Peer Review File

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Reviewer A

Thank you for submitting the manuscript entitled Liposomal Bupivacaine Intercostal Block Placed Under Direct Vision 1 Reduces Morphine Use in Thoracic Surgery.
It is interesting that morphine consumption is lower in LB group 24-48 hours after surgery.
A little hard to convince the result and methods, I found and pointed out some questions and problems as below.

【Major points】

1. As the author said, the patients enrolled in the two groups are different in physical status including complication and respiratory function. There are big biases to compare. The surgeon possibly selected the high-risk patients for the TEA group because they expected strong analgesic effects. At least, the author should perform the comparison of the same physical status patients again, even if there were no differences in the additional analysis of respiratory function.
Comment: thank you for this comment, this is a valid point to emphasize and clarify.
Reply 1: The Charlson Comorbidity Index was not different between the 2 groups, as shown in Table 1. We also added ASA class comparison between the two groups and also found no significant differences between the group.
Changes in the text: Added ASA class comparison in Table 1

2. About the analgesic method, the TEA group's regimen is not sufficient in local anesthetic concentration and infusion dose compared to the LB group. It was hard that we expected equal analgesic effects.
Reply: Practices at our institution have changed more recently. TEA regimen is decided by our expert thoracic anesthesiologists. At the time this study was conducted, this was the dose that was frequently administered to our patients.
Changes in the text: none

3. Longer hospital stay may be due to catheter insertion, not epidural analgesia itself. If the epidural single shot of LB was used, LOS and analgesic effects would be totally different from this study.
Comment: thank you, this is a valid point.
Reply: We did not mention this in the original manuscript, but the length of chest tube duration was similar between the two groups. Furthermore, it was similar to the average duration of epidural catheters. Therefore, we don't believe that the length of the epidural catheter itself was a significant predictor of prolonged length of stay in the TEA group.
Changes in the text: page 11. Line 232.

4. Intercostal nerve block has a higher risk of analgesic toxicosis, furthermore, longer longer-acting drugs such as LB using intercostal block, the risk would be increased, which is why I am not able to agree on intercostal block using LB is more effective.
Comment: we appreciate your viewpoint. This is why this topic is still relevant and is worth further investigation.
Changes in the text: none

【Minor points】

1. The author should provide how to decide the patient's number enrolled in this retrospective study.
2. The flow chart of this study should be shown in Fig1

Comment: thank you for the comment. We included all patients undergoing a lung resection at our institution over an 8 month period. Everyone receives either a TEA or LB. No exclusion criteria were applied when determining eligibility. However, when conducting our 48-hour pain score analysis, we did exclude 69 patients who were discharged on POD1 (page 7, line 160).
Reply: We added a flow chart depicting overall cohort
Changes in the text: figure 1

Reviewer B

This is an interesting manuscript and adds to the ongoing dialogue regarding best practices in perioperative anesthesia.

My concerns are minor and at the Editors discretion to have them addressed prior to being published in this Journal.

1. The study, as mentioned by the authors, has significant selection bias. Patients with severe preoperative FEV1 were more likely to be chosen for TEA. Surgeons who perceived a more difficult resection opted for TEA which may account for the increased pain scores and LOS. It would be interesting to evaluate pain scores based on intraoperative time and intraoperative anesthesia which was admittedly varied.

   Comment: thank you for this comment. This is a valid point.
   Reply: The retrospective, observational design of this study does have certain limitations including bias. We had emphasized this in our Limitations section. However, it is noteworthy that ASA class and the comorbidity index, two measures of frailty and baseline comorbidities, were equivalent between the two groups. We added the ASA comparison in Table 1. Any individual selection biases that were present did not translate when comparing whole groups.
   Changes in the text: none

2. I think it is very important that you have highlighted the importance of

visualization of a subpleural weal, and the difference that technical administration may have in affecting postoperative outcomes. Especially, given the previous
Comment: thank you!
Changes in the text: none

3. It should be noted that while the authors review previous studies of liposomal bupivacaine (References 22 and 23). These studies have differing results because of the difference in administration. Both Kelley et al and Parascandola et al uses 20 ml of liposomal bupivacaine with normal saline at a dose of 13.3 mg/ml. While Kelley et al, administers 5 cc of liposomal bupivacaine at the beginning of the VATS procedure at every accessible rib space from T2 inferiorly, Parascandola et al, evenly distributes 20 cc of liposomal bupivacaine from levels T3 to T10 at the end of the procedure. Thus, the amount of medication and the content of the block is significantly different from the liposomal bupivacaine mixed with 0.25% bupivacaine, as studied in this manuscript.

Comment: thank you for this comment.
Reply: Our purpose in referencing these studies was to provide examples of other work that has been done focusing on the association between liposomal bupivacaine and opioid consumption post-operatively. Optimal doses can differ among institutions. What's more interesting is that our findings add to the body of literature supporting LB over TEA for post-operative pain control, despite the differing doses and methods of administration.
Changes in the text: page 14, lines 305 – 310

Reviewer C

Thank you for the opportunity to review this retrospective study comparing liposomal bupivacaine to TEA. TEA seems to be falling out of favor especially in cases where thoracotomy is not planned since there are alternative pain management techniques that are showing to be equally as good if not better. While this topic is timely, the approach would have to be significantly improved. Currently, the manuscript is only descriptive, and conclusions presented should not be made based on presented data and "analysis". I suggest major revision. Please see my specific comments below.
From the introduction, it is unclear what the primary and secondary outcomes are. Please be more specific.
Comment: thank you for this suggestion
Response: Our primary outcome was to compare post-operative opioid consumption between patients receiving TEA vs. LB. Our secondary outcomes were to compare post-operative pain, adverse events, and hospital length of stay.
Changes in the text: last paragraph of the introduction, page 5, lines 111 – 114

