Original Article

Local Infiltration of Liposomal Bupivacaine in Isolated Traumatic Rib Fractures

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Abstract

Introduction: Adequate pain control is essential in the management of traumatic rib fractures. Local infiltration of liposomal bupivacaine (LB) to provide intercostal nerve block has been added to the multimodal pain control regimens. We explored the effectiveness of LB infiltration around the site of rib fracture on pain score and total opioid use.

Methods: Patients with isolated rib fractures receiving additional infiltration of LB at the fracture site were compared to patients receiving only conservative treatment. A linear mixed model was performed to evaluate the impact of LB on pain score and total opioid use [morphine milligram equivalent per day (MME)].

Results: Patients in the LB group experienced slightly, but insignificantly, greater pain scores. The adjusted mean MME was significantly higher compared to the control (44.6 vs 24.4, p= 0.01) and increased over time (Δ=5.7 and 6.6, p= 0.03 respectively at ~48h and ~96h, respectively).

Conclusion: No significant reductions in pain score and opioid requirement were achieved by additional local infiltration of LB in patients with isolated traumatic rib fractures.

Keywords: Liposomal bupivacaine, intercostal nerve block, rib fracture, pain score, total opioid dose

Background

Rib fractures are the common traumatic thoracic injuries associated with increased morbidity and mortality which is directly related to the number of fractured ribs and associated pain.[1] While patients with multiple fractured ribs (≥ 3 rib fractures) are expected to have concomitant lung injury, even isolated fractures can cause prolonged pain, leading to complications.[2] The associated pain limits the patient's ability to breathe deeply and to cough, restricting tidal lung volume and preventing the clearance of airway secretions, leading to atelectasis and pneumonia.[3] Therefore, early intervention with adequate pain management is the cornerstone of rib fracture management. Most rib fractures are treated conservatively without surgery, with adequate pain control,

physiotherapy, and respiratory assistance.[2,3] Different analgesic modalities and interventions are used in practice.

Multimodal analgesia- combining different classes of drugs, remains the standard for effective pain control.[4] Use of NSAIDs, acetaminophen, muscle relaxants, and low-dose narcotics have demonstrated improved outcomes in pain control.[5] Regional intercostal, paravertebral blocks, along with epidural analgesia, have shown benefit. Current studies have demonstrated bupivacaine, a widely used local anesthetic, inhibits NMDA pain receptors, thereby preventing pain sensitization.[6] Bupivacaine is a local anesthetic drug with a very short duration of action. Using DepoFoam extended drug delivery technology, the active drug bupivacaine is packaged in multivesicular liposomes (liposomal bupivacaine, [LB]). After infiltration, the lipid membranes are slowly absorbed, providing prolonged release and duration of action of bupivacaine.[6] Studies have shown the efficacy of LB in a variety of surgical procedures. However, only a few studies have investigated the use of LB injection as infiltration for nerve block in the control of rib fracture pain.

Objective

This study evaluated the effect of local LB administration in controlling pain in patients with isolated rib fractures treated non-surgically. In particular, we investigated whether LB provides better pain control and decreases the need for opioid analgesics.

Methods

Study type:

This was a retrospective study performed on patients admitted to a Level II Trauma Center in Lubbock, Texas, who were diagnosed with isolated rib fractures between January 1, 2016, and December 31, 2020. All work was conducted in compliance with Institutional Review Board Committee requirements.

Study Population:

The Trauma Registry was used to identify patients aged 18-89 years with a diagnosis of isolated rib fracture. Patients requiring surgery or presenting with complications such as hemothorax, pneumothorax, or massive pleural effusion were excluded. Additionally, patients who were intubated, pregnant, or incarcerated were excluded.

Data Collection:

Data were extracted from the electronic medical records of eligible patients, including demographic variables (age, sex, race, smoking history), rib fracture variables (mechanism of injury, laterality, number of ribs fractured), treatment variables, and in-hospital outcome variables. X-ray and CT scan reports were used to identify the number of rib fractures. The development of in-hospital post-fracture complications like pneumonia, adult respiratory distress syndrome, pleural effusion, atelectasis, and pneumothorax were retrieved from patient chart documentation and imaging reports.

