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# Liposomal Bupivacaine is NOT Better than Bupivacaine in Limited Incision Thoracic Surgery

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BACKGROUND: The prolonged bioavailability of liposomal bupivacaine suggests it might have a therapeutic advantage over bupivacaine in saline. This is a retrospective analysis of limited incision thoracic surgery patients to evaluate if liposomal bupivacaine provided better pain control and altered outcomes compared to similar administration of bupivacaine in saline. This will give out a way to conduct future prospective randomized control trials to compare both LB and BS is superior to bupivacaine in saline. METHODS: Study group patients were limited to those undergoing wedge or segmental resection or lobectomy via VATS or Robot Assisted approaches. Forty-four patients received liposomal bupivacaine (LB) while 63 patients who received bupivacaine in saline (BS). RESULTS: For each group (LB v BS) the average length of stay (3.75 v 3.51 days), oral morphine equivalents (232 v 241 mg), and time to rescue narcotic dose (269 v 212 minutes) were not significantly different. CONCLUSIONS: Liposomal bupivacaine is considerably more expensive than bupivacaine in saline and did not demonstrate superior pain control and didn't change clinical outcomes.

Keywords: VATS; Bupivacaine; Thoracic Surgery; Pain

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## INTRODUCTION

Video-assisted thoracic surgery (VATS) utilizes limited muscle division and avoids rib spreading. Although no large prospective, randomized, controlled trial has compared VATS lobectomy with thoracotomy, well-designed retrospective studies have consistently shown that VATS has comparable oncologic outcomes and is associated with fewer complications, reduced length of hospital stay, improvement in patient quality of life, and superior tolerance of adjuvant therapies. [1-3]

The adoption of VATS has resulted in altered analgesic regimens in the postoperative period. Current pain management strategies for thoracic surgery range from continuous infusion via an epidural catheter or a para-spinal catheter, intercostal nerve blockade, paravertebral blockade, and wound infiltration. [1-2] Single injection local anesthetics have been considered adequate for short term pain control only, due to their relatively short half-life. Continuous infusion of local anesthetic to the surgical site via an indwelling catheter has had variable results. [1] The use of epidural catheters requires frequent monitoring and is often associated with hypotension, urinary retention, immobility and dislodgment. These interventions target peripheral nerves for pain relief, and often require supplementation by centrally acting oral or intravenous analgesics, mainly opioids and non-steroidal anti-inflammatory drugs.

Our standard protocol for postoperative analgesia after VATS is posterior intercostal nerve block with a long acting local anesthetic and postoperative pain management with opioid derivatives and ketorolac.

Liposomal bupivacaine was approved for clinical use in 2011, available in a single-dose vial at a 1.3% concentration (266 mg/20 mL). Its pharmacokinetic profile relies on the liposomal formulation, allowing slow release of bupivacaine, with an anesthetic effect reported to persist for up to 96 hours following injection. [1] Liposomal bupivacaine was found to be comparable to epidural analgesia for thoracic surgical patients (thoracotomy and VATS). [1] However, liposomal bupivacaine is considerably more expensive than bupivacaine in saline. The average wholesale price (AWP) of one 20-mL liposomal bupivacaine (Exparel) vial is $359.99 compared to the $2 to $8 average whole sale price of a vial of standard bupivacaine. [1-2]

Prior to April 2014 we had used 0.5% bupivacaine in saline. At that time, we began to use liposomal bupivacaine, replacing bupivacaine in saline for the posterior intercostal block. The purpose of this retrospective study is to assess whether liposomal bupivacaine provided better pain control and altered outcomes compared to similar administration of bupivacaine in saline. This will give out a way to conduct future prospective randomized control trials to compare both LB and BS.

## METHODS

Following Institutional Review Board approval and following HIPAA guidelines, using a prospective database, we conducted chart review of all patients who underwent minimally invasive thoracic surgery between January 2012 and September 2014. Only patients who underwent a primary procedure of wedge resection, lobectomy, or both, using a VATS or Robotic assisted surgical approach were included. Data collected from medical records included patient demographics, co-morbid conditions, and postoperative complications.

Surgical technique - After induction of general anesthesia, patients were positioned in a lateral decubitus position, prepped and draped in standard fashion. A double lumen tube or bronchial blocker was used for all procedures. For VATS a 4-5 cm $4^{th}$ or $5^{th}$ interspace access incision and a 12-mm $8^{th}$ interspace thoracoscopy port were placed, an additional posterior basal 10 mm $8^{th}$ interspace port was placed in some patients. For robotic procedures, 4 port sites were placed in the $7^{th}$ or $8^{th}$ interspaces with a subcostal access port. At the end of the procedure, under thoracoscopic guidance, a multilevel posterior intercostal nerve block was performed using 22G spinal needle placed over the superior border of ribs with injection of 2 cc into each interspace. Injections extended from 1 interspace above the access incision to the interspace below the lowest intercostal port incision usually encompassing 7-8 interspaces. The remaining bupivacaine was injected into the muscle and skin of all port sites. Morphine equivalents were administered via direct injection or PCA pump.

