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RESEARCH ARTICLE

Pain control using liposomal bupivacaine versus bupivacaine for robotic assisted thoracic surgery

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Abstract

Background Despite a trend towards minimally invasive thoracic surgeries over thoracotomies, patients can still experience significant post-operative pain. Literature on the use of liposomal bupivacaine in patients undergoing robotic surgeries is lacking. *Objective* To compare pain control via intercostal nerve block with liposomal bupivacaine to bupivacaine for patients undergoing robotic assisted thoracic surgery. *Setting* A 455 bed community hospital. *Methods* This was a prospective observational study with a historical control group of 96 patients who underwent robotic lung resection. Patients in the control group received bupivacaine, while the intervention group received liposomal bupivacaine. *Main outcome measure* Average pain scores 24, 48, and 72 h after surgery. *Results* There were no significant differences in average pain scores between groups. The frequency of ketorolac use on the first post-operative day was lower for those who received liposomal bupivacaine. There were no significant differences in opioid requirements, length of stay, or rate of complications. *Conclusions* There was no significant difference in post-operative pain control between patients receiving liposomal bupivacaine and bupivacaine for robotic assisted surgery.

Keywords Liposomal bupivacaine · Nerve block · Pain control · Robotic surgery · Thoracic surgery

Impacts on practice

- There seem to be no significant differences in average pain scores, opioid requirements, or length of stay in patients who received liposomal bupivacaine versus bupivacaine during robotic assisted thoracic surgery.
- In robotic assisted thoracic surgery, liposomal bupivacaine does not seem to have an advantage over bupivacaine for pain control.

Introduction

Management of pain following thoracic surgery is a necessary part of post-operative care. Pain originates from pleural and muscular damage as well as intercostal nerve damage that occurs during surgery. Adequate pain control permits early mobilization and prevents complications such as deep venous thrombosis and pulmonary embolism. Furthermore, pain control allows patients to clear respiratory secretions, thus preventing complications such as hypoventilation and pneumonia [1].

Thoracic epidural analgesia has historically been the gold standard for post-thoracotomy pain [2]. However, open thoracotomies have become less common in favor of minimally invasive procedures, such as video assisted and robotic assisted thoracoscopic surgeries. These less invasive approaches offer advantages including less post-operative pain and reduced length of stay [3–6]. For these reasons, alternatives to thoracic epidural analgesia are necessary.

Paravertebral nerve blockade, intercostal nerve block, and intrapleural analgesia have been studied for pain relief following thoracic surgery. Paravertebral nerve blockade is achieved using ultrasound guidance to inject local

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anesthetic into the paravertebral space, thus producing analgesia over several thoracic segments. Studies found paravertebral block to provide comparable pain relief with fewer side effects and pulmonary complications compared to thoracic epidural anesthesia [7, 8]. Intercostal nerve block is achieved via injection of local anesthetic into the intercostal nerves, while intrapleural analgesia is achieved via injection of local anesthetic into the pleural space. Unfortunately, the short duration of action of local anesthetics precludes their use for prolonged pain relief. Continuous infusions of local anesthetic through an indwelling catheter can provide extended pain relief, although this method is costly, requires catheter insertion, is prone to occlusion, and allows the opportunity for infection.

Liposomal bupivacaine (Exparel) was approved by the Food and Drug Administration (FDA) in 2011 for single-dose infiltration into a surgical site to produce postsurgical analgesia [9]. In 2018, liposomal bupivacaine received an additional indication for interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Bupivacaine is an amide anesthetic with a half-life of 3 h that exerts its analgesic effects by preventing the influx of sodium along the axon. Liposomal bupivacaine is formulated in a carrier matrix composed of aqueous bupivacaine containing chambers separated by lipid membranes. Over time, erosion and reorganization of the lipid membranes causes steady drug release. A single infiltration of liposomal bupivacaine results in plasma levels of bupivacaine that can persist for 72 h.

Liposomal bupivacaine has been studied for intercostal nerve block in patients undergoing thoracic surgery, although most of the literature has included patients undergoing open thoracotomy. Rice et al. compared liposomal bupivacaine to thoracic epidural analgesia in patients undergoing lung resection via thoracotomy, video assisted thoracic surgery, or robotic assisted thoracic surgery. They found no significant differences in post-operative pain scores, narcotic utilization, or complications, but a significant reduction in length of stay with liposomal bupivacaine [10]. Khalil et al. compared liposomal bupivacaine to thoracic epidural analgesia in patients undergoing thoracotomy. They reported significantly lower mean pain scores with liposomal bupivacaine but no difference in narcotic utilization [11].

