A GUIDELINE FOR THE USE OF BLOOD AND BLOOD COMPONENTS IN THE MANAGEMENT OF MASSIVE HAEMORRHAGE

Issued by the National Blood Users Group
November 2002

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Position Statement

Rapid and continuing loss of blood is life-threatening. Ensuring that tissue oxygenation is maintained at a level consistent with avoidance of critical ischaemic organ damage and irreversible organ failure demands speed and skill. The knowledge base for that skill is the subject of this Guideline.

Massive haemorrhage does not easily lend itself to clinical trials. Randomised and controlled trials are extremely difficult to design and conduct and blinding of investigators is clearly impossible. Nevertheless several careful studies have been reported that provide a basis for identifying current best practice in massive haemorrhage.

Many questions are unanswered, and may continue to be so. For example controversy persists over which fluids to use for initial resuscitation or maintenance of the intravascular volume. The timing and extent of initial resuscitation in certain types of patients with rapid and severe blood loss have also been questioned.

In this setting, an evidence-based Guideline is likely to undergo modification in the future as our understanding of the treatment of severe haemorrhage develops. The requirement for teamwork, early involvement of senior staff and a planned and practised approach is unlikely however to be superseded for a very long time. All hospitals should have protocols for the management of massive haemorrhage, and all clinicians who are likely to deal with massive haemorrhage should be aware of these protocols. Prompt action and clear communication between hospital staff and departments involved in the care of these patients are essential.

Summary

Definition of Massive Haemorrhage

(i) An ongoing transfusion requirement in an adult of more than 150 ml per minute.

(**ii)** Replacement of more than 50% of blood volume in 3 hours or less.

(iii) Replacement of one blood volume, or transfusion of 10 units or more of red cells in a 24 hour period.

Management of massive haemorrhage:

Prompt action and good communication are essential

The following are the essential steps in managing patients with massive bleeding:

General

1. Perform interventions according to a planned protocol, and **in parallel as appropriate.**

2. Send for senior help **early**.

3. Make sure that the relevant laboratory staff are aware that a massive haemorrhage is in progress.

Specific

- **Provide adequate ventilation and oxygenation**
- **Control the source of haemorrhage**
- **Restore the circulating volume**
- **Start blood component therapy:**

- Early transfusion of red cells will be required
- Anticipate coagulopathy

- **Maintain or restore normothermia.**
- **Evaluate the therapeutic response.**
- **Know and implement specific local procedures for dealing with the logistic demands of massive transfusion.**

Management of massive haemorrhage in patients who refuse blood transfusion.

Introduction

Avoidable deaths from massive haemorrhage are well recognised and have been reported in both obstetrical and surgical practice.[1,2] Early and effective intervention in the initial 'golden hour' has a major impact on the eventual outcome after major haemorrhage. Planned protocols for the management of life-threatening situations have been designed to improve management in cardiac and trauma emergencies.[3,4] We recommend that such protocols should be established to deal with massive haemorrhage and be specific both for the speciality, and for the hospital or clinical unit. Important considerations such as how long it takes to get crossmatched blood and blood components late at night or at the weekend, when severe life-threatening trauma is more common, will vary from hospital to hospital.

This Guideline is intended to provide a basis to enable Hospital Transfusion Committees (HTC) to construct specific hospital protocols (Table 1).

Several definitions have been proposed for the broad ranging clinical scenarios that constitute massive haemorrhage. These include an ongoing blood loss of more than 150 mls per minute, the replacement of 50% of the circulating blood volume in 3 hours or less and blood loss requiring the replacement of the patient's total blood volume within 24 hours, or transfusion of 10 units of red cells within 24 hours.[5,6] These are arbitrary definitions but the first has the benefit of allowing early recognition of major blood loss and of the need for effective intervention to prevent haemorrhagic shock and other complications of massive haemorrhage.

The priorities and goals in resuscitating the bleeding patient are:

- the provision of adequate ventilation and oxygenation
- the control of haemorrhage
- the restoration of perfusion to vital organs
- the correction of coagulopathy by appropriate blood component therapy

The haemodynamic, haemostatic and metabolic derangements will vary with the clinical condition and the speed and effectiveness of the resuscitation. Management of the patient must be tailored on an individual basis taking into account the cause of the haemorrhage and the physiological disturbance. The metabolic disturbance associated with a gradual loss of a large volume of blood will differ from that resulting from the acute massive loss of major trauma. Massive haemorrhage in obstetrics is often complicated by coagulopathies that arise in conditions such as placental abruption, placenta praevia and postpartum haemorrhage. Patients with prolonged hypoxia or hypovolaemia are also at risk for coagulopathy. Early diagnosis is essential and treatment of the coagulopathy is necessary with fresh frozen plasma, cryoprecipitate and platelets.