Outcome Measures:

The primary outcomes of interest were pain score over time and MME/day over time.

1. Pain

The self-reported pain scores assessed using a numerical 11-point scale, ranging from 0-10, with higher scores meaning greater pain, were retrieved from the nursing assessment chart. The assessment record

was performed at discrete and irregular time intervals. However, the scores were retrieved close to the time point specified. The initial pain score retrieved was taken close to 24 hours post-admission, while subsequent scores were taken at 24-hour intervals at ~48, ~72, ~96, and ~120 hours.

2. Pain medications

Pain was controlled using a multiple pain control strategy using oral or injectable opioids, non-opioids, and gabapentin analgesics. The type, amount, and route of administration of opioid medication were extracted from the chart at the same time intervals as the pain score. The daily total opioid dose was calculated from all the opioid-containing analgesics, converted to a standard morphine milligram equivalent (MME) calculator- MDCalc.

For fentanyl, the calculation of MME was adjusted according to the route of administration. When delivered by continuous IV drip or a patch, the recommended conversion factor of 2.4 was used. For example, when 100µg/hour fentanyl was delivered, the calculated MME is 100µg (dose/hour) *24 (hours) *2.4 (conversion factor) = 240mg/day MME. When delivered by IV bolus or nasal spray at 0.1-0.2mg, 10µg fentanyl IV is equivalent to 1mg IV morphine.

The timing and dose of LB were collected from patients who received infiltration of LB at the fracture site. LB was administered by infiltration around the site of fracture under the guidance of ultrasound or computed tomography (CT) (Figure 1).

