Medical management of bleeding in critically ill patients

Saxon Ridley MD FRCA
B. Taylor BSc FRCA FFANZCA FJFICM
K. Gunning MBBS MA FRCS FRCA

Key points

Medical management of bleeding is defined as the use of pharmaceutical agents, such as desmopressin and antifibrinolytic agents, or blood products [e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen, platelets, and coagulation factors] to improve coagulation.

Control of bleeding by conventional surgical techniques or by interventional radiology is essential and must be considered before using medical therapy.

General measures to improve coagulation including correction of dilutional anaemia, hypothermia, and acidosis must be performed.

Saxon Ridley MD FRCA
Consultant in Anaesthesia and Intensive Care
Glan Clwyd Hospital
Rhyl
Denbighshire LL18 5UJ, UK
Tel: +44 1745 583910
Fax: +44 1745 583143
E-mail: saxon@ridley.waitrose.com
(for correspondence)

B. Taylor BSc FRCA FFANZCA FJFICM
Consultant in Anaesthesia and Intensive Care
Department of Critical Care
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Southwick Hill Road
Portsmouth PO6 3LY, UK

K. Gunning MBBS MA FRCS FRCA
Consultant in Anaesthesia and Intensive Care
Addenbrooke's Hospital
Hills Road
Cambridge CB2 2QQ, UK

Medical management of bleeding in critically ill patients may involve pharmaceutical agents (e.g. desmopressin, antifibrinolytic agents) and various blood products, such as fresh frozen plasma (FFP), cryoprecipitate, fibrinogen, platelets, and coagulation factors (e.g. prothrombin complex concentrates, Factor VIII, and Factor VIIa). However, before considering these therapeutic options, meticulous attention to control of bleeding by conventional surgical techniques such as packing, tamponade, ligation, and diathermy or by interventional radiology (embolization and coiling) is essential. Pharmacological and therapeutic options for bleeding control are not a substitute for interventional methods; they should be considered as part of the whole management strategy, since therapeutic options alone are unlikely to control active bleeding.

General measures to control bleeding

The following general principles should be considered as they may improve not only the patient's general condition but also coagulation function.

(i) Dilutional anaemia should be avoided as red cells are required for clot formation. Although lower transfusion triggers are now widely used, the evidence supporting 'permissive anaemia' is based on haemodynamically stable patients;[1] for management of active bleeding, a target haemoglobin concentration above 10 g litre^{-1} is appropriate.

(ii) As hypothermia impairs coagulation, laboratory tests are measured at 37°C. The most temperature-sensitive, the prothrombin time (PT), is depressed at temperatures <35°C and the activated partial thromboplastin time (APTT) <33°C.[2] At such temperatures, altered enzyme kinetics equate to a 33% reduction in normal clotting factors.[3] Hypothermia also reduces platelet function[4] and increases fibrinolysis.

(iii) Acidaemia results in enzyme and platelet dysfunction, with a pH reduction from 7.4 to 7.0 leading to a 70% reduction in activation of prothrombin (Factor II).[4] Activity of Factor VII/tissue factor complex is reduced by 60% and recombinant Factor VIIa (rFVIIa) activity by 90%.[4]

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue (1-deamino-8-D-arginine vasopressin) of the antidiuretic hormone L-arginine-vasopressin; it has less vasoconstrictive activity but retains some antidiuretic properties. It promotes the release of von Willebrand's Factor from endothelial storage sites (called Weibel-Palade bodies), so increasing exposure at damage sites.[5] It also increases the density of platelet surface glycoprotein receptors (improving adhesiveness[6]) and increases plasma activity of Factor VIII and levels of plasminogen activator antigen.[7]

Although desmopressin improves haemostasis in healthy subjects and also reduces bleeding time in patients with coagulopathy related to uraemia, cirrhosis, non-steroidal anti-inflammatory drugs, and aspirin,[8,9] its effect in massive coagulopathic bleeding is uncertain. The dose is 0.3 μg kg^{-1}; it may cause facial flushing, transient headache, and small decrease in blood pressure.[10] Repeat doses should be limited to 6 h intervals to allow replenishment of von Willebrand's Factor storage sites.[11] Desmopressin can result in water retention and hyponatraemia (with the risk of seizure activity, especially in infants and children). Meta-analyses of the use of desmopressin in cardiac surgical patients suggest that there is no change in mortality, re-thoracotomy, or myocardial

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infarction rate,[12] raising questions about its efficacy in this setting. In patients with pre-existing coronary artery disease, its residual vasoactive effect[13] may occasionally cause acute coronary syndrome.

