Restrictive red blood cell transfusion strategies in critical care: does one size really fit all?

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ABSTRACT

Many intensive care patients receive red blood cell transfusions. International clinical practice has recently changed, with a decrease in the "trigger" haemoglobin concentration used for red blood cell transfusions in critically ill patients. This change has been driven by increasing awareness of the infectious and non-infectious complications of allogeneic red blood cell transfusion, the perennial blood supply shortages, and most importantly by the Transfusion Requirements in Critical Care (TRICC) study, which suggested that a restrictive transfusion strategy (a transfusion trigger of 70g/L and a post-transfusion goal of 70–90 g/L) may be equivalent to a liberal transfusion strategy (a transfusion trigger of 100g/L and a post-transfusion goal of 100–120 g/L) in non-shocked ICU patients.

However, patients with ischaemic heart disease may benefit from red blood cell transfusion at a haemoglobin trigger level higher than advocated by such a restrictive transfusion strategy. This assertion is supported by animal studies, retrospective clinical studies and a post-hoc subgroup analysis of the patients with ischaemic heart disease in the TRICC trial.

Despite this, and a number of important methodological issues that limit the generalisation of the TRICC results to patients with ischaemic heart disease, the TRICC authors, subsequent guidelines and recent reviews have recommended a restrictive strategy in ICU patients with ischaemic heart disease. This conclusion and the change in clinical practice that followed these publications are premature. In determining the appropriate trigger for transfusion of allogeneic blood, the physician should ideally weigh the risk–benefit profile for each individual patient, for each unit of blood administered.

Crit Care Resusc 2008; 10: 323–327

Anaemia is common in patients managed in intensive care units.[1-4] It has been shown that 35%–45% of ICU patients have anaemia sufficient to require red blood cell transfusion, and they receive on average almost 5 units.[1,4] The causes of this anaemia are multifactorial and include blood loss, haemodilution, and the anaemia of critical illness, which reduces red blood cell production.[1-4] Controversially, red blood cell transfusions have been used to improve the peripheral delivery of oxygen,[5] even in patients with haemoglobin (Hb) concentrations more than 100 g/L.[6,7] More recently, early goal-directed therapy — a component of the current 2008 Surviving Sepsis guidelines for critically ill patients with severe sepsis and septic shock — includes as a target maintaining the haematocrit over 30%.[8,9]

Recent clinical trials suggested that clinical practice is changing, and that the "trigger" haemoglobin concentration for blood transfusion in critically ill patients fell over the past decade.[10-13] This apparent change in practice has been driven by increasing awareness of infectious and non-infectious complications of allogeneic blood transfusion, by the perennial blood supply shortages, and by the suggestion based on an intensive care trial that more liberal blood transfusion strategies may not improve outcomes in critically ill patients.[14] However, it is important to note that selected patients, such as those with ischaemic heart disease, may benefit from higher haemoglobin concentrations.

In determining the appropriate trigger for allogeneic blood transfusion, physicians need to weigh the risk–benefit profile for each individual patient and for each unit delivered. To aid this clinical decision, it is useful to consider the risk profile of the product to be administered, the transfusion trigger used by the clinician, and the presence of comorbidities (particularly coronary artery disease) that might alter this risk–benefit profile.

The blood product transfused

It is important for the safe transfusion of blood and the interpretation of clinical trials conducted in different countries to note that what we broadly refer to as a "unit" of red blood cells can differ significantly. The unit definition is currently used interchangeably to describe not only whole blood and packed red blood cells, but also red blood cells of differing age, stored in differing anti-coagulant preparations, in differing volumes, as well as both leukodepleted and non-leukodepleted preparations. There has been considerable recent speculation that some of these factors affect clinically relevant outcomes independent of the haemoglobin transfusion trigger used.[15-24]

The determination of shelf life for red blood cells is based on data from studies of red blood cell corpuscular integrity

24 hours after transfusion.[21] The shelf life of red blood cells is currently 42 days. Laboratory data suggest that red blood cells stored under standard conditions for 28 days are not efficacious in improving tissue oxygen consumption or other measures of tissue hypoxia when compared with fresh red blood cells (stored < 5 days).[25-27] Three large retrospective clinical studies also suggest an association between prolonged storage and adverse clinical outcomes.[22,24,28] However, the results of three randomised controlled trials — all small — were contradictory.[23,29,30] Large prospective randomised controlled trials are needed to determine whether the age of red blood cells transfused is an independent predictor of outcome in critically ill patients. In the absence of such trials, blood transfusion services will continue to provide red blood cell products of widely differing ages, determined solely by logistic issues of supply and demand.

