



Blood Transfusion and the Anaesthetist

Blood Component Therapy

2005

Published by
The Association of Anaesthetists of Great Britain and Ireland,
21 Portland Place, London W1B 1PY
Telephone: 020 7631 1650, Fax: 020 7631 4352
E-mail: info@aagbi.org Website: www.aagbi.org

December 2005

MEMBERSHIP OF THE WORKING PARTY

Dr D Thomas	Chairman
Dr D J Wilkinson	Vice President
Dr S K Greenwell	Vice President
Dr R W Buckland	Past Honorary Secretary
Dr R Verma	Council Member
Dr I H Wilson	Council Member
Dr C Connolly	GAT Representative
Dr J Isaac	Royal College of Anaesthetists Representative
Prof M Murphy	BSH Representative
Dr D O'Shaughnessy	DOH Representative
Dr L Williamson	BBTS Representative

Ex Officio

Prof M Harmer	President
Dr P G M Wallace	Past President
Dr R J S Birks	Honorary Treasurer
Prof W A Chambers	Honorary Secretary
Dr D K Whitaker	President Elect
Dr D Bogod	Editor-in-Chief, <i>Anaesthesia</i>
Dr D E Dickson	Honorary Membership Secretary

Contents

- Section 1. Recommendations for blood component use
- Section 2. Introduction
- Section 3. Component production
- Section 4. Component use
- Section 5. Co-morbidity predisposing to increased bleeding
- Section 6. Drugs that increase blood loss
- Section 7. Drugs that decrease blood loss
- References and useful web addresses
- Appendices

SECTION 1. RECOMMENDATIONS

- Assessment of haemostasis in the pre-operative period can reduce peri-operative blood loss.
- Red cell concentrates do not contain coagulation factors or platelets, so the use of blood components (fresh frozen plasma [FFP] and platelets) needs to be considered early in managing a patient with massive haemorrhage.
- Emergency use of blood components requires assessment of haemostasis in advance of administration even if empirical use is necessary.
- The use of near-patient testing devices can improve decision-making on the use of blood components.
- Thawed FFP can be stored at 4°C and can be used safely within 24 hours.
- Thawed FFP kept at room temperature must be infused within 4 hours.
- Vitamin K +/- prothrombin complex concentrate (PCC) is recommended to reverse warfarin. FFP is indicated when there is severe bleeding or when PCC is unavailable.
- Platelet transfusion in the bleeding patient, or a patient requiring urgent surgery, is indicated at a platelet count $<50 \times 10^9 \cdot l^{-1}$ but in stable non-bleeding patients in intensive care, a trigger of $10 \times 10^9 \cdot l^{-1}$ is acceptable.
- Component therapy should not be used to make regional anaesthesia possible if there are alternative anaesthetic methods available.

SECTION 2. INTRODUCTION

This booklet advises on the appropriate use of blood components other than red cells. This advice is required since red cell concentrates do not contain coagulation factors or platelets. The booklet also discusses pharmacological agents and their impact on coagulation and haemostasis.

The following information, when used in conjunction with the companion booklet 'The Anaesthetist and Blood Transfusion: Red Cell Transfusion', will provide guidance on best transfusion practice.

SECTION 3. COMPONENT PRODUCTION

All blood components used in the UK and Ireland since October 1999 have been leucodepleted in an attempt to decrease the potential risk from transfusion-transmitted variant Creutzfeldt-Jakob disease (vCJD).

The 99.99% (4-log reduction) removal of white blood cells means that there are still up to 10^{-6} white cells present in the blood supplied.

Albumin, anti-D and other fractionated blood products have been sourced from USA plasma since 1999.

All children born since 1st January 1996 (a time when risk from contaminated foods was removed) who require plasma receive FFP sourced from the USA to minimise vCJD transmission. This FFP is methylene-blue treated to minimise the risk of viral infection.

The decision that all FFP used in the UK should be imported and virally inactivated has not yet been taken. In Ireland, attempts have been made to ensure that virally inactivated product is available for all patients who require it but there have been ongoing difficulties with supply.

From August 2004, anyone who has, or is believed to have, received a blood transfusion in the UK since 1980 cannot donate blood.

SECTION 4. COMPONENT USE

The use of component therapy during the operative period will be required if

haemorrhage occurs to an extent that requires correction of coagulopathy or a low platelet count. This would normally be after a loss of at least one blood volume, or if unexpected bleeding occurs despite surgical control.

- Emergency use of blood components requires concurrent assessment of haemostasis.
- The availability of near-patient testing equipment can provide useful information to guide component therapy, e.g. thromboelastogram (TEG).
- The ongoing requirement for component therapy in the postoperative period will only be effective if all surgical causes of bleeding have been rectified.

