Randomized trial of bupivacaine with epinephrine versus bupivacaine liposome suspension in patients undergoing minimally invasive lung resection

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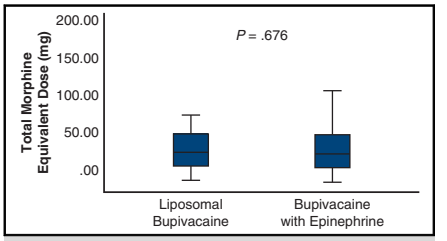
ABSTRACT

Objectives: Thoracic surgery can cause significant pain, and multiple strategies have been developed to control pain after surgery. We compared 2 bupivacaine formulations given intraoperatively: bupivacaine with epinephrine (1,200,000) or liposomal bupivacaine.

Methods: This was a randomized, open-label study (NCT03560362). Eligible patients were adults scheduled for a minimally invasive lung procedure. Incision sites were injected with bupivacaine with epinephrine or liposomal bupivacaine before incision, and each intercostal space was injected with 1 mL of bupivacaine with epinephrine or liposomal bupivacaine entering the thoracic cavity. Patient-controlled analgesia was initiated in the recovery room. Pain was recorded using a visual analog scale. The primary outcome was the amount of narcotics taken during the postoperative hospital stay.

Results: We recruited 50 patients; 25 received bupivacaine with epinephrine, and 25 received liposomal bupivacaine. The treatment groups were similar in age, histology, and procedure performed. There were no statistical differences between the treatment groups in the amount of narcotics required during the hospital stay (36.3 mg for bupivacaine and 38 mg for liposomal bupivacaine) or in pain assessed the day of surgery (5 and 5), the first day (3.5 and 2.3), second day (3 and 2.6), 2 weeks (0 and 1), or 3 months (0 and 0) postoperatively. Hospital length of stay and complications were also similar.

Conclusions: In a small, randomized study, we did not find significant differences between bupivacaine with epinephrine or liposomal bupivacaine in mitigating pain after minimally invasive lung resection. We currently favor using the less expensive nonliposomal bupivacaine preparations until additional data are available. (J Thorac Cardiovasc Surg 2021;161:1652-61)



Narcotic use after intraoperative bupivacaine with epinephrine or liposomal bupivacaine.

CENTRAL MESSAGE

In a small, randomized study, we were unable to demonstrate that liposomal bupivacaine is better than standard bupivacaine with epinephrine at relieving pain after minimally invasive thoracic surgery.

PERSPECTIVE

In patients undergoing minimally invasive lung surgery, liposomal bupivacaine, a pricey extended-release formulation, did not have an advantage over traditional bupivacaine with epinephrine. Until larger randomized studies are available, the bupivacaine with epinephrine should be the drug of choice in patients undergoing minimally invasive surgery because it is less expensive.

See Commentary on page 1662.

Minimally invasive thoracic surgery results in fewer complications, shorter hospital stays,[1] and less narcotic use compared with thoracotomy, but it still can be associated

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Abbreviations and Acronyms
MED = morphine equivalent dose
PCA = patient-controlled analgesia
VATS = video-assisted thoracic surgery

with significant postoperative pain.[2] Pain management strategies after minimally invasive thoracic surgery have varied and include epidural analgesia, paravertebral block, and intercostal nerve block. Applying an intercostal nerve block in combination with local infiltration of skin incisions with analgesia is a popular option for surgeons performing minimally invasive surgery,[3] because it is a simple and quick procedure that avoids the potential complications of an epidural catheter.[4] Bupivacaine with epinephrine (1:200,000) is often used for intercostal nerve block because of the simplicity and low cost of the agent. Unfortunately, the duration of the block, typically 6 to 8 hours, is relatively short.[5]

Liposomal bupivacaine is a water-soluble bupivacaine formulation with analgesic-filled chambers separated by lipid membranes. This formulation allows continuous steady release of the drug for up to 96 hours.[6] Liposomal bupivacaine was approved by the US Food and Drug Administration in 2011 for single-dose, surgical-site administration and in 2018 for interscalene brachial plexus blocking. Liposomal bupivacaine appears safe when used as an intercostal nerve block.[7] However, liposomal bupivacaine costs $325 (US dollars, https://www.exparel.com/hcp/cost) per vial, making it approximately 50 times more expensive than bupivacaine with epinephrine, which costs $6 or less (https://www.drugs.com/price-guide/bupivacaine-epinephrine) per vial.

The effectiveness of liposomal bupivacaine was studied in randomized studies in other specialties with mixed results; some studies showed benefits,[8,9] and others did not.[10-13] There is only 1 randomized study in the cardiothoracic surgical literature[14] that compared liposomal bupivacaine applied parasternally with placebo in patients undergoing coronary artery revascularization and did not show a benefit of liposomal bupivacaine.

Multiple retrospective studies examining pain management after minimally invasive thoracic surgery have shown decreased opioid use and shorter hospital stays with the use of liposomal bupivacaine when compared with different preparations of bupivacaine.[15-17] However, there are no randomized studies comparing liposomal bupivacaine with bupivacaine with epinephrine in the thoracic surgical literature. The goal of our study was to compare liposomal bupivacaine and bupivacaine with epinephrine in thoracic surgical patients undergoing minimally invasive lung procedures in a well-designed, randomized trial.

