparisons between the bupivacaine and placebo groups (drug treatment effect, Rx) were assessed using two-sample t-tests or Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data, as appropriate. Mixed effects models utilizing a log-normal distribution were used to evaluate the longitudinal data. To determine whether the potential impact of analgesia drugs, pain scores and respiratory outcomes differs over time or treatment, a time analysis

evaluating treatment effect alone and treatment effect over time was performed. Where the interaction was non-significant, it was removed from the model and the average values over time were compared by treatment instead. When the interaction was significant, post hoc mean comparisons were conducted using the Scheffe adjustment for multiple comparisons. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) with two-sided p-values <0.05 considered statistically significant.

Results

Demographics and baseline injury characteristics of the enrolled patients

Patients were well balanced between groups for demographics, injury, and comorbidities. Of all the study participant 47% were female; 100% were non-Hispanic / non-Latino. Participants sustained on average 7 ± 4 rib fractures with 4 ± 3 being right sided and 4 ± 3 left sided fractures. Study participants had 5 ± 4 co-morbid pre-injury medical diagnoses per person (**Table 1**). Randomization provided well balanced groups as noted by adjusted AIS greater than or equal to 3 and injury severity score (ISS) being similar between groups (**Table 1**).

Ribs Injected by Treatment Group

There were no differences in the number or distribution of targeted intercostal injections between groups, as seen in **Table 1** and **Supplemental Digital Content 1**, http://links.lww.com/TA/C199. The average time from hospital admission to intercostal injection with either liposomal bupivacaine or normal saline was 1.10 ± 0.59 days.

Comparison of Analgesia Use

The mean analgesia use in MME is graphed; however, several outliers skewed the means, as shown in **Figures 2,3**. Therefore, median MME was included for a more accurate reflection of the group analgesia use. Overall, there was a significant decrease in MME administration over time (p=0.02) (**Figure 3**). The trajectory of MME administration was similar regardless of treatment group (p-value for interaction=0.57), and MME values over time were also similar by treatment group (**Figure 3).**

A subgroup analysis of MME use was performed based upon the number of rib fractures sustained; ≤6 rib fractures (n=46), 7-12 rib fractures (n=43), or ≥13 rib fractures (n=11). Patients with ≤6 rib fractures displayed no significant difference in MME use between treatment groups, although there was a significant decrease in MME use amongst both study groups over time (p<0.001) **(Figure 2).** Patients with 7-12 rib fractures or ≥13 fractures did not demonstrate any significant differences in MME use between treatment groups or difference in MME use over time (**Figure 2**).

The trajectories of acetaminophen, gabapentin, lidocaine patches, tramadol, hydrocodone, methadone, IV morphine, and IV fentanyl use were similar regardless of treatment group (p-value for interactions>0.05), and mean values over time were also similar by treatment group except for acetaminophen (Rx p=0.02), and were without a difference in the trajectory over time (Rx*time p=0.11) (**Figure 3**). In addition, there were no differences from time of injection to time of first breakthrough analgesic agent received (187 ± 266 min bupivacaine vs 262 ± 318 min placebo).

The trajectory of oxycodone use was significantly different by treatment group (p-value for interaction=0.02). Post hoc analysis showed the liposomal bupivacaine group had a trend toward higher oxycodone use at day 2 (p=0.07) and day 4 (p=0.09) but not a statistically significant difference (**Figure 3**). The trajectory of hydromorphone use was also significantly different by treatment group (p-value for interaction=0.009) (**Figure 3**). Post hoc analysis showed that the liposomal bupivacaine group had higher hydromorphone use at day 1 (p=0.04) and day 4 (p=0.02) (**Figure 3**).

Pain Scoring

There were no differences between bupivacaine and control groups for pain experienced, based on mean verbal NRS levels assessed daily before and after the injections, as demonstrated in **Table 2**.

Secondary Endpoints and Adverse Events

Randomization resulted in no significant physiologic differences between bupivacaine and control groups, except for a higher respiratory rate in the bupivacaine group (19 ± 5 bpm bupivacaine vs. 17 ± 4 bpm placebo, p=0.02) (**Tables 1 and 3**). After treatment, pulmonary physiology and performance was notable for higher incentive spirometry volumes achieved and respiratory rate over the first two days in the bupivacaine group, without a difference in trajectory over time for either parameter (**Table 3**).

