Peer Review File
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Reviewer A

I congratulate authors for this study investigating a very important aspect of the thoracic surgery and lung resection. Pain management play a key role in achieving good outcomes not only according to patients' perspective, but also in oncology. Debate is open on which method should be used to optimize pain management, reduce the use of opioids and ensure low rate of complications related to the procedure itself, to the surgery and to the use of drugs.
The whole scientific community agrees in a single aspect which is absolutely mandatory: the use of a regional anesthesia.

I do have some comments.
Comment 1. Most important concern I have is about to methodology. Perhaps, might be a personal limit, but it is not clear to me how you designed the study. In the abstract it is written that "both groups received routine SAP block with ropivacaine at 24h". Does this mean that every patient, despite being allocated to intervention group or control group received the block? In methods you described that the randomization was unblinded by opening the envelope with allocation at 24 h, and you describe the use of ropivacaine vs saline depending on group allocation. Perhaps, I do not understand the labelling of drug A and drug B. Overall the procedure is not well described, and this represents a major limitation.
Reply: Thank you for you for your comment, our abstract reads "90 patients undergoing video-assisted thoracic surgery (VATS) were randomized to receive ultrasound-guided second SAP block with 15ml 0.375% ropivacaine (SAP block group) or 15ml normal saline (control group) 24hours after both groups received routine SAP block with 15ml 0.375% ropivacaine. The study investigated whether addition of a second shot SAP block has analgesic benefit to patients undergoing VATS. Just before surgery, all patients received first short SAP block with 15ml 0.375% ropivacaine .24hours later, experiment group received second short SAP block with 15ml 0.375% ropivacaine while control group received placebo (15ml normal saline). The labeling of drug A and drug B was done to cement the blinding procedure.
Changes in text: None
Comment 2. I appreciate the in-depth description of the anesthetic procedure, but I find the description of surgery extremely poor. Also indication and patients' characteristics are not well reported.
Reply: Thank you for your comment. In table 1 we presented patient characteristics and various types of surgery carried out on both groups including surgery duration which is as one of the factors relating to pain after thoracic surgery. Moreover, on line 136-138 we described the surgical aspects which are more likely relate to pain after thoracic surgery like length of surgical incision, location of surgical incision etc. The type of surgery administers depended on patients condition and surgeon team

preference, Since all surgical team were blinded to group allocation, this did affect the results.

Changes in text: None

Comment 3. On line 194 you describe that "patients were visited every day or alternative day to assess complication". Is it the standard of care? Visiting patients every second day? I cannot accept it as good standard.

Reply: Thank you for your feedback. We have revised this section to read as below

Changes in text: Patients were assessed daily for any incidence of perioperative complication(see highlight in page 6).

Comment 4. You also wrote: chest x-ray taken 24h before removal of chest tube and CT scan performed 24h after. This is not standard of practice. There is no mention at all in the published literature about this practice in thoracic surgery patients. Can you justify it?

Reply: Thank you for your comment, We have revised this section as indicated below

Changes in text: This was supplemented by hospital routine postoperative chest imaging practice, comprising of a chest x-ray (taken 24h before removal of chest tube) and computed tomography(taken 24h after chest tube removal)(see highlight in page 6)

Comment 5. The parameter Hypoxemia does not carry and absolute meaning. It depends on the amount of lung removed and it can also depend on the functional status of the patients before surgery. You did not report any functional characteristic of patients undergoing lung resection.

Reply: Thank you for your observation, we have added data on functional characteristic of patients from both groups in table 1

Changes in text:see table 1

Comment 6. There is no mention at all on the surgical procedures. No mention about lymph node dissection, number of chest tubes, criteria to remove the drains, drainage system, perioperative care, physiotherapy etc.

Reply: Thank you very much for your comment, this study was not powered to compare impact of various surgical procedures on postoperative pain. It's worth noting however, that we did highlight the surgical aspects which are more likely to influence postoperative pain (see line 136-138 and table 1). The type of surgery administered was dictated by patient condition and attending surgeon preference. Two chest tubes were indwelled at the lateral chest wall at the end of surgery. Criteria to remove chest tube was based on department standard; no air leakage and drainage volume of less than or equal to 200ml

Changes in text: None

Comment 7. You started the paper stating that insufficient pain management leads to complications and prolong the length of stay in hospital, which is not confirmed by your data. Please, do not report "lower incidence of postoperative complications" as a result of your study.

Reply: Thank you for your feedback, we have revised this section accordingly

Changes in text: we have deleted line 332-347

Comment 8. You stated that the use of a second shot of ropivacaine at 24h prolog the effect of analgesia which is not the target of your study. You compared day zero and

day one shot of regional anesthesia with no regional anesthesia at all (or some blocks over previous block vs some blocks over nothing, but, as I said, this point is not clear). You do not have data on declaring that an additional block at 24h improves results.

