Risks of perioperative blood transfusions

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Abstract

It has been estimated that up to 40% of blood transfusions are given to surgical patients. Despite transfusion being safer than it ever has been, it still poses significant risks. These can be enhanced in the perioperative period where identifying complications can also be more challenging. This article outlines the risks associated with perioperative transfusions and discusses the current recommendations for transfusion and use of alternatives to blood transfusion.

Keywords Blood; perioperative; transfusion

Royal College of Anaesthetists CPD Matrix: 2A05.

Blood transfusions can be life saving, but despite ever increasing safety, transfusions still pose significant risks. In 2017, 3230 events were reported to the UK Serious Hazards of Transfusion (SHOT). The haemovigilance group's annual report noted 1671 incidents, 442 pathological reactions and 21 deaths attributable to blood transfusion.[1] It is therefore essential that unnecessary transfusions are minimized and that clinicians are highly vigilant for signs of transfusions reactions.

Serious complications of allogeneic blood transfusion are outlined in Table 1 and are discussed in more detail below. Identifying adverse reactions can be more challenging in the perioperative setting, as their presentation is often non-specific and can initially mimic other conditions, such as haemorrhage. All adverse reactions attributable to transfusions should be reported using existing local clinical governance systems.

SHOT was established in 1996 as a voluntary haemovigilance system for collating data relating to adverse events affecting recipients. The EU Blood Safety and Quality Directive 2005/61/EC legally mandated haemovigilance for hospital blood banks and blood establishments; in the UK this is facilitated through the MHRA (Medicines and Healthcare products Regulatory Agency) using the SABRE reporting system (Serious Adverse Blood reactions and Events). The transfusion of ABO incompatible blood is considered to be a never event.[2]

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Learning objectives

After reading this article, you should be able to:

- describe the risks associated with perioperative transfusions
- outline the indications for a blood transfusion including the current transfusion threshold
- discuss the alternatives and adjuncts to blood transfusion

Antibody-mediated transfusion reactions

A summary of all types of antibody-mediated reactions are found in Table 2. The most serious of these are the haemolytic transfusion reactions. These result from interactions between antibodies in the recipient's plasma and surface antigens on donor red cells. There are numerous red cell antigens but they differ in their potential for immunization resulting in a spectrum of haemolytic reactions (Figure 1).

The most serious haemolytic reactions are caused by ABO-incompatible red cell transfusions and are associated with major morbidity and mortality, 30% and 5–10%, respectively.[3] They are predominantly caused by human error.[1] Recent estimates suggest that 1:2000 samples received by the laboratory are labelled with the wrong patient's information (wrong blood in tube).[4] If an acute haemolytic reaction is suspected, the blood transfusion should be stopped with supportive care and temperature monitoring instituted. Investigations should be sent to the laboratory, including full blood count, urea and electrolytes, liver function tests, lactate dehydrogenase, direct antiglobulin test and a repeat group and screen sample. The implicated unit should also be returned to the laboratory. The transfusion laboratory must be informed immediately as another patient may be at risk of receiving the wrong blood if a sampling or selection error has occurred.

Transfusion-associated circulatory overload (TACO)

TACO is defined as acute or worsening pulmonary oedema within 6 hours of transfusion. Management involves stopping the transfusion and administering oxygen and diuretics/nitrates as appropriate.

This preventable complication of transfusion was the commonest cause of transfusion-related major morbidity and mortality reported to SHOT in 2017.[1]

The SHOT report recommended a pre-transfusion risk assessment for transfusion associated circulatory overload assessment whenever possible in 2016 and 2017.[1] TACO is much more common in patients who weigh less than 50 kg or those with a previous history of fluid overload secondary to renal or cardiac disease. Weight-adjusted dosing should be used to guide the volume of transfusion administered (4 ml/kg of red cells will produce a Hb rise of approximately 10 g/l). Haemodynamically stable patients should be clinically reassessed and have their haemoglobin levels checked following each unit of blood with regard to effectiveness of transfusion and side effects.[5] A restrictive post transfusion target of 70–90 g/l will minimize total volume transfused.[5]

Complications of blood transfusions

Acute (within 24 hours)	Early (within 2 weeks)	Late (after 2 weeks)
Acute haemolytic reactions	Delayed haemolytic reactions	Transmission of infection
Allergic reactions	Post-transfusion purpura	Transfusion-associated graft-versus-host disease
Bacterial contamination of blood unit	Transfusion induced immunomodulation	Transfusional iron overload
Febrile non-haemolytic reactions		Alloimmunization
Transfusion-related acute lung injury		Transfusion induced immunomodulation
Transfusion-associated circulatory overload		
Delays in transfusion leading to under resuscitation		

Table 1

Transfusion-related acute lung injury (TRALI)

TRALI is characterized by acute respiratory distress within six hours of transfusion. Cases commonly present with acute dyspnoea, hypoxia, fever and hypotension. Bilateral pulmonary infiltration is seen on the chest X-ray (CXR). Treatment is supportive and ventilatory support is often required. Most cases recover within 72 hours, predominantly without long-term consequences. TRALI may be misdiagnosed as cardiogenic pulmonary oedema and treatment with diuretics may worsen outcomes.