Acute major haemorrhage may develop into progressive cardiovascular collapse. Initial compensation is via neurohumoral pathways mediated by the release of catecholamines and angiotensin. This causes an increase in peripheral resistance and redistribution of blood into the central circulation, mainly from the skin and splanchnic circulations. A 10% reduction in blood volume can be compensated for by vasoconstriction. With blood loss of more than 1.5L, cardiac output and blood pressure fall and with more than 30% loss of blood volume, hypovolaemic shock develops. Inadequate perfusion sets off a neurohumoral cascade that may result in end-organ failure.

A successful outcome requires prompt action and good communication between clinical specialities, diagnostic laboratories and blood bank staff. The establishment of a massive transfusion alert system, similar to the cardiac arrest call, that would notify the relevant staff of the emergency situation should be considered. When the estimated blood loss has reached 1-1.5 litres and the bleeding is ongoing, the massive haemorrhage protocol should be initiated.[7] **Early consultation with experienced surgical, anaesthetic and haematological colleagues is essential.** The Hospital Transfusion Committee should provide a forum in which a rapid and effective communication system can be organised and massive transfusion episodes should be audited.

The following Grades of Recommendation are used in the guidelines issued by the Blood Users Committee.

Grade A: (evidence levels Ia, Ib): Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

Grade B: (evidence levels IIa, IIb, III): Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

Grade C: (evidence level IV): Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

Management of Massive Haemorrhage

The comprehensive management of massive haemorrhage requires the following:

General

Perform interventions according to a planned protocol, and in parallel as appropriate.

The specific steps detailed below must be performed as expeditiously as possible. This requires co-ordination and good communication between the different departments e.g. A&E, theatre and laboratory and the different specialities of surgery, anaesthesia and haematology. The clinician in charge of the patient at the time must be responsible for detailing essential tasks to specific individuals, such as ordering blood and communicating with the laboratory. As the patient is moved from one clinical area to another and different clinicians take over the care of the patient, all details of prior management (fluids/blood given and ordered) must be clearly recorded and transferred.

Send for senior help early.

Clinical situations that have the potential for exsanguination should be recognised early and the most senior available clinicians with experience in such emergencies should be informed without delay. Enquiries into maternal deaths from haemorrhage in the United Kingdom (UK) have shown that substandard care and avoidable mortality frequently relates to failure to involve senior clinicians.[1]

Make sure that the relevant laboratories are aware that a massive haemorrhage is in progress.

Laboratories need to be specifically informed. This allows the staff to consider their other priorities, to assess their stock levels against possible demand, to prepare for large, repeated and urgent requests for blood and components, and to summon back-up help early if required. **Direct contact and briefing is essential:** writing comments such as ASAP on the blood order form has been rendered completely useless by decades of inappropriate use.

Specific

- **Provide adequate ventilation and oxygenation.**
  Establish a patent airway and give 100% oxygen.

- **Control the source of haemorrhage and set up intravenous access.**
  The control of obvious haemorrhage and the establishment of adequate intravenous access are the priorities.

Identify and control the source of haemorrhage

Definitive control of haemorrhage, surgical or radiological, should be implemented immediately. **Patients should be transferred urgently to an area where definitive intervention for diagnosis and treatment can occur.** If facilities for specific management are not available locally, the bleeding area should be packed if possible, in order to control bleeding and the patient transferred to the appropriate referral centre.

Venous access

It is important to establish intravenous access that allows a reliable, rapid rate of transfusion. The size, number and site of intravenous lines are dictated by the degree of shock, the apparent rate of

bleeding and the type of injury. Short large bore cannulae, 14 gauge or larger, should be used. The site and type of access used should be determined by the skill and expertise of the person inserting the line. Venous access should never be initiated in an injured limb. If the source of haemorrhage is below the diaphragm, at least one intravenous line should be in the upper limb or neck. Patients with upper thoracic and neck injuries should have large bore access in the lower extremities. In patients with severe multiple injuries, in whom thoracoabdominal trauma is suspected, one access site should be above the diaphragm and one below the diaphragm.