There were no differences between groups in hospital LOS (6.7 ± 4.5 days bupivacaine,

7.5 ± 6.7 days placebo) or ICU LOS (4 ± 4.3 days bupivacaine, 3.9 ± 2.7 days placebo). There was no significant difference in epidural catheter placement (2 [4.%] bupivacaine, 1 [2%] placebo) or rate of pneumonia (3 [6%] bupivacaine, 1 [2%] control group).

The rates of overall and severe adverse events were not significantly different between groups, with a low rate of severe AEs in both groups. In addition, most AEs were determined to be unrelated or unlikely related to the drug or injection procedure (**Supplemental Digital Content 2**, http://links.lww.com/TA/C200).

Discussion

This prospective randomized double blinded placebo-controlled trial evaluated the impact of liposomal bupivacaine injection in traumatic rib fracture patients. This study demonstrated that percutaneous liposomal bupivacaine injection is a safe method of analgesia; however, is not effective to reduce pain compared to placebo injection. Patients in the liposomal bupivacaine group experienced comparable pain scores to the placebo group and maintained a similar overall clinical course with no significant changes noted in rates of pneumonia, hospital LOS, and ICU LOS between groups.

One of the observed benefits of liposomal bupivacaine injection was the improvement in early incentive spirometry values on post injection days 1 and 2. Subjects injected with liposomal bupivacaine were noted to have significantly increased incentive spirometry volumes compared to placebo groups, along with a significantly increased respiratory rate that was no longer observed by day 3. These pulmonary function assessments were made by both the

standard incentive spirometry portable device and the non-invasive thoracic impedance respiratory monitor, further confirming early pulmonary improvement in the liposomal bupivacaine group. Loss of this difference over time may reflect the waning pharmacologic effect of the injected drug by 48 hours and suggests that ongoing multimodal analgesia remains important in sustaining pulmonary function in this patient population.

Our results stand in contrast to some of the previous studies in the literature on liposomal bupivacaine injection. A study by Sheets et al. found that patients who received intercostal nerve block with liposomal bupivacaine required fewer in-hospital intubations, and experienced shorter ICU and hospital LOS compared with epidural analgesia [(26)]. While the authors suggested that liposomal bupivacaine injection was superior to epidural catheter placement, the study was retrospective. Additionally, physicians made independent decisions regarding placement of liposomal bupivacaine intercostal nerve block versus epidural catheter placement at the bedside, which may have contributed to selection bias on analgesic medication choices made. By contrast, in our study, both patient and physician were blinded to treatment regimen further minimizing bias in the results. Further, a recent study by Leasia et al. provided more evidence that single injection of liposomal bupivacaine provides comparable analgesia to a continuous peripheral nerve plane analgesia catheter in patients undergoing rib fracture surgical stabilization with no significant reductions in opiate use(32).

This study demonstrated that liposomal bupivacaine intercostal injection was a safe alternative for analgesic rib fracture management. This finding has been consistently verified in the literature. Rice et al. published a study comparing patients who underwent lung resection

using intraoperative liposomal bupivacaine injection versus thoracic epidural analgesia [33]. This study revealed that there were no significant changes in perioperative complications, postoperative pain scores, or opioid use between liposomal bupivacaine injection and thoracic epidural catheter placement. However, these authors did conclude that liposomal bupivacaine injection was a safe and possible alternative for lung resection patients[33]. Mehran et al. performed a similar study in lung resection patients and compared intraoperative liposomal bupivacaine to epidural catheter placement. They found that liposomal bupivacaine was a safe adjunct and was non-inferior to epidural catheter placement with regards to peri- and post-operative complications including wound infection and pneumonia[34]. These results are different than what we observed in the trauma population. One possible explanation is that liposomal bupivacaine is more effective in managing pain from a controlled incision and rib resection but may be less effective in addressing pain from uncontrolled and persistently mobile traumatic rib fractures.

