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Whole blood versus component therapy for haemostatic resuscitation of major bleeding: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction There is a renewed interest in the use of whole blood (WB) to manage patients with life-threatening bleeding. We aimed to estimate mortality and complications risk between WB and blood component therapy for haemostatic resuscitation of major bleeding.

Methods We will conduct a systematic review and meta-analysis of studies published between 1 January 1980 and 1 January 2020, identified from PubMed and Scopus databases. Population will be patients who require blood transfusion (traumatic operative, obstetric and gastrointestinal bleeding). Intervention is WB transfusion such as fresh WB (WB unit stored for less than 48 hours), leukoreduced modified WB (with platelets removed during filtration), warm fresh WB (stored warm at 22°C for up to 8 hours and then for a maximum of an additional 24 hours at 4°C). The primary outcomes will be the 24-hour and 30-day survival rates (in-hospital mortality). Comparator is blood component therapy (red blood cells, fresh-frozen plasma and platelets given together in a 1:1:1 unit ratio). The Cochrane risk of bias tool for randomised controlled trials and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) for observation studies will be used to assess the risk of bias of included studies. We will use random-effects models for the pooling of studies. Interstudy heterogeneity will be assessed by the Cochran Q statistic, where $p<0.10$ will be considered statistically significant and quantified by I^2 statistic, where $I^2 \geq 50\%$ will indicate substantial heterogeneity. We will perform subgroup and meta-regression analyses to assess geographical differences and other study-level factors explaining variations in the reported mortality risk. Results will be reported as risk ratios and their 95% CIs.

Ethics and dissemination No ethics clearance is required as no primary data will be collected. The results will be presented at scientific conferences and published in a peer-reviewed journal.

Strengths and limitations of this study

► The systematic review and meta-analysis will update the available evidence on mortality and morbidity risk associated with whole blood use compared with component therapy in treating life-threatening bleeding.
► We adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines to ensure transparency of the study.
► Between-study heterogeneity is a limitation. We will use random-effects meta-regression models to characterise the sources of heterogeneity.

INTRODUCTION

Over the past three decades, there is a renewed interest in using whole blood (WB) to manage patients with life-threatening bleeding. Robertson initially established the foundation for blood transfusions for traumatic injuries during the First World War when blood banking during military combat became available.[1] However, civilian establishment of organised blood banking lagged by several decades and became readily accessible during the Second World War. Stored WB was the mainstay of transfusion through the beginning of the Vietnam era. In 1965, during the Vietnam War, blood component therapy was introduced, and by the 1970s, WB resuscitation had nearly ceased.[2] Component therapy, including packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets (PLT), has been adopted as the gold standard for both military and civilian trauma resuscitation.

Strategies in component resuscitation have evolved over the past several decades, with the adoption of damage control resuscitation (DCR). DCR principles include early administration of blood products in a balanced ratio, prevention and correction of coagulopathy, and minimisation of crystalloid fluid resuscitation.[3] Typical initial resuscitation using a massive transfusion protocol uses component therapy from universally compatible donors before laboratory testing. The concept of a balanced component resuscitation that supports achieving haemostasis with

transfusion of PRBC, FFP and PLT that approximates WB has been largely supported by recent evidence.[4 5] While component therapy has dominated civilian resuscitation of haemorrhagic shock, fresh WB (stored at 22°C for 24 hours) has continued to be used in military trauma resuscitation in austere environments where the storage of component therapy is unavailable. In fact, over 6000 units of type-specific warm fresh WB were transfused during the Iraq and Afghanistan conflicts to patients with severe haemorrhage, and these patients showed increased 24-hour and 30-day survival and decreased transfusion requirements.[6 7] However, warm fresh WB still only comprised 4% of transfusions during this era, reflecting the current practice of using component therapy when available.[6]

Civilian interest in the use of WB for resuscitation of traumatic haemorrhagic shock has resurged in the past decade. Unlike in austere military environments, civilian usage of WB has been in the form of cold-stored WB, stored for up to 21 days between 1°C and 6°C. Stored WB has an established safety profile; over 350 000 units were transfused during the Vietnam war with low rates of haemolysis.[8] Low-titre, leucocyte-reduced, PLT-sparing group O WB has been used in several small series at three level 1 trauma centres in the USA with initial published data suggesting a trend towards decreased transfusion requirements, but studies have been small and underpowered to detect a survival benefit.[9 10] However, these studies did establish a safety profile for the practice of transfusing group O WB, with no reports of transfusion reactions or differences in serum haptoglobin as a marker of haemolysis.[10 11] The risk of haemolysis caused by the transfusion of group O low-titre WB to a non-group O recipient is low.[8 12]

There has been preliminary investigation by one series into coagulation markers as assessed by thromboelastography, with improvement in markers of coagulopathy seen in groups receiving WB and PLT transfusion.[13] However, there still remains a paucity of literature assessing the effects of WB in the resuscitation of haemorrhagic shock on mortality, total transfusion requirements and need for damage control. Systematic reviews assessing the effect of WB transfusion versus component therapy on outcomes have limitations, including selection bias, age groups studied, limited outcomes assessed and did not address sources of heterogeneity in results using random-effects meta-regression and subgroup analyses.[14–16] In this study, we seek to fill this gap by evaluating mortality rates and identifying potential complications of WB transfusion, including haemolysis and thrombotic events. We propose to assess sources of heterogeneity (which are very common in meta-analysis) through random-effects meta-regression and subgroup analyses.

Objectives
This study aims to present a protocol for systematic review and meta-analysis to compare 24-hour and 30-day survival

in WB use and component therapy for haemostatic resuscitation of major bleeding.

