6: Alternatives and adjuncts to blood transfusion

Transfusion alternatives were mostly developed to reduce blood use in surgery but have much wider application. They are most effective when used in combination and as part of a comprehensive patient blood management programme. Predeposit autologous blood donation before surgery is of uncertain benefit and now has very restricted indications in the UK. Intraoperative cell salvage (ICS) is effective (and may be life-saving) in elective or emergency high blood loss surgery and management of major haemorrhage. Postoperative cell salvage (PCS) and reinfusion can reduce blood use in joint replacement and scoliosis surgery. ICS and PCS are usually acceptable to Jehovah's Witnesses. Tranexamic acid (antifibrinolytic) is inexpensive, safe and reduces mortality in traumatic haemorrhage. It reduces bleeding and transfusion in many surgical procedures and may be effective in obstetric and gastrointestinal haemorrhage. Off-label use of recombinant activated Factor VII (rFVIIa) for haemorrhage does not reduce mortality and can cause serious thromboembolic complications.

Erythropoiesis stimulating agents (ESAs), such as erythropoietin, are standard therapy in renal anaemia and can support blood conservation in some cancer chemotherapy patients and autologous blood donation programmes. They may also be effective in selected patients with myelodysplasia. ESAs may cause hypertension and thromboembolic problems. Careful monitoring is required to keep the haematocrit below 35%.

Safe parenteral iron preparations are now available and may produce more rapid and complete responses in iron deficiency anaemia. Indications include intolerance of oral iron, support for ESA therapy and as an alternative to transfusion in perioperative and postpartum anaemia.

Transfusion alternatives have largely been developed to reduce donor red cell transfusion in surgery, where they are most effective as part of a comprehensive ‘patient blood management’ programme (see Chapter 7). Many of these techniques have wider application, ranging from traumatic and obstetric haemorrhage to patients who do not accept blood transfusions. This chapter briefly describes the commonly available transfusion alternatives and their rationale. Their use in specific clinical indications is covered in Chapters 7–10 and 12.

6.1: Autologous blood transfusion (collection and reinfusion of the patient’s own red blood cells)
6.1.1: Predeposit autologous donation (PAD)

This is the banking of red cell units from the patient before planned surgery.

PAD was stimulated by concerns about viral transmission by donor blood, especially during the HIV epidemic of the early 1980s. With a red cell storage-life of 35 days at 4°C, most healthy adult patients can donate up to three red cell units before elective surgery. Patients may be given iron supplements, sometimes with erythropoietin, to prevent anaemia or allow more donations to be collected. The Blood Safety and Quality Regulations (BSQR, 2005) require that donations for PAD must be performed in a licensed blood establishment, rather than a routine hospital setting. The donations must be processed and tested in the same way as donor blood and are subject to the same requirements for traceability.

Given the current remote risk of viral transfusion-transmitted infection by donor blood in developed countries, the rationale, safety and cost-effectiveness of routine PAD has been severely questioned (see 2007 British Committee for Standards in Haematology (BCSH) Guidelines for Policies on Alternatives to Allogeneic Blood Transfusion. 1. Predeposit Autologous Blood Donation and Transfusion – https://b-s-h.org.uk) and the procedure is now rarely performed in the UK. Although PAD may reduce exposure to donor blood, it does not reduce overall exposure to transfusion procedures or protect against wrong blood into patient episodes due to identification errors at collection from the blood bank or at the bedside. Indeed, the availability of autologous blood may increase the risk of unnecessary transfusion. Most Jehovah’s Witnesses will decline PAD (see Chapter 12). Clinical trials of PAD are mainly small and of low quality and do not provide strong evidence that the risks outweigh the benefits. The BCSH guideline on PAD only recommends its use in ‘exceptional circumstances’, and lists the following indications for PAD:

- Patients with rare blood groups or multiple blood group antibodies where compatible allogeneic (donor) blood is difficult to obtain.
- Patients at serious psychiatric risk because of anxiety about exposure to donor blood.
- Patients who refuse to consent to donor blood transfusion but will accept PAD.
- Children undergoing scoliosis surgery (in practice, most specialist units now use other blood conservation measures).

