To transfuse, or not to transfuse: that is the question

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ABSTRACT

Transfusion practice, like medical practice in its entirety, has evolved rapidly over the past few decades. Recent research on clinical outcomes has examined the impact of blood transfusion on critically ill patients, patients with trauma, those undergoing cardiac surgery, those experiencing acute coronary syndromes, oncology patients and others.
Evidence is mounting of adverse outcomes associated with blood transfusion in a wide variety of clinical contexts. Here, we highlight the deficit in the current literature guiding transfusion practice, and call for an Australasian study to fill this deficit.

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Transfusion has revolutionised multiple aspects of modern medicine for more than 100 years, since Landsteiner defined blood group compatibilities in 1900, yet evidence guiding the decision to transfuse a patient is perhaps less clear than ever. Blood transfusion has a clearly defined role in the management of haemorrhagic shock and presumably is beneficial in situations where a critically low haematocrit contributes to oxygen-supply dependency.[1] While blood and blood products are safer today than ever before, the risks of allogeneic blood transfusion are becoming more apparent,[2-4] as are the many transfusion-associated complications, such as lung injury,[5,6] immunomodulation,[7] and cellular hypoxia.[8]

The question of transfusion is one of the risk–benefit ratio. As the risks of transfusion become clearer, high-quality evidence delineating where the benefit outweighs the risks is less forthcoming. The risk–benefit equation of transfusion medicine encompasses at least three factors:

- The risks secondary to anaemia that depend, in turn, on the patient's capacity to compensate for it.
- The efficacy of allogeneic red blood cell (RBC) transfusion to correct these risks, a consideration which is all too often assumed but has not been well demonstrated.
- The risks associated with transfusion themselves.

Recent research on clinical outcomes has examined the impact of blood transfusion on critically ill patients, trauma patients, patients undergoing cardiac surgery, patients with acute coronary syndromes, oncology patients and others. These studies provide additional evidence of adverse outcomes associated with blood transfusion in a wide variety of clinical contexts. The aim of this article is to highlight the deficit in the current literature guiding transfusion, and to call for an Australasian study to fill this "chasm".

Prospective randomised trials

As identified by Nichol in the previous issue of the Journal, there are very few prospective randomised trials assessing risk versus benefit of transfusions in the critically ill.[9] The largest single prospective randomised trial was conducted over a decade ago. The Transfusion Requirements in Critical Care (TRICC) trial,[10] a prospective randomised trial, was the first quality study to demonstrate a causal link between blood transfusion and adverse outcomes in critically ill patients. When patients were randomised to liberal (haemoglobin [Hb] transfusion threshold of < 100 g/L) or restrictive (transfusion threshold < 70 g/L) transfusion groups, cardiac and pulmonary complications increased significantly, and a trend existed toward increased mortality in the liberal transfusion group. When younger (< 55 years of age) or less critically ill (Acute Physiology, Age, Chronic Health Evaluation [APACHE] score < 20) patients were considered, a statistically significant ($P < 0.03$) increase in mortality was present in patients who were more liberally transfused.

A subsequent subgroup analysis of 375 patients with cardiovascular disease demonstrated a trend toward increased survival in the liberal transfusion group, but transfusion also resulted in a statistically significant increase in pulmonary oedema and multiorgan system dysfunction.[11] A recent randomised trial in critically ill children using a design similar to the TRICC trial found that patients randomised to liberal or to restrictive transfusion strategies experienced similar outcomes.[12]

Two other prospective studies conducted in patients undergoing coronary artery bypass grafting (CABG) surgery,[13,14] with triggers at either 80 g/L or at 90 g/L, showed no significant differences between the restrictive and more liberal haemoglobin triggers. Bracey et al,[13] in a study of 428 patients undergoing coronary artery bypass grafting (CABG), concluded that a lower Hb threshold of 80 g/L does not adversely affect patient outcome. Moreover, RBC resources can be saved with no increased risk to the patient.

Two large prospective studies[15,16] assessed the effect of leukodepleted versus non-leukodepleted blood transfusion and concluded there was no difference in mortality between

the two groups. There was similarly no discernible difference in length of stay in hospital or in the intensive care unit, hospital costs, antibiotic usage and readmission rates. The only significant difference was a reduction in febrile reactions in those who received leukodepleted blood.