Laboratory tests.

Blood samples should be obtained, while establishing venous access, for blood grouping, antibody screening and cross matching of six (6) units of red cells and baseline laboratory tests:

- full blood count,
- prothrombin time (PT),
- activated partial thromboplastin time (APTT),
- fibrinogen,
- urea and electrolytes

The initial resuscitation should not be delayed trying to obtain an arterial blood gas sample, but blood gas and lactate analysis are useful monitors of ongoing resuscitation. The laboratory tests should be repeated at least four hourly or after replacement of one third of blood volume, to assess the efficacy of treatment. If a coagulopathy is detected expert advice should be obtained from the haematologist for interpretation of results and optimum corrective therapy.

• Restore the circulating volume

In parallel with intervention to control the source of the haemorrhage, intravascular volume should be restored to maintain

perfusion pressure. Prolonged hypoperfusion results in acidosis, increased capillary permeability, consumption of clotting factors in the microvasculature and release of inflammatory mediators. These changes contribute to the development of a coagulopathy and secondary end-organ injury.

The clinical endpoint to be achieved in restoring the circulating volume is not well defined. In patients with penetrating torso injuries an improved outcome was shown in those who did not have aggressive fluid resuscitation until operative intervention for bleeding control was undertaken.[8] Proposed mechanisms for the detrimental effect of fluids given before surgical control of bleeding include pressure disruption of an effective thrombus, dilution of coagulation factors and lowering blood viscosity, thereby decreasing resistance to flow around an incomplete thrombus.[8] It is not the value of fluid resuscitation that is being debated, but rather the volume, timing and extent of that resuscitation for certain patients. Immediate management of arterial bleeding should focus on control of the haemorrhage.

General guidelines for fluid resuscitation, in the early phase, recommend an initial fluid bolus of one to two litres in an adult. Further interventions are determined by the patient's response. Failure to respond requires immediate surgical intervention to control exsanguinating haemorrhage.

As control of haemorrhage becomes more established, the clinical goals in fluid resuscitation are evidence of improved organ blood flow and tissue perfusion. **A combination of heart rate, blood pressure, central venous pressure (CVP) and urinary output (>30 mls/hr or 0.5ml/kg/hr) are used initially. An increase in blood pressure, particularly if achieved with the use of inotropes, does not necessarily equate with improved perfusion.**

Intravenous fluid administration.

The use of albumin, and other colloids versus crystalloids for volume replacement continues to be the subject of debate after two recent meta-analyses.[9,10]

Crystalloids are cheap, easy to administer, are not associated with adverse reactions and, in large volumes, do not effect coagulation. The large volumes which are required (3-4 times the deficit) cause a reduction in colloid oncotic pressure (COP) and the duration of volume expansion is short.[11] Extensive tissue oedema occurs with their use. The clinical significance of this has not been established but microvascular blood flow may be restricted and thus tissue oxygenation.[12]

Colloids (nonalbumin) produce a more efficient expansion of intravascular volume, have a more prolonged intravascular persistence, better preservation of oncotic pressure and improve microvascular blood flow. The disadvantages of colloids include the risk of allergic/anaphylactic reactions, adverse effects on coagulation and on renal function. The incidence of adverse effects varies between the different types of colloid available.

Hydroxyethyl starch (HES) causes fewer reactions than gelatins but is associated with a greater interference in blood coagulation, shows evidence of long-term tissue storage and produces a dose dependent pruritus. There is the concern about the use of doses, which exceed those recommended by the manufacturers. The manufacturer's data sheets recommend that the volume administered should be limited to 1.5 litres per 24 hours in an adult. Short-term use of large doses of HES in massive haemorrhage, appears to have a less deleterious effect on coagulation than moderate daily doses.[13]

Current practice for resuscitation often involves a combination of warmed crystalloids and colloids on the basis that crystalloids re-establish fluid homeostasis and colloids provide plasma expansion and

improved microvascular perfusion. In the initial management of haemorrhagic hypotension in trauma patients, the use of small volumes (4ml/kg) of hypertonic saline hyperoncotic solutions (such as 7.5% saline/dextran 70) appears to reduce morbidity and mortality in certain subgroups, particularly those with head injuries.[14,15]

