Liposomal bupivacaine versus bupivacaine/epinephrine after video-assisted thoracoscopic wedge resection†

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Abstract

OBJECTIVES: The purpose of this research is to compare liposomal bupivacaine and bupivacaine/epinephrine for intercostal blocks related to analgesic use and length of stay following video-assisted thoracoscopic wedge resection.

METHODS: A retrospective study of patients undergoing video-assisted thoracoscopic wedge resection from 2010 to 2015 was performed. We selected patients who stayed longer than 24 h in hospital. Primary outcomes were length of stay and postoperative analgesic use at 12-h intervals from 24 to 72 h.

RESULTS: Intercostal blocks were performed with liposomal bupivacaine in 62 patients and bupivacaine/epinephrine in 51 patients. A Wilcoxon signed-rank test evaluated differences in median postoperative analgesic use and length of stay. Those who received liposomal bupivacaine consumed fewer analgesics than those who received bupivacaine/epinephrine, with a statistically significant difference from 24 to 36 h (20.25 vs 45.0 mg; \( P = 0.0059 \)) and from 60 to 72 h postoperatively (15.0 vs 33.75 mg; \( P = 0.0350 \)). In patients who stayed longer than 72 h, the median cumulative analgesic consumption in those who received liposomal bupivacaine was statistically significantly lower than those who received bupivacaine/epinephrine (120.0 vs 296.5 mg; \( P = 0.0414 \)). Median length of stay for the liposomal bupivacaine and bupivacaine/epinephrine groups were 45:05 h and 44:29 h, respectively. There were no adverse events related to blocks performed with liposomal bupivacaine.

CONCLUSIONS: Thoracic surgery patients who have blocks performed with liposomal bupivacaine require fewer analgesics postoperatively. This may decrease complications related to poor pain control and decrease side effects related to narcotic use in our patient population.

Keywords: Video-assisted thoracoscopic surgery • Liposomal bupivacaine • Pain management

INTRODUCTION

Pain management following thoracic surgery is imperative in preventing morbidity and mortality in our patients. Inadequate pain control following thoracic surgery not only leads to decreased patient satisfaction and quality of life but also to poor cough and clearance of respiratory secretions, leading to atelectasis, pneumonia and hypoxemia [1]. Additionally, inadequate pain control hinders patient mobilization, increasing the risk for deep venous thrombosis and pulmonary embolism [1].

One method for post-surgical anaesthesia is posterior intercostal nerve blockade. This method eliminates the need for indwelling catheters and reduces the technical failure rate seen with epidural infusions [2]. Historically, bupivacaine hydrochloride (HCl) in epinephrine (BE) has been used in intercostal blocks for postoperative pain control and has been shown to have a duration of action of 8–12 h following a single bolus [3]. However, the relatively short duration of action of bupivacaine may lead to ineffective postoperative pain control and increase the need for additional rescue analgesia.

In 2011, the US Food and Drug Agency approved multivesicular liposomal bupivacaine (MVLB) (Exparel, Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA), an extended-release formulation of bupivacaine that is exclusively indicated for single-dose...
administration into the surgical site for postsurgical anaesthesia [4]. The drug is not currently indicated for use in peripheral nerve blocks. MVLB is encapsulated within lipid-based particles, allowing for slow release and prolonged diffusion from the injection site [5]. Slow release from its delivery system and longer elimination half-life of MVLB results in prolonged post-surgical anaesthesia for up to 72 h [5]. Although studies exist demonstrating the use of MVLB as an alternative to thoracic epidural anaesthesia [6], there are limited data on the comparison of MVLB and BE for the management of pain following thoracic surgery. Our hypothesis is that patients who receive MVLB intercostal blocks following video-assisted thoracic surgery (VATS) require fewer postoperative rescue narcotics than those who receive BE.

