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LETTER

Methodological Considerations on the Retrospective Cohort Study of Remifentanil-Propofol versus Propofol Alone in Severe Traumatic Brain Injury [Letter]

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Dear editor

We read with interest the recent retrospective cohort study by Zhu et al[1] comparing remifentanil-propofol with propofol-alone maintenance anesthesia in 113 patients undergoing surgery for severe traumatic brain injury (TBI) The authors report a three-month Good Recovery rate on the Glasgow Outcome Scale (GOS) of 54.39% in the remifentanil-propofol group versus 25.00% in the propofol-alone group (P = 0.001), together with differences in extubation time, awakening time, and several serum biomarkers. We commend the authors for addressing a clinically relevant question but wish to raise seven methodological considerations that, in our view, preclude the conclusions drawn.

First, the magnitude of the reported outcome difference is biologically implausible. A near-doubling of Good Recovery at three months (54.39% vs 25.00%) attributable to intraoperative maintenance anesthetic choice alone would represent one of the largest single-intervention effect sizes ever reported in severe TBI. Established prognostic models for severe TBI—IMPACT and CRASH[2,3]—demonstrate that age, admission Glasgow Coma Scale motor score, pupillary reactivity, hypoxia, hypotension, and computed tomography findings together explain the majority of long-term outcome variance. Major therapeutic interventions recommended by current Brain Trauma Foundation guidelines[4] typically yield effect sizes of 5–10 absolute percentage points on dichotomized functional outcomes. An absolute 29-point difference arising from anesthetic maintenance alone, without corresponding differences in intracranial pressure management, surgical timing, osmotherapy, temperature control, or intensive care delivery, warrants extraordinary scrutiny rather than acceptance at face value.

Second, the mechanism of group allocation is not described. In a retrospective cohort, patients receiving different maintenance regimens almost certainly differed systematically in baseline severity, surgeon or anesthesiologist preference, admission hemodynamics, or institutional protocol era. The authors report baseline characteristics but do not address the fundamental question of why one patient received remifentanil and another did not. Without this information, confounding by indication cannot be excluded, and the reported outcome difference may reflect selection rather than a treatment effect.

Third, the "propofol alone" label is misleading. Both groups received fentanyl at induction, and the study examined only the choice of intraoperative opioid maintenance. The contrast is therefore not "opioid versus no opioid" but "continuous remifentanil infusion versus intermittent fentanyl as needed." This distinction is clinically important and should be reflected in the title, abstract, and discussion so that readers do not misinterpret the comparison as one of opioid avoidance.

Fourth, the observed differences in extubation and awakening times are pharmacokinetically expected and do not constitute a novel finding. Remifentanil's context-sensitive half-time remains approximately 3–5 minutes regardless of

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infusion duration, whereas intermittent fentanyl accumulates with repeated dosing. Faster emergence with remifentanil-based maintenance has been consistently demonstrated across surgical populations for more than two decades. Presenting this as a benefit specific to TBI anesthesia risks overstating the clinical novelty of the finding and conflates a well-characterized pharmacokinetic property with a mechanism of neuroprotection.

Fifth, the study reports more than ten outcome comparisons—extubation time, awakening time, multiple serum biomarkers (TNF-α, IL-6, S-100β, NSE), Glasgow Outcome Scale categories, and adverse events—without a pre-specified primary endpoint or any consideration of multiple testing. While there is legitimate debate regarding the need for multiplicity adjustment in observational research,[5] the combination of no pre-specification, no correction, and uniformly "positive" findings across heterogeneous outcomes raises concern that the reported P values may overstate the evidence against the null. A pre-specified primary endpoint, with remaining comparisons reported as exploratory, would substantially clarify the inference.

Sixth, the serum neuro-inflammatory and neuronal injury biomarkers (TNF-α, IL-6, S-100β, NSE) are surrogate outcomes whose relationship to patient-important endpoints in severe TBI is incompletely established. Short-term reductions in circulating inflammatory or structural markers do not reliably translate into improved functional recovery, and their inclusion alongside the GOS risks conflating mechanistic plausibility with clinical benefit.

Seventh, the five-category Glasgow Outcome Scale is subject to substantial inter-rater disagreement, with misclassification rates of 10–20% reported even in controlled clinical trial settings.[6] At three months, when transitions between the "Moderate Disability" and "Good Recovery" categories are most frequent, misclassification can inflate or deflate the reported Good Recovery rate by a magnitude comparable to the effect the authors attribute to remifentanil. Compounding this concern, the manuscript does not report adherence to the STROBE statement for observational research,[7] and definitions of the exposure window and follow-up period are not clearly specified—features that are prerequisites for ruling out immortal time bias in pharmaco-epidemiological comparisons.[8]

We do not dispute that remifentanil-propofol maintenance may offer intraoperative advantages over intermittent fentanyl in TBI surgery; a faster, smoother emergence is clinically valuable. We do, however, suggest that the authors' inference—that anesthetic maintenance choice alone nearly doubles three-month Good Recovery in severe TBI—substantially exceeds what the design, sample size, and analysis can support. We would encourage re-analysis with adjustment for established IMPACT/CRASH prognostic covariates, pre-specification of a single primary endpoint, and a tempered conclusion that reflects the observational nature of the data.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this Letter, the authors used Claude Opus 4.7 (Anthropic PBC, San Francisco, California, USA) to assist with language refinement and with the organization and formatting of reference information. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data Sharing Statement

Data sharing is not applicable to this Letter, as no new datasets were generated or analyzed. All claims pertain to the published article by Zhu et al (Drug Des Devel Ther. 2025;19:10561–10569).

Author Contributions

K.Ş.: Conceptualization; Writing – original draft; Writing – review and editing. S.H.: Methodology; Writing – review and editing. M.T.P.: Investigation; Writing – review and editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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