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 I trauma center as a Food and Drug Administration investigational new drug study. Enrollment criteria included patients 18 years or older admitted to the intensive care unit with blunt chest wall trauma who could not achieve greater than 50% goal inspiratory capacity. Patients were randomized to liposomal bupivacaine or saline injections in up to six 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: One hundred patients were enrolled, 50 per cohort, with similar demographics (Injury Severity Score, 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 (1095 mL, 1063 mL bupivacaine vs. 900 mL, 866 mL control). Hospital and intensive care unit lengths of stay were similar and there were no differences in postinjection pneumonia, use of epidural catheters or adverse events bet ween groups.

CONCLUSION: 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. (*J Trauma Acute Care Surg.* 2022;92: 266–276. Copyright © 2021 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/care management, Level II.

KEY WORDS: Liposomal bupivacaine; rib fracture; opioid; intercostal injection.

Blunt chest wall trauma remains the second most common injury observed in nonintentional 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.f[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, posttraumatic 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, nonopioid 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 hours 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 with 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.

PATIENTS AND 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 or older admitted to the University of Cincinnati Medical Center, an urban American College of Surgeons–verified Level I trauma center, were screened for

Submitted: July 30, 2021, Revised: October 29, 2021, Accepted: November 1, 2021, Published online: November 15, 2021.

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This study was presented at the 80th Annual Meeting of AAST and Clinical Congress of Acute Care Surgery, September 28 to October 2, 2021 in Atlanta, GA.

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DOI: 10.1097/TA.0000000000003462

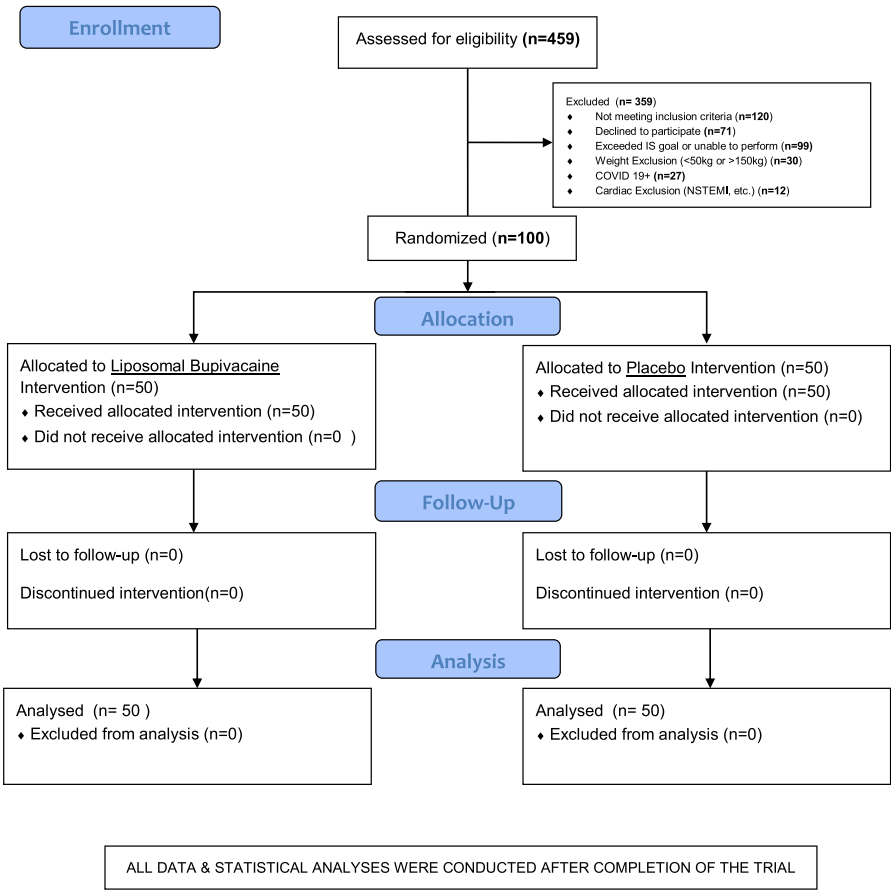

Figure 1. CONSORT diagram of study participants in clinical trial Intercostal Liposomal Bupivacaine for the Management of Blunt Chest Wall Trauma, NCT02749968.

