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Transfusion in Trauma 4

Transfusion of blood and blood components is a fundamental part of our treatment of injured patients. Approximately 40 per cent of 11 million units of blood transfused in the United States each year are used in emergency resuscitation. Despite this, there is little level I evidence to provide a rationale for administration of packed red blood cells (pRBCs) to trauma patients.

4.1 INDICATIONS FOR TRANSFUSION

Anaemia is a decrease in the O_2-carrying capacity of blood, and is defined by a decrease in circulating red cell mass (to below 24 mL/kg in females and 26 mL/kg in males). Anaemia will result in an increase in cardiac output at a haemoglobin (Hb) level of <7 g/dL (4 mmol/L). Oxygen extraction increases as O_2 delivery falls, ensuring a constant O_2 uptake by the tissues. The threshold for O_2 delivery is at a haematocrit of 10 per cent and an Hb level of 3 g/dL (1.8 mmol/L) when breathing 100 per cent O_2 and with a normal metabolic rate.

4.2 TRANSFUSION FLUIDS

Normal humans can survive an 80 per cent loss of red cell mass if they are normovolaemic. Volume-dependent markers such as packed cell volume and Hb are poor indicators of anaemia because of the effect of dilution after fluid transfusion on their values (i.e. they are relative values).

4.2.1 Colloids

4.2.1.1 STARCHES

The use of starches is contraindicated in the actively bleeding patient, since all starches deplete the von Willebrand/factor VIII complex[1], and may make the actively bleeding patient more coagulopathic from both factor depletion and dilution coagulopathy. Hydroxyethyl starch is an independent risk factor for acute kidney injury and death after blunt trauma[2].

4.2.1.2 ALBUMIN

Human albumin is produced from blood donors but is also contraindicated in trauma patients. The Saline versus Albumin Fluid Evaluation (SAFE) study in 2007 tested saline versus albumin and demonstrated an increased mortality in trauma patients and in particular in patients with traumatic brain injury (TBI). Albumin is no longer used in the acute resuscitation of a patient with trauma or burns.

4.2.2 Fresh Whole Blood

The human being is an O_2-dependent organism, and O_2 depletion causes major damage within minutes. Thus, in the exsanguinating patient, blood is transfused, in order to improve O_2 transport. Evidence from the Iraq and Afghan wars and recent studies in civilian trauma have highlighted the advantage of fresh whole blood (FWB) in the resuscitation and survival of the exsanguinating patient[3]. The rationale is that FWB has more function than purely that of an O_2 carrier, providing:

- Oncotic pressure (from plasma and stored fresh frozen plasma [FFP]).
- Coagulation function (clotting factors in FFP and platelets [PLT]).
- Temperature homeostasis (from warm circulating fluid).
- Fresh whole blood offers blood at close to 37°C, RBCs, plasma and platelets in natural proportions, to cover the need of the exsanguinating patient for

O_2 and oncotic pressure, and to minimize the acute coagulopathy of trauma shock (ACoTS). A 500-mL unit of FWB has a haematocrit of 38–50 per cent, 150 000–400 000 fully functional platelets/mm^3 and 100 per cent activity of clotting factors diluted only by the 70 mL of anticoagulant. In addition, the viability and flow characteristics of fresh RBCs are better than their stored counterparts that have metabolic depletion and membrane dysfunction[3]. However, FWB, unless in a military environment with a large number of healthy, screened, young blood carriers, is generally not available.

4.2.3 Packed Red Blood Cells

Previous haemorrhage management transfused excessive amounts of crystalloids and packed red blood cells (pRBCs), which diluted native clotting factors, causing hypocoagulation[4]. This additional fluid aggravated the coagulopathy initiated from the moment of injury due to:

- The injury itself, and in proportion to its extent (hypoperfusion resulted in increased activated protein C levels, leading to increased tissue plasminogen activator and increased fibrinolysis).
- Loss of warm blood and replacement with cooler fluid, resulting in decreased body temperature.
- Hypoperfusion, resulting in anaerobic metabolism, increased lactic acid production and a decrease in pH.

Biochemical reactions within the body require a specific and narrow temperature and pH range to proceed. The coagulation cascade does not proceed, even in the presence of all the clotting factors, when the tissue pH is below 7.2 and temperature below 34°C. This is defined as acute coagulopathy of trauma-shock (ACoTS)[5] (also known as trauma-induced coagulopathy [TIC]), and differs from disseminated intravascular coagulopathy, which may develop after hours or days, when the septic component adds its consequences to trauma.

Fresh whole blood can, if warmed, be transfused within 24 hours. It is, however, considered still fresh if stored at 4°C for 48 hours[3]. If it is less than 8 hours old, it can be refrigerated for 3 weeks[2], remaining transfusable but not fresh.

The levels of clotting factors V and VIII decline quickly for 24 hours after collection. The rate of decline then slows until clinically subnormal levels are reached within 7–14 days. It is because FWB contains these factors that it is recommended for massive transfusion and is so effective in the correction of coagulopathy. The other clotting factors remain stable in stored blood. Fresh whole blood has lost most of its platelets after 3 days of storage.

4.2.4 Component Therapy (Platelets, Fresh Frozen Plasma, Cryoprecipitate)

4.2.4.1 PLATELETS

A fall in platelet count occurs somewhat later than the loss of clotting factors. Unfortunately, a platelet count is not helpful, unless very low levels are documented, since it is a poor clinical indicator of the function of the remaining platelets. Hypothermia affects platelet adhesion more than enzymes, above 33°C, while hypothermia affects all aspects of coagulation below 33°C. There is some evidence in which there appears to be a survival advantage of receiving approximately 0.8 units of platelets per unit of RBCs during massive transfusion[6]:

- Prophylaxis: if the platelet count <15 000/mm.
- Pre-surgery: platelet count <50 000/mm^3.
- Active bleeding: platelet count <100 000/mm^3.
- One unit increases the platelet count by 10 000/mm^3 platelets.
- One mega-unit (five units) of apheresis platelets increases the platelet count by 50 000/mm^3.