PAD should only be considered in surgery with a significant likelihood of requiring transfusion, operation dates must be guaranteed and the patient’s ability to donate safely must be assessed by a ‘competent clinician’, usually a transfusion medicine specialist. Adverse events and reactions associated with PAD (or other autologous transfusion systems) should be reported to the Serious Hazards of Transfusion (SHOT) haemovigilance scheme and the Medicines and Healthcare Products Regulatory Agency (MHRA).

6.1.2: Intraoperative cell salvage (ICS)

This is the collection and reinflation of blood spilled during surgery.

Commercially available, largely automated devices are available for ICS and are now widely used in hospitals for both elective and emergency surgery with significant blood loss and in the management of major traumatic or obstetric haemorrhage. The machines must always be used and maintained according to the manufacturer’s instructions by appropriately trained staff. A 2010 Cochrane Collaboration review of randomised trials of ICS, mainly in cardiac and orthopaedic surgery, showed a 20% reduction in donor blood exposure (an average saving of 0.7 units per patient). Much useful information about clinical indications and use of ICS, policies for implementation, staff training/competency assessment and patient information has been prepared by the UK Cell Salvage Action Group (UKCSAG) (http://www.transfusionguidelines.org.uk/Index.aspx?Publication=BBT&Section=22&pageid=7507).
Blood lost into the surgical field is filtered to remove particulate matter and aspirated into a collection reservoir where it is anticoagulated with heparin or citrate. If sufficient blood is collected and the patient loses sufficient blood to require transfusion, the salvaged blood can be centrifuged and washed in a closed, automated system. Red cells suspended in sterile saline solution are produced, which must be transfused to the patient within 4 hours of processing. The reinfusion bag should be labelled in the operating theatre with the minimum patient identifiers derived from the patient’s ID band (UKCSAG has developed a suitable label for this purpose). The red cells are transfused through a 200 µm screen filter, except in those instances where a leucodepletion filter is indicated (see below). The transfusion should be prescribed, documented and the patient monitored in the same way as for any transfusion. Patients undergoing elective procedures where ICS may be used should give informed consent after provision of relevant information.

Indications for ICS in adults and children (for whom low-volume processing bowls are available) are as follows:

- Surgery where the anticipated blood loss is >20% of the patient’s estimated blood volume.
- Elective or emergency surgery in patients with risk factors for bleeding (including high-risk Caesarean section) or low preoperative Hb concentration.
- Major haemorrhage.
- Patients with rare blood groups or multiple blood group antibodies for whom it may be difficult to provide donor blood.
- Patients who do not accept donor blood transfusions but are prepared to accept, and consent to, ICS (this includes most Jehovah’s Witnesses).

ICS should not be used when bowel contents contaminate the operation site and blood should not be aspirated from bacterially infected surgical fields.

Because of concerns about cancer cell reinfusion and spread, manufacturers do not recommend ICS in patients having surgery for malignant disease. However, extensive clinical experience suggests this is not a significant risk although it is recommended to reinfuse the red cells through a leucodepletion filter.

ICS is now widely used in women at high risk of postpartum haemorrhage during Caesarean section and in the management of major obstetric haemorrhage and is supported by many specialist and national guideline groups (http://guidance.nice.org.uk/IPG144/). Theoretical concerns about amniotic fluid embolism have not been borne out in practice, although gross fluid contamination should be aspirated before blood collection and the harvested red cells should be reinfused through a leucodepletion filter.

6.1.3: Postoperative cell salvage (PCS)

PCS is mainly used in orthopaedic procedures, especially after knee or hip replacement and in correction of scoliosis. Blood is collected from wound drains and then either filtered or washed in an automated system before reinfusion to the patient.

The simple filtration systems for reinfusion of unwashed red cells are mainly used when expected blood losses are between 500 and 1000 mL. With these infusion volumes concerns about adverse effects on blood coagulation have not been confirmed in routine practice. Clinical staff must be trained and competency assessed to use the device, accurately document the collection and label the pack at the bedside. Collection of salvaged blood must be completed within the manufacturer’s specified time (usually 6 hours) and the reinfusion must be monitored and documented in the same way as donor transfusions.
PCS is relatively cheap, has the potential to reduce exposure to donor blood and is acceptable to most Jehovah’s Witnesses. It remains unclear whether it adds significantly to a comprehensive blood conservation programme which includes preoperative optimisation of Hb, haemostatic/antifibrinolytic measures during surgery and strict postoperative transfusion thresholds.

