7.3: Transfusion management of major haemorrhage

Major haemorrhage is variously defined as:

- Loss of more than one blood volume within 24 hours (around 70 mL/kg, >5 litres in a 70 kg adult)
- 50% of total blood volume lost in less than 3 hours
- Bleeding in excess of 150 mL/minute.

A pragmatic clinically based definition is bleeding which leads to a systolic blood pressure of less than 90 mm Hg or a heart rate of more than 110 beats per minute.

Early recognition and intervention is essential for survival. The immediate priorities are to control bleeding (surgery and interventional radiology) and maintain vital organ perfusion by transfusing blood and other fluids through a wide-bore intravenous catheter. Recent research has focused on major traumatic haemorrhage, influenced by the increased survival of military casualties using ‘damage control resuscitation’ and early transfusion of fresh plasma and red cells (see below).

Successful management of major haemorrhage requires a protocol-driven multidisciplinary team approach with involvement of medical, anaesthetic and surgical staff of sufficient seniority and experience, underpinned by clear lines of communication between clinicians and the transfusion laboratory. Useful information on the development of major haemorrhage protocols can be found on the UK Blood Transfusion and Tissue Transplantation Services website and the Association of Anaesthetists’ guideline on management of massive haemorrhage (http://www.aagbi.org/sites/default/files/massive_haemorrhage_2010_0.pdf).

Major haemorrhage protocols should identify the key roles of team leader (often the most senior doctor directing resuscitation of the patient) and coordinator responsible for communicating with laboratories and other support services to prevent time-wasting and often confusing duplicate calls. In an emergency situation it is essential to ensure correct transfusion identification procedures for patients, samples and blood components are performed (see Chapter 4) and an accurate record is kept of all blood components transfused. Training of clinical and laboratory staff and regular ‘fire drills’ to test the protocol and ensure the rapid delivery of all blood components are essential.
An example of a practical algorithm for the transfusion management of major haemorrhage is given in Figure 7.2.

### 7.3.1: Red cell transfusion in major haemorrhage

Red cell transfusion is usually necessary if 30–40% blood volume is lost, and rapid loss of >40% is immediately life threatening. Peripheral blood haematocrit and Hb concentration may be misleading early after major acute blood loss and the initial diagnosis of major haemorrhage requiring transfusion should be based on clinical criteria and observations (see Figure 7.2).

For immediate transfusion, group O red cells should be issued after samples are taken for blood grouping and crossmatching. Females less than 50 years of age should receive RhD negative red cells to avoid sensitisation. The use of Kell negative red cells is also desirable in this group. Group O red cells must continue to be issued if patient or sample identification is incomplete or until the ABO group is confirmed on a second sample according to local policy (see Chapter 2).

ABO-group-specific red cells can usually be issued within 10 minutes of a sample arriving in the laboratory. Fully crossmatched blood is available in 30 to 40 minutes after a sample is received in the laboratory. Once the volume of blood transfused in any 24 hour period is equivalent to the patient's own blood volume (8–10 units for adults and 80–100 mL/kg in children), ABO and D compatible blood can be issued without the need for a serological crossmatch.

**Figure 7.2 Algorithm for the management of major haemorrhage (adapted from the BCSH Practical Guideline for the Management of Those With, or At Risk of Major Haemorrhage (2014) with permission)**
Recognise blood loss and trigger major blood loss protocol

Take baseline blood samples before transfusion for:
- Full blood count, group and save, clotting screen including Clauss fibrinogen
- Near-patient haemostasis testing if available

If trauma and <3h from injury, give tranexamic acid 1 g bolus over 10 minutes followed by IV infusion of 1 g over 8h (consider tranexamic acid 1 g bolus in non-traumatic)

Team leader to coordinate management and nominate a member of team to liaise with transfusion laboratory
- State patient unique identifier and location when requesting components
- To limit use of Group O NEG: until patient group known, use O NEG units in females and consider O POS in males
- Use group-specific blood as soon as available
- Request agreed ratio of blood components (e.g. 6 units RBS and 4 units FFP). Send porter to lab to collect urgently

If bleeding continues

Until lab results are available:
- Give further FFP 1L (4 units) per 6 units red cells
- Consider cryoprecipitate (2 pools)
- Consider platelets (1 adult therapeutic dose (ATD))