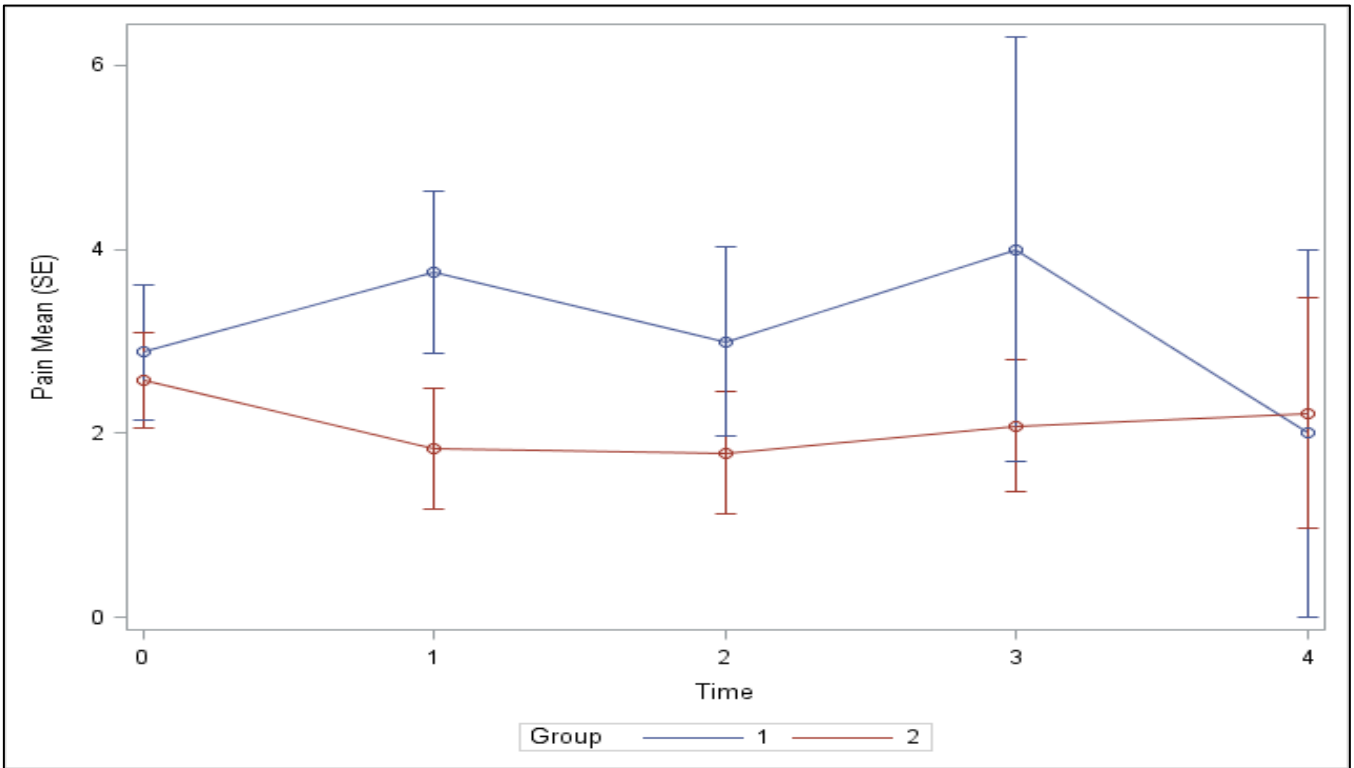

Figure 1. Comparison of mean Pain Score in LB (Group-1) vs conventional treatment (Group-2) over time. Time points 0, 1, 2, 3 & 4 indicate the days from admission in hours (~24h, ~48h, ~72h, ~96h, ~120h)

	Pain Score	
Time	Group 1	Group 2
24h	2.8 (3.1)	2.6 (3.2)
48h	3.7 (3.2)	1.9 (3.2)
72h	3.0 (2.5)	1.8 (2.9)
96h	4.0 (4.0)	2.1 (2.5)
120h	2.0 (3.5)	2.2 (3.8)

Statistical Analysis

Data were collected by retrospective chart review for patients who received LB + conventional treatment (Group_1) and a control group of patients who received only conventional treatment (Group_2). The differences in baseline demographics and characteristics were described using mean ± standard deviation or median with interquartile range for continuous variables and frequency count (%) for categorical variables. The associations of categorical variables between the groups were analyzed with Pearson's Chi-Square or Fisher Exact test. Wilcoxon rank-sum tests were used for continuous variables.

A linear mixed model was used to evaluate the impact of LB on pain score and MME over time while accounting for random effects. The random intercept (Subject) describes the pain score and MME/day for each patient and accounts for subject-specific variation. Age, sex, and treatment group were included in the model as fixed effects.

The change in population mean was examined using the plots of the individual profiles against time. All analyses were conducted using R (R Core Team, 2021; RStudio, version 4.1.2) and SAS.

Results

A total of 78 patients were identified with isolated rib fractures, of whom 20 received additional LB injection (Group_1) compared to 58 who received conventional treatment only (Group_2). The majority of patients (77%) were white males who sustained fractures mostly due to falls (72%) and road traffic accidents (23%). Most (92%) had fewer than six rib fractures. There was no significant difference in age, body mass index (BMI), smoking status, number, and laterality of rib fractures between the groups (Tables 1 and 2).

Table 1. Demographic Characteristics of Rib Fracture Patients

	Group 1	**Group 2**	**p value**
	Received LB (n=20)	**Not received LB (n=58)**	
Age (years)	68.6 ± 16.5	66.6 ± 19.1	0.86[+]
Sex			0.47[*]
Male	11 (55%)	39 (67%)	
Female	9 (45%)	19 (33%)	
Race			0.68[**]
White	15 (75%)	45 (78%)	
African	0	2 (3%)	
Hispanic	3 (15%)	4 (7%)	
Other	2 (10%)	7 (12%)	
Ethnicity			0.65[**]
Non-Hispanic or Latino	14	43	
Hispanic or Latino	5	14	
Declined to answer	1	1	
BMI (kg/m^2)	29.1 ± 5.12	26.7 ± 6.32	0.06[+]
Smoking			0.68[**]
Active Smoker	5 (25%)	8 (14%)	
Past Smoker	4 (20%)	14 (24%)	
Non Smoker	10 (50%)	31 (53%)	
Unknown	1 (5%)	5 (9%)	
[+] *Wilcoxson rank-sum Test* [*] *Chi square Test* [**] *Fisher Exact*			