enrollment (Fig. 1). Based on institutional ICU admission criteria for chest wall injury, the study inclusion criteria were 18 years or older, two or more rib fractures or sternal fracture, inability to achieve greater than 50% of predicted inspiratory capacity on incentive spirometry, and anticipated hospital LOS at least 72 hours. Those meeting the inclusion criteria were approached for informed consent, which was obtained prior to enrollment and any study procedures being initiated. Exclusion criteria included younger than 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 less than 55 mm Hg, active myocardial ischemia, or non-ST elevation myocardial infarction, weight less than 50 kg or greater than 150 kg, pregnant, prisoner, severe traumatic brain injury, Glasgow Coma Scale score less than 8, greater than 20 rib fractures, or being a candidate for surgical rib fixation. Patient demographics and traumatic injury and treatment characteristics were obtained, including Abbreviated Injury Scale (AIS), hospital LOS, ICU LOS, placement of epidural analgesic catheter, adverse events (AEs) 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. In addition, 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. Because of this limitation, study personnel were only permitted to inject up to six 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, and pulse oximetry in the surgical ICU (SICU). Blood pressure and respiratory rate were measured every 5 minutes

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, electrocardiogram, 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 six 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 six intercostal spaces were injected in total, allowing for use of up to 18 of the 20 mL in the supplied vial. Ultrasound was used

TABLE 1. Subject and Admission Characteristics (n (%), Mean ± SD (Median: IQR)

	All (N = 100)	Bupivacaine (n = 50)	Control (n = 50)	*p*	SMD
Demographics					
Female	47 (47%)	25 (50%)	22 (44%)	0.69	
Non-Hispanic	100 (100%)	50 (100%)	50 (100%)	1.0	
Age (y)	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
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 (mm Hg)	125.85 ± 19.98 (123:29)	127.5 ± 18.5 (128:28)	124.2 ± 21.41 (120:32)	0.31	0.16
Diastolic BP (mm Hg)	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 (mm Hg)	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 (mm Hg)	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	17.76 ± 7.39 (17:9)	17.88 ± 8.14 (17:9) n = 50	17.64 ± 6.64 (17:9)	0.85	
AIS (> or = 3)					
AIS head, n = 26	15 (15%)	10 (20%)	5 (10%)	0.16	0.02
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

Data in boldface indicate statistical significance.

IQR, interquartile range; ISS, Injury Severity Score; SMD, standardized mean difference; SD, standard deviation; Po_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; O_2, oxygen; Fx, fracture.

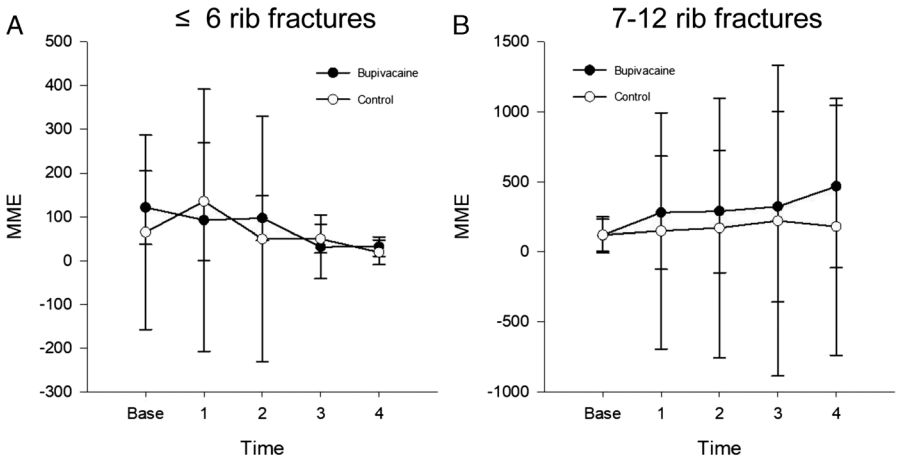

Figure 2. Comparison of MME use based upon number of rib fractures (*A*) ≤6 or (*B*) 7–12 in liposomal bupivacaine group versus control group, *$p < 0.05$. Base (baseline time point) 1, 2, 3, 4 indicate days poststudy injection with either liposomal bupivacaine or placebo.

