

Peer Review File

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Reviewer A

Thank you very much for the helpful comments on improving sentence structure and flow as well as providing quite relevant references on the possible mechanism behind erector spinae plane blocks. We have made the suggested changes and included the references.

Comment 1: Page 4 Line 76 Inadequate analgesia compounds these changes related to splinting with reduced tidal volumes, impaired admission (1,2). This sentence is too long. Please try to separate it into two or more sentences.

Reply 1: The sentence has been restructured and separated into two distinct sentences to improve clarity (Page 4, Lines 76-81).

Changes in text: “Inadequate analgesia amplifies the negative effects of splinting including reduced tidal volumes, impaired cough and clearance of secretions, and increased atelectasis. Altogether, this may increase the risk of postoperative pulmonary complications including hypoxemia, hypercarbia, pneumonia, possible need for prolonged mechanical ventilatory support, reintubation, and intensive care unit (ICU) admission (1,2).”

Comment 2: Page 7 Line 141. It inhibits cyclooxygenase (COX), when used in appropriate doses (13). This sentence is too long. Please try to separate it into two or more sentences.

Reply 2: This sentence has been reworded to improve clarity (Page 7, Lines 146-150).

Changes in text: “Although the exact analgesic mechanism of action remains unknown, it inhibits cyclooxygenase (COX) and may affect multiple central nervous system pathways involved in pain. It has little to no anti-inflammatory activity, does not affect platelet function, renal perfusion, or gastrointestinal (GI) tract mucosal integrity, and has an extremely safe profile when used in appropriate doses (13).”

Comment 3: Page 22 line 498

One possible explanation for evidence supporting and sympathetic chain.

You should provide references for your explanation. It may be appropriate to include references regarding anatomical (cadaveric) study for these blocks.

For example,

J. Ivanusic, Y. Konishi, and M. J. Barrington, “A cadaveric study investigating the mechanism of action of erector spinae blockade,” *Regional Anesthesia and Pain Medicine*, vol. 43, no. 6, pp. 567–571, 2018.

S. D. Adhikary, S. Bernard, H. Lopez, and K. J. Chin, “Erector spinae plane block versus retrolaminar block: a magnetic resonance imaging and anatomical study,” *Regional Anesthesia and Pain Medicine*, vol. 43, no. 7, pp. 756–762, 2018.

H. Yang, Y. J. Choi, H. Kwon, J. O, T. H. Cho, and S. H. Kim, “Comparison of injectate spread and nerve involvement between retrolaminar and erector spinae plane blocks in the thoracic region: a cadaveric study,” *Anaesthesia*, vol. 73, no. 10, pp. 1244–1250, 2018.

Reply 3: Thank you for providing these pertinent references to provide more evidence for the possible mechanism behind the ESPB. The sentence has been restructured to reflect this and now includes the above references (Page 24, Lines 532-540).

Changes in text: “One possible explanation for evidence supporting improved analgesia with ESPB compared to SAPB could be the postulated spread to the paravertebral space with coverage of dorsal and ventral rami and sympathetic chain similar to a paravertebral block, which may block noxious stimuli related to chest wall muscles, pleura, and thoracic viscera which is transmitted by muscular branches of the intercostal nerve, dorsal rami, and sympathetic chain. This is in contrast to the SAPB, which may only directly affect the lateral cutaneous branches of the intercostal nerves and not (Figure 1). However, there are some conflicting results on whether the ESPB reliably or actually spreads to the paravertebral and epidural spaces (138-140).”

Reviewer B

Comment 1: It is well-performed review and with interesting results which can be of scientific and practical values.

