

Peer review file

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Reviewer A

Comment 1: VATs procedures and some detail is given in the introduction and perhaps in Fig 1, but nothing about what is included is actually given in Methods.

Reply 1: We agree with you and have reflected this comment.

Changes in the text: We reviewed electronic medical records of patients undergoing minor VATS procedures under general anesthesia.

(see Page 4, line 62-64)

We enrolled the patients with American Society of Anesthesiologists physical status (ASA-PS) 1- 2 who were scheduled for minor VATS procedures (bullectomy, partial lung resection and mediastinal tumor resection)

(see Page 9, line 151-153)

Comment 2: The first paragraph contributes nothing, Just start with the 2nd paragraph, but add a little more to opening sentence related to the purpose of current study.

Reply 2: We agree with you and have reflected this comment. We have deleted the sentence and added a sentence for risk of TEA and TPVB.

Changes in the text: TPVB has similar contraindications including coagulation disorders and anticoagulation (3) (7), and other major complications such as serious neurologic injuries same as TEA (3).

(see Page 6, line 99-101)

Comment 3: Were patients able to self-administer local via pump. Also, a range of infusion rates were described. How were they chosen? Could they be changed? Who changed them over the course of hospitalization?

Reply 3: You have raised an important question. We have added some sentences to answer this question. We also showed the infusion dose of local anesthetics in Result.

Changes in the text: The responsible anesthesiologists decided the choice of analgesia and dose for continuous infusion of local anesthetics. Patient controlled regional analgesia was not performed in this study. If adverse events such as PONV occurred, the local anesthetic flow was stopped or decreased until the event subsided, and then the flow was resumed. The decision was made by the anesthesiologists or surgeons.

(see Page 11, line 187-191)

The initial infusion dose of local anesthetics was significantly higher in the RLB group than in the TEA group (10.0 [9.0-10.0] ml/h in the RLB group and 5.0 [4.0-5.0] ml/h in the TEA group, ($p<0.01$)). The infusion dose of local anesthetics at POD 1m were significantly higher in the RLB group than in the TEA group (8.0 [6.0-10.0] ml/h in the RLB group and 4.0 [3.0-5.0] ml/h in the TEA group, ($p<0.01$)).
(see Page 19, line 333-337)

Comment 4: The paper indicates 10 primary outcomes. This is potentially a statistical problem that is not addressed. Using the definition that THEY use, most of the "primary outcomes" would be encompassed by the 95% confidence interval. I do not know if the definition they used (not described) has been used elsewhere for non-inferiority trials.

Reply 4: You have raised an important question. We have changed the primary outcome of this study to resolve these issues. The statistical analysis, we used in this study was described in the recently published paper entitled "Comparison of ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia after video-assisted thoracic surgery: a randomized controlled non-inferiority clinical trial. Reg Anesth Pain Med. 2020;45(1):10-5" (References 21). Please refer to this article.

Changes in the text: The primary outcome was the median differences in the numerical rating scale (NRS) scores during rest between the groups at the morning of postoperative day 1 (POD 1m).

(see Page 4, line 64-66)

The median differences in NRS scores during rest between the two groups at POD 1m were under 1, which indicates non-inferiority of RLB.

(see Page 4, line 71-73)

The analgesic effects of continuous ultrasound-guided RLB were non-inferior to those of TEA for minor VATS procedures.

(see Page 5, line 75-76)

The primary outcome of this study was the median differences in the NRS scores between the TEA and RLB groups during rest at the morning of postoperative day 1 (POD 1m). The secondary outcome parameters were NRS scores at rest and when coughing, postoperative initial narcotic rescue usage, rescue analgesics requirement in the ward, and adverse effects including incidence of hypotension, pruritus, urinary retention, postoperative nausea and vomiting (PONV), and the length of postoperative hospitalization.
(see Page 13, line 233-239)

The 95% CI of the median differences in NRS scores between the two groups are shown in Figure 2. The 95% CI of the median differences in NRS scores during rest between the

two groups at POD 1m were under 1, which indicates non-inferiority of RLB.

(see Page 18, line 322-325)

Our study suggested that the analgesic effects of continuous ultrasound-guided RLB were non-inferior to those of TEA for minor VATS procedures.

(see Page 24, line 428-429)

Comment 5: The term "comparable" as this was not an equivalence trial. Simply say it was non-inferior.

