

Is an age-of-blood transfusion trial in trauma patients in Australia and New Zealand feasible?

Cecile Aubron, Kirsi-Maija Kaukonen, Zoe McQuilten, Peter Cameron, Michael Bailey and D Jamie Cooper

An increasing body of literature on the clinical consequences of the storage duration of red blood cells (RBCs) in various patient groups highlights the importance of this issue to clinicians and blood services. Lelubre and Vincent recently published a systematic review including 55 clinical studies on the effect of age of RBCs on various clinical outcomes.¹ This review, with others,^{2,3} emphasises the heterogeneity in the methodology of studies. In addition, it supports equipoise concerning the clinical effects of RBC storage duration, and the need for large randomised controlled trials (RCTs). There is currently only one large published RCT that addresses the issue of the age of blood in 377 critically ill patients. The Age of Red Blood Cells in Premature Infant (ARIP) RCT showed no difference in mortality combined with major neonatal morbidity in very low birthweight premature infants receiving fresher blood (<7 days old) compared with standard practice.⁴ The negative result provides evidence that a fresh blood transfusion is not associated with a better outcome in this patient group, but the same question in adults is not answered and there are no definitive trials in trauma patients.⁴

Trauma patients and RBC storage duration

The two-hit hypothesis, supported by animal models, suggests that pre-existing pathological changes associated with inflammation and oxidative stress enhance the adverse effects related to the RBC storage duration.⁵⁻⁷ Critically ill patients are highly heterogeneous in terms of pathological processes and clinical states. In contrast, critically ill trauma patients are predominantly young, often free of comorbidities and victims of a well defined injury. Among the 18 studies evaluating the effects of the age of blood that have been conducted in trauma patients, 15 found a negative impact of older blood on patient outcomes, suggesting that this patient group may be particularly susceptible to the potential effect of RBC storage duration.¹ The large volume of blood that they receive in a short time and/or the systemic inflammatory response syndrome secondary to trauma may contribute to the potential association between age of blood and outcome.

The two large RCTs which are currently being conducted do not focus on trauma patients. The Age of Blood Evaluation (ABLE) trial (ISRCTN44878718) and the Standard

Issue Transfusion versus Fresher Red Blood Cell Use in Intensive Care (TRANSFUSE) trial (ACTRN12612000453886) enrol heterogeneous critically ill patients who did not receive blood before intensive care unit admission.^{8,9} By design, there will be few trauma patients included in both these trials. If these ongoing RCTs fail to show an overall benefit from fresher RBCs, the question of whether RBC storage duration has an effect on the outcomes of critically ill patients will probably be closed.

Nonetheless, trauma patients are more likely to receive massive transfusions and to be more exposed to RBC storage duration effects than other critically ill patients. The question of whether fresher RBCs are beneficial to trauma patients will remain unresolved. In addition, if transfusion of fresher blood is found to have an impact on outcome, the health economic consequences will be highly relevant, because trauma patients are younger than other critically ill patients.

Before designing a trauma TRANSFUSE RCT

The TRANSFUSE RCT is a large, randomised, double-blinded trial studying the effect of freshest available RBC transfusion compared with standard RBC transfusion on 90-day mortality in mixed critically ill patients and is currently being conducted in Australia, New Zealand, Finland and Ireland.

To investigate this effect in trauma patients with acute severe haemorrhage, a similar, large RCT would be required, but several issues must be addressed to ensure its feasibility. First, the sample size based on trauma patient mortality and on the incidence of severe traumas in Australia needs to be determined and feasible. Mortality in trauma patients overall is lower (by about 12%–15%) than in other critically ill patients, when patients admitted after elective surgery are removed from analysis.^{10,11}

In addition, a retrospective review of the Victorian State Trauma Outcomes Registry Monitoring (VSTORM), linked with hospital laboratory and transfusion data, indicated that the annual incidence of trauma patients in Victoria requiring at least one unit of RBCs in the first 48 hours after the trauma occurred was around 407 per year. The incidence of severe trauma requiring five or more units of RBCs in the first 48 hours was 170 patients per year. The hospital mortality in these trauma patients was 17% and 24%, respectively.

