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 darbepoietin 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.
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>
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<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.