Table 2. Rib Fracture Characteristics

	Group 1	Group 2	p value
	Received LB (n=20)	**Not received LB (n=58)**	
Mechanism of fracture			0.25**
Fall	12(60%)	44(76%)	
RTA	6(30%)	12(21%)	
Blunt trauma	2(10%)	2(3%)	
Number of fractures			
<2	8 (40%)	28 (48%)	
3-6	11 (55%)	25 (43%)	
>7	1 (5%)	5 (9%)	
Laterality of fracture			0.19**
Right	8 (40%)	35 (60%)	
Left	11 (55%)	22 (38%)	
Bilateral	1 (5%)	1 (2%)	
** *Fisher Exact*			

Out of 58 in the control group, seven had an initial X-ray finding of- atelectasis (5) and pleural effusion (2) at presentation, of whom only 3 developed persistent atelectasis and/or effusion complications. Similarly, of 20 in the LB group, eight had initial X-ray findings of atelectasis (4), effusion (3), and both atelectasis and effusion (1), of whom two developed complications of pneumonia, and one had increased pleural effusion and atelectasis.

None of the patients in either group required admission for ventilation support. There was no significant difference between the groups in length of hospital stay (3.4 ± 2.3 vs 3.15 ± 2.5, p=0.58) (Table 3).

Table 3. Hospital Outcomes of Rib Fracture Patients

	Group 1	Group 2	p value
	Received LB (n=20)	**Not received LB (n=58)**	
LOHS (days)	3.4 ± 2.3	3.15 ± 2.5	0.58+
Discharge			
Home	17	49	0.84**
Rehabilitation	3	7	
Nursing home	0	2	
+ *Wilcoxson rank-sum Test* ** *Fisher Exact*			

Almost all patients received opioid analgesics, 19/20 (95%) in the LB group compared with 52/58 (90%) in the conventional treatment group. One patient in the LB group, with one rib fracture, received LB only and left the hospital. Out of six patients who did not receive opioid analgesics in the conventional group, 2 left the hospital the same day, 3 received acetaminophen, and 1 received acetaminophen and ketorolac. The most commonly prescribed non-opioid drugs were acetaminophen (APAP), ketorolac, ibuprofen, celecoxib, naproxen, and lidocaine. Opioid prescriptions, both oral or parenteral medications calculated in morphine milliequivalent units (MME) were morphine, hydromorphone, hydrocodone, oxycodone, tramadol, fentanyl, codeine, and methadone. Two patients in the conventional treatment group received additional gabapentin compared to the LB group, in which three patients received gabapentin and four patients received pregabalin.

In the majority of patients, a single shot of LB was administered. The mean time to administer LB was 11.9 (±7.7) hours. One patient received LB on day 4, and another

patient received two doses on days 2 and 3. Most patients were discharged home. There were no deaths reported in either group. The adjusted means for pain score and MME over time were obtained using linear mixed models with random intercept. The within-subject covariance structure was modeled as instructed. The interaction of group and time was removed from both models due to insignificance. The final model included age, gender, and BMI to adjust for differences in demographic profile between the two comparison groups.

The pain scores did not change over time. Patients in the LB group, in general, appeared to experience slightly greater pain than those in the control group (Figure 2). However, the difference was not statistically significant (Table 4). In the model where MME was treated as the outcome, the adjusted mean of MME in the LB group was 20.2 units higher compared to that of the control group (44.6 vs 24.4, p=0.0111).

MME also changed over time, with the greatest change in MME observed at 48h and 96h (Δ=5.7 and 6.6, respectively) (Table 5).