MATERIALS AND METHODS

This was a prospective, randomized, single-blinded, open-label study (clinicaltrials.gov, NCT03560362). The trial opened in July of 2015 and was closed in September of 2018. The University of Tennessee Health Science Center approved the study, and all patients gave informed consent for the study and the surgical procedure.

Patients

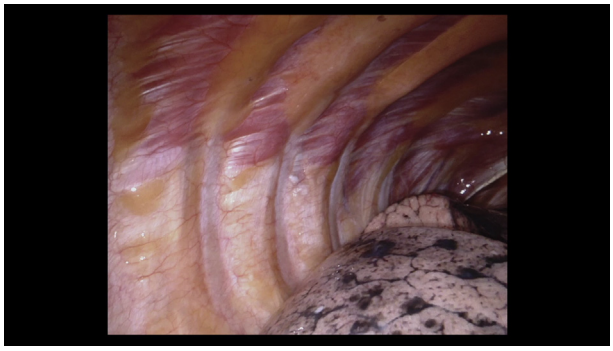
Eligible patients were 18 years of age or older and scheduled for an elective minimally invasive therapeutic or diagnostic lung procedure. Procedures included robotic- or video-assisted thoracic surgery (VATS) lobectomy, segmentectomy, or wedge resection. Exclusion criteria included emergency or urgent surgery, previous thoracic surgery, chronic narcotic use, a history of alcohol abuse, a diagnosis of fibromyalgia, use of gabapentin for any reason, significant known liver disease (Child-Pugh score B or C or the presence of ascites), renal failure (serum creatinine level >1.5 mg/dL), significant cardiac disease (ejection fraction <50%), or significant chronic obstructive pulmonary disease (forced expiratory volume in 1 second or diffusing capacity for carbon monoxide <50% predicted). Patients who could not communicate in English were also excluded.

Study Design

Patients were randomly assigned to receive intraoperative analgesia with either bupivacaine with epinephrine (1:200,000) (control arm) or with liposomal bupivacaine (Exparel; Pacira Pharmaceutical Inc, Parsippany, NJ) (experimental arm). The randomization sequence was known only to the research coordinator. On the day of surgery, the surgeon was notified which agent to use.

Pain Management Strategy

During surgery, bupivacaine with epinephrine or liposomal bupivacaine was injected into the skin before incision at the sites for all ports. Upon entering the thoracic cavity, 1 mL of the randomly assigned drug was injected in each intercostal space percutaneously, starting with the second or third intercostal space and continuing to the 11th intercostal space (Video 1). After surgery, all patients received patient-controlled analgesia (PCA) with morphine or hydromorphone (Dilaudid; Purdue Pharma, Stamford, Conn) starting in the recovery room. Patients who had significant pain in the postoperative period also received intravenous ketorolac (Toradol; Pfizer Pharmaceutical, New York, NY), 15 mg every 6 hours for 48 hours. Patients were not given any other medications, such as Cox-2 inhibitors, gabapentin, or acetaminophen, preoperatively for pain management. Patients received PCA until the chest drain was removed and were then transitioned to oral oxycodone



VIDEO 1. Intercostal nerve block and the use of bupivacaine with epinephrine versus liposomal bupivacaine. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30752-2/fulltext.

(5 mg) with acetaminophen (325 mg) (Percocet; Endo Pharmaceuticals Inc, Malvern, Pa) every 6 hours.

Surgical Procedure

Robotic procedures were performed as previously described[3] with a slight modification to the port placement. Briefly, 4 arms were used with ports approximately 8 cm apart in the eighth intercostal space. The port closest to the spine was placed at least 4 cm from the spinous processes. A fifth port for the assistant surgeon was placed on top of the 11th rib, between the most anterior port and the camera port.

Thoracoscopic procedures were performed with 2 ports as previously described.[18] Briefly, a 10-mm camera port was placed on the eighth intercostal space at the mid-axillary line, and a 3- to 4-cm access incision was placed on the fifth intercostal space at the anterior axillary line.

At our institution, we use a digital chest drainage system. We removed the chest drain from our patients when it was draining less than 400 mL of fluid per 24 hours and less than 20 mL/min of air for more than 4 hours.

Study End Points and Assessment

The primary end point of the study was the amount of narcotics administered during the hospital stay converted to morphine equivalent dose (MED) in morphine milligram equivalent. The total narcotics administered included narcotics administered by PCA, extra doses given for breakthrough pain, and all oral narcotic forms. Secondary end points included pain score, which was recorded using a Visual Analog Scale, on postoperative day 1, at the first postoperative visit after discharge, and 3 months after surgery. The Visual Analog Scale is an easy to use and reproducible method to assess pain.[19] Patients estimated their pain level using an 11-number scale varying from zero, which indicated no pain, to 10, which indicated unbearable pain. Nurses recorded the pain score once each 12-hour shift, and we averaged each 24-hour period postoperatively.

Statistical Analysis

Sample size. Before beginning the trial, we performed a retrospective review of our last 20 patients to undergo a minimally invasive thoracic procedure. We determined that the mean MED during the hospital stay for these patients was 27 $\pm$ 10.1 mg. Using this information, we designed this trial with an alpha equal to 0.05 and a 90% power to detect an expected 25% decrease in the total MED. A sample size of 86 patients was needed, and we planned to recruit 100 patients, 50 in each group, to complete the trial. The trial was closed early because of poor accrual and relocation of the primary investigator after recruitment of 51 patients.