Platelets

The greatest demand for platelet transfusion is for haemato-oncology patients. The risk of transmission of bacterial infection is high (1 in 12,000). The Serious Hazards of Transfusion (SHOT) scheme has shown that bacterial infection is a serious complication of the transfusion of platelets that have been stored for 3 days or more (20 cases in six years in the UK).

The reasons for this are:

- Bacteria can enter the pack from the donor skin at the time of collection.
- Platelets are stored in an oxygen permeable bag kept at 22°C. This helps preserve platelet function but may encourage bacterial growth.

The longer the platelets are kept prior to transfusion, the higher is the risk of bacteraemia.

There is a high incidence of transfusion-related acute lung injury (TRALI) associated with platelet transfusions. This is usually due to an interaction between leucocyte antibodies in donor plasma and the corresponding antigen in the patient. Blood Centres are working to minimise the incidence of TRALI by suspending donated pooled platelets in male plasma that seems to carry a lower risk. Apheresis platelets are currently sourced from both male and female donors.

Preparation:

Platelets for transfusion are collected in two ways: -

- From the pooled buffy coats of the whole blood donated by four donors to make one adult pack (suspended in male plasma)
- Individual donor apheresis (from a previously tested donor) can yield up to three adult packs.

Storage:

Platelets may be stored for up to 5 days on an agitator at 22°C.

Volume: usually 250-350ml.

Platelet count in pack: $> 2.4 \times 10^{11}$ per adult dose.

Platelets should be inspected prior to infusion. Packs must be rejected, or referred for further opinion, if there is any unexpected appearance such as discolouration or flocculation (i.e. large clumps of white debris).

Availability:

On-site storage of platelets will vary from one hospital to another and will depend upon demand and the distance from the nearest Blood Centre. Anaesthetists need to be aware of local arrangements and the normal time interval for obtaining platelets in an emergency. Local protocols may be developed through the Hospital Transfusion Team.

Indication for transfusion:

The appropriate use of platelet transfusion can reduce the volume of red blood cells transfused. When contemplating platelet transfusion, the quality of the endogenous platelets needs to be considered as well as the patient's platelet count.

In stable patients, a platelet count of $>10 \times 10^9 \cdot l^{-1}$ in the absence of active bleeding does not warrant platelet transfusion.

Invasive intervention in a patient with a platelet count $<50 \times 10^9 \cdot l^{-1}$, e.g. surgery, insertion of a chest drain, percutaneous tracheostomy or central venous line, will require a platelet transfusion to increase the platelet count to $>50 \times 10^9 \cdot l^{-1}$.

In the operating theatre in a patient who is actively bleeding, platelet transfusion is required to keep the platelet count $>50 \times 10^9 \cdot l^{-1}$.

Platelet transfusion should not be used to make regional anaesthesia possible if there are alternative anaesthetic methods available.

Dose:

Platelets are administered in adult bag equivalents. Each adult therapeutic dose can be expected to raise the platelet count by approximately $20 \times 10^9 \cdot l^{-1}$ in most adult patients.

Cost:

Approximately £200.00 per adult dose.

Fresh Frozen Plasma

The use of FFP has increased significantly in the past few years and there is concern about the appropriateness of its use. It is frequently used in cases of excessive bleeding or to prevent bleeding in those patients with abnormal coagulation. Administration needs to be guided by tests of haemostasis.

Preparation:

In the UK and Ireland, FFP is produced by centrifugation of whole blood from a previously tested donor and frozen to achieve factor VIII concentration $> 0.7 \text{ iu.ml}^{-1}$

Storage:

Collected plasma from donated packs or plasmapheresis and frozen to -30°C .

Frozen packs are brittle and need to be handled with care.

FFP can be thawed using a dry oven (10 minutes), microwave (2-3 minutes) or in a waterbath (20 minutes).

Thawed FFP is best used immediately but may be stored at 4°C and infused within 24 hours - provided it is kept at this temperature or returned to blood bank for storage within 30 minutes of being removed from a 4°C fridge or transport box.

Indications for transfusion:

FFP may be necessary as the empirical treatment of an acquired coagulopathy with prolonged INR/APTT in the absence of warfarin or heparin.

Dose:

The dose is 12-15 ml.kg⁻¹. In a 70-kg person, this is equivalent to three to four 300-ml packs of FFP.

Cost:

£30 for 300 ml.

All children born since 1st January 1996 who require plasma now receive imported methylene blue treated FFP. It may be decided to exclude all UK and Irish plasma from use and to import all plasma from abroad. This will inevitably increase the cost of a unit of FFP to over £100 per pack, i.e. £400 per four-pack dose.