MATERIALS AND METHODS

Study design

An institutional review board approved study (no. 2012-064) was performed using the patients of a single surgeon’s consecutive VATS wedge resections from 1 January 2010 to 1 December 2015. Each patient was formally consented regarding the off-label use of MVLB. There was no separate reimbursement for MVLB. BE was routinely used for the intercostal blocks from January 2010 until March 2013. Starting from March 2013, MVLB was the primary agent for the placement of intercostal blocks in all patients undergoing VATS wedge resections. In patients from both groups, intercostal blocks were placed intraoperatively following VATS wedge resection. The blocks were placed under direct vision, evenly distributed from the level of T3 to T10 using either 0.5% bupivacaine in 1:100 000 epinephrine or 20 ml of 13.3 mg/ml of MVLB (off-label use, approved by hospital institutional review board).

Inclusion criteria were all VATS wedge resection patients who were hospitalized for >24 h. Exclusion criteria included patients who stayed <24 h, administration of thoracic epidural anaesthesia, incomplete electronic medication reconciliation records, conversions to open thoracotomy and transfers to the intensive care unit. All procedures from 2010 to 2015 were performed under the guidance of the same attending surgeon with different trainees and featured 3 ports with a 5-mm 30° camera. Each trainee was instructed on how to place the intercostal block by one attending surgeon. Port distribution was similar for both groups and a utility port of 12–20 mm was used in all patients. The scope size remained the same throughout the duration of the study. All patients underwent VATS wedge metastectomies for diagnostic purposes.

A total of 113 patient medical records were reviewed. Patient characteristics identified were age, gender, body mass index and comorbidities including hypertension, hyperlipidaemia, coronary artery disease, arrhythmias, chronic obstructive pulmonary disease, diabetes mellitus type 2 and smoking history. Primary data points included postoperative inpatient narcotic use and length of stay. Perioperative results including acute cardiac or neurological events and rates of postoperative complications including pneumonia, persistent air leak >3 days, cardiac arrhythmias, deep vein thromboses, pulmonary emboli, nausea and emesis, constipation >7 days postoperatively, urinary tract infections and urinary retention were also assessed as secondary end-points.

Narcotic requirement assessment

In the immediate postoperative period, pain control in all patients was typically managed using hydromorphone patient-controlled analgesia. Once the patient was tolerating intake of clear liquids by mouth, they were transitioned to a combination of slow and immediate release oxycodone with intravenous hydromorphone as needed for breakthrough pain. Additionally, ketorolac was administered every 6 h for up to 12 doses. No ketorolac was administered if preoperative creatinine >1.4. Pain was initially assessed hourly while the patient recovered in the post-anesthesia care unit. Once the patient was transferred to the ward, pain was assessed with the patients’ vital signs every 4 h by nursing staff and all use of oral, intravenous and patient-controlled analgesia narcotics was recorded. These data were independently entered into the patient’s medical record by the nursing staff. Total postoperative analgesic use was calculated by converting each dose of narcotic into equianalgesic doses of IV morphine and adding the equivalent dose for every 12-h interval from 24 h to 72 h postoperatively. No changes were made to perioperative protocol between the groups. Additionally, no patient in either population had a documented allergy to opioid narcotics.

Length of stay measurement

The date and time each patient entered the post-anaesthesia care unit following their procedure as well as the date and time of their discharge was recorded. The length of stay was calculated as hours. If a patient’s length of stay was >72 h, only the first postoperative 72 h of opioid use were recorded.

Statistical analysis

The primary end-points measured in this study were interval and cumulative analgesic use and length of stay. A Wilcoxon signed-rank test evaluated differences in median postoperative analgesic use and length of stay. Non-normal data are presented as median [interquartile range (IQR): 25th–75th percentiles]. Secondary end-points were frequency of pulmonary, cardiovascular, gastrointestinal, haematologic and genitourinary complications. This information was gathered by examining hospital discharge summaries as well as outpatient postoperative visit records. These data were analysed using contingency table methods.

Comparisons were considered statistically significant at an alpha of \( P < 0.05 \).

One attending surgeon developed this protocol, including the instruments and techniques used and the postoperative pain pathway. In those included in data analysis, there was no deviation from the protocol between the 2 groups.

