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RESPONSE TO LETTER

Statistical Issues in the Oliceridine versus Sufentanil Trial for Elderly Thoracoscopic Surgery [Response to Letter]

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Dear editor

We sincerely thank Dr. Xu D, Ma H, and Hou D for their thoughtful and constructive methodological comments on our article entitled "The satisfactory analgesia and minimal emesis of elderly patients after thoracoscopic lung surgery: oliceridine versus sufentanil in a randomized controlled trial". We greatly appreciate the opportunity to clarify these important statistical issues and to strengthen the presentation of our findings. Below, we respond point-by-point to the raised concerns.

Primary Analysis on the per-Protocol Set Rather Than Intention-to-Treat

Given that only one patient was lost to follow-up in the present study, and this loss was not due to issues related to adherence or protocol deviations, it is unlikely to result in a notable overestimation of the treatment effect. Accordingly, we opted to use the Per-Protocol Set (PPS) as the primary analytical approach. Nevertheless, we agree with Dr. Xu and colleagues regarding the utility of the Intention-to-Treat (ITT) analysis as a sensitivity measure to assess the robustness of our results.

Sample Size Calculation Based on a Small Pilot Study

In the study design phase, a lack of sufficient information is often the prevailing condition; the sample size of 15 cases per group was all the information we had prior to the trial, accounting for 12% of the final sample size, which is still within an acceptable range. It is often difficult to require that the final effect size be completely consistent with the initial estimates. In this study, the estimated values and the final effect sizes were in the same direction, which is entirely acceptable.

However, as pointed out by Dr. Xu, the fact that the lower limit of the confidence interval for the results is close to zero does deserve attention, and it is therefore necessary to examine the robustness of the results.

Furthermore, regarding Dr. Xu's suggestion to estimate statistical power based on the observed effect size, from a statistical perspective, this approach is not particularly recommended, as it can only provide limited useful information.

Multiplicity Issues in Secondary Outcomes

It should be emphasized that our trial only had one pre-specified primary endpoint: the overall rate of patients meeting the satisfactory analgesia with minimal emesis (SAME) criteria within the first 3 postoperative days (PODs). The daily SAME rates on POD 1, 2 and 3 are just subgroup descriptive data of the primary endpoint, rather than three independent endpoints. Given only one primary hypothesis was tested, Bonferroni correction is not necessary for these daily stratified results.

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As detailed in the statistical methods section, the post-hoc pairwise comparisons for the longitudinal NRS and QoR-15 data were performed using repeated measures ANOVA and GEE, with automatic multiplicity adjustment embedded in SPSS. Thus, all reported *P* values are already corrected, and no additional α modification was applied.

Additional Minor Clarifications

Definition of "within the first 3 postoperative days": this was defined as 0–72 hours after surgery, and postoperative day 1 referred to the first 24 hours after surgery; Calculation of daily average cough NRS score: this was calculated as the arithmetic mean of three assessments conducted at 8-hour intervals each day.

We fully agree with your comments on the statistical assumptions of repeated-measures ANOVA. In our analysis of NRS scores, we strictly assessed the normality of residuals and sphericity of the dataset in advance. The Mauchly's test was used to examine sphericity, and Greenhouse-Geisser correction was adopted whenever the sphericity assumption was violated. We acknowledge that these detailed statistical procedures were not fully elaborated in the article.

The registration number of this randomized controlled trial is ChiCTR2500102213, and the official registration date is May 12, 2025. In strict compliance with the requirements of the CONSORT, the recruitment and enrolment of all participants commenced after the trial was formally registered.

Conclusion

We sincerely thank the Dr. Xu D, Ma H, and Hou D for their interest in our work and their critical review of our statistical methods. After a thorough re-evaluation, we do not believe that our statistical methods have any major issues, and we remain confident in the appropriateness of our analytical approach. Likewise, we recognize that your comments remain highly valuable for reference and have helped us reflect on alternative perspectives. This exchange has enhanced the transparency of our reporting. We hope our reply adequately resolves the concerns and we remain open to further scholarly discussion.

Disclosure

The authors report no conflicts of interest in this communication.

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