Editorial

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Blood transfusion in anaesthesia and critical care: Less is more!

As perioperative physicians, anaesthesiologists are commonly confronted with the management of perioperative anaemia and blood loss before, during and after surgery. Fresh frozen plasma, cryoprecipitate and platelets are vital products in the management of coagulopathic patients, and transfusion of blood and blood products is a common intervention in the operating rooms and critical care unit. This post-graduate issue is, therefore, important, relevant and contemporary, as it deals with all the aspects of blood and blood product transfusion and coagulation management in anaesthesia and critical care.

Acute haemorrhage during surgery or trauma is an important indication for packed red blood cell transfusion (PRBCT). While restoration of fluid volume with fluids is vital in the management of hypovolemic shock, PRBCT can raise the haemoglobin (Hb) and oxygen carrying capacity of blood. No randomised controlled trials (RCTs) are available comparing PRBCT with no transfusion in such situations. However, observational studies in Jehovah's witnesses and other circumstances where blood could not be transfused tell us that low Hb values are associated with worse outcomes. In a study of 300 Jehovah's Witness patients undergoing major non-cardiac surgeries, there was a demonstrable link between the lowest post-operative Hb levels and outcome.[1] The composite outcome of 30 days in-hospital mortality or major morbidity ranged from 100% in patients with Hb values <2 g/dl to 58% with Hb values 4.1–5.0 g/dl and 29% with Hb levels between 5.1 and 6 g/dl. There were no deaths if the lowest Hb was >7 g/dl.Transfusion of PRBCs in anaemic adults leads to a significant increase in their exercise capacity, objectively documented by increase in the anaerobic threshold and other parameters on cardiopulmonary exercise testing.[2] However, blood and blood products are scarce resources and must be used sparingly, only when necessary.[3] We recently documented that in our cancer centre, PRBCT occurred in 16% of operations and that 51% of transfused patients had a post-transfusion Hb >10 g/dl, indicating over transfusion. Significantly, single-unit transfusions were not associated with over transfusion, implying that the minimum amount of blood required to reach the target Hb must be used; a single unit of PRBCs may often be adequate.[4] Transfusion itself is not free from problems and complications. While advances in blood banking practices and diagnostics have greatly minimised the risks of mismatched transfusions and transmission of infection, transfusion induced immunomodulation, transfusion-associated acute lung injury and graft versus host disease are being increasingly recognised. It must also be kept in mind that all transfusion services in India may not be observing the same standards of screening for infectious diseases as in the West. A Cochrane review of 17 trials found an association between PRBCT and adverse outcomes, including increased morbidity, infections, stroke and complications.[5] There is a known association between recurrence of cancer and blood transfusion for colon cancer surgery, but this has not been well demonstrated for other cancers.[6] It must be pointed out that the association is not the same as causation. It may be argued that patients with more locally aggressive tumours, more extensive and difficult resections are the ones more likely to get blood transfusions, as well as recurrence. However, blood transfusion is an independent variable affecting outcome in most of these studies, suggesting that the association of transfusion with adverse outcome remains significant even after accounting for these

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factors.The adverse outcomes of anaemia and blood transfusion have been summarised in an excellent review.[7] It would appear that there is a range of Hb values that are well-tolerated, and that at levels below this, the risks of anaemia outweigh the risks of transfusion, while at levels above these, the risks of transfusion are greater. Most centres have adopted a restrictive transfusion policy that tolerates anaemia till a transfusion trigger is reached, usually around 7 g/dl.[8] What is the validity and evidence supporting such an approach? Should the decision to transfuse be based only a number, or take into account other factors including patient comorbidities and some physiological targets or indicators of tissue perfusion? In this editorial, we will examine the literature including the results of very recently published trials, to answer some of these questions.

The early goal-directed therapy (EGDT) study was a single-centre RCT in patients with severe sepsis and septic shock.[9] Transfusion of PRBCs to a haematocrit of 30% was one of the interventions used in the EGDT arm to raise the central venous oxygenation saturation ($ScvO_2$) >70%. The $ScvO_2$ is an index of the balance between oxygen supply and consumption, with a low $ScvO_2$ indicating a deficiency of oxygen supply relative to the demand. Patients in the EGDT group received more PRBCTs and had an improved mortality compared to those patients receiving standard resuscitation measures for severe sepsis and septic shock. This trial demonstrated both physiological benefit (increased $ScvO_2$ and lower lactate levels) and outcome benefit (reduced mortality) in patients receiving EGDT including liberal PRBCTs. These results have not been confirmed by two recent multicentre RCTs (Process Investigators *et al*.[10] and ARISE Investigators *et al.)*.[11] In both studies, no mortality benefit was observed in patients assigned to EGDT.