Fresh frozen plasma

In the UK, FFP is prepared by centrifuging whole blood from previously tested donors or by apheresis. UK donors are screened for high titres of ABO antibodies. FFP is also collected from pooled donations (up to 2500 donors) in Germany and the USA; when frozen at −30°C, it can be stored for up to 1 yr. The volume of a typical unit, which contains all the coagulation factors, is 200 ml, but this may vary between 180 and 400 ml.[14]

Pathogen-reduced plasma (e.g. 'Octoplas') is generated by treating FFP with a solvent/detergent to inactivate lipid-coated viruses. This inactivates Hepatitis B and C, but not non-lipid coated Hepatitis A or Parvovirus B19. Solvent/detergent-treated plasma also lacks the large multimers of von Willebrand's Factor and Factor VIII. In the UK, pathogen-reduced plasma can also be created by adding methylene blue to FFP obtained from ABO screened donors; it contains low levels of Factor VIII and fibrinogen. Solvent/detergent treatment appears to eliminate the risk of transfusion-related acute lung injury[14] (TRALI) with the responsible leucocyte alloantibodies being diluted by the large pooled donation volume.

Uses of FFP

FFP can be used to replace single inherited clotting factor deficiencies for which no virus-safe product is available, or for multiple factor deficiencies associated with severe bleeding and disseminated intravascular coagulation. In critical care, FFP is also used for plasma exchange in thrombotic thrombocytopenia purpura.[15]

Water baths are often used to re-warm FFP; they have the advantage of being capable of thawing large volumes simultaneously, but the procedure takes approximately 20 min and strict infection control measures are essential. Dry ovens reduce this time to 10 min to defrost two units, and microwaves to 2 min, but there is a danger of 'hot spot' formation. After thawing, FFP can be stored at 4°C; UK recommendations state that infusion should be completed within 4 h; 24 h is permissible in the USA.[14] The haemostatic effect of FFP declines progressively after thawing; within 24 h, von Willebrand's Factor, antithrombin III, Factors XIII, XII, XI, X, and IX decrease. Only Factors V, VIII, VII, II, and fibrinogen remain reasonably stable (Fig. 1).

FFP is only indicated for surgical bleeding when there is a proven associated coagulopathy. Coagulation is not normally disturbed unless clotting factors decreased below 30% of their normal levels or the fibrinogen concentration below 0.75 g litre^{-1}. Consequently, FFP replacement aims to exceed the minimum of

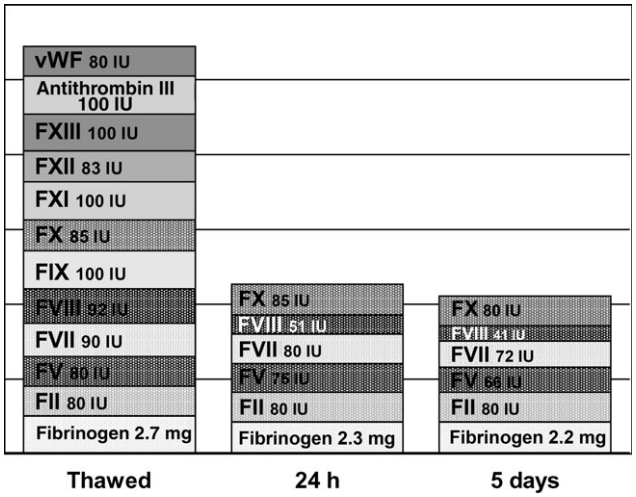

Fig. 1 The decay in clotting factor activity in FFP with time after thawing (vWF, von Willebrand's Factor).

30% of normal plasma factor concentrations. This can usually be achieved with a transfusion of 10–15 ml kg^{-1}; four units of FFP (i.e. about 800 ml) will produce approximately a 10% increase in coagulation factors.[11] The acute reversal of warfarin requires only 5–10 ml kg^{-1}.

Allergic phenomena are well-recognized complications of FFP therapy; in the first 6 yr of the Serious Hazards of Transfusion reporting mechanism, 23 allergic reactions and 25 anaphylactic reactions[16] have been recorded. The clinical picture of TRALI (defined as acute dyspnoea with hypoxia and bilateral pulmonary infiltrates occurring during or in the 24 h after the transfusion with no apparent other cause[16]) is similar to the acute respiratory distress syndrome. Since 1996, 109 patients suspected of developing TRALI suffered a mortality of 30%. This diagnosis should be considered in any patient who develops severe respiratory compromise after FFP therapy.

The leuco-depletion process involved in FFP production may lead to allergic conjunctivitis or 'red eyes'. Although freezing does not inactivate Hepatitis A, B, or C, HIV, or Parvovirus B19, the risk of viral transmission from FFP is very low (1 in 10^7 for HIV, 0.2 