A post hoc sample size calculation based on the mean MED of 47 $\pm$ 5.4 mg in the bupivacaine with epinephrine control group indicated that a sample size of 25 patients per arm had the 90% power to detect a 10% decrease in the MED administered to the experimental arm compared with the MED in the control arm. This sample size calculation was performed using PASS 2014 (NCSS, Kaysville, Utah) using the Mann–Whitney *U* test assuming equal variance.

Data Analysis

Patient characteristics are reported using median and range for continuous variables and frequencies and percentages for categoric variables. Mann–Whitney *U* test was used to compare continuous variables, and the Fisher exact test was used to compare categoric variables. For continuous data, we obtained median differences and 95% confidence interval using median regression, and for categoric outcome variables, we obtained percent differences and 95% confidence interval using a 2-sample difference of proportions z interval. All comparisons were 2-tailed. SPSS version 25 (IBM Corp, Chicago, Ill) was used for statistical analysis.

RESULTS

The trial's CONSORT diagram is depicted in Figure 1. We screened 239 patients and excluded 188. The remaining 51 patients were randomized; 26 received bupivacaine with epinephrine, and 25 received liposomal bupivacaine. After randomization, 1 patient who was assigned to the bupivacaine with epinephrine arm was excluded after he developed severe delirium on the first postoperative day and required intubation. On further questioning, we discovered he was a heavy daily drinker, and his last alcohol intake was 2 days before surgery. There were 50 evaluable patients in the final cohort: 25 in the bupivacaine with epinephrine control arm and 25 in the liposomal bupivacaine experimental arm. Three-month follow-up was completed for all patients.

The patients in the 2 study arms were similar in age, sex, histology, and procedure performed (lobectomy, segmentectomy, or wedge resection) (Table 1). The majority of patients in both arms had robotic anatomic lung resection for lung cancer. Four patients in the control arm underwent VATS wedge resection, 2 for the treatment of lung metastases and 2 for the diagnosis of interstitial lung disease. Three patients in the experimental arm underwent VATS wedge resection, 2 for the treatment of lung metastases and 1 for the diagnosis of interstitial lung disease.

There were no perioperative mortalities or mortalities within 90 days. Complications were similar between the 2 groups with the most common complications being prolonged air leak (Table 2), and 74% (n = 37) of the patients did not have any complications. There were no significant pulmonary complications, including pneumonia, atelectasis, or the need for toilet bronchoscopy. The median length of hospital stay for the patients who received bupivacaine with epinephrine was 2.0 days and not significantly different (P = .605) from the stay length of the patients who received liposomal bupivacaine (2.0 days).

There were no significant differences in the amount of narcotics taken during hospital stay between the study arms. On day 0, the day of surgery, MED was 21.5 mg for patients who received liposomal bupivacaine and 18 mg for patients who received bupivacaine with epinephrine. On postoperative day 1, MED was 12 mg for patients with liposomal bupivacaine and 13 mg for patients bupivacaine with epinephrine, and on postoperative day 2, it was 1.7 mg for liposomal bupivacaine and 8.8 mg for bupivacaine with epinephrine (Table 3). Patients who were treated with liposomal bupivacaine with epinephrine during their surgery used a median MED of 38.0 mg during their hospital stay, and patients treated with bupivacaine with epinephrine used 36.3 mg during the hospital stay (P = .676) (Figure 2). One patient in each group received ketorolac in the postoperative period. The median pain score on postoperative day 0 was 5 in patients treated with liposomal bupivacaine and 5 in patients treated with bupivacaine with

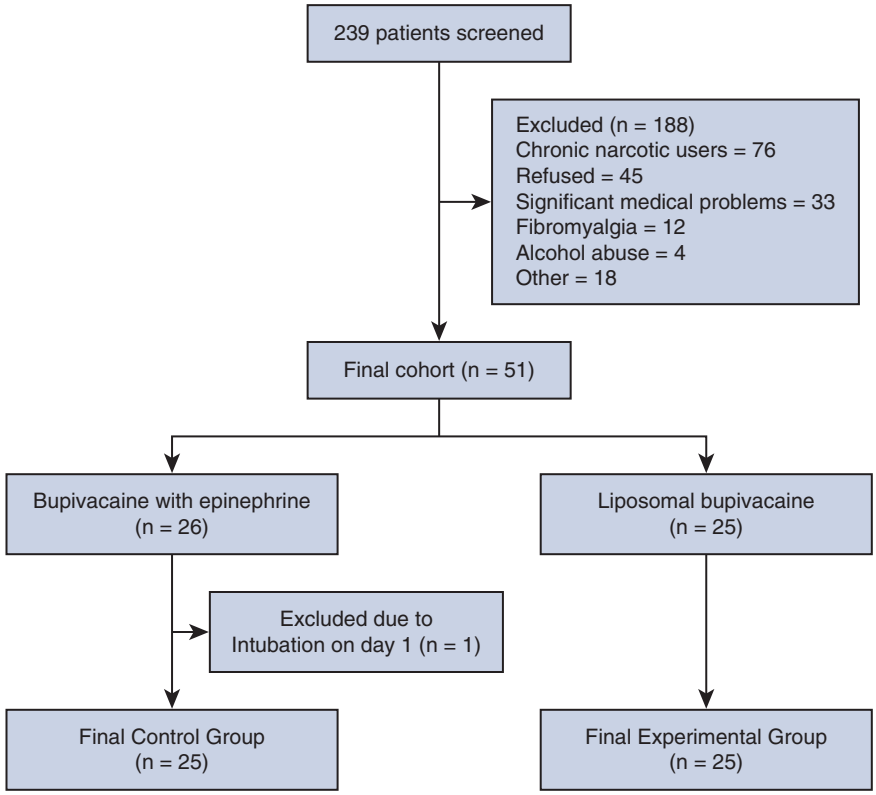


FIGURE 1. CONSORT diagram detailing study recruitment and patient inclusion and exclusion criteria.

