Peer Review File

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Reviewer A

Comment 1: Please emphasize a bit more that improvement of functional status is an important requirement to evaluate the effectiveness of treatment for pain in older adults
Reply 1: Please see the paragraph emphasizing the importance of functional status during pain assessment and pain control.

"An area of importance when considering the pain control of the older adult VATS patient, though often disregarded, is the preoperative assessment and optimization of functional status. While chronological age has historically been a focus when assessing perioperative risk, a patient's physiological or biological age, performance status, functional status, and frailty may better assess risk. Frailty, a term used to describe the decline of physiological function, is used as a measure of perioperative risk in older patients. Specifically, frail surgical patients carry an increased risk of adverse events and poor outcomes (2–4) and 68.8% of thoracic surgical patients are prefrail or frail(Beckert et al. 2017). The preoperative performance status score, as defined by the Eastern Cooperative Oncology Group, correlates to the experience of postoperative pain in thoracic surgical patients (Fagundes et al. 2015). Patients with low preoperative functioning or frailty benefit from targeted preoperative therapy, a practice commonly seen in cardiac surgery. This therapy focuses on physiologically, psychologically, and physically optimizing patients prior to their surgical experience. In frail patients undergoing VATS, the pain benefit of prehabilitation is not clearly defined though benefits may be seen in the identification and optimization of patients with cognitive disorders to allow appropriate pain assessment perioperatively. "

Reviewer B

Comment 1: Lines 19-20 consider adding that the benefits in frail and advanced age older adults are unclear.
Reply 1: Added, please see manuscript.

Comment 2: Line 68 & 92 please consider changing reference number 8: "Yezierski RP. The effects of age on pain sensitivity: preclinical studies. Pain Med. 2012 Apr;13 423 Suppl 2(Suppl 2):S27–36" for a more adequate one. This reference reviews previous studies on animal models. Although it can be an appropriate reference in a case of Phase I Clinical Trial. It is not appropriate as a background of techniques and treatments already used on human persons.
Reply 2: Please see adjustments to references "**Additionally, nerve fibers associated with pain have been shown to decrease and alter with age resulting in varied neuropsychological responses (Chakour et al. 1996; Tinnirello et al. 2021). "**

Comment 3: Lines 196-198 the way the sentence is formulated two or more references are expected. Consider changing to "Acute pain management guidelines acknowledge this benefit…"
Reply 3: Updated. Please see manuscript.

Comment 4: Lines 211-213 please include a reference or reference the data used to conclude this acetaminophen dosage.
Reply 4: Please see the following updates: **"The maximum daily dose is four grams (gm) per day in most adults, with experts recommending reduced dosing of three gm per day (Cornelius et al. 2016) or weight-based dosing (Maximum 75 mg/kg/day) in frail older adults (less than 50 kilograms (kg)(FDA 2015). "**

Comment 5: Lines 278, 279 consider including a more exhaustive list of ketamine side effects.
Comment 6: Line 285 please consider enumerating the counterindications that can limit the use of

ketamine.
Reply 5&6: Please see the following paragraph
" Ketamine is a non-competitive N-methyl-d-aspartate (NMDA)/glutamate receptor complex antagonist that decreases pain by diminishing central sensitization. Ketamine is recommended to be considered as a component of multimodal analgesia in the general adult population for perioperative and opioid-tolerant patients (16,18,28). **Notable short-term adverse effects of intravenous ketamine include hemodynamic instability, emergence reactions, respiratory depression, drug-induced liver injury and increased cerebrospinal fluid pressure (Schwenk et al. 2018; FDA 2022). The most common and medication-limiting adverse effects are the neuropsychological manifestations, with labeled contraindications limited to patients who can not tolerate significant elevations in blood pressure and those with known hypersensitivity to ketamine(FDA 2022). "**

Comment 7: Line 312 consider adding a paragraph discussing the phenomenon of rebound pain and its management, since it is described to frequently occur after peripheral nerve blocks.
Comment 8: Lines 325-335 consider describing some other potential but rare complications such as nerve injury, spinal cord injury, pneumothorax, and persistent symptoms of nerve dysfunction. Also consider discussion counterindications (history of previous thoracic surgery or infection that may have caused scarring of thoracic paravertebral space).