The total dose of liposomal bupivacaine for each patient was 266 mg, and total dose of bupivacaine in saline was 150 mg. Both were dosed using a total of 30 cc's. To reach this volume the liposomal bupivacaine was diluted with 10 cc of normal saline

to reach the final volume. All patients received bupivacaine in saline until April 2014 when we switched to liposomal bupivacaine. Outcome measures were chosen based on end points (standard in the literature), including the 1) length of stay, 2) total oral morphine equivalents consumed (based on standard relative potencies) and 3) time to first narcotic postoperative rescue dose, (defined as first narcotic medication given following recovery in post anesthesia care unit). Student's t-test and Fisher's exact test were used for statistical analysis.

## RESULTS

A total of 160 patients were identified, of which 115 underwent either pulmonary wedge or sub-lobar resection or lobectomy. Only scheduled elective procedures were included. 44 patients received liposomal bupivacaine, while 63 patients received bupivacaine in saline. Demographics and comorbidities are shown in Table 1. The liposomal bupivacaine group had a higher percentage of patients with a diagnosis of depression or anxiety, COPD, and a history of smoking, whereas the bupivacaine in saline group was older.

The average length of stay, average oral morphine equivalent consumed, and time to first rescue dose are detailed in Table 2. There was no statistically significant difference between the groups.

Complications amongst study patients are detailed in Table 3. Overall morbidity rate for the liposomal bupivacaine group was 19.0% and for the bupivacaine in saline group 27.4%, p = 0.48.

**Table 1: Demographics and Comorbidities** * Student's t-test, ** Fisher's Exact Test

| | Liposomal Bupivacaine | Bupivacaine in Saline | p-value |
|---|---|---|---|
| Number of Patients | 44 | 63 | |
| Age (Years) | 61.8 | 66.7 | 0.048* |
| Robot Assisted (n, %) | 6, 14% | 21, 33% | 0.024** |
| Female Sex (n, %) | 31, 70% | 35, 56% | 0.158** |
| Weight (Kg) | 72.0 | 76.7 | 0.21* |
| Depression/Anxiety (n,%) | 12, 27% | 6, 10% | 0.02** |
| COPD (n, %) | 9, 20% | 5, 8% | 0.08** |
| Obese (BMI>30) (n, %) | 7, 16% | 6, 10% | 0.38** |

| | | | |
|---|---|---|---|
| H/o Smoking (n, %) | 36, 82% | 36, 57% | 0.01** |

**Table 2: Outcomes** * Student's t-test

| | Liposomal Bupivacaine | Bupivacaine in saline | p-value* |
|---|---|---|---|
| Number of Patients | 44 | 63 | |
| Oral Morphine Equivalents (mg) | 232.61 | 241.52 | 0.942 |
| Time to Rescue dose (Minutes) | 269 | 212 | 0.628 |
| Length of Stay (Days) | 3.75 | 3.51 | 0.499 |

**Table 3: Complications in study group patients**

| AGE / SEX | LOS (days) | Access | Procedure | Group | OR time H:M | Final Diagnosis | Complications |
|---|---|---|---|---|---|---|---|
| 77F | 7 | VATS | Lobectomy, Wedge | LB | 3:14 | Squamous Cell Carcinoma | A-fib, superficial venous thrombus |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 65F | 7 | VATS | Lobectomy, Wedge | LB | 1:53 | Adenocarcinoma | Chest tube dislodged |
| 75F | 2 | VATS | Wedge | LB | 1:21 | Metastatic malignant melanoma | Surgical site infection, cellulitis |
| 58M | 2 | VATS | Wedge | LB | 2:11 | Small cell lung cancer | Chylothorax |
| 68M | 2 | VATS | Wedge | LB | 1:29 | Squamous Cell Carcinoma | ER visit for chest pain - CT shows Small Pneumohemothorax - patient discharged, Not admitted. |
| 54F | 5 | VATS | Wedge x2 | LB | 2:39 | Foreign body giant cell reaction | COPD exacerbation - readmission |
| 62F | 5 | VATS | Lobectomy | LB | 2:07 | Squamous Cell Carcinoma | mucous plug- resolved with bronchoscopy |
| 62F | 3 | Robot Assist | Lobectomy | LB | 2:35 | Adenocarcinoma | Post-operative Pneumothorax |
| 72F | 5 | VATS | Lobectomy | BS | 3:28 | Adenocarcinoma | Complicated by collapse LLL that resolved |
| 79F | 6 | Robot Assist | Lobectomy | BS | 4:25 | Adenocarcinoma | Medication error |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 50M | 6 | Robot Assist | Lobectomy, sleeve | BS | 4:57 | Neuroendocrine Carcinoma | RML collapse requiring bronchoscopy |
| 67M | 3 | VATS | Lobectomy, Wedge | BS | 1:20 | Adenocarcinoma | ER visit for pleuritic pain |
| 67F | 4 | VATS | Lobectomy, Wedge | BS | 2:22 | Adenocarcinoma | Fevers, health care associated pneumonia-readmission |
| 86M | 3 | Robot Assist | Lobectomy | BS | 2:28 | Adenocarcinoma | Urinary retention |
| 81F | 3 | Robot Assist | Lobectomy | BS | 2:14 | Adenocarcinoma | ER visit for anorexia |
| 69M | 4 | Robot Assist | Lobectomy | BS | 2:52 | Adenocarcinoma | Pneumothorax, Constipation - readmission |
| 64F | 3 | VATS | Wedge | BS | 0:47 | Adenocarcinoma | Postoperative SBO requiring exploratory laparotomy |