• Start blood component therapy

Blood transfusion with red cells and other blood components will invariably be required in the patient with life-threatening haemorrhage and continuing bleeding. Each patient has to be assessed on an individual basis with respect to specific requirements for blood and blood components. In massive transfusion, the requirements for blood components should be anticipated by assessing the clinical situation. **This should be the responsibility of a senior, experienced member of staff.** The delivery time, the size of the local inventory and the distance to the nearest blood bank are all factors that have to be considered. **In the emergency situation, protocols for the checking and administration of blood must be adhered to, as most transfusion related morbidity is due to incorrect blood being transfused.**

Red Cells.

In ongoing massive haemorrhage, red cells will be urgently required. Blood loss is usually underestimated. Haemoglobin and haematocrit values should be checked regularly. The Hb level may not accurately reflect the degree of blood loss in patients with massive haemorrhage as it will be affected by haemoconcentration and haemodilution. The decision on the rate of transfusion needs to take these factors into account as well as the rate of bleeding and the vital signs of the patient.

In an extreme emergency where a critical oxygen deficit is developing due to blood loss, group O uncrossmatched red cells should be used if the blood group is unknown. In females of child bearing potential,

Table 1 Acute massive blood loss: template guideline*

Goal	Procedure
• Arrest bleeding	• Early surgical or obstetric interven • Upper G/1 tract procedures • Interventional radiology
• Contact key personnel	• Consultant in charge • Duty anaesthetist • Blood bank • Duty haematologist
• Restore circulating volume. Resuscitate to a level that restores or maintains vital organ perfusion but restoration of normal blood pressure should not be attempted until definitive measures have been taken to control haemorrhage.	• Insert wide-bore peripheral cannul • Give adequate volumes of warmed • Aim to maintain adequate BP and u (or 0.5ml/kg/hour)
• Request laboratory investigations	• FBC, PT, APTT, fibrinogen; blood-ba biochemical profile, blood gases or • Ensure correct sample identity • Repeat FBC, PT, APTT, fibrinogen ev 1/3 blood volume replacement. • Repeat after blood component infu
• Request suitable red cells	• Timelines determine choice • Blood needed immediately- use 'Em • Blood needed in 15-60 minutes- ur group-specific will be provided wh • Blood needed in 60 minutes or lon • When time permits use blood warr • Employ blood salvage if available an
• Request platelets 10ml/kg body weight for a neonate or small child, otherwise one adult therapeutic dose (one pack)	• Allow for delivery time from blood • Anticipate platelet count <50 x 10^9 volume replacement
• Request FFP 15 ml/kg body weight = 1 litre or 4 units for an adult)	• Anticipate coagulation factor deficie loss of 1.5 x blood volume • Aim for PT and APTT <1.5x me • Allow for 30 min thawing time
• Request cryoprecipitate (1-1.5 packs/10 kg body weight)	• To replace fibrinogen and factor • Aim for fibrinogen >1.0 g litre • Allow for delivery time plus 30
• Suspect DIC	• Treat underlying cause if possibl

*Adapted from Stainsby et al[24] and The Handbook of Transfusion Medicine.[28]

	Comments
tion	
ae crystalloid/ colloid/ blood rine output >30 ml/ h in adults	• 14 G or larger • Blood loss is often underestimated • Monitor central venous pressure (CVP) • Refer to Advanced Trauma Life Support guidelines[4] • Keep patient warm
nk sample, pulse oximetry very 4 hrs or after sion	• Take samples at earliest opportunity as results may be affected by colloid infusion • Misidentification is commonest transfusion risk • May need to give FFP and platelets before the FBC and coagulation results available
ergency stock' group O Rh D neg crossmatched ABO en blood group known ger - fully crossmatched blood mer and/or rapid infusion device. d appropriate	• Emergency use of Rh D pos blood is acceptable if patient is male or postmenopausal female. • Laboratory will complete cross-match after issue • Further cross-match not required after replacement of 1 blood volume (8-10 units) • Blood-warmer indicated if large volumes are transfused rapidly. • Salvage contraindicated if wound heavily contaminated
centre litre after 2 x blood	• Target platelet count: >100 x 10^9/L for multiple/CNS trauma or if platelet function abnormal • >50 x 10^9/L for other situations • May need to use platelets before laboratory results available- take FBC sample before platelets transfused
ency after blood ean control	• PT and APTT >1.5x mean control correlates with increased surgical bleeding • May need to use FFP before laboratory results available- take sample for PT/APTT, fibrinogen before FFP transfused
VIII min thawing time	• Fibrinogen <0.6-0.8g/L strongly associated with microvascular bleeding • Fibrinogen deficiency develops early when plasma-poor red blood cells used for replacement
e	• Shock, hypothermia, acidosis leading to risk of DIC • Mortality from DIC is high

