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Risks from, and appropriate use of, blood products

[1]LM Manson, [2]GC Preston
[1]Consultant, Blood Transfusion Centre, Royal Infirmary of Edinburgh; [2]Specialist Registrar, Department of Haematology, Western General Hospital, Edinburgh, UK

ABSTRACT Transfusion medicine has come a long way since the discovery of ABO blood groups by the Austrian scientist Karl Landsteiner in 1900. There has been continual improvement in the quality and safety of blood products available for clinical use, but, as with any treatment, there are associated risks. However, the UK national haemovigilance scheme has shown that most of those related to blood products are due to human error and could be prevented. Indeed, the most frequently reported category of transfusion reaction is 'incorrect blood component tranfused', which is nearly always due to an error of patient identification or prescribing, and can be fatal. Junior doctors are most often implicated, as they are delegated responsibility for blood-product prescribing and many mistakes arise due to lack of knowledge. While a lot of media emphasis has been put on the risk of viral and, more recently, prion transmission, transfusion-transmitted infections are very rare. In the UK there have only been four cases of confirmed variant Creutzfeldt-Jakob disease due to blood transfusion, and the risk of HIV transmission is approximately one per four million units transfused. Other problems, such as febrile, allergic and haemolytic reactions, are much more common. The use of red cells, platelets, fresh frozen plasma and cryoprecipitate requires understanding both of their content and of the clinical situations in which they are used. Doctors need to be aware of these issues in order to use blood products appropriately.

KEYWORDS Anaemia, blood products, transfusion

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Correspondence to ***GC Preston, Department of Haematology, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK***

tel. ***+44 (0)131 537 1000***
e-mail ***gavinpreston@nhs.net***

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INTRODUCTION

Blood products are a valuable and often life-saving treatment. In 2006, 2.1 million blood donations were made across England and Wales to meet demand. There is, however, the potential for great harm and even death if products are used inappropriately. Furthermore, most of the risks associated with blood transfusion are partly or completely avoidable. This article aims to inform clinicians how to avoid these risks and how to make appropriate use of blood products.

RISKS OF BLOOD TRANSFUSION

In the UK, there is a voluntary reporting scheme for clinical incidents involving blood transfusion. This is published annually as the *Serious Hazards of Transfusion* (SHOT) report. In 2006 there were four deaths as a direct result of blood transfusion, two of which were entirely preventable.

Cases of death directly due to clinical transfusion error

Case 1

A very sick premature infant was scheduled for surgery. The platelet count was 48 x 10^9/L. The drug chart stated '1 pool of platelets' but did not specify a volume. A junior doctor gave a telephone instruction to give '15 ml per kg'. The message was misheard as '50 ml per kg' and 300 ml of platelets were given over 30 minutes. The infant suffered a cardiac arrest and was transferred to paediatric intensive care where she died two days later.

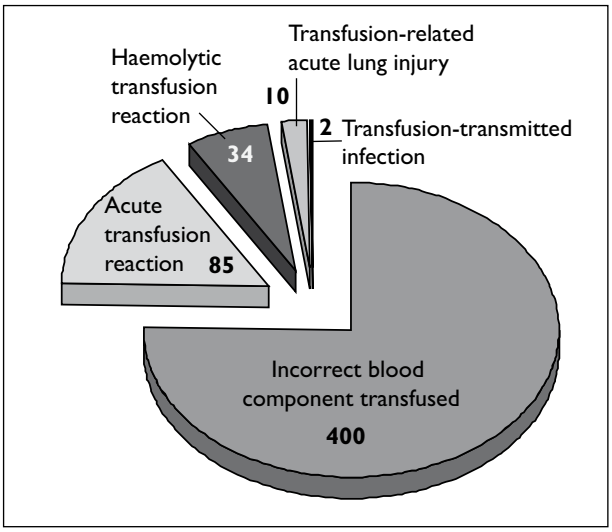

FIGURE 1 Adverse events from blood transfusion in the UK (2006 SHOT report data).

