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CORRESPONDENCE

Network meta-analysis of isolated patient blood management interventions leads to uncertain interpretation. Comment on Br J Anaesth 2021; 126: 149–56

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Editor—We read with interest the recent network meta-analysis of patient blood management interventions by Roman and colleagues[1] in the *British Journal of Anaesthesia*. The authors reported that patient blood management interventions resulted in a reduction in exposure to red blood cells without statistically significant effects on 30-day or hospital mortality. The authors also performed a network meta-analysis that did not demonstrate additive benefits from the use of one of several additional interventions (e.g. preoperative treatment of anaemia, restrictive transfusion protocol, tranexamic acid, cell salvage, or point-of-care tests of coagulopathy). No randomised trial demonstrated that patient blood management, as defined by the authors, was cost-effective, leading the authors to conclude that patient blood management interventions do not have important clinical benefits beyond reducing bleeding and transfusion. We think the results reported in the network meta-analysis and the authors' conclusion should be interpreted with caution.

A valid network meta-analysis relies on the assumption that the studies included in the analysis are similar, on average, in all important factors that may affect the relative effects. In this analysis, the authors pooled studies that assessed the effect of single interventions on exposure to blood products and all-cause mortality, rather than the totality of interventions that, together, constitute comprehensive patient blood management. As recently demonstrated by Trentino and colleagues[2] in their meta-analysis of restrictive and liberal haemoglobin thresholds for red blood cell transfusion, key clinical differences exist among RCTs comparing transfusion strategies. Trentino and colleagues[2] summarised unique concerns specific to transfusion strategies: (1) haemoglobin thresholds selected for transfusion differ between studies without the ability to take patient characteristics into consideration (e.g. degree of tolerance to anaemia), (2) the absolute difference of pre-transfusion haemoglobin concentrations (e.g. what if the restrictive threshold is already too liberal), (3) time to randomisation (resulting in transfusion administered before randomisation or patients being excluded because of bleeding), and (4) comparable transfusion dosing regimens. The same critical limitations exist for studies that assessed the efficacy of preoperative anaemia management (different iron preparations, dose and route of administration, variation in the use of erythropoiesis stimulating agents and timing and duration of treatment), antifibrinolytics (e.g. different drugs and different dosage), cell salvage (e.g. different devices), and point-of-care coagulation monitoring (e.g. different tests and different strategies to replace coagulation factors). Adding the mean effect of study interventions performed on heterogeneous populations based on variable study designs in a network meta-analysis violates the condition of a valid network meta-analysis that all important factors that may affect the relative effects be similar and does not allow any conclusion on the additive effect of those interventions.

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The beneficial effect of patient blood management relies not only on the reduction of transfusion, but on how multimodal perioperative patient-specific interventions synergistically improve clinical outcomes. The implementation of patient blood management targets more than mortality, which thankfully is a very rare endpoint, but any perioperative complications, such as hospital-acquired infection and hospital-acquired anaemia, that could affect patients' perioperative course, resource utilisation (not only cost), and long-term health. Because patient blood management is a clinical 'bundle' promoting implementation of a patient-centred and multimodal strategy,[3] it does not lend itself to being studied in the same manner as a single therapy (such as preoperative treatment of anaemia, restrictive transfusion protocol, tranexamic acid, cell salvage, or point-of-care tests of coagulopathy) in the context of a network meta-analysis. Although, RCTs are important to assess the efficacy of a specific treatment in a specific population (e.g. can restrictive transfusion thresholds 'work' under a specific set of circumstances), alternatives are required to assess the effectiveness of a comprehensive bundle of clinical strategies in real-world circumstances. The effectiveness and cost-effectiveness of the implementation of patient blood management have been demonstrated in several analyses of data obtained from institutional or national programs.[4–8] Those results might not be based on randomised designs, but described real-life effects of implementing a bundle of perioperative patient-specific interventions. None of those real-life experiences were considered in Roman and colleagues'[1] network meta-analysis.

The results reported by Roman and colleagues[1] should be interpreted with caution as they highlight the numerous limitations of the network meta-analysis design. We disagree with the authors' conclusion that patient blood management interventions do not have important clinical benefits beyond reducing bleeding and transfusion in people undergoing major surgery, clinical benefits that have been shown with a design more appropriate to studying patient blood management. We believe patient blood management interventions have a synergistic effect such that the effectiveness of patient blood management interventions on outcome (beyond mortality) and resource utilisation (beyond costs) can only be studied through patient-centred analysis of multimodal interventions.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Interpretation of network meta-analysis of isolated patient blood management interventions. Response to *Br J Anaesth* 2021; 126: e1–2

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