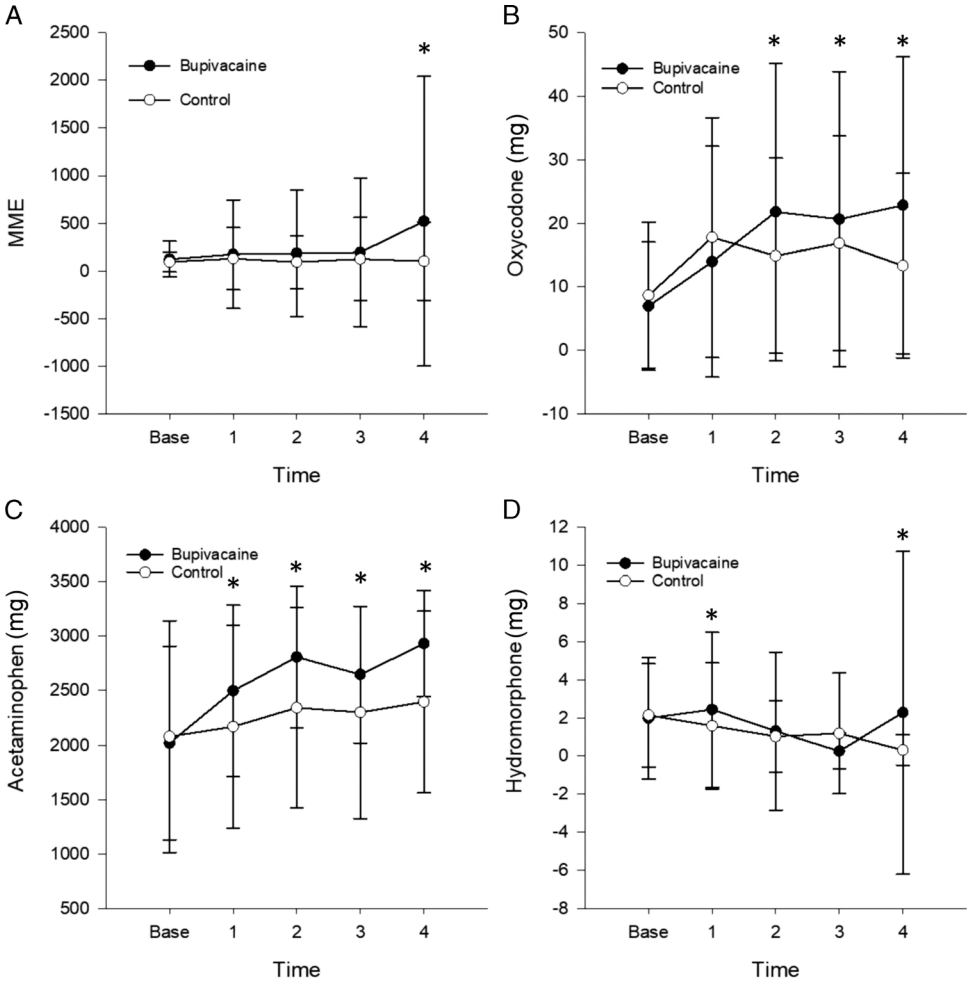

Figure 3. Opiate analgesic use over time between treatment and control groups. (*A*) MME use overtime. (*B*) Oxycodone use. (*C*) Acetaminophen use. (*D*) Hydromorphone use *$p < 0.05$. Base (baseline time point) 1, 2, 3, 4 indicate days poststudy injection with either liposomal bupivacaine or placebo.

at the administering provider's discretion to localize the intended intercostal space, and was only used in five patients.

Primary Endpoint-Assessment of Inpatient Pain and Morphine Milligram Equivalent Use

The primary endpoint was oral morphine milligram equivalents (MMEs) 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; nonsteroidal 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, a 0 to 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 to detect potential respiratory depression or distress during study period. While in the SICU, all study subjects were additionally monitored with a noninvasive 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 MMEs 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. Because of the 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 (Fig. 1). Based on the final study population of 100 patients, a 45% change in baseline MME would provide a statistical power of 86%. The initial data were reviewed for safety per FDA IND guidelines after 50 patients were enrolled.

Data were reported as mean ± standard deviation, as well as median with interquartile range 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 χ^2 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 nonsignificant, 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 less than 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 participants, 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 comorbid preinjury 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 being similar between groups (Table 1).

