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Perioperative vasoactive drugs in patients undergoing major abdominal surgery. Comment on *Br J Anaesth* 2020; 124: 513–24

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Keywords: cardiovascular; goal-directed therapy; haemodynamics; major abdominal surgery; perioperative care; postoperative outcome; vasoconstrictor agents

Editor—I read with great interest the article by Deng and colleagues[1] on assessing the effect of *vasoactive drugs* in patients undergoing major abdominal surgery. Their systematic review and meta-analysis claims that perioperative vasoactive drugs reduce postoperative complications and the length of hospital stay. Although the authors openly discuss the limitations of their findings, I would like to point out methodological concerns and the need for some data to be validated and revised.

First, I am concerned about the authors' assertion that missing outcome data are at a low risk of bias (risk-of-bias figure in Supplementary material 2[1]). The authors assumed that no trial included in their meta-analysis had missing outcome data. However, the study by Sandham and colleagues,[2] the largest RCT included, reported that 1 yr mortality rates were 163/910 (17.9%) in the intervention group and 155/941 (16.5%) in the control group. In accordance with the principle of intention-to-treat analysis, the number for each group should be 997 vs 997 not 910 *vs* 941. Patients lost to follow-up (87/997 missing from the intervention group and 56/997 missing from the control group) can result in incomplete outcome data; the high risk of attrition bias is arguably inevitable. As including an appraisal of the risk of bias in studies is an integral part of systematic review methods, the authors should report the reason(s) for these missing data and evaluate whether missingness in the outcome could depend on its true value.[3] In addition, the authors should clearly state any assumptions or imputation methods used to handle the missing data.

Second, there is no equipoise regarding comparison of trials with different study protocols, resulting in important methodological limitations. Although pre-specified eligibility criteria were applied in this systematic review and meta-analysis, the characteristics of protocolised vasoactive support interventions varied. Some trials had different objectives for vasopressor and inotrope support interventions. For example, in the study of Stens and colleagues[4] included in this systematic review, the clinical effectiveness of additional cardiac index (CI) and pulse pressure variation (PPV)-guided haemodynamic therapy and that of conventional MAP-guided fluid therapy were compared. Their study adopted protocolised vasoactive management therapy; however, this study did not mean to compare the vasoactive management strategy. Thus, there are substantial differences in the way vasoactive agents were initiated, titrated, and weaned between trials. In fact, in the study of Stens and colleagues,[4] there were substantial differences amongst groups that received vasopressor or inotropic agents (64–78% in the CI–PPV group *vs* 35–38% in the control group), suggesting that the intervention group did not necessarily receive vasoactive agents and *vice versa*. Therefore, the authors' hypothesis that 'the perioperative administration of vasoactive drug therapy, with or without goal directed therapy, reduced mortality, morbidity'[1] does not seem to be compatible with their protocol for this systematic review and meta-analysis. To explain this major concern regarding heterogeneity, pre-established protocols[5] should be described in detail.

Lastly, I would like to see the overall quality of the evidence assessed via the Grading of Recommendations, Assessment, Development and Evaluations framework for relevant outcomes.[6]

I believe that considering the aforementioned factors would have improved the quality and credibility of this study.

Declaration of interest

The author declares that they have no conflicts of interest.

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Perioperative use of vasoactive drugs on postoperative outcomes after major abdominal surgery. Response to *Br J Anaesth* 2020; 125: e353–4

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Editor—We thank Yonekura[1] for his interest in our systematic review,[2] and would like to address his comments.

Firstly, we accept that the denominator in our meta-analysis was inconsistent with the intention to treat principle. We have repeated the analysis with updated denominators reflecting intention to treat or modified intention to treat principles. This did not change the results of the meta-analysis (risk ratio of mortality at longest follow-up in intervention compared with control group of 0.83, 95% confidence interval 0.63–1.10, P=0.20). For missing data, 1851 of 1994 randomised participants in the study by Sandham and colleagues[3] had completed 1 yr of follow-up. Of those with missing long-term outcome data, 88 participants were excluded after randomisation as they did not meet the *a priori* inclusion criteria, and 55 were lost to follow-up (only 2.9% of the modified intention to treat population). We made a considered judgement that this does not represent significant loss to follow-up as the overall mortality rate was in the range of 16–18%. There is no evidence to suggest that the missingness is systematic (non-random). Furthermore, it is the original authors' responsibility to report the reason(s) for missing data and any assumptions or imputation methods used to handle missing data.

Secondly, we agree with Yonekura's[1] concern that heterogeneity posed a major limitation in our systematic review, as we had highlighted in our discussion. The aim of our systematic review was to assess whether the protocolised administration of vasoactive agents had an effect on postoperative outcome, which included studies comparing vasoactive medications as part of haemodynamic targeting with routine care. It would be considered unethical not to treat severe hypotension in the controlled arm of a trial, and as such the use of vasoactive agents in both arms of an intervention such as this is not surprising. This is not an equipoise problem, rather, methodological limitations of individual studies which we had addressed in our discussion.

Thirdly, we disagree that the Grading of Recommendations Assessments, Development and Evaluation (GRADE) framework is useful in this context. We did not publish clinical guidelines, but rather a synthesis of previously published research.

Declarations of interest

PM is an Australian National Health and Medical Research Council practitioner fellow and an editor of the *British Journal of Anaesthesia*. CD declares no conflict of interest.

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