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Comparison of cost and outcomes in patients receiving thoracic epidural versus liposomal bupivacaine for video-assisted thoracoscopic pulmonary resection

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ABSTRACT

Background: Thoracic Epidural has long been the most recommended treatment for postoperative pain management in general thoracic surgery. This study compares liposomal bupivacaine (LB) as an alternative method for pain control and compares it to the standard.

Methods: LB was compared to thoracic epidural bupivacaine hydrochloride (TE BH) in 387 patients who underwent video-assisted thoracoscopic pulmonary resection (VATS-R) at our institution. Patients received either continuous TE BH or intraoperative LB at a predetermined dose. A total of 237 patients received TE BH from April 2010 to March 2014 and 143 patients received LB from April 2014 to March 2016. After propensity matching, 95 patients in each group had similar demographics and clinical characteristics including gender, age, race, American Society of Anesthesia (ASA) classification, Zubrod scores, and FEV1 and DLCO percent predicted measurements. Outcome measures included hospital costs, length of stay (LOS), adverse events, postoperative opioid medication use, and pain scores.

Results: Compared to the TE BH group, the LB group had significantly lower pain scores (average visual analogue scale the day of surgery: 3.9 versus 4.5, $p < 0.05$), decreased postoperative opioid medication (morphine equivalent dose during the first 3 days: 344.5 versus 269.5, $p < 0.05$), and lower total and direct hospital costs ($2906 and $1865 respectively, $p < 0.05$). Although a shorter LOS in the LB group was not statistically significant (4.3 versus 5.1 days, $p = 0.156$), more patients in the LB group were discharged directly home than the control group (44.2% versus 28.4%, $p < 0.05$). There was no difference noted in overall adverse events including 30-day readmissions between the two groups.

Conclusion: LB is a viable alternative for pain management in patients undergoing VATS-R. With recent scrutiny on healthcare costs and the opioid epidemic, these results are encouraging and should be further investigated.

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Introduction

Pain management in thoracic surgery is an ongoing challenge. Pulmonary function, postoperative activity and quality of life are all positively affected with optimized pain control.[1] Pain plays a primary role in both hospital costs and our country's increasing opioid epidemic.[2] Inadequate pain control may consequently lead to significant postoperative sequelae, including pneumonia, atelectasis and deep venous thrombosis.[3] Standard practices at various institutions consist of preoperative placement of a thoracic epidural with continuous infusion of 0.125% bupivacaine hydrochloride.[4–8] Although highly effective in many cases, TE carry known risks of hypotension, urinary retention, temporary peripheral paresthesia, epidural leak, and hematoma or abscess formation.[5,6] Additional drawbacks include patient body habitus and operator dependency

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as TE placement is generally carried out preoperatively by an anesthesiologist and runs continuously via pump until discontinued postoperatively.

Liposomal bupivacaine (LB) (Exparel®, Pacira Pharmaceuticals Inc., Parsippany, NJ) is an extended-release formulation of bupivacaine indicated for intraoperative administration into the surgical site. It is designed to allow for slow drug diffusion from the injected site for up to 72 h and to provide adequate local postoperative analgesia.[9] More recently, LB has been utilized for pain management in various surgical procedures within the thoracic, orthopedic, colorectal, and plastics literature. Previous studies have shown posterior intercostal nerve blockades using LB are safe and effective for patients undergoing thoracic surgery.[10] Additionally, studies have compared LB to paravertebral catheters as well as to bupivacaine hydrochloride injection alone within thoracic surgery patient populations.[4,11] There is very limited literature however, that compares outcomes in Video-Assisted Thoracoscopy Pulmonary Resection Patients (VATS-R) receiving LB versus TE BH and no literature was found comparing costs.

The objective of this retrospective, patient cohort, single-center study was to assess length of ICU and hospital stay (LOS), hospital cost, pain scores, and morphine equivalent dose (MED) of opioid use in patients undergoing VATS-R who received a multimodal pain regimen that included intraoperative LB compared with those who received TE BH. Additionally, adverse events and 30-day readmissions were analyzed. We hypothesized that surgeon-administered, intraoperative intrathoracic intercostal nerve block using LB would decrease total length of stay, hospital costs, postoperative pain scores, opioid use, complications and adverse events.