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

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

TABLE 3. Pulmonary Function Baseline and Posttreatment: Mean ± SD (Median:IQR)

	All (N = 100)	Bupivacaine (n = 50)	Control (n = 50)	*p*
O_2 (L/min)				
Baseline	3.4 ± 4.09 (2:1)	3.26 ± 2.98 (2:1)	3.52 ± 4.88 (2:2)	Rx, $p = 0.24$
1	4.49 ± 9.22 (2:2)	5.78 ± 12.19 (2:2)	3.5 ± 6.11 (2:2)	Interaction
2	5.15 ± 10.26 (2:2)	4.7 ± 10.74 (2:1.5)	5.48 ± 10.08 (2:3)	$p = 0.25$
3	4.91 ± 6.79 (2.25:3)	7 ± 10.29 (2:2)	3.62 ± 2.84 (2.5:3)	
FIO_2				
Baseline	31.16 ± 14.43 (27:4.5)	32.38 ± 15.39 (27:3)	30.1 ± 13.73 (27:6)	Rx, $p = 0.62$
1	32.63 ± 13.15 (27:6)	34 ± 12.36 (27:9)	31.56 ± 13.84 (27:7.5)	Interaction
2	30.36 ± 6.83 (27:6)	30.09 ± 6.68 (27:3)	30.57 ± 7.06 (27:7.5)	$p = 0.68$
3	33.69 ± 13.72 (29.5:9)	32.33 ± 7.25 (30:13)	34.67 ± 17.03 (29:9)	
Respiratory rate				
Baseline	18.01 ± 4.7 (17:6)	19.17 ± 4.72 (18.5:8)	16.87 ± 4.44 (17:6)	Rx, $p = 0.02$
1	18.02 ± 3.99 (17:6)	18.58 ± 3.58 (20:5)	17.45 ± 4.34 (17:7)	Interaction
2	18.55 ± 5.03 (19:7)	18.9 ± 4.55 (20:5)	18.17 ± 5.54 (18:9)	$p = 0.61$
3	18.95 ± 5.71 (18:6.5)	19.24 ± 4.82 (18:6)	18.68 ± 6.5 (17:7)	
Tidal volume (ExSpiron)				
Baseline	512.76 ± 229.48 (473:212)	505.3 ± 231.3 (448:189)	520.01 ± 230 (508:236)	Rx, $p = 0.57$
1	468.07 ± 187.13 (428:219)	466.04 ± 169.2 (432:195)	470.15 ± 205.66 (420:254)	Interaction
2	473.39 ± 163.41 (458:198)	458.76 ± 145.49 (450:145)	489.15 ± 181.35 (485:235)	$p = 0.92$
3	526.47 ± 205.69 (493:254.5)	532.41 ± 229.07 (488:222)	520.90 ± 184.85 (498:264)	
Minute ventilation (ExSpiron)				
Baseline	8.81 ± 3.14 (8.6:3.8)	9.03 ± 2.76 (8.7:3.2)	8.39 ± 3.47 (8.4:4)	Rx, $p = 0.17$
1	8.05 ± 2.91 (7.5:3.1)	8.52 ± 3.26 (8.1:3.2)	7.58 ± 2.43 (7.1:3.1)	Interaction
2	8.57 ± 3.18 (8.3:4.1)	8.37 ± 2.57 (8.6:3.9)	8.79 ± 3.75 (8:5.4)	$p = 0.48$
3	9.63 ± 3.51 (9.6:4.7)	10.01 ± 3.73 (9.5:4.8)	9.27 ± 3.22 (9.74.5:)	
Spirometry volume (ExSpiron)				
Baseline	747.47 ± 290.31 (750:500)	992.29 ± 442.1(750:375)	737 ± 292.17 (700:500)	Rx, $p = 0.03$
1	995.68 ± 439.97 (1000:500)	1095.29 ± 464.58 (1000:500)	900.32 ± 396.85 (1000:600)	Interaction
2	965.8 ± 456.03 (950:500)	1063.07 ± 538.85 (975:650)	866.28 ± 329.41 (750:525)	$p = 0.13$
3	1020.2 ± 422.5 (1000:500)	992.29 ± 442.15 (1000:475)	1047.4 ± 406.5 (1050:625)	

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 ($p = 0.02$) (Fig. 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 (Fig. 3**).**

A subgroup analysis of MME use was performed based upon the number of rib fractures sustained; six rib fractures or less (n = 46), 7 to 12 rib fractures (n = 43), or 13 rib fractures or more (n = 11). Patients with 6 rib fractures or less displayed no significant difference in MME use between treatment groups, although there was a significant decrease in MME use among both study groups over time ($p < 0.001$) (Fig. 2). Patients with 7 to 12 rib fractures or 13 fractures or more did not demonstrate any significant differences in MME use between treatment groups or difference in MME use over time (Fig. 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, $p = 0.11$) (Fig. 3). In addition, there were no differences from time of injection to time of first breakthrough analgesic agent received (187 ± 266 minutes bupivacaine vs. 262 ± 318 minutes placebo).