Case 2

An 80-year-old female patient had surgery for a fractured neck of femur. A post-operative haemoglobin (Hb) was reported as 39 g/L. The pre-operative Hb was 95 g/L, and

TABLE 1 Some common indications for cytomegalovirus-negative and irradiated components

Indications for CMV-antibody-negative components CMV	CMV-antibody-negative pregnant women[1]
To prevent CMV disease in the recipient	CMV-antibody-negative recipients of autologous or allogeneic stem cell transplant[2]
	CMV-antibody-negative recipients of solid organ transplants
	Intrauterine transfusions
	Patients with HIV
Indications for gamma-irradiated components	Patients who have received purine analogues (e.g. fludarabine)
To prevent transfusion-associated graft versus host disease in the recipient	All recipients of haematopoietic stem cell transplants
	Transfusions to stem cell donors during the harvest period
	Hodgkin's disease (all stages of disease)
	HLA-selected platelets
	Intrauterine transfusion (IUT)
	Neonatal transfusion if previous IUT[1]
	Congenital immunodeficiency of cell-mediated immunity (e.g. severe combined immunodeficiency)
	Transfusions from first- or second-degree relatives

[1]CMV negative and irradiated products are often issued by blood banks as standard for all pregnant women and neonates as a 'catch all' safety net.
[2]Most haematology units have a policy for giving CMV-negative units to all CMV-antibody-negative patients who might in the future have a stem cell transplant.

there had been little intraoperative blood loss. Eight hours following surgery the patient was less well, hypotensive and tachycardic. A junior doctor prescribed six units of red cells, all of which were administered over a 16-hour period. The post-transfusion Hb was 182 g/L and the patient subsequently died from cardiac failure. It was later realised that the immediate post-operative blood sample had been diluted by an intravenous infusion.

The majority of errors reported to SHOT come under the 'incorrect blood component transfused' category (see Figure 1). This includes patient identification errors and incorrect prescribing. Human errors in correct patient identification, either when taking the blood sample for cross-matching or when commencing transfusion, can result in fatal incidents. Such errors are the most common cause of a patient with blood group O being transfused group A red cells. This will cause an acute haemolytic reaction due to the naturally occurring anti-A antibodies in the group O recipient. Such ABO incompatibility reactions have a high mortality rate.

Junior doctors are most often involved in making transfusion errors, since they are delegated the responsibility for most clinical transfusions. Common problems are:

- Over-reliance on laboratory results
- Failure to review results in the context of previous results or to relate to the clinical condition of the patient
- Transfusion of patients with haemoglobin above the transfusion trigger
- Lack of awareness of the need for cytomegalovirus (CMV)-negative or irradiated products (see Table 1)
- Failure to recognise the symptoms and signs of a transfusion reaction
- Lack of knowledge about the contents, volume and use of products

There are, of course, complications that may arise from the transfusion of appropriately selected blood products (see Table 2). Febrile non-haemolytic transfusion reactions are most common, occurring in up to 5% of red cell transfusions. If symptoms or signs of a reaction develop, the transfusion should be stopped and the transfusion laboratory informed. An appropriate sample for red cell grouping and antibody screening ('group and save') should be sent along with the remains of the blood product and a transfusion reaction form to allow full investigation. It is now a legal requirement that all serious transfusion reactions are reported to the Medicines and Healthcare Devices Regulatory Authority by blood transfusion services.

RED CELLS

Whole blood is very rarely used in current practice. Red cell concentrate contains very little white cells and plasma. This is particularly important to remember in a major haemorrhage situation, as other blood products will be needed in addition to red cells. One unit of red cells (approximately 250–350 ml) will raise the