Due to these mixed and varying results for optimal pain management strategies of traumatic rib fractures and noted improvements in patient morbidity and mortality with operative fixation, the Eastern Association for the Surgery of Trauma guidelines have begun to shift recommendations towards operative fixation[35]. A review of operative rib fracture fixation by Girsowicz et al. revealed that surgical stabilization of patients with multiple non-flail and painful rib fractures experienced improvements in early reduction in pain and disability, and shorter duration of time before restarting normal daily activity[36]. Similarly, a study by Nirula et al. revealed that in comparing operative and non-operative rib fracture stabilization, there was a trend toward fewer ventilator days in the operative fixation group compared to controls[37]. One

further study by Leinicke et al. also demonstrated the benefit of operative fixation compared to controls with reductions noted in ventilator days, inpatient mortality, pneumonia, and rates of tracheostomy[38]. As data continues to emerge around operative fixation for rib fracture management, the use of simultaneous liposomal bupivacaine injection intra-operatively is another avenue for analgesic management that could be pursued for future use.

This study has some notable limitations. First, we were unable to recruit as many patients as we had intended, as noted in the power analysis. The COVID-19 pandemic limited our capability to enroll patients, as the risk of researcher exposure and patient participation was deemed to be higher than the benefit of further study recruitment. Second, as an FDA approved IND study the protocol was modified so that the liposomal bupivacaine was unable to be diluted limiting the total injectable volume to 6 intercostal spaces. The average number of rib fractures within our study population was 7, potentially limiting the ability to achieve the intended regional analgesic effect. Previous publications in abdominal and thoracic surgery have provided evidence that diluting liposomal bupivacaine is a safe and effective means for increasing the area of injectable analgesia which may have further benefited patients included in our study [39, 40]. Third, a change was made in the study protocol so that patients who were candidates for operative rib fracture fixation were excluded from the study. As such, the enrollment, which was intended for 200 patients, was reduced to 100 patients putting the study at risk for a type 2 error although unlikely after further analysis of data showing many similarities between the two groups in the outcomes. Fourth, the age of our study population was noted to be significantly higher (60.5 years) compared to the mean age of our blunt chest trauma population (53 years) and ICU admitted blunt chest trauma population (55 years). The increase in age of our recruited study population

may have impacted our ability to observe further pulmonary and analgesic benefits of liposomal bupivacaine use. Lastly, one of the most common reasons for patient refusal to enroll in the study was attributed to the injection requirement. This last point leads to a further limitation of liposomal bupivacaine in general as a widespread analgesic agent, as patients may prefer to have a non-procedural analgesic modality rather than additional perceived pain with intercostal injections.

In conclusion, intercostal injection with liposomal bupivacaine is a safe method for analgesia in traumatic rib fracture patients; however, its use did not provide adequate analgesia when used independently. As the prevalence of traumatic rib fractures continues to increase there is a need for consensus on analgesic recommendations to improve patient outcomes, as well as the role that operative fixation may play. Further evaluation into the defined use of liposomal bupivacaine as a multimodal agent intra-operatively to reduce acute inpatient and subsequent outpatient opioid use may be needed.

The stated authors have no conflicts of interest to disclose.

The views published in this article are those of the authors and do not necessarily reflect the official policy or position of the United States Air Force, the Department of Defense or the U.S. Government.

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Figure Legend

Figure 1: CONSORT diagram of study participants in clinical trial "Intercostal Liposomal Bupivacaine for the Management of Blunt Chest Wall Trauma, NCT02749968

Figure 2: Comparison of MME use based upon number of rib fractures A. ≤6 or B. 7-12 in liposomal bupivacaine group versus control group, * indicates $p<0.05$. *Base (Baseline time point) 1,2,3,4 indicate days post study injection with either liposomal bupivacaine or placebo.*

Figure 3: Opiate Analgesic use Over Time Between Treatment and Control Groups. A MME use overtime. B Oxycodone use. C. Acetaminophen use. D. Hydromorphone use

*indicates $p<0.05$. *Base (Baseline time point) 1,2,3,4 indicate days post study injection with either liposomal bupivacaine or placebo.*

Figure Legend Supplemental Digital Content

Supplemental Digital Content 1: Location of Injection and Proportion of Ribs Injected. A. Bupivacaine group B. Control group. L=left sided rib fractures, R=right sided rib fractures

Supplemental Digital Content 2: Adverse Events/Protocol Deviations (N(%), Mean ± SD (Median)

Figure 1: CONSORT diagram of study participants in clinical trial "Intercostal Liposomal Bupivacaine for the Management of Blunt Chest Wall Trauma, NCT02749968