epinephrine ($P = .387$). The pain scores on postoperative day 1 were 2.3 and 3.5, and on day 2 were 2.6 and 3 for patients treated with liposomal bupivacaine and bupivacaine with epinephrine respectively (Table 3). Pain did not differ significantly at any time point examined. At the first postoperative clinic visit, typically 2 weeks after surgery, the median pain score was 1 in patients treated with liposomal bupivacaine and 0 in patients treated with bupivacaine with epinephrine. There were also no significant differences in pain score 3 months after surgery (Table 3).

DISCUSSION

In a randomized study comparing bupivacaine with epinephrine with liposomal bupivacaine, we did not find significant differences in mitigating pain after minimally invasive lung resection. Although the study closed early and our cohort was relatively small, our post hoc analysis determined that this trial was powered to detect a 10% decrease in MED. We did not observe even this small difference overall or at any of the time points we examined (Figure 3).

TABLE 1. Patient characteristics

Characteristic	Control arm (bupivacaine with epinephrine)	Experimental arm (liposomal bupivacaine)	*P* value
Age, median in y (IQR)	63 (56-67.5)	63 (55-73)	.614
Sex, n (%)			.085
Male	7 (28%)	14 (56%)	
Female	18 (72%)	11 (44%)	
Surgery type			.684
Lobectomy or segmentectomy, n (%)	21 (84%)	22 (88%)	
Wedge, n (%)	4 (16%)	3 (12%)	
Surgical approach			1.000
Robotic surgery, n (%)	22 (88%)	21 (84%)	
VATS, n (%)	3 (12%)	4 (16%)	

IQR, Interquartile range; *VATS*, video-assisted thoracoscopic surgery.

TABLE 2. Postoperative complications

Complication, n (%)*	Control arm (bupivacaine with epinephrine)	Experimental arm (liposomal bupivacaine)	*P* value	% difference (95% CI)
None	20 (80%)	17 (68%)	.333	−12 (−35 to 12)
Prolonged air leak	4 (16%)	6 (24%)	.480	8 (−14 to 30)
Atrial fibrillation	1 (4%)	2 (8%)	.552	4 (−13 to 21)
Ileus	0 (0%)	2 (8%)	.149	8 (−7 to 25)
Urinary retention	0 (0%)	1 (4%)	.312	4 (−10 to 20)
Chylothorax	1 (4%)	0 (0%)	.312	−4 (−20 to 10)
Pneumothorax	1 (4%)	0 (0%)	.312	−4 (−20 to 10)
Acute renal injury	0 (0%)	1 (4%)	.312	4 (−10 to 20)

Complications defined as per Society of Thoracic Surgeons definitions. *CI*, Confidence interval. *Three patients had more than 1 complication.

Early randomized studies comparing liposomal bupivacaine with other methods of mitigating pain were performed on patients undergoing hemorrhoidectomy. Gorfine and colleagues[20] reported a multicenter randomized trial comparing liposomal bupivacaine with placebo. Pain scores were significantly decreased after hemorrhoidectomy in patients who received liposomal bupivacaine. Haas and colleagues[21] randomized patients undergoing hemorrhoidectomy to liposomal bupivacaine or 0.25% bupivacaine with epinephrine. Cumulative pain scores and opioid consumption were lower in patients who received liposomal bupivacaine. However, both studies used cumulative pain scores, and a careful analysis suggested that the effect of the drug was not significant 12 hours after surgery.[22]

The effectiveness of liposomal bupivacaine in reducing pain and narcotic use after surgery in other specialties is still controversial. Three randomized trials compared periarticular injection of liposomal bupivacaine with standard 0.25% bupivacaine (without epinephrine) in patients undergoing total knee arthroplasty. Two of the 3 studies did not show differences in pain scores or postoperative narcotic use.[10,23] The third trial[24] showed a reduction in pain scores and reduced opioid use. Contradicting results were also obtained after breast surgery[9,13] and urologic surgery.[12,25]

To our knowledge, there is only 1 other published randomized trial addressing the use of liposomal bupivacaine for analgesia in cardiothoracic surgery. Lee and colleagues[14] randomized patients undergoing coronary artery bypass through a median sternotomy to intercostal and parasternal injection of liposomal bupivacaine or saline. The primary end points were pain over the first 72 hours after surgery, assessed using a nonverbal pain scale, and total

