Peer Review File

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Reviewer A

Congratulations to the authors on your brilliant clinical study. However, there are several questions causing the acceptance of your article in doubt. The following are my personal opinion and comments.

Comment 1: (1) It is a retrospective study in which bias in patients' selection and treatment could not be avoided.

Reply 1: Unfortunately, the bias is partially true and inevitable because the population of patients with mediastinal tumors or cysts is limited even though it was a prospective study.

Comment 2: (2) Are there something wrong about the total number of patients, enrolled into this study, 172 or 182 ? (line 76 and 166).

Reply 2: Sorry for typo, 172 is correct. We correct line 76.

Changes in the text: L76 "182⇒172"

Comment (3) I could not find out table 1-3.

Reply 3: We attached the tables of excel files. It was impossible to read. We attached again the file reformed by the word file.

Comment (4) I could not find out the solid evidence of fentanyl or acetaminophen doses during operation to prove the difference between groups.

Reply 4: as mention above, I attached the tables in words.

Comment (5) How to explain the incidence of PONV are more in TEA than in TB ? Is there standard formula of PCA for TEA ? This study showed the benefit of thoracic epidural analgesia after robotic-assisted surgery, but there were still some pitfall of the patient profile and clinical data collections

Reply5: Thank you for your valuable comments**,** as your comments, the incidence of PONV is much more in TEA than TB in this retrospective study, because the postoperative continuous epidural infusion regimen of our institution usually includes opioids such as morphine. On the other hand, in TB group, postoperative intravenous fentanyl in PCA bottles can be adjusted mainly for the patients' requirements. We think that is why TEA group had more incidence of PONV. We have to reconsider the regimen of TEA to reduce PONV postoperatively.

Change in the text5: we referred that in L238" This suggests the need for improving PCA regimes, such as by using dexmedetomidine (26), or for improving TEA regimes by omitting opioids."

Reviewer B

The authors conducted a retrospective study of 169 patients who underwent video-assisted thoracic surgery for mediastinal disease. They compared postoperative pain in the first 48 hours (based on NRS), rescue analgesic requirements and side effects of anesthesia and analgesia in

three groups of patients: GA alone, GA + TEA, GA + ultrasound-guided thoracic block. They concluded that TEA provided better analgesia but that thoracic blocks might also provide adequate postoperative analgesia.

I would like to thank the authors for sharing the results of this study and congratulate them on the clarity of their writing. In particular, the methodology is very clearly specified.

I have a few comments/questions:

Comment1: - Methods: The authors first mention 182 patients (line 76) and then 172 (line 166) as shown on the flow chart. Have ten patients been excluded? Why were they excluded? Please, explain.
Reply1: Sorry for typo, 172 is correct. We correct line 76.
Changes in the text: L76 "182⇒172"
Comment 2: - Methods, lines 88-91: The peroperative combination of remifentanil and fentanyl is unusual. Do the authors have a comment on this?
Reply2: Thank you for the valuable comment**,** we usually add fentanyl on propofol-remifentanil anesthesia to prepare postoperative analgesia and to reduce intraoperative remifentanil concentration, which may cause postoperative shivering.
Comment 3: - Methods, lines 92-93: Doesn't the wound infiltration by the surgeon only in some but not all patients in the AG alone group bring confusion? In how many patients was this performed? Please, comment in the manuscript.
Reply3: Thank you for your valuable comment**.** In almost all cases they did the local anesthetics but the dose of it was varied. And we replace the phrase as below
Change in the text: L92-93 "In twenty-three cases, the surgeons performed local anesthetic infiltration with 0.25% levobupivacaine (3-10 mL) ~~or ICB for each incision~~**"**
Comments 4- A limitation of the study is that there was no standard baseline analgesia protocol. Indeed, intraoperative acetaminophen were not administered basally in all patients. NSAIDs were given as rescue medication in the postoperative period but was a dose of NSAIDs given pre- or intraoperatively? The lack of systematic basal pre- or intraoperative analgesia with acetaminophen and NSAIDs, as recommended by some scientific societies (e.g. ESRA's PROSPECT initiative), is an important limitation of the study and should be clearly mentioned.
Reply4: We agree with your opinion. Your opinion should improve our manuscript.
Chang in the text: L244-249: The second limitation of the study is that there was no standard baseline analgesia protocol. Indeed, intraoperative acetaminophen was not administered basally in all patients. NSAIDs were given as rescue medication in the postoperative period but not pre- or intraoperative period. Since systemic basal pre- or intraoperative analgesia with acetaminophen and NSAIDs is recommended by some scientific societies, we should reconsider our protocol in the near future. Third,
Comments5: - Discussion, lines 230-231: the authors mention "the incidence of postoperative hypotension was not different between groups" but 8 patients in the TEA group experienced hypotension while none in the other two groups (table 4). The p-value = 0.06 is very close to the statistical significance level. This should be detailed.
Reply5: Yes, it is close to significantly different. If we used the statistic method which was not