Materials and methods

This was an IRB-approved (799915–5), retrospective study that involved adult patients (aged 18 years of age and older) undergoing a primary VATS-R at OSF Saint Francis Medical Center in Peoria, IL between April 1, 2010 and October 31, 2016. VATS-R procedures included lobectomy, segmentectomy, wedge resection, and pneumonectomy. LB was introduced to VATS-R in April 2014, thus the patients with VATS-R between April 1, 2014 and October 31, 2016 were assigned into the experimental, LB group ($n = 143$) and the rest were considered as historical control subjects, TE BH group ($n = 237$). The LB group was also retrospectively reviewed. In order to minimize possible biases, a propensity score matching methodology was used to select 190 patients (95 patients in each group) for further analyses.

The two groups of patients were identified from the Epic Systems Corporate electronic medical record (EMR) system as well as from the Society of Thoracic Surgery General Thoracic Surgery Database, maintained by the Duke Research Institute. Each eligible patient's data was extracted and stored directly into an excel file by the research coordinator, then only de-identified data was used for analysis.

Primary outcomes included an assessment of total length of ICU and overall hospital stay, hospital costs, pain scores (0–10, visual-analog scale), morphine equivalent requirements and adverse events in patients undergoing VATS-R who received a multimodal pain regimen that included intraoperative LB compared with those who received TE BH. Hospital costs were adjusted by the 2016 Medical Care Consumer Price Index. We also reported 30-day readmissions and adverse events including atelectasis, pneumonia, intubation, new heart dysrhythmia, myocardial infarction, deep vein thrombosis, hypotension, sepsis, surgical site infection, and death. The distribution of types of resections were not analyzed in this chart review due to pain being presumably related to surgical approach (VATS vs thoracotomy) as opposed to the type of resection (lobectomy, wedge resection, etc.) in our study.

Covariates involved age, gender, race, body mass index (BMI), cigarette smoking, American Society of Anesthesiologists physical status classification (ASA), diffusing capacity of carbon monoxide in patient's lungs (DLCO), calculated percentage from respiratory tests reflective of the volume of air exhaled by a patient, creatinine, hemoglobin, steroids use, and comorbidities, such as chronic obstructive pulmonary disease (COPD), hypertension, heart failure, coronary artery disease, peripheral vascular disease, cerebrovascular history, and diabetes. These covariates were considered in the propensity score matching.

Intraoperative intrathoracic intercostal nerve rib blocks were performed during VATS-R with a long laparoscopic needle. According to our protocol, 20 cc of 1.3% LB diluted in 30 cc of saline to produce 50 cc. Approximately 5 cc were infiltrated into the intercostal space for up to 8 rib spaces. The remaining 10 cc were locally infiltrated into the mini-thoracotomy site used for extraction of the specimen. The method of administration was consistent amongst the two included surgeons. Postoperative pain management regimen included nonsteroidal anti-inflammatory drugs (NSAIDs), musculoskeletal relaxant, and oral opioids. For patients with unrelieved pain, patient controlled analgesia (PCA) was ordered on an individual basis. For the NSAID, ketorolac 15–30 mg IV (if not contraindicated by age or renal function) was given initially and then converted to ibuprofen by mouth (PO) when able to tolerate oral intake. The musculoskeletal relaxant given was scheduled orphenadrine 30–60 mg IV followed by cyclobenzaprine 5–10 mg PO three times daily. If used, PCA was discontinued at the time of chest tube removal, usually on postoperative day 1 or 2.