The majority of cases of TRALI are caused by antibodies in the donor blood reacting against human leucocyte antigens (HLA) and human neutrophil antigens (HNA) in the recipient. This results in damaged pulmonary endothelial cells due to sequestration of the inflammatory cells in the lungs, causing capillary leak into the alveolar spaces (non-cardiogenic pulmonary oedema). Patients with raised levels of pro-inflammatory cytokines, such as during the perioperative period, are more susceptible. In suspected cases of TRALI the donor unit should be investigated for the presence of HLA and HNA antibodies.

The incidence of TRALI is approximately 1 in 150, 000 units transfused, which is a significant reduction since routine red cell leucodepletion (removal of majority of white cells) was introduced.[1] It is more common with plasma-rich blood components.

Transfusion-associated dyspnoea (TAD)

A relatively new term, transfusion associated dyspnoea (TAD) has been used to describe respiratory distress temporally associated with transfusion which does not meet the diagnostic criteria for TACO, TRALI or allergic reaction.

Transfusion transmitted infections

Bacterial

Bacterial contamination of blood components is a rare complication but can result in septic shock with high mortality rates (25% mortality since 1996 in UK).[1] Contamination commonly arises from the donor arm during venepuncture and proliferates during storage. There were no reported incidents of bacterial infection in 2017 in the UK following routine introduction of bacterial screening of units.[1]

Cases typically present shortly after commencing the transfusion with pyrexia (usually >2°C above baseline), rigors and haemodynamic compromise. Blood cultures need to be obtained and immediate administration of resuscitative measures including broad-spectrum intravenous antibiotics (covering both gram-positive and gram-negative pathogens) is essential. All implicated units should be sealed and returned to the transfusion laboratory. The blood product manufacturer will promptly withdraw all other components from the original donor to reduce the risk of further occurrences.

Viral

The risk of transfusion-related viral infections is now minimal within the UK following the introduction of routine screening and donor selection. Currently all donor blood is routinely tested for hepatitis B, hepatitis C, hepatitis E, human immunodeficiency virus (HIV), and human T-cell lymphotrophic virus (HTLV), and the bacterium *Treponema pallidum (syphilis)*.[3,6] If screening occurs in the 'window period' before there is a detectable antibody response in the donor, there is a risk of infectious products entering the blood supply. Emerging viruses likely to be transmitted by transfusion include zika virus and West Nile virus. Donors with potential exposure to these viruses are deferred from donating.

Cytomegalovirus (CMV) can be transmitted by transfusion but rarely has any clinical implications in the general population. However, it can be life threatening in fetuses, neonates and immunocompromised individuals. Routine leucodepletion has significantly reduced the risk of transfusion-related CMV and the only groups that currently require CMV negative products are fetuses (intra-uterine transfusions), neonates and pregnant women.[7]

Prions

Variant Creutzfeldt-Jakob disease (vCJD) was identified in the UK in 1996 and four cases of transfusion-transmitted vCJD have been identified. Various measures have been instigated to minimize this risk, including leucodepletion of all blood products, importation of all plasma for fractionated blood products and importation of FFP for all transfusion recipients born after 1st January 1996 when dietary transmission of vCJD is assumed to have ceased.

Transfusion-related immunomodulation (TRIM)

The immunomodulatory effects of blood transfusions have been appreciated for a number of years. Indeed in the pre-immunosuppressant era of renal transplantation allograft rejection was reduced in those who received transfusions.

Antibody-mediated transfusion reactions

Reaction	Description	Antibody	Haemolysis	Frequency	Timing	Clinical features	Management
Acute haemolytic reactions	Transfusion of ABO incompatible blood resulting in DIC, haemoglobinuria and acute renal failure	IgM	Intravascular Haemolysis of transfused and recipient red cells	1:180,000	Immediately after transfusion of 5 ml red cells	DIC, Acute kidney injury, haemoglobinuria, shock	Stop transfusion, notify laboratory immediately. Supportive measures including dialysis, inotropes
Delayed haemolytic reactions	Transfusion of red cells expressing antigens to which the donor has pre formed antibodies (commonly RH, Kidd)	IgG	Extravascular destruction of transfused antigen positive cells only	1:40,000	24 hours to 10 days following transfusion	Falling Hb, jaundice, rarely haemoglobinuria	Supportive management
Allergic reactions	Sensitivity to donor plasma proteins	IgE	Non-haemolytic	1:100	Usually during or immediately following transfusion	Pruritis, urticaria	Antihistamines
Anaphylaxis	Anaphylaxis, usually in IgA deficient individuals who have anti IgA in their plasma.	IgA	Non-haemolytic	1:40,000	Usually during or immediately following transfusion		Management of anaphylaxis as per UK resuscitation council guidelines.
Febrile non-haemolytic transfusion reactions	Pyrexia ($<38^{\circ}$C but $>2^{\circ}$C above baseline)	Cytokine accumulation during cell storage	Non-haemolytic	1:100	During transfusion	Pyrexia, chills, myalgia	Slow or stop transfusion, antipyretics