TABLE 2 Adverse events related to blood products

Adverse event	Symptoms and signs	Specific management
Immediate/early		
Febrile non-haemolytic transfusion reaction	Fever, tachycardia	Paracetamol
Acute haemolytic transfusion reaction	Fever, loin pain, dyspnoea, pain at infusion site, jaundice, haemoglobinuria, disseminated intravascular coagulation, renal failure	Maintain renal perfusion, transfer to high-dependency setting
Allergic reactions	Urticaria, angioedema, wheeze Anaphylaxis may occur	Chlorpheniramine, hydrocortisone, salbutamol, adrenaline
Transfusion-associated circulatory volume overload	Signs of cardiac failure	Diuretics
Transfusion-associated acute lung injury (TRALI)	Acute respiratory distress syndrome within six hours of transfusion	Respiratory support
Bacterial contamination	Signs of sepsis that develop during or shortly after transfusion	Blood cultures, antibiotics
Late		
Delayed haemolytic transfusion reaction	Fall in haemoglobin 5–10 days after transfusion	Repeat group and save Supportive
Transfusion-associated graft versus host disease	Fever, skin rash and gastrointestinal symptoms developing 4–30 days after transfusion	Steroids Mortality approaches 100%
Transfusion-transmitted infection	Development of disease caused by viral, prion or other agent	Recall of products from donor and tracing of other recipients
Post-transfusion purpura	Severe thrombocytopenia 5–10 days after transfusion	Intravenous immunoglobulin
Alloimmunisation (red cell, platelet and HLA antibody formation)	Haemolytic transfusion reactions, haemolytic disease of the newborn, refractoriness to platelet transfusions	Give products negative for the relevant antigen
Iron overload (patients receiving regular transfusion support)	Cardiomyopathy, arthritis, hepatic and endocrine dysfunction	Iron chelation

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haemoglobin concentration by 10 g/L in an average adult. The paediatric dose is 15 ml/kg.

The indications for receiving red cells are in essence simple:

- Haemorrhage
- Anaemia (where there is no other correctable cause)

It is important to think about the whole clinical picture, not just the haemoglobin, when considering transfusion. In the past there has been too much reliance on an arbitrary haemoglobin threshold to determine when to transfuse red cells. This approach results in both over- and under-transfusion of red cells to different groups.

Factors to consider prior to red cell transfusion

- Ability to tolerate anaemia (cardiac and respiratory function)
- Symptoms of anaemia
- Predicted trajectory of haemoglobin concentration
- Absolute haemoglobin concentration
- Risks of red cell transfusion
- Alternative treatments for anaemia
- Patient's wishes with regard to blood products

In haemorrhage, the priority is the maintenance of adequate circulatory volume. Studies on fit and healthy volunteers that induced acute isovolaemic anaemia to a haemoglobin concentration of 50 g/L produced no signs of inadequate tissue oxygenation. Loss of 30–40% of circulatory volume (up to 2 L for an average adult) can be safely treated with crystalloid alone.

In anaemia it is crucial to establish the cause. Iron deficiency, megaloblastic anaemia and autoimmune haemolytic anaemia can often be treated without any need for transfusion. Symptoms of anaemia are a helpful guide both as an indication for transfusion and to gauge response. Angina or symptoms of cardiac failure related to anaemia are important indicators for red cell trans-fusion, even if the anaemia is relatively mild. Isolated fatigue as a symptom of anaemia is unlikely to improve with red cell transfusion. Patients with reduced cardiorespiratory reserve tolerate anaemia less well and are more likely to require red cell transfusion in all situations.

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TABLE 3 Recommended platelet count for medical/surgical procedures in adults

Type of procedure	Recommended minimum platelet count (x 10^9/L)
Dental surgery (e.g. tooth extraction)	30
Lumbar puncture, epidural anaesthesia, gastroscopy, arterial and central venous line insertion, liver biopsy, transbronchial biopsy, laparotomy	50
Surgery to critical areas, e.g. brain or eyes	100

Alternatives to allogeneic red cells

There are a number of strategies that can be employed to reduce the need for allogeneic red cell use. In surgery, there has been successful use of intraoperative red cell salvage for both elective and emergency procedures. This has seen a dramatic fall in the use of allogeneic red cells, especially in cardiothoracic and vascular cases. Autologous red cell donation pre-operatively has specific indications and limited availability. Much research has gone into synthetic oxygen transport molecules, but none has shown adequate safety and efficacy for regular clinical use. Recombinant erythropoietin is useful in certain situations, particularly in renal disease.