group O RhD negative red cells should be used unless they are in such short supply that delays would endanger life[16] in which case group O RhD positive blood should be given. Delay in red blood cell transfusion is a continuing cause of maternal mortality.[1] In males and post menopausal females whose blood group is unknown, group O RhD positive red cells can be given. Group specific red cells should be given at the earliest opportunity, as group O blood is a scarce resource.

When one blood volume has been replaced quickly (8-10 units in an adult), cross-matching is usually not needed and suitable group compatible blood can be used.

Red Cell Salvage. Whenever possible intraoperative cell salvage should be used. HTCs should endeavour to provide resources so that cell salvage is readily available in hospitals at all times. This will reduce the demand on blood bank supplies. Cell salvage provides red cell concentrate with a Hct of 55-75%. Cell salvage systems should only be used under well-established protocols.

Fresh Frozen Plasma (FFP) & Cryoprecipitate.

Component therapy with fresh frozen plasma and cryoprecipitate would normally be guided by laboratory testing. In large volume gradual bleeding as may occur with major surgery, this practice should be followed. However, with the logistics of the delays associated with taking a blood sample, waiting for the results and then waiting for the appropriate component to be prepared and delivered, it is necessary, on occasion and especially with rapid large volume loss, to order components in advance based on judgement of the overall situation.

Haemostatic defects in massive transfusion

The haemostatic defects complicating massive transfusion are complex involving both dilution and consumption and the complete laboratory profile has not been well described. The haemostatic changes are related to the type and volume of blood and other fluids transfused, the presence of pre-existing haemostatic abnormalities, the effects of hypothermia, the extent of tissue injury and hypovolaemic shock.[17] For adults dilution of coagulation factors occurs when there has been replacement of an entire blood volume with red blood cells (RBCs) and crystalloids or colloids; moderate reductions in platelet count and clotting factors and prolongations of the PT and APTT are usually present.

Currently all RBCs issued by blood transfusion services, including the IBTS, are suspended in an optimal additive solution with virtually no plasma. Massive blood loss followed by replacement with only RBCs, crystalloid and/or colloid will often dilute coagulation factors to levels insufficient to provide adequate haemostasis. Until recently most published clinical studies and guidelines on massive transfusion have been based on the use of whole blood or plasma reduced red cells which contained significant amounts of plasma that provided some coagulation factors.[5,16,18] Thrombocytopenia was then quite accurately considered as the cause of the ensuing bleeding diathesis in massive transfusion.[19] Since RBCs now contain negligible amounts of plasma, deficiency of fibrinogen appears first followed by other coagulation factor deficits and later by thrombocytopenia.[19,20]

- In a prospective study of patients having major surgery associated with massive blood loss, where resuscitation was with red cell concentrates and colloid, the initial cause of the coagulopathy was due to a dilutional effect. The critical fibrinogen concentration of 1.0g/L was reached after a blood loss of 1.5 blood volumes. Dangerously low levels of other clotting

factors, including platelets, were approached after a blood loss of more than 2 blood volumes.[20]

Prolongation of the activated partial thromboplastin time (APTT) and prothrombin time (PT) occur commonly in the massively transfused patient.