Methods

Methodology lacks sample size estimation, and adjusted comparison of outcomes between the two groups.
Inclusion, exclusion criteria clearly specified.
Comment: thank you for the suggestion
Reply: we added a flowchart to depict our cohort. All the patients undergoing a lung resection at our institution receive either TEA or LB. Our objective was to look at these patients over an 8 month period at our institution. We did not apply any exclusion criteria when determining eligibility. However, when conducting our 48-hour pain score analysis, we did exclude 69 patients who were discharged on POD1 (page 7, line 160).
Changes in the text: Figure 1

What is the rationale of injecting LA at the port site? Isn't this supposed to be covered by the intercostal blocks?
Comment: this is a good point
Reply: there is no specific rationale for this. This is just what our surgeons often do. There is no harm.
Changes in the text: none

Non-surgical readership may not be familiar with the postoperative complications grading system used in this manuscript (Clavien-Dindo). I suggest explaining what this is. Perhaps creating a supplementary table with explanations/examples that reader can refer to.
Comment: great suggestion
Reply: we have added a Supplementary Table 1 describing the grades of complications and their definitions
Changes in the text: Supplementary Table 1

Results
Add consort diagram please.
Comment: thank you for this suggestion
Changes in the text: see figure 1

Table 1, add **ASDs** instead of p values please.
Response: our statisticians are not familiar with this term.
Changes in the text: none

More patients in the epidural group had resections done for malignant lesion. Could these patients be more likely to have more generalized pain issues thus confounding your findings?
Comment: this is a valid point
Reply: we compared indication of surgery (for benign vs. malignant disease) between the two groups and found no difference. We included this new comparison in Table 1.
Changes in the text: Table 1.

Results should be restructured. If the primary focus of this article is to demonstrate that TEA and LB are similar in terms of postoperative pain management, then I would really like to see those results first vs reading about conversion rates, postoperative complications etc.
Comment: Thank you, this is great advice.
Reply: We have restructured our results to describe our primary outcome (pain scores and postoperative opioid consumption) before describing our secondary outcomes.
Changes in the text: starting at page 8

I find the whole paragraph on postoperative complications difficult to read because it is long and hard to place into context. Since this is not the primary outcome, I would consider listing these complications in a separate table format to get a sense of comparison between the groups. Just listing all these complications in its current form is very descriptive and I don't see the correlation between these complications and the groups studied. I would focus on those complications that may be at least somewhat directly related to the TEA or LB, examples: hypotension, A fib, respiratory failure, urinary retention, toxicity etc…
Comment: thank you for this suggestion
Reply: We simplified the description to now only mention the overall number of patients in each group who experienced a specific grade complication. Additional breakdown in shown in Table 4.
Changes in the text: page 11, lines 233 - 239. Table 4.

It is not informative to say that for example more patients who received TEA experienced grade II complications compared to LB group when there is no adjustment in analysis. If you have a group of older patients in TEA, that in and of itself could explain these findings.
Comment: Thank you for your comment, this is a valid point.
Reply: Our analysis focusing on ASA class and charlson comorbidity index (CCI) demonstrates no difference in baseline comorbidities and physical characteristics between the two groups. We believe this is more important than age alone when predicting who might be at risk for postoperative complications.
Changes in the text: none

Results page 9. 69 patients discharged on POD1 (68 of these were in LB group), then table 1, under "a" 323 patients had LOS >2 days. I find this somewhat confusing, perhaps stating under "a" 68 excluded from LB group, and 1 from TEA group due to discharge on POD 1, or simply list new "N" for both groups, it seems more transparent that almost none of the TEA patients had early discharge.
Comment: this a great clarifying suggestion
Reply: Under "a" in Table 1, we added the number of patients excluded from LB and TEA group
Changes in the text: table 1

Please include pain scores and SD as well as MMEs for both groups in results.
Comment: thank you for your suggestion
Response: added
Changes in the text: starting at page 9

Why was multivariable analysis only done on median hospital LOS?
Reply: Hospital LOS was significantly different between the two groups. Our analysis included several confounding variables that could be influencing LOS, such as grade of complication. Therefore, before concluding that type of analgesia is the only factor influencing LoS, we wanted to do a multivariable analysis acknowledging these other variables.
Changes in the text: none

Discussion
First paragraph statements are not supported by presented analysis and results.
Comment: We reworded it to focus on our findings. We moved the sentence "LB may be a good alternative to TEA for postoperative pain control in patients undergoing minimally invasive lung resections" from the introduction to later in the conclusion.
Changes in the text: page 12, first paragraph of the discussion. Page 15 – concluding statements.

Please add references page 11, line 239.
Response: this page is describing our results. We are not referencing any articles in this section.
Changes in the text: none

96 hours duration of LB has been challenged in the most recent literature.
Comment: this is a valid point
Reply: We removed the 96 hour duration as an explanation
Changes in the text: removed the '96 hour' explanation

Conclusion
Too strong. The study is retrospective in nature, primary outcome is not well defined, sample size analysis has not been presented, there is no adjusted analysis to compare the outcomes on (example, propensity matching), therefore, presented results can be viewed as heavily biased.
Comment: thank you for your comment
Reply: The retrospective, observational nature of this study does come with certain biases. We included this in our limitations. However, our goal was to provide additional insight into the LB vs. TEA ongoing discussions because results are still contradictory among studies. We encourage readers to conduct additional literature review when determining best practices.
Changes in the text: none