RESULTS

Eight hundred and twenty-one patients underwent VATS between 1 January 2010 and 1 December 2015, of which 194 underwent VATS wedge resections. Excluded were patients who were discharged within 24 h (29 in BE and 20 in MVLB), patients with an incomplete medication administration record or received thoracic epidural anaesthesia (29 in BE and 1 in MVLB) or patients whose procedures were converted to thoracotomy and were transferred...
to the intensive care unit (4 in BE and 2 in MVLB). In the remaining 113 patients, intercostal blocks were performed in 62 patients and BE in 51 patients.

Patient demographics and comorbidities were similar between the BE and MVLB groups (Table 1). There were 39 females (62.9%) and 23 males (37.1%) in the MVLB group and 32 females (62.7%) and 19 males (37.3%) in the BE group. The average age was 62.6 years (SD = 15.7) and 61.8 (SD = 13.8) years for the MVLB and BE groups, respectively.

At every interval postoperatively, those who received MVLB consumed fewer interval analgesics than those who received BE. The median narcotic consumption was 20.25 mg IV MSO₄ (IQR: 12.5–39.0), while the consumption in those who received BE was 33.75 mg IV MSO₄ (IQR: 30.0–52.5), with a statistically significant difference in the 12-h intervals (P < 0.05). The 25th and 75th percentile values are represented by the lower and upper ends of each box, respectively.

In patients who stayed >72 h, the median cumulative analgesic consumption was 120.0 mg IV MSO₄ (IQR: 112.5–272.5) in those who received MVLB and 296.5 mg IV MSO₄ (IQR: 212.25–414.0) in those who received BE, P = 0.0414. Median narcotic use between the 2 populations at each time interval is depicted in Fig. 2.
Perioperative outcomes are shown in Table 3. Perioperative outcomes in both groups were gathered by review of the intraoperative anaesthesia records, operative dictations, inpatient electrocardiograms, inpatient discharge summaries and outpatient follow-up records. There were no differences in perioperative pulmonary, cardiovascular, gastrointestinal, haematologic or genitourinary complications between the 2 groups. However, it is noteworthy to mention that there were 4 cases of pneumonia identified in the BE population within 30 days of their procedure. Each patient was treated with oral fluoroquinolones. Additionally, 2 patients in the BE group experienced an episode of persistent atrial fibrillation in the postoperative period, for which they each were discharged on oral anti-arrhythmic medication. No acute cardiac or neurological adverse events related to MVLB administration were observed.

![Graph showing postoperative cumulative opioid requirements in IV MSO4 equivalents. The blue and red circles represent cumulative opioid consumption in the bupivacaine/epinephrine (BE) and multivesicular liposomal bupivacaine (MVLB) groups, respectively. Wilcoxon signed-rank test.

**Figure 2:** Postoperative cumulative opioid requirements in IV MSO4 equivalents. The blue and red circles represent cumulative opioid consumption in the bupivacaine/epinephrine (BE) and multivesicular liposomal bupivacaine (MVLB) groups, respectively. Wilcoxon signed-rank test.

<table>
<thead>
<tr>
<th>Perioperative results</th>
<th>MVLB n (%)</th>
<th>BE n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0%)</td>
<td>4 (6.9%)</td>
</tr>
<tr>
<td>Air leak &gt;3 days</td>
<td>2 (3.3%)</td>
<td>3 (5.2%)</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>2 (3.3%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular arrhythmia</td>
<td>0 (0.0%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cardiac arrests</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and emesis in hospital</td>
<td>2 (3.3%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Constipation &gt;7 days postoperative</td>
<td>1 (1.6%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (1.6%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Urinary retention leading to recatheterization</td>
<td>1 (1.6%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>1 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

**Table 3:** Perioperative results

MVLB: multivesicular liposomal bupivacaine; BE: bupivacaine/epinephrine.