- In a retrospective review of 22 massively transfused patients, resuscitated primarily with red cells and crystalloid, PT values greater than 1.5 times normal were reported in all patients who received 12 or more units of RBCs and in 36% of patients who received less than 12 units.[21]

- Abnormal bleeding in patients given packed red cell replacement for major blood loss occurred in those with PT or APTT values greater than 1.5 times normal.[22,23]

- Marked prolongations of the PT/APTT (greater than 1.8 times the control value) were indicative of clotting factor levels below 20% and were good predictors of diffuse microvascular bleeding in the massively transfused patient.[18]

- The same study showed that a fibrinogen level <0.6-0.8g/L may prolong the PT/APTT even when other clotting factors are adequate.[18]

In massive haemorrhage, we recommend (Grade C):

- FFP in a dose of 15/ml/kg (4-6 units), should be considered after loss of one blood volume (5 L or 70 ml/kg) and definitely be given before 1.5 blood volumes have been lost.[19]

- Further administration of FFP should be aimed at maintaining the PT ratio < 1.5 normal.[24]

- Early use of FFP may avoid the need for cryoprecipitate but if fibrinogen levels are critically low at or below 1g/L, cryoprecipitate should be given. The minimum dose in an adult should be 10 packs containing 1.5-3g fibrinogen in total.

(Note: FFP contains all of the coagulation factors. Cryoprecipitate contains fibrinogen, Factor VIII and von Willebrand factor. 5 units of FFP (1250 ml) contains, approximately, the same quantity of fibrinogen as 10 packs of cryoprecipitate (approx. 150 ml).*

Fibrinogen concentrate. A virally inactivated fibrinogen concentrate is available which may provide an alternative to cryoprecipitate in patients with afibrinogenaemia or very low fibrinogen levels. However it is not licensed for use in Ireland and has to be used on a named patient basis.

Platelets

A platelet count of 50 x 10^9 /litre or less can be anticipated when approximately 2 blood volumes have been replaced but the individual variation is great.[20,24] In a study of 39 massively transfused patients, platelet counts less than 50 x 10^9/L were found in 75% of patients who received 20 or more units of RBCs and in no patients who received less than 20 units.[21] As well as simple dilution, thrombocytopenia in a massively transfused patient may be due to consumption of platelets in disseminated intravascular coagulation

* The IBTS has discontinued the use of single donor Irish FFP, which has been replaced by Solvent Detergent (SD) treated plasma. The volume of each unit of SD plasma is 200 mls.

(DIC). *In assessing the requirement for platelets, frequent measurements are needed and when necessary platelets should be requested from the blood centre at levels above the desired target to ensure their availability when required.*[24] This is particularly true for hospitals that do not hold a stock of platelets. The delivery time of platelets should be assessed by the HTC in each hospital in formulating their guidelines for massive transfusion.

Platelets are now issued by the IBTS in bags each containing a single adult dose of approximately 2.4 x 10^{11}/bag suspended in around 250 mls of fresh plasma. One platelet adult pack would be expected to increase the platelet count by at least 20 x10^9/L.

In massive haemorrhage we recommend (Grade C):

- Platelets should be administered to maintain a platelet count > 50x10^9/L[25] or > 100x10^9/L if the patient has multiple high-energy trauma or an intracranial injury [26,27].

- A platelet count of 50x10^9/L or less can be anticipated when approximately 2 blood volumes have been replaced, but the individual variation is great. Anticipation of platelet requirements should allow for delivery time.

- When platelet function is abnormal as after cardiopulmonary by-pass or patients on aspirin or clopidrogel therapy, empirical platelet transfusion may be required.

Management of disseminated intravascular coagulation (DIC) in the major haemorrhage/ massive transfusion setting

Despite immediate appropriate intervention, a severe coagulopathy can occur. DIC can also be a consequence of delayed or inadequate resuscitation.[16] DIC is manifested by the onset of microvascular bleeding in the operative field and oozing from venepuncture sites.[17]

Patients at particular risk are those with prolonged hypovolemia or tissue hypoxia, patients with extensive tissue damage or penetrating head injury, obstetric patients with complications, e.g abruptio placentae, uterine rupture and amniotic fluid embolism.

Laboratory evidence of DIC should be sought before microvascular bleeding becomes evident so that aggressive action can be taken to address the underlying cause. Prolongation of PT and APTT ratio (>1.8) beyond that expected by dilution, accompanied by a significant thrombocytopenia (platelets < 50 x 10^9/L and a low fibrinogen (< 0.8 g/L) are consistent with DIC. Aggressive treatment with FFP, cryoprecipitate and platelets should be given sooner rather than later.

If DIC is suspected in the major haemorrhage /massive transfusion setting, we recommend (Grade C):

- Avail of expert haematological advice as soon as possible

- If coagulation tests are not readily available to guide component therapy, 4-6 units of FFP, one adult pack of platelets and 10 units of cryoprecipate should be ordered and transfused empirically.