Statistical analysis

Data were cleaned and analyzed in the SAS 9.4 (SAS Institute In. Cary, NC, USA). Demographics and clinical characteristics were reported as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Chi-square test, *t*-test, and Wilcoxon rank sum test were used under different circumstances in the univariate analyses. The 1:1 matching between LB and TE BH patients was performed based upon the greedy method that was developed by Bergstralh and Kosanke.[12]

In multivariable analyses, generalized linear mixed models were employed to compare the differences of LOS, pain scores, MED of opioid use, and costs with a certain distribution (normal, lognormal, or gamma) as well as a random effect by matching identifiers. Aside from daily average pain score, the area under the pain score curve within 24, 48, and 72 h after surgery was calculated. Conditional logistic regression models were conducted to examine the likelihood differences of ICU use, disposition of home with self-care, 30-day readmissions, and overall adverse events.

Results

Both LB and TE BH groups had similar demographics and clinical characteristics after propensity score matching. Among 190 patients, the average age was 65.4 (±10.9) years old with a range of 19–87 years, half were female, and the majority (94.7%) were Caucasians.

The average LOS in the LB group (4.3 ± 3.5 days) was not significantly shorter than in the TE BH group (5.1 ± 5.3 days) with an adjusted p value of 0.227. Likewise, the differences of ICU utilization were not significant, either (14.7% LB group vs 9.5% TE BH group, adjusted $p = 0.272$). However, patients receiving LB were more likely to be discharged to home for self-care compared to TE BH (44.2% vs. 28.4%, adjusted $p = 0.039$).

The LB group had significantly lower pain score at rest scenarios on the day of surgery (3.6 ± 2.3 vs. 4.6 ± 2.0, adjusted $p = 0.002$) even though the LB group consumed less opioids (1.8 ± 6.9 vs. 5.4 ± 23.2, adjusted $p = 0.032$) prior to surgery. No differences of pain score between the two groups were noted on the following postoperative days, likely due to the TE BH group using more opioids than the LB group (MED within 72 h after surgery 336 ± 268 vs. 263 ± 214, adjusted $p = 0.031$). Similar results were also found utilizing the area under the pain score curve (Table 1).

The cost analysis shows that both total cost and direct cost were lower in the LB group compared to TE BH group (saving $2906 and $1609, respectively; adjusted $p < 0.05$ for each). As shown in Table 2, the saving of direct cost in the LB group could be mainly explained by lower medical cost (saving $1791, adjusted $p < 0.001$).

Additionally, this study did not find any difference between LB and TE BH groups in overall adverse events (26.3% vs. 21.1%, adjusted $p = 0.413$) and 30-day readmissions (10.5% vs. 8.4%, $p = 0.638$). Each group had one patient who died within 30 days after surgery.

Discussion

Using evidence-based medicine as a driving force, we noted an opportunity to objectively study the impact of LB. This study suggests that equally effective pain control could be achieved with the use of LB for analgesia in postoperative thoracoscopic surgery patients and was associated with overall improved surgical recovery, pain management and cost savings. Consequently, we have made the transition from TE BH pain management to LB in all general thoracic surgery patients while virtually eliminating PCA use and noting that our patients are rarely requiring IV opioids after leaving the post-anesthesia care unit. The VATS-R in our study included lobectomy, segmentectomy, wedge resection, or pneumonectomy. Though specific specimen pathologies were not analyzed, it is unlikely that it alone would have had a significant impact on pain control.

The current opioid epidemic has inspired a nationwide push to address the overuse of opioids. Our data noted an overall decrease in the use of opioid pain medication but no statistically significant difference in the reported pain scores. Given our findings, one could infer that the same subjective pain control could be achieved utilizing less opioids. This finding can be of great impact to the surgical community as it can provide an alternative adjunct for postoperative pain management.

