

Peer Review File

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Reviewer A

I thank the editors for the opportunity to review this manuscript. The study is a non-randomized retrospective analysis of patients undergoing 3 incision VATS lobectomy, by three different surgeons. Patients had three formulations of bupivacaine administered. The authors noted that patients receiving blocks with liposomal bupivacaine and regular bupivacaine with epi did the best for LOS and for pain.

Studies such as this prove that we all improve our outcomes with time and experience. The decreased LOS may be just as attributable to the team's processes for chest tube removal as the pain control. I do not discount the fact that pain control is important. (For full disclosure, this reviewer has published on this topic, and is cited in the references in this manuscript.)

The paper's conclusions regarding LOS may be prone to bias. The factor least likely to be altered is the actual amount of morphine used by the patient.

Were any adjuncts such as IV acetaminophen or ketorolac or ketamine used? How about gabapentin. The authors should be very clear as to any adjuncts administered by their anesthesia colleagues.

Was the block done at the beginning or end of the case? In my own experience, timing matters. Was this uniform across all three surgeons.

Overall, I thank the authors for submitting this manuscript. It is useful information. This drug has changed postoperative thoracic surgery care for the better.

Comment 1: The decreased LOS may be just as attributable to the team's processes for chest tube removal as the pain control.

Reply 1: Although our practice pattern remained unchanged during the study period other than type of intercostal agent used, we acknowledge the retrospective nature of the study makes it impossible to state unequivocally that confounders do not exist. We have added to our limitations in the discussion to clarify this point.

Changes in the text: page 9 "Still, given the study design, it is impossible to rule out all potential confounders that may have emerged over the time period of the study."

Comment 2: The paper's conclusions regarding LOS may be prone to bias.

Reply 2: Given that no single measure is perfect for assessing post-operative pain, we chose LOS because we believe that if a patient has better controlled pain that allows

them to ambulate and perform activities of daily living sooner after surgery, they are more likely to be discharged sooner. Additionally, it highlights a factor in overall hospital cost when considering the addition of a potentially costly therapy.

Changes in the text: Page 6 Methods, Outcomes section: “This was chosen as a measure of pain control because an improvement in post-operative pain allows patients to meet discharge criteria such as ambulation and activities of daily living sooner. Additionally, it highlights a factor in overall hospital cost, which is important when considering the addition of a potentially costly therapy.”

Comment 3: The factor least likely to be altered is the actual amount of morphine used by the patient.

Reply 3: We agree opioid measurement is imperfect on its own, but given an otherwise stable pain regimen (detailed under perioperative management section in Methods), it is still another surrogate marker for pain control.

Changes in the text: n/a

Comment 4: Were any adjuncts such as IV acetaminophen or ketorolac or ketamine used? How about gabapentin. The authors should be very clear as to any adjuncts administered by their anesthesia colleagues.

Reply 4: This is discussed in the perioperative management section within Methods on page 5, but the distinction between perioperative use of adjuncts by anesthesia and our own management on the floor is now emphasized in the text.

Changes in the text: Page 5 Methods, Perioperative management section
“Preoperatively, our anesthesiologists consistently provide oral acetaminophen with or without gabapentin. Intraoperatively, they administer ketamine in addition to the surgeon-performed INB. While in recovery, the anesthesiologists again administer acetaminophen with or without gabapentin and celecoxib. Upon transfer to the floor, we follow a standard protocol as follows: scheduled acetaminophen, scheduled gabapentin, oxycodone as needed, and hydromorphone as needed for breakthrough pain.”

Comment 5: Was the block done at the beginning or end of the case? In my own experience, timing matters. Was this uniform across all three surgeons.

Reply 5: As noted in the technique section under methods on page 4, we perform the block at the end of the case under thoracoscopic visualization, prior to chest tube placement. This was uniform across all three surgeons.

Changes in the text: Page 5 Methods, Technique section INB was uniformly performed percutaneously at the end of each operation under thoracoscopic visualization, prior to chest tube placement.

Comment 6: Overall, I thank the authors for submitting this manuscript. It is useful information. This drug has changed postoperative thoracic surgery care for the better.

Reply 6: We thank you for your time and comments in reviewing our work.

Reviewer B

Thank you for submitting the manuscript entitled “Intercostal Nerve Blockade with Liposomal Bupivacaine Reduces Length of Stay after VATS Lobectomy”

It is well constructed.

The reviewer would like to point out and ask the followings,

- It is valuable that you limited the patients who underwent lobectomies, it is more preferable and informative that the details of lobectomies (RU, RM...LU)and surgical time are shown in the table 1. In particular, surgical time can affect invasiveness.