I suggest cite the following references “Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. *J Clin Anesth*. 2021 Feb;68:110071.”, “Lee J, Lee DH, Kim S. Serratus anterior plane block versus intercostal nerve block for postoperative analgesic effect after video-assisted thoracoscopic lobectomy: A randomized prospective study. *Medicine (Baltimore)*. 2020 Dec 4;99(49):e22102.”, “Qiu Y, Wu J, Huang Q, Lu Y, Xu M, Mascha EJ, Yang D, Ince I, Sessler DI. Acute pain after serratus anterior plane or thoracic paravertebral blocks for video-assisted thoracoscopic surgery: A noninferiority randomised trial. *Eur J Anaesthesiol*. 2021 Aug 1;38(Suppl 2):S97-S105.” and “Guerra-Londono CE, Privorotskiy A, Cozowicz C, Hicklen RS, Memtsoudis SG, Mariano ER, Cata JP. Assessment of Intercostal Nerve Block Analgesia for Thoracic Surgery: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2021 Nov 1;4(11):e2133394..”

Reply 1: Thank you for providing these additional recent references which are quite pertinent and add to the evidence base for this manuscript. They have now each been included in their appropriate sections.

Changes in text:

- Pages 9-10, Lines 205-208: “Ketamine potentiates the analgesic effects of opioids, can improve analgesia and reduce opioid-consumption in the immediate postoperative period, may prevent acute opioid tolerance and central sensitization to nociceptive signaling, and reduce inflammation related to surgery (34-38).”
- Page 21, Lines 477-483: “However, a small randomized trial failed to find any difference in pain scores or opioid consumption in patients who receive either SAPB or ICNB for VATS (124). Interestingly, a recent randomized non-inferiority trial of SAPB and PVB for VATS showed no significant difference in post-operative pain scores at two hour between the two approaches, but also no difference in pain scores for either compared to no block at 24 or 48 hours, and no difference in 24 hour post-operative opioid consumption (125).”
- Page 18, Lines 394-396: “More recently, a large systematic-review and meta-analysis demonstrated that ICNB has benefits including improved pain control and reduced opioid consumption in the first 24 hours after thoracic surgery compared to systemic therapy alone (102).”

Reviewer C

Comment 1: I believe the significance of this type of review paper is not to enumerate the results of previous papers, but to conclude in a certain direction.

Fundamentally, it is very difficult to read in the current form.

For example, by showing the summary of advantages and disadvantages of each anesthesia method reported in numerous trials, the flowchart to select anesthesia methods (especially combination multiple approaches) according to the site and surgical method, or the transition of anesthesia method and trends along the timeline in a chart, I think it will be a little easier to read.

Reply 1: Thank you for your constructive feedback on the overall organization and effect of the manuscript. We agree that the overall goal of the paper should not be to simply summarize the known body of literature on the subject, but rather to take that information to guide clinical decisions and propose questions for the future of the field. We have taken your comment as well as the comments of multiple other reviewers, notably Reviewer D, to change some of the organization and structure of the paper to better reflect this and make it more readable. We have changed the tables with more detail regarding each specific medication and regional anesthesia

technique to also address this point. Although a flow-chart delineating how to select a specific type of analgesic approach according to surgical approach would be helpful, the nature of both individual patient factors and the mostly unknown superiority of any specific approach for any specific surgery would make this difficult to do with confidence. I hope that our tables and the text provide readers with information to make a tailored approach for their specific case.

Changes in text: multiple changes to overall structure, content, and table organization detailed in prior and subsequent responses to other reviewers

Reviewer D

Thank you very much for your thoughtful and constructive comments, they were very useful in reorganizing the paper into a more effective format, as well as adding to content that is essential to the focus of the paper.

Comment 1: Introduction:

I would leave Table 1 to the Discussion/results section

Reply 1: We have taken this comment and your below comments on Table 1 to make changes including moving the table to the results/ discussion section, as well as splitting the table into two separate tables detailing systemic analgesics and regional anesthesia options for thoracic surgery, as detailed below.

Changes in text : Table 1, Table 2

Comment 2: Methods:

I would suggest you clearly describe the choice for your study design in the methods section. A sentence or two explaining why, in your opinion, a narrative review suits your purpose better than systematic review, would be helpful.

Reply 2: Thank you for this suggestion, the changes have been incorporated and help to better define our overall goal and approach to the review (Page 6, Lines 127-130). We chose a narrative review with a goal of providing an overall summary of the wide variety of systemic analgesic and regional anesthetic approaches to thoracic surgery. We felt that a narrative review better fit with this goal, as the topic seems to broad for a systemic review, which would be better suited for a more narrow focused review answering a specific question in the field.