4.2.4.2 FRESH FROZEN PLASMA

Most massively bleeding trauma patients will need FFP early. This is different from most recommendations, which are based on more controlled circumstances, and is founded on computer simulation of the amount of FFP required to avoid excessive plasma dilution compromising haemostasis. Current evidence suggests that most patients will require one unit of FFP for every unit of blood transfused. A unit of FFP also contains most of the citrate anticoagulant from the unit of blood from which it was originally derived. It contains about 0.5 g fibrinogen, and normal levels of pro- and anticoagulants. Solvent-detergent-related/freeze-dried plasma carries about 20 per cent less of the above per unit given. Potential advantages are:

- It contains all coagulation factors, but not all in equal concentrations.
- It is preferred to cryoprecipitate, which contains 50 per cent of coagulation factors (especially of fibrinogen, factor VIII and von Willebrand factor).

4.2.4.3 CRYOPRECIPITATE

Cryoprecipitate contains fibrinogen, von Willebrand factor/factor VIII complex and fibrin stabilising factor/factor XIII. Cryoprecipitate may not be required in all cases of trauma. One unit (250 mL) of FFP contains 0.5 g fibrinogen; one unit of cryoprecipitate contains 0.25 g fibrinogen, but in 10 mL (rather than 250 mL). Therefore, in most cases, FFP will meet the needs required. However, if a rapid increase in the amount of fibrinogen is required, cryoprecipitate is a useful adjunct.

4.2.4.4 FIBRINOGEN CONCENTRATE

Fibrinogen concentrate can be used to correct acquired hypofibrinogenaemia in trauma. There are several guidelines, but evidence is lacking regarding the treatment efficacy and safety in trauma. So far no level I evidence supports the use in trauma.

4.3 EFFECTS OF TRANSFUSING BLOOD AND BLOOD PRODUCTS

Stored pRBCs (stored for a maximum of 42 days with current US Food and Drug Administration [FDA]-approved storage solutions) develop defects proportionate to the duration of storage that assume greater clinical significance when transfused rapidly, or in large quantities, such as in critically ill patients[4].

4.3.1 Metabolic Effects

Stored packed red blood cells (pRBC) (stored for a maximum of 42 days with current FDA-approved storage solutions) develop defects proportionate to the duration of storage that assume greater clinical significance when transfused rapidly.

- There is a storage-related decreased ATP which precedes red blood cell membrane deformability and its survival during storage.
- Degradation of 2,3-diphosphoglycerate (2,3-DPG) occurs after 7–10 days in storage. 2,3-Diphosphoglycerate is an enzyme affecting the affinity of Hb for O_2. After 7 days of storage, the O_2-transporting ability of Hb drops by two-thirds. Adenine added to pRBCs may restore levels of 2,3-DPG *in vivo* after transfusion, although there is limited level I evidence in this respect.
- Increased ammonia release occurs due to the release of intracellular protein after disruption of the red cell membrane during storage.

4.3.2 Effects of Microaggregates

This remains controversial; however, microfilters are no longer used.

- Red cell membrane instability leads to cell rupture.
- Increased amounts of microaggregates (platelets/leukocytes/fibrin debris) are found in the buffy coat.
- Impaired pulmonary gas exchange and adult respiratory distress syndrome (ARDS) and transfusion-related lung injury (TRALI) can occur.
- Reticuloendothelial system (RES) depression can occur.
- Activation of complement and coagulation cascades may occur.
- Vasoactive substances may be produced.
- Antigenic stimulation may occur.
- Acute-phase response may be seen.

4.3.3 Hyperkalaemia

Serum potassium levels rise in stored blood as the efficiency of the Na^+/K^+ pump decreases. Transfused blood may have a potassium concentration of >40 mmol/L. Transient hyperkalaemia may occur as a result but often does not need correction.

4.3.4 Coagulation Abnormalities

Fresh frozen plasma contains all the clotting factors of the coagulation cascade. Thawed plasma is FFP brought to 4°C and stored for 5 days, this timeline being based on the lifetime of factors V and VIII. Recent studies have shown that thawed plasma stored at this temperature retains significant clotting function for up to 14 days[1]. More recent evidence promotes the use of liquid (never frozen) plasma, retaining the clotting factors' efficacy for even longer.

- Thrombocytopenia and a loss of factors V and VIII in stored blood may contribute to the coagulopathy. Platelets have a short half-life, and their functioning is usually minimal after 3–5 days of storage.
- Levels of clotting factors V and VIII decline quickly for 24 hours after collection. The rate of decline

slows until clinically subnormal levels are reached at 7–14 days. It is because FWB contains these factors that it is recommended for massive transfusion, although it is generally not available outside the military for cost and legal reasons. The other clotting factors remain stable in stored blood.

- Packed red cells do not contain platelets as these are generally spun off, and whole blood has lost most of its platelets after 3 days of storage. Spontaneous bleeding rarely occurs if the platelet count is greater than 30 000/mm^3. Levels as low as this are seen after the replacement of one to two times the total blood volume, and may result from dilution. Despite this, the body has large reserves of platelets, sequestrated in the spleen, liver and endothelium, that are mobilized when there is a need.
- In whole blood, platelets may contribute to microaggregates that find their way to the lungs. Their presence is less evident in packed red cells. Transfusion of pooled platelets carries a greater risk of infection, as several donors have contributed to a single pack of platelets.

Ideally, the transfusion of blood components should be guided by viscoelastic laboratory tests of clotting function, such as thromboelastography (TEG). This is most relevant where surgical bleeding is controlled. However, in the face of continued bleeding, despite surgical control, blood products may need to be given empirically.