A number of countries have introduced leukodepletion of all red blood cell products. This expensive and laborious removal of most leukocytes in the red blood cell products was introduced initially to reduce the potential for transmitting the causative agent of variant Creutzfeldt–Jakob disease.[31] However, additional clinically relevant benefits have been found, including reduced risk of transfusion-related acute lung injury and reduced renal dysfunction.[16,17,19,20] Furthermore, a recent retrospective before-and-after study in Canada showed that leuokodepletion of red blood cell products resulted in a significant reduction in mortality in a cohort of 14 786 intensive care (surgical and trauma), hip fracture and cardiac surgery patients.[32] It has therefore been suggested that leukodepleted blood may have a more favourable risk–benefit profile than non-leukodepleted blood. Furthermore, it has been suggested that the leukocyte burden may significantly affect the storage lesion that occurs on prolonged storage of red blood cells,[33] further worsening the risk–benefit profile of non-leukodepleted blood.

In summary, in the interpretation of previously conducted red blood cell transfusion trials, it is important to consider the characteristics (eg, age, and leukodepletion status) of the blood product administered. Future prospective randomised controlled clinical trials will determine whether these factors influence the clinician's bedside assessment of the risk–benefit profile for red blood cell transfusion in critically ill patients.

The transfusion trigger

Although the American College of Physicians recommended in 1992 against use of red blood cell transfusion prompted by an arbitrary transfusion trigger,[34] many clinicians and much of the literature have adopted this approach. The Transfusion Requirements in Critically Care (TRICC) study published in 1999[14] suggested that a restrictive strategy is at least equivalent in outcome to a more liberal transfusion strategy in volume-resuscitated ICU patients. The study randomly allocated 838 patients who were not actively bleeding but had a haemoglobin (Hb) concentration < 90 g/L to receive either a restrictive (transfusion trigger of 70g/L and a post-transfusion goal of 70–90 g/L) or a liberal (a transfusion trigger of 100g/L and a post-transfusion goal of 100–120 g/L) transfusion strategy. The results were essentially negative, with no significant difference in the death rate from all causes between the two strategies in the 30-day period after ICU admission (18.7% in the restrictive group v 23.3% in the liberal group; $P = 0.11$). Although survival rates were similar for the patient group as a whole, the rates of death were significantly lower in the restrictive group compared with the liberal group in the subgroup of patients with an APACHE II score ⩽ 20 ($P = 0.02$) and in the subgroup aged under 55 years ($P = 0.02$). These findings prompted the authors to recommend that critically ill patients receive red blood cell transfusions when Hb concentration falls below 70 g/L, and that Hb concentration should be maintained between 70 and 90 g/L.

The TRICC study,[14] in combination with concerns about the complications of red blood cell transfusion had a significant impact on the attitudes of the critical care community and contemporary clinical transfusion practice in intensive care medicine. This is evidenced by recent clinical trials that have documented a decreasing mean haemoglobin concentration at which blood transfusions occur,[10,11,13] suggesting that more restrictive transfusion strategies are being widely implemented clinically. While the TRICC study was well conducted and has rationalised the administration of red blood cells to young healthy patients, the widespread adoption of a restrictive transfusion strategy may be harmful in selected patient groups.

Patients with coronary artery disease

Patients with coronary artery disease may benefit from a higher haemoglobin concentration. This is evidenced by animal studies suggesting that myocardial dysfunction and ischaemia either occur earlier or are more severe in anaemic animals with coronary artery stenosis.[35,36] In a retrospective cohort study of patients undergoing surgery who refused blood transfusion for religious reasons, it was demonstrated that the odds-adjusted mortality increased exponentially with Hb levels below 100 g/L in patients with cardiovascular disease compared with those without.[37] Furthermore, two large ICU cohort studies found that an increasing severity of anaemia was associated with a disproportionate increase in

mortality rate among patients with ischaemic heart disease,[38,39] and that blood transfusion appeared to decrease this risk.[39] These findings suggest that a restrictive transfusion strategy may be deleterious in patients with ischaemic heart disease. Based on these and other considerations, conventional wisdom has guided the common practice of maintaining the haemoglobin concentration of patients with ischaemic heart disease at a level of at least 80 g/L, and often 100 g/L.

