Propofol curtails survival in perioperative and critically ill patients by a relative reduction of 10%: should propofol be abandoned?

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Introduction

The release of the meta-analysis by Kotani *et al.* generated a significant response in the anesthesiology and intensive care unit (ICU) community. According to the 252 randomized controlled trials (RCTs) comprising more than 30,000 patients included in this meta-analysis, the use of propofol is associated with a potential increase of 10% in mortality in comparison to other sedative strategies (1). It is important to note that this study is not definitive and further research is needed to confirm these findings. Nevertheless, this analysis has highlighted limitations. Some of these limitations could have been addressed by conducting a large RCT comparing propofol with another sedative strategy and distinguishing patients undergoing surgical procedures and those in the ICU (1).

Potential mechanisms and pathophysiology of propofol side effects

Propofol has numerous benefits, including rapid onset and elimination, short duration of action, rapid recovery from anesthesia, a very low incidence of adverse effects, and an absence of mutagenic or teratogenic effects, establishing it as an optimal hypnotic agent (1). Moreover, research indicates a higher incidence of postoperative delirium with inhalational agents compared to propofol following major oncological surgeries (2,3).

Nonetheless, propofol is not devoid of detrimental effects, such as propofol-related infusion syndrome (PRIS) and the risk of accidental microbial contamination (4-7). In terms of drug interactions, various meta-analyses have revealed that total intravenous anesthesia (TIVA) is associated with increased mortality rates in specific cardiac surgery populations when compared to volatile anesthetic agents. This is attributed to propofol's lack of the pharmacological ischemic preconditioning effect that is characteristic of halogenated agents (8,9). Furthermore, propofol usage has been linked to a heightened incidence of nephrogenic diabetes insipidus, similar to the effects observed with sevoflurane (10).

Limitations of the meta-analysis

Only two out of the 252 studies included in the meta-

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analysis reported a significantly higher mortality rate in the propofol group. One of these studies, conducted by Likhvantsev *et al.* (11), involved 900 patients undergoing elective coronary artery bypass grafting (CABG) and presented a high mortality rate in both groups, making it a significant outlier for this meta-analysis (12). However, it should be noted that an error was made in the data extraction; the corrected 1-year mortality rate in this study is 17.8% (52 out of 292) in the sevoflurane group and 24.8% (81 out of 326) in the propofol group. These results differ from those reported in the meta-analysis by Kotani *et al.*, which documented rates of 11.6% (52 out of 450) and 18% (81 out of 450) respectively, not accounting for the large amount of loss of follow-up (13,14). It is important to note that the study by Likhvantsev *et al.* is the only RCT in the cardiac surgery subgroup analysis that does not cross the line of no effect, thereby carrying a cumulative weight of 61% in the forest plot (11,13). In a subsequent study, two of the authors compared the use of volatile anesthetic in patients undergoing elective CABG (2,709 patients) versus TIVA (2,691 patients) in a 5,400-patient RCT (15). This study did not demonstrate a significant difference in 1-year mortality between the groups [relative risk, 0.94; 95% confidence interval (CI): 0.69 to 1.29; P=0.71]. Notably, this negative RCT was not included in the meta-analysis (12).

The authors employed a fixed-effect model, which should be used only if it is reasonable to assume that all studies share the same common effect. The authors chose this model based solely on heterogeneity index. However, the low heterogeneity index reported here results from studies with small sample sizes, few events, and wide confidence intervals. In the random-effect model meta-analysis (additional file 1), there is no significant difference in mortality between the groups (relative risk, 1.05; 95% CI: 0.98 to 1.13; P=0.17).

Initially, the primary endpoint of the meta-analysis was 30-day mortality. However, less than 10% of the studies provided this data. Consequently, the outcome was modified to the longest follow-up, which was found to be very heterogeneous (hospital, perioperative, ICU, 30 days, 1 year), thus precluding a qualitative comparison.

Moreover, the authors excluded studies with a high risk of bias, which, while prudent, would have benefited from a leave-one-out analysis to ensure that the results were not unduly influenced by the studies of Likhvantsev *et al.* (11) and de la Gala *et al.* (16).

The authors' recommendations are not applicable to ICU patients due to the lack of significant statistical differences observed in that setting (14). Another significant limitation is the absence of a clearly defined comparative group for propofol (17). Additionally, Kotani *et al.* extracted data for 1-year mortality, despite initially planning to assess 30-day mortality in their PROSPERO registration (CRD42022323143). They later updated the registration to 1-year mortality (13). 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 (13). 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).

Are Kotani *et al.*'s statements on the use of propofol still relevant today?

Kotani *et al.*'s recommendations on the use of propofol remain a topic of debate. Their suggestion that physicians consider alternative hypnotic agents, implement hypnotic rotation strategies in the ICU, and attempt propofol dose reduction while awaiting large RCTs, has been criticized for potentially being premature and misleading, categorized under 'spin' language. This term describes the practice of presenting findings in a biased manner without adequate evidence, a prevalent issue in approximately 40% of all RCTs in anesthesia (14,19).

A significant counterpoint to Kotani *et al.*'s stance is provided by a large RCT published by Pasin *et al.* in 2015 (20), which included 133 studies with 14,516 patients. This meta-analysis found no significant difference in mortality between patients receiving propofol [349/6,957 (5.0%)] versus those receiving any comparator [340/7,559 (4.5%)], with a risk ratio of 1.05 (95% CI: 0.93 to 1.18; P=0.50). 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 (20).

An important shortcoming in Kotani *et al.*'s meta-analysis is the selection of studies included. The 2015 meta-analysis by Pasin *et al.* (20) 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 (20). However, this effect was not

discussed in Kotani *et al.*'s 2023 article, raising questions about the omission of such a significant detail (20).

What should be the next steps?

Given the numerous limitations of the current meta-analysis, abandoning propofol is not advisable. A more productive approach would be to conduct a network meta-analysis. Unlike standard meta-analyses that require a well-defined comparator group, network meta-analyses enable multiple comparisons among various treatment groups, provided certain methodological conditions are met (17,21).

In their conclusion and response to criticism, Kotani *et al.* emphasized the need for future trials to compare propofol with propofol-free anesthesia strategies to confirm the results of the present meta-analysis (1,22). They suggest a multinational, not-for-profit, large-scale trial led by researchers to mitigate bias and enhance the generalizability of the findings (1).

Conclusions

This meta-analysis presents limitations that preclude abandoning or reducing the use of propofol in anesthesia and ICU. The primary takeaway is to highlight a potential risk associated with the utilization of propofol, suggesting that further investigation is necessary. A more definitive answer could be achieved through a network meta-analysis or a large-scale RCT that compares propofol with a standard or multiple comparators.

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Footnote

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