Upon review of the literature, obtaining optimal pain control using systemic, regional or combination of both modalities after thoracic surgery have been utilized; TE, patient controlled analgesia, local anesthetic site infiltration, paravertebral and intercostal nerve blocks are among those reported. Systemic analgesics can include the use of NSAIDs, opioids, or ketamine. Alzahrani et al. provides a comprehensive review of techniques including intrapleural analgesia, serratus anterior plane block, and intercostal nerve block.[13] As far as the gold standard for postoperative thoracotomies, a TE is often employed.[4–8] In a 2016 Cochrane review, paravertebral nerve blockades showed no difference in 30-day mortality, major complications, or LOS when compared to TE blockade in thoracotomies.[14] However, TE have associated sequelae, most notably potential site infection, hypotension and urinary retention in addition to an oftentimes-needed dedicated pain service team for management. As more minimally-invasive thoracic approaches are used to reduce postoperative pain, pain though reduced, is still an important factor in reducing postoperative morbidity.

Regional analgesia has arguably fewer side effects. Other modalities include the use of lidoderm patches which have been reported in robotic cardiac surgery as adjuncts to pain control,[15] though with limited literature reports. Cryoanalgesia was also tested however, was reported to have associations with increased chronic neuropathic pain.[16] Catheter-based pain pumps that continuously infuse local anesthetic around the surgical site, commonly known as the OnQ Pain Relief System, have also been employed after thoracotomy.[17] We have had our subjective experience using the OnQ system for approximately 2–3 years and although we did not perform a formal outcome and analysis review comparing its use with, for example TE BH, we did not note a clinical difference in pain scores and opioid need at that time. In

Table 1
Pain score in visual analogue scale and opioid use.

	BH group (n = 95)	LB group (n = 95)	Unadjusted P value	Adjusted P value[a]
Average pain score (Activity)				
The day of surgery	4.5(2.6)	3.9(2.4)	0.169	0.147
First day after surgery	4(2.2)	3.5(1.8)	0.081	0.083
Second day after surgery	3.1(2.2)	3.1(1.8)	0.904	0.902
Third day after surgery	3(2.0)	2.9(1.9)	0.774	0.699
Average pain score (Rest)				
The day of surgery	4.6(2)	3.6(2.3)	0.003	0.003
First day after surgery	3.2(2)	2.9(1.7)	0.191	0.193
Second day after surgery	2.4(1.6)	2.5(1.7)	0.522	0.523
Third day after surgery	2.3(1.7)	2.2(1.8)	0.645	0.581
Area under the pain score curve (Activity)				
0–24 hrs after surgery	99.9(59.1)	88.8(49.7)	0.168	0.165
0–48 hrs after surgery	92.5(50.7)	82.7(41.1)	0.146	0.147
0–72 hrs after surgery	87.2(45.5)	78.4(39.6)	0.158	0.160
Area under the pain score curve (Rest)				
0–24 hrs after surgery	92.9(51.4)	78.7(46.2)	0.048	0.049
0–48 hrs after surgery	79.2(39.7)	69.4(39.9)	0.093	0.094
0–72 hrs after surgery	72.1(37.8)	65.7(38.0)	0.244	0.245
Morphine equivalent dose of opioid use				
Pre-surgery	5.4(23.2)	1.8(6.9)	0.149	0.032
Intra-operation	2.8(9.6)	2.3(10.1)	0.745	0.461
0–24 hrs after surgery	68.3(55.8)	59.6(56.6)	0.286	0.290
0–48 hrs after surgery	225.4(168)	188.3(153.6)	0.115	0.105
0–72 hrs after surgery	336.2(267.6)	262.8(214.1)	0.038	0.031

[a] Generalized linear mixed model with a normal (or lognormal) distribution and a random effect by matching identifiers.

Table 2
Hospital costs in 2016 US dollars.

Variable	BH group (n = 95, median and interquartile range)	LB group (n = 95, median and interquartile range)	Cost saving	Unadjusted P value	Adjusted P value[a]
Total costs	18301 (14971–22080)	15395 (13964–18503)	2906	0.024	0.024
Direct costs	11215 (9413–13631)	9607 (8537–11372)	1609	0.019	0.020
Pharmacy costs	496 (381–783)	801 (654–967)	−305	0.103	0.082
Medical costs	10335 (8767–11751)	8545 (7415–9835)	1791	0.003	0.011
Medical surgery supplies	185 (122–255)	110 (68–174)	75	0.003	0.002
Lab costs	642 (441–830)	487 (319–561)	155	<0.001	<0.001
Diagnostic radiology[a]	163 (123–208)	170 (127–226)	−6	0.595	0.583
Operation room costs	6138 (5046–7680)	5406 (4241–6085)	732	0.002	<0.001
Anesthesia	102 (90–118)	123 (97–150)	−21	0.005	<0.001
Pathology[b]	319 (200–455)	233 (160–311)	86	<0.001	<0.001
General room care	2182 (1526–3052)	1712 (1171–2773)	471	0.035	0.013