It is important to detect trauma-induced coagulopathy as early as possible. Conventional coagulation tests, such as prothrombin time/international ratio (PT/INR), activated partial thromboplastin time (APTT), fibrinogen concentration and platelet counts, have traditionally been used. However, there is a striking lack of evidence to support the use of conventional coagulation tests (CCTs) to monitor resuscitation, although thresholds based on CCTs have been suggested.

On the other hand, the enthusiasm and literature around viscoelastic haemostatic assays (VHAs) like rotational thromboelastometry (ROTEM) and TEG in the trauma setting are increasing. The VHA may be performed bedside and provide results within minutes. Over the last years various papers have been published trying to identify VHA patterns and thresholds characterizing ATC and need for massive transfusion in trauma patients. However, the evidence to prove its superiority and practical use in identifying ATC or predicting the need for transfusions in the acute setting is still not conclusive. (See Section 4.4.6.2.)

4.3.5 Other Risks of Transfusion

4.3.5.1 TRANSFUSION-TRANSMITTED INFECTIONS

- Hepatitis A, B, C and D.
- Human immunodeficiency virus 'window period'.
- Cytomegalovirus.
- Atypical mononucleosis and a swinging temperature that can be present for 7–10 days post-transfusion.
- Malaria.
- Brucellosis.
- Yersinia.
- Syphilis.

4.3.5.2 HAEMOLYTIC TRANSFUSION REACTIONS

- Incompatibility: ABO, rhesus (type the blood) and 26 other surface antigens (screen for these).
- To very cold blood, overheated blood or pressurized blood.
- Immediate generalized reaction (plasma).

4.3.5.3 IMMUNOLOGICAL COMPLICATIONS

- Major incompatibility reaction (usually caused by 'wrong blood' due to administrative errors).
- Graft-versus-host disease: Transfusion-related acute lung injury (TRALI).
- Immunomodulation: Reports on transplant and oncology patients have provided evidence that transfusion induces a regulatory immune response in the recipient that increases the ratio of suppressor to helper T cells. These changes may render the trauma patient more susceptible to infection.

4.3.5.4 FACTORS IMPLICATED IN HAEMOSTATIC FAILURE

- Hypothermia: Blood is stored at 4°C but body temperature is 37°C, so the body needs to provide 1255 kJ of energy to heat each unit of blood to body temperature.
- Acidosis (from citrate and lactate).
- Dilution, depletion and decreased production of red cells and platelets.
- Diffuse intravascular coagulation: There is a consumption of clotting factors and platelets within the circulation, which are trapped in the microvascular thrombi created due to fibrin disposition.
  - Extrinsic: Tissue thromboplastins, for example blunt trauma and surgery, and burns.
  - Intrinsic: Endothelial injury, endotoxin, hypothermia, hypoxia, acidosis and platelet activation.
  - Fibrinolysis.
  - Consumption of red cells and platelets.
  - Protein C activation.

Despite the extensive list quoted above, there is no level I evidence regarding the risks of pRBC transfusion. There is level II evidence that pRBC transfusion is an independent risk factor for:

- Increased nosocomial infections (wound infection, pneumonia, sepsis).
- Multiple organ failure and systemic inflammatory response syndrome.
- Longer length of intensive care unit (ICU) and hospital stay, increased complications and increased mortality.

Additionally, there is level II evidence that

- Pre-storage leucocyte depletion of RBC transfusion reduces complication rates, some studies showing a reduction in infectious complications.
- There is a relationship between transfusion and TRALI and ARDS.

So blood has effects and side effects, some of which are 'bad', and we should use it in a rational and restrictive way in most patients. In trauma haemorrhage, there is no good alternative so far and prioritizing balanced transfusion as part of haemostatic resuscitation secures clotting and oxygenation. The less 'bad' blood may be FWB, and its surrogate components transfusion (which amounts to a reconstitution of whole blood). However, FWB is not generally available outside the military context and may be logistically difficult to obtain in civilian practice.

4.4 CURRENT BEST TRANSFUSION PRACTICE

4.4.1 Initial Response

1. Aggressively pursue the diagnosis and treatment of haemorrhage.
2. Titrate administered fluids to maintain a lower than normal blood pressure (hypotensive resuscitation), until control of haemorrhage.
3. Measure and closely follow serum lactate and arterial pH as indicators of the state of systemic perfusion.
   - If normal, attempt to maintain perfusion.
   - If abnormal, attempt a gradual improvement without elevating the blood pressure and aggravating the haemorrhage.
4. Maintain normothermia.
5. Control ventilation to achieve O_2 saturation of 99–100 per cent and a normal end-tidal carbon dioxide level.
6. Aim for a target Hb of 7–9 g/dL (4–5.5 mmol/L) and a normal prothrombin time at the time that haemorrhage is controlled. Consider maintaining a higher Hb concentration in older patients and in those with known ischaemic disease.
7. If massive transfusion is likely, attempt from the outset to maintain intravascular composition. Use early RBC, plasma and platelet transfusion.

Blood pressure and heart rate are the current standard-of-care monitors of shock resuscitation in the field and in the emergency department when associated with serum lactate or base excess (base deficit). Both, however, are insensitive markers of early compensated shock; alternative monitors are needed for assessing the adequacy of tissue perfusion, with a view to avoiding both under-resuscitation and over-resuscitation. The challenge is to identify as early as possible those patients who are not responding to early interventions. Blind and aggressive volume loading in the hope of normalizing blood pressure and heart rate, without appropriate emphasis on the control of haemorrhage, sets the stage for the so-called bloody vicious cycle, the abdominal compartment syndrome or multiple organ failure (MOF).

4.4.2 Reduction in the Need for Transfusion

Blood is a scarce (and expensive) resource and is also not universally safe. Reducing the need for transfusion[4] is the best way to limit the complications:

- Treat the cause, i.e. undertake urgent surgery to stop bleeding, and avoid hypothermia and acidosis.
- Treat deficiencies and complications as they arise. There is no evidence to support prophylactic therapy with FFP, platelets, etc.[7], however, replacement of components becomes of great importance in massive transfusion. (See Section 4.7.)