PLATELETS

There are at least 240 x 10^9 platelets in an adult therapeutic dose in a volume between 200–300 ml. This generally raises the platelet count by 20–40 x 10^9/L. In most situations one unit of platelets is adequate, but more may be needed in life-threatening haemorrhage (see Table 3). The recommended paediatric dose is 15 ml/kg. The indications for platelets are:

- Treatment of bleeding associated with thrombocytopenia or platelet function defect
- Prophylaxis of bleeding associated with thrombocytopenia or platelet function defect
- Prior to or during a medical or surgical procedure
- Where the risk of spontaneous haemorrhage is high:
  - platelet count <10 x 10^9/L in well patient
  - platelet count <20 x 10^9/L in febrile/septic patient

In some conditions with thrombocytopenia, platelet transfusions are relatively contraindicated. In these situations, such as heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenia purpura (TTP), platelet transfusions can cause potentially fatal acute thrombosis.

FRESH-FROZEN PLASMA

All of the normal plasma proteins are found in fresh-frozen plasma (FFP), including coagulation factors and fibrinogen. The therapeutic dose for children and adults is 10–15 ml/kg. This approaches 1 L for most adults and the total volume to be transfused must be considered. The indications for FFP are:

- Treatment of bleeding associated with coagulation factor deficiency
- Prophylaxis of bleeding associated with a coagulation factor deficiency prior to or during a medical/surgical procedure
- Plasma exchange (particularly TTP)

The most common indications are in patients with liver disease and major haemorrhage. Use in clinical practice is guided by the activated partial thromboplastin time (aPTT), prothrombin time (PT) and fibrinogen. If the fibrinogen is very low (<1.0 g/L), cryoprecipitate provides more effective replacement than FFP. It is inappropriate to give FFP simply to correct prolonged clotting times, as found, for example, in liver disease or disseminated intravascular coagulation. This is because the bleeding risk in such situations is usually small and the haemostatic effect of FFP lasts only a few hours. It is also important to remember that the aPTT and PT may be prolonged for a multitude of reasons other than coagulation factor deficiency, the most common being heparin contamination of the sample and a phospholipid-dependent inhibitor (e.g. lupus anticoagulant).

In bleeding situations the most important endpoint is clinical haemostasis. For prophylaxis it is recommended that the patient/control ratio for both the aPTT and PT is less than 1.5 and the fibrinogen is maintained above 1.0 g/L. As with platelets, many surgeons will want these figures to be as close to normal as possible prior to surgery in critical areas. There is, however, little useful evidence to support clinical practice.

CONCLUSION

Discussion of appropriate indications and risks of any treatment would be incomplete without mentioning consent. Informed consent is often overlooked in the use of blood products. It is good medical practice to document such a discussion in the patient's medical notes; this should include the likely risks and benefits associated with transfusion, and available alternatives. This should also apply to discussion regarding elective surgery or chemotherapy regimens where there is likely to be a need for blood product support. As such, doctors have a duty to be aware of issues relevant to blood transfusion.

KEY POINTS

- In the UK, more than 2.5 million blood donations are required each year to support the clinical use of blood products. Appropriate use of this resource benefits patients and is frequently life-saving.
- Most of the risks from transfusion arise as a consequence of human error.
- Junior doctors are usually delegated the task of prescribing blood products and often have inadequate knowledge to perform this safely.
- The use of blood products is a clinical decision, which should take into account all relevant patient factors. Over-reliance on laboratory results leads to errors.
- All serious transfusion reactions should be managed in collaboration with haematology medical staff and the hospital blood bank. It is a legal requirement for these to be reported.

FURTHER READING

- British Committee for Standards in Haematology. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; 113:24–31.
- British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; 122:10–23.
- British Committee for Standards in Haematology. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryo-supernatant. *Br J Haematol* 2004; 126:11–28.

All of the above guidelines are available online at: http://www.bcshguidelines.com. See also http://www.learnbloodtransfusion.org.uk

- McClelland DBL. *Handbook of transfusion medicine*. 4th edition. London: The Stationery Office; 2007.
- *Serious Hazards of Transfusion* reports available from: http://www.shotuk.org/home.htm

Originally published as part of the Haematology module in the RCPE Online Continuing Medical Education Programme. Online CME, including self-asessment MCQs, is available to Fellows and Members at: http://www.rcpe.ac.uk

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