Observational studies

The CRIT Study[17] was undertaken to quantify the incidence of anaemia and RBC transfusion practice in critically ill patients and the relationship to clinical outcomes. This was a prospective, multicentre observational cohort study of ICU patients in the United States, which demonstrated that RBC transfusions are independently associated with longer ICU and hospital stay and increased mortality. Overall, there were more complications in the patient cohort, and the number of RBC units transfused was an independent predictor of worse clinical outcome.

The ABC study (Anaemia and Blood Transfusion in the Critically Ill) was performed in 146 western European ICUs,[18] with a similar design to that of the CRIT Study: 37.0% of the 3534 patients were transfused, with a mean pre-transfusion haemoglobin concentration of 84 g/L. Mortality was higher for transfused patients than for non-transfused patients with similar organ dysfunction as assessed by the Sequential Organ Failure Assessment (SOFA) score. After matching patients by propensity scores for being transfused (and thus controlling for SOFA and APACHE II scores, among other variables), 28-day mortality was significantly higher in patients with transfusions (22.7% versus 17.1%, $P = 0.02$).

A recent observational study, the SOAP (Sepsis Occurrence in Acutely Ill Patients) study,[19] enrolled 3147 patients, of whom 33% received an RBC transfusion. Patients receiving transfusions were older and generally sicker, and consequently the observed increase in mortality was not surprising. There was a direct relation between the number of blood transfusions and mortality, but in multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. Moreover, in 821 pairs matched according to a propensity score, there was a higher 30-day survival rate in the transfusion group than in the other patients ($P = 0.004$). Vincent et al[19] concluded that this study does not support the view that blood transfusions are associated with increased mortality rates in acutely ill patients.

Meta-analyses

Two meta-analyses have assessed general and post-surgery patients, and demonstrated that RBC transfusion slightly worsens outcome or has no effect.[20,21] Carson and colleagues[22] identified nine other randomised control trials that used a clearly defined restrictive or liberal transfusion strategy, giving a total of 1780 patients in 10 trials. The Hb transfusion triggers evaluated in these trials ranged from 70 g/L to 100 g/L. Data on mortality or hospital length of stay were available in only six of these trials. Conservative transfusion triggers were not associated with an increase in mortality; on average, mortality was a fifth lower (relative risk, 0.80; 95% CI, 0.63–1.02) with the conservative versus the liberal transfusion strategy. Likewise, cardiac morbidity and length of hospital stay did not appear to be adversely affected by the lower use of RBC transfusions. Of the 1780 patients, 892 (50%) had cardiovascular disease. On analysis, there were no differences in the combined odds of death or cardiac events using restrictive strategies as compared with more liberal approaches. There were insufficient data on other potentially relevant clinical outcomes, such as stroke, thromboembolism, multiorgan failure, delirium, infection, or delayed wound healing to perform any pooled analysis. Carson et al concluded there were insufficient data to address the full range of risks and benefits associated with different transfusion thresholds, particularly in patients with coexisting disease. They also noted that their meta-analysis was dominated by a single trial: the TRICC trial, which enrolled 838 patients, and was the only individual trial identified that was adequately powered to evaluate the impact of different transfusion strategies on mortality and morbidity.

The meta-analysis by Chung et al,[23] which included 20 trials representing 5236 patients with colorectal carcinoma, supported the hypothesis that perioperative blood transfusion increases the risk of disease recurrence, cancer death and death, with an estimated cumulative odds ratio of a negative outcome of 1.69.

Retrospective database analysis

Coronary artery disease

Rao and colleagues[24] collected data from three large trials in patients with acute coronary syndromes to determine the association between blood transfusion and outcomes among patients who developed moderate to severe bleeding, anaemia, or both during hospitalisation. The study analysed 24 111 participants in the GUSTO IIb, PURSUIT, and PARAGON B trials. Patients were grouped according to whether they received a blood transfusion during hospitalisation; 2401 (10%) patients received at least one blood transfusion during hospitalisation. The rates for three predetermined outcomes (30-day mortality, heart attack, and composite mortality/heart attack) were significantly higher among patients who received a transfusion (30-day mortal-

ity, 8% in transfused patients versus 3.08% in non-transfused patients; 30-day heart attack, 25.16% versus 8.16%; 30-day composite mortality/heart attack, 29.24% versus 10.02%). Transfusion was associated with a nearly fourfold higher risk of 30-day mortality and a threefold increase in incidence of death/myocardial infarction within 30 days. In further analysis that included procedures and bleeding events, transfusion was associated with a trend toward increased risk of death.