Specific aims
► Compare differences between 24-hour and 30-day survival in groups of patients receiving WB or blood components (pRBC, PLT and FFP).
► To estimate morbidity such as acute kidney injury, sepsis, venous thromboembolism, acute respiratory distress syndrome, 24 hours transfusion volume, coagulation abnormality, intensive care unit (ICU) length of stay and ventilation days in a group receiving WB compared with component therapy.

Review question
What is the 24-hor and 30-day survival rates following the use of WB or blood component therapy?

METHODS
This protocol was reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.[17 18] See online supplemental table 1.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Eligibility/ inclusion criteria
Studies will be selected according to the PICO criteria: Patient (P), Intervention (I), Comparator (C), and Outcome(s) of interest (O). We will exclude patients who received WB outside the above clinical settings.

Patients
Adult and paediatric patients who require blood transfusion (symptomatic anaemia with large-volume deficits, traumatic operative, obstetric and gastrointestinal bleeding). Patients will be eligible regardless of age, sex or geographical location. Randomised controlled trials (RCTs) and observational studies will be included in this meta-analysis. Studies published between 1 January 1980 and 1 January 2020 will be screened, and no language limitation will be imposed. We will exclude studies not conducted in humans and meeting abstracts, review papers and commentaries.

Intervention
WB transfusion such as fresh WB (WB unit stored for less than 48 hours), leucoreduced modified WB (with PLT removed during filtration), warm fresh WB (stored warm at 22°C for up to 8 hours and then for a maximum of an additional 24 hours at 4°C).

Outcome (S) of interest

The primary outcomes will be the 24-hour and 30-day survival rates (in-hospital mortality). Secondary outcomes will include acute kidney injury, sepsis, venous/arterial thromboembolism, acute respiratory distress syndrome, 24 hours transfusion volume, coagulation abnormality, haemolysis, ICU length of stay and ventilation days.

Comparator

Blood component therapy ((RBCs, fresh-FFP, and PLTs given together in a 1:1:1 unit ratio).

Database searches

The following databases will be searched: PubMed (MEDLINE), Scopus, OVID (HEALTH STAR), OVID (MEDLINE) and Joanna Briggs Institute EBP databases. We will use a snowballing method to search the citation lists of included papers using the 'cited by' tool in Google Scholar. We will contact corresponding authors of published or ongoing studies for information regarding missing data.

Search terms

Our keyword search will be based on Medical Subject Headings (MeSH) with various combinations of the main search: "Whole blood" OR "Component Therapy" AND "transfusion." We will tailor the search terms with each database using Boolean operators, truncations, proximity operators, and Medical Subject Headings. For a complete list of search terms used for MEDLINE database, see online supplemental table 2.

Title, Abstract and full-text screening

The citations will be downloaded into the Endnote software, and we will exclude duplicate articles. Two reviewers (AES and EH) will independently screen studies in two stages. In the first stage, the reviewers will independently screen titles and abstracts and document reasons for exclusion if applicable. In the second stage, full-text versions of selected abstracts will be downloaded/retrieved and assessed independently by the two reviewers (AES and EH).

Data extraction

Data will be extracted from eligible papers. Disagreements will be discussed with a third reviewer (PS) to reach a consensus. If a publication is not available in English, reviewers will seek translation. We will extract the following information: first author, country in which the study was conducted, year of publication, study period, hospital specialty, whether resuscitation was indicated, research methodology, total sample size, survival rates, complications rates, percent of study sample that was male, mean age at transfusion, risk ratios (RR) of mortality and secondary outcomes. In case of missing data, one attempt will be made to contact the corresponding author of the associated study by email.

Assessment of methodological quality of the papers

Two authors (AES and EH) will independently assess the quality of the papers included in the review. The Cochrane risk of bias tool for randomised control trials (RCT) and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) for observation studies. Meta-regression analysis will be conducted to assess the effect of the study quality on the primary outcome.

Data synthesis and analysis

The primary outcomes will be mortality risk associated with WB and component therapy. We will use random-effects models for the pooling of studies.[19] We will separate civilian from military patients during the analysis and reporting of the result. Interstudy heterogeneity will be assessed by the Cochran Q statistic, where $p < 0.10$ will be considered statistically significant and quantified by I^2 statistic, where $I^2 \geq 50\%$ will indicate substantial heterogeneity. We will perform subgroup and meta-regression analyses to assess geographical differences and other study-level factors that could explain variations in the reported mortality risk. These will include median/mean age, race and sex proportions, civilian versus military patients and the compositions of component therapy. Results will be reported as RR and their 95% CIs. Publication bias will be assessed by visual inspection of funnel plots and the Egger and Begg tests when ≥ 10 study comparisons are available. In the presence of publication bias, adjustment for funnel plot asymmetry will be done by imputing missing study data using the Duval and Tweedie trim-and-fill method.

Additional analyses

Several blood components will be documented in the table format. If too much heterogeneity exists in the component therapy, we will not pool the results in a meta-analysis. Nevertheless, supposing enough publications are included, various blood components and RBC, PLT and plasma ratios will be used as regressors or groups in meta-regression and subgroup analysis, respectively.

Ethics and dissemination

No ethics clearance is required as no primary data will be collected. The results of this systematic review and meta-analysis will be presented at scientific conferences and published in a peer-review journal.

Presentation of results and reporting

The results of the final manuscript will be reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Potential amendments

The protocol was written in 2020, and the study is expected to be completed by 2021. We do not foresee the need for amendments to this protocol, but they will be registered and reported if they arise.

CONCLUSION

In this systematic review and meta-analysis, we will synthesise the current literature on WB use versus PRBC, PLT

and FFP component therapy to manage life-threatening haemorrhage. This meta-analysis will include RCT and observational studies to assess the association of blood transfusion types with mortality and morbidity. This study will inform haemostatic resuscitation of major bleeding when assessing which blood therapy optimises survival and reduce morbidity.

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