- If the patient continues to ooze, despite surgical control of bleeding, packing the operative sites and deferring of wound closure until the coagulopathy is corrected should be considered.

In all massive haemorrhage situations, blood samples should be sent regularly to assess coagulation status (Hb/Hct, platelets, PT, APTT, fibrinogen). Flow sheets should be kept of the time samples were taken, the results and the interventions in the interim, so that appropriate management can be determined. *Monitoring, including coagulation screens, should continue after apparent resolution of the acute bleeding episode and should be intensified if bleeding recurs.*
The different clinical scenarios that are associated with massive

haemorrhage will require different priorities in the management of resuscitation. These priorities cannot be guided by a single protocol.

Obstetric bleeding may be unpredictable and massive and is frequently associated with DIC in which hypofibrinogenaemia and thrombocytopenia are the most consistent findings. Failure to diagnose and treat coagulopathy continues to be a contributory factor in maternal deaths from haemorrhage as emphasised in the reports on Confidential Enquiries into Maternal Deaths in the UK.[1,34,35] DIC is always secondary to an underlying process. Treatment should be directed at the precipitating cause.[28] **If DIC is strongly suspected in a bleeding obstetric patient, do not delay blood and blood component therapy while waiting for the results of coagulation tests. In addition to FFP and platelets as above, give a higher dose of cryoprecipitate, at least 15 packs.**

A management option in the situation that develops with the rupture or laceration of a major vessel is to maintain blood volume with crystalloids/colloids and oxygen carrying capacity with red cell concentrates until the haemorrhage shows signs of control by surgical intervention. When this occurs, appropriate components should then be administered to correct haemostatic abnormalities.

In patients who have a massive haemorrhage associated with multiple injuries, where there can be a combination of major vessel laceration, soft tissue injury and haematoma formation not amenable to surgical intervention, the early and regular use of blood components should be considered to ensure that the concentration of coagulation factors and platelets are optimised simultaneously.

Recombinant Factor VIIa. Isolated case reports have recently described the use of recombinant Factor *VIIa*, at a dose of 90 micrograms/kg, in patients with massive haemorrhage who failed to respond to conventional therapy. Controlled clinical trials are planned and at present this treatment must be regarded as investigational and can only be given with the guidance of a Coagulation consultant at the National Haemophilia Centre, St James's Hospital, Dublin.

• Maintain or restore normothermia

Hypothermia occurs with massive transfusion due to low ambient temperatures, large open wounds, initial infusion of room temperature fluids and cold blood. Hypothermia gives rise to significant complications that can exacerbate the clinical situation. These complications include an increased blood loss, prolonged PT and APTT, platelet dysfunction, enhanced fibrinolysis, decreased breakdown of citrate and lactate, increased affinity of haemoglobin for oxygen and an increased release of red blood cell potassium.[29,30] A report on trauma patients with hypothermia <32°C was associated with 100% mortality, irrespective of severity of injury, fluid replacement and duration of hypothermia.[31] **Hypothermia constitutes an extremely important reversible haemostatic defect.** This defect is not reflected in the patient's PT and APTT values, as they are performed at a temperature of 37°C.

Core temperature should be monitored, preferably by using a nasal probe. Warm all intravenous fluids from the beginning, with a fluid warmer that is effective at moderate and high flow rates. **The use of a rapid infusion and an in-line counter current warming system is recommended for the patient requiring massive warmed infusion of fluids and blood components.** They must be correctly serviced and maintained and used strictly according to the instructions supplied. Blood products must not be warmed by improvisations such as putting the pack into hot water, in a

microwave or on a radiator. Forced air warming blankets and thermal drapes should be used wherever possible to keep the patient warm.

- **Evaluate the therapeutic response**

The main goal in resuscitation is the prompt restoration of tissue perfusion and organ function. The initial assessment is usually based on pulse and blood pressure which are non-specific in assessing volume status. Invasive monitoring, including an arterial line, central venous line and urinary catheter are required to monitor physiological deficits. The degree of metabolic acidosis, central venous oxygen saturation and serum lactate are helpful in assessing the degree of shock and the response to resuscitation. Regular haemoglobin and haematocrit assessment and coagulation screens are necessary. Details of the blood components used must be recorded. It is also advisable to record the time laboratory samples are taken, the results of the tests and the timing and volume of the components given.