**DISCUSSION**

From this analysis, our data show that patients who receive MVLB require fewer postoperative analgesics than those who receive BE. As was anticipated, MVLB and BE provided similar analgesia within the first 24 h postoperatively. However, while the effects of BE are relatively transient, the prolonged release of MVLB appears to provide up to 72 h of improved pain control. For several years, surgeons at our institution have been injecting bupivacaine in epinephrine under direct supervision into the T3–T10 posterior intercostal spaces at the end of each thoracic surgery case. However, this intervention has a short duration of action that may not provide adequate analgesia after surgery. Liposomal bupivacaine has been used since March 2013 with the intent of providing a prolonged analgesic effect in comparison with BE. To our best knowledge, no studies have evaluated differences in pain control between bupivacaine and the extended-release multivesicular liposomal bupivacaine.

Several studies have validated the use of intercostal nerve blockade over thoracic epidural anaesthesia, citing equivalent pain control with reduced risk for systemic side effects and lower failure rate. In 2015, Rice et al. demonstrated that MVLB is equivalent to thoracic epidural anaesthesia with regard to postoperative pain scores, opioid use and perioperative complications [6]. Likewise, Khalil et al. concluded that intraoperative MVLB during thoracotomy was associated with significantly better pain control postoperatively compared with epidural analgesia [7]. Our analysis contributes to the larger body of literature that supports the use of MVLB for prolonged post-surgical analgesia. In addition, there were no adverse events reported with the use of MVLB. These data alone represent a significant contribution to the literature as MVLB has only been in use since 2013.

The consequences of poor pain control postoperatively are numerous. Uncontrolled pain following thoracic surgery can reduce forced expiratory volume, leading to atelectasis, hypoxia or pneumonia. Reduced ambulation also contributes to a higher risk for thromboembolic disease. While VATS has been shown to reduce postoperative pain when compared with thoracotomy, patients who undergo VATS still experience a significant amount of discomfort following their procedure. Additionally, the opioid narcotics that are administered to address this postoperative pain are associated with a wide range of side effects including gastrointestinal distress, hypotension, neurologic disturbances and urinary retention. Thus, it is of utmost importance to develop a pain management regimen that will adequately address their pain while placing them at the lowest risk for complications or side effects.

As with most studies that seek to assess adequacy of pain control, the highly subjective nature of pain was a limitation of the study. While other studies have sought to quantify postoperative pain using the numerical pain score, there can be discrepancies between numerical pain scores and actual narcotic use [7]. Additionally, while numerical pain scores are recorded at our institution upon administration of opioid narcotics, missing data, particularly in the older medical records, and the absence of how the pain score changed following delivery of pain medication made collecting numerical pain scores impractical in this study. Future studies should consider examining the change in pain score before and after narcotic administration as another means of assessing pain control. Additionally, this study includes only the inpatient narcotic requirements. Collection of outpatient
narcotic requirements would be useful in better characterizing the adequacy of pain control. Narcotic use is easily quantified and provides an objective and standardized evaluation of the very subjective sensation that is pain. However, as with all assessments of pain, factors such as variable pain thresholds, allergies to particular agents and opioid tolerance can be confounding when analysing narcotic use.

Unlike interval and cumulative narcotic use, there was no significant difference in length of stay between the MVLB and BE groups. While adequate pain control is one criterion that patients must meet before discharge, their time of discharge is contingent upon a multitude of variables related to the perioperative management strategies of the team of residents and nurses caring for them, specifically regarding advancement of diet, encouragement of ambulation and use of incentive spirometry. Because this was a retrospective analysis, it is difficult to ascertain the limiting factor in determining a patient's duration of hospitalization. Using retrospectively collected length of stay data from medical record abstraction, despite various known or unknown confounding factors, is a limitation of any retrospective observational study, ours included. In this study, length of stay is our best reasonable surrogate measure of pain control in the setting of narcotic administration.

Therefore, while patients in the MVLB group required fewer narcotics, it is unclear which confounding factors related to perioperative management may have influenced their length of stay.

This study only included patients who underwent VATS wedge resections, while excluding other thoracic procedures including lobectomies and thoracotomies. At our institution, VATS wedge resections are among the most commonly performed procedure within the Division of Thoracic Surgery, and thus able to generate well-powered, homogenous, data to be used in the study. We felt that the inclusion of other procedures would add additional variables to our data, making our conclusions less clear. Hence, the narrowed scope can be viewed as a limitation of the study. However, while this study focused on only one procedure, our aim in future research is to reproduce these improved pain control across all thoracic surgery procedures.