strict, a significant difference might be acquired. We added the phrases as below.

Change in the text: L231-236 Although only in TEA group, 8 patients experienced postoperative hypotension, while the other groups were not, the incidence of postoperative hypotension was not significantly different among the groups (P=0.06). This is possible because our TEA method successfully reduced the amount of local anesthetic administered by combining epidural opioids with local anesthetics in most patients (84/102) in Group TEA.

Comments6: - Figure 2: The p-values could be incorporated into the figure to show which differences are statistically significant in the pain scores. Also, some differences in pain scores are minor (less than 1/10) for example between the no-block group and the TEA group at 0, 3, 12 and 18h. If the difference is statistically significant, is it clinically relevant? This must be discussed in the discussion section.

Reply6: Thank you for your valuable comment. We added the asterisks in Figure2 as a mark of significant difference. And we added the phrase about whether the slight difference in low NRS is clinically relevant as follows.

Chane in the text: L227 Even though there were significant differences between NB and TEA at 6hr and 12hr after surgery, the differences are so slight in the low scores, whether clinically relevant should be investigated in the next prospective study.

Reviewer C

Review of the manuscript Postoperative analgesia in patients undergoing robot-assisted thoracic surgery (RATS) for mediastinal disease: retrospective comparative study of general anesthesia alone, combined with epidural analgesia, and with ultrasound-guided thoracic block.

Comments1: I would like to compliment the authors for their effort to search for a regional anesthesia technique to improve postoperative pain in patients undergoing RATS. However, there is too much heterogeneity in the groups to conclude this. The patients within groups are too different and the main result (postoperative pain) is not clinically different.

Reply1: Thank you for evaluating our efforts and providing valuable comments.

And we added the phrase about whether the slight difference in low NRS is clinically relevant as follows.

Chane in the text: L227 Even though there were significant differences between NB and TEA at 6hr and 12hr after surgery, the differences are so slight in the low scores, whether clinically relevant should be investigated in the next prospective study.

Comment1: Title: Thoracic block is not a regularly used term. The ASRA and ESRA have published a standardized nomenclature and thoracic block is not one of them. (El-Boghdadly K, Wolmarans M, Stengel AD, et alStandardizing nomenclature in regional anesthesia: an ASRA-ESRA Delphi consensus study of abdominal wall, paraspinal, and chest wall blocksRegional Anesthesia & Pain Medicine 2021;46:571-580).

Reply1: Thank you for the recommendation of Delphi, I confirmed it, and reconsider how to solve your pointing out. We inserted “paraspinal” to “Thoracic block” in the title and other places in the manuscript.

Change in the text: L3” Postoperative analgesia in patients undergoing robot-assisted thoracic surgery (RATS) for mediastinal disease: retrospective comparative study of general anesthesia alone, combined with epidural analgesia, and with ultrasound-guided thoracic paraspinal block ”

Comment2: Abstract: The design of the study is a retrospective cohort study on 3 groups, with a follow up of 48hrs. The groups differ in size. There are approximately 170 patients in the study. Pain scores differ but this is not clinically relevant. Also 30% of patients with an epidural needs rescue analgesia; does the epidural work appropriately in these patients?

Reply2-1: Thank you for evaluating our efforts and providing valuable comments.
And we added the phrase about whether the slight difference in low NRS is clinically relevant as follows.