Reply: This study compared the analgesic efficacy of single shot SAP block to double shot(second SAP block).We investigated whether the addition of a second block 24 hours after the first block prolongs its analgesic effect thereby supplementing its limitation of short duration of action. Our results confirmed this hypothesis as patients in the intervention group experienced significantly less pain burden (**see figure 2,and supplementary table 1**), this less pain burden was manifested by significantly lower opioids consumption(**see figure 3**) which are the main stay drugs for managing pain after surgery. Moreover, significantly less opioid consumption brought by the study intervention was manifested by significantly less incidence of nausea and vomiting side effects in SAP block group **(see table 4)**, side effects that are strongly associated with opioid consumption. Furthermore, the prolonged analgesic effects brought by addition of second SAP block at POD 1 yielded higher pain scores as part of QoR-40 questionnaire therefore raising the overall score, hence better quality of recovery.

Changes in text: Addition supplementary table 1

Comment 9. Finally, you did compare regional anesthesia with systemic analgesia (maybe???) which is not the standard of care for thoracic surgery (Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, Ljungqvist O, Petersen RH, Popescu WM, Slinger PD, Naidu B. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019 Jan 1;55(1):91-115. doi: 10.1093/ejcts/ezy301. PMID: 30304509. https://doi.org/10.1111/anae.15609)

Reply: Thank you for your comment. You are correct that the study did not compare regional anesthesia to systemic analgesia, which is the standard of care for thoracic surgery(Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, Ljungqvist O, Petersen RH, Popescu WM, Slinger PD, Naidu B. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019 Jan 1;55(1):91-115. doi: 10.1093/ejcts/ezy301. PMID: 30304509. https://doi.org/10.1111/anae.15609). The purpose of the study was to compare the efficacy of regional anesthesia to placebo in patients undergoing thoracic surgery. This study was not powered to compare regional anesthesia with systematic analgesia. However, the study does provide evidence to support the use of regional anesthesia for thoracic surgery, which we mentioned in the introduction part of the manuscript are local, effective and efficient.

Changes in text: None

Reviewer B

your study underlines the importance of adequate analgesia after thoracic surgery and states, that repeat regional anesthesia is a valuable tool to reduce the sequelae of postoperative pain.

After reading the manuscript, I still have some substantial questions:
Methods:
Comment 1. You applied 0.3mg Sufentanil per kg bodyweight, which is a pretty high dose for anesthesia induction.
Reply: Thank you for your observation, we sincerely apologize for this error, we meant 3μg/kg
Changes in text: We have made correction accordingly, see page 4
Comment 2. oxygen requirement, non-invasive ventilation, intensified physio- and respiratory therapy, which certainly relate to the effects of adequate pain control? Instead, you only list the incidence of hypoxemia or respiratory depression without any necessary interventions.
Reply: Thank you for your comment. while we acknowledge that the said factors have certain impact on postoperative pain, going by the results of 48h Adverse effects incidences displayed in table 4, even if these factors existed, there were not big enough to cause statistical significance. Otherwise, the treatment of these side effects was based on attending surgeon preference.
Changes in text: None
Comment 3. You mention two type of analgesia/ pain assessment. Can you relate these more clearly?
Reply: Thank you for your comment, The NRS and the pain domain of the QoR-40 was used together to provide a more complete picture of a patient's pain experience. The NRS provided quick and frequent pain assessments at various time interval as reported in figure 2, while the pain domain of the QoR-40 assessed pain intensity and impact on patient recovery over follow-up period.
Changes in text: None
Postoperative outcomes:
Comment 4. Are there really any clinically relevant differences? Looking at the Pain scores from the QoR-40 scores, the result demonstrates a statistic difference, but do the represent clinical importance?
Reply: Thank you for your comment, simple answer is yes, Higher pain scores from experiment group (SAP block) implied that these patients have better pain control which translated to less postoperative opioids consumptions leading to clinically less incidence of opioid associated side effects such as nausea and vomiting.
Changes in text: None
Comment 5. The QoR as a composite outcome shows differences, but looking int the single parameters, minor differences though some of statistical difference, become visible.
Apart from the physical comfort on day 1, no real differences in physical independence representing recovery from physical, functional impairment can be seen, reducing the value of the reduction in pain mentioned.
Reply: Thank you for your comment, breakdown of the results of each composite of QoR-40 is as follows, statistical significant differences in physical comfort on POD 1，statistical significant differences in Emotional status and pain scores between both groups on both POD 2 and POD 3.However, just like previous studies(Li Z, Lin Q, Lin

L, Wu Q, Ke P, Chen H, Lin C, Yu Y. Efficacy and safety of thoracoscopic-guided multiple paravertebral block for video-assisted thoracoscopic lobectomy surgery: a randomized blinded controlled study. Front Surg. 2023 Oct 24;10:1267477. doi: 10.3389/fsurg.2023.1267477. PMID: 37942003; PMCID: PMC10628487; Kim DH, Oh YJ, Lee JG, et al. Efficacy of Ultrasound-Guided Serratus Plane Block on Postoperative Quality of Recovery and Analgesia After Video-Assisted Thoracic Surgery: A Randomized, Triple-Blind, Placebo-Controlled Study. Anesth Analg. 2018;126(4):1353-61.), our results did not find the statistically significant difference in physical independence and psychological support.

