Editorial

# Liposomal bupivacaine in minimally invasive thoracic surgery: something is rotten in the state of Denmark

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In the last decade, incorporation of minimally invasive approaches for a vast array of thoracic procedures has improved perioperative patient outcomes, however adequate postoperative pain control for thoracic patients remains a challenge. Inadequate pain control may result in adverse sequelae such as hypoventilation, retained secretions, respiratory failure, decreased mobility, and prolonged hospital stay (1). There is ample evidence in the literature of the effect these adverse events can have on postoperative morbidity and mortality.

Intercostal nerve blockade eliminates the need for more invasive analgesia (2). Historically, blocks performed with bupivacaine have been shown to have a duration of action of 8 to 12 hours following single bolus (3). Although this method provides adequate initial pain control, it may lead to ineffective prolonged postoperative pain control and need for additional rescue analgesia. Liposomal bupivacaine is a delayed-release formulation with a duration of action of up to 96 hours (4). There is now evidence validating the use of liposomal bupivacaine nerve blockade over epidural anesthesia in patients undergoing a thoracotomy and minimally invasive thoracic surgery (5,6). However, due to costs concerns, many institutions prohibit the use of this drug.

Dominguez *et al.* report the results of a retrospective study comparing liposomal versus standard bupivacaine in minimally invasive thoracic surgery, with the primary outcome being its effect on hospital stay (7). Secondary outcomes included 24-hour pain scores, opioid utilization, and time to ambulation. The authors evaluated patients undergoing video-assisted thoracoscopic surgery (VATS) wedge resections, VATS lobectomy, and minimally-invasive esophagectomy (MIE). They report an overall shorter length of hospital stay in the liposomal bupivacaine group compared to the standard bupivacaine group (1.35 *vs.* 2.45 days, P<0.0001) and this finding remained after stratification by type of surgery. Interestingly, the liposomal bupivacaine group had higher 24-hour pain scores compared to standard bupivacaine (P=0.002), although they did not find a difference in 24-hour postoperative opioid usage (P=0.664). Patients in the liposomal bupivacaine group had overall higher rates of ambulation at 24 hours after surgery compared to the standard bupivacaine group (P=0.003). Finally, readmission rates were 25% and 20% in the liposomal and standard bupivacaine groups, respectively (P=0.592).

Although the findings by Dominguez *et al.* contribute to the growing body of evidence supporting the use of liposomal bupivacaine for postoperative analgesia in patients undergoing thoracic surgery, their conclusions in the face of the data presented are of concern. Primarily, it is critical variables that are not accounted for in this study. First, the authors include patients who underwent VATS wedge resection, VATS lobectomy and MIE with limited details on the technical aspects of the operation. The authors state all operations were performed by three different thoracic surgeons, but it is unclear if the operations were performed all the same way. In the group of patients undergoing MIE, it is unclear if all cases were performed with a minimally invasive abdominal and thoracic approach following an Ivor-Lewis style of procedure. The operative times reported by the authors for such a procedure seem relatively short for the complete operation. Additionally, in the MIE group,

the authors do not include whether local analgesia was used for the thoracic incisions as well as the abdominal incisions. Moreover, the length of stay for the MIE patients in the liposomal bupivacaine group was exceedingly short (1.57 *vs.* 4.37 days). How can the authors explain this as it is not reflective of the current standards? Finally, the authors report quite high readmission rates in the two study groups but do not provide details relating to those readmissions or stratify by type of surgery. It is unclear if patients were readmitted due to surgical complications or for pain management.

Although the authors attempt to account for the heterogeneity of their cohort by presenting their data stratified by surgery type, this remains a significant limitation. For instance, MIE patients and patients undergoing VATS wedge resection and VATS lobectomy can have different sources of discomfort in the postoperative phase. MIE patients have thoracic and abdominal incisions and additional chest tubes compared to patients undergoing VATS wedge resection and lobectomy. Typically, for patients undergoing VATS wedge resection and lobectomy, duration of chest tube correlates to postoperative pain (8). There is no data on chest tube duration provided by the authors. This is a variable that one would expect to have significant impact on the pain scores, especially in the first 24 hours after surgery. The higher 24-hour pain scores in the liposomal bupivacaine group cited by the authors may have been driven by the MIE patients as one would expect 24-hour pain scores to differ between patients undergoing an MIE *vs.* VATS wedge resection or VATS lobectomy. More details about the procedures and stratification by surgery type could have provided further insight into this finding.

The authors did not find a difference in opioid usage in the first 24 hours after surgery and noted higher 24-hour pain scores in the liposomal bupivacaine group. Liposomal bupivacaine has an approximate duration of action of 96 hours and it is possible they would have observed differences had they included data past the first 24 hours after surgery. In contrast to the findings by Dominguez *et al.*, in a recent study by Kelley *et al.* there is reduced usage of postoperative opioids in the first 24 hours after minimally invasive thoracic surgery in patients receiving liposomal bupivacaine nerve blockade compared to standard bupivacaine, however they did not find a difference between 24 and 72 hours (9). We have also previously reported our own retrospective data on the use of liposomal bupivacaine and postoperative pain control in patients undergoing VATS wedge resections (10). We found patients who received liposomal bupivacaine consumed fewer opioid analgesics than those who received standard bupivacaine, with a statistically significant difference in the 12-hour intervals between 24 and 36 hours and 60 and 72 hours postoperatively. In addition, the cumulative use of opioid analgesics at 72 hours postoperatively was significantly less in the liposomal bupivacaine group. We did not find differences in length of stay or perioperative complications between the two groups. The conflicting data among these three studies are likely the result of multiple factors such as patient populations, operative procedures, and study design. However, to better understand the effect of liposomal bupivacaine on postoperative pain it is important to trend its efficacy over an extended period (i.e., longer than 24 hours) due to its long duration of action.

Dominguez *et al.* conclude liposomal bupivacaine is associated with a shorter length of stay after minimally invasive thoracic surgery. However, the seemingly aberrant data and abovementioned limitations prohibit the reader from arriving at the same conclusion. The authors report the study took place during a period of transition from standard bupivacaine to liposomal bupivacaine at their institution. One wonders whether this period of transition coincided with other institutional improvements in postoperative recovery protocols which have become more commonplace in the last decade. Improvement in surgeon technique is also unaccounted for, although it can be challenging to quantify. Finally, although the data on liposomal bupivacaine in minimally invasive thoracic surgery currently comes from retrospective studies, there is increasing evidence in the literature of its effectiveness in controlling postoperative pain. In the era of minimally invasive approaches for increasingly complex thoracic procedures and widespread implementation of enhanced postoperative recovery protocols, liposomal bupivacaine nerve blockade can have an impact. Ultimately, large randomized studies are needed to confirm its role in patient recovery.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

 

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