

COMMENT

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Comment on Propofol and survival: an updated meta-analysis of randomized clinical trials

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Dear Editor,

We wish to add further comment to the recent publication by Kotani et al. [1]. Firstly, we would like to thank the authors for undertaking a thorough and detailed meta-analysis on a clinically important topic suggesting propofol is associated with increased mortality (RR 1.10, 95% CI 1.01–1.20, $p=0.03$). We would, however, like to add to the comments of Benavides-Zora et al. [2] and Hansel [3] regarding the meta-analysis.

Mortality outlier study

As already highlighted by Benavides-Zora et al. [2] and Hansel [3], there is an error in the data extraction regarding the mortality rate from the manuscript by Likhvantsev et al. [4]. The corrected one-year mortality rate in this study is 52/292 (17.8%) in the sevoflurane group and 81/326 (24.8%) in the propofol group, rather than 52/450 (11.6%) and 81/450 (18%), respectively, as detailed in the Kotani et al. meta-analysis. As detailed by Hansel, this artificially inflates the estimated risk ratio of the study in the meta-analysis.

On closer analysis of the Likhvantsev et al. study, the mortality rate in both groups is very high and a significant outlier in the meta-analysis. The study included 900 patients undergoing elective coronary artery bypass grafting (CABG) with “patients who had a recent or ongoing myocardial infarction” excluded. The study authors comment that their “1-year mortality was extremely high in this cohort of patients” and their “hypotheses to explain these findings was that patients’ adherence to cardiologic medication was extremely poor after hospital discharge”. In comparison, the crude one-year mortality for “all cardiac surgery” in the UK is 3.78% [5]. This study is one of only two out of 252 studies included in the meta-analysis demonstrating increased mortality in a propofol group. With such a markedly high mortality rate, this study is a clear outlier and has the potential to influence the meta-analysis results, in addition to the data extraction error.

Study not included in the analysis

Further investigation of the 900-patient study by Likhvantsev et al. [4] shows that two authors (Likhvantsev and Landoni) went on to perform a 5400-patient randomized control trial comparing maintenance of anaesthesia in patients undergoing elective CABG with volatile anaesthetic (2709 patients) to total intravenous anaesthetic (TIVA, 2691 patients) [6]. This later paper demonstrated no significant mortality difference at 1 year (relative risk, 0.94; 95% [CI] 0.69 to 1.29; $p = 0.71$). Mortality rates in this study were 2.8% in the volatile group and 3.0% in the TIVA group, markedly different to the 17.8% and 24.8% reported in the previous 900 patient study of Likhvantsev et al. and more in keeping with contemporary reports [4].

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We must highlight that whilst the 900-patient study of Likhvantsev et al. [4] is included in the meta-analysis, the 5,400-patient study of Landoni et al. [6] is not. This may be due to the concise literature search strategy used in the meta-analysis in which the Landoni et al. paper does not appear as the intervention was documented as TIVA and not propofol. In the TIVA group, however, anaesthetic was maintained by a propofol infusion in 2297/2665 (86.9%) patients allowing comparison against 2709 patients with volatile anaesthetic maintenance. It is therefore surprising that this study was not included in the meta-analysis given; the detailed data collection methods described, it is mentioned in the discussion section and, most surprisingly, that the first author (Landoni) is a co-author in this meta-analysis [1].

Spin

Again, we wish to add to the comment of Benavides-Zora et al. [2] in regard to the “spin” of the presentation of results. In Kotani et al.’s discussion of the difference between the meta-analysis and the 5400 patient Landoni et al. study, they comment, “*We hypothesize that the use of propofol in the majority of patients who were randomized to the volatile group [crossover between treatment groups] blunted the detrimental effect of propofol on survival in this trial*”. This contradicts a sub-group analysis in their paper that showed no difference in mortality between groups in studies where propofol was not used in the comparator arm (RR 1.03, 95% CI 0.94–1.14, $p = 0.50$).

As Hansel commented, Kotani et al. “*stop short of addressing the elephant in the room*” of the impact of the 900 patient Likhvantsev et al. on the overall meta-analysis results. In addition, we felt that they fail to address the white elephant in the room of the 5400-patient study of Landoni et al. which mysteriously does not feature in the meta-analysis at all.

Summary

In summary, we believe that the readers of *Critical Care* should be cautious in their interpretation of the results of this important meta-analysis and would no doubt appreciate re-analysis without the significantly outlier in mortality of the Likhvantsev et al. study and including the mortality data from the 5400-patient Landoni et al. study.

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AG wrote the main manuscript text. PM and BS reviewed and contributed to the final manuscript.

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Declarations

Ethical approval and consent to participate

Not applicable.

Competing interests

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