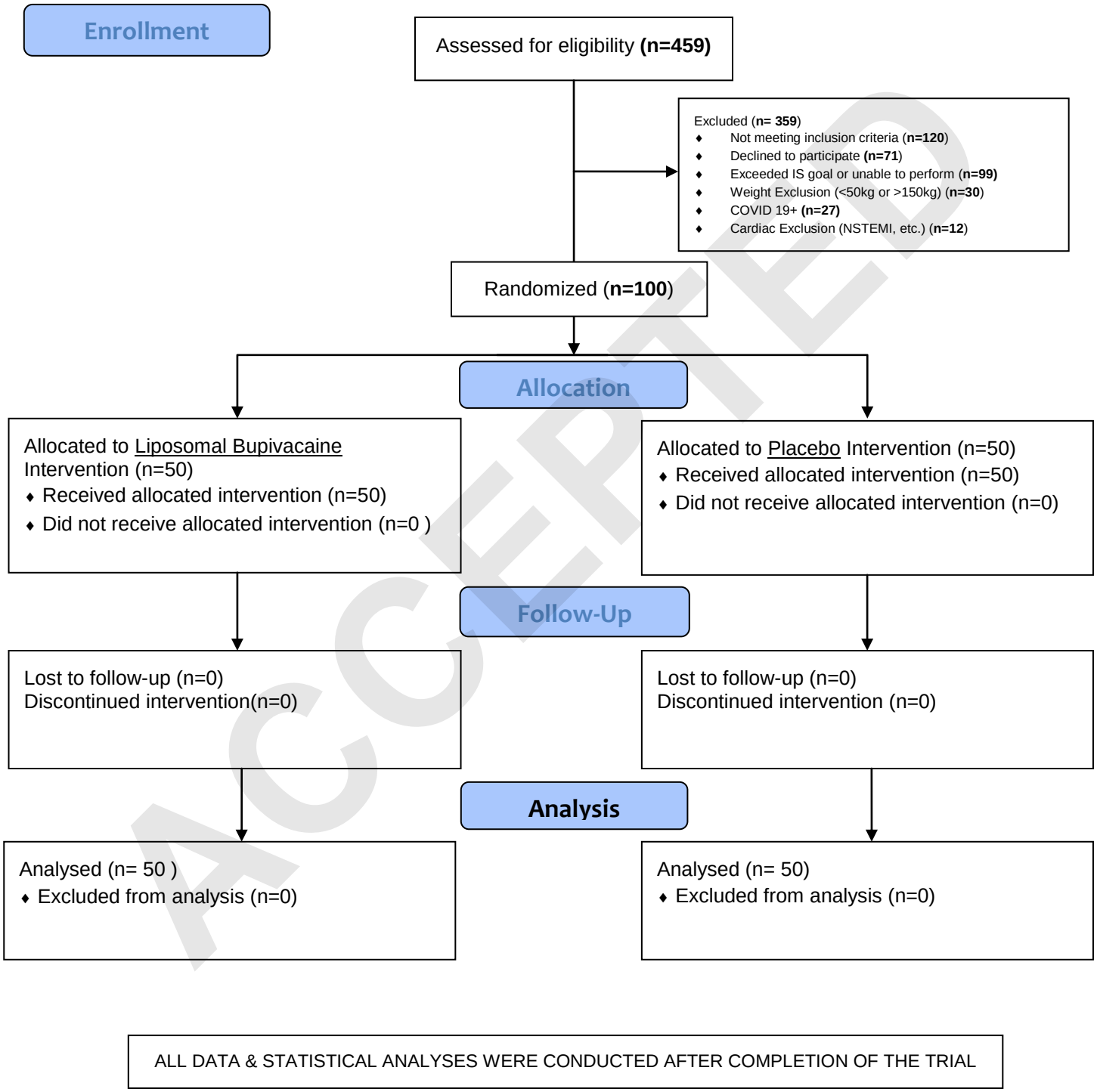


Table 1: Subject and Admission Characteristics (N (%), Mean ± SD (Median:IQR)