Changes in text: “The manuscript was prepared as a Narrative Review, with a goal of providing a broad overview of the evidence for various systemic analgesic and regional anesthesia approaches for treating pain related to thoracic surgery, rather than the more narrow and targeted focus of questions addressed in a systematic review.”

Comment 3: Discussion:

Your results are divided into 2 main areas: discussing (potential) agents in multimodal systemic analgesic intra-operative approach. I very much like your approach to present general information, as well as evidence specific to minimally invasive and thoracotomy.

I think this section could benefit from its own summary: How to approach multi modal analgesia? What are the interactions/synergistic effects? Somewhat the one you start in line 570. Table 1(a) would fit here nicely.

Reply 3: Thank your for this helpful comment on both the organization and content of our discussion section. We have included a more specific summary in each section here after reviewing the available options, by moving some summary text from the conclusion to the discussion and expanding. We have also separated Table 1 into two separate tables and moved it from the introduction to the discussion here as recommended (Page 14, Lines 304-313, Table 1)

Changes in text: “Summary of Multimodal/Systemic Analgesics (Table 1)

Acetaminophen and NSAIDs can have synergistic effects and should be routinely utilized perioperatively unless contraindicated. Ketamine has its merits in patients with chronic pain or opioid tolerance as well as in patients undergoing thoracotomy who are unable to receive regional anesthesia, but caution is warranted in elderly patients given psychomimetic effects. Gabapentin may have some opioid-sparing effect, but can cause sedation and synergistic respiratory depression with opioids, and should not be routinely used in naïve patients. Although the utility of IV lidocaine is unclear in thoracic surgery, glucocorticoids including dexamethasone have multiple benefits including analgesia and should be used unless contraindicated.”

Comment 4: Are there any adjuncts/agents you found to little evidence for to include; it would be useful to know you looked at them, but excluded them from your review.

Reply 4: We did focus on the most commonly used systemic multi-modal analgesics, with a focus on those with data specifically for thoracic surgery. Although certain other adjuncts are used in a variety of surgical patients including in thoracic surgery, we did not find a significant body of evidence specifically for analgesics effects of other agents in thoracic surgery. Although medications such as dexmedetomidine are used for analgesia, this and other adjuncts seemed outside of the scope of this already large review. One change that we did make related to your comment was including the use of magnesium for analgesia as a non-opioid adjunct, by incorporating it into the ketamine section and retitling the section to “NMDA receptor antagonists” to be more inclusive (Page 10, Lines 212-214).

Changes to text: “Magnesium also has NMDA receptor antagonist properties and is used as a non-opioid analgesic with possible benefits including improved pain and reduced opioid requirements with few adverse effects (40-42).”

Comment 5: In addition to the multimodal approach, there is a choice in regional and neuraxial options you describe.

Apart from liposomal Bupivacaine, you do not elaborate on the different choices of local anaesthetic agents, nor the use of adjuncts to prolong duration of regional blocks. This would be a helpful addition to your already big effort to summarise and structure this mountain of evidence.

Reply 5: Thank you for this suggestion, as the use of adjuncts to blocks is an interesting component with some data to guide its use. We initially only included liposomal bupivacaine as the only specific local anesthetic, as it has an area of active research for the past few years with conflicting results and controversial opinions. Beyond comparisons of liposomal bupivacaine with bupivacaine, we are not aware of any significant body of literature comparing other types of long-acting local anesthetics in thoracic surgery. We have added a statement regarding this in the summary of the regional anesthesia section (Page 27, Lines 608-611). We have also included a section on the use of additives for regional blocks (Page 26, Lines 684-699)

Changes to text:

