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LETTER

Interpreting Reduced Postoperative hs-cTnT After Intraoperative Esketamine: Methodological Considerations [Letter]

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Dear editor

We read with interest the recent randomized trial by Zhou et al reporting that intraoperative low-dose esketamine reduced postoperative high-sensitivity cardiac troponin T (hs-cTnT) concentrations in elderly patients undergoing Ivor Lewis esophagectomy.[1] This is an important question, as perioperative myocardial injury remains a major concern in high-risk thoracic surgery. We appreciate the authors' effort to address this issue prospectively. Still, several aspects of the study deserve closer attention before these findings are applied in practice.

First, the primary endpoint was a surrogate biomarker rather than a clinical outcome. Although postoperative troponin elevation is clearly associated with prognosis,[2] a lower hs-cTnT concentration does not necessarily mean that patients experience fewer meaningful cardiovascular events. The trial was not powered for differences in myocardial injury after noncardiac surgery, major adverse cardiovascular events, or mortality. In addition, patients who met criteria of myocardial injury after non-cardiac surgery (MINS) do not appear to have undergone systematic electrocardiographic or echocardiographic evaluation. Without formal blinded adjudication, it remains difficult to distinguish ischemic myocardial infarction from type 2 injury or other forms of non-ischemic troponin release.[3,4] That distinction matters, because these entities differ in both mechanism and clinical implications.

Second, the observed reduction in hs-cTnT may reflect indirect rather than direct cardioprotection. Compared with controls, patients in the esketamine group received 22% less ciprofol, 43% less sufentanil, and 22% less remifentanil, spent significantly less time with mean arterial pressure below 80% of baseline, and required less norepinephrine. Each of these differences independently modulates myocardial oxygen supply-demand balance and represents a recognized risk factor for MINS.[5,6] The trial design cannot distinguish whether hs-cTnT fell because esketamine directly protected cardiomyocytes — as preclinical data suggest — or simply because the esketamine group experienced less hemodynamic stress and less opioid-related cardiovascular depression. A design with tighter anesthetic standardization, or mediation analysis, would help clarify this point.

Third, the issue of anesthetic depth was not fully addressed. Although bispectral index (BIS) monitoring was used, the manuscript did not report group-wise BIS data, time-weighted mean values, or the proportion of time spent at deeper levels of anesthesia. If patients in the esketamine group were maintained at a lighter anesthetic plane, part of the observed benefit could be explained by differences in autonomic tone and hemodynamic stress rather than by the study drug itself. Reporting achieved BIS values and incorporating them into adjusted analyses would strengthen the internal validity of the findings.

Fourth, the biomarker findings should also be interpreted in light of limited generalizability. hs-cTnT can be influenced by renal function,[7] yet renal handling was not clearly incorporated into the analysis. Moreover, patients with recent major cardiovascular events were excluded, even though they are among those at highest risk for

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perioperative myocardial injury.[8] This makes it harder to know whether the same findings would apply to a broader and more vulnerable surgical population.

Finally, the proposed mechanism remains speculative. The lower postoperative inflammatory markers reported in the esketamine group are interesting, but single time-point measurements of nonspecific markers are not enough to support a clear anti-inflammatory explanation.[8] Likewise, whether a short-term biomarker signal translates into better medium- or long-term recovery remains unknown.

Overall, this study provides an interesting signal and supports further investigation of esketamine in major thoracic surgery. At the same time, the current findings are best interpreted as preliminary. Larger multicenter trials with adjudicated cardiovascular outcomes, and more rigorous control of anesthetic and hemodynamic variables will be needed before a true cardioprotective role can be established.

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