- Follow a restrictive transfusion policy in ICU. One large multicentre trial[5] documented a significantly lower mortality rate for critically ill patients managed with a restrictive transfusion strategy and a transfusion threshold of 7 g/dL (5 mmol/L) Hb[8]. However, this assumes normovolaemia, absence of ongoing bleeding and an absence of pre-existing cardiovascular disease or severe brain injury.
- Develop a capacity for cell salvage.

4.4.3 Transfusion Thresholds

There is no level I evidence indicating the ideal trigger for transfusion in trauma patients. In general, the following guidelines apply[9]:

1. Identify the critically ill patient with a Hb less than 7 g/dL (5 mmol/L) or a haematocrit below 21 per cent.
2. If the Hb is less than 7 g/dL, transfusion with pRBCs is appropriate. For patients with severe cardiovascular disease, and trauma patients with ongoing bleeding or haemodynamic instability, a higher threshold of 8–10 g/dL (6–7 mmol/L) is appropriate.
3. If the Hb is less than 7 g/dL, assess the patient for hypovolaemia. If this is found, administer intravenous fluids to achieve normovolaemia, and reassess the Hb level.
4. If the patient is not hypovolaemic, determine whether there is evidence of impaired O_2 delivery.
5. If impaired O_2 delivery is present, consider cardiac output monitoring.
6. If impaired O_2 delivery is not present, monitor Hb as appropriate.

4.4.4 Transfusion Ratios

While principle largely favours fresh whole blood, blood component transfusion is the best feasible alternative in most civilian situations.

Military clinical research[3] and newer studies on civil trauma[9] suggest transfusing pRBC:FFP:platelets in a proportion of 1:1:1, with life-threatening bleeding.

Volumes and content of blood products vary between countries.

Consider an example of a combination of blood products: the mixture of one pRBC unit (335 mL) with a haematocrit of 55 per cent, one unit of platelets (50 mL) with 5.5 × 10 platelets[10], and one unit of FFP (275 mL) with 80 per cent coagulation factor activity. This combination results in 660 mL of fluid with a haematocrit of 29 per cent, 88 000 platelets per mm^3 and 65 per cent coagulation factor activity.

The optimal ratio of RBCs to FFP remains, however, controversial. Currently, an initial two units pRBCs followed by a 1:1:1 ratio of RBC:FFP:platelets appears to be reasonable. If apheresis platelets (usually containing five or six units of platelets) are supplied, this ratio will become 5:5:1 or 6:6:1.

4.4.5 Adjuncts to Enhance Clotting

There has been extensive interest in the provision of adjuncts to enhance clotting as part of the resuscitation of the trauma patient. These include the following.

4.4.5.1 RECOMBINANT ACTIVATED FACTOR VII

Interest has focused on recombinant activated factor VIIa (NovoSeven). This was initially developed as an adjunct for the treatment of haemophilia. However, following its successful use in controlling the bleeding in a trauma patient, there was considerable interest in its use. A large multicentre trial in 2005[11] showed a reduction in red cell transfusion requirements in blunt trauma patients, and the drug has been used extensively 'off-label'. A further large multicentre trial in 2008 showed a reduction in blood product usage of 3.6 units in blunt injury, but there was no significant effect on mortality or for penetrating injury[12]. Although not widely used in the era of better understanding and assessment of the clotting process, it is still utilized in certain countries and in some military situations. A suitable protocol appears in Table 4.5.

4.4.5.2 TRANEXAMIC ACID

Tranexamic acid is indicated for prolonged bleeding (empirically) or when there is evidence of hyperfibrinolysis (measured using TEG or ROTEM). It is given at a dose of 10–20 mg/kg every 6 hours.

The CRASH-2 trial showed a significant reduction in mortality with the use of tranexamic acid[13]; however, although the trial involved very large numbers of subjects, fewer than half the patients require red cell transfusion, and in those who were transfused, the two arms utilized the same amount of blood, and the mortality rate for either arm did not correlate with that in other studies. In addition, no injury severity comparisons were included. Therefore, further studies are in progress. However, a recent study indicated that the majority of severely injured patients have a fibrinolysis shutdown, and therefore tranexamic acid may have no effect[14].

Tranexamic acid's greatest use may be where increased clot lysis is shown to be present (e.g. using thromboelastography).

4.4.5.3 DESMOPRESSIN

Desmopressin potentiates the function of platelets and is indicated only for functional platelet disorders, secondary to platelet inhibitors such as aspirin, clopidogrel, ticagrelor, prasugrel, etc., renal or hepatic failure, haemophilia-A and von Willebrand disease.

4.4.5.4 APROTININ

Aprotinin has no indication in trauma, and was withdrawn from the market in 2008.

4.4.6 Monitoring the Coagulation Status

Ideally, the use of blood components should be guided by laboratory tests of clotting function[5]. This is part of the concept of personalized medicine or in trauma is part of the concept of goal-directed therapy giving the patient only what is needed and avoiding transfusions not needed. Haemostasis according to the cell-based model is described in the phases of initiation, amplification and propagation, from clot formation to clot lysis, with participation of all circulating plasmatic and cellular components. Thrombin generation is central for clot development and strength. It primarily occurs on the surface of activated platelets and, hence, platelets and thrombin generation are closely related to the development of coagulopathy.

4.4.6.1 TRADITIONAL ASSAYS

- Fibrinogen degradation products.
- International normalized ratio (INR) – extrinsic.
- Partial thromboplastin time (PTT) – intrinsic.
- D-dimer values (fibrin deposition).

