Why we must "TRANSFUSE"

Cecile Aubron, Guillaume Carteaux and D James Cooper

To reduce mortality of patients admitted to intensive care units, rather than seeking a new, clever and perhaps expensive medication, we may be better off trying to tackle a common and well known clinical procedure whose safety has recently been questioned. Red blood cell (RBC) transfusion is one such daily ICU treatment with potentially lifesaving benefits, but which also has an increased risk of morbidity and mortality in critically ill surgical and trauma patients.[1,2] Although this published association may reflect a variety of factors, attention has increasingly focused on the possible adverse effect of transfusing RBCs that have been stored for a prolonged time.[3,4] However, it is not known whether fresher RBCs are better than older ones, and a large randomised controlled trial (RCT) is needed to provide level 1 evidence to guide clinical practice.

Why blood transfusion is an important issue in intensive care medicine

Anaemia is very common among critically ill patients, and up to 90% become anaemic by the third day of their ICU stay.[5] Moreover, severe anaemia is associated with poor outcomes and is typically treated with RBC transfusion.[6] The RBC transfusion rate in ICUs varies between 20% and 40%,[5,7,8] with a mean of 2.0 to 4.8 RBC units transfused per patient,[7,8] despite a decrease in transfusion since the introduction of the latest clinical guidelines.[8] In Australia, a mean of around 140 000 RBC units are delivered by the Australian Red Cross Blood Service to critically ill patients every year.[9,10]

RBC transfusion is aimed at restoring haemoglobin concentration to levels sufficient to maintain adequate oxygen delivery to vital organs, but it is clear that it is also associated with an increased risk of nosocomial infection, transfusion-related acute lung injury, sepsis, multiple organ failure, increased duration of mechanical ventilation, increased length of stay in ICU and hospital, and increased mortality.[1,2,7,11] Moreover, a restrictive transfusion threshold is also associated with decreased hospital mortality (28.1% v 22.2%; $P=0.05$).[1]

Fresh or old red blood cells — does it matter?

Current transfusion practice calls for the delivery of the oldest available RBCs in most Australian centres to avoid wastage. However, storage of RBCs for longer periods could play a role in the occurrence of harmful effects. Over a 42-day storage period, metabolic, biochemical and molecular changes occur. These include depletion of ATP and 2,3-diphosphoglycerate, membrane phospholipid vesiculation and protein oxidation and lipid peroxidation of RBC membranes.[12,13] Over time, RBC shape changes, followed by increased osmotic fragility and loss of deformability.[12] Decreased membrane flexibility may compromise microcirculatory flow and leads to increased interactions between red cells and endothelial cells, with activation of inflammation. Critically ill patients may be especially susceptible to potentially deleterious effects of RBC storage because they frequently have disease states that lead to impaired microcirculatory blood flow. Therefore, the transfusion of fresher blood may decrease mortality compared to standard care among ICU patients.

Over the past two decades, clinical studies conducted among trauma patients, ICU patients and patients undergoing cardiac surgery have supported the hypothesis that transfusing older red cells may be injurious, and showed a negative impact of prolonged RBC storage on clinical outcome or tissue oxygenation parameters. However, these studies have not been sufficiently powered to confirm any clinical impact of the duration of RBC storage, and consequently have not changed transfusion practice. Accordingly, a systematic review[3] and a meta-analysis[4] have been inconclusive.

Nevertheless, in the past few years, four large studies have reported that transfusing older compared to fresher blood increases patient mortality and morbidity. First, in 2008, Koch and colleagues reported increased time of mechanical ventilation (9.7% v 5.6%; $P<0.001$), incidence of sepsis (4% v 2.8%; $P=0.01$) and mortality in 6002 cardiothoracic patients transfused with older RBCs.[11] Transfusion of older RBCs was also independently associated with an increased risk-adjusted rate of a composite of serious adverse events (25.9% v 22.4%; $P=0.001$).[11] In 2010, a Canadian prospective observational study of 4933 acute care cardiovascular patients reported an adjusted relative risk for death of 1.48 (95% CI, 1.07–2.05) for patients in the highest quartile of maximum age of blood compared with those in the lowest quartile.[14] Also in 2010, two prospective paediatric ICU studies, of 455 and 296 patients, respectively, reported an independent association between duration of blood storage and morbidity and mortality.[15,16] Despite limitations, these recent large studies suggest that transfusion of fresher blood may be better — leaving clinicians concerned but uncertain regarding current transfusion practice in ICU. Moreover, our preliminary data in Australia and New Zealand, including a prospective observational study, found a clear relationship between the age of RBC and

mortality of 757 ICU patients (Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, and the Australian and New Zealand Intensive Care Society Clinical Trials Group, unpublished data).