Reply 5: Thank you for your suggestion. We have reflected this comment.

Changes in the text: Our study suggested that the analgesic effects of continuous ultrasound-guided RLB were non-inferior to those of TEA for minor VATS procedures.

(see Page 24, line 428-429)

Reviewer B

Comment 1: At least redefine a continuous nerve blockade in the introduction.

Reply 1: Thank you for your suggestion. We agree with you and have incorporated this suggestion in the introduction.

Changes in the text: Continuous infusion of local anesthetics through catheter prolong the analgesic effects. However, there were no clinical reports that compare the analgesic efficacy of continuous RLB with that of TEA after thoracic surgery. We hypothesized that ultrasound-guided continuous RLB might provide analgesia as effective as that of TEA for minor VATS procedures. Thus the purpose of this retrospective propensity-matched study was to compare the postoperative analgesic efficacy and adverse effects of ultrasound-guided continuous RLB with those of TEA in patients undergoing minor VATS procedures.

(see Page 7, line 123-130)

Comment 2: Do the rates of TEA and RLB change in the post-operative period and if so, what parameters would affect such change. Were changes in rates recorded in your data?

Reply 2: You have raised an important question. We have added some sentences to answer this question.

Changes in the text: If adverse events such as PONV occurred, the local anesthetic flow was stopped or decreased until the event subsided, and then the flow was resumed. The decision was made by the anesthesiologists or surgeons.

(see Page 11, line 189-191)

The initial infusion dose of local anesthetics was significantly higher in the RLB group than in the TEA group (10.0 [9.0-10.0] ml/hr in the RLB group and 5.0 [4.0-5.0] ml/hr in the TEA group, ($p<0.01$)). The infusion dose of local anesthetics at POD 1m were significantly higher in the RLB group than in the TEA group (8.0 [6.0-10.0] ml/hr in the RLB group and 4.0 [3.0-5.0] ml/hr in the TEA group, ($p<0.01$)).
(see Page 19, line 333-337)

Comment 3: Were the doses of rescue analgesia recorded? How is the NRS being recorded? Is it asked by the same nursing team responsible for providing rescue analgesia? If so, it may bias the results whereby patient would over-rate their pain in order to ensure rescue medications.

Reply 3: Thank you for raising this important point. We administered two types rescue analgesics when the pain was not well controlled despite TEA or RLB uses. We recorded each doses of rescue analgesia. Because flurbiprofen equivalent dose for acetaminophen is not known, we compared the frequency of rescue analgesics uses between the two groups. NRS was recorded by the nursing staff. It might bias the result. We add the sentence in the method and limitation.

Changes in the text: In routine practice, the nursing staff asked the patients about pruritus, urinary retention, nausea and pain intensity. (see Page 14, line 239-240)

Fifth, the NRS scores were recorded by the nursing staffs, it might bias the results by which patient would overrate their pain in order to ensure rescue medications administered by the same nursing team. (see Page 24, line 421-423).

Comment 4: The methods who or what algorithm is used to decide if a patient receives an epidural or a RLB. Is this all anesthetist dependent? Are there known factors at your institution that may affect this choice?

Reply 4: Thank you for raising this important point. We have added a sentence in the method section who decide the choice of analgesia. We described in the limitation that propensity score matching analysis may have reduced the risk of bias and improved the validity of our analysis, selection bias was not eliminated.

Changes in the text: The responsible anesthesiologists decided the choice of analgesia and dose for continuous infusion of local anesthetics.
(see Page 11, line 187-188)

Comment 5: There are a total of 10 primary outcomes (pain scores at 5 different times in 2 different contexts, at rest and coughing), yet there is not adjustment for multiple

comparisons.

Reply 5: You have raised an important question. We have changed the primary outcome of this study to resolve this issues referring to the recently published paper entitled “Comparison of ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia after video-assisted thoracic surgery: a randomized controlled non-inferiority clinical trial. Reg Anesth Pain Med. 2020;45(1):10-5” (References 21).

Changes in the text: The primary outcome was the median differences in the numerical rating scale (NRS) scores during rest between the groups at the morning of postoperative day 1 (POD 1m).

(see Page 4, line 64-66)

The median differences in NRS scores during rest between the two groups at POD 1m were under 1, which indicates non-inferiority of RLB.