Table 2

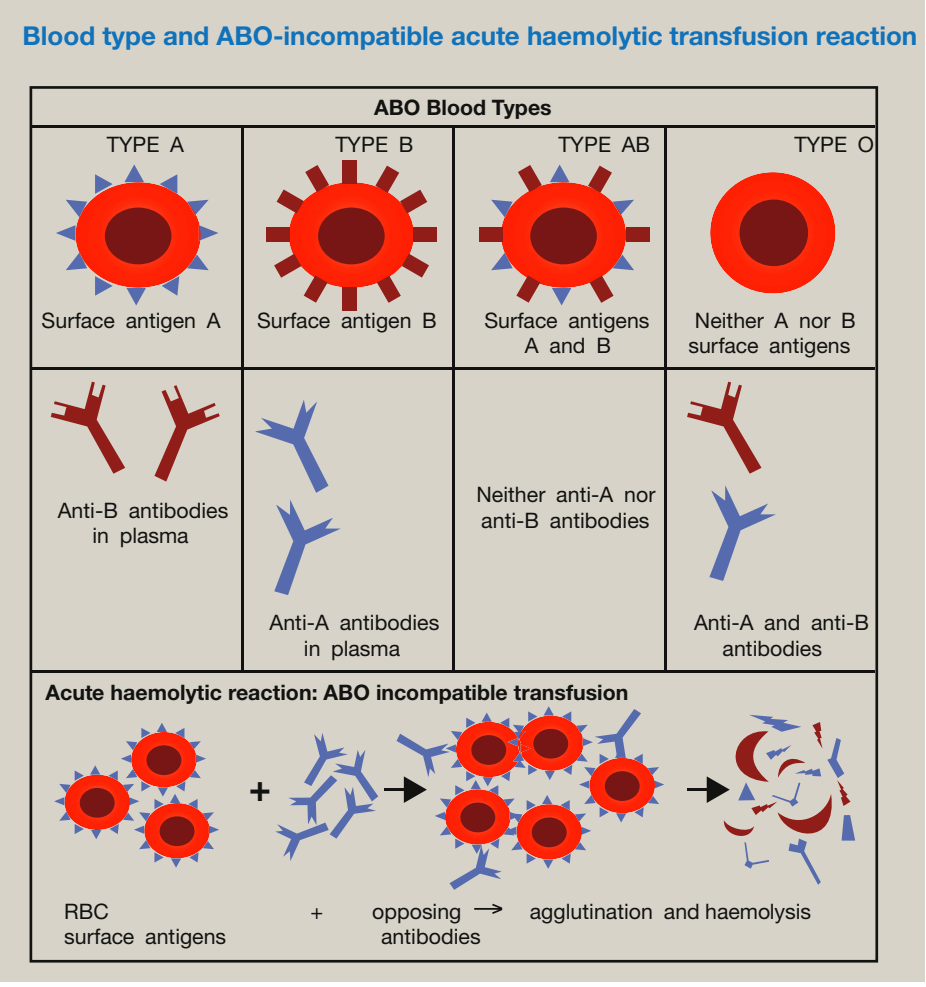

Figure 1

The mechanisms of TRIM are multifactorial. Contributory factors are likely to include immunosuppressive effects such as suppression of cytotoxic cells/monocyte activity and release of prostaglandins together with pro-inflammatory factors including cytokine production (Th1 and Th2 type cytokines, IL-6, etc).[8]

In the perioperative setting it has been speculated that this immunomodulatory effect increases the risk of postoperative infections[8] and cancer recurrence rates after curative resections.[9] However, this remains controversial as the circumstances under which patients require perioperative transfusions are likely to significantly impact on these complications. The potential confounding variables include type of malignancy, resectability, duration and type of anaesthesia, blood loss and perioperative stress response.

Massive blood transfusion

Massive transfusion is defined as replacement of a patient's total blood volume in <24 hours or replacement of 50% of total blood volume within 3 hours.[2] There are specific risks associated with massive transfusion, in addition to the potential complications already mentioned.