	All (n=100)	Bupivacaine (n=50)	Control (n=50)	p-value	SMD
Demographics					
Female	47 (47%)	25 (50%)	22 (44%)	0.69	
Non-Hispanic	100 (100%)	50 (100%)	50 (100%)	1.0	
Age (years)	60 ± 18 (62:24)	60 ± 18 (62:29)	61 ± 18 (64:21)	0.75	0.05
Medical History (sum per pt)	5 ± 4 (4)	6 ± 5 (4.5)	5 ± 4 (4)	0.79	0.22
Body Mass Index (BMI) (kg/m^2)	28.4 ± 6.7 (26.9:10)	29.29 ± 7.1 (27.1:11)	27.54 ± 6.3 (26.9:7)	0.26	0.27
Baseline Clinical Parameters					
Incentive Spirometry Volume	17.76 ± 7.39 (17:6)	17.88 ± 8.14 (17:6)	17.64 ± 6.64 (17:6)	0.85	0.04
Systolic BP (mmHg)	125.85 ± 19.98 (123:29)	127.5 ± 18.5 (128:28)	124.2 ± 21.41 (120:32)	0.31	0.16
Diastolic BP (mmHg)	73.16 ± 12.46 (72:17)	74.3 ± 12.88 (72.5:19)	72.02 ± 12.04 (72:17)	0.51	0.18
Mean Arterial Pressure (mmHg)	86.11 ± 12.18 (87:18.5)	86.66 ± 11.78 (88:18)	85.56 ± 12.66 (86:21)	0.80	0.09
Heart Rate (bpm)	83.5 ± 17.42 (82:21.5)	86.16 ± 17.09 (85.5:18)	80.84 ± 17.51 (77:25)	0.11	0.31
PO_2 (mmHg)	95.74 ± 2.83 (96:4)	95.74 ± 2.66 (96:4)	95.74 ± 3.01 (96:4)	0.88	0
O_2 (L/min)	3.4 ± 4.09 (2:4)	3.27 ± 2.98 (2:4)	3.52 ± 4.88 (2:4)	0.32	0.06
FIO_2	31.16 ± 14.4 (27:4.5)	32.38 ± 15.39 (27:3)	30:.1 ± 13.72 (27:6)	0.24	0.15
Respiratory Rate	18. ± 5 (17:6)	19 ± 5 (18:5)	17 ± 4 (17:6)	**0.02**	0.44
Tidal Volume (ExSpiron)	512.76 ± 229.5 (473:212)	505.3 ± 231.3 (448.5:189)	520 ± 230 (508:236)	0.52	0.06
Minute Ventilation (ExSpiron)	8.71 ± 3.14 (8.6)	9.03 ± 2.76 (8.75:3.3)	8.38 ± 3.47 (8.4:4)	0.17	0.19
Spirometry Volume (ExSpiron)	747.5 ± 290.31 (750:500)	758.16 ± 291.03 (750:375)	737 ± 292.2 (700:500)	0.35	0.07
Traumatic Injury Characteristics					
ISS (Injury Severity Score)	17.76 ± 7.39 (17:9)	17.88 ± 8.14 (17:9) n=50	17.64 ± 6.64 (17:9)	0.85	0.02
AIS (> or =3)				0.16	
AIS Head n=26	15 (15%)	10 (20%)	5 (10%)		
AIS Face n=10	0	0	0		
AIS Neck n=4	1 (1%)	1 (2%)	0	1.0	

AIS Chest n=99	97 (97%)	48 (96%)	49 (98%)	1.0	
AIS Abdomen n=26	14 (14%)	8 (16%)	6 (12%)	0.56	
AIS Spine n=41	7 (7%)	2 (4%)	5 (10%)	0.24	
AIS Upper Extremity n=41	1 (1%)	0	1 (2%)	1.0	
AIS Lower Extremity n=31	9 (9%)	3 (6%)	6 (12%)	0.49	
Number Rib Fx n=100	7.28 ± 3.59 (7:4)	6.82 ± 3.0 (7:4)	7.74 ± 4.03 (7:4)	0.41	0.24
Number Right Sided Rib Fx n=100	4 ± 3 (4:6)	3 ± 3 (4:6)	4 ± 3 (3.5:7)	0.82	0.33
Number Left Sided Rib Fx n=100	4 ± 3 (3:7)	3 ± 3 (3:7)	4 ± 3 (4:7)	0.23	0.33

SMD (Standardized Mean Difference)

PO_2 (partial pressure of oxygen)

O_2 (oxygen)

FiO_2 (fraction of inspired oxygen)