TABLE 3. Postoperative characteristics and pain assessment

Variable	Control arm (bupivacaine with epinephrine)	Experimental arm (liposomal bupivacaine)	*P* value	Difference in median (95% CI)
Operative time, median (IQR)	135 (101-151)	130 (110-184)	.655	−5.0 (−39.9 to 29.9)
Histology (%)			.713	
NSCLC (%)	20 (80)	21 (84)		
Lung metastasis	2 (20)	3 (12)		
Benign	3 (12)	1 (4)		
Length of stay, median in d (IQR)	2.0 (2-3)	2.0 (2-4)	.605	.0 (−1.2 to 1.2)
Narcotics administered, median in MME (IQR)				
MED day 0	18.0 (10.0-35.0)	21.5 (7-28.5)	.528	3.5 (−9.0 to 16.0)
MED day 1	13.0 (3.7-24.6)	12.0 (2.6-19.0)	.337	−1.0 (−11.5 to 9.5)
MED day 2	8.8 (1.3-37)*	1.7 (0-18.8)†	.103	−6.9 (−25.4 to 11.6)
Total MED	36.3 (16.0-66.8)	38.0 (15.5-63.6)	.676	1.7 (−29.2 to 32.6)
Postoperative pain, median VAS score (IQR)				
Postoperative day 0	5.0 (2.2-7.2)	5.0 (0.6-6.0)	.387	0.0 (−3.1 to 3.1)
Postoperative day 1	3.5 (2.6-4.5)	2.3 (1.2-4.9)	.326	−1.2 (−2.9 to 0.6)
Postoperative day 2	3 (1.5-4.7)*	2.6 (1.7-3.9)†	.226	−0.4 (−3.2 to 2.4)
First postoperative visit (∼2 wk operatively)	0.0 (0-2)	1.0 (0-4)	.092	1.0 (−1.0 to 3.0)
3-mo postoperative visit	0.0 (0.8)	0.0 (0-1)	.663	0.0 (−0.5 to 0.5)

CI, Confidence interval; *IQR*, interquartile range; *NSCLC*, non–small cell lung cancer; *MME*, morphine milligram equivalents; *MED*, morphine equivalent dosage; *VAS*, Visual Analog Scale. *A total of 14 evaluable patients. †A total of 12 evaluable patients.

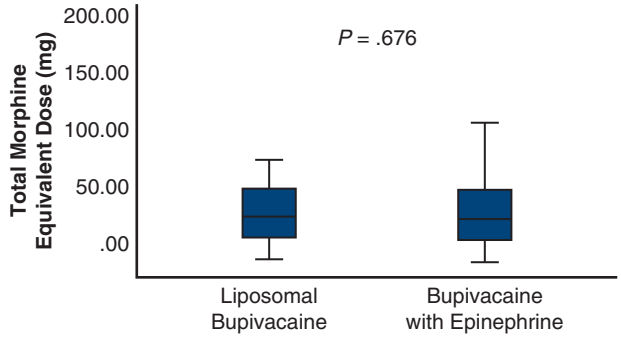


FIGURE 2. Median MED used during the entire hospital stay in patients receiving bupivacaine with epinephrine or liposomal bupivacaine intraoperatively. *Box plot* depicts median MED, interquartile range, and lowest and highest MED for each group.

amount of pain medication used. There were 39 patients in the treatment arm and 39 patients in the control group. Except for the intraoperative liposomal bupivacaine, pain management regimens were similar between the 2 groups. There were no differences in pain scores at each of the time points examined, but overall, pain scores were lower in the treatment arm. Despite an initial reduction in opioid use 2 hours after surgery in the patients who received liposomal bupivacaine, the liposomal bupivacaine did not significantly reduce narcotic use during the first 3 postoperative days. Likewise, in our randomized controlled trial, we did not see any differences in pain scores or narcotic use on postoperative days 1 and 2. Another study, published as an abstract in 2018,[26] compared bupivacaine with liposomal bupivacaine in patients undergoing VATS lung resection and also failed to demonstrate differences in pain score or MED between the 2 groups. The abstract included little information on sample size or methods but appears to corroborate our work.

It is not clear that liposomal bupivacaine works as advertised in other specialties either as noted earlier. In patients undergoing minimally invasive thoracic surgery, our trial and the trial by Khandhar and colleagues[26] were both negative. It is possible that the potential advantages of liposomal bupivacaine are less important in patients undergoing minimally invasive procedures. However, there are multiple retrospective studies comparing pain management after intercostal nerve block with liposomal bupivacaine, intercostal nerve block with bupivacaine, or epidural analgesia in thoracic surgery. Two retrospective studies compared epidural analgesia with injection of liposomal bupivacaine in patients who underwent thoracotomy or thoracoscopy.[7,27] Both studies had similar results, namely, no difference in pain scores or narcotic used between patients who received epidural analgesia