- If the comparison of LOS is the primary outcome, the frequency of the postoperative complications should be shown in the result . Ideally, preoperative pulmonary function should also be shown or the definition of COPD is necessary. Because these parameters could influence on the outcome.

- The author described that patients receiving LB INB left the hospital a full day earlier than those receiving SB INB. The discharge criteria should be shown in the Methods part.

- The reviewer think the intraoperative opioid dosage can affect postoperative analgesia. I think the anesthetic methods and intraoperative opioid usage in the groups should be shown, at least, it should be mentioned in the Limitation part.

- Did you investigate the frequency of the other perioperative available analgesics including gabapentin, ketamine, celecoxib, oxycodone, and NSAID among the three groups?

Comment 1: It is valuable that you limited the patients who underwent lobectomies, it is more preferable and informative that the details of lobectomies (RU, RM... LU)and surgical time are shown in the table 1. In particular, surgical time can affect invasiveness.

Reply 1: The specific lobe resected as well as surgical times have been obtained and are now included in table 1. It should be noted that surgical times were, in fact, shorter among patients in the MIX group than each of the other two groups, however, there was no statistical difference in times between the SB and LB groups (the two groups with statistically different LOS).

Changes in the text: Table 1: Lobe resected as well as median procedure time for each type of bupivacaine has been added to Table 1. This is discussed in Methods, data

collection, page 6 “The specific lobe resected was extracted from the operative notes.” It is also added to Results, cohort characteristics, page 7 “The distributions of specific lobe resected were not different. The procedure times among the three groups were significantly different. Specifically, procedure time in the MIX cohort was significantly shorter than in each of the other two cohorts. There was no statistical difference between procedure time in the SB cohort compared to the LB cohort.” The procedure time difference is again addressed in the discussion on page 9, “There is an overall difference in the procedure times among the three groups. However, between the two groups with statistically different LOS, SB and LB, the procedure times were not statistically different.”

Comment 2: If the comparison of LOS is the primary outcome, the frequency of the postoperative complications should be shown in the result.

Reply 2: After looking back at all of our data and electronic medical records, we were unable to accurately extract this data at this time.

Changes in the text: n/a

Comment 3: Ideally, preoperative pulmonary function should also be shown or the definition of COPD is necessary. Because these parameters could influence on the outcome.

Reply 3: We are unable to retrieve pulmonary function testing results at this time. However, the text has been modified to define how a patient in our system is diagnosed with COPD.

Changes in the text: page 6, methods, data collection section “Comorbidities were electronically extracted. Specifically, chronic obstructive pulmonary disease is listed as a diagnosis in the patient’s chart only after a primary care physician or pulmonologist has verified the diagnosis based on symptoms and pulmonary function testing.”

Comment 4: The author described that patients receiving LB INB left the hospital a full day earlier than those receiving SB INB. The discharge criteria should be shown in the Methods part.

Reply 4: The discharge criteria has been added to the Methods section under perioperative management.

Changes in the text: Page 5 Methods, perioperative management “Patients are deemed suitable for discharge when they are able to manage their pain with minimal oral opioid medication, tolerate a normal diet, and perform near to their baseline level of activities of daily living. The decision regarding readiness for discharge is made by the attending surgeon.”

Comment 5: The reviewer think the intraoperative opioid dosage can affect postoperative analgesia. I think the anesthetic methods and intraoperative opioid

usage in the groups should be shown, at least, it should be mentioned in the Limitation part.

Reply 5: Anesthetic methods have been more clearly defined in the methods under perioperative management. Our anesthesiologists utilize ketamine for intraoperative pain control and do not use opioids.

Changes in the text: Page 5 Methods, perioperative management “Preoperatively, our anesthesiologists consistently provide oral acetaminophen with or without gabapentin. Intraoperatively, rather than opioid, our anesthesiologists administer ketamine in addition to the surgeon-performed INB. While in recovery, the anesthesiologists again administer acetaminophen with or without gabapentin and celecoxib.”

Comment 6: Did you investigate the frequency of the other perioperative available analgesics including gabapentin, ketamine, celecoxib, oxycodone, and NSAID among the three groups?

Reply 6: While exact dosages of gabapentin and acetaminophen were not recorded, our protocol involves standardized, scheduled dosing of both of these medications. Intra-operatively, ketamine is used for every case based on the patient’s height and weight. Post-operatively, NSAIDS are used on a case by case basis throughout the study period (mentioned in methods perioperative management section). All opioid use is tracked and reported as morphine equivalents.

Changes in the text: n/a