AIS (abbreviated injury score)

Fx (fracture)

Table 2: Pain Scores vs Drug Group: Mean ± SD (Median:IQR)

	All (n=100)	Bupivacaine (n=50)	Control (n=50)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
24 Hour				
Base	6.38 ± 2.82	6.32 ± 2.73 n=50	6.44 ± 2.93 n=50 (7:4)	Rx p=0.73
1	(7:3)	(7:3)	5.84 ± 3.07 n=50 (7:5)	Interaction
2	5.57 ± 2.94	5.31 ± 2.8 n=50	5.58 ± 2.54 n=44 (6:3)	p=0.54
3	(6:5)	(6:4)	5.73 ± 3.06 n=40 (6:3)	Time
4	5.45 ± 2.88	5.28 ± 3.19 n=47	5 ± 3.44 n=30 (6:8)	P=0.35
	(6:5)	(6:5)		
	5.51 ± 2.94	5.32 ± 2.84 n=41		
	(6:4)	(6:4)		
	5.61 ± 3.17	6.45 ± 2.59 n=24		
	(7:4)	(7:4)		

Rx (interaction based upon treatment)

Table 3: Pulmonary Function Baseline and Post Treatment: Mean ± SD (Median:IQR)

	All (n=100)	Bupivacaine (n=50)	Control (n=50)	p-value
O_2 (L/min)				
Baseline	3.4 ± 4.09 (2:1)	3.26 ± 2.98 (2:1)	3.52 ± 4.88 (2:2)	Rx
1	4.49 ± 9.22 (2:2)	5.78 ± 12.19 (2:2)	3.5 ± 6.11 (2:2)	p=0.24
2	5.15 ± 10.26 (2:2)	4.7 ± 10.74 (2:1.5)	5.48 ± 10.08 (2:3)	Interacti
3	4.91 ± 6.79 (2.25:3)	7 ± 10.29 (2:2)	3.62 ± 2.84 (2.5:3)	on
				p=0.25
FiO_2				
Baseline	31.16 ± 14.43	32.38 ± 15.39 (27:3)	30.1 ± 13.73 (27:6)	Rx
1	(27:4.5)	34 ± 12.36 (27:9)	31.56 ± 13.84	p=0.62
2	32.63 ± 13.15 (27:6)	30.09 ± 6.68 (27:3)	(27:7.5)	Interacti
3	30.36 ± 6.83 (27:6)	32.33 ± 7.25 (30:13)	30.57 ± 7.06 (27:7.5)	on
	33.69 ± 13.72		34.67 ± 17.03 (29:9)	p=0.68
	(29.5:9)			
Respiratory				
Rate	18.01 ± 4.7 (17:6)	19.17 ± 4.72 (18.5:8)	16.87 ± 4.44 (17:6)	**Rx**
Baseline	18.02 ± 3.99 (17:6)	18.58 ± 3.58 (20:5)	17.45 ± 4.34 (17:7)	**p=0.02**
1	18.55 ± 5.03 (19:7)	18.9 ± 4.55 (20:5)	18.17 ± 5.54 (18:9)	Interacti
2	18.95 ± 5.71 (18:6.5)	19.24 ± 4.82 (18:6)	18.68 ± 6.5 (17:7)	on
3				p=0.61
Tidal Volume				
(ExSpiron)	512.76 ± 229.48	505.3 ± 231.3	520.01 ± 230	Rx
Baseline	(473:212)	(448:189)	(508:236)	p=0.57
1	468.07 ± 187.13	466.04 ± 169.2	470.15 ± 205.66	Interacti
2	(428:219)	(432:195)	(420:254)	on
3	473.39 ± 163.41	458.76 ± 145.49	489.15 ± 181.35	p=0.92
	(458:198)	(450:145)	(485:235)	
	526.47 ± 205.69	532.41 ± 229.07	520.90 ± 184.85	
	(493:254.5)	(488:222)	(498:264)	
Minute				
Ventilation				
(ExSpiron)	8.81 ± 3.14 (8.6:3.8)	9.03 ± 2.76 (8.7:3.2)	8.39 ± 3.47 (8.4:4)	Rx
Baseline	8.05 ± 2.91 (7.5:3.1)	8.52 ± 3.26 (8.1:3.2)	7.58 ± 2.43 (7.1:3.1)	p=0.17
1	8.57 ± 3.18 (8.3:4.1)	8.37 ± 2.57 (8.6:3.9)	8.79 ± 3.75 (8:5.4)	Interacti
2	9.63 ± 3.51 (9.6:4.7)	10.01 ± 3.73 (9.5:4.8)	9.27 ± 3.22 (9.74.5:)	on
3				p=0.48
Spirometry				
Volume				
(ExSpiron)	747.47 ± 290.31	992.29 ±	737 ± 292.17	**Rx**