- **Know and implement the specific local procedures for dealing with the logistic demands of massive transfusion.**

Each institution should have guidelines and agree a protocol/s for the management of massive transfusion. Such protocols must be specific both for the speciality and the clinical unit. This should be based on the realistic local time required for acquiring blood and its components, both from the supplier's and the user's viewpoint. Where an elective procedure is likely to be associated with major blood loss, the availability of back-up services should be considered in advance.

The Hospital Transfusion Committee has a central role in constructing specific hospital protocols. As recommended by the Report on Confidential Enquiries into Maternal Deaths in the UK,[1] hospitals should have a multidisciplinary protocol for the management of massive haemorrhage which should be updated and

rehearsed regularly in conjuntion with the blood bank. Guidelines for the management of patients who refuse blood transfusion for religious or other reasons should also be available. The Hospital Transfusion Committee should ensure that all massive transfusion episodes are audited.

Management of massive haemorrhage in patients who refuse blood transfusion

Every patient has to be treated with respect and staff should be sensitive to their individual needs, acknowledging their values, beliefs and cultural background. Patients of the Jehovah's Witness faith are not allowed by their religion to receive allogeneic blood or blood products. Medical and nursing staff should be aware of Jehovah's Witnesses' beliefs and know of the non-blood medical alternatives to transfusion that may be required. Each Jehovah's Witness patient should be given the opportunity to discuss treatment options with the responsible doctor under a guarantee of strict clinical confidentiality. Concerns have been recently expressed about the need to ensure that the decision not to accept transfusion is that of the patient themselves, not their relatives or the liaison committee and the need for strict medical confidentiality should the patient choose to be transfused. These concerns were addressed recently in the British Medical Journal following on changes in the approach taken by the Witnesses themselves in excluding individuals from membership who have received a blood transfusion.[32] The Jehovah's Witnesses usually have individuals who are keen to work constructively with patients, relatives and hospital staff in these difficult circumstances. The patient's decision concerning refusal of blood transfusion should be documented. In the case of minors who refuse transfusions, the best interests of the child takes precedence.

A court order may be obtained but essential treatment should not be delayed.[33]

The technique of blood salvage using a cell saver where the patient's blood is collected and washed, concentrated and returned to the patient is acceptable to Jehovah's Witnesses provided that a continuous closed circuit is maintained. For safe and effective use, this requires active management by a lead clinician and adherence to standard operating procedures. The use of cell-saver autotransfusion will allow rapid collection and transfusion of autologous red cells in major intraoperative and post operative haemorrhage.

The Confidential Enquiries into Maternal deaths in the United Kingdom have recommended that all maternity hospitals should have guidelines for the management of patients who refuse blood products.[1,34,35] This should be documented at the first antenatal visit and the patient should be booked for delivery in a unit which has all the facilities for prompt management of haemorrhage, including hysterectomy. During pregnancy the patient's haemoglobin and iron stores should be optimised and oxytocic drugs should be given at delivery.

Massive obstetric haemorrhage occurs usually in the form of postpartum haemorrhage. The principle of management is to avoid delay. Rapid decision making may be necessary particularly with regard to surgical intervention. Dextran should be avoided because of its possible adverse effect on haemostasis. Crystalloid and plasma expanders should be used and Vitamin K given intravenously. Hysterectomy is normally the last resort in the treatment of obstetric haemorrhage, but delay will increase the risk and the patient's life may be saved by timely hysterectomy. The patient should be transferred to an intensive care unit and management should include iron therapy and erythropoietin to maximise haemoglobin synthesis.

An official article published in the June 15, 2000 issue of The Watchtower, the main journal of Jehovah's Witnesses, confirms that the primary components of blood that must be refused are red cells, white cells, platelets and plasma but leaves the decision on fractions of these primary components up to the Witness's own conscience.

Blood substitutes (eg perfluorocarbons, haemoglobin solutions) are under development. Their role in the management of acute anaemia is unclear[36] and they are currently not licensed. As the haemoglobin solutions are not primary components but fractions of primary components they may be acceptable to some Witnesses. Perfluorocarbons will be acceptable to Witnesses if and when they are licensed for clinical use. Recombinant haemoglobin may also become an option in the future.

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