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Red blood cell transfusion in the treatment and management of anaemia: the search for the elusive transfusion trigger

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Therapeutic red blood cell (RBC) transfusion is widely utilized in the management of anaemia. Critically ill intensive care unit (ICU) patients in particular, as well as medical and haematology–oncology patients, are among the largest groups of users of RBC products. While anaemia is common in these patients, its treatment and management, including appropriate thresholds for RBC transfusion, remain controversial. We review here the function of RBCs in oxygen transport and physiology, with a view to their role in supporting and maintaining systemic tissue oxygenation. Adaptive and physiological compensatory mechanisms in the setting of anaemia are discussed, along with the limits of compensation. Finally, data from clinical studies will be examined in search of evidence for, or against, a clinically relevant transfusion trigger.

Introduction

Red blood cell (RBC) transfusion constitutes one of the mainstays of therapy in the management of anaemic patients. With a prevalence of anaemia as high as 95% in intensive care unit (ICU) patients by day 3, critically ill ICU patients along with other medical and haematology–oncology patients are among the largest users of RBC products [1–4]. Twenty to fifty percent of all ICU patients, and 85% of those remaining in the ICU for greater than 1 week, receive at least one RBC transfusion, and more than two-thirds of ICU transfusions are given for indications other than acute blood loss [3,5]; among surgical patients, patterns of RBC usage regionally show an increase in transfusion rate over the past decade [4]. Prospective observational studies in Western Europe and the USA surveying blood use in critically ill patients [6,7] reveal that 'low haemoglobin' is by far the most commonly cited indication for transfusion, in as many as 90% of cases, as reported by clinicians [7]. While anaemia is common in these patients, its treatment and management, including appropriate thresholds for RBC transfusion, remain controversial. Data from experimental as well as clinical studies have contributed greatly to the understanding of the physiology of anaemia and have shaped changes in guidelines for RBC transfusion; consistent application of these guidelines to routine clinical practice, however, has yet to achieve success.

The historical and empirical '10/30 rule', which has biased many decades of transfusion practice, was first proposed by Adams and Lundy in 1942 as one of many perioperative suggestions aimed specifically at improving outcome in surgical patients with poor anaesthesia risk [8]. Too often the 'rule' has been cited inappropriately and applied too broadly. Four decades later, an effort to examine factors influencing the physician's decision to transfuse blood led to use of the term 'transfusion trigger' [9], a term that has inadvertently implied the existence of a haemoglobin threshold level below which transfusion should be initiated. Early efforts to curb unnecessary transfusion practices were spurred on by the recognition of adverse events, first the newly identified infectious disease risks associated with allogeneic blood, and more recently concerns about immune-mediated risks and the suspected toxicity of stored red cells. The more fundamental question remains one of efficacy: when, and how much, transfusion is indicated.

We review here the function of RBCs in oxygen transport and physiology, with a view to their role in supporting and maintaining systemic tissue oxygenation. Adaptive and physiological compensatory mechanisms in the setting of

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anaemia are discussed, along with the limits of compensation. Finally, data from clinical studies will be examined in search of evidence for, or against, a clinically relevant transfusion trigger.

RBC physiology and oxygen transport

RBCs constitute the principal means by which oxygen transport occurs. Under normal circumstances, oxygen is carried through circulating blood primarily bound to haemoglobin, with a negligible amount, approximately 2%, dissolved in plasma; in the severely anaemic patient breathing supplemental O_2; however, physically dissolved O_2 comprises as much as 20% of blood oxygen content. Accordingly, anaemia is commonly treated by RBC transfusion to restore oxygen-carrying capacity and avoid compromised peripheral tissue oxygenation. Yet decreases in haemoglobin do not always result in changes in oxygen delivery (DO_2) and oxygen consumption (VO_2); physiological compensatory mechanisms exist to counter mild to moderate changes in haemoglobin. Under normal conditions with adequate coronary artery reserve, cardiac output increases as arterial oxygen content (CaO_2) decreases such that DO_2 is maintained; this mechanism is dependent on coronary vascular dilation allowing for increased coronary blood flow. Oxygen consumption (VO_2) is, in turn, further buffered by the ability of peripheral tissues to alter oxygen extraction (EO_2) in hypoxemic states by altering microvascular blood flow, resulting in lower venous oxygen content (CvO_2) and stable tissue pO_2 [10].