All of the above are cost effective if frequently done, but specimens are heated to the normal *in vivo* temperature of 37°C. All are time-consuming. Therefore, the conventional approach is inappropriate for the hypothermic trauma patient, whose coagulation status is altered. The TEG/ROTEM therefore is more effective at covering the assessment need in the trauma patient.

4.4.6.2 VISCOELASTIC HAEMOSTATIC ASSAYS (VHAS): THROMBOELASTOGRAPHY (TEG)/ROTATIONAL THROMBOELASTOMETRY (ROTEM)

The VHA technology results in a visual profile, or trace, and variables with a reference value (Figure 4.2)[15,16]. Briefly, the collected whole blood sample is placed in a special designed small cup (approximately 1 cc). Inside the cup is suspended a pin connected to a detector system (a torsion wire in TEG, an optical detector in ROTEM), and the cup and pin are oscillated relative to each other with movement initiated from either the cup (TEG) or the pin (ROTEM). As fibrin strings form between the cup and pin, the transmitted rotation from the cup to pin (TEG) or the impedance of the rotation of the pin (ROTEM) are detected at the pin, and a trace is generated as seen in Figure 4.2. The standard assays are with kaolin activation in TEG, kaolin + tissue factor in

Table 4.1 Interpretation of the Parameters of the TEG and ROTEM

TEG Parameter (Normal Range)	ROTEM Parameter (Normal Range)	Measurement
R time (3–8 min)	CT_{EXTEM} (38–79 sec) CT_{INTEM} (100–240 sec)	Clotting factor activity
α (alpha) angle (55–69 degrees)	$A10_{EXTEM}$ (43–65 mm)	Rate of increase in clot strength
K time (1–3 mm)		Kinetics to maximum clot strength
MA (51–69 mm)	MCF_{EXTEM} (50–72 mm)	Maximum strength of the clot
Ly30 (<4%)	LI30 (94–100%)	Fibrinolysis at 30 minutes
FF_{MA} (14–24 mm)	FibTEM MCF (9–16 mm)	Fibrinogen activity (level)

Note: Thromboelastograph (TEG): *R*, reaction time; MA, maximum amplitude, Ly30, hyperfibrinolysis after 30 min; FFMA, functional fibrinogen. Rotational thromboelastometry (ROTEM): CT, clotting time; A10, amplitude after 10 min; MCF, maximum clot firmness; Li30, hyperfibrinolysis after 30 min.

RapidTEG and tissue factor or kaolin activation, respectively, in the ExTEM and InTEM assays in ROTEM, and several other dedicated assays are available from both technologies. The contribution of fibrinogen to clot strength can be evaluated in the Functional Fibrinogen assay in TEG and the FibTEM assay in ROTEM. The VHAs are portable bedside devices, but there are several advantages in running these in a standardized lab by skilled technicians.

The result is available within 3–10 minutes, in the form of a curve (Figure 4.1a or 4.1b). A number of parameters can be measured (Table 4.2):

- *R* time (reaction time)/clotting time – the latency from the time at which the blood is placed in the cup until the clot begins to form.
- Alpha angle – the progressive increase in clot strength.
- *K* time (kinetic time) – the *K* time starts where the *R* time ends, and ends when the curve is at 20-mm amplitude.
- MA (maximum amplitude) – the maximal clot strength.
- Ly30 – lysis at 30 minutes; thrombolysis in 30 minutes.

The VHAs allow for goal-directed haemostatic therapy, thereby only treating with what is needed. See Table 4.2 for one of several international validated algorithms. Furthermore, it is possible to decide if the bleeding is surgical or coagulopathic/pathological, which clotting factors are missing, the function of platelets and whether fibrinolysis is evolving normally. Transfusion of blood components, coagulation factors and additional medication can be administered rationally, based on the results.

The TEG offers substantial support to decision making during the resuscitation, as it gives real-time accurate information on the coagulation status of the trauma patient and facilitates the differentiation between pathological abnormality and surgically correctable bleeding.

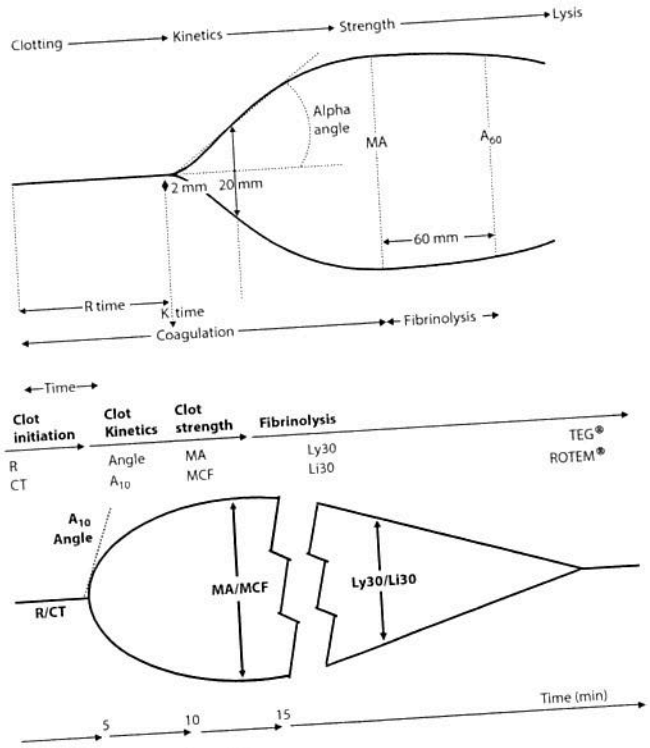

Figure 4.1 Thromboelastogram.