Few studies focus solely on the use of liposomal bupivacaine for minimally invasive procedures. A recent study by Parascandola et al. [12] compared liposomal bupivacaine and bupivacaine/epinephrine for intercostal blocks in video assisted thoracoscopic wedge resection. In this retrospective cohort study, those who received liposomal bupivacaine used significantly fewer analgesics than those who received bupivacaine/epinephrine 24–36 h postoperatively (20.2 vs. 45.0 mg ME; $p = 0.006$) and 60–72 h postoperatively (15.0 vs. 33.8 mg ME; $p = 0.04$). Median length of stay did not significantly differ between the groups.

Data comparing liposomal bupivacaine to bupivacaine in patients undergoing robotic assisted thoracic surgery are lacking.

Aim of the study

The purpose of this study was to compare pain control via intercostal nerve block with liposomal bupivacaine to bupivacaine for patients undergoing lung resection via robotic assisted thoracic surgery.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from participants included in the study.

Method

Study design

This was a prospective observational study with a historical control conducted at a 455 bed community hospital. Adult patients who underwent robotic assisted lung resection (wedge, segment, or lobe) performed by a single surgeon between January 1, 2017 and May 31, 2018 were eligible for inclusion. Patients were excluded from this study if they were less than 18 years old, required pneumonectomy, required extended resections (chest wall or diaphragm), or were converted to open thoracotomy. Bupivacaine was used for intercostal nerve block from January 2017 to October 2017. Beginning November 2017, liposomal bupivacaine was used.

All surgeries were performed using the da Vinci Surgical System. An incision was made at the eighth intercostal space, and an 8 mm robotic trocar was placed into the chest. Through that, an endoscope was passed. Under direct visualization, two more incisions were made anteriorly and laterally, and through that, 12 mm trocars were placed. Then another 12 mm trocar was placed at the 11th intercostal space anteriorly.

Patients in the control group received intercostal nerve blocks intraoperatively after lung resection. The blocks were placed under direct visualization with 40 mL bupivacaine 0.25% evenly distributed over the 4th intercostal space to

8th intercostal space. Patients in the intervention group received intercostal nerve blocks intraoperatively prior to lung resection due to the delayed onset of liposomal bupivacaine. Liposomal bupivacaine 1.3% 20 mL was diluted with 50 mL of sodium chloride 0.9%. From this dilution, 20 mL was injected into the four incisions sites, and the remainder was evenly distributed from the 4th intercostal space to 8th intercostal space.

Immediately following surgery, patients were transferred to the post-anesthesia recovery unit. Once stable, patients were then transferred to the stepdown unit. Patient reported pain scores were assessed by a nurse every four hours using a numeric scale (0–10). A post-operative pain protocol was utilized to minimize deviation between the groups. All patients received the physician's standard of care post-operative analgesic regimen which included intravenous and oral opioids, acetaminophen, tramadol, ketorolac (if appropriate based on renal function), and meloxicam. The amount of analgesics received in the step-down unit was recorded for the first 72 post-operative hours.

The study protocol was approved by the institution's Institutional Review Board (File #20171006). Patient characteristics, pain scores, and complications data were extracted from patient's records with the assistance of the institution's outcomes department. Complications were reported in accordance with the definitions set forth by the Society of Thoracic Surgeons National Database. All other data were collected via retrospective chart review.

Statistical analysis

The primary endpoint of this study was the average daily pain scores 24, 48, and 72 h after surgery. Secondary endpoints included length of stay, chest tube duration, home oxygen requirements, opioid utilization, coanalgesic utilization, pulmonary complications (atelectasis requiring bronchoscopy, pneumonia, bronchopleural fistula, reintubation), and surgical complications (atrial fibrillation, myocardial infarction, deep vein thrombosis, pulmonary embolism, urinary tract infection, renal failure, bleeding, surgical site infection, ileus). The pharmacy department at our institution provided the liposomal bupivacaine utilized in this study which was specifically allotted for research purposes. The sample size was determined by the amount of liposomal bupivacaine available. The investigators used a similar number of patients in the control group to match the intervention arm of the study. Due to the lack of published data on liposomal bupivacaine in minimally invasive thoracic surgeries with pain scores as the primary outcome, a power calculation was not performed. A p value < 0.05 was considered statistically significant.