As tissues vary in their percentage of oxygen extracted from circulating blood at baseline, so too does the extent of their ability to increase EO_2 under anaemic conditions. The heart, with the largest baseline EO_2 of 60%, is least able to compensate for hypoxemia, in comparison to tissues with lower baseline extraction rates such as the brain (30%), kidney (< 10%) and skin (< 10%). In addition to the greater workload of providing increased cardiac output to peripheral tissues under anaemic conditions, increased coronary blood flow is necessary to maintain stable cardiac tissue pO_2. Accordingly, cardiac function dictates the limit of anaemia clinically tolerated in any given patient.

Equations describing CaO_2, DO_2 and VO_2, as well as EO_2, are listed in Table 1. In the search for clinically relevant thresholds for RBC transfusion, the term 'critical DO_2' (DO_2crit) has been defined as the level of DO_2 below which VO_2 cannot be maintained and begins to decrease. At the DO_2crit, signs of oxygen impairment become apparent, both globally, as indicated by increased lactic acid production, as well as regionally, by tissue-specific markers of hypoxia such as ST-segment changes on electrocardiogram and P300 latency on electroencephalogram. As DO_2 approaches DO_2crit, so also does the compensatory increase in O_2 extraction approach its maximum limit (EO_2crit). EO_2crit, which varies between tissues, influences DO_2crit; tissues with a lower EO_2crit have a higher DO_2crit. In addition, DO_2crit is also influenced by VO_2, with DO_2crit necessarily higher to support metabolism when VO_2 is higher [10].

Table 1 Equations for oxygen transport and utilization

Arterial oxygen content	$CaO_2 = (Hb \times 1{\cdot}34 \times SaO_2) + (PaO_2 \times 0{\cdot}003)$
Oxygen delivery	$DO_2 = CO \times CaO_2$
Oxygen consumption	$VO_2 = CO \times (CaO_2 - CvO_2)$
	$VO_2 = CO \times ([Hb \times 1{\cdot}34 \times (SaO_2 - SvO_2)] + [(PaO_2 - PvO_2) \times 0{\cdot}003])$
Oxygen extraction	$EO_2 = VO_2/DO_2$

CO, cardiac output; Hb, haemoglobin; PaO_2, arterial oxygen pressure; PvO_2, venous oxygen pressure; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation.

Experimental studies – towards finding the limits of compensation

Data from studies in experimental animal models and in humans have shed light on the limits of physiological compensation in anaemia. In the 1970s, experimental models of anaemic haemodilution found a DO_2crit of 10 ml O_2/kg·min in anaesthetized dogs, corresponding to a critical haematocrit of 10% [11,12]. Subsequent canine studies under similar conditions placed the DO_2crit lower, at 7·9 ml O_2/kg·min [13], and even lower in anaesthetized pigs [14]. Critical haemoglobin in anaesthetized pigs subject to acute isovolemic haemodilution was demonstrated to be 3·9 to 4·0 g/dl, below which VO_2 became delivery-dependent [15,16]. Although the absolute values obtained from these experimental studies cannot be extrapolated to humans, critical haemoglobin across species appears to be remarkably constant, at approximately 20–25% of normal resting haemoglobin [10].

In humans, the first report of such measures was documented in an 84-year-old Jehovah's Witness who refused transfusion and died postoperatively at a haemoglobin concentration of 1·6 g/dl; DO_2crit in this patient under anaesthesia was 4·9 ml O_2/kg·min for a VO_2 of 2·4 ml O_2/kg·min, and occurred at haemoglobin of 4·0 g/dl. The oxyhaemoglobin dissociation curve, after correction for changes in pH and PCO_2, shifted rightward at a haematocrit of 8%, indicating compensatory decrease in haemoglobin oxygen affinity as a mechanism of facilitating oxygen offloading to peripheral tissues during extreme anaemia [17]. Similarly in sedated critically ill patients after discontinuation of life support, DO_2 ranged between 3·8–4·5 ml O_2/kg·min for a VO_2 of 2·4 ml O_2/kg·min; EO_2crit reached approximately 60% [18].

Given that DO_2crit level varies with different baseline metabolic requirements, subsequent studies undertook measurements during conscious states in which VO_2 is higher.

