Peer Review File

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Reviewer A

AQ 1 A Editorial on paper is descriptive but lacks much further insight than previously published letters. Although appropriately referenced large parts of the editorial are regurgitation of criticism that I and others have written.

AQ 1 B I struggle to see relevance of the paragragh on treatment of PRIS with ECMO.

AQ 1 C To publish this would need the insight and commentary significantly improved.

Reply AQ 1 A> Thank you for your comment. Many reviews have indeed already been conducted on this study. However, given the numerous debates it has sparked within the scientific community and at conferences, we believe it is important to continue highlighting the various weaknesses of the article to avoid drawing premature conclusions.

Reply AQ 1 B > Regarding your comment on the relevance of mentioning ECMO in the PRIS section, we have removed the paragraph.

Changes AQ 1 B in the text : We have removed the paragraph about PRIS and ECMO.

~~In cases of severe refractory cardiogenic shock due to Propofol-related infusion syndrome (PRIS), urgent discontinuation of propofol and aggressive supportive treatment are required [10]. In this case, Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) may offer temporary cardiac support and potential reversibility in PRIS-induced cardiogenic shock [10]. However, ECMO is not always safe and recent case studies have demonstrated a risk of PRIS after liberation from Extracorporeal Membrane Oxygenation (ECMO) [11].~~

Reply AQ 1 C > To publish this, we need to significantly enhance the insight and commentary. Therefore, we have added more detailed insights to improve the commentary.

Changes AQ 1 C in the text:

Additionally, Kotani et al. extracted data for one-year mortality, despite initially planning to assess 30-day mortality in their PROSPERO registration (CRD42022323143). They later updated the registration to one-year mortality [17]. It appears they extracted data as intention-to-treat (n = 450 per arm as the denominator), when it would have been more appropriate to use the number of patients for whom

follow-up data were available, further inflating the estimates [17]. Lastly, given the considerable underlying clinical heterogeneity, the choice of a fixed-effect model is questionable; a random-effects model would have been more suitable [18].

A significant counterpoint to Kotani et al.'s stance is provided by a large RCT published by Landoni et al. in 2015, which included 133 studies with 14,516 patients. This meta-analysis found no significant difference in mortality between patients receiving propofol [349/6957 (5.0%)] versus those receiving any comparator [340/7559 (4.5%)], with a risk ratio of 1.05 (95% CI, 0.93 to 1.18; P = 0.5). The conclusion was that despite theoretical concerns, propofol does not negatively impact survival, according to the largest meta-analysis of randomized trials on hypnotic drugs ever conducted [21].

An important shortcoming in Kotani et al.'s meta-analysis is the selection of studies included. The 2015 meta-analysis by Landoni et al. highlighted that the subgroup of patients who did not receive a loading dose of propofol before infusion had a higher mortality rate compared to those who did receive a loading dose. This finding is likely because most studies without a loading dose were conducted in ICU or cardiac surgery settings, where mortality rates are inherently higher [21]. However, this effect was not discussed in Kotani et al.'s 2023 article, raising questions about the omission of such a significant detail [21].

Reviewer B

Fair arguments!
Please cite (PMID: 37474241; PMID: 30115258) and discuss the advantages of propofol over inhalational agents in decreasing neurological complications further improving surgical outcomes.

Reply 2 A: Thank you for your very stimulating comment. We have adjusted our text as advised.

Changes 2 A in the text: We have added a note regarding the interest of propofol compared to inhalational agents for reducing the risk of postoperative delirium (see lines 5, 6, 7, and 8 of the paragraph titled "Potential Mechanisms and Pathophysiology of Propofol Side Effects").