Results are reported as means with standard deviations. Dichotomous outcomes are reported as n (%). Results were analyzed using the t test for continuous variables and the Chi squared test for categorical variables. SPSS (version 25) was used for all analyses. Normality for data was assessed both visually and by using the Shapiro–Wilk test in SPSS.

Results

Study population

A total of 96 patients were included. Demographics and baseline characteristics are summarized in Table 1. The average age of participants was 66 years, and the population was 55% female and 95% white. There were no significant differences in baseline characteristics between patients who received bupivacaine and liposomal bupivacaine.

Outcomes

In regards to our primary outcome, there were no significant differences in average daily post-operative pain scores between groups. The average pain score on the first post-operative day was 5 in each group ($p = 0.211$). The average pain score on the second post-operative day was 3 in the bupivacaine group and 4 in the liposomal bupivacaine group ($p = 0.082$). The average pain score on the third post-operative day was 2 in the bupivacaine group and 3 in the liposomal bupivacaine group ($p = 0.763$). Patients who received liposomal bupivacaine used fewer IV morphine equivalents per day than patients who received bupivacaine, although none of the between group differences achieved statistical significance. Patients in the bupivacaine group received 22 mg IV morphine equivalents compared to 18 mg in the liposomal bupivacaine group on post-operative day 1 ($p = 0.099$). On post-operative day 2, patients in the bupivacaine group received 16 mg IV morphine equivalents compared to 12 mg in the liposomal bupivacaine group ($p = 0.087$). On post-operative day 3, patients in the

Table 1 Baseline characteristics

	Control (n = 53)	Intervention (n = 43)	p value
Age (years)	66 ± 11	66 ± 10	0.863
Gender, n (%)			0.914
Male	24 (45)	19 (44)	
Female	29 (55)	24 (56)	
Race, n (%)			0.252
White	49 (92)	42 (98)	
Black	4 (8)	1 (2)	
Weight (kg)	78 ± 19	81 ± 21	0.293
Height (cm)	168 ± 8	170 ± 10	0.388
BMI (kg/m^2)	27.9 ± 6.5	29.0 ± 6.4	0.404

Table 2 Analgesic utilization

Medication, n (%)	Control (n = 53)	Intervention (n = 43)	*p* value
Acetaminophen day 1	42 (79)	31 (72)	0.414
Acetaminophen day 2	6 (11)	7 (16)	0.480
Acetaminophen day 3	7 (13)	4 (9)	0.550
Ketorolac day 1	26 (49)	11 (26)	0.019
Ketorolac day 2	10 (19)	10 (23)	0.600
Ketorolac day 3	2 (4)	3 (7)	0.482
Tramadol day 1	3 (6)	1 (2)	0.416
Tramadol day 2	4 (8)	1 (2)	0.252
Tramadol day 3	3 (6)	0 (0)	0.113
Meloxicam day 1	3 (6)	1 (2)	0.416
Meloxicam day 2	2 (4)	1 (2)	0.685
Meloxicam day 3	0 (0)	1 (2)	0.264

bupivacaine group received 8 mg IV morphine equivalents compared to 7 mg in the liposomal bupivacaine group ($p = 0.675$). Table 2 depicts differences in coanalgesic use between the groups for each day. The frequency of ketorolac use on the first post-operative day was significantly lower for those who received liposomal bupivacaine compared to bupivacaine (26% vs. 49%, $p = 0.019$). There were no significant differences in use of other analgesics between groups.

Other secondary outcomes are listed in Table 3. There was a trend towards shorter length of stay in liposomal bupivacaine group, but it was not statistically significant (3.7 vs. 4.4 days, $p = 0.690$). For patients who had their chest tubes removed after discharge, the duration was significantly shorter in the liposomal bupivacaine group (9 vs. 15 days, $p = 0.027$). Pulmonary and surgical complications are found in Table 4, and there were no significant differences between groups. There were no medication related adverse events reported by patients in either group.