Table 4.2 Goal-Directed Administration of Haemostatic Products and Medication, Based on TEG and ROTEM

TEG	ROTEM	Coagulopathy	Treatment Options
R 10–14 min	ExTEM CT 80–100 sec InTEM CT 200–240 sec	Coagulation factors ↓	FFP 20 mL/kg
R >14 min	ExTEM CT >100 sec InTEM CT >240 sec	Coagulation factors ↓↓	FFP 30 mL/kg rFVIIA (see Table 4.5)
FF_{MA} 7–14 mm	FibTEM MCF 6–9 mm	Fibrinogen ↓	FFP 20 mL/kg or cryoprecipitate 3 mL/kg or fibrinogen concentrate 20 mg/kg
FF_{MA} 0–7 mm	FibTEM MCF 0–6 mm	Fibrinogen ↓↓	FFP 30 mL/kg or cryoprecipitate 5 mL/kg or fibrinogen concentrate 30 g/kg
K (kinetic) time	>4 min		cryoprecipitate 5 mL/kg or fibrinogen concentrate 30 mg/kg or rFVIIA (see Table 4.5)
α angle	<65°		Cryoprecipitate 5 mL/kg or fibrinogen concentrate 30 mg/kg or rFVIIA (see Table 4.5)
MA 45–49 mm and FF_{MA} >14 mm	ExTEM A_{10} 35–42 mm and FibTEM ≥10 mm ExTEM MCF <50 mm and FibTEM ≥10 mm	Platelets ↓	Platelets 5 mL/kg
MA <45 mm and FF_{MA} >14 mm	ExTEM A_{10} <35 mm and FibTEM ≥10 mm	Platelets ↓↓	Platelets 10 mL/kg
Ly30 >3 (– 8)%	ExTEM Li 30 <94%	Hyperfibrinolysis	TXA 1–2 g IV or 10–20 mg/kg
Difference in R Hep TEG versus standard TEG *R* >2 min	InTEM CT/HepTEM CT >1.25	Heparinization	Protamine 50–100 mg or FFP 10–20 mL/kg

Note: TXA, tranexamic acid, FFP, fresh frozen plasma; rFVIIA: recombinant factor VIIa; sec, seconds.

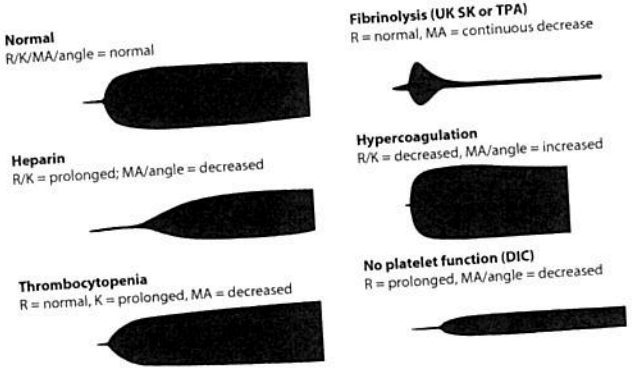

Figure 4.2 Abnormal appearances of the ROTEM.

4.5 AUTOTRANSFUSION

Intra-operative and post-operative blood salvage and alternative methods for decreasing transfusion may lead to a significant reduction in allogenic blood usage.

Autotransfusion eliminates the risk of incompatibility and the need for cross-matching; the risk of transmission of disease from the donor is also eliminated. Autotransfusion is a safe and cost-effective method of sustaining RBC mass while decreasing demands on the blood bank. However, cell salvage in trauma patients is fraught with difficulty as, in the trauma patient, autotransfusion typically involves the collection of blood shed into wounds, body cavities and drains.

Modern autotransfusion devices are basically of two types:

- Collection of blood that is mixed with an anticoagulant, filtered and returned. The blood is collected, anticoagulated with heparin or citrate and then run through a system in which it is washed and centrifuged, before being retransfused.
- Reinfusion after filtration is less labour intensive and provides blood for transfusion quickly. Whole blood is returned to the patient with platelets and proteins intact, but free Hb and procoagulants are also reinfused. A high proportion of the salvaged blood is returned to the patient, and the most recent devices do not require mixing of the blood with an anticoagulant solution. In-line filters are absolutely essential when autotransfusion devices are used. These filters remove gross particles and macroaggregates during collection and reinfusion, thus minimizing microembolization[17].

Cell washing and centrifugation techniques require a machine and (usually) a technician to be the sole operator. This latter requirement can limit the utility of the devices in everyday practice. The cell washing cycle produces red cells suspended in saline with a haematocrit of 55–60 per cent. This solution is relatively free of free Hb, procoagulants and bacteria. However, bacteria have been shown to adhere to the iron in the Hb molecule, and washing therefore does not eliminate the risk of infection.

To a degree, the simpler the system, the less likely it is that problems will occur. In elective situations, nurses, technicians or anaesthesia personnel can participate in the autotransfusion process. In emergency situations without additional personnel, such participation may not be possible. Systems that process reclaimed RBCs may require trained technicians, particularly if the procedure is used infrequently.

In practical terms, bleeding from the chest seems ideal for immediate autotransfusion as the contents of thoracic cavity are sterile, in contrast with abdominal bleeding, where visceral injury and contamination may coexist. The simplest effective method is to use the sterile chest drain container. Use saline to create the fluid valve at the end of a chest drainage tube, to which is added 1000 IU fractionated heparin. The contents of the bottle may be hung and (using a microfilter to collect microaggregates) immediately reintroduced intravenously.

Autotransfusion is generally contraindicated in the presence of bacterial or malignant cell contamination (e.g. an open bowel, infected vascular prostheses, etc.) unless no other RBC source is available and the patient is in a life-threatening situation. However, there are several studies showing the practice may not be as unreasonable as previously thought[18].

Cell salvage techniques have been shown to be cost-effective and useful in some trauma patients (e.g. in splenic trauma with significant blood loss), but further studies are indicated to clarify the indications.

4.6 RED BLOOD CELL SUBSTITUTES

The ideal pRBC substitute is cheap, has a long shelf life, is universally compatible and well tolerated and has an O_2 delivery profile identical to that of blood. Significant effort has been made to find a suitable substitute that could, essentially, be treated as an artificial O_2 carrier.