The transfusion requirements in critical care (TRICC) study was a landmark trial published in 1999.[12] Euvolemic patients in the intensive care unit (ICU) with Hb <9 g/dl were randomized to a restrictive transfusion strategy for transfusion of PRBCs (transfused if Hb <7 g/dl to maintain Hb between 7 and 9 g/dl) or a liberal strategy (transfused if Hb <10 g/dl to maintain Hb 10–12 g/dl). Mortality was similar in both groups, indicating that liberal transfusions were not beneficial. In fact in subgroups such as less severely ill patients with an Acute Physiology and Chronic Health Evaluation 2 score <21, and patients ≤55 years age, mortality as well the incidence of complications was higher in patients assigned to the liberal transfusion strategy. The authors concluded that a restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

The apparent contradiction between the EGDT study (recommending a haematocrit of 30%) and TRICC study can be resolved if one recognizes that the EGDT study enrolled patients with severe sepsis or septic shock requiring fluid resuscitation in the first 6 h after presentation to the emergency department, while the TRICC trial enrolled stable, euvolemic patients within 72 h of admission to the ICU. Thus during acute haemodynamic resuscitation in severe sepsis, a liberal Hb target was beneficial, and once the patient had stabilized, a restrictive target was appropriate. The Sepsis Occurrence in Acutely Ill Patients, a multicentre, observational study of sepsis in European ICUs.[13], surprisingly, found that patients who received blood transfusions had improved outcome compared with non-transfused patients. It was suggested that the use of leucodepleted blood in Europe may have avoided some of the adverse effects of PRBCT while maintaining the benefits.The recently published transfusion requirements in septic shock RCT[14] included 1005 patients in the ICU who had septic shock and a Hb concentration ≤9 g/dl; they were randomized to receive one unit of leukoreduced RBCs when the Hb level was ≤7 g/dl (lower threshold) or when the level was 9 g/dl or less (higher threshold) during the ICU stay. At 90 days after randomization, mortality was 43% in the lower-threshold group, versus 45% in the higher-threshold group ($P = 0.44$). Notably, there was no increase in complications with the liberal transfusion strategy. These patients were probably well-resuscitated, as the median time from ICU admission to randomisation was at least 20 h, lactate levels were mostly <2 mmol/l and $ScvO_2$ >65%. However, this study again strongly suggests that even with leucoreduced blood, there is no benefit to a liberal transfusion strategy.The FOCUS trial was probably the only RCT in the perioperative period and enrolled patients at high risk of ischemic cardiovascular events.[15] Patients with Hb <10 g/dl after hip-fracture surgery were randomised to a liberal transfusion strategy (Hb target of 10 g/dl) or a restrictive transfusion strategy (symptoms of anaemia or at physician discretion for a Hb level of <8 g/dl).

There was no difference in mortality, complications or inability to walk across the room without human assistance on 60-day follow-up between the two groups. There was no increase in complications, contrary to the results of several observational studies. Finally, there was no difference in the incidence of myocardial ischaemia between the groups, suggesting that a Hb target of 8 g/dl was safe in patients with cardiovascular disease or risk factors.There is only one recent RCT performed in patients with acute bleeding. This trial, performed in patients with acute gastrointestinal bleeding, found that a restrictive strategy (PRBCT when Hb <7 g/dl) resulted in greater survival and fewer complications at 6 weeks compared to a liberal transfusion strategy (PRBCT when Hb <10 g/dl).[16] What are the implications of these studies for anaesthesiologists managing the bleeding patient in the OR? It is difficult to determine when a particular Hb level has been reached during ongoing bleeding during surgery. It requires that frequent Hb estimations are made by point-of-care testing to determine when transfusion should be initiated. Severe anaemia could result from overenthusiastic attempts at conserving blood, or if the Hb level is estimated too late and transfusion is not initiated in time. Perhaps continuous Hb monitoring using pulse oximetry might help make decision-making. Two commercial pulse oximeters measure the total Hb. While their accuracy for a single reading is not adequate to determine the Hb concentration, they can be used to determine the trend of Hb values during acute haemorrhage.[17] The trend can then be used to guide when a point-of-care test should be performed. As this technology is further refined, it will help in determining not only when the Hb level should be tested, but also in guiding blood transfusion. Till then, assessment of ongoing blood losses, haemodynamic status and the anaesthesiologists experience will continue to guide Hb testing as well as blood transfusion in bleeding patients. The bottom line appears to be that liberal transfusion using higher Hb thresholds and targets should be avoided. Hb targets of 7–9 g/dl are good enough! However, patients should be monitored to ensure that tissue perfusion is not impaired.Restrictive transfusion is not an end in itself but should be part of an overall patient blood management plan. This includes the diagnosis of the cause and correction of pre-operative anaemia, as anaemia is not harmless. This may mean delaying surgery where possible. It is not appropriate to transfuse blood to merely make the patient 'fit for surgery' early. Similarly, operating on a patient with a low Hb level increases the chance of receiving an intraoperative transfusion. The newer intravenous iron carboxy-maltose preparations are safe and allow for rapid infusion and correction of anaemia.[18] Efforts to conserve blood during surgery, including autologous blood transfusion, surgical techniques to minimise blood loss and restrictive transfusion strategies should all form part of the patient blood management plan.[19] Finally, transfusions and outcomes must be audited to make sure that the current best practices are followed, and to take corrective action when problems are discovered.

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