Weiskopf *et al.* [19] demonstrated that healthy resting humans are able to tolerate acute isovolemic haemodilution down to a haemoglobin level of 5 g/dl, although mild reversible reduction in mental acuity is seen at this level [20–22]. In 32 conscious individuals at rest, no significant change in VO_2 or plasma lactate concentration were found despite decreases in oxygen transport (DO_2) during progressive isovolemic haemodilution with 5% albumin and/or autologous plasma down to a haemoglobin level of 5 g/dl. Two subjects developed significant electrocardiographic ST changes, although these were noted in younger volunteers and were attributed to body position or activity and increased heart rate, respectively, and both resolved without sequelae [19]. The same investigators demonstrated in another study of conscious healthy young volunteers that for VO_2 of 3·4 ml O_2/kg·min, DO_2crit during acute haemodilution with 5% albumin and autologous plasma was lower than 7·3 ml O_2/kg·min and haemoglobin 4·8 g/dl [23].

In the presence of coronary artery disease, however, the haemoglobin threshold increases. Evidence of cardiac dysfunction in animal models has been reported at a level of 7 g/dl in the presence of 75% coronary artery stenosis [24]. Other studies in dogs with critical stenosis of the left anterior descending artery show the lowest median haemoglobin tolerated without myocardial contractile dysfunction was 7·5 g/dl. This effect was reversible and corrected by RBC transfusion which increased arterial haemoglobin by 1·9 g/dl and was able to restore regional oxygen consumption, oxygen extraction, as well as myocardial contractile function [25]. Using radioactive microspheres to evaluate myocardial blood flow and its transmural distribution, assessment of myocardial oxygen consumption (MVO_2), lactate production and reactive hyperaemic response to assess coronary vasodilator reserve, cardiac failure during isovolemic haemodilution in anaesthetized dogs was found to occur at a much higher haematocrit in the presence of critical stenosis of the left anterior descending artery compared to intact left anterior descending artery (17% vs. 9%) [26]. Results from these and other experimental studies, however, cannot be easily extrapolated to the clinical setting in which patients have coexisting comorbidities that cannot be readily modelled in animals and that change characteristics of the oxygen supply–demand balance. Critical stenosis produced by ligation of an artery, for example, differs physiologically from stenosis in the presence of generalized atherosclerosis.

Anaemia in the clinical setting – aetiology and impact

Several aetiological factors underlie the anaemia seen in the clinical setting. Critically ill ICU patients have decreased erythropoietin levels, along with insufficient reticulocyte production relative to the degree of anaemia observed. Suppression of endogenous erythropoietin production has been shown to be mediated by EPO gene inhibition in the presence of cytokines and other inflammatory mediators [2,27,28].

With regard to iron metabolism, greater than 90% of ICU patients have abnormal iron studies, with low serum iron (Fe), total iron binding capacity (TIBC) and Fe/TIBC ratio, while ferritin is normal to elevated [2,29,30]. Iron dysregulation arises partly from nutritional deficiency, but primarily as a result of functional iron deficiency related to acute inflammation and chronic disease [31,32]. Studies in mice and in humans demonstrate an upregulation of liver hepcidin production in response to interleukin-6. This increase in hepcidin, in turn, mediates reduced intestinal iron absorption as well as decreased iron availability via suppression of iron release from macrophages [33].

In addition, impaired bone marrow function also plays a role in the development of ICU anaemia. Experimental studies revealed morphological changes in bone marrow histology after shock and fluid resuscitation, impacting cell differentiation and demonstrating increased apoptosis [34]. With multifactorial aetiologies underlying failed erythropoiesis, including nutritional/metabolic and hormonal derangements as well as bone marrow compromise, critically ill patients in particular are prone to develop anaemia and its attendant consequences. These are compounded further by blood loss – both pathological (gastrointestinal or other haemorrhage) and iatrogenic from frequent phlebotomy or interventional procedures, exacerbating anaemia in the critically ill [6].

The risks of anaemia, and the degree at which clinical outcome is affected, have been subject to heated controversy. In studies of resuscitation protocols in patients with severe sepsis and septic shock, early goal-directed haemodynamic therapy, including transfusion, has been proven effective in improving outcomes and has subsequently been incorporated into guidelines for sepsis management, despite problems in the interpretation of these findings (e.g. the absence of haemoglobin data with which to correlate outcomes, and the use of a unique patient demographic population with more severe comorbidities) [35]. Particularly during sepsis, when demand for tissue oxygenation is critical, and tissue oxygen extraction is thought to be impaired by microcirculatory failure, an area of some controversy [36] – decreases in oxygen-carrying capacity are implicated as contributing to end-organ failure. To what degree the expected anaemia in the critically ill impacts outcomes, and evidence for whether, and to what extent, it should be corrected, shall be the focus of the remainder of this review.

