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Determining influences of intraoperative s-ketamine on postoperative delirium and cognitive function: methodology is important

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Abstract

The letter to the editor was written in response to the recent article by Wang et al. "The influence of low-dose s-ketamine on postoperative delirium and cognitive function in older adults undergoing thoracic surgery", which is published in *Journal of Cardiothoracic Surgery.* 2024; 19(1):324. This article concludes that intravenous low-dose S-ketamine during thoracic surgery in older patients significantly reduces the incidences of postoperative delirium and cognitive dysfunction, indicating a potential neuroprotective effect of intraoperative low-dose S-ketamine. In view to the retrospective nature of this study and their inconsistent findings with the results of a recent randomized controlled trial performed in patients undergoing non-cardiac thoracic surgery, we believe that several methodological issues and potential confounders in this study deserve further clarification and discussion before accepting their conclusions. Our main concerns include lacking the times and number of delirium monitoring per postoperative day, alone use of the Confusion Assessment Method form for delirium screening, not providing the factors related to the occurrence of postoperative delirium in the ICU stay, and application of a non-standard definition for postoperative cognitive impairment. We believe that clarification of these issues is useful for improving the transparency of their methodology and facilitating the interpretation of their results.

To the Editor

By conducting a retrospective cohort study of 140 elderly patients with a mean age of 76.9 years or more who underwent elective thoracic surgery, Wang et al. [1] demonstrated that a continuous intravenous infusion of low-dose S-ketamine (<0.5 mg/kg/h) during surgery significantly decreased the incidences of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). These results are different from the findings of a recent randomized controlled trial performed in patients undergoing non-cardiac thoracic surgery, in which a small-dose S-ketamine does not provide obvious postoperative cognitive benefits assessed by the Confusion Assessment Method (CAM) and Mini-Mental

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State Examination [2]. Furthermore, a recent systematic review and meta-analysis including 9 randomized controlled trials with a total of 573 patients demonstrates that intraoperative subanesthetic dose of ketamine/S-ketamine compared with controls has no advantage in preventing POCD in patients, or in elderly patients [3]. Other than the retrospective nature of Wang et al.' study may limit the ability to make the causal inferences from the observed associations, we believe that several methodological issues and potential confounders in this study deserve further clarification before accepting their conclusions.

First, the delirium monitoring in this study was performed by the CAM form during the 7 days postoperatively. However, the readers were not provided with the starting time of the POD assessment. As POD may occur immediately after emergence from anesthesia and usually presents around 24 h postoperatively, 2017 guideline recommendations from the European Society of Anaesthesiology emphasize that delirium screening should start as early as the emergence is completed and delirium occurring in the period from the completion of emergence to the morning of first postoperative day should have been included in the results [4]. Other than the CAM form interview, it was also unclear if the chart review was combined for POD assessment. In fact, POD is a fluctuating condition that often manifests late at night. POD occurring at night may be missed if only day CAM form interviews are carried out. The available literature indicates that the CAM form interview combined with the chart review can increase the sensitivity and specificity in detecting incident delirium in postoperative period [5]. Since a chart review obtains information from a readily available source, it has been combined with the CAM form interview for POD assessment in previous study [6]. We are concerned that these unknown factors would have underestimated the incidence of POD reported in this study.

Second, the median length of intensive care unit (ICU) stay was 4 days, which accounted for about 60% of a 7-day delirium monitoring period. However, mechanical ventilation time, extubation time, postoperative pain management, occurrence of complications and sedation strategy during the ICU stay were not provided in this study. It has been shown that duration of tracheal intubation, mechanical ventilation time, inadequate pain control, hypotension, hypoxemia, pulmonary complications, acute infection, acute kidney injury and sleep disorder during the ICU stay are associated with significantly increased risks of POD in elderly surgical patients [7, 8]. Furthermore, the use of sedative and analgesic medications including opioids and benzodiazepines is significantly attributable to the occurrence of POD in the ICU [9]. Thus, we argue that these unknown factors would have biased their main findings.

Finally, this study only applied the Montreal Cognitive Assessment scale to assess perioperative cognitive function and defined a decrease of 2 points or more in the Montreal Cognitive Assessment score as "POCD". This definition of "POCD" is evidently outmoded. As early as 2018, the International Nomenclature Consensus Working Group recommended that cognitive impairments associated with anesthesia and surgery should be named as "perioperative neurocognitive disorders". Especially, the new recommendations require that definitions of perioperative neurocognitive disorders used in clinical studies must meet the diagnostic criteria of neurocognitive disorders recommended in the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition [10]. Due to the use of a non-standard definition for postoperative neurocognitive impairment, we cannot determine if intravenous low-dose S-ketamine may really reduce the occurrence of postoperative neurocognitive impairments in the elderly patients undergoing elective thoracic surgery. Considering the above-mentioned design issues, we believe that further studies are needed to validate the conclusion of this retrospective study regarding the potential benefits of intraoperative low-dose S-ketamine in decreasing POD occurrence and enhancing neurocognitive function after elective thoracic surgery. As this study did also not assess any outcomes of enhanced recovery after surgery practices for thoracic surgery, such as the time to first ambulation, quality of postoperative recovery and length of hospital stay, we do not agree with the authors that their findings have significant clinical significance, potentially contributing to the enhancement of postoperative recovery quality.

Abbreviations

POD	Postoperative delirium
POCD	Postoperative cognitive dysfunction
CAM	Confusion Assessment Method
ICU	Intensive care unit

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Data availability
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Declarations

Ethics approval and consent to participate
As our paper is just a letter to the editor that comments a article published in journal, ethics approval and consent are unnecessary.

Consent for publication
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The authors declare no competing interests.

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