However, the TRICC study[14] — the only multicentre randomised controlled transfusion trial in ICU to date — suggested that a restrictive transfusion strategy may be as safe as a liberal transfusion strategy in patients with cardiovascular disease (which included ischaemic heart disease but not acute coronary syndromes). Furthermore, a subsequent post-hoc subgroup analysis by Hebert and colleagues, designed to identify the 257 patients with severe ischaemic heart disease randomised in the original TRICC study,[14] demonstrated a non-significant ($P = 0.3$) trend towards decreased mortality in the liberal transfusion group compared with the restrictive group in patients at risk of this disease.[38] The authors concluded that a restrictive strategy was safe in most ICU patients, including those with ischaemic heart disease.[38] These conclusions[14,38] and the subsequent change in clinical practice that followed these publications are premature, given a number of methodological concerns about the TRICC trial.

First, there was an inherent selection bias in the initial TRICC trial,[14] which may have confounded the results in patients with cardiovascular disease. There was an increased prevalence of cardiovascular disease (26%) in patients whose participation in the trial was refused (by either physician or next of kin) after they met eligibility criteria, compared with the group who were subsequently entered into the trial (20%). This difference may have reflected Canadian physician bias towards the potential deleterious effects of a restrictive transfusion strategy in patients with ischaemic heart disease.[40]

Second, the TRICC trial[14] recruited patients between 1994 and 1997, when the Canadian blood transfusion service used non-leukodepleted blood. As the Australian blood transfusion service moves towards a full national leukodepleted service in 2008, the risk–benefit ratio of transfused red blood cells may improve. This potentially important difference between the original TRICC study and contemporary practice in many developed countries further suggests that a liberal transfusion strategy incorporating leukodepleted blood may confer additional benefits beyond those previously demonstrated in patients with ischaemic heart disease.[38] Future trials will have to test this hypothesis prospectively.

Third, before conducting the TRICC trial, the investigators surveyed the attitude to transfusion practice of 193 Canadian critical care physicians.[40] The survey found that blood transfusions in critically ill patients were titrated on the basis of many indicators of health status.[14,40] In clinical practice, only 3% of physicians would have prescribed the restrictive trigger (70 g/L) that was tested for patients with ischaemic heart disease, whereas only 12% of physicians would have prescribed the liberal trigger (100 g/L) for healthy young patients.[14,41,42] This formed non-comparable subgroups in both study arms, who received care different and opposite from titrated care — in other words, practice misalignments were created.[43] These practice misalignments may have confounded the ability of the original TRICC study to demonstrate the superiority of one transfusion strategy in patients with ischaemic heart disease.

Fourth, while the initial TRICC trial randomised 838 patients,[14] the subsequent post-hoc analysis identified only 257 patients with ischaemic heart disease.[38] Among the latter, 30-day mortality was 21% in the liberal transfusion group and 26% in the restrictive transfusion group (5% absolute difference in mortality). The small cohort size resulted in a significant underpowering (type 2 error) of this post-hoc analysis and confounded its ability to detect a statistically significant difference in mortality.

Finally, an intriguing recent post-hoc analysis of the TRICC study conducted by Deans et al showed that the effect of a transfusion strategy on mortality depends on the presence or absence of pre-randomisation of ischaemic heart disease.[43] The effects of transfusion thresholds on 30-day mortality were significantly different and opposite, depending on the presence or absence of ischaemic heart disease pre-randomisation (Breslow–Day test; $P = 0.03$).[14,38] In patients with ischaemic heart disease ($n = 257$), the use of a restrictive transfusion strategy increased mortality compared with the use of a liberal strategy. In patients without ischaemic heart disease ($n = 581$), the use of a restrictive transfusion strategy decreased mortality compared with the use of a liberal strategy.

Conclusion

It is therefore clear that the question whether to use a restrictive transfusion strategy in patients at risk of ischaemic heart disease is far from answered. Despite some very recent reviews calling for the use of a restrictive transfusion strategy in patients with ischaemic heart disease without acute coronary syndromes in the critical care unit,[44] it seems premature to recommend such a restrictive strategy as safe in these patients.[45] As almost two-thirds of the general population over 65 years of age have heart, stroke or vascular conditions,[46] and the prevalence of these condi-

tions increased by 18.2% over the past decade, it is critical to determine the optimal red blood cell transfusion strategy for patients with ischaemic heart disease. The most prudent advice for clinicians in the absence of a prospective study that addresses this issue is to establish the individual risk of the blood product being transfused and the patient's risk of ischaemic heart disease to determine the ideal transfusion trigger. The irony is that the TRICC investigators survey[40] demonstrated that Canadian clinicians were doing (or at least saying they were doing) exactly this before they commenced their randomised controlled trial!

Acknowledgements

A modified version of this article was presented at the Joint Faculty of Intensive Care Medicine Annual Scientific Meeting 2008 and was distributed in the accompanying booklet *Blood and blood product usage in the ICU*.

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