Artificial O_2 carriers can be grouped into perfluorocarbon (PFC) emulsions and modified Hb solutions. The native Hb molecule needs to be modified in order to decrease its O_2 affinity and to prevent rapid dissociation of the native alpha$_2$–beta$_2$ tetramer into alpha$_2$–beta$_2$ dimers.

4.6.1 Perfluorocarbons

Perfluorocarbons are carbon–fluorine compounds that are completely inert and have low viscosity, but dissolve large amounts of gas. They do not mix with water and therefore need to be produced as emulsions. Unlike the sigmoid relationship of Hb, they exhibit a linear relationship with O_2, therefore their efficacy relies on maintaining a high PaO_2; however, PFCs unload O_2 well. They do not expand the intravascular volume and can only be given in small volumes as they overload the reticuloendothelial system. Once thought to hold potential, they have so far not been found to confer additional benefit compared with crystalloid solutions, especially as there is a significant incidence of side effects.

4.6.2 Haemoglobin Solutions

Although free haemoglobin can transport O_2 outside of the red cell membrane, it is too toxic to be clinically useful. Techniques have been developed to remove the need for the red cell membrane and create haemoglobin-based oxygen carriers (HBOCs).

4.6.2.1 LIPOSOMAL HAEMOGLOBIN SOLUTIONS

These are based on the encapsulation of Hb in liposomes. The mixing of phospholipid and cholesterol in the presence of Hb yields a sphere with Hb at its centre. These liposomes have O_2 dissociation curves similar to red cells, with low viscosity, and their administration can transiently produce high circulating levels of Hb.

Problems associated with HBOCs relate to effects on vasomotor tone, which appears to be modulated by the carriers' interaction with nitric oxide, causing significant vasoconstriction.

4.6.2.2 POLYMERIZED HAEMOGLOBIN SOLUTIONS (HUMAN-OUTDATED/BOVINE RBCS)

Techniques have been developed for cross-linking the haemoglobin molecules, initially with a di-aspirin link and recently as a haemoglobin polymer. Both human and bovine Hb have been used.

Considerable research has taken place in the past decade with regard to the development of synthesized Hb solutions. Bovine-derived Hb (Hemopure) is approved for clinical use in South Africa. Currently, the products have not been licensed for use in the trauma patient.

No level I evidence has yet appeared to support the use of Hb substitutes instead of blood.

The O_2 transport characteristics of modified Hb solutions and PFC solutions are fundamentally different (Table 4.3). The Hb solutions exhibit a sigmoid O_2 dissociation curve similar to that of blood, while PFC emulsions are characterized by a linear relationship between the partial pressure and the content of O_2. Haemoglobin solutions therefore provide O_2 transport and unloading characteristics similar to blood. This means that at a

Table 4.3 Advantages and Disadvantages of Haemoglobin-Based Solutions Compared with Hydrocarbons

Haemoglobin-Based Solutions	PFC-Based Emulsions
Advantages	**Advantages**
• Carries and unloads O_2 • Sigmoidal O_2 dissociation curve • 100% FiO_2 not mandatory for maximum potency • Easy to measure	• Carries and unloads O_2 • Few and mild side effects • No known organ toxicity
Disadvantages	**Disadvantages**
• Side effects o Vasoconstriction o Interference with laboratory methods (colorimetric)	• 100% FiO_2 is mandatory for maximal efficacy • Additional colloid is often necessary, with potential side effects

relatively low arterial O_2 pressure, substantial amounts of O_2 are being transported. In contrast, relatively high arterial O_2 partial pressures are necessary to maximize the O_2 transport of PFC emulsions (Figure 4.2).

Note that 5 per cent O_2 can be offloaded by both blood and PFCs, PFC O_2 being more completely offloaded than blood-transported O_2.

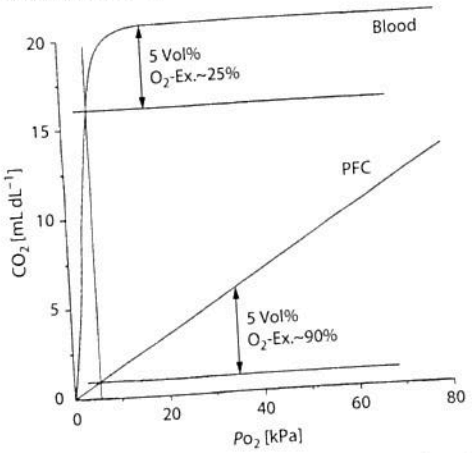

Figure 4.2 Oxygen transport characteristics of haemoglobin and perfluorocarbons.

4.7 MASSIVE HAEMORRHAGE/ MASSIVE TRANSFUSION

4.7.1 Definition

Blood volume is approximately 70 mL/kg. Massive transfusion[19] is defined as:

- The replacement of 100 per cent of the patient's blood volume in less than 24 hours.
- The administration of 50 per cent of the patient's blood volume in 1 hour.

There is a danger of death when blood loss is more than 150 mL per minute or 50 per cent of blood volume in 20 minutes. Each trauma unit should have a policy for massive transfusion, which should be activated as soon as a potential candidate is admitted.

Also germane to the initial period of massive blood transfusion are the potential complications of acidosis, hypothermia and hypocalcaemia. Hypothermia (<34°C) causes platelet sequestration and inhibits the release of platelet factors that are important in the intrinsic clotting pathway. In addition, it has consistently been associated with a poor outcome in trauma patients. Core temperature often falls insidiously because of exposure at the scene and in the emergency department, and because of the administration of resuscitation fluids stored at ambient temperature.