Changes in text: None

Comment 6. The NRS-score at rest shows differences at the respective time intervals, are they the effects of the regional anesthetic intervention or rather the effect of a inadequate analgesia in the placebo group, the postoperative morphine equivalents at 48 and 72 hours do not reflect substantial differences considering the low opioid consumption. The use of the PCA in a sense of pressing times might be reduced, but still, is necessary in SAP-group patients. I cannot find any statistical details on the NRS scores.

Reply: Thank you for your comment, NRS at rest were significantly lower in the experiment group due to prolonged analgesia brought by addition of second short SAP block. We have added the statistical analysis data of NRS score to supplementary table 1.

Changes in text: Added supplementary table 1

Comment 7.A reduction in adverse events is related to the regional technique in your article. The duration of action of the SAP-Technique is usually 6-12 h. Could you reference shorter time intervals for the NRS, not only pain at rest, but also with cough/ mobilization, so the true effects are probably missed.

Reply: Thank you for your comment. We agree that it is important to measure pain during activities that are typically more painful, such as coughing or moving around. However, we believe that the true benefit of regional analgesia was not lost in our study, because we also assessed pain using the pain section of the QoR-40.The QoR-40 is a validated patient-reported outcome measure that assesses pain severity, pain interference, and quality of life. The pain section of the QoR-40 includes questions about pain at rest, as well as pain during activities

In our study, we found that the regional technique significantly reduced pain scores on the QoR-40, both at rest and during activities. This suggests that the regional technique was effective in reducing pain, even during activities that are typically more painful.

We acknowledge that our study may have the limitation of not measuring NRS pain during specific activities such as coughing or moving around. However, we believe that the QoR-40 used provides a comprehensive assessment of pain that captures the impact of pain on patients' daily lives hence more comprehensive.

Changes in text: None

Comment 8. Apart from the postop QoR-40, I can only identify the incidence of PONV significantly differing, apart from the PCA pressing times.

Reply:Thank you for your comment. This study found that application of a second SAP

block at POD 1 yielded statistically significant differences between the two groups in the following outcomes:

- Quality of recovery (QoR-40) ($p < 0.05$)
- Postoperative opioid consumption ($p < 0.05$)
- Postoperative pain scores ($p < 0.05$)
- PCA pressing times ($p < 0.05$)
- Incidence of postoperative nausea and vomiting (PONV) ($p < 0.05$)

These differences are clinically meaningful because they indicate that patients in the SAP block group experienced better recovery, less pain, and reduced need for opioids compared to patients in the control group.

Changes in text: Addition of statistical data of NRS, see supplementary table 1

Comment 9. In the discussion section, you state a lower incidence of pneumonia and atelectasis and CPTP. The study is not powered to demonstrate differences in PPC considering the low incidence, and the differences are far from any statistical difference (0 vs. 1 for atelectasis, 1 vs. 4 for pneumonia), which might cast doubts about these conclusions.

Reply: Thank you for your suggestion: We have deleted line 332-347,In terms of CPTP, while there was no statistically significant difference in CPTP between the two groups in our study, we strongly believe that our results are still clinically significant for the following reasons:i)Our results in the control group are similar to existing literature, which suggests that our study population and methods are comparable to other studies that have reported CPTP rates.ii)The results in the experiment group were lower than the control group, although not statistically significant. This suggests that the intervention may have had a beneficial effect on CPTP prevalence, even if this effect was not large enough to reach statistical significance.iii)CPTP is a serious complication that can lead to reduced quality of recovery and increased morbidity and mortality. Even a small reduction in CPTP prevalence could have a significant impact on patient outcomes.

Chanes in text: None

Comment 10. Neither the prevalence of CPTP or clinically relevant outcomes. CPTP is usually defined as pain lasting > 3month (WHO-definition), and you state a possible reduction in opioid dependence? Can you provide any details about the opioid use confirming your hypothesis, is there really a significant reduction in pain at 2/3 month?

Reply: Thank you for your feedback, based on current literature, the prevalence of CPTP post VATS is around 30% which is similar to 32.5%and 27.5% reported by patients in the control group arm of our study at 2^{nd} and 3^{rd} postoperative month respectively. On the other hand, patients in SAP block arm registered a much lower CPTP prevalence of 16.2% and 14% at 2nd and 3rd month and therefore we believe the intervention led to significant clinical improvement in lowering CPTP prevalence. By the virtue that the study reported clinical meaningful reduction on the incidence of CPTP at 3rd month postoperative points to lower chance of consuming opioid medication in relation to treatment of surgery related pain

Changes in text: None