Wu et al[25] assessed transfusion in emergency patients in a retrospective study of data on nearly 79 000 Medicare beneficiaries aged 65 years or older who were hospitalised with acute myocardial infarction, from a database of more than 230 000 patients. The authors noted that the group with lower haematocrit values on admission had higher 30-day mortality, and that blood transfusion was associated with a reduced 30-day mortality among those with a haematocrit in the range, 0.05–0.24.The authors concluded that blood transfusion was associated with a lower short-term mortality rate among older patients (over 65 years) with myocardial infarction if the admission haematocrit was 0.30 or lower, and might be effective in patients with a haematocrit as high as 0.33 on admission.

In an accompanying editorial, Hébert and Fergusson[26] contrasted the findings of the above two studies and commented that Rao and colleagues included only younger individuals who required aggressive intervention. Younger patients may derive less benefit from transfusions because of a more preserved ability to augment cardiac output, along with a more aggressive approach to revascularisation, and greater use of statins and antiplatelet agents. It is also possible that younger patients can better adapt to anaemia. Specific concerns about the study of Wu et al included the low rate of RBC transfusion, limited statistical adjustments made in the multivariable analysis, analysis based on the admission haematocrit value rather than the value associated with the transfusion, no consideration for the time-dependent use of RBCs, and residual confounding because RBC use was intimately linked to haematocrit values (confounding by indication). Moreover, the observed benefits of transfusion did not persist for patients with an admission haematocrit between 0.301 and 0.33, and in a secondary analysis that excluded patients who died within 2 days of admission.

The REPLACE-2 (Randomised Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial analysed transfusion-related mortality in all patients as a secondary outcome measure. It is noteworthy that the adjusted odds ratio for 1-year mortality was increased fourfold in transfused patients who underwent percutaneous coronary intervention in this trial, most of whom had stable ischaemic heart disease.[27]

Singla et al[28] reported on 370 patients in a tertiary hospital who presented with anaemia and a suspected acute coronary syndrome. After risk adjustment, the risk of myocardial infarction or death was increased by a factor of 2.5 in patients who received blood. Jani et al[29] reported on 4623 anaemic patients undergoing percutaneous coronary intervention 1 week after myocardial infarction. Men with a pre-procedure Hb level < 130 g/L and women with a pre-procedure Hb level < 120 g/L were classified as anaemic. After propensity matching and multiple regression analysis, transfused patients were about twice as likely to die in hospital.[29]

Coronary artery bypass graft surgery

Engoren et al found that blood transfusions during or after CABG were associated with increased long-term mortality.[30] The decrement seen in the survival curves in the transfused population persisted after both multivariate analysis and propensity analysis. Koch et al in 2006 similarly concluded that perioperative RBC transfusion is associated with adverse long-term sequelae in patients with isolated CABG.[31] After risk adjustment, the number of units transfused remained the most important determinant of mortality and prolonged mechanical ventilation. Kuduvalli et al also concluded that perioperative RBC transfusion appears associated with an increase in 30-day and 1-year mortality in patients undergoing CABG.[32] A multicentre study in the US by Spiess et al[33] (which included 2202 patients who underwent CABG at 25 different centres) found reduced mortality, and rate of myocardial infarction and severe left ventricular dysfunction for post-CABG patients whose haematocrit on arrival in the ICU was < 0.24.

Data analysed at our centre on 5342 post-cardiac surgery patients (unpublished study) showed that median time to death was significantly shorter for patients who received transfusions: 1.15 years in those transfused with packed RBCs, and 0.83 years in those transfused with any blood product, compared with 4.68 years in the non-transfused group. Global 30-day mortality in this population was 1.7%, but mortality in those transfused was significantly higher than in the non-transfused group (3.6% v 0.3%, $P < 0.001$). The 1-year mortality was also significantly higher in the transfused group compared with the non-transfused group (7.3% transfused v 1.3% non-transfused, $P < 0.001$). Transfused patients had almost twice the 5-year mortality (16% v 7%) compared with non-transfused patients. After correction for co-morbidities and other factors, transfusion was still associated with a 66% increase in mortality.