To definitively resolve this issue, we now plan to conduct a large, pivotal RCT in Australia and New Zealand to determine whether, compared with standard care, transfusion of the freshest available RBCs decreases mortality rates among ICU patients. Our study design will not include an arbitrary cut-off age for defining fresher RBCs, as others have proposed, but instead will compare the "freshest available" RBCs with standard care. This pragmatic design aims to make the intervention realistic and feasible, as well as to allow it to be easily and widely implemented in case of any proven benefit among ICU patients.

If transfusion of freshest available RBCs to critically ill patients leads to decreased patient mortality, current transfusion practices, particularly including expiry dates for RBCs, would need to be re-evaluated. Perhaps, and even more importantly, if we found no difference between the two treatment arms, an expensive and wasteful nationwide practice change would be avoided.

This study question is of major importance to ICU clinicians, transfusion specialists and the Australian Red Cross Blood Service. Changes to blood transfusion practice to supply fresher blood to critically ill patients would be challenging, but are conceivable. There is also a real risk that without our study, in response to perceived public concerns, scientifically unjustified practice and policy changes may occur with major and expensive consequences to the supply of blood in Australia.

This concern is strengthened by our Australian experience in the past with universal leukodepletion. Leukodepletion was introduced in 2010 to align Australia with an international standard of practice. However, a double-blind phase 3 RCT demonstrating a clinically important benefit has never been undertaken. Now there is a recurrent cost to government of almost $40 million annually, which is of unproven clinical benefit and value.[17] Furthermore, as most transfusions are now leukodepleted, it is no longer possible for an RCT of leukodepletion to be undertaken in Australia at all. It would be unfortunate if this experience were repeated with the transfusion of older red cells. Further, it would be equally unfortunate if patients were disadvantaged by continued transfusion of older RBCs simply because of insufficient high-quality evidence.

These observations make the proposed "TRANSFUSE" (Standard Issue Transfusion versus Fresher Red Blood Cell Use in Intensive Care) randomised trial of the greatest priority. If appropriate funding is obtained in the 2011 funding rounds, in 2012 the Australian and New Zealand intensive care community is committed to "TRANSFUSE".

Author details

Cecile Aubron, Senior Research Fellow
Guillaume Carteaux, Research Fellow
D James Cooper, Director
Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
Correspondence: Jamie.Cooper@monash.edu

References

1 Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340: 409-17.
2 Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med* 2008; 36: 2667-74.
3 Lelubre C, Piagnerelli M, Vincent JL. Association between duration of storage of transfused red blood cells and morbidity and mortality in adult patients: myth or reality? *Transfusion* 2009; 49: 1384-94.
4 Vamvakas EC. Meta-analysis of clinical studies of the purported deleterious effects of "old" (versus "fresh") red blood cells: are we at equipoise? *Transfusion* 2010; 50: 600-10.
5 Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill — current clinical practice in the United States. *Crit Care Med* 2004; 32: 39-52.
6 Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348: 1055-60.
7 Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288: 1499-507.
8 Investigators TBOS. Transfusion practice and guidelines in Australian and New Zealand intensive care units. *Intensive Care Med* 2010; 36: 1138-46.
9 McQuilten ZK, Schembri N, Polizzotto M, et al. Hospital blood bank information systems accurately reflect patient transfusion: results of a validation study. *Transfusion* 2010. [Epub ahead of print]. doi: 10.1111/j.1537-2995.2010.02931.x
10 Australian Red Cross Blood Sevice. Annual report 2009 to 2010. http://www.donateblood.com.au/files/documents/ARCBS_AR_2010.pdf (accessed Mar 2011).
11 Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008; 358: 1229-39.
12 Chin-Yee I, Arya N, d'Almeida MS. The red cell storage lesion and its implication for transfusion. *Transfus Sci* 1997; 18: 447-58.
13 Wolfe LC. The membrane and the lesions of storage in preserved red cells. *Transfusion* 1985; 25: 185-203.
14 Eikelboom JW, Cook RJ, Liu Y, Heddle NM. Duration of red cell storage before transfusion and in-hospital mortality. *Am Heart J* 2010; 159: 737-43.
15 Gauvin F, Spinella PC, Lacroix J, et al. Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients. *Transfusion* 2010; 50: 1902-13.
16 Karam O, Tucci M, Bateman ST, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. *Crit Care* 2010; 14: R57.
17 Cleemput I, Leys M, Ramaekers D, Bonneux L. Balancing evidence and public opinion in health technology assessments: the case of leukoreduction. *Int J Technol Assess Health Care* 2006; 22: 403-7. ❑