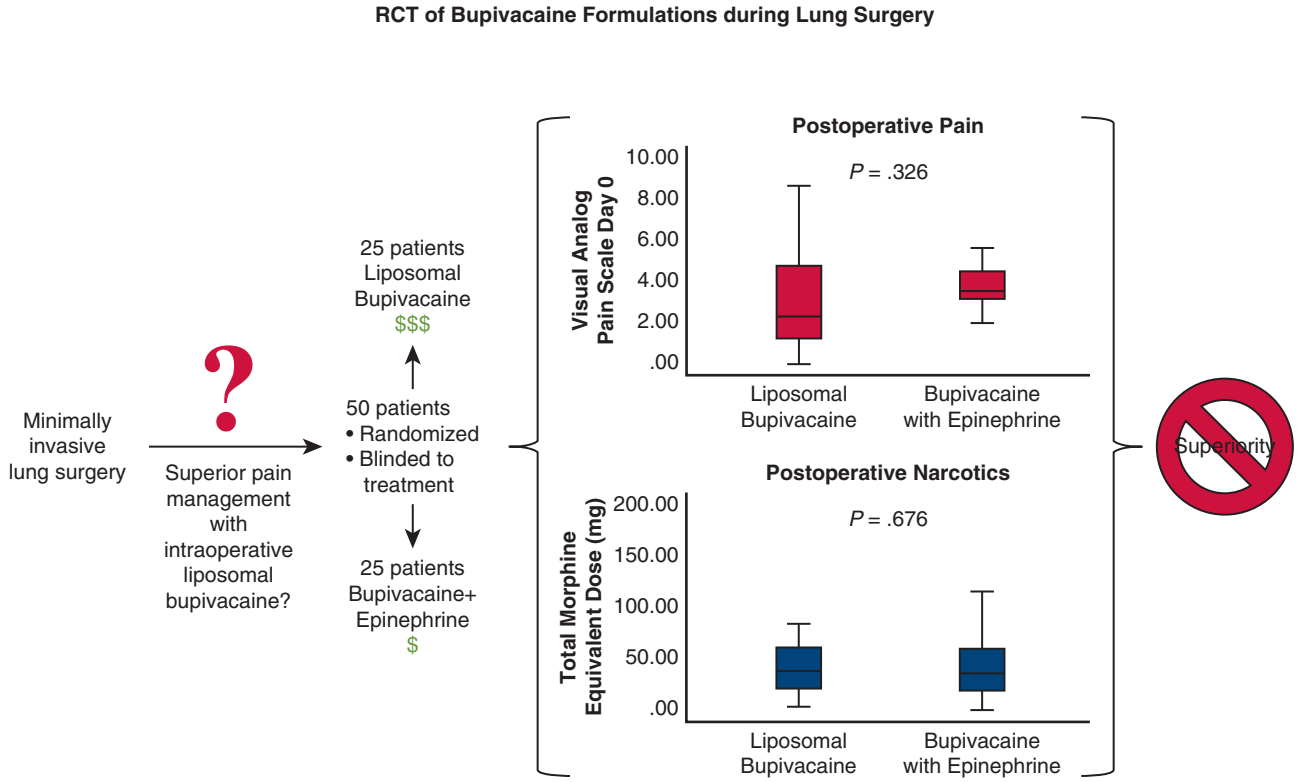


FIGURE 3. A randomized controlled trial of intraoperative administration of 2 different bupivacaine formulations that differ greatly in cost enrolled and treated 25 patients in the experimental arm (liposomal bupivacaine) and 25 patients in the control arm (bupivacaine with epinephrine). There were no differences in postoperative pain or narcotic use. Liposomal bupivacaine was not superior to bupivacaine with epinephrine. *RCT*, Randomized controlled trial.

and patients who received liposomal bupivacaine, but shorter hospital stays after intercostal liposomal bupivacaine administration. These 2 studies included patients who underwent a minimally invasive or open thoracic procedure.

In patients undergoing minimally invasive thoracic procedures, 4 retrospective studies compared intercostal nerve blocks using liposomal bupivacaine with intercostal nerve blocks using bupivacaine with epinephrine or bupivacaine alone. The major shortcoming in these studies is their retrospective nature, often using historical controls. Parascandola and colleagues[15] compared intercostal nerve block with liposomal bupivacaine with 0.5% bupivacaine with epinephrine (1:100,000) in patients undergoing VATS wedge resection. Patients who received liposomal bupivacaine consumed less analgesic during their hospital stay. Kelley and colleagues[16] studied the use of intercostal block with liposomal bupivacaine in patients undergoing thoracoscopic surgery and compared it with standard bupivacaine and lidocaine. Patients who received intercostal liposomal bupivacaine used less narcotics 6 and 24 hours after surgery, but this difference was not evident 48 and 72 hours after surgery. Ketorolac use was more common in the patients who received bupivacaine and lidocaine. Dominguez and colleagues[17] retrospectively analyzed 80 patients undergoing minimally invasive procedures; 40 received intercostal block with liposomal bupivacaine, and 40 received 0.25% bupivacaine with epinephrine (1:100,000). Although not significant, there was a strong trend toward longer surgeries in the control group. Pain scores 24 hours after surgery were lower for the control group compared with the liposomal bupivacaine group, and there was no difference in morphine use. However, length of hospital stay was shorter in the patients who received intercostal liposomal bupivacaine, and more patients were ambulatory 24 hours after surgery. Rincavage and colleagues[28] compared intercostal nerve block with liposomal bupivacaine with 0.25% bupivacaine in patients undergoing robotic thoracic surgery. There were no differences in pain scores or opioid use between the 2 groups.

A recent Cochrane Collaboration group literature review evaluating liposomal bupivacaine found that, despite a few positive studies, the level of evidence to support the use of liposomal bupivacaine was low.[29] A critical review of the clinical data reported for studies of liposomal bupivacaine noted that the evidence supporting benefits beyond the first 12 hours is weak, and there are potential biases contained in the available studies.[22]

Our study attempted to address some of the criticisms of previous studies. Our prospective randomized design, with the patients blinded to their group assignment, mitigated the possibility of a placebo effect and potential biases. We also attempted to isolate the effect of the study drug by not providing patients with pregabalin or other agents that could influence postoperative pain and excluding patients from the study who might be taking pain medications or other agents that could affect the study outcomes. Our initial sample size calculation was based on a retrospective chart analysis, and we found a mean MED use of 27 mg. However, during the trial, the MED was significantly higher at 47 mg. Although the reasons for this are not entirely clear, we believe that the difference stems from incomplete chart documentation of PCA use, which was corrected because the research protocol demanded accurate documentation.