Transfusion of large volumes of red cells can lead to dilutional coagulopathy as packed red cells do not contain platelets or coagulation factors. Expectant replacement of coagulation factors and platelets with FFP, cryoprecipitate and platelets is essential. Coagulation is also impaired by hypothermia, acidaemia and hypocalcaemia which are also associated with massive transfusion.

Full guidance on management of massive haemorrhage is beyond the scope of this article.

The use of perioperative blood transfusions

Definitions for a restrictive versus liberal strategy for blood transfusion vary in the literature but the general consensus is supportive of a restrictive approach using a transfusion threshold of Hb $\leq$70–80 g/l or haematocrit $\leq$25% in haemodynamically stable, non-bleeding patients.[1,10] However, a more liberal approach in the more elderly population might produce better 30 and 90 day mortality outcomes in surgical patients.[11]

The NICE guideline NG24, published in 2015, suggested a transfusion threshold of 70 g/l increasing to 80 g/l in patients with acute coronary syndrome.[5] These values should provoke consideration of a transfusion but the decision to transfuse should be based on the patients' clinical condition and not the Hb level alone. Patients who are not actively bleeding should be

Summary of methods to reduce transfusion in surgical patients

Preoperative optimization	• Identify if anaemic and investigate and treat in a timely manner prior to surgery • Identify if at increased risk of bleeding (personal history, coagulation screen), discontinue anticoagulant or antiplatelet drugs if possible
Minimizing blood loss at surgery	• Blood-sparing surgical and anaesthetic techniques should be used • Antifibrinolytic drugs, tissue sealants and intraoperative cell salvage procedures should be used when appropriate
Avoiding unnecessary transfusion after surgery	• Use a restrictive transfusion threshold if clinically appropriate • Minimise blood loss from blood tests • Use iron and other stimulates to red cell production as needed

Table 3

transfused with a single unit of red cells and then reassessed prior to further transfusions being administered.

Delayed transfusion, or undertransfusion, are now also recognized as emerging complications of blood transfusion. In 2017 SHOT reported that 6 deaths and 1 case of major morbidity were secondary to this.[1]

Adjuncts and alternatives to red cell transfusions

In recognition of the above guidance along with preoperative correction of anaemia, the use of alternatives to blood transfusions and developments of blood-sparing surgical techniques, surgical blood usage has decreased by more than 20% since 2000. However, 15–50% of surgical red cell transfusions could be avoided, in a range of surgical procedures, and there is considerable variation in transfusion practice with fourfold to fivefold variability in the use of blood for the same operations.[3,12] Patient blood management programmes should be utilized to reduce the need for transfusion and for the greatest impact should be instigated at the beginning of the patient pathway which is often in primary care (Table 3). ◆

REFERENCES

1 Serious Hazards of Transfusion (SHOT). Annual SHOT report, 2017.

2 Never Events Policy and Framework. NHS improvements. Jan 2018, https://improvement.nhs.uk/documents/2265/revised_never_events_policy_and_framework_final.pdf (accessed 29 October 2018).

3 United Kingdom Blood Services. Handbook of transfusion medicine. 5th Edition. TSO, 2013.

4 Milkens C, Berryman J, Cantwell C, et al. Guidelines for pretransfusion compatibility procedures in blood transfusion laboratories. British Committee for Standards in Haematology. *Transfus Med* 2012; **23:** 3–35. and 2017 addendum.

5 NICE guidelines NG24 Blood transfusion, 2015.

6 Recommendations from the expert advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) on measures to protect patients from acquiring hepatitis E virus via transfusion or transplantation. http://hospital.blood.co.uk/media/28794/sabto-recommendations-nov-2016.pdf. (Accessed 29 Oct 2018).

7 SABTO (advisory committee on the safety of blood, tissues and organs. Report of cytomegalovirus steering group). 2011, https://www.gov.uk/government/uploads/system/uploadas/attachment_data/file/215126/dh_132966.pdf (accessed 27 June 2015).

8 Cata JP, Wang H, Gottumukka V, et al. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. *Br J Anaesth* 2013; **110:** 690–701.

9 Wu HL. The impact of blood transfusion on recurrence and mortality following colorectal cancer resection. A propensity score analysis of 4030 patients. *Nat Sci Rep* 2018; **8:** 13345.

10 Carson JL, Terrin ML, Noveck H, et al. Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair. *N Engl J Med* 2011; **365:** 2453–62.

11 Simon GI, Craswell A, Tom O, et al. Outcomes of restrictive versus liberal transfusion strategies in older adults from 9 randomised controlled trials: a systematic review and a meta analysis. *Lancet Haematol* 2017; **4:** e465–74.

12 Wells AW, Mounter PJ, Chapman CE, et al. Where does blood go? Prospective observational study of red cell transfusion in north England. *Br Med J* 2002; **325:** 803.