Baseline	(750:500)	442.1(750:375)	(700:500)	**p=0.03**
1	995.68 ± 439.97	1095.29 ± 464.58	900.32 ± 396.85	Interacti
2	(1000:500)	(1000:500)	(1000:600)	on
3	965.8 ± 456.03	1063.07 ± 538.85	866.28 ± 329.41	p=0.13
	(950:500)	(975:650)	(750:525)	
	1020.2 ± 422.5	992.29 ± 442.15	1047.4 ± 406.5	
	(1000:500)	(1000:475)	(1050:625)	

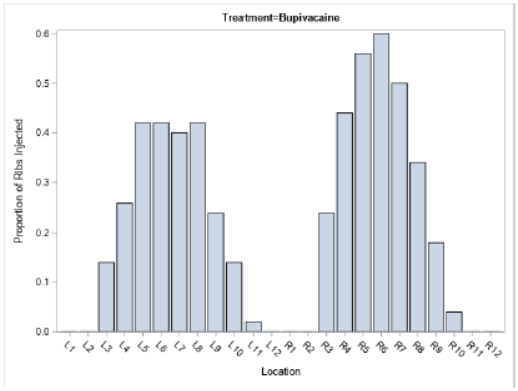
O_2 (oxygen)

FiO_2 (fraction of inspired oxygen)

Rx (interaction based upon treatment)

Supplemental Digital Content 1

A



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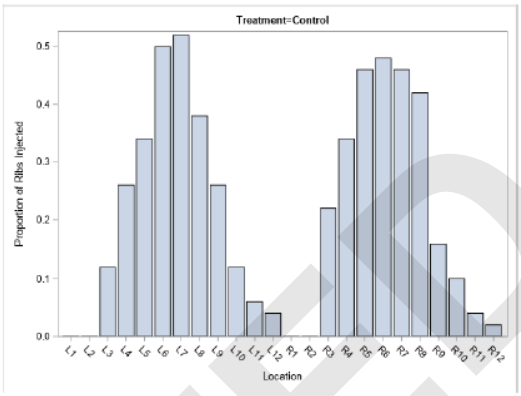

Supplemental Digital Content 2: Adverse Events/Protocol Deviations (N(%), Mean ± SD (Median)

	All (n=100)	Bupivacaine (n=50)	Control (n=50)	p-value
Adverse Events (sum per pt)	0.50 ± 0.50 (0.50)	0.54 ± 0.50 (1)	0.46 ± 0.50 (0)	0.43
AE Severity				0.48
Mild	62 (68%)	28 (62%)	34 (74%)	
Moderate	19 (21%)	11 (25%)	8 (17%)	
Severe	10 (11%)	6 (13%)	4 (9%)	
AE Related to Drug				0.57
Not	88 (97%)	44 (98%)	44 (96%)	
Unlikely	3 (3%)	1 (2%)	2 (4%)	
AE Related to Severity				0.67
Possibly related	5 (6%)	3 (7%)	2 (4%)	
Unlikely related	15 (16%)	6 (13%)	9 (20%)	
Not related	71 (78%)	36 (80%)	35 (76%)	
AE change				
No Change	91 (100%)	45 (100%)	45 (100%)	
AE outcome				0.16
Recovered/Resolved	74 (81%)	34 (76%)	40 (87%)	
Recovering/Resolving	17 (19%)	11 (24%)	6 (13%)	
AE Ongoing				
Yes	27 (30%)	18 (40%)	9 (20%)	**0.03**
No	64 (70%)	27 (60%)	37 (80%)	
Protocol Deviations (sum per pt)	0.87 ± 1.05 (1)	0.82 ± 1.06 (1)	0.92 ± 1.05 (1)	0.56

AE (adverse events)

SD (standard deviation)

Visual Abstract