Study Limitations

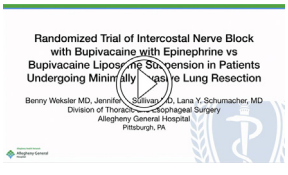
Our study is not without flaws. Perhaps the most glaring limitations are the small number of patients included in the trial and the fact that it was performed at a single center. Another important shortcoming was the strict inclusion criteria, which may have selected out patients with more complex pain problems, such as those taking chronic narcotics and pregabalin, and may limit the real-life applicability of the study. Although not statistically significant, there were more women in the control arm (bupivacaine with epinephrine). Although not well studied, sex differences in pain sensitivity and perception may be important and were not accounted for in our study. It is also worth mentioning that although there was no statistical difference in any of the variables examined, there are differences that may be clinically relevant, such as the difference in pain score on postoperative day 1 and the 2 mg difference in total MED during the hospital stay.

CONCLUSIONS

In a small, randomized study, we were unable to demonstrate that liposomal bupivacaine is better than standard bupivacaine with epinephrine at relieving pain after minimally invasive thoracic surgery. Larger studies are needed to confirm our findings. Until then, we advocate using the least expensive available formulation of bupivacaine in patients undergoing minimally invasive thoracic surgery, which is currently bupivacaine with epinephrine, and avoiding a more costly formulation without clear advantage.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Sunday_May5/203BD/203BD/S62%20-%20Doing%20the%20right%20thing%20I/S62_7.mp4.



Conflict of Interest Statement

Dr Weksler is proctor for Intuitive Surgery and Speaker for AstraZeneca. Schumacher is a proctor for Intuitive Surgery. All other authors have nothing to disclose with regard to commercial support.

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Key Words: postoperative pain, minimally invasive surgery, randomized trial

Discussion

Presenter: Dr Benny Weksler

Dr Sudish C. Murthy *(Cleveland, Ohio)*. Dr Weksler and colleagues present a small but randomized trial of conventional versus liposomal bupivacaine as the primary or principal source of initial pain control for patients undergoing minimally invasive lobectomy: VATS and robotic lobectomy. This is a timely report given the urgency to develop more effective narcotics-sparing pain regimens for our patients. However, in the push to do this, there are cost-containment

issues that seem to run in a counter direction. Navigating both of these issues can be difficult given that they seem to be intersecting tangents, if you excuse that oxymoron, but that is critical. This is precisely where this study seems to fit. As pointed out, the cost of liposomal bupivacaine is, conservatively, 30 to 50 times more expensive than the non-liposomal equivalent. In fact, for many of us who work in high-volume thoracic surgery centers that have liberally used liposomal bupivacaine, it is almost certainly the highest of your elective pharmacy charges. It is easy to beat this study up on the size, which is unfortunate, and I'm not sure we can really hold the investigators too responsible for the fact that it poorly recruited or that there was a job change by a senior faculty during the study. I understand that, and I'm sure you know, that this was probably not initially powered accurately, and you had slightly larger ambitions and the audience needs to know that, but let's just take the data for the data and not worry so much about the power calculations. I will let others in the audience address this. I just have one question for you. You have superb results in both groups with a length of stay of 2 to 2.5 days, and I'm wondering whether there is something else you are doing from your operative technique or from your institutional ERAS programs that is reducing pain in these patients, and, consequently, the contribution of pain as a surrogate for length of stay? Could there be something that you can identify in your lobectomy technique or perhaps port placement that might be contributing to these surprisingly good results in both arms? With that, I will step back and listen to your answer. Thank you for the honor to discuss this.

Dr Benny Weksler *(Pittsburgh, Pa)*. I don't know that I can take credit for anything different that we do. During the study period, we did not use any ERAS protocol. The idea was to try to isolate the effect of liposomal bupivacaine. The majority of our cases were robotic. We put ports on 1 single intercostal space, and the assistant port is almost below the diaphragm. If that's a contributor or not, I don't know, but from what I've seen the majority of people are using similar port placement. I do want to comment briefly in regard to power—and those are the things that happen in randomized studies sometimes—so we took the last 20 patients before we initiated the trial, and they had a mean morphine equivalent dosage use of 27 mg $\pm$ 3. We needed 86 patients for the study to establish within 90% power a difference of 25%, which I thought would be reasonable considering the cost difference between the 2 drugs. So what happened is when we did the randomized study, the mean morphine equivalent dosage in the control group was 47 $\pm$ 5, which means—and that's not appropriate statistically, Dr Katie Nason is looking at me waiting for me to say it—but theoretically at this level this study would be powered to detect a 20% difference in morphine equivalent dosage. So yes, it's underpowered because we didn't plan it like that, but I would not dismiss it offhand.

Dr M. Blair Marshall *(Boston, Mass)*. Benny, I enjoyed your talk. In your slides, you showed at the early time point, the pain scores were higher in the liposomal bupivacaine group. We noticed the same in our study. Because of the delayed onset of action of liposomal bupivacaine, many institutions have started to mix liposomal bupivacaine with bupivacaine. When you compared bupivacaine with bupivacaine with epinephrine, the latter has a more durable effect. So, I'm wondering if we can not only mix liposomal bupivacaine with bupivacaine but also with epinephrine to get the maximal effect?

Dr Weksler. It's possible. My pharmacy people are going to have a stroke if I propose that.

Dr Marshall. It's very safe to mix liposomal bupivacaine with bupivacaine; that's all been published.