The use of bicarbonate in the treatment of systemic acidosis remains controversial. Moderate acidosis (pH <7.20) impairs coagulation, myocardial contractility and oxidative metabolism. Acidosis in the trauma patient is caused primarily by a rise in lactic acid production secondary to tissue hypoxia and hypothermia, and usually resolves when the volume deficit has been corrected and the efficiency of the circulation restored. Administration of sodium bicarbonate may cause a leftward shift of the oxyhaemoglobin dissociation curve, reducing tissue O_2 extraction, and may worsen intracellular acidosis caused by carbon dioxide production. On the other hand, adrenergic receptors may become desensitized with protracted acidosis. Bicarbonate infusion, therefore, should be limited to persons with protracted shock.

Hypocalcaemia caused by citrate binding of ionized calcium does not occur until the blood transfusion rate exceeds 100 mL per minute (equivalent to one unit every 5 minutes). Decreased serum levels of ionized calcium depress myocardial function before impairing coagulation. Calcium gluconate or calcium chloride should be reserved for cases in which there is ECG evidence of QT interval prolongation or, in rare instances, for cases of unexplained hypotension during massive transfusion.

4.7.2 Protocol

An algorithm of coordinated action incorporating many hospital departments (surgery, blood bank, ICU, anaesthesiology) is activated upon the arrival of a trauma patient with massive haemorrhage. The protocol provides roles for the personnel, actions to be taken, medications and blood products to be transfused. The target is the increase of survival of these patients. The basis of these protocols has been the knowledge recently acquired from modern battlefields, which has dramatically changed the way we manage these patients (Tables 4.4 and 4.5).

Table 4.4 Guidelines for Massive Transfusion

Definition

Replacement of the whole blood volume within 24 hours, or 50% of the blood volume in 3 h.

Activation

The protocol will be activated **automatically by the blood bank** after two units of packed red blood cells (pRBCs) have been issued to a patient, *and* a request for a further four units of blood or more is subsequently requested within any 24-h period. A prospective tool utilizing PR >120 bpm and BP <90 + free blood in the abdomen can be used[17]. Activation can also be done at the discretion of the treating physician.

Blood Specimens

Group and cross-match

- Leukodepleted blood should be used wherever it is available.
- Cross-matched blood if available.
- Un-cross-matched group O blood.

The following **baseline blood specimens** are required:

- Full blood count including platelets.
- Prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time, international normalized ratio (INR), fibrinogen, D-dimer, thromboelastography (TEG) or rotational thromboelastometry (ROTEM).

The following are required **after every six units of transfused blood**:

- Repeat baseline blood samples.
- Full TEG or ROTEM.

Avoid hypothermia (patient and transfused fluid)

- Use an appropriate blood warmer.
- Keep the patient warm using an appropriate patient-warming device.
- Maintain a warm environment.

Blood and Blood Products

The blood bank will issue the following products (as part of a two- or six-unit 'massive transfusion pack'):

(*Note*: Multiple **two-unit packs** are preferable as they can be returned if the 'cold chain' is intact.)

- Two units or six units of pRBC s using the *freshest blood available*.
- Two units or six units of **thawed** fresh frozen plasma (FFP).
- Two units or six units of platelets *or*
- For every six units of blood issued, one apheresis unit of platelets ('platelet mega-unit') (*Note*: This may be five or six units of pooled platelets.)

Administration

Microaggregate filters are **not** advised.

Once administration of the 'massive transfusion pack' blood is begun, administer all the above in a **1:1:1 ratio** (blood:FFP:platelets) or **6:6:1/5:5:1/4.4.1** (blood:FFP:apheresis mega-platelet unit – depends on local interpretation of a 'megaplatelet unit'). After every six units of red cells, if ongoing bleeding or need for transfusion is present:

- Give a further four units of FFP if PT or APTT is >1.5 times mid-normal or according to TEG/ROTEM.
- Give 10 units of cryoprecipitate if fibrinogen <1 g/L or according to TEG/ROTEM.
- Give 10 mL 10% calcium chloride ***only*** if the above additional doses are given.
- Give at least one megaunit of pooled platelets if the platelet count is <75 000 /mm^3.

Return all unused 'massive transfusion packs' to the blood bank as soon as possible.

Endpoints of Transfusion

- Any active surgical bleeding has been controlled.
- No further need for red cells.
- Temperature >35°C.
- pH >7.3.
- Fibrinogen >1.5 g/L.
- INR better than 1.5, PT less than 16 sec., aPTT less than 42 sec.
- Haemoglobin 8–10 g/dL (4–6 mmol/L).

Table 4.5 Guidelines for Use of Recombinant Activated Factor VII (rFVIIa) in Trauma

Definition

This guideline describes the use of rFVIIa as an *adjunct* in the management of coagulopathy following trauma with massive bleeding or the need to enter the massive transfusion protocol.

Issue

The blood bank will issue the required rFVIIa for administration immediately **after completion** of the 6th and 12th units of transfused blood.

Limitation

rFVIIa should **only** be used:

- **If all surgical bleeding has been controlled**
- **In the presence of active bleeding**
- **Where possible, its use should be backed up with a thromboelastogram (TEG)**
  Increased R (reaction) time despite fresh frozen plasma
- After transfusion of >6 units of blood
- If the platelet count is >50 000/mm^3
- If the pH is >7.2
- If the temperature is >34° C

Blood specimens

Disseminated intravascular coagulopathy screen:

- Full blood count and platelets
- Prothrombin time, activated partial thromboplastin time, thrombin time, International Normalized Ratio, D-dimer
- Fibrinogen
- TEG or rotary thromboelastomer

Dose

The dose of rFVIIa should be 90 µg/kg

- Round UP to the nearest 1.2 mg
  (Example: a 75-kg male receives 75 × 90 µg/kg = 6.75 mg rFVIIa. Round UP to 7.2 mg.)

If the patient continues to bleed:

- Repeat the dose after 1 h and after 3 h from first dose
- Repeat the dose after completion of the **12th** unit of transfused blood

End points of administration

The first of:

- Cessation of bleeding
  or
- Three doses

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