If lab results are available:

<table>
<thead>
<tr>
<th>IF</th>
<th>GIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falling Hb</td>
<td>Red cells</td>
</tr>
<tr>
<td>PT ratio &gt;1.5</td>
<td>FFP 15–20 mL/kg</td>
</tr>
<tr>
<td>Fibrinogen &lt;1.5 g/L</td>
<td>Cryoprecipitate (2 pools)</td>
</tr>
<tr>
<td>Platelets &lt;75×10⁹/L</td>
<td>Platelets 1 ATD</td>
</tr>
</tbody>
</table>

Continue cycle of clinical and laboratory monitoring and administration of ‘goal-directed’ blood component therapy until bleeding stops
The use of intraoperative cell salvage devices reduces the need for donor red cells in appropriate cases. When bleeding is controlled and the patient enters the critical care unit, a restrictive red cell transfusion policy is probably appropriate.

7.3.2: Coagulation and major haemorrhage

The transfusion of large volumes of red cells and other intravenous fluids that contain no coagulation factors or platelets causes dilutional coagulopathy. Major traumatic haemorrhage is often associated with activation of the coagulation and fibrinolytic systems (‘acute traumatic coagulopathy’). Plasma fibrinogen predictably falls to sub-haemostatic levels (<1.5 g/L) after 1 to 1.5 blood volume replacement (earlier in the presence of coagulopathy and hyperfibrinolysis). Coagulation is also impaired by hypothermia, acidosis and reduced ionised calcium ($Ca^{2+}$) concentration (which can be measured on many blood gas analysers). Ionised hypocalcaemia may be caused by rapid transfusion of blood components containing citrate anticoagulant, although this is uncommon in the presence of normal liver function.

Traditional ‘massive transfusion’ guidelines use laboratory tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) to guide blood component replacement. The usefulness of these tests is reduced by the significant delay between sampling and returning results to the clinical team. If a PT can be made available with a rapid turnaround time that allows it to reflect the clinical situation it can be used to aid decisions regarding FFP infusion. The Clauss fibrinogen assay should be used in preference to a fibrinogen estimated from the optical change in the PT (PT-derived fibrinogen) that can be misleading in this setting.

Point of care testing (POCT) has an increasing role in providing ‘real time’ laboratory data to guide blood component replacement. It is essential to ensure appropriate calibration and quality assurance of POCT devices. Assays of clot formation, clot strength and lysis, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM), have been used for many years to inform plasma and platelet transfusion in liver transplantation and cardiac surgery. Their value in the management of major haemorrhage is uncertain and is the subject of current research.

FFP should be transfused in doses of 12–15 mL/kg (at least four units in the average adult) to maintain the PT ratio (compared to ‘normal pooled plasma’) less than 1.5. Fibrinogen levels should be maintained above 1.5 g/L (Table 7.5).

Table 7.5 Options for fibrinogen replacement

<table>
<thead>
<tr>
<th>Source of fibrinogen</th>
<th>Dose to raise fibrinogen by about 1 g/L in adult patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>4 units (about 15 mL/kg)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>2 five-unit pools</td>
</tr>
<tr>
<td>Fibrinogen concentrate$^a$</td>
<td>3 to 4 g</td>
</tr>
</tbody>
</table>

$^a$ Currently not licensed in the UK for acquired hypofibrinogenaemia
The early transfusion of FFP in a fixed ratio to red cells (‘shock packs’) in traumatic haemorrhage, to reverse coagulopathy and reduce bleeding, has been extrapolated from military to civilian practice but the true value of this approach is uncertain. Retrospective studies are confounded by ‘survivorship bias’ (the most severely injured patients do not survive long enough to be transfused) and the non-military trauma population is older and less fit. Transfusion policy is just one component of an integrated, multidisciplinary response to major trauma. Large-volume FFP transfusion carries increased risks of circulatory overload (TACO), allergic reactions and transfusion-related acute lung injury (TRALI), and further clinical research is required to clarify its role.

Once haemostasis is secured, prophylactic anticoagulation with low molecular weight heparin should be considered because of the risk of thromboembolic complications.

