

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-50>

Reviewer A

Comment 1: typo in title on "patient", please fix as well as in the intro section.

Reply: Thank you for pointing the typos out. We fixed all the typos.

Changes in the text: In "Title page" section, Page 1, we modified the typo in Title.

Changes in the text: In "Abstract" section, Page 1, we modified the typo in background, line 4.

Changes in the text: In "Introduction" section, we modified the typo in Para 2, line 4 and Para 4, line 2 and 9.

Comment 2: The anesthesiologists were not blinded, do you think this made an impact on perioperative opioid and management

Reply: We didn't mask the anesthesiologists in operating room due to several reasons:

(1) The primary difference between the two groups is paravertebral blocks+ultra sparing opioids in Opioid-sparing group and routine opioid-based anesthesia during the operation. We were unable to blind anaesthesiologists who performed the blocks in operating room. However, patients were blinded, as the blocks were performed after induction of general anaesthesia.

(2) We implemented strict anesthesia and analgesia protocols to let the local anesthesiologists follow in OR. In Opioid-sparing group, patients were given blocks and remifentanil, and remifentanil doses were adjusted to objective variables as SPI between 20-50. In routine opioid-based anesthesia, local anesthesiologists uses sufentanil also adjusted to SPI between 20-50. Therefore, the intraoperative opioid use may not be affected.

(3) After surgery, patients may use the patient-controlled anesthesia pump in PACU and surgical ward where the PACU anesthesiologist and surgeons were both blinded to group assignment. Therefore, the postoperative opioid use may not be affected.

In summary, we didn't think unmasked anesthesiologists may affect the perioperative opioid management.

Comment 3. The addition of PCA pumps to both groups may skew the results somewhat, did the authors ever discuss not adding the PcA group in the paravertebral block group and then use as an outcome failed PCA or did fine without PCA, that would provide further insight that paravertebral blockade does indeed provide better pain control?

Reply: Thank you for your advice. We agree with you and added the changes in discussion per your advice. We used PCA to both groups as to mask patients and surgeons in surgical ward in postoperative pain management. As you mentioned, paravertebral blockade may provide better pain control compared to routine anesthesia after surgery . In our previous publication, paravertebral blockade extended the onset of perceivable pain from 12 hours to 16 hours after surgery (Eur J Anaesthesiol 2021; 38 (Suppl 2):S97–S105.) Not adding the PcA to both group may enlarge the difference between groups, with respect to pain control or recovery.

Changes in the text: We added the sentence “ The addition of PCA pumps to both groups may skew the results somewhat, and not adding the PCA to both group may enlarge the difference between groups, with respect to pain control or recovery.” in Discussion, limitation, Page 19, para 2, line 10-13.

Comment 4: can the authors also include a table or chart for the quality and OBAS scores to have p values with it, i see it in the text but not in the figures?

Reply: Dear professors, we have Quality and OBAS scores in Table 2 (Please check the review panel updated on February 24), with median Difference and P value between groups. Because of technique problems, the tables was missed in the first version, but finally editorial office fixed that problem on February 24. So we have all the data you required (The primary and secondary outcome in Table 2).

Comment 5: is there a reason why routine VATS lobectomies are NOT extubated in the OR right after surgery, it seems as though all patients are extubated in the PACU,

these findings could also throw off some of the data about postop pain control?

Reply: Thanks for your question. Owing to the large surgical volume in our institute, we have 5-8 thoracic cases in one OR. To enhance the OR efficiency, we extubate patients routinely in PACU.

Comment 6: Did the authors think about using a routine postop pain PO regimen for both groups thus that would provide a more controlled postop pain management profile, and decrease treatment biases?

Reply: PCA technique is a validated and frequently used delivery method providing self-administered doses of analgesic medication to relieve postoperative pain. In thoracic postoperative analgesia, PCA is still the mainstay for postoperative pain management, so we used intravenous PCA in our trial as a means to control postoperative pain. Postop pain PO regimen for both groups may be feasible, and Oral-PCA has become an adaptive dispenser using tablets that are to be swallowed.

A recent published study concluded that Oral-PCA by PCoA® Acute provides pain control and usability which is noninferior to that achieved by the IV-PCA for postoperative analgesia after hysterectomy and limb surgeries. However, the analgesics efficacy of Oral-PCA compared to PCA in thoracic surgery has not been confirmed.