(see Page 4, line 71-73)

The analgesic effects of continuous ultrasound-guided RLB were non-inferior to those of TEA for minor VATS procedures.

(see Page 5, line 75-76)

The primary outcome of this study was the median differences in the NRS scores between the TEA and RLB groups during rest at the morning of postoperative day 1 (POD 1m). The secondary outcome parameters were NRS scores at rest and when coughing, postoperative initial narcotic rescue usage, rescue analgesics requirement in the ward, and adverse effects including incidence of hypotension, pruritus, urinary retention, post operative nausea and vomiting (PONV), and the length of postoperative hospitalization.

(see Page 13, line 233-239)

The 95% CI of the median differences in NRS scores between the two groups are shown in Figure 2. The 95% CI of the median differences in NRS scores during rest between the two groups at POD 1m were under 1, which indicates non-inferiority of RLB.

(see Page 18, line 322-325)

Our study suggested that the analgesic effects of continuous ultrasound-guided RLB were non-inferior to those of TEA for minor VATS procedures.

(see Page 24, line 428-429)

Comment 6: This is just a style preference, but often two sentences are used in the results when one could suffice.

Reply 6: Thank you for your suggestions. We have reflected this comment.

Changes in the text: The duration of general anesthesia was significantly longer in the

RLB group than in the TEA group (124.0 [112.5-133.0] min in the RLB group and 96.0 [85.0-111.0] min in the TEA group, ($p<0.01$)). Intraoperative remifentanyl consumption was significantly higher in the RLB group than in the TEA group (1.3 [1.1-1.7] mg in the RLB group and 1.0 [0.7-1.3] mg in the TEA group, ($p<0.01$)). There were no significant differences in the intraoperative fentanyl consumption between the two groups (200.0 [100.0-250.0] μ g in the RLB group and 150.0 [100.0-200.0] μ g in the TEA group, ($P=0.13$)). There were no significant differences in the duration of postoperative thoracic drainage between the two groups (2.0 [2.0-4.0] day in the RLB group and 2.0 [2.0-3.5] day in the TEA group, ($P=0.345$)). There were no significant differences in the length of postoperative hospitalization between the two groups (6.0 [5.0-8.5] day in the RLB group and 5.0 [4.0-8.0] day in the TEA group ($P=0.226$)). (see Page 17, line 303-315)

Comment 7: It would be preferable to see unmatched results as well as matched results to compare the two.

Reply 7: Thank you for your suggestion. We have added a supplemental table for unmatched results.

Changes in the text: Postoperative NRS scores between the TEA group and the RLB group before propensity score matching is available in the Supplemental Material. (e-Table)

(see Page 17, line 296-298)

Comment 8: 438 records may have been reviewed, it is incorrect to say that 438 records were enrolled. Only 192 patient records met your inclusion criteria, and thus this constitutes your enrolment.

Reply 8: Thank you for the advice. We have changed this sentence as suggested.

Changes in the text: A total of 192 relevant records of patients were enrolled in this study. (see Page 4, line 62)

Comment 9: Line 16: it is not necessary to justify the reasoning behind your choice of a non-inferiority design.

Reply 9: Thank you for the advice. We have removed this sentence as suggested.

Comment 10: Line 39-41: Please correct the statement or reference appropriate studies.

Reply 10: Thank you for noticing this mistake. We have corrected the statement and

reference.

Changes in the text: TEA and TPVB provide comparable pain relief after thoracic surgery (4) (6). TEA protect against pulmonary complications than intravenous opioid administration (2).

(see Page 6, line 93-95)

Comment 11: TPVB has less contra-indications to TEA. Please describe the contra-indications and complications that you are referring to.

Reply 11: Thank you for the advice. We have described the contra-indications and complications.

Changes in the text: TPVB has similar contraindications including coagulation disorders and anticoagulation (3) (7), and other major complications such as serious neurologic injuries same as TEA (3).

(see Page 6, line 99-101)

Comment 12: Reference 9 is an editorial, it does not have original data to suggest VATS is associated with moderate-severe pain

Reply 12: Thank you for the advice. We have removed this sentence as suggested.

Comment 13: Line 56-58: back up this statement with a reference. the syntax of the sentence is incorrect.

Reply 13: Thank you for the advice. We have revised the sentence, and added the reference.