Additives for regional blocks

There have been a number of additives investigated for prolonging or enhancing the analgesic effect of neuraxial and peripheral blocks. In addition to the routine use of epinephrine as an additive to local anesthetics for regional anesthesia, some of the most commonly used additives include dexamethasone and alpha-2 agonists including dexmedetomidine. Although both intravenous and perineural dexamethasone may both improve analgesia quality and duration upper extremity peripheral nerve blocks, there is no conclusive data suggesting its effectiveness in other regional anesthesia techniques outside of its systemic benefits detailed above (163). Similarly, dexmedetomidine may prolong the duration of analgesia in upper limb nerve blocks; however, it also increases the risk of transient hypotension and bradycardia and may contribute to sedation, and its effectiveness in regional anesthesia techniques for thoracic surgery is not well-investigated (164). However, limited evidence suggests that magnesium and dexmedetomidine added to paravertebral bupivacaine may enhance the analgesic effect after thoracic surgery (165-167). Although such additives may prolong the effect of certain regional blocks, it is unclear if this is related to perineural or systemic effects, and more investigations are needed to determine if their routine use in thoracic surgery patients is beneficial.”

“Beyond LB, there is no real data comparing different types of local anesthetics, but utilizing long-acting agents such as bupivacaine or ropivacaine within their safe dose range offers optimal analgesia, especially for single-shot techniques.”

Comment 6: Regarding the structure, I would suggest the same approach and advise a separate summary: how to approach regional/neuraxial analgesia? Table 1(b) here?

Reply 6: As mentioned above, we thank you for your guidance on improving the structure and organization of the paper. A summary of the regional anesthesia techniques has been included here, and the second part of the initial Table 1 was expanded upon in a separate Table 2 and included here (Page 27, Lines 600-611, Table 2)

Changes to text: “Summary of Regional Anesthesia (Table 2)

Regional and neuraxial anesthesia should be strongly considered in patients undergoing thoracic surgery. Thoracotomy patients should have either TEA or continuous PVB. For VATS, PVB targeting the origin of intercostal nerves and the sympathetic chain can attenuate pain signals from somatic and visceral sources, and have demonstrated advantages over other chest wall blocks. Fascial plane blocks and ICNB can be considered in patients with contraindications for PVB who are undergoing VATS, however the comparative efficacy or optimal block is still not clear. The data on the utility of LB for blocks for thoracic surgery is mixed, and future studies are needed to clarify its role in this field. Beyond LB, there is no real data comparing different types of local anesthetics, but utilizing long-acting agents such as bupivacaine or ropivacaine within their safe dose range offers optimal analgesia, especially for single-shot techniques.”

Comment 7: Conclusion and future directions:

Timing of analgesic interventions, new and emerging analgesic agents are exciting prospects. However, you rightfully address the importance of defining the right, clinically relevant, outcome measures in future research. Perception of pain is also influenced by patient expectations and education. A mention of the broader context of pain management, including education, would fit here.

Reply 7: We agree that patient perspectives on pain and proper education on expectations of postoperative pain and its management are crucial for optimal patient care. We have included this in our conclusion and added a relevant reference (Page 28, Lines 634-636)

Changes to text: “Also, preoperative discussions with patients focused on determining beliefs around pain, coping strategies, and expectations both of post-operative pain and the planned strategies to mitigate it, are essential for optimal patient care (170).”

Reviewer E

Comment 1: Nice job on summarizing all the studies out there with regards to pain after thoracic surgeries. The summary is presented in a very organized method and will be an easy read for many readers.

I would suggest that you remove table 2. LB should be included as just a one line summary in Table 1, just like all the other treatment modalities. Having a table summarizing all the studies surrounding LB seems unnecessary and put the focus on a treatment modality that doesn't really show too much clinical benefits.

Reply 1: Thank you for your overall comments and recommendations on removing Table 2. We acknowledge that the initial Table 2 did not fit as well as similar tables for other techniques were not included. We initially included it as, although there is no conclusive data on its effectiveness for regional anesthesia techniques for thoracic surgery, it remains a controversial topic and active area of research. However, we agree that Table 2 did not add greatly to the impact of the manuscript, and have removed it, and instead summarized it in the text (Page 25, Lines 560-563).

Changes to text: “There are several retrospective studies comparing ICNB with bupivacaine or LB: three out of seven studies failed to show any significant benefits, while the others demonstrated benefits at different time points (151-157).”