Comment 7: I agree with the authors that the Quality of life surveys may not be the best way to assess pain by the patient even 24 hours after surgery, as many patients are still incapacitated and not able to answer survey related questions, with that being said, how were the surveys filled out? by patient, by family member, by research associate? how many actually completed surveys at 6 hours vs. 24 hours, i imagine less so for 6 hours postop?

Reply: We filled out almost all the patients after randomization. 80/80 patients in routine anesthesia group and 79/80 in opioid-sparing anesthesia group at 6 hours and 24 hours. Because Quality of life surveys are our primary and secondary outcome, so we assigned an independent well-trained research nurse to conduct the survey in surgical ward. Therefore, the surveys at 6 hours vs. 24 hours were all complete.

Comment 8. Was there consideration for exparel use by thoracic surgeons there?

Reply: Thanks for your pointing it out. Exparel is a long-lasting local anesthetics approved by FDA, but it was still not approved in China now. Although a recent study showed that Liposomal Bupivacaine may provide better pain control, we were unable to use this local anesthetics. Further, we may try to investigate it after being approved by Chinese authorities.

Comment 9. Why paravertebral blocks vs. epidural blocks at your instiution?

Reply: Thank you for your advice.

In our institution, 90% of thoracic surgeries are VATS and 60% cases were given paravertebral blocks. Thoracic epidural analgesia has been considered the gold-standard of pain management after open thoracotomy. However, in recent years, paravertebral blocks have gained significant popularity, especially under ultrasound guidance. The current guidelines strongly recommend the use of a regional anesthetic technique, favoring paravertebral blocks because of their improved side-effect profile (Teeter EG, Kolarczyk LM, Popescu WM. Examination of the enhanced recovery guidelines in thoracic surgery. *Curr Opin Anaesthesiol.* 2019 Feb;32(1):10-16).

Comment 10. Is that true, 19,000 thoracic cases per year, that is a LOT of cases, is that a typo?

Reply: Yes, the number is absolutely correct. We have the largest surgical volume in Chinese thoracic specialty and actually the number is still growing with average 1800 thoracic cases per month.

Comment 11. Were your thoracic surgeons involved in this plan or just anesthesia?

Reply: No, thoracic surgeons were blinded to the group assignment.

Comment 12. who managed the patients afterwards, thoracic surgeons, hospital based medicine docs, anesthesia docs? or a combination of?

Reply: For the postoperative pain management, patients were given PCA after transferred from PACU, and if they claimed severe pain, the thoracic surgeons may

prescribe rescue medications.

Comment 13. Do the authors have a plan to just look at lobectomy patients only? i do think 60% of sublobar resections is a lot and i agree that you would not see a huge benefit in these patients w/ paravertebral blocks?

Reply: Yes, we agree with you on this point. Lobectomy may be a further interesting hypothesis to address the benefits of our opioid-sparing scheme, due to its more invasive procedures.

Changes in the text: We add the sentence “Lobectomy may be a further interesting hypothesis to address the benefits of our opioid-sparing scheme, due to its more invasive procedures.” in discussion, para 6.

Comment 13. Also were the authors able to see or r/o patients included in the study if they had severe chronic pain or on pain meds prior to the surgery, as this would skew the results as well, was this factored in?

Reply: Thanks for your reminder. We didn't enroll any patients with preoperative chronic pain or taking pain medicine, or have thoracic surgery before which may have bias on patients selection.

Changes in the text : We added this sentence “or converted to open thoracotomy, have chronic pain or take pain medicine prior to surgery, or undergone thoracic surgery before” in Text, “Materials and Methods” section, para 3, line 2-4.

Comment 14: Overall this is a nice study as it is randomized and I applaud the authors on using paravertebral blocks, however can more quantitative data be showed in the figures/charts/tables section?

Reply: Dear Pro. we have all the data uploaded by editorial office on February 24(Tables). Please check it and any questions please contact us.

Reviewer B

This is very important work and should help move all of us to less use of opioid based analgesics.

Comment 15: Is there a reason why everyone didn't receive paravertebral blockade?

Unfortunately, introducing this variable makes it hard to make conclusions about the effectiveness of simply changing anesthetic management to avoid opioids.

Reply: Recently, an increasing number of anesthesiologists have incorporated ultrasound-guided TPV blockade into their routine practice, especially for in-plane transversal technique. Ultrasound-guided TPV blockade could provide better pain control, but it also requires more practice to obtain a good view of TPV space, so that not all patients received paravertebral blockade. Moreover, this approach. It's imperative that ultrasound-guided TPV blockade are subjective to a critical evaluation based on reported outcomes of effectiveness and safety in clinical trials, therefore, we aimed to validate the advantage of TPV blockade in promoting patients' recovery. We hope our present data may help in better comprehension and application of ultrasound-guided TPV blockade

Comment 16:Also, can you explain why the first 6 hours didn't show any difference? The addition of paravertebral blockade should have improved this.

