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Patient blood management interventions lead to important benefits for major surgery. Comment on *Br J Anaesth* 2021; 126: 149–56

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Editor—Systematic reviews and meta-analyses provide clinicians and policymakers with valuable, simple, and reliable summary measures to guide decisions on various conditions and treatments. In our opinion, the recent meta-analysis by Roman and colleagues[1] on certain patient blood management (PBM) interventions misses the mark. We have concerns about potentially far-reaching negative impacts of the conclusions that are not wholly supported by the evidence.

In their meta-analysis,[1] the authors focused on three outcome domains and clearly showed the effectiveness of the studied PBM measures in two (measures of transfusion/bleeding and measures of resource use). Conversely, they failed to detect efficacy in the domain of clinical effectiveness, led by mortality.[1] Finally, the authors were only able to identify a single RCT addressing cost-effectiveness of a PBM modality that showed significant cost reduction, but the results were not fully consistent with four other model-based studies.[1] Consequently, the authors concluded that 'PBM interventions did not lead to important clinical benefits or cost-effectiveness' as indicated in the title of their manuscript and highlighted in the abstract.[1] Titles and abstracts are often the first (and sometimes, only) parts of a paper seen by many clinicians, and the message conveyed, that PBM does not work, cannot be any more clear. That message is inconsistent with their findings.

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PBM modalities reduce allogeneic blood transfusions and surgical blood loss.[1] Both are quality measures.[2] Blood transfusions are independently linked to worse clinical outcomes, as shown by several studies.[3] Therefore, it is not unreasonable to expect that measures leading to reduced transfusions would also lead to improved clinical outcomes. We think the reason this was not supported in the meta-analysis by Roman and colleagues[1] lies in the design and power of the primary studies included.

Although clinical outcomes such as mortality are very important, given their low occurrence rate, they can be challenging to assess in clinical studies.[4] To design a study sufficiently powered to assess an outcome that occurs in a few percent of cases, thousands of patients are needed. The findings of the meta-analysis by Roman and colleagues should be interpreted in the context of many primary studies that are severely under-powered to detect improvements in low incidence clinical measures such as mortality.

Meta-analyses can address the power limitations of smaller studies by pooling and analysing the raw data from multiple studies in what is known as an individual participant data (IPD) approach. Conversely, if a meta-analysis pools the treatment effects of the individual studies instead of the raw data (known as the aggregate data [AD] approach), it may fail to show statistically significant improvements when individual studies report non-significant treatment effects.[5] The results from the AD and IPD approaches are more likely to be in agreement when the individual studies are sufficiently powered,[6] but many trials on PBM modalities are not adequately powered for clinical outcomes such as mortality,[4] passing the limitation on to the aggregate parameter estimates of meta-analyses.

Heterogeneity is a common concern in meta-analyses, and statistical tests (such as tau,[2] I^2 statistics, and Cochran's Q) are used to assess for it. Nonetheless, these tests primarily address statistical heterogeneity. Clinical heterogeneity that arises from differences in patient, intervention or outcome characteristics is more difficult to assess, and no statistical method can adjust for it if present.[7] The studies included in this network meta-analysis span vastly different patient populations, procedures, and interventions. Efficacy of some PBM treatments can be highly sensitive to patient and procedure characteristics. For example perioperative red blood cell recovery is more effective in procedures associated with higher blood loss.[8] Similarly, iron therapy is more likely to help when iron deficiency is present. PBM strategies advocate an individualised approach tailored to each patient's specific needs and conditions,[9] and it can be challenging to pool the results of heterogeneous studies with one-size-fits-all approaches to assess the impact of PBM strategies as was attempted in this meta-analysis.[1]

Improvement in clinical outcomes remains the ultimate endpoint of PBM.[10] Assessment of clinical outcomes requires properly designed and adequately powered studies, however. In the absence of such studies, meta-analyses using the IPD approach may compensate for limited sample size of individual studies, but those using the AD approach such as the one by Roman and colleagues[1] run the risk of propagating the limitations of the primary studies.[4] In the meantime, surrogate endpoints such as transfusion rate and volumes can serve as lower hanging fruit to demonstrate the effectiveness of PBM modalities.[4]

We find it inaccurate (if not irresponsible) to declare PBM modalities 'ineffective' despite clear evidence supporting their positive impact on reducing perioperative transfusion and bleeding, and shortening length of stay.[1] As clinicians, we can reasonably expect the improved clinical outcomes to follow when transfusion is reduced, bleeding is controlled, and anaemia is managed.

Declarations of interest

MJ has been a consultant for the Society for the Advancement of Blood Management (SABM) and Gauss Surgical. SO is a board member and is currently serving as the President of SABM. JFH is secretary–treasurer of the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) and is consultant for Nordic Pharma and Pharmacosmos.

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