Table 4. Linear Mixed Model of Pain Score

	Pain Score		
	Estimate (SE)	**Change (SE)**	***p value***
Baseline (24h)	2.8 (0.7)		0.5823
Time 2 (48h)	2.5 (0.7)	-0.3 (0.6)	
Time 3 (72h)	2.3 (0.8)	-0.5 (0.7)	
Time 4 (96h)	2.7 (0.8)	-0.1 (0.8)	
Time 5 (120h)	1.8 (0.9)	-1.0 (0.8)	
Group 1 (LB)	2.8 (0.9)		0.3664
Group 2 (Control)	2.0 (0.7)	-0.8 (0.8)	

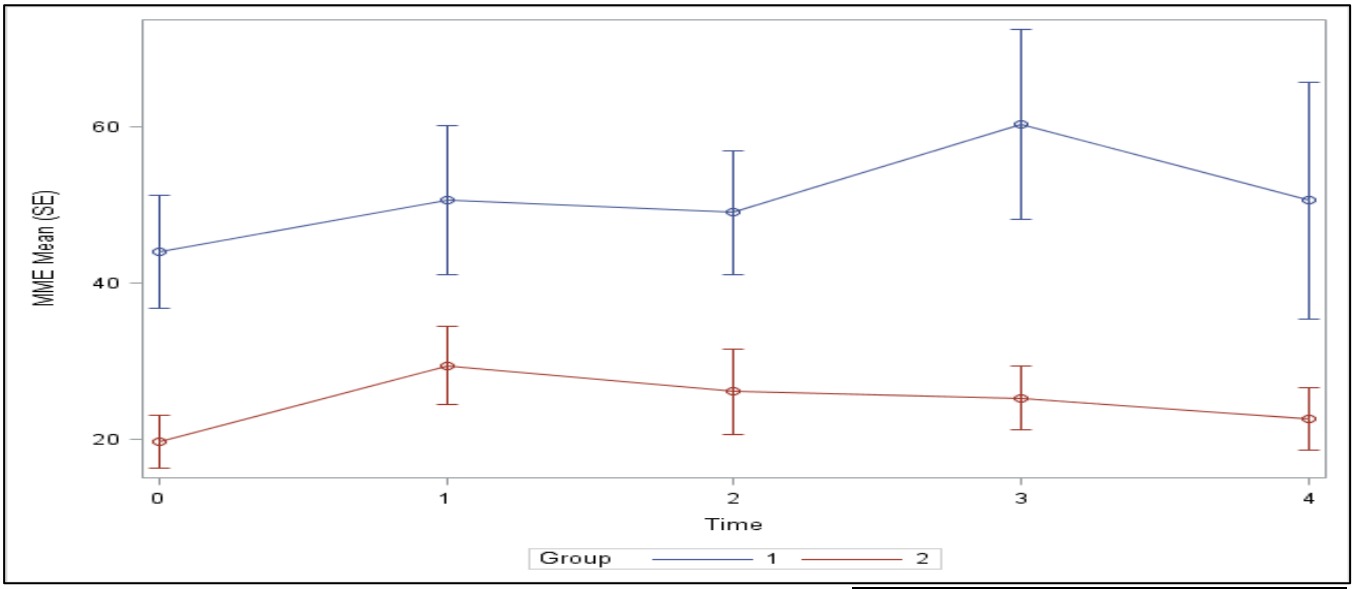

Figure 2. Comparison of mean MME/day in LB (Group-1) vs conventional treatment (Group-2) over time. Time points 0, 1, 2, 3 & 4 indicate the days from admission in hours (~24h, ~48h, ~72h, ~96h, ~120h)

	MME	
Time	Group 1	Group 2
24h	44.0 (31.3)	19.7 (24.7)
48h	50.7 (40.3)	29.5 (32.5)
72h	49.1 (29.7)	26.1 (28.7)
96h	60.3 (34.4)	25.4 (18.3)
120h	50.6 (33.8)	22.6 (16.5)

Table 5. Linear Mixed model of Morphine milligram Equivalents (MME)