Changes in the text: Minor VATS procedures, including VATS bullectomy and wedge resection for lung cancer, were performed using smaller incisions and leading to shorter hospital stay compared to those of VATS lobectomy (12).

(see Page 7, line 111-113)

Comment 14: The relationship between post-operative pain and type of procedure may be more complex and such statement would therefore require empirical evidence to support it.

Reply 14: You have raised an important question. We could not find out the evidence that support minor VATS procedures are associated with less perioperative pain scores compared with that of VATS lobectomy. Thus, we have rewritten the sentence.

Changes in the text: Although it is not known whether minor VATS procedures are associated with less perioperative pain scores compared with that of VATS lobectomy,

(see Page 7, line 113-115)

Comment 15: If RLB can be performed without ultrasound, why did you chose to use ultrasound at your center? Is it easier/safer with ultrasound?

Reply 15: Thank you for the advice. We have added the new sentence.

Changes in the text: Although RLB can be performed without ultrasonography, ultrasound images allow for visualization of the needle and local anesthetic distribution.

(see Page 7, line 119-121)

Comment 16: Line97-98: “where the main surgical incision was to be made” if the block is performed after surgery is completed what is this incision that will be made?

Reply 16: Thank you for noticing this error. We have changed the sentence.

Changes in the text: where the main surgical incision was made.

(see Page 10, line 170-171)

Comment 17: rakuraku should be capitalized.

Reply 17: Thank you for the advice. We have reflected this comment.

Changes in the text: Rakuraku

(see Page 10, line 176)

Comment 18: Line 131: what conversion factors were used to convert narcotics to MME?

Reply 18: Thank you for the advice. We have added the conversion factors with reference.

Changes in the text: Narcotic rescue usage is standardized to morphine milligram equivalent (MME; morphine: pethidine: fentanyl = 1:10:0.01) (20).

(see Page 12, line 209-211)

Comment 19: I would recommend changing the term to “when coughing.”

Reply 19: Thank you for the advice. We agree with you and have incorporated this suggestion throughout our paper.

Changes in the text: when coughing

(see Page 13, line 222) (see Page 14, line 236) (see Page 18, line 319) (see Page 18, line 320) (see Page 19, line 325) (see Page 19, line 327) (see Page 21, line 366)

Comment 20: typo? “the all surgeries”

Reply 20: Thank you for noticing this error. We have changed the word.

Changes in the text: All surgeries

(see Page 13, line 229)

Comment 21: It seems odd to measure this as an outcome

Reply 21: Thank you for raising this important point. We have deleted from the outcome.

Comment 22: Line 159: How was urinary retention measured? How are the other secondary outcomes measured?

Reply 22: Thank you for your advice. We have reflected this comment by adding the sentence.

Changes in the text: In routine practice, the nursing staff asked the patients about pruritus, urinary retention, nausea and pain intensity.

(see Page 14, line 239-240)

Comment 23: Line 167: I believe you mean multivariable instead of multivariate.

Reply 23: Thank you for noticing this error.

Changes in the text: To estimate the propensity score, a multivariable logistic regression analysis was used based on the following covariates

(see Page 14, line 248-249)

Comment 24: Line 188: I believe the correct term is Hodges-Lehmann (not Lehman).

Reply 24: Thank you for noticing this error.

Changes in the text: NRS scores using the Hodges-Lehmann estimator.

(see Page 15, line 268-269)

Comment 25: Line 189: Reference 19 used total postoperative oxycodone consumption as its outcome and used a difference of 10 as their non-inferiority margin. It is incorrect to say it used “1.0” as the difference. Also, please state that the 1.0 mentioned is a difference in reported pain scores.

Reply 25: Thank you for your suggestion. We have referred the article entitled “Comparison of ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia after video-assisted thoracic surgery: a randomized controlled non-inferiority clinical trial. Reg Anesth Pain Med. 2020;45(1):10-5” (References 21). We defined an acceptable non-inferiority margin as 1.0 according to the previous study (21).

(see Page 15, line 269)

Comment 26: Line 194: I don't think the word enrolment is appropriate for a retrospective study. I believed the correct wording would be “438 records were reviewed”

Reply 26: Thank you for the advice. We have reflected this comment.