Discussion

In this prospective cohort study with a historical control, the average daily pain scores were not significantly different between groups. The milligrams of IV morphine equivalents used were numerically lower for each post-operative day in the liposome bupivacaine group compared with the bupivacaine group. However, none of the between group

Table 3 Secondary endpoints

	Control (n = 53)	Intervention (n = 43)	*p* value
Length of stay (days)	4.4 ± 3.6	3.7 ± 1.9	0.690
Chest tube removed prior to discharge, n (%)	37 (70)	36 (84)	0.112
Inpatient chest tube duration (hours)	67 ± 48	79 ± 68	0.390
Outpatient chest tube duration (days)	15 ± 5	9 ± 5	0.027
Home oxygen required, n (%)	4 (8)	3 (7)	0.915

Table 4 Pulmonary and surgical complications

	Control (n = 53)	Intervention (n = 43)	*p* value
Pulmonary, n (%)			
Atelectasis requiring bronchoscopy	1 (2)	2 (5)	0.439
Pneumonia	2 (4)	3 (7)	0.482
Bronchopleural fistula	2 (4)	0 (0)	0.198
Reintubation	1 (2)	0 (0)	0.365
Surgical, n (%)			
Atrial fibrillation requiring treatment	10 (30)	6 (14)	0.521
Myocardial infarction (MI)	0 (0)	0 (0)	–
Deep vein thrombosis (DVT) requiring treatment	0 (0)	0 (0)	–
Pulmonary embolism (PE) requiring treatment	0 (0)	0 (0)	–
Urinary tract infection (UTI)	0 (0)	0 (0)	–
Renal failure-RIFLE criteria[a]	0 (0)	0 (0)	–
Unexpected return to OR for bleeding	0 (0)	0 (0)	–
Surgical site infection	0 (0)	0 (0)	–
Ileus	1 (2)	1 (2)	0.881

[a]Risk, injury, failure, loss of kidney function, and end-stage kidney disease [13]

differences reached statistical significance. The amount of morphine received in our study is less than that reported in the literature for patients undergoing video-assisted lung resections. In the study by Parascandola et al. [12] the median IV morphine equivalents used in the first 24 h was 90 mg in the bupivacaine/epinephrine group and 70.9 mg in the liposomal bupivacaine group. This difference in narcotic use may be due to the improved maneuverability of the robotic arm compared to the human arm, resulting in reduced pressure on the chest wall, less damage to the intercostal nerves and surrounding tissues, and less pain. The frequency of ketorolac use on the first post-operative day was lower for those who received liposomal bupivacaine compared to bupivacaine. This difference may be attributable to the use of liposomal bupivacaine, although one would expect to still see the effect of bupivacaine in the control group on the first post-operative day.

The mean post-operative length of stay was shorter in the liposomal bupivacaine group compared with the bupivacaine group, but this difference was not statistically significant. Adequate pain control is only one criterion that patients must meet prior to discharge, and there are numerous other variables which may have impacted time to discharge. We cannot attribute the disparity in length of stay to improved pain control with liposomal bupivacaine, as pain scores did not significantly differ between the groups. The chest tube duration for those patients who had their tubes removed in the outpatient setting was significantly shorter for the liposomal bupivacaine group. However, given the duration of action of liposomal bupivacaine, it is difficult to attribute this difference to the study drug.

Strengths of this study include our restriction for admission into the study to those patients who had robotic assisted lung resections performed by a single physician. This restriction was done in order to control for confounders in our study. Additionally, we attempted to reduce bias through the use of a post-operative pain protocol. An additional strength of our research is that we studied liposomal bupivacaine for robotic assisted thoracic lung resections, a novel patient population which has not previously been described in the literature.

Limitations of this study include small sample size and the lack of a true sample size calculation. Our study may have been underpowered, which increases the possibility of type 2 error. There was also potential for bias, as the study was not blinded. Another limitation of this study is that our results may have been impacted by a national opioid shortage which coincided with the use of liposomal bupivacaine. Furthermore, our study only accounted for inpatient use of analgesics. Additionally, our primary outcome was patient reported pain scores, which has limitations due to the subjective nature of pain. Lastly, we did not perform any pharmacoeconomic assessments on whether the cost of liposomal bupivacaine could be offset by its benefits.

Liposomal bupivacaine has the potential to provide extended pain relief from a single dose without the risk of complications that come with an epidural or indwelling catheter, or the adverse effects associated with systemic analgesics. Our study adds to the growing body of literature on the use of liposomal bupivacaine as part of a multimodal pain approach for post-operative analgesia in thoracic surgery. Larger, prospective studies on the use of liposomal bupivacaine in robotic assisted thoracic surgeries are needed. Additionally, cost–benefit analyses are needed to provide insight for hospitals when deciding whether liposomal bupivacaine should be on formulary.

Conclusion

In patients undergoing robotic assisted thoracic lung resection, there was not a significant difference in post-operative pain control between patients receiving liposomal bupivacaine and bupivacaine.

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Conflicts of interest All authors declare that they have no conflicts of interest.

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