Clinical studies – towards finding a transfusion threshold

Retrospective observational studies have examined the impact of anaemia in surgical and critical care patients. Experience

with patients declining blood transfusion has enabled a view into the limits of human tolerance of severe anaemia. A retrospective chart review of Jehovah's Witness medical and surgical patients [37] identified 50 deaths, of which 23 were attributable to anaemia. With the exception of three who died after cardiac surgery, all of the patients whose deaths were attributable to anaemia had haemoglobin levels of 5 g/dl or less. Despite this, 25 patients survived even with haemoglobin of 5 g/dl or less.

When cardiac risk factors are considered, however, the critical haemoglobin threshold becomes more elusive. In a retrospective observational cohort study of 1958 surgical patients refusing RBC transfusion for religious reasons, Carson *et al.* [38] found that overall mortality increased with decreasing preoperative haemoglobin. This mortality increase occurred at higher haemoglobin levels in patients with ischaemic heart disease. Similarly, in a study of 4470 critically ill ICU patients, patients with cardiac disease manifested a trend towards increased mortality when haemoglobin levels fell below 9·5 g/dl (55% vs. 42%; $P = 0{\cdot}09$). However, anaemic patients with Acute Physiology and Chronic Health Evaluation (APACHE) II score of > 20 and a cardiac diagnosis had a significantly lower mortality rate when given 1–3 or 4–6 units of allogeneic RBCs compared to no transfusion (35% vs. 32% vs. 55%, respectively; $P = 0{\cdot}01$) [39], suggesting that RBC transfusion under these circumstances may be beneficial. Despite associations that are statistically significant, however, no cause-and-effect conclusions can be drawn from these and other retrospective analyses in which confounding factors cannot be excluded.

In a very large retrospective observational study using Medicare billing data of 78 974 patients hospitalized for confirmed acute myocardial infarction, Wu *et al.* [40] found that elderly patients with acute myocardial infarction and lower haematocrit on admission had higher 30-day mortality rates. RBC transfusion was beneficial for short-term survival, being associated with lower 30-day mortality rate among those with haematocrit below 30% to 33%. Regardless of large study size and wide representation of patients with acute myocardial infarction; however, no direct relationship between transfusion and improved outcome (30-day mortality) can be concluded; timing of transfusions and their impact on haematocrit was not assessed in the study, and associations were based solely on admission haematocrit. Furthermore, use of the Medicare billing database relies on accuracy of diagnosis coding. Contrary to these findings, Rao *et al.* [41] in a post-hoc analysis of three large international clinical trials of 24 112 acute coronary syndrome (ACS) patients, found RBC transfusion to be associated with an increased hazard for 30-day mortality and 30-day mortality/myocardial infarction (MI), with predicted probability of 30-day death higher at haematocrit level above 25%. To complicate the picture further, Sabatine *et al.* [42], in another post-hoc analysis of 41 637 ACS patients enrolled in 16 Thrombolysis in Myocardial Infarction (TIMI) trials, found increased risk of major cardiovascular events to be associated with different haemoglobin thresholds in patients with ST-elevation myocardial infarction (haemoglobin below 14 g/dl and greater than 17 g/dl) compared to non-ST elevation myocardial ACS (haemoglobin below 11 g/dl and greater than 16 g/dl).

In other particular subsets of non-cardiac patients, various thresholds for an increased cardiovascular risk of anaemia have been reported. In a prospective randomized trial examining the safety of perioperative blood conservation strategies with regard to anaemia and cardiac complications, the relationship between haemoglobin levels and episodes of myocardial ischaemia was studied in 190 elderly patients undergoing radical prostatectomy randomized to either preoperative autologous blood donation, acute normovolemic haemodilution (ANH), or a combination of preoperative erythropoietin therapy with ANH. In these patients who did not have known underlying cardiovascular disease, postoperative haematocrit levels less than 28% were associated with significantly higher likelihood of developing myocardial ischaemia both during and up to 24 h after surgery, and haematocrit levels were associated with duration of ischaemic episodes. After adjusting for other risk factors, haematocrit less than 28%, and similarly intraoperative tachycardia, remained independently associated with risk of intraoperative and postoperative myocardial ischaemia [43]. Patients in this study however, which was aimed at evaluating blood conservation strategies, were not prospectively and randomly allocated to maintain specific and differing haematocrits. Precise temporal relationships were also not recorded for the observed ST changes, tachycardia and haematocrits, which together limit the study's conclusions. In a small case–control study of 27 high-risk vascular surgery patients, Nelson *et al.* [44] also found that a postoperative haematocrit level less than 28% was significantly associated with myocardial ischaemia ($P = 0{\cdot}001$) and morbid cardiac events ($P = 0{\cdot}0058$), and that this was not attributable to any significant differences in baseline or event-related heart rate. By contrast, in another study of older subjects without known cardiac disease, 20 patients over 65 years were demonstrated to tolerate haemodilution down to a haemoglobin of 8·8 g/dl, maintaining stable VO_2 with no ST-segment changes in lead II, although the appearance of slightly less negative ST-segment deviations in lead V5 indicated this level of haemodilution to be near the threshold of tolerance in this patient population [45].