Dr Weksler. Yes, I know. I really don't have an answer to your comment. What I do know, and it's important to know, is it is possible that minimally invasive surgery changed some of those paradigms a bit, and in a manuscript that I think is in press in the *Journal*, the ERAS pain protocol did not make a difference in patients undergoing minimally invasive thoracic surgery. I don't know if we're talking as much about the bupivacaine or the fact that we're doing more and better minimally invasive thoracic surgery.

Dr Stephen G. Swisher *(Houston, Tex)*. It's an interesting observation. Our OB/GYN group recently did its randomized study, and they observed dramatic improvement with implementation of ERAS, but there was no difference when they randomize between these 2 cohorts. So this may be due to your minimally invasive or implementation of ERAS.

Dr Weksler. Thank you.

Dr Raphael Bueno *(Boston, Mass)*. Nice study. Question and a comment. The question is: Should pain score really be the primary objective of this comparison trial? Because as Dr Murthy pointed out, the real objective question is financial, and we might as well address that, and that is measured in length of stay. I wonder if that would give you a better answer and will help us give a better answer to the bean counters who are controlling the drugs. As far as the comment: I think you're significantly underpowered. With Dr Jaklitsch in our group, we developed a prospective database and we were put in the situation that Sid Murthy

discussed, and we looked at it, and it took 350 patients in each arm—and a prospective database not a randomized trial—to show a real significant difference in all those things. I worry about being underpowered, putting something underpowered out there, and that potentially adversely affecting one way or another how we practice without really having sufficient data to show where we are. The question is: Is the pain score a good primary objective?

Dr Weksler. Regarding your question, I think you could go either way. Morphine equivalent dosage is a surrogate of pain score because patients in this trial, and it's described in the manuscript, because of time constraint, I did not say it here—they all used PCA. So if they have pain they press the button. I believe that is a good surrogate. In regard to your comment, we were planning to get to 100 patients, and we didn't get there, but I would not dismiss our results, which are in line with some other retrospective studies in minimally invasive surgery. There is one on patients undergoing robotic surgery that was retrospective, granted, but didn't show any difference. There are studies on knee replacement that have not shown any difference, and others on mammoplasty. There are plenty of data that question how good this thing is. In the manuscript, I've also quoted a critical article on the approval process of liposomal bupivacaine in which the only studies that were used compared it with placebo and not with normal bupivacaine, so I think there are some problems.

Dr Linda W. Martin *(Charlottesville, Va)*. I didn't hear any description of your technique. When did you inject it, how many interspaces, did you go transcutaneous or transpleural? I think those things are extraordinarily important in assessing the effect. Second, I was curious as to why you only recorded pain scores and morphine equivalents until day 1 if your patients were there until day 2 or 3, and obviously we would think that the plain (nonliposomal) bupivacaine has to run out, and we're going to see those pain scores change. I think those pain scores for the entire hospital stay are interesting and important to report along with this, and it's not telling the whole story if that's not there. Last but not least, I think it's great that you never have to convert to open, but to the rest of us that happens every so often. Using the liposomal bupivacaine at the beginning of the case gives you that flexibility.

Dr Weksler. The way that we did that is properly described in the manuscript, and we injected the skin before incision. As soon as we got in the chest in robotic cases, we did it through the skin and intercostal nerve block from the second or third intercostal space all the way down to the diaphragm. In VATS cases, we did it through the chest with one of those big needles. VATS cases were the minority of the cases. I really can't take any credit for not converting. Those were the 50 that we didn't convert. That doesn't mean that I don't have conversions. But your point I think is more toward the fact that there is more evidence that the liposomal bupivacaine is more helpful in open cases. But again, no randomized trials. There was one more question that I forgot. I'm sorry.

Dr Martin. I was wondering why you only recorded your outcomes at day 1 and 2 weeks. What happens on days 2 and 3 when the plain stuff runs out and they start to hurt.

Dr Weksler. We recorded these on days 0, 1, and 2. We have data on day 3 as well, but there were not a lot of patients still in house on day 3. Our median length of stay was 2.5 days, which makes that data a little weaker. So we recorded it, but didn't present it here.

Unidentified Speaker. Were you using any other adjuncts? Ketorolac, intravenous acetaminophen, gabapentin, and were they distributed evenly between the groups?

Dr Weksler. The short answer is no. The only agent that could be used for breakthrough pain was ketorolac, and that was used in a few patients and was equally distributed between the 2 groups.

Unidentified Speaker. You said they had a PCA?

Dr Weksler. Everybody had a PCA.

Dr Katie S. Nason *(Pittsburgh, Pa)*. A good way to get at the comment that Blair brought up about the effectiveness of the liposomal bupivacaine being several hours after injection would be to look at when the most PCA use occurred over the time that they had the PCA. Did you look at that to see if it was highest where you know in the postanesthesia care unit or the nurses are giving them doses because they're in a ton of pain because they didn't have the effect of the bupivacaine occurring yet? And then it tapers off, or is it is it the same distribution of both groups? Because that may argue for a mixture and overall reduce in the morphine equivalents as opposed to looking equivalent, but maybe when they took them was not equivalent, we just weren't seeing. Because I've operated with you and I know you know a lobectomy is relatively quick in your hands. So you could get in and out before the liposomal bupivacaine would even be working.

Dr Weksler. No, I think it's a good question, Katie. I don't have the answer to your question. We did not look at the data. I don't have the distribution of the morphine only the total dose. I may be able to get a better sense as this paper goes through review. People ask me that question on pain scores distributed through the day through day zero. So it is possible that we can gauge that variance.