Editorial III

Blood transfusion in critical illness

Transfusing blood to treat anaemia in normovolaemic, critically ill patients, is common practice. It has been estimated that one-third of all patients admitted to intensive care units in the developed world receive blood transfusions.[1] Most intensivists prescribe blood with the belief that it enhances oxygen transport and may, therefore, relieve covert tissue hypoxia. Increasing an anaemic, critically ill patient's plasma haemoglobin concentration by transfusion undoubtedly increases global oxygen delivery but there is no guarantee that an increase in regional oxygen delivery will follow. It is even less certain if increased oxygen delivery after transfusion can promote increased oxygen consumption to relieve tissue hypoxia (pathological supply dependency).

Investigators have tried to establish the existence of pathological supply dependency and define optimal oxygen transport goals in both critically ill and perioperative patients.[2 3] However, they manipulated oxygen transport using fluid, inotropic and vasoactive treatments rather than blood transfusion. A transfusion threshold of 10 g dl^{-1} was standard in these studies. Furthermore, a systematic review suggested that although some perioperative patients may benefit from augmented oxygen delivery, there was little evidence to support this approach in critically ill patients.[4] There have been numerous studies evaluating the effects of blood transfusion on oxygen kinetics in a wide variety of critically ill patients.[5–10] However, all of these studies had small patient numbers and only modest total volumes of blood were administered. Although an increase in oxygen delivery following transfusion was a consistent finding, an associated rise in oxygen consumption was observed only occasionally. A decrease in plasma lactate following transfusion was reported in only one of the studies. These results raised many questions, which include the on-going controversy over the very existence of pathological supply dependency, but it can nevertheless be concluded that there is little evidence that blood transfusion relieves tissue hypoxia in critically ill patients.

Many factors influence a clinician's decision to prescribe blood for a normovolaemic, critically ill patient including: how acutely the anaemia developed, the severity of the associated symptoms, age, and comorbidity. Most intensivists use a numeric transfusion trigger, usually a plasma haemoglobin value, as a threshold below which transfusion is indicated.[11] However, this approach has been criticized as physiological variability, in terms of compensatory increases in cardiac output and oxygen extraction in response to anaemia, limits the usefulness of a single laboratory number as a general transfusion guide. This has led other workers to suggest that clinicians should use a physiological trigger, such as an oxygen extraction ratio greater than 50%, in anaemic patients as an indication for blood transfusion.[12] However, this physiological trigger was calculated from studies of non-critically ill animals in which anaemia was induced by controlled euvolaemic haemodilution. Furthermore, impaired oxygen extraction is not uncommonly observed in human critically ill subjects. Even if the oxygen extraction ratio were a reliable indicator of sub-optimal oxygen delivery resulting from anaemia, it would remain difficult to define a number that could be utilized safely as a transfusion trigger in critically ill patients. Such difficulties surrounding physiological triggers have contributed to the widespread adoption of numerical transfusion triggers in clinical practice.

In 1982, Allen and colleagues suggested the 10/30 rule (10 referring to plasma haemoglobin of 10 g dl^{-1} and 30 to the haematocrit) as a clinically useful transfusion trigger.[13] Although the 10/30 rule was derived from perioperative patient studies, the rule was enthusiastically adopted throughout medical practice. It became particularly popular in critical care medicine because: the daily measurement of plasma haemoglobin was a cheap and routine investigation; a haemoglobin of 10 simplified oxygen kinetic calculations; and it was an easy number to remember! Nevertheless, the 10/30 rule as a transfusion trigger in the critically ill has never been supported by a randomized controlled trial.

Despite the 10/30 rule's past popularity in critical care medicine, the increasing costs and decreasing availability of blood products have forced clinicians to reconsider the rule and ask if a transfusion trigger of less than 10 g dl^{-1} could be used safely. Other reasons to reconsider transfusion triggers include the rare but well-recognized risks of transfusion such as infection with human immunodeficiency and infectious hepatitis viruses, and ABO mismatch. There are three other risks of transfusion that are particularly relevant to critically ill patients. First, blood transfusion can cause leucocytosis that may be of uncertain pathological significance but can certainly cause diagnostic confusion.[14] Secondly, microcirculatory risks may also follow transfusion because storage of blood decreases red cell 2,3-diphosphoglycerate concentrations thus impairing the deformability of the cell. Poorly deformable red cells flow through the microcirculation inefficiently and this may partly explain the poor correlation between blood transfusion and increased oxygen consumption. Marik and colleagues demonstrated increased splanchnic ischaemia following transfusion with old blood in patients with sepsis.[8] Furthermore, in a rat sepsis model, transfusion with fresh blood increased oxygen consumption whereas old blood failed to do so.[15] In summary, blood transfusion

(particularly with old blood) can paradoxically decrease microcirculatory oxygen delivery and contribute to tissue hypoxia.

Thirdly, *in vitro* studies have suggested that blood transfusion causes immunosuppression by decreasing cell-mediated immunity, reducing non-killer cell activity, suppressing macrophage antigen presentation, altering T-cell ratios, and decreasing the concentrations of cytokines (TNF, IFN-γ, and GM-CSF) that are vitally important in immune responses.[16] Randomized controlled trials studying the effects of allogeneic transfusion in colorectal surgery, demonstrated a correlation between volume of transfusion and the incidence of postoperative infections.[17 18] Although these were perioperative patient studies, they nevertheless suggest that transfusion-associated immunosuppression may occur in critically ill patients. There is evidence that the white cells present in transfused blood are the cause of this immunosuppression.[16] In another study of colorectal surgery patients, there was a lower incidence of post-operative infections in patients transfused with leucocyte-depleted blood.[19] Although leucocyte depletion is a costly process, it has been widely adopted throughout Europe.