	MME		
	Estimate (SE)	**Change (SE)**	***p value***
Baseline (24h)	31.2 (3.7)		0.0351
Time 2 (48h)	36.8 (4.5)	5.7 (2.5)	
Time 3 (72h)	33.8 (4.0)	2.7 (2.8)	
Time 4 (96h)	37.7 (4.4)	6.6 (2.8)	
Time 5 (120h)	33.1 (4.5)	1.9 (2.9)	
Group 1 (LB)	**44.6 (6.5)**		**0.0111**
Group 2 (Control)	**24.4 (4.1**)	**-20.2 (7.7)**	

Discussion

This retrospective study evaluated the effect of adding LB infiltration to conventional multimodal analgesic treatment of patients with isolated rib fractures. There was no significant reduction in pain score with added LB infiltration at the fracture site compared to conventional treatment using oral or parenteral opioids and non-opioid analgesics. The patient reported pain score was higher in the LB group, which, although not significant, was sustained at the same level over time. Moreover, a higher MME/day level was administered in the LB group compared to the conventional treatment group.

Adequate pain control remains the cornerstone in the non-surgical management of rib fractures for early ambulation and prevention of the development of pulmonary complications. LB (herein: Exparel; Pacira Pharmaceuticals) is a form of bupivacaine where the drug is formulated in microvesicles, which, upon administration, will slowly release the drug at a constant rate for an extended period of time for up to 96 hours with a single dose infiltration.[7-9] Previous studies have shown the efficacy of LB in providing effective analgesia in many orthopedic, colorectal, and plastic surgeries and has, too, been used in thoracic surgeries.[9] However, our study stands in contrast to those. Similar to this study, a recent prospective randomized trial comparing LB intercostal nerve block (ICNB) against peri-intercostal subcutaneous infiltration of saline demonstrated no significant difference in pain score and MME usage.[10] In addition, another randomized clinical trial comparing LB ICNB to continuous infusion of plain bupivacaine through an indwelling catheter in surgical stabilization of rib fracture showed no difference in the Sequential Clinical Assessment of Respiratory Function (SCARF) score. There was a lower opioid requirement in the LB group on postoperative days 2 to 4, but this was also not significant.[11]

Additionally, a randomized clinical trial of LB used as infiltration ICNB compared to epidural infusions in thoracic surgery (minimally invasive surgery or open thoracotomy) demonstrated no significant difference in mean pain score and opioid requirements[7]. Moreover, a retrospective study of surgical rib stabilization was conducted, in which LB added to ICNB with bupivacaine HCl was compared with bupivacaine with or without epinephrine. The outcome was non-inferior pain scores and non-significant differences in opioid use, leading to the conclusion that there was no benefit in adding LB to conventional treatment. Furthermore, there are other studies where the use of LB in different procedures/surgeries, such as robotically assisted thoracic procedure or video-assisted thoracoscopic surgery, showed no significant difference in pain scores, especially after the first 24 hours.[12, 13]

While regional nerve block has been shown

to be beneficial in various surgical settings, it is of interest to consider why intercostal nerve block using LB has been shown, in this study and those discussed above, to be ineffective. The perception of pain is subjective. Because this was not a randomized trial, it is possible that those patients who were administered the additional LB infusion were those who had self-reported higher pain scores. The use of opioid and non-opioid medications was not uniform, meaning that patients were given a variety of analgesics, making generalizations less certain. The absence of standard guidelines on the use of LB in these patients may have created a potential selection bias in surgeons' choice of LB infusion. Hence, the retrospective design is a limitation of this study.

Other issues include the wide range in the number of fractured ribs as a potential confounder affecting the outcome. There was only one case where infiltration of LB to multiple fracture sites was not achieved due to the distant location of fracture sites. The data were not available for patients who were discharged from the hospital before the specified time period to collect the reported pain score and MME use. The pain score data was collected from nursing assessment records and not from a protocol, although the pain scores were uniformly recorded in the medical record at specified time points.

Conclusion and Future Perspectives

Pain management is crucial to prevent complications of rib fractures. However, this study found that adding liposomal bupivacaine infiltration at the site of rib fracture neither reduced the pain score nor helped in reducing the total adjusted dose of opioid analgesics. Future prospective randomized clinical trials are required to confirm this effect.

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