Reply 7&8: See paragraph: "Despite the proposed benefit of regional anesthesia techniques on pain control in the patient undergoing VATS, complications such as rebound pain, pneumothorax, and nerve injury should be recognized and considered. Rebound pain is a well-recognized but understudied complication of these techniques, especially in the VATS population. Rebound pain is the experience of severe acute pain following the resolution of peripheral anesthetic block. While the underlying pathophysiology is not well understood, up to half of patients who receive a peripheral nerve block in the ambulatory setting may experience rebound pain, with younger age being a risk factor for experiencing rebound pain (Barry et al. 2021). With the use of ultrasound guidance for paravertebral and peripheral blocks, the incidence of pneumothorax and nerve injury has plummeted. One prospective study of 1427 thoracic paravertebral injections placed via ultrasound guidance showed no occurrences of pneumothorax or pleural injury (Pace et al. 2016)."

See final two sentences in the following paragraph, addressing the contraindications.

Utilization of interventional approaches with local anesthetic medication can avoid complications seen with other methods of pain control in the perioperative patient and must be considered in the older adult population. Targeted pain management in the postoperative VATS patient can decrease the cardiopulmonary risk seen with general anesthesia in high-risk patients such as frail older adults. For example, thoracoscopic procedures using local anesthetic blocks and sedation allow the surgeon to perform procedures through less physiological stressing means for patients. These approaches are effective for patients undergoing VATS and are stable from a cardiopulmonary standpoint (37). In older adult patients requiring targeted peripheral pain control, a serratus anterior plane block is an appropriate adjunct to a multimodal pain regimen (38). When comparing TEA to opioids administered systematically via systemic IV, TEA provides improved pain control and postoperative pulmonary function (39) and improved quality of life scores (40) following lobectomy. **The specific approach and choice of block requires consideration of the overlying anatomy. For instance, prior interventions, scars, or overlying infections should be considered when planning an interventional pain approach.**

Comment 9: Line 327 consider stating that LAST is more frequent in older adults with sarcopenia and older adults with small body size.
https://pubmed.ncbi.nlm.nih.gov/29356773/

Reply 9: "This population is also at increased risk of adverse effects of LAST, especially those with liver and cardiac disease (41) and those of low weight or with sarcopenia (Neal et al. 2018)."

Comment 10: The team of authors does not include any anesthesiologist. My training includes general medicine, but I am not an expert in anesthesiology. Since this article directly affects the scope of an anesthesiologist's work which includes pain management in perioperative patients, and the performance of interventional methods for pain control, I recommend that an anesthesiologist reviews this paper either as a reviewer or part of the team of authors, prior to publication.
Reply 10: Thank you for this insight. In response, we have invited Greg Sinos, CRNA to review our paper and provide comments. He did not recommend any additional changes. He is recognized at the end of the manuscript.

Further review by Reviewer B:

Please remove (Table 2) from header. Add a third sentence to the paragraph (e.g. "The most frequently used medication agents for perioperative pain management in older adults are included in Table 2.").- Complete

Page 8. Line 25. Please separate the sentence in two: "…3 gm per day (14). A maximum weight-based dosing of 75 mg/kg/day should be considered in frail older adults with weight of less than 50 kg (24)."- Complete

Page 9. Lines 1-4. The first two sentences are redundant, please combine them into one single sentence stating the number of different NSAIDs available and their mechanism of action.- Complete - See edited sentence: "Twenty different non-steroidal anti-inflammatory drugs (NSAIDs) are commercially available which work by inhibiting cyclooxygenase (COX) and decreasing prostaglandin precursors formation, leading to antipyretic, analgesic, and anti-inflammatory effects."

Page 9. Line 2. Consider introducing COX abbreviation after first use in text.- Complete, see above

Page 9. Lines 9-10. Please mention that COX-2 selective inhibitors still maintain renal and cardiovascular side effects, such as acute kidney failure, hyperkalemia, hypertension, heart failure and edema. All of which are more likely to occur in older adults. - Complete. "However, COX-2 selective inhibitors maintain renal and cardiovascular side effects, such as acute kidney failure, hyperkalemia, hypertension, heart failure, and peripheral edema. "

Page 13. Lines 26-27. Since the third author of this article has a relevant article on this topic please consider stating: "Despite all of the previous considerations the use of local anesthesia and sedation for VATS was shown to be safe and well tolerated." Katlic MR, Facktor MA. Video-assisted thoracic surgery utilizing local anesthesia and sedation: 384 consecutive cases. Ann Thorac Surg. 2010;90(1):240-245. doi:10.1016/j.athoracsur.2010.02.113-Complete. "Despite the aforementioned considerations, local anesthesia and sedation have been shown to be safe in patients undergoing VATS (49)."

Page 16. Reference 14 is a 113-page Guideline on Acute Pain Management in Older Adults. In its bibliography it cites more than 200 different sources. This reference is cited 18 times in the article. Please consider citing the original source in each instance or the specific relevant pages of the Guideline for each citation. Complete. See manuscript with some sources updated as individual references, others being referenced through Guideline page reference.