Previous studies suggest that the number of old RBC units have a direct impact on outcomes for trauma patients.¹²⁻¹⁷ As Australian massive transfusion protocols are based on ≥ 5 RBC units transfused, a possible future RCT would ideally be focused on trauma patients who require a large transfusion volume (≥ 5 RBC units in 48 hours). Based on 90% power to detect a 25% decrease in relative risk of mortality (24% versus 18%) with a conventional two-sided *P* of 0.05, the sample size needed would be about 2000 patients. About 25% of the Australian population live in Victoria and assuming that Victoria is representative of Australia, and that all eligible patients could be included into the study, the recruitment for this trauma TRANSFUSE study would take at least 5 years.

These assumptions and timelines are not realistically achievable. Based on this estimation, mortality may not be the appropriate outcome for a study including a young and previously healthy population. Trauma has been shown to be a leading cause of functional limitation in young people.¹⁸ On the other hand, studies in trauma brain injury suggest that blood product transfusion may have an impact on patient functional outcome.¹⁹⁻²¹ Functional outcomes such as long-term quality of life, including the EuroQol-5D (EQ-5D) measure of health status, may also be more relevant in trauma patients than mortality. In addition, these functional scores would allow a health economic assessment. A major economic impact has already been shown in a study of normal saline versus albumin 4% in traumatic brain injury in this young and previously healthy population.²²

The second issue to address is the complex trauma setting which involves the emergency department, operating room and ICU. Effective recognition and randomisation of trauma patients in these three different places before transfusion may be challenging. Randomisation of trauma patients by the hospital massive transfusion protocol activation or by the use of scoring systems for prediction of massive bleeding in trauma patients²³ could be effective. However, methods to identify eligible patients must first be validated, because scoring systems have been developed in retrospective patient cohorts and have not been validated in large prospective studies.²⁴

An observational study

A prospective observational study in trauma patients is desirable and would enable:

- accurate determination of the incidence and mortality of massively bleeding trauma patients in Australian and New Zealand trauma centres
- estimation of the proportion of these patients eligible for a trauma TRANSFUSE RCT

- prospective validation of the feasibility of identifying accurately all eligible patients with the massive transfusion protocol and/or a scoring system for prediction of massive bleeding
- study of the relevance and usefulness of alternative outcomes (EQ-5D) as the primary or coprimary outcome measures
- accurate sample size calculations.

If an observational study supports the feasibility of an RCT, a pilot study may then be required to ensure feasibility of:

- a screening method including the use of predictive scoring for massive bleeding
- delivery of RBC units to the patient according to the study group, even in the presence of heavy bleeding.

A successful observational study could be achieved in several ways. First, the Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH) study is a multicentre randomised trial which will evaluate prehospital tranexemic acid administration in coagulopathic trauma patients in Australia. It will provide demographic data including outcomes of trauma patients. Second, existing national trauma and massive transfusion registries could also contribute to characterising the epidemiology of trauma patients and massive transfusion in Australia and New Zealand.

Conclusion

Trauma patients are a distinct subgroup of critically ill patients; they are younger, more often healthy before injury, and likely to be exposed to a large volume of blood products. If transfusion of fresh blood improves outcomes for these patients, the economic impact of the change of transfusion practices will be significant. There are clear obstacles which limit the capacity to conduct an RCT in bleeding trauma patients in Australia, and its feasibility is uncertain. An RCT with mortality as the end point will probably require an international collaboration, while an RCT with functional end points may be feasible in Australia and New Zealand. An observational study is required as the first step.

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Competing interests

None declared.

Author details

Cecile Aubron, Senior Research Fellow, Australian and New Zealand Intensive Care Research Centre¹

Kirsi-Maija Kaukonen, Senior Research Fellow¹

Zoe McQuilten, Postgraduate Student,¹ and Clinical Fellow²

Peter Cameron, Professor of Emergency Medicine,¹ and Chair³

Michael Bailey, Head Statistician¹

D Jamie Cooper, Director¹

¹ Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.

² Research and Development, Transfusion Research Unit, The Australian Red Cross Blood Service, Melbourne, VIC, Australia.

³ Emergency Medicine, Hamad Medical Corporation, Doha, Qatar.

Correspondence: Cecile.aubron@monash.edu

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