The trajectory of oxycodone use was significantly different by treatment group (p value for interaction = 0.02). Post hoc analysis showed that 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 (Fig. 3). The trajectory of hydromorphone use was also significantly

different by treatment group (p value for interaction = 0.009) (Fig. 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) (Fig. 3).

Pain Scoring

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

Secondary Endpoints and AEs

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 2 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 AEs 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 with 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 postinjection Days 1 and 2. Subjects injected with liposomal bupivacaine were noted to have significantly increased incentive spirometry volumes compared with 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 noninvasive 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.[26] 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. While the authors suggested that liposomal bupivacaine injection was superior to epidural catheter placement, the study was retrospective. In addition, 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.[32] 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.

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.[33] published a study comparing patients who underwent lung resection using intraoperative liposomal bupivacaine injection versus thoracic epidural analgesia. 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.[34] 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 noninferior to epidural catheter placement with regards to perioperative and postoperative complications including wound infection and pneumonia. 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 toward operative fixation.[35] A review of operative rib fracture fixation by Girsowicz et al.[36] revealed that surgical stabilization of patients with multiple nonflail and painful rib fractures experienced improvements in early reduction in pain and disability, and shorter duration of time before restarting normal daily activity. Similarly, a study by Nirula et al. revealed that in comparing operative and nonoperative rib fracture stabilization, there was a trend toward fewer ventilator days in the operative fixation group compared with controls.[37] One further study by Leinicke et al.[38] also demonstrated the benefit of operative fixation compared with controls with reductions noted in ventilator days, inpatient mortality, pneumonia, and rates of tracheostomy. As data continue to emerge around operative fixation for

rib fracture management, the use of simultaneous liposomal bupivacaine injection intraoperatively 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 six 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 with 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 nonprocedural 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 intraoperatively to reduce acute inpatient and subsequent outpatient opioid use may be needed.

AUTHORSHIP

T.E.W. participated in the literature search, data analysis/interpretation, writing. K.E.S. participated in the literature search, writing. A.T.M. participated in the study design, data collection. K.P.A. participated in the study design, data collection. A.S. participated in the data analysis. M.E.D. participated in the study design and protocol development, grant submission, article revision. R.S. participated in the data collection. C.A.D. participated in the study design and protocol development, grant submission, IND procurement, literature search, critical revision. M.D.G. study design and protocol development, grant submission, IND procurement, critical revision, writing, data collection, data analysis

DISCLOSURE

The authors declare no conflicts of interest.

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.
Clinical Trial Registration: "Intercostal Liposomal Bupivacaine for the Management of Blunt ChestWallTrauma"NCT02749968, https://clinicaltrials.gov/ct2/show/NCT02749968?term=NCT02749968&draw=2&rank=1
This work was funded by grant number FA8650-16-2-6G04 from the United States Air Force School of Aerospace Medicine, Aeromedical Research Department. The United States Air Force Research Laboratory, 711th Human Performance Wing (Aeromedical Research Department, 2510 Fifth St. Building 840, Wright-Patterson Air Force Base, OH 45433) was the awarding and administering acquisition office.

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DISCUSSION

ANDREW KERWIN, M.D. (Memphis, Tennessee): Good afternoon, Drs. West and Michetti, members and guests. I'd like to start by thanking the AAST for the privilege of discussing this paper.

I'd also like to congratulate Dr. Wallen and her colleagues on an excellent presentation and a well-designed study and a concise and a well-written manuscript. I appreciate them sending it to me well in advance of the meeting so I could review it.

So I want to commend Dr. Wallen and colleagues for designing a single-center, prospective, double-blind, randomized, placebo-controlled trial to determine the utility of liposomal bupivacaine in managing pain following blunt chest trauma.

This is an important study for us because this is a common problem that we all have to deal with and we're all searching for the best way to provide analgesia for our patients while limiting opioid use.

I was very excited to read this study in hopes that they had come up with the analgesic solution for these challenging patients. However, it appears the liposomal bupivacaine injections did not reduce the morphine milligram equivalent for patients in the intervention group.

In fact, the intervention group had a trend towards higher oxycodone use – I think this was in the manuscript – and a statistically-significant increase in hydromorphone use at Day 1 and Day 4. So I want to make sure I have that correct and so if I got that correct, then why do you think this occurred?

You described the technique for the injection very nicely in the paper and mentioned there was training for those performing the intervention. I was wondering if you could comment on the additional training required for those performing the injections.