In contrast to the abundance of evidence that allogeneic blood transfusion may be detrimental, there is a paucity of literature addressing how well critically ill patients tolerate anaemia. It has been documented that healthy animals and surgical patients cope well with profound anaemia.[20] Other authors have suggested that perioperative bleeding is a more important factor than plasma haemoglobin concentrations in determining postoperative mortality and morbidity. In a surgical study, plasma haemoglobin values as low as 6 g dl^{-1} were well tolerated provided operative blood loss was less than 500 ml.[21] In a large study of Jehovah's Witness patients undergoing major surgery, a 1.4% mortality was attributed to anaemia, with 90% of the deaths occurring in patients undergoing cardiovascular surgery.[22] These studies suggest that plasma haemoglobin measurements significantly less than 10 g dl^{-1} are generally well tolerated by surgical patients. However, it remains unclear if this applies to critically ill patients.

At what plasma haemoglobin concentration do the risks of anaemia outweigh the potential risks of blood transfusion in critically ill patients? When is blood transfusion justified? Until 2 yr ago, there had been only five randomized controlled studies comparing different transfusion strategies in critically ill and perioperative patients.[23–27] Perhaps not surprisingly all of these small studies failed to answer this question. Until recently the only published studies available to help clinicians decide when to transfuse anaemic critically ill patients have been either observational or small, poorly controlled, clinical studies based on peri-operative rather than critically ill patients.

Two years ago, an attempt was made to answer this question when the Transfusion Requirements in Critical Care (TRICC) Investigators, on behalf of the Canadian Critical Care Trials Group, published the results of a large multicentre, randomized, controlled clinical trial of transfusion requirements in critical care.[28] After conducting an observational study to assess transfusion practice variation throughout Canada,[29] the investigators enlisted 838 patients over 3 yr from 25 centres. Only normovolaemic, anaemic (plasma haemoglobin <9 g dl^{-1}) patients who were expected to stay in the intensive therapy unit for more than 24 h were included in the study. Important exclusion criteria were evidence of active bleeding (>3 units transfusion over 24 h), chronic anaemia (plasma haemoglobin <9 g dl^{-1} in the preceding month) and patients undergoing cardiac surgery. The enlisted patients were randomized to receive either a restrictive transfusion strategy (transfusion trigger of 7 g dl^{-1} and a maintenance range of 7–9 g dl^{-1}) or a liberal strategy (transfusion trigger of 10 g dl^{-1} and a maintenance range of 10–12 g dl^{-1}). Single unit transfusions were administered and plasma haemoglobin checked before further transfusion was considered.

The procedures were applied successfully as average daily haemoglobin concentrations were 8.5 and 10.7 g dl^{-1} in the restrictive and liberal strategy groups, respectively. On average, a total of 2.6 units of blood were administered to patients randomized to the restrictive strategy group compared with 5.6 units for patients in the liberal strategy group. Patients in the restrictive strategy group received 54% less blood by volume than patients in the liberal strategy group. One-third of the patients in the restrictive strategy group did not require transfusion whereas all patients in the liberal strategy group were transfused. There was a non-significant trend towards decreased 30-day all-cause mortality (the primary outcome measure), in favour of patients in the restrictive strategy group and the same pattern was observed for the secondary outcome measures of 60-day all-cause and ICU mortalities. Also, there was a significantly lower adjusted multiple organ dysfunction score (secondary outcome measure), again in favour of patients in the restrictive strategy group. Subgroup analysis revealed that young patients (<55 yr old), and patients with APACHE II <20 were the only subgroups to have a significantly better primary outcome measure after randomization to the restrictive strategy group. There was no significant difference between the two strategies for any other subgroups including patients with septic shock and with cardiovascular disease. There were significantly fewer cardiac complications, including acute myocardial infarction and pulmonary oedema, observed in patients in the restrictive strategy group.

The TRICC investigators concluded that a restrictive strategy is at least comparable with a liberal strategy in critically ill patients and may be better because it is associated with: a trend towards improved 30-day all-cause mortality; a significant decrease in hospital mortality, adjusted multiple organ dysfunction score, and cardiovascular complications; and decreased transfusion by 54% and transfusion exposure by 33%. The TRICC investigators recommended the restrictive strat-

egy as best practice for most patients including those with cardiovascular disease, but with the possible exception of critically ill patients with on-going coronary ischaemia. Doubt about the appropriateness of a restrictive strategy approach for such patients was supported by the publication of a later subgroup analysis that suggested that patients with severe cardiac disease randomized to the restrictive strategy group had a non-significant increase in 30-day all-cause mortality.[30] Unfortunately, the TRICC study excluded patients with chronic anaemia and those undergoing cardiac surgery and so it remains difficult to recommend a transfusion strategy for either of these groups on the basis of this study.

Most studies addressing transfusion practice in critically ill patients have been conducted in North America. However, a prospective, epidemiological survey of anaemia and transfusion practice in Western Europe (Anaemia and Blood Transfusion in Critical Care Study) has been completed but the results await publication. In the long term, new therapies such as human recombinant erythropoietin and artificial blood substitutes may decrease blood transfusion requirements. However, at this moment the simplest, safest, and most cost-effective way to reduce transfusion requirements in critically ill patients is the adoption of a lower transfusion trigger as suggested by the TRICC investigators, rather than the premature introduction of clinically unproven, expensive, new treatments with uncertain safety profiles.

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