Cryoprecipitate

This is the cryoglobulin fraction of plasma obtained by thawing a single donation of FFP at 4°C. There is no virally-inactivated preparation.

Preparation:

UK and Irish Blood Centres prepare cryoprecipitate in volumes of 20-40 ml.

Precipitable cryoproteins are rich in Factor VIII, von Willibrand Factor (VWF), factor XIII, fibronectin and fibrinogen. Packs contain at least 150-300 mg of fibrinogen and 70 iu of factor VIII.

Indication for transfusion:

In patients with an acquired coagulopathy related to haemorrhage, trauma or sepsis, cryoprecipitate is normally only used to correct a fibrinogen level of $<1 \text{ g.dl}^{-1}$ if further large volumes of FFP are not otherwise indicated. A dose of 10 packs may provide 1.5-3 g of fibrinogen compared with 1.5-4.5 g in three packs of FFP.

Dose:

It is issued by the hospital blood bank as 10 prepared units of cryoprecipitate (300-ml volumes). It may be pooled in one bag.

Cost:

One unit costs £33. A dose of 10 units costs £330.

SECTION 5. CO-MORBIDITY PREDISPOSING TO INCREASED BLEEDING

Liver disease

The patient with obstructive jaundice may be deficient in vitamin K dependent coagulation factors (II, VII, IX & X) and have a coagulopathy. This should be reversed before surgery with oral or parenteral vitamin K.

Patients with acute or chronic liver failure may have a more complex coagulopathy with decreased levels of most coagulation factors, and decreased platelet numbers and function.

Renal disease

The uraemic patient may have a prolonged bleeding time and abnormal platelet aggregation despite a normal platelet count. Dialysis should correct this and is the mainstay of treatment. Desmopressin (DDAVP) therapy, given intranasally or intravenously, will increase circulating von Willebrand factor levels and will improve platelet aggregation in these patients. In an emergency situation when bleeding is a problem, cryoprecipitate can be used to increase von Willebrand factor levels in the uraemic patient. It should be remembered that correction of anaemia will also help correct the prolonged bleeding time.

Congenital coagulopathies

Patients with inherited coagulation disorders, e.g. haemophilia, will require concentrated factor infusion to cover the peri-operative period. This should be managed with guidance from a haematologist.

SECTION 6. DRUGS THAT INCREASE BLOOD LOSS

Antiplatelet agents

An increasing number of patients take antiplatelet agents. Non-steroidal anti-inflammatory drugs, dipyridamole, aspirin and clopidogrel are all implicated in increased surgical blood loss. Ideally, these drugs should be stopped before surgery to allow platelet function to return to normal. The time required for platelet function to return to normal after cessation of anti-platelet agents varies.

- NSAIDs provide reversible inhibition of cyclo-oxygenase, and their antiplatelet effects are half-life dependent (usually hours).
- Dipyridamole has a short antiplatelet effect (hours).
- Aspirin and clopidogrel lead to irreversible inhibition of platelet aggregation for the life span of the platelet (~10 days).
- Clopidogrel causes platelet inhibition via a different mechanism to aspirin and, following coronary stenting, the two drugs are increasingly being prescribed together.

Clopidogrel is a pro-drug. The active metabolite circulates for approximately 18 hours after the most recent dose and permanently inhibits any platelets present during this time (whether endogenous or transfused). Platelet therapy during this time is unlikely to be helpful. If possible, emergency surgery is best delayed for at least 24 hours after the last dose of clopidogrel.

There is growing evidence that haemorrhagic risk is increased when aspirin and clopidogrel are taken concomitantly. These drugs need to be stopped for 7 days to be confident of adequate platelet function. However, due consideration must be given to the risks associated with stopping these drugs in surgical patients, particularly those with drug-eluting coronary artery stents.

Many patients presenting for emergency coronary revascularisation have had failed coronary stenting procedures. These patients have usually received aspirin and clopidogrel. Haemorrhage during the subsequent emergency surgery is a major problem. The combination of platelet transfusions and aprotinin therapy has been used to decrease blood loss.

Patients who have received clopidogrel within 7 days of the proposed date of surgery should, where possible, have their surgery postponed. If the surgery is a genuine emergency, platelets should be made available for transfusion, and use of aprotinin should be considered. Delaying for 24 hours after the last dose of clopidogrel will improve the response to platelet transfusion.

Anticoagulants

Patients taking warfarin who present with a surgical emergency should receive vitamin K (either orally or parenterally) if rapid reversal of their anticoagulation is required.