[a] The slight increase in cost of diagnostic radiology is reflective of an increase in radiology costs in the time frame during the study.
[b] The decrease in pathology costs are reflective of a decrease in pathology reports during the study time frame.

addition, catheter-based pumps have their associated nuances such as the need for removal of the catheter postoperatively, dislodgement, catheter occlusions, infection risk,[18] and components such as pharmacy, nursing and patient factors that may contribute to its associated morbidity.[19] LB studies have been employed for various surgical subspecialties; earlier 2015 reports of its use in thoracic surgery consider it a viable alternative to TE BH[10,11] and is becoming more widespread in its use.

There were other unexpected positive outcomes of our study using LB as well. Patients managed with LB were more likely to discharge to home or self-care while the TE BH patients had increased skilled nursing or rehab facility requirements. Patient disposition was determined by postoperative clinical status taking into account pain control, physical and occupational therapy rehabilitation needs, and nursing cares. As the patients were propensity matched prior to analysis we doubt that there is a bias in this result. Patient dispositions are unlikely due to a potential Hawthorne effect given the retrospective nature of the study; the patients were unaware at the time that outcomes were being reviewed and the two groups were reviewed in separate time frames. Optimized pain control plays a role in shorter time to ambulation and activity and decreased deconditioning, leading to an overall improved postoperative physical condition. This allows patients to return to home near their preoperative baseline negating the need for specialized care. Although we did not find a statistically significant decrease in the length of stay, the raw data suggested there was an almost 1-day earlier discharge in the LB group compared to the TE BH group, future studies may prove to be statistically significant with a larger sample size.

An unintended, though impressive finding was the large fiscal savings within the LB group with a total cost savings of $2906 per patient admission. In relation to costs incurred by the hospital, the initial cost of the LB may be higher ($285–315 per vial of LB compared to $1–3/vial bupivacaine hydrochloride), however the end return on overall investment in savings outweighs these seemingly high initial costs. There was no additional charge by surgeon for the intraoperative administration of LB. Healthcare costs are forever under scrutiny and we have found an alternative that not only lowers overall costs but improves patient comfort without adverse events. There is also an assumed additional savings that we were unable to capture for anesthesia provider services since they were a separate billing entity. Additional cost savings not included in our financial analysis revealed average anesthesia provider charges for epidural placement and management which approximated $1499.

This study has several limitations. First, this was a single center study and extrapolation of the findings may not be generalizable to broader population. Data on patient outcomes at our institution may not be generalizable to other institutions because factors that may have an impact on postsurgical outcomes, such as patient demographics, baseline comorbidities, surgical technique performed, and the postsurgical pain management protocol used, may differ between patient populations. Extrapolation of the findings herein to a larger or more heterogeneous population may be limited. For example, geographic location and hospital volume can affect readmission rates. Secondly, there is an initial learning curve (incision injection vs intercostal injection) with administration technique of LB. Knowing this, our data shows equal or improved pain control postoperatively even in the initial stages of the LB intercostal nerve rib blocking procedure, despite this associated learning curve. Thirdly, this was a retrospective study using historical controls and future randomized control trials should be done to further evaluate the efficacy of LB versus TE BH. Further comparison studies are needed to delineate what factors play a role in determining the benefit of cost reduction, but our results are promising.

LB is a strong adjunct in postoperative pain control, but its initial cost is often a deterrent for institutions to implement its use. This report may encourage a change in the postoperative pain management of thoracic patients at other institutions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.10.026.

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