## DISCUSSION

Adequate postoperative analgesia is key to safe performance of lung surgery. When a thoracotomy is the approach, a thoracic epidural is regarded as gold standard for analgesia. Due to the reduction of tissue injury associated with smaller incision techniques, requirements for postoperative analgesia have been reduced. Compared to epidural anesthesia, paravertebral blocks have similar efficacy of pain relief after thoracotomy, with fewer side effects, however due to the short half-life, pain relief may be unsustained. [1-2] Liposomal bupivacaine has also been shown to be comparable to a thoracic epidural in certain situations without the attendant complications. [8]

Liposomal bupivacaine with its increased half life was felt to offer an alternative to thoracic epidural analgesia. It has a similar safety profile as bupivacaine in saline. [1] Liposomal bupivacaine has been shown to provide as effective analgesia as other local analgesics or compared to placebo, though none have shown conclusive evidence for a long-term analgesic effect of up to 96 hours. [1-5]

We began to use liposomal bupivacaine in hopes of seeing enhanced pain control reducing opiate usage and shortening length of stay. Anecdotal observation suggested a similar profile to bupivacaine in saline. Some patients had prolonged pain relief whereas in others the pain relief was

short lived. These observations led to the current retrospective study.

Our data shows that patients who received liposomal bupivacaine did not have enhanced pain control and the length of stay, total opiate requirement and time to first opiate dosage was similar. This observation is consistent with the assessment of Uskova and O'Connor that current data do not provide superior clinical results for liposomal bupivacaine over conventional bupivacaine. [1]

It is interesting that despite higher total amount of bupivacaine administered with liposomal bupivacaine, pain relief was similar. It is possible that the delayed release of bupivacaine in the liposomal form may not allow adequate release in the first 24-hour period when pain is most acute. Perhaps a combination of liposomal bupivacaine and bupivacaine in saline might provide superior pain control.

This study is limited by the fact that it is retrospective and not randomized. In addition, pain scores were not collected.

Liposomal bupivacaine is substantially more expensive than bupivacaine in saline. The average wholesale price (AWP) of one 20-mL liposomal bupivacaine (Exparel) vial is $359.99 compared to the $2 to $8 average whole sale price of a vial of standard bupivacaine. [9-10] Until there is clear evidence for its superior effect showed by some prospective randomized control trial its use cannot be justified.

## REFERENCES


1. Cheng AM, Wood DE. Minimally invasive resection of early lung cancers. Oncology (Williston Park, NY). 2015;29:160.166.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395.409.
3. Klapper J, D'Amico TA. VATS versus open surgery for lung cancer resection: moving toward a minimally invasive approach. J Natl Compr Canc Netw. 2015;13:162.164.
4. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116:248.273.
5. Joshi, G.P., Bonnet, F., Shah, R. et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg. 2008;107:1026.1040
6. Gebhardt, R., Mehran, R.J., Soliz, J., Cata, J.P., Smallwood, A.K., Feeley, T.W. Epidural versus ON-Q local anesthetic-infiltrating catheter for post-thoracotomy pain control. J Cardiothorac Vasc Anesth. 2013;27:423.426.
7. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. J Pain Res. 2012;5:107.116
8. Rice DC, Cata JP, Mena GE, Rodriguez-Restrepo A, Correa AM, Mehran RJ. Posterior intercostal nerve block with liposomal bupivacaine: An alternative to thoracic epidural analgesia. Ann Thorac Surg 2015:99;1953.60.
9. Liposomal bupivacaine: drug information. UpToDate. Waltham, MA: UptoDate; 2014. www.uptodate.com. Accessed December 24, 2014.
10. Bupivacaine: drug information. UpToDate. Waltham, MA: UptoDate; 2014. www.uptodate.com. Accessed December 24, 2014.



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