Also, you mentioned the injections were performed by trained trauma and acute care surgeons. Can you tell me, is this attendings only or are the residents and fellows also performing these injections?

It appears the interventions took place while the patients were in the SICU. I was wondering if you had any data regarding the time after the first injections were done in regards to their time of admission.

In other words, the patient received their injection of the liposomal bupivacaine shortly after the initial trauma evaluation and stabilization? Did you control the pain better and reduce opioid use more than if the injection occurred hours later when the patient was settled into the surgical ICU?

You demonstrated there was an overall decrease in opioid use in both groups during this study. Can you comment on the reason for this overall decrease in the opioid use?

Is it just the fractures got better and the patients felt better? And, additionally, was there a standardized approach to the use of multi-modality analgesic regimens during the study?

Finally, while you demonstrated safety of liposomal bupivacaine use, you did not identify any outcome benefits other than improved incentive spirometry values on Day 1 and Day 2. Do you think this justifies its use for rib fracture patients?

I think you pointed out in one of your slides it's about 100 times difference in the cost between the liposomal bupivacaine and the marking. So could you address that cost there and tell me how you think that should factor into the management of these patients?

Are you still using this in your practice? And then if so how would we approach our pharmacy about having this medication available for us to use in patients, given the discrepancy in cost?

Thank you and I, again, congratulate you on a very well done study.

THOMAS J. SCHROEPPEL., M.D. (Colorado Springs, Colorado): Perhaps I misunderstood the semantics of the study design but you said it was a placebo-controlled, double-blinded, randomized study.

You said the FDA would not allow you to inject saline in the same space that you injected the bupivacaine so the injection technique would be different, therefore, the people injecting it would have to be un-blinded. Could you please clarify for me.

DEREK BENHAM, M.D. (San Diego, California): Hi, there. I'm Derek Benham from San Diego, California. Congratulations on a good study. I did have a question for you.

Given the Pacira recent lawsuit against our colleagues in anesthesia who have found similar findings, did that affect your study at all or affect your reporting of your findings at all?

Thank you.

DENNIS ASHLEY, M.D. (Macon, Georgia): Just a follow-up to the location question of injection, if it truly was a subcutaneous injection, do you have any data that shows that that works just as well as getting it in the muscle and near the nerve?

So just maybe some clarification on exactly where that injection was because if it truly was just in the subcutaneous tissue then can you be sure that you really didn't give analgesia to that nerve or maybe over time it infiltrates that nerve. I just don't know.

Thank you. Very nice study.

TAYLOR E. WALLEN, M.D. (Cincinnati, Ohio): Okay. Thank you for all of the questions. First, I'll address Dr. Kerwin's questions.

There was an increase in oxycodone use in both groups over time and we attributed this just simply to the fact that the patients had substantial pain from their rib fractures. Unfortunately, a majority of the patients did have greater than seven rib fractures and we were only able to inject up to six of those rib fractures so it makes sense that they had increased oral medication usage over time. And, actually, there was a decrease in hydromorphone use over time in both of the cohorts.

For your second question, all procedures were performed by acute care surgery care attendings except for two performed by a surgical critical care fellow. No residents were involved in the injections.

Our average time from admission to injection was 1.1 days. We do utilize a standardized protocol for all of our blunt chest wall trauma patients with multi-modal analgesia agents, including tramadol, acetaminophen, hydromorphone and oxycodone, which we wean over time, converting more to oral medications throughout the hospital stay.

In addressing the question of how do we optimize the use of this very expensive medication in all patients, it must be considered that this is a heterogeneous population with variations in rib fractures so it may not be optimal for all patients. However, we do think there is potential utility and there has been a previous study in operative rib fractures where Exparel was beneficial. So there may be better utility for Exparel in operative rib fracture candidates, where you are stabilizing the rib because the drug is a significant cost.

And then for Dr. Schroeppel, all of the physicians who performed the injections were obviously un-blinded, however, they were not participating in the care of the patients that they injected. They were acute care surgery attendings but they were not directly involved in the care of those patients.

Finally, the Exparel injection was peri-intercostal and the placebo drug was subcutaneous so the ACS attending at the time was just given a plain vial but was told either to inject it subcutaneously or peri-intercostal.

To Dr. Benham, the current lawsuit with Pacira actually started about a year ago and it did not impact any of the methods or results in our study.

And then to Dr. Ashley, as mentioned the Exparel injections were peri-intercostal, not subcutaneous. The subcutaneous injection was just for our placebo medication.

Thank you.