General surgical patients

A large database assessed the relationship between transfusion, infection and mortality in a general surgical population[34] and found that with each unit of blood transfused there was a statistically detectable increase in both infection and mortality (odds ratios, 1.06 and 1.08, respectively).

Trauma and burns patients

Data collected prospectively on 15 534 trauma patients at Maryland Shock Trauma Centre revealed that blood transfusion was independently associated with a threefold increase in mortality in the trauma population.[35] A recent study of 8215 patients with blunt trauma further supported the existence of a dose–response relationship between transfusion and mortality.[36] Boral et al,[37] in an analysis of 1615 burns patients, described a fivefold increase in mortality among the transfused patients with comorbidities compared with the non-transfused group. Patients with burns to < 20% total body surface area were more likely to be transfused if they had comorbidities.

Systematic reviews

Marick and Corwin[38] recently published a systematic review of 45 observational studies that analysed a median of at least 687 patients per study. In 42 of the 45 studies, the risks of RBC transfusion outweighed the benefits; in another two studies, the risk was neutral; and in the remaining study, the benefits outweighed the risks in a subgroup (elderly patients with acute myocardial infarction and a haematocrit < 0.30). Seventeen of 18 studies demonstrated that RBC transfusions were an independent predictor of death; the pooled odds ratio (12 studies) was 1.7 (95% CI, 1.4–1.9).

Twenty-two studies examined the association between RBC transfusion and nosocomial infection; all found that blood transfusion was an independent risk factor for infection. The pooled odds ratio (nine studies) for developing an infectious complication was 1.8 (95% CI, 1.5–2.2). RBC transfusions similarly increased the risk of developing multiorgan dysfunction syndrome (three studies) and acute respiratory distress syndrome (six studies). The pooled odds ratio for developing acute respiratory distress syndrome was 2.5 (95% CI, 1.6–3.3).

The authors concluded that, in adult ICU, trauma and surgical patients, RBC transfusions are associated with increased morbidity and mortality, and therefore current transfusion practices may require re-evaluation. The risks and benefits of RBC transfusion should be assessed in every patient before transfusion.

Recently, Gerber[39] reviewed the current literature on the utility of, and complications associated with, transfusion of packed RBCs in medical and surgical patients with ischaemic heart disease. He concluded that, despite the variability in data sources and study design, the preponderance of data indicate that transfusion of packed RBCs in the population of patients with ischaemic heart disease is of limited clinical utility, and may carry the potential for serious adverse consequences.

Experience of Jehovah's Witness patients

Case reports and series of patients who refuse blood transfusions for religious reasons show that Hb levels of 60 g/L to 80 g/L are routinely well tolerated.[40,41] Spence et al found that Hb level was not a significant predictor of outcome of operations on Jehovah's Witnesses unless it was below 30 g/L.[42] A 1994 literature review[43] sought reports on Jehovah's Witnesses with an Hb level < 80 g/L or haematocrit < 0.24. With the exception of three patients who died after cardiac surgery, all the deaths attributed to anaemia occurred when Hb level was lower than 50 g/L. There were 25 survivors with an Hb level of 50 g/L or less, adding to the anecdotal evidence of human tolerance to anaemia. In a retrospective cohort study, Carson et al showed that the risk of death was low in patients with postoperative Hb levels of 71–80 g/L, although 9% had morbidity. As postoperative blood counts fall, the risk of mortality or morbidity rises, and becomes extremely high below 50–60 g/L.[44]

Leukodepletion

Leukodepletion was introduced in the hope that it would reduce the possible risk of transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Secondary benefits of leukodepletion may include a reduction in the incidence of other adverse effects, such as non-haemolytic transfusion reactions, cytomegalovirus transmission, alloimmunisation, graft versus host disease, and transfusion-associated immunosuppression.[45] Hébert and colleagues[46] conducted a study before and after universal leukodepletion in 14 786 patients who were undergoing cardiac surgery or repair of a hip fracture, or required intensive care after surgical intervention or multiple trauma. The authors documented a 1% decrease in mortality rate associated with the implementation of universal leukodepletion, without observed changes in serious infections. The overall cost-effectiveness of universal leukodepletion has yet to be proven, especially in lower-risk populations. In addition, studies[47] suggest that the incremental benefits provided by leukodepletion may not be mediated through immunomodulation, but rather through decreased stimulation of the inflammatory cascade.