6.1.4: Acute normovolaemic haemodilution (ANH)

In ANH several units of blood are collected into standard blood donation packs immediately before surgery (usually in the operating room) and the patient’s blood volume is maintained by the simultaneous infusion of crystalloid or colloid fluids. The blood is stored in the operating theatre at room temperature and reinfused at the end of surgery or if significant bleeding occurs. ANH is most often used in cardiac bypass surgery where the immediate postoperative transfusion of ‘fresh whole blood’ containing platelets and clotting factors is seen as an advantage. Reported hazards of ANH include fluid overload, cardiac ischemia and wrong blood into patient errors. Mathematical modelling suggests ANH is most effective as a blood conservation measure in surgery with major blood loss – now uncommon in elective cardiac surgery. Systematic reviews of published trials have found no significant reduction in exposure to donor transfusions compared to standard care or other blood conservation techniques and the safety of ANH remains unclear.

6.2: Pharmacological measures to reduce transfusion

6.2.1: Antifibrinolytic and procoagulant drugs

6.2.1.1: Tranexamic acid

Tranexamic acid, a synthetic lysine derivative, inhibits fibrinolysis (the breakdown of blood clots) by reducing the conversion of plasmin to plasminogen. It is low cost and can be used by the oral or intravenous route. It is closely related to, but more potent than, the older agent aminocaproic acid (EACA).

A recent systematic review of trials in many forms of surgery confirms that tranexamic acid reduces both the risk of receiving a blood transfusion (by around 30%) and the need for further surgery due to re-bleeding. A small increase in the risk of thromboembolic events could not be excluded but there was no increase in mortality in patients receiving tranexamic acid. Many different dosages were used in surgical trials, but low-dose protocols appeared equally effective (see the list below).

The international CRASH-2 randomised trial of more than 20 000 patients with major traumatic haemorrhage showed a significant reduction in mortality in patients receiving tranexamic acid within 3 hours of trauma and there was no increase in thromboembolic events (including patients with traumatic brain injury). A major international trial of tranexamic acid in 15 000 women with major postpartum haemorrhage (the WOMAN trial) is being conducted and trials are also in progress in gastrointestinal haemorrhage.

In view of these findings, many experts agree that tranexamic acid should be included in major traumatic haemorrhage protocols and may safely be used in most surgical blood conservation programmes.

Examples of published tranexamic acid doses are as follows:

- Cardiac surgery: 10 mg/kg intravenously (IV) immediately pre-op followed by IV infusion of 1 mg/kg/h.
- Traumatic haemorrhage in adults (CRASH-2): 1 g IV within 3 hours of the event followed by 1 g infused over 8 hours.
- Traumatic haemorrhage in children: 15 mL/kg (maximum 1000 mg) IV over 10 minutes followed by 2 mg/kg/h (max 125 mg/h) by IV infusion until haemorrhage is controlled.
- Postpartum haemorrhage (WOMAN trial): 1 g IV followed by a further 1g if bleeding continues or recurs.
6.2.2: Aprotinin

Aprotinin inhibits many proteolytic enzymes and reduces fibrinolysis. It is bovine in origin and severe allergic reactions, occasionally fatal, occur in up to 1 in 200 patients on first exposure. Repeat administration is not advised within 12 months. Aprotinin is mainly used in cardiac surgery where it appears to be more effective than tranexamic acid in reducing blood loss and blood transfusion. However, several retrospective studies have shown an increase in thromboembolic events, renal failure and overall mortality compared to other antifibrinolytic drugs. It was temporarily withdrawn from prescription in 2007 and is now recommended for use only in those patients with a particularly high risk of bleeding in whom the benefits are believed to exceed the risks. Aprotinin is significantly more expensive than tranexamic acid.