In the absence of severe bleeding, FFP should not be used for the reversal of warfarin anticoagulation. Prothrombin complex concentrate (PCC) may be required. This should be discussed with a haematologist as some PCCs do not contain factor VII and in severe bleeding, FFP and PCC may be required. .

Peri-operative management of warfarin anticoagulation

Low Risk

Patients with atrial fibrillation. Anticoagulation can be safely stopped 3 days before surgery

Intermediate Risk

Patients with a history of venous thrombo-embolism.

Either

- Give unfractionated heparin 5000 units three times a day until 2 hours before the operation. The same regimen should be administered after surgery until warfarin has been recommenced and the INR has returned to 2.5 for 2 days.

or

- Give low molecular weight heparin (LMWH) at a prophylactic dose until 12 hours before surgery. After surgery, it should be continued with warfarin until the INR is satisfactory.

It is recommended that the following doses be used as a daily dose: -

Bemiparin 3500 iu

Certoparin 3000 iu

Dalteparin 5000 iu

Enoxoparin 40 mg

Reviparin 1432 iu

Tinzaparin 3000 iu

High Risk

e.g. patients with mechanical heart valves.

Infusion of unfractionated heparin should be started when INR is <2.5 at a dose depending on APTT (often 24 000 per day) to achieve an APPT ratio of 2.5 - 3.5.

SECTION 7. DRUGS THAT DECREASE BLOOD LOSS

Antifibrinolytics

Antifibrinolytic drugs such as tranexamic acid and aprotinin have been used to reverse established fibrinolysis, in the setting of massive blood transfusion.

Prophylactic aprotinin therapy can decrease blood loss in major surgery (e.g. cardiac and liver transplant surgery), and may also offer anti-inflammatory properties.

Dose:

Varies by procedure.

Recombinant Factor VIIa

This drug has been used since 1996 to treat active bleeding, or as prophylaxis for surgery, in haemophiliacs who have inhibitors. More recently, it has been used in a variety of unlicensed indications, e.g. as a 'universal haemostatic agent' in cases of massive blood transfusion. The drug is expensive but may prove lifesaving in this setting, but only when attempts have already been made to correct surgical and haemostatic problems as described above.

Dose:

The most widely used dose is 90 $\mu\text{g.kg}^{-1}$.

REFERENCES AND USEFUL WEB ADDRESSES

Association of Anaesthetists Great Britain and Ireland (2001) Blood Transfusion and the Anaesthetist: red cell transfusion. Association of Anaesthetists of Great Britain and Ireland, London. www.aagbi.org

BCSH (2003) Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant. www.bcshguidelines.org

British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003; 122:10-23. www.bcshguidelines.org

Horlocker TT, Wedel JW, Benzon H, et al. Regional Anaesthesia in the anticoagulated patient: Defining the Risks (The second ASRA Consensus Conference on Neuroaxial Anesthesia and Anticoagulation). *Regional Anesthesia and Pain Medicine* 2003; 28: 172.

SHOT report (Serious Hazards of Transfusion) 2001-2002 ISBN 0 9532 789 5 6.

Stainsby D, MacLennan S, Hamilton PJ . Commentary. Management of massive blood loss: a template guideline. *British Journal of Anaesthesia* 2000; 85: 487

Cordery R, Royston R. Pharmacological Approaches In: A Manual of Blood Conservation. 2004 eds: Thomas D, Thompson J, Ridler B. tfm publishing Ltd. www.tfmPublishing.com

www.blood.co.uk

www.bbts.org.uk

www.aagbi.org

www.transfusionguidelines.org.uk

www.bcshguidelines.com

APPENDIX 1

Laboratory investigation in common bleeding disorders (from the Oxford Handbook of Anaesthesia)

Disorder	Platelet count	INR	APTT	TT	Fibrinogen	Other
Haemophilia A	Normal	Normal	↑	Normal	Normal	↓ VIII
Haemophilia B	Normal	Normal	↑	Normal	Normal	↓ IX
von Willebrand's	Normal (usually)	Normal	↑	Normal	Normal	↓ VIII, vWF ↑ bleeding time
Liver disease	Normal or ↓	↑	↑	Normal	Normal or ↓	↓ V
Vitamin K deficiency	Normal	↑	↑	Normal	Normal	↓ II, VII, IX, X
DIC	Normal or ↓	↑	↑	↑↑	Normal or ↓	↑ FDPs, d-dimers ↓ II, V, VIII
Massive transfusion	↓	↑	↑	Normal or ↑	Normal or ↓	Normal FDPs
Heparin (unfractionated)	Normal (rarely ↓)	Normal or ↑	↑↑	↑↑	Normal	↑ anti-Xa
Heparin (LMW)	Normal (rarely ↓)	Normal	Normal	Normal	Normal	↑ anti-Xa
Warfarin	Normal	↑↑	↑	Normal	Normal	↓ II, VII, IX, X
Lupus anticoagulant	Normal	Normal or ↑	↑↑	Normal	Normal	DRVVT +ve, cardiolipin antibody