Red blood cell storage and outcome

The inability to define optimum and minimum transfusion thresholds and to reliably measure tissue oxygenation has made it difficult to study the efficacy of different RBC products. Consequently, the determination of RBC shelf life has been based on the maintenance of corpuscular integrity and post-transfusion 24-h survival.[48] Stored RBCs are deficient in 2,3-diphosphoglycerate and consequently less

adept at unloading oxygen. It has also been proposed that loss of nitric oxide activity in banked blood impairs the vasodilatory response to hypoxia,[49] although the clinical significance of this finding is controversial.[50] Stored RBCs are also less deformable, possibly leading to sludging and capillary occlusion. If stored RBCs have greater affinity for oxygen, and capillary flow is impaired, blood transfusion could increase mixed venous oxygen saturation while decreasing tissue oxygen delivery.[51]

Retrospective clinical studies have documented an association between prolonged storage times and adverse clinical outcomes, including mortality,[52] pneumonia,[53] serious infections,[54] and length of stay[55] in many patient populations, including those with multiple trauma, critically ill patients, and those undergoing cardiac surgical procedures. Two randomised controlled trials in adults have been reported. Walsh and colleagues[56] evaluated changes in gastric pHi, a measure of gastric perfusion, in 22 critically ill patients who were undergoing mechanical ventilation and required an RBC transfusion. The authors were unable to detect any adverse consequences for pHi or changes in the arterial–gastric mucosal carbon dioxide gap with an RBC storage time >20 days compared with <5 days. These results contradicted earlier observations in a before-and-after study conducted by Marik and Sibbald,[57] who documented an inverse relationship between the age of transfused RBCs and gastric pHi ($r=-0.71$, $P<0.001$). However, it should be noted that patients in the study of Walsh et al received leukodepleted RBCs. Koch et al[58] retrospectively evaluated the impact of differences in duration of RBC storage. Patients who received blood that was stored for more than 2 weeks before transfusion had a statistically significant increase in in-hospital mortality, prolonged intubation, renal failure and sepsis or septicaemia.[58]

Current guidelines

In an effort to conserve a limited and expensive resource and to minimise the injury caused by transfusion therapy, committees from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists developed a practice guideline.[59] This emphasises that the benefits of transfusion have not been adequately demonstrated and that existing evidence is an imperfect guide to transfusion decisions. It suggests a transfusion trigger of Hb level less than 70 g/L in postoperative cardiac surgery patients (Class IIa recommendation). However, it simultaneously suggests (Class IIb recommendation) that it is "not unreasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischaemia (e.g. central nervous system and gut) whose Hb levels are as high as 10 g/dL [100 g/L], but more evidence to support this recommendation is required".[59] Given the growing evidence of an association between transfusion and ischaemic outcomes, this last recommendation appears to be flawed.

Conclusions

Based on the current literature, there appears to be no indication for routine transfusion in patients with non-ST-elevation acute coronary syndrome, although anaemic patients with ST-elevation myocardial infarction may benefit from this intervention. However, the specific indications for transfusion in this population remain ill defined. To date, blood transfusion in this group has been driven by well-intentioned beliefs and advice from older practitioners that patients with coronary artery disease *must* have a higher haematocrit — not by science.

Transfusion medicine is a developing and changing field. It is physiologically incontrovertible that there is some "cut-off" Hb or haematocrit value below which tissue oxygenation is inadequate. The clinician therefore needs an evidence base to decide whether "to transfuse, or not to transfuse". The individual intensivist, surgeon or anaesthetist proposing to transfuse a patient should consider carefully exactly what is to be accomplished with a transfusion, and the balance of risks. What is emerging from the literature is a crying need for prospective randomised trials.

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