In interventional studies of haemodilution tolerance in coronary artery disease patients, reports have demonstrated adequate cardiovascular compensation at mild levels of induced anaemia. A prospective case–control study of 50 patients undergoing coronary artery bypass graft (CABG) surgery and treated with beta blockers showed no evidence

of myocardial ischaemia by electrocardiogram and transoesophageal echocardiogram in patients who underwent ANH down to a haematocrit of 28%. Despite reduced systemic oxygen delivery, left ventricular systolic and diastolic function remained intact, as evidenced by unchanged left ventricular end-systolic wall stress and preload-adjusted maximal power (contractility) [46]. Similarly, in 20 patients with coronary artery disease randomly assigned to undergo either ANH vs. control/no ANH, Licker *et al.* [47] found that ANH down to a haemoglobin of 8·6 g/dl was well tolerated, with primarily haemodynamic changes related to reduced blood viscosity, such as greater central venous return, increased cardiac preload and higher cardiac output.

Evidence exists in many cases for not only adequate physiological compensation for mild anaemia in cardiovascular disease, but in some instances, superior outcomes in mildly anaemic patients. In a prospective randomized controlled trial, the same investigators found better outcome measures in 43 CABG patients randomized to undergo ANH down to a haemoglobin of 28% compared to 41 patients assigned to standard care management, with the former exhibiting lower postoperative troponin I and creatinine phosphokinase levels, reduced need for inotropic support, and fewer numbers of patients experiencing atrial fibrillation, atrioventricular conduction blockade or combined disorders [48]. These findings matched results obtained in a rat model of myocardial infarction, in which rats assigned to undergo ANH down to a haematocrit of 30% prior to induction of left coronary artery occlusion followed by 48 h of reperfusion demonstrated fewer fatal ventricular tachyarrhythmias, lower troponin I levels, decreased myocardial infarct size (tetrazolin staining) and overall higher survival rates at 48 h post-reperfusion [49]. An earlier smaller prospective randomized study showed similar cardioprotective effects of preoperative normovolemic haemodilution, although statistical significance was not achieved, possibly owing to small sample size. In 20 coronary artery disease patients scheduled to undergo aortic surgery and randomized to receive either preoperative ANH or no ANH, Catoire *et al.* found that the negative effects of aortic clamping (increased systemic vascular resistance and arteriovenous oxygen difference, as well as decreased cardiac index) were lessened by haemodilution, suggesting improved haemodynamic tolerance to aortic clamping in patients undergoing ANH. Four patients in the control group and only one in the ANH group developed new segmental wall motion abnormalities intraoperatively [50].

Similarly, despite increased risk seen in cardiovascular disease, elderly and other higher-risk patients, primarily at haematocrit levels below 28%, Spiess *et al.* [51] concluded that low haematocrit levels in patients undergoing CABG surgery conferred a cardioprotective effect. Data from 2202 patients enrolled in a prospective observational study of patients undergoing CABG with or without other concurrent cardiac procedures revealed that higher haematocrit levels (34% or greater) on ICU admission was associated with significantly increased rates of both myocardial infarction and severe left ventricular dysfunction compared to medium (25–33%) and lower (24% and less) haematocrit levels (8·3% vs. 5·5% vs. 3·6%; $P = 0{\cdot}03$, and 11·7% vs. 7·4% vs. 5·7%; $P = 0{\cdot}006$, respectively). On multivariate analysis, high haematocrit remained an independent predictor, and the most significant predictor, of adverse outcomes. These findings, which might be explained by improved oxygen delivery stemming from the favourable haemodynamics of reduced blood viscosity, could not be replicated in a subsequent study by Klass *et al.* [52], in which a trend, but no significant association, was found between high haematocrit (33% or greater) on ICU entry and increase in either perioperative myocardial infarction rate or hospital mortality. Although intraoperative RBC and fresh frozen plasma (FFP) transfusions were similar between the groups, postoperative RBC and FFP transfusions were significantly higher in the low haematocrit group (27% or less), and cannot be excluded as a factor contributing to the lower mortality rates seen in the low haematocrit group. Similar to the study by Spiess *et al.*, analyses in the Klass study, a retrospective chart review of 500 CABG surgery patients, were performed on a single haematocrit at the time of ICU admission; without monitoring changes in haematocrit throughout ICU stay, inferences about the role of haematocrit in influencing cardiac outcomes cannot be made.