6.2.3: Tissue sealants

Also known as ‘biological glues’ or ‘tissue adhesives’, tissue sealants may be derived from human or animal clotting factors such as fibrinogen (sometimes activated by thrombin in the syringe immediately before administration) or synthetic hydrogel polymers. They are sprayed on surgical fields or raw surfaces to promote haemostasis and reduce blood loss. Clinical trials show that they can reduce surgical bleeding and exposure to donor blood, the effect being most significant in orthopaedic surgery.

6.2.4: Recombinant activated Factor VII (rFVIIa, NovoSeven™)

rFVIIa directly activates blood-clot formation at sites of exposed tissue factor in damaged blood vessels, bypassing other clotting pathways. It is only licensed for the treatment of bleeding in patients with haemophilia A or B with inhibitors. However, more than 95% of its use worldwide is off label in patients with major haemorrhage or as ‘last ditch’ treatment in bleeding refractory to other treatment. The main off-label uses are in cardiac surgery, trauma, intracranial haemorrhage and liver/abdominal surgery. It is an extremely expensive drug and the appropriate dose for non-haemophilia bleeding is unknown. Acidosis, common in major traumatic haemorrhage, reduces its effectiveness and adequate levels of fibrinogen are needed for clot formation.

Reports of the effectiveness of off-label rFVIIa are distorted by positive publication bias – mainly case reports of spectacular results and small, underpowered trials. Registry studies are less encouraging. They show little, if any, reduction in mortality and a significant incidence of serious venous and arterial thromboembolic events, especially in older patients and those with vascular disease. A recent Cochrane Collaboration systematic review of randomised controlled trials of prophylactic or therapeutic rFVIIa in patients without haemophilia also found no evidence of reduced mortality and, at the most, a modest reduction in blood loss or transfusion (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005011.pub4/abstract). Higher doses were no more effective and it is not a substitute for coagulation factor replacement. In view of this, the routine use of rFVIIa for non-haemophilia bleeding cannot be recommended outside well-designed clinical trials, and hospitals should have clear local protocols for its use (or not) in emergency settings.

6.2.5: Desmopressin (DDAVP)

Desmopressin causes the release of Factor VIIIc and von Willebrand factor (vWF) from endothelial cells and is used to treat or prevent bleeding in patients with mild type I von Willebrand’s disease or haemophilia A. It may reduce bleeding in patients with uraemia and platelet dysfunction due to kidney failure. The standard dose for this indication is 0.3 µg/kg subcutaneously or intravenously. The template bleeding time is shortened within 60 minutes and the effect lasts less than 24 hours. Repeat doses may be less effective as stores of vWF are depleted. It may also cause headaches and facial flushing.
6.2.6: Erythropoiesis stimulating agents (ESAs)

Erythropoietin (Epo) is produced in the kidneys and increases red blood cell production in the bone marrow in response to reduced oxygen delivery to the tissues. Recombinant human erythropoietin (rHuEpo) was initially licensed for treating the anaemia of renal failure and longer-acting forms, such as darbopoietin alfa, have now been introduced. Other licensed indications include treating anaemia and reducing transfusion requirements in some cancer patients undergoing chemotherapy, increasing the yield of blood in PAD programmes and reducing exposure to donor blood in adults undergoing major orthopaedic surgery. Some patients with ‘low-risk’ myelodysplasia have also been successfully treated with rHuEpo off-label. ESAs are expensive and more research is needed to develop guidelines for their use in combination with other blood conservation measures.

Table 6.1 Licensed indications and summary of dosage recommendations for the major erythropoiesis stimulating agents used in blood conservation

