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LETTER

Methodological Considerations in the Evaluation of Ciprofol's Effect on Postoperative Delirium in Elderly Patients [Letter]

Yanfei Lu[1,2], Fang Cai[1,2]

[1]Center for Rehabilitation Medicine, Department of Anesthesiology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou, Zhejiang, People's Republic of China; [2]Research Institute of Anesthesiology and Perioperative Medicine, Hangzhou Medical College, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Fang Cai, Email gumpy@126.com

Dear editor

We read with great interest the randomized controlled trial by Chen et al investigating the effect of ciprofol on postoperative delirium (POD) in elderly patients undergoing hip surgery.[1] The study provides valuable insights into the potential benefits of ciprofol over propofol in reducing POD incidence and its correlation with SIRT3 expression. However, we have several methodological concerns that may affect the interpretation of the results and warrant further clarification.

First, a major methodological concern in this study is the inadequate control for established confounding variables that significantly influence POD risk. Although basic demographic and intraoperative measures were reported, the authors did not provide comparative data on key preoperative comorbidities—such as hypertension, diabetes, coronary artery disease, atrial fibrillation, or history of stroke—all of which are risk factors for POD.[2,3] Furthermore, although both groups received identical multimodal analgesia protocols—including regional nerve blocks and patient-controlled intravenous analgesia—systematic assessment of postoperative pain using validated scales (e.g, VAS or NRS) was lacking. Postoperative pain is a strong precipitant of delirium, particularly in elderly patients undergoing major orthopedic surgery. It may contribute to POD through mechanisms such as sleep disruption, anxiety, and systemic inflammatory activation.[4] It is noteworthy that the reduction in POD incidence in the ciprofol group was most pronounced on postoperative day 1, which coincides with the period of highest pain intensity. This temporal association raises the possibility that the observed difference in POD incidence may be attributable to imbalances in patient vulnerability or analgesic efficacy rather than a direct neuroprotective effect of ciprofol. Therefore, we recommend that the authors provide detailed between-group comparisons of preoperative comorbidities and pain scores, and perform multivariate regression analyses adjusting for these potential confounders. Only through rigorous control of these variables can a more reliable causal relationship between ciprofol and reduced POD risk be established.

Second, the predictive value of SIRT3 should be interpreted with caution. The reported AUCs were based on very few outcome events—10 delirium cases on postoperative day 1 and only 4 cases on day 3. Such small numbers lead to unstable estimates and wide confidence intervals (95% CI: 0.6968–1.000 on day 1), limiting the precision of the analysis. The finding on day 3, with a higher point estimate (AUC 0.8703) but no statistical significance ($P>0.05$), further reflects the lack of power inherent in such a limited dataset. Moreover, these analyses were conducted using univariate regression without adjustment for other known risk factors of delirium, leaving the possibility of confounding. The proposed cut-off value of 1.565 ng/mL, derived from this small sample, is also unlikely to be reliable and would require validation in independent cohorts. Taken together, the current results suggest that SIRT3 remains an interesting candidate biomarker, but its predictive role should be regarded as preliminary until confirmed in larger studies with sufficient events and multivariable adjustment.

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Third, the authors used the 3D-CAM scale to assess postoperative delirium (POD) but did not stratify delirium by severity using specialized assessment tools such as the Memorial Delirium Assessment Scale (MDAS). This omission is particularly relevant given their investigation of SIRT3 as a biomarker. Delirium severity is clinically meaningful because it correlates with outcomes such as duration of hospitalization, functional decline, and long-term cognitive impairment.[5] More importantly, Serum SIRT3 levels may not only predict the occurrence of delirium but also correlate with its severity. As a key regulator of mitochondrial function and neuroinflammation, SIRT3's expression levels likely reflect the intensity of underlying pathophysiological processes. Severe delirium may represent more profound mitochondrial dysfunction that would correspond to lower SIRT3 activity. By analyzing only a binary outcome, the authors missed an opportunity to explore whether SIRT3 could serve as a quantitative biomarker for delirium severity.

Finally, delirium is an acute cerebral dysfunction characterized by fluctuating symptoms, with the majority of cases occurring within seven days after surgery.[6] In this study, assessments were conducted only on postoperative days 1 and 3, and only once per day,which likely missed late-onset delirium cases. This design significantly increases the risk of "false negatives" potentially leading to an underestimation of the overall incidence of postoperative delirium (POD) and obscuring potential differences between the two interventions. We recommend adopting a more intensive assessment frequency (e.g, twice or three times daily) and extend the follow-up period to at least the seventh postoperative day to more accurately capture the true profile of delirium.

Disclosure

The authors report no conflicts of interest in this communication.

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