Changes in the text: A total of 438 relevant records of patients were reviewed in this study.
(see Page 17, line 291-292)

Comment 27: Line 226: Although one can figure out what “POD 1m” stands for (POD1 morning) it is never explained in the text and only explained in Table 2 caption.

Reply 27: Thank you for the advice. We agree with you.

Changes in the text: The primary outcome of this study was the median differences in the NRS scores between the TEA and RLB groups during rest at the morning of postoperative day 1 (POD 1m).

(see Page 13, line 233-235) NRS scores were recorded 6 and 12 hours after surgery, POD 1m, the evening of POD 1 (POD 1e) and the morning of POD 2 (POD 2m).

(see Page 14, line 240-242)

Comment 28: Line 236: were rescue narcotics available for patients and just not consumed? Or were they never available? Your data suggests no patients in either group used narcotics.

Reply 28: Thank you for the advice. Narcotics were only available for patients in the operating room. These results compare the narcotic rescue usage in the operating room. We have added the sentence.

Changes in the text: Narcotics were only available for patients in the operating room.

(see Page 12, line 210-211)

There were no significant differences in the narcotic rescue usage (MME) in the operating room between the two groups.

(see Page 19, line 330-332)

Comment 29: Please state the p-values from Table 3 when saying there is no significant differences in frequency of rescue analgesics and incidence of PONV.

Reply 29: Thank you for the advice. We have added the p-values.

Changes in the text: There were no significant differences in the frequency of rescue analgesics use between the two groups ($P=0.87$). There were no significant differences in the incidence of PONV between the two groups ($P=0.17$).

(see Page 19, line 339-341)

Comment 30: Line 254-255 is redundant and the exact repeat of the prior paragraph. I recommend removing it altogether.

Reply 30: Thank you for the advice. We have removed the sentence.

Comment 31: Line 260: syntax

Reply 31: Thank you for noticing this error.

Changes in the text: porcine cadaver models
(see Page 21, line 375)

Comment 32: Line 263: syntax error

Reply 32: Thank you for noticing this error.

Changes in the text: Although our dosage used in this study provided effective analgesia comparable to that of TEA for minor VATS procedures, the optimal dosage of local anesthetic required for achieving effective analgesia is still not clear.
(see Page 21, line 377-379)

Comment 33: Line 265-266: This sentence is redundant and simply paraphrasing the prior sentence.

Reply 33: Thank you for the advice. We have removed the sentence.

Comment 34: What about elector spinae blocks as mentioned on line 299?

Reply 34: Thank you for the advice. We have removed the elector spinae blocks from the sentence.

Changes in the text: RLB are considered to be safer maneuvers than TEA and TPVB.
(see Page 23, line 411-412)

Comment 35: Is it possible to review “total anesthesia time” in order to clarify if TEA+GA is significantly different from GA including RLB?

Reply 35: Thank you for raising this important point. Unfortunately, we did not measure the time for TEA in our patients. Therefore, we are unable to “total anesthesia time” comments.

Comment 36: Line 280-282: this sentence seems unfinished or has a syntax error

Reply 36: Thank you for noticing this error.

Changes in the text: The longer duration of anesthesia was accompanied with higher intraoperative remifentanyl consumption in the RLB group compared to that of TEA group.
(see Page 22, line 392-394)

Comment 37: I do not agree that minimally invasive surgery necessarily requires less invasive analgesia.

Reply 37: Thank you for the advice. We have removed the sentence.

Comment 38: The authors do not discuss the safety profile compared to TPVB or elector spinae blocks.

Reply 38: Thank you for the advice. We have added the sentence about discussing the safety profile of RLB compared to TPVB. We have deleted the words of elector spinae blocks from the sentence.

Changes in the text: RLB could also reduce the risk of pneumothorax and incidental epidural injection of local anesthetics considered as a complication of TPVB (15). RLB are considered to be safer maneuvers than TEA and TPVB.

(see Page 23, line 409-411)

Comment 39: it would be appropriate to say chi-square, fisher exact or Wilcoxon rank sum was used as appropriate for the distribution as the distributions would affect whether parametric or non-parametric testing is used.

Reply 39: Thank you for the of advice. We have reflected this comment.

Changes in the text: χ^2 test, or Fisher's exact test or Mann-Whitney U test was used as appropriate for the distribution as the distributions would affect whether parametric or non-parametric testing is used.

(see Table 1)