7.3.3: Platelets and major haemorrhage

The platelet count usually remains above 50×10^9/L (the generally accepted haemostatic level) until 1.5 to 2.5 blood volumes have been replaced. Many hospitals do not store platelets on site and the time for transfer from the blood centre must be factored into local protocols. Therefore, an adult therapeutic dose should be requested when the count falls to 75×10^9/L.

7.3.4: Pharmacological treatments in major haemorrhage

The CRASH-2 trial published in 2010 clearly showed that early administration of the antifibrinolytic drug tranexamic acid improves the survival of patients with major traumatic haemorrhage or at risk of significant bleeding after trauma (Chapter 6). Tranexamic acid should be given as soon as possible after the injury in a dose of 1 g over 10 minutes followed by a maintenance infusion of 1 g over 8 hours. Evidence is emerging of the value of tranexamic acid in other forms of major haemorrhage, including obstetric and surgical haemorrhage. Given its good safety profile, ease of administration and low cost, tranexamic acid should be considered as a component of most major haemorrhage protocols.

Recombinant activated Factor VII (rFVIIa, NovoSeven™) is widely used off-label as a ‘last ditch’ therapy for patients with major haemorrhage (see Chapter 6). Systematic reviews and registry studies show no good evidence of improved survival, and life-threatening arterial and venous thromboembolic complications may occur, particularly in older patients with vascular disease. Several national guidelines no longer recommend its use outside research studies. Local protocols that include rFVIIa should require advice and authorisation from a haematologist or coagulation specialist and ensure that adverse effects are monitored and recorded.

7.3.5: Acute upper gastrointestinal bleeding

Acute upper gastrointestinal bleeding (AUGIB) is common and has a case fatality of around 10%. Some 35% of bleeds are caused by peptic ulcer disease but the most severe haemorrhage and highest mortality is seen in the 10% of cases presenting with bleeding from oesophageal or gastric varices. Treatment of AUGIB consumes around 14% of red cell units issued in the UK. Evidence-based guidelines for management were published in 2012 by the National Institute for Health and Care Evidence (NICE – http://www.nice.org.uk/nicemedia/live/13762/59549/59549.pdf).

Initial resuscitation of patients with massive gastrointestinal haemorrhage should include transfusion of red cells, platelets and clotting factors according to the local major haemorrhage protocol. In patients who are actively bleeding, the platelet count should be maintained >50×10^9/L, PT ratio >1.5 and fibrinogen >1.5 g/L. PCC and intravenous vitamin K should be used if immediate warfarin reversal is needed. It may be logical to administer PCC, which contains the liver-derived clotting Factors II, VII, IX and X, in bleeding patients with liver failure, but its use in this situation is off-label.
Once the patient is haemodynamically stable, and in patients with less severe initial haemorrhage, over-transfusion may increase the risk of recurrent bleeding (probably by increasing portal venous pressure) and increase mortality. In a recent large randomised trial in patients with severe (but not massive) upper gastrointestinal haemorrhage in Spain (Villanueva et al., 2013), mortality and re-bleeding was lower in patients randomised to a restrictive rather than a liberal red cell transfusion policy (transfusion trigger 70 or 90 g/L). There were more adverse events (reactions and circulatory overload) in the liberal group. Of note, the trial excluded patients with a history of ischaemic heart disease, stroke or vascular disease and the results may not be generalisable, especially to older patients. Transfusion strategy in AUGIB is the subject of a current UK multicentre randomised trial (TRIGGER – http://www.nhsbt.nhs.uk/trigger) which is recruiting unselected cases in six hospitals.

7.3.6: Major obstetric haemorrhage

See section 9.4.

7.3.7: Audit of the management of major haemorrhage

Audit is important to assess adverse events, timeliness of blood component support, patient outcome and component wastage. There should be multidisciplinary review of cases that trigger the major blood loss protocol to ensure it is being applied appropriately and effectively. Serious adverse reactions (SAR), serious adverse events (SAE) or incidents of patient harm due to delay should be reported to the Serious Hazards of Transfusion (SHOT) scheme (http://www.shotuk.org) (SAE and SAR must also be reported to the Medicines and Healthcare Products Regulatory Agency, MHRA).