One concern in using local anaesthetic for intercostal block is the high rate of systemic reabsorption, increasing the likelihood of developing cardiac and central nervous system toxicities. Recently, Ilfeld et al. examined safety data from 6 controlled (Phases I–III) trials involving off-label use of MVLB in peripheral nerve blocks in 575 patients after various procedures including thoracotomy [8]. Among patients who received the FDA maximum approved MVLB dose of 266 mg in the Phase III studies, the most common adverse effects were nausea, pyrexia, pruritus and constipation. The most common treatment-related central nervous and cardiac toxicities were hypotension and bradycardia, respectively. The incidence of adverse effect (AE) was similar among bupivacaine HCl and placebo groups [8]. In our population, there were no acute neurologic or cardiac adverse events recognized in the postoperative period following administration of MVLB. Adverse events with MVLB in thoracic surgery has not been studied or published widely, so the demonstrable lack of adverse events is a significant contribution to the literature by itself. While retrospective studies are, by nature, subject to flaws, attempts to control for bias as best as possible in a consecutive population were made by maintaining strict adherence to the same postoperative protocol, excluding patients who fell outside of it, performing the block in the same way in all patients, despite being performed by different trainees in our teaching institution, and providing evidence of similar patient characteristics in both populations. Although additional study of its use is warranted, MVLB appears safe for intercostal block.

Perioperative outcomes were a secondary objective in this study. Pulmonary, cardiovascular, gastrointestinal, haematologic and genitourinary complications and side effects were similar between groups. While there were no significant differences in incidence of narcotic-associated side effects, it is noteworthy to mention that our study was not powered to detect differences in frequency of AE. Our small sample size limited our finding to statistically significant differences in frequency of AEs. A matched-case-control study has analytic limitations to sufficiently match a large enough sample for robust statistical testing as well as lack of collection of unexplained confounding data. Large, prospective double-blind randomized control trials are needed to examine more robustly the question of incidence rates of AE associated with MVLB versus BE. Currently, at our institution, we are collecting data as part of a larger prospective study aimed at providing more robust scientific data.

Among the most formidable barriers in adopting the widespread use of MVLB is its prohibitive cost. The average wholesale price of a 20–ml vial of MVLB is $285, significantly more expensive than bupivacaine HCl which has an average wholesale price of $1 to $3 per vial [9]. However, while there have not been any formal economic analyses on thoracic surgery patients, several studies have shown cost-effectiveness in using a MVLB-based, multimodal analgesia regimen in patients undergoing colorectal surgery. In a Phase IV health economic trial in patients undergoing open colectomy, Cohen observed that a MVLB-based multimodal regimen resulted in lower hospital costs, as well as shorter lengths of stay and less narcotic consumption compared with a standard opioid-based regimen in patients undergoing open colectomy [10]. Additionally, the open-label, multicentre IMRPOVE Phase IV health economics trial conducted by Marcket et al. demonstrated that a MVLB-based regimen was associated with a statistically significant reduction in inpatient costs, narcotic consumption and length of stay when compared with an IV narcotic-based pain control regimen in patients undergoing ileostomy reversal [11]. Currently, there are no large published data comparing cost-effectiveness of MVLB in thoracic surgery. While the patients in our study required fewer narcotics postoperatively and experienced lower rates, albeit not statistically significantly, of postoperative complications, larger studies are needed to derive the true economic impacts of utilizing MVLB in thoracic surgery patients. Although the data regarding reduction in hospitalization costs is found in other fields other than thoracic surgery and these studies do not necessarily represent the patients in this study, the results are encouraging and will hopefully drive further economic analyses in patients undergoing thoracic surgery who receive MVLB.

This study demonstrated that thoracic surgery patients who have blocks performed with MVLB following VATS wedge resection required less analgesics postoperatively than those who receive BE. The use of MVLB for intercostal blockade may help to achieve the highly sought after balance between efficacy and safety in pain management.

**Conflict of interest:** none declared.

**REFERENCES**