APPENDIX 2

Acute Massive Blood Loss Template (from *British Journal of Anaesthesia* 2000; 85: 487)

Table1

Acute Massive Blood Loss - A Template guideline

GOAL	PROCEDURE	COMMENTS
<ul style="list-style-type: none"> Restore circulating volume 	<ul style="list-style-type: none"> Insert wide bore peripheral cannulae Give adequate volumes of warmed crystalloid, ?colloid, blood Aim to maintain normal BP and urine output >30ml/hr 	<ul style="list-style-type: none"> 14G or larger Monitor CVP Blood loss is often underestimated Refer to Advanced Trauma Life Support guidelines Keep patient warm
<ul style="list-style-type: none"> Contact key personnel 	<ul style="list-style-type: none"> Clinician in charge Duty anaesthetist Blood bank Duty haematologist 	<ul style="list-style-type: none"> Nominated co-ordinator should take responsibility for communication and documentation.
<ul style="list-style-type: none"> Arrest bleeding 	<ul style="list-style-type: none"> Early surgical or obstetric intervention Interventional radiology 	

<ul style="list-style-type: none"> • Request laboratory investigations 	<ul style="list-style-type: none"> • FBC, PT, APTT, Fibrinogen; blood bank sample, biochemical profile, blood gases or pulse oxymetry • Ensure correct sample identity • Repeat FBC,PT, APTT,Fibrinogen every 4 hrs, or after 1/3 blood vol replacement • Repeat after blood component infusion 	<ul style="list-style-type: none"> • Take samples at earliest opportunity as results may be affected by colloid infusion • Misidentification is commonest transfusion risk. • May need to give components before results available
<ul style="list-style-type: none"> • Request suitable red cells 	<ul style="list-style-type: none"> • Un-crossmatched group O Rh neg • In extreme emergency • No more than 2 units • Un-crossmatched ABO group specific • when blood group known • Fully crossmatched • if irregular antibodies present • When time permits use blood warmer and/or rapid infusion device • Employ blood salvage if available and appropriate 	<ul style="list-style-type: none"> • Rh pos is acceptable if patient is male or postmenopausal female • Lab will complete crossmatch after issue • Further crossmatch not required after replacement of 1 blood volume (8 - 10 units) • Blood warmer indicated if flow rates >50 ml/kg/hr in adult • Salvage contra-indicated if wound heavily contaminated

<ul style="list-style-type: none"> • Request platelets 	<ul style="list-style-type: none"> • Allow for delivery time from blood centre • Anticipate platelet count $<50 \times 10^9 /l$ after 2 x blood volume replacement 	<ul style="list-style-type: none"> • Target platelet count <ul style="list-style-type: none"> • $>100 \times 10^9 /l$ for multiple/CNS trauma or if platelet function abnormal • $>50 \times 10^9 /l$ for other situations
<ul style="list-style-type: none"> • Request FFP (12-15 ml/kg body wt=1 litre or 4 units for an adult) 	<ul style="list-style-type: none"> • Aim for PT & APTT $< 1.5 \times$ mean control • Allow for 30 mins thawing time 	<ul style="list-style-type: none"> • PT/APTT $>1.5 \times$ mean control correlates with increased surgical bleeding
<ul style="list-style-type: none"> • Request cryoprecipitate (1-1.5 packs/10kg body wt) 	<ul style="list-style-type: none"> • To replace fibrinogen & FVIII • Aim for fbg $> 1.0g/L$ • Allow for delivery time + 30 mins thawing time 	<ul style="list-style-type: none"> • Fbg <0.5 strongly associated with microvascular bleeding • Fbg deficiency develops early when plasma poor RBCs used for replacement
<ul style="list-style-type: none"> • Suspect DIC 	<ul style="list-style-type: none"> • Treat underlying cause if possible 	<ul style="list-style-type: none"> • Shock, hypothermia, acidosis lead to risk of DIC • Mortality of DIC is high



THE ASSOCIATION OF ANAESTHETISTS
of Great Britain & Ireland

21 Portland Place, London W1B 1PY
Tel: 020 7631 1650
Fax: 020 7631 4352
Email: info@aagbi.org
www.aagbi.org