Chane in the text: L227 Even though there were significant differences between NB and TEA at 6hr and 12hr after surgery, the differences are so slight in the low scores, whether clinically relevant should be investigated in the next prospective study

Reply2-2: The epidural work is routinely checked by cold test before general anesthesia induction. However, since it is checked at one or two points, it might be possible that the analgesic area was not spreading and insufficient for invasiveness.

Comment 3: Methods: Consent: in line 74 is stated that informed consent was waved. Do the patients not need to consent to using their data for research?

Reply3: In our institution, an opt-out system is applied for retrospective study. We disclose what and how research is being done, the target period, eligible patients, privacy policy and contact addresses in HP.

Comment4: Three groups are studied. The first group received general anesthesia alone. However, some patients received wound infiltration which makes me wonder if this is wound infiltration or intercostal blocks? My concern is that this group may be the same as the third group.

Reply4: Thank you for valuable comment. It was wound infiltration, so we delete “or ICB” in the sentence.

Comment5: The second group received an epidural. Sometimes they received fentanyl during surgery. Sometimes there was fentanyl or morphine in the epidural mixture. And sometimes there were opioids in the continuous epidural mixture they received postoperatively. I find this confusing and I’m concerned about the diversity in this group.

Reply5: your concern is true, actually I would like to further analyze at least each opioid group in the epidural mixture, but the sample size was too small for that. This time, it is just a retrospective study as our institutional protocol is decided by each anesthesiologist’s preference. We would like to plan further study based on your comments, thank you.

Comment6: The third group is the thoracic block group. Patients have received a block via 1 to 3 intercostal spaces. It is unclear what kind of block this is.

Reply6: we chose to perform MTP, ESP, or TPVB via 1-3 intervertebral spaces
depending on each anesthesiologist’s preference. Most patients (33/42) were MTP (table4).

Comment7: Collected data and statistical analysis: what is the main outcome parameter? This is not mentioned in the power calculation.

Reply7: Thank you for your comment, the main outcome is a numerical rating scale (NRS), so power calculation was based on the NRS. It was described L144and 169.

Comment8: Results: In line 168 it is stated that the first group received an ICB by the surgeon. Therefore, there is no real difference anymore between the first and third group of patients.

Reply8: This comment is the same as the reviewer2 since the surgeon's procedure was only infiltration around the skin, ICB is inappropriate and we deleted "ICB".

Comment9: In line 170 it is stated that the thoracic block is a collection of erector spinae plane block, paravertebral block and MTB block. A very diverse group.

Reply9: Thank you for pointing this out, we would like to conduct the prospective study in the near future precisely, this time, just the retrospective study, and the analgesic method was decided by each anesthesiologist. Even this time, consequently, since any block was performed by a single shot using 0.25% levobupivacaine, the block duration was the same.

Comment10: In line 177 and 178 there are two groups mentioned, not three.

The results are difficult to interpret considering the very different analgesia regimes that were applied, even within groups.

Reply 10: thank you for pointing out the mistake. About different regimes are permissive in this time because another aim of this study is to investigate current analgesic situation for RATS mediastinal disease in our institution. Based on this study, we would like to more precise prospective studies including your comments.

Change in the text: " three" in L179

Comments11: Discussion: In the discussion I would like to see a summary of the findings and a comparison with other studies. How does it fit in? What is new? In this manuscript to me this is not clear.

Reply1: It is true that there are no specific fitting and new articles in the discussion. Because there is few articles about analgesia for RATS mediastinal disease. We mentioned it in L220.

Comments12: Limitations: it appears that there are two surgical approaches studied. This adds to the heterogeneity.

Reply 12: My appologies for any misunderstanding, in this study, we have one approach, the lateral intercostal approach. We added the phrase in the last sentence of the discussion.

Change in the text: , which is not included in this study,

Comments13: Also I think the studied groups are too small to state something about side effects. This should be added to the limitations.

Reply13: Thank you for your suggestion, I added the limitation as follows.

Change in the text: And lastly, this study may be small enrollment to state something about side effects. We should increase the patients' number in the next study.