Reply: We aimed to find the benefits of our opioid-sparing strategy on quality of recovery in the first 6 hours which is our primary outcome. Even paravertebral blockade truly improved pain and opioid-related side effects, including dizziness, nausea and vomiting, but we failed to find the clinically meaningful difference of QoR-15 owing to some reasons (**addressed in the Discussion section, Para 2**): among the QoR-15 questionnaires, pain, physical comfort, physical independence, emotional distress, and psychological support all constituted the components of QoR-15. Even pain and nausea were under control, the other domains of QoR-15, especially physical independence and psychological support (Been able to enjoy food, Able to look after personal toilet and hygiene, Able to return to work or usual home activities) both still had lower scores; Second, being an indicator reflecting patients' recovery, **change of 8** in QoR-15 as the minimally clinically important difference were based on an observational study of 204 patients, none of whom underwent thoracic surgery [24]. Although the difference between groups was 4 which reached statistical difference, but it didn't reach clinical meaningful difference of 8. Therefore, it remains unclear whether QoR-15 could detect the minor changes in the immediate postoperative period for thoracic patients.

Comment 17: Lastly, I think it will be important to emphasize education in the recovery room as the initial few hours rarely reflect longer term outcomes, as you've demonstrated.

Reply: Yes, we absolutely agree with you on this point.

Changes in the text: We added your advice in "Discussion section, para 2": "Third, it should be more active to emphasize patients' education before the surgery and in the recovery room as the initial few hours rarely reflect longer term outcomes".

Reviewer C

It is unclear to me why QoR-15 at 6 hours after surgery is shown to be statistically significant ($p=0.000$) on table 2 (page 26), yet most of the components of QoR-15 at 6 hours after surgery as shown on table 3 (page 27) are statistically insignificant, and the conclusion is that "opioid-sparing anesthesia was not superior to routine anesthesia on patient-reported QoR-15, at 6 hours after surgery" (last paragraph, page 19). As QoR-15 at 6 hours after surgery is the designated primary outcome of the study (2nd para of Outcomes, on page 9), this inconsistency is of major significance, and needs to be clarified.

Comment 18

Reply: Thanks for your question. QoR-15 at 6 hours after surgery is statistically significant, with the median difference of 4 between groups, reaching to statistical significance, but not clinical meaningful significance (changes of 8 in QoR-15). Here, QoR-15 score is referring to the global score of QoR-15, not the components of QoR-15 (we clarified this definition in Methods section, outcome, page 7 in Text). We found the difference of QoR-15 global score was only 4 between groups at 6 hours after surgery, then we analyzed the reason which components were significant or not. Most of the components of QoR-15 at 6 hours after surgery are statistically insignificant, with only 3 survey were significant (20%). And that may explain why we only got the median difference of 4 in the global scores.

Changes in the text: We clarified this point and made changes in the first para in Discussion section: "In this randomized assessor- and patient-masked trial, we found that our opioid-sparing anesthesia regime was not superior to routine anesthesia on the global score of QoR-15 at 6 hours after surgery in patients having VATS lung resection.

The median difference in the global score of QoR-15 between groups was 4 and it appeared unimportant given the minimum clinically important difference for QoR-15 of 8 [17]”.

Reviewer D

Comment 19. Overall, an interesting study. This further contributes to the growing literature supporting the use of blocks in thoracic surgery to minimize postoperative opioid use. The authors could have provided more information about the operations performed to give the readers a sense of the extent of surgeries performed - a simple VATS wedge is different from a VATS lobe with regards to operative time which can result in more pain given the manipulation of the VATS ports. In addition, although the QOL questionnaires used are useful, it would have been more objective to use other measures to quantify patient outcomes such as the 6-min walk distance mentioned by the authors.

Reply: We agree with you.

Changes in the text: We have add the sentence in Discussion section, para 4, limitations: “Lobectomy may be a further interesting hypothesis to address the benefits of our opioid-sparing scheme, due to its more invasive procedures. ”.

“Although the QOL questionnaires used are useful, it would have been more objective to use other measures to quantify patient outcomes such as the 6-min walk distance mentioned.”