<table>
<thead>
<tr>
<th>ESA</th>
<th>Licensed (non-renal) indications</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoietin alfa</td>
<td>Treatment of anaemia and reduction of transfusion in adult patients receiving chemotherapy for solid tumours, lymphoma or myeloma</td>
<td>Initial dose (subcutaneous injection): 150 IU/kg 3 times weekly or 450 IU/kg once weekly</td>
</tr>
<tr>
<td></td>
<td>Preoperative autologous donation (of up to four units collected over 3 weeks)</td>
<td>600 IU/kg intravenous 2 times weekly for 3 weeks prior to surgery</td>
</tr>
<tr>
<td></td>
<td>Prior to major orthopaedic surgery in adults</td>
<td>600 IU/kg subcutaneously on days −21, −14, −7 and day of surgery</td>
</tr>
<tr>
<td>Epoietin beta</td>
<td>Symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy</td>
<td>Initial dose (subcutaneous injection) 30 000 IU once weekly (approximately 450 IU/kg)</td>
</tr>
<tr>
<td></td>
<td>Preoperative autologous donation</td>
<td>2 times weekly for 4 weeks by subcutaneous or intravenous injection using manufacturer’s algorithm for dosing (see SPC)</td>
</tr>
<tr>
<td>Darbopoietin alfa</td>
<td>Symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy</td>
<td>Initial dose 500 µg (6.75 µg/kg) subcutaneously once every 3 weeks</td>
</tr>
</tbody>
</table>
Higher haematocrits may cause thromboembolic complications. Guidelines recommend that a haematocrit of 35% (Hb approximately 120 g/L) should not be exceeded. ESAs may also increase the risk of tumour growth or recurrence in certain cancers. There have been rare cases of pure red cell aplasia associated with rHuEpo treatment.

The dosage, scheduling and licensed indications for use in blood conservation vary between different ESAs (Table 6.1) and prescribers should refer to the current Summary of Product Characteristics (SPC) for each preparation, the British National Formulary and expert haematological and pharmacological advice when developing local protocols. It is usually necessary to co-administer oral or intravenous iron with Epo to support the increase in red cell production.

### 6.3: Thrombopoietin mimetics

These increase platelet production by stimulating the receptor for the hormone thrombopoietin (THPO). Romiplostim (Nplate™) is given by subcutaneous injection and Eltrombopag (Promacta®) is an oral agent. Both are licensed for the treatment of idiopathic thrombocytopenic purpura (ITP). Research is in progress to assess their ability to prevent bleeding and reduce platelet transfusions in aplastic anaemia, myelodysplasia and chemotherapy-induced thrombocytopenia. Early encouraging results are tempered by concerns about a possible increased risk of thromboembolic events, bone marrow fibrosis and a theoretical risk of stimulating malignant cells. Therefore, these agents should only be used off-label in the context of clinical trials.

### 6.4: Parenteral iron

Oral iron is the preferred, and safest, first-line therapy for most patients with iron deficiency anaemia but many users experience gastrointestinal side effects and compliance with treatment is poor. In patients receiving ESA, oral iron replacement is often inadequate and ‘functional iron deficiency’ limits the response to treatment. Parenteral iron produces more rapid responses and better repletion of iron stores in several clinical settings but, until recently, its use was limited by a significant risk of severe, occasionally fatal, allergic reactions with the available preparations (especially high molecular weight iron dextran). The currently available preparations have a very low incidence of serious reactions and have brought parenteral iron back into mainstream practice. Common indications for the use of intravenous iron include:

- Iron deficiency anaemia with intolerance of oral iron, especially in inflammatory bowel disease, or where oral iron is ineffective.
- To support the use of erythropoiesis stimulating agents (including patients on renal dialysis).
- As an alternative to blood transfusion when a rapid increase in Hb is required (e.g. perioperative anaemia, severe anaemia in late pregnancy or postpartum anaemia).

Several parenteral iron preparations are now licensed in the UK. Some, such as iron sucrose (Venofer®), are given up to three times weekly by slow intravenous injection or short infusion and may need several weeks of treatment for a full replacement dose to be administered. Others, such as low molecular weight iron dextrans (Cosmofer®), may be given as a single total dose infusion over several hours. More recently introduced agents, such as ferric carboxymaltose (Ferinject®) or iron isomaltoside (Monoferr®) have the advantage of administering large replacement doses more rapidly (15 to 60 minutes).

The newer preparations are more expensive and clinical experience is still limited. Parenteral iron is contraindicated in the first trimester of pregnancy. The availability of individual parenteral iron preparations varies between hospitals and they should be used according to local guidelines and policies. Detailed information about dose and administration is available in the individual Summary of Product Characteristics and the British National Formulary (http://bnf.org/bnf).

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