Taken together, these findings collectively suggest that while patients with cardiac disease may have greater risk of adverse outcomes associated with anemia, the risk occurs predominantly at haematocrit levels below 28%, while by contrast, higher haematocrit level, above 33–34%, likewise may confer increased risk of poorer outcomes, and must be taken into account in decisions to initiate RBC transfusion.

More clinical data – when to transfuse?

In a retrospective analysis examining the effects of perioperative transfusion on postoperative mortality, Carson *et al.* [53] studied 8787 elderly patients undergoing hip fracture repair. In patients with haemoglobin levels 8·0 g/dl or higher, postoperative transfusion was found not to influence 30-day and 90-day mortality after adjusting for trigger haemoglobin level, cardiovascular disease and other risk factors. Preoperative transfusion similarly did not impact 30-day mortality in patients with haemoglobin levels 8·0 g/dl or higher, suggesting that a haemoglobin threshold of 8·0 g/dl is safe in this population, although only mortality was assessed and cardiac morbidity was not addressed.

In a widely cited and the largest randomized controlled trial to date investigating the safety of restrictive vs. liberal transfusion strategies (Transfusion Requirements in Critical

Care, TRICC), Hébert *et al.* [54] studied 30-day all-cause mortality in 838 euvolemic ICU patients with haemoglobin levels less than 9 g/dl within 72 h of ICU admission. Of these patients, 418 were randomized to a restrictive arm in which haemoglobin was maintained between 7·0 and 9·0 g/dl, and RBC transfusion given when haemoglobin levels fell below 7·0 g/dl, while 420 patients were assigned to a liberal arm in which haemoglobin was maintained between 10·0 and 12·0 g/dl, and RBC transfusion was given when haemoglobin levels fell below 10·0 g/dl. The results showed no significant difference in 30-day mortality between the two groups (18·7% vs. 23·3%; $P = 0{\cdot}11$); however, the in-hospital mortality rate was lower in the restrictive than the liberal group (22·2% vs. 28·1%; $P = 0{\cdot}05$). In subgroup analyses, 30-day mortality rates were significantly lower in the restrictive treatment arm in patients who were younger and less ill. In patients less than 55 years of age, mortality rates were 5·7% vs. 13·0% in the restrictive and liberal arms, respectively (95% confidence interval [CI] 1·1 to 13·5%; $P = 0{\cdot}02$), and in patients with APACHE II scores of 20 or less, 30-day mortality rates were 8·7% and 16·1% (95% CI 1·0 to 13·6%; $P = 0{\cdot}03$), suggesting that in at least these subsets of patients in this setting, a more restrictive RBC transfusion strategy should be employed. No significant mortality differences were found between the two treatment groups in the remaining subgroup analyses done, including patients with cardiac disease (primary or secondary diagnoses), severe infection and septic shock, and trauma [54].

Although no significant mortality differences between treatment groups were seen in the TRICC subgroup analyses of trauma, septic shock, severe infection and cardiovascular disease patients, data from some observational studies, although not directly comparable, suggest worse outcomes with transfusion in some of these subgroups. Prospective observational data on 15 534 trauma patients admitted to a level I trauma centre showed blood transfusion to be a strong independent predictor of mortality, ICU admission, and ICU and hospital lengths of stay after stratifying by serum lactate level, base deficit, anaemia and shock index [55]. In major burn patients (a retrospective cohort analysis of 666 patients from 21 burn centres), blood transfusions were similarly found to be associated with increased mortality and infection, with an increasing number of infectious episodes reported per unit of blood transfused, after adjusting for indices of burn severity [56]. Finally, in a prospective observational cohort study of 11 963 CABG surgery patients, RBC transfusion was associated with increased risk of postoperative morbid events, ranging from renal failure, prolonged ventilatory support, severe infection, cardiac complications, neurological events and overall mortality [57].

Paralleling the design of the TRICC trial, Lacroix *et al.* [58] studied transfusion rates and outcomes in 637 stable critically ill paediatric patients whose haemoglobin levels were below 9·5 g/dl within 7 days of ICU admission. No significant differences in adverse events and mortality were found between 320 children randomized to a restrictive strategy group with transfusion threshold of 7·0 g/dl, vs. 317 children in the liberal strategy group with transfusion threshold of 9·5 g/dl. Collectively, 44% fewer RBC transfusions were given in the restrictive group compared to the liberal group, and a significant percentage of patients were spared transfusions altogether (54% vs. 2% not transfused in the restrictive and liberal arms, respectively; $P < 0{\cdot}001$), demonstrating both safety and benefit of a restrictive transfusion strategy in paediatric patients, similar to that seen in adult critical care patients.

In a post-hoc analysis using data derived from the TRICC trial, Hébert *et al.* [59] examined 357 critically ill patients with cardiovascular disease for the effect of restrictive vs. liberal transfusion strategies in cardiac disease patients. In the overall analysis, which included a broad range of very different cardiac and vascular diagnoses (arrhythmias, uncontrolled hypertension, cardiac arrest, cardiogenic and other forms of shock, myocardial infarction, angina, congestive heart failure, in addition to cardiac and vascular procedures such as abdominal aortic aneurysm repair and peripheral vascular surgery), all mortality rates were similar between the two groups, including 30-day, 60-day, ICU and in-hospital mortality. Complication rates for shock, myocardial infarction, unstable angina and cardiac arrest were comparable between the groups; only acute pulmonary oedema was significantly different (9% vs. 18%; $P = 0{\cdot}01$). While multiple-organ dysfunction (MOD) scores were initially similar between both groups, there was significantly lower change in MOD score from baseline in the restrictive group than in the liberal group. Of note, however, despite similar outcomes in cardiovascular disease patients overall, the subset of 257 patients with severe ischaemic heart disease showed lower absolute survival in the restrictive treatment group compared to the liberal group; this trend did not reach statistical significance. The findings suggest that management of ICU anaemia among cardiovascular disease patients should take into account the specific cardiac diagnosis and its severity, and that the use of a restrictive transfusion strategy may be possible, with the exception of patients with unstable angina or acute myocardial infarcts.

Discussion

Most clinicians agree that patients are at increasing risk as haemoglobin concentration falls below 6 g/dl and that few non-bleeding patients benefit from RBC transfusion when haemoglobin exceeds 10 g/dl. With only one large adequately powered randomized clinical trial assessing outcomes of restrictive vs. liberal transfusion strategies in adult critical care patients, much-needed data are still lacking on optimal

RBC transfusion thresholds across varying clinical settings. A systematic review of the literature, analysing 10 randomized clinical trials totalling 1780 patients from five surgical, three trauma/acute blood loss and two ICU studies, found no differences in mortality, cardiac events and lengths of hospital stay in patients receiving a restrictive transfusion strategy, while being associated with a 42% reduction in RBC transfusion and a reduction in RBC volume transfused by 0·93 units [60,61]. Most of the data on clinical outcomes, however, were derived from a single trial [54].

While findings of the TRICC trial showed no difference in 30-day mortality between restrictive and liberal treatment groups, the validity/interpretability of these results has been questioned on the basis of flaws in trial design in which non-comparable practice-misaligned treatment subgroups were inadvertently created within each treatment arm, i.e. the randomization of patients into fixed treatment arms with absolute transfusion thresholds that are contrary to current clinical practice [62]. Although the incorporation of a 'current practice control group' with transfusion therapy titrated to patient disease severity would be ideal, the precise patient characteristics (with the exception of presence of cardiovascular disease), as well as the appropriate dosing schedule with which to adjust therapy, are the very factors that are the subject of continued study and have yet to be clearly identified, thus complicating the design of clinical trials for RBC transfusion practice.

Although the benefits of RBC transfusion have never been directly proven, current practice indicates consistently higher use of transfusions in patients with ischaemic heart disease, comprising up to 14·3% of all RBCs given [63]. Avoiding an increase in cardiac workload in the face of anaemia appears prudent, as physiological studies suggest that ischaemic myocardium, despite retaining inotropic reserve, undergoes protective downregulation of contractile function in proportion to decreased blood flow, which allows for metabolic adaptation in areas of compromised coronary perfusion [64,65]. The true benefit of improving oxygen-carrying capacity in such patients via RBC transfusion can only be determined in future randomized controlled trials restricted to, or stratified for, varying degrees of cardiac disease. In the construction of titrated 'standard of care' control groups, consensus guidelines and surveys often do not represent true current clinical practice, and several examples illustrate their ineffectiveness in modifying clinical practice [66–69]. With respect to RBC transfusion in particular, nearly two-thirds of resident physicians reported regularly transfusing RBCs in settings they deemed likely unnecessary, at least as frequently as once a month [70], and wide variation in medical faculty's transfusion practices with respect to the weight attached to different clinical factors used in transfusion decision-making also attests to the difficulty of characterizing current practice [71].

In the meantime, data from more recent observational studies continue to yield inconsistent results. In a prospective multivariate analysis of 2085 medical/surgical ICU patients, number of RBC transfusions was independently associated with nosocomial infection after controlling for patient age, maximum storage age and number of transfusions, and remained statistically significantly associated with infection risk after correction for survival probability based on Mortality Prediction Model scores. Mortality, ICU length of stay and hospital length of stay were significantly higher in transfused patients even when corrected for illness severity [72]. By contrast, in a recent large multicentre prospective observational study of 3147 adult patients admitted to 198 European ICUs, RBC transfusion was not associated with a higher mortality rate on multivariate analysis; moreover transfused patients had a higher 30-day survival rate than non-transfused patients in 821 pairs matched according to propensity scores [73]. Finally, although a recent systematic review of the literature [74] incorporating results of 45 observational cohort studies of 272 596 high-risk hospital patients classified 42 of 45 studies as evidence for greater risk of transfusion than benefit, two of 45 studies as neutral, and only one study as showing benefits outweighing risks, it should be noted that none of the analysed studies utilized leucoreduced RBCs, which has been correlated in some studies with better outcomes [75], particularly in the setting of cardiac surgery, where patients transfused with leucoreduced RBCs have fewer postoperative infectious complications associated with mortality compared to those transfused with non-leucoreduced RBCs [76,77]. Quality of the stored RBC component remains another poorly understood variable, among other defined risks of blood transfusion [78,79].

In summary, a survey of the available literature for evidence of the best RBC transfusion threshold yields a plethora of data attesting to the need for multifactorial considerations in the decision to transfuse. It would be helpful and convenient if some physiological test or set of tests could be used to predict which patients will benefit from red cell transfusion. Unfortunately, no such test or algorithm has been found. Validated metabolic markers of global tissue hypoperfusion, such as serum lactate (indicating anaerobic metabolism) and base deficit (a surrogate marker for lactic acidosis), are easily measured but are each confounded by a range of conditions as well as resuscitative therapies. Mixed venous oxygen saturation has been proven useful in guiding critical care management, but is limited by the need for invasive monitoring using a pulmonary artery catheter or right atrial central line. Central venous oxygen saturation, a more easily measured approximation of mixed venous saturation, and currently a marker used to guide early goal-directed therapy in adult septic shock patients, can be misleading, since elevated values can be seen in severe sepsis which is characterized by low O_2

extraction. Clinical signs at the bedside have likewise been proven insensitive and are non-specific markers of hypoxia; blood pressure and heart rate in adults are not uncommonly within normal limits in the face of elevated lactate levels and alterations in venous oxygen saturation. Changes in mental status and urine output similarly suffer confounding factors in their interpretation, and are thus unreliable indicators of tissue hypoperfusion in anaemia [80,81]. Finally, even in experimental, maximally controlled settings, discordance has been seen between metabolic markers of cardiac ischaemia (ATP content, ratio of phosphocreatine to ATP, lactate content and lactate production) and contractile function evidenced by decreases in regional left ventricular systolic wall thickening, suggesting possibly that existing metabolic tests are insensitive markers for the onset of cardiac dysfunction in anaemia [65].

If the decision to initiate RBC transfusion is best guided by individual physiological need, the threshold for treatment continues to be a moving target that still relies on a combination of clinical tools – signs and symptoms at the bedside together with laboratory data and available measures that best signify changes in tissue oxygenation. Significant advances in blood safety and manufacturing have reduced many of the previous risks associated with allogeneic blood. The introduction of leucoreduced RBCs and newer molecular, serological and microbial testing which have since been employed in more recent studies, calls into question past findings of detrimental outcomes associated with transfusion [73]. Controversy over the magnitude of risks of RBC transfusion remains. As practitioners await development and validation of more accessible, practical and reliable physiological markers to guide therapy, the decision to transfuse RBC continues to rely on evaluation of the individual patient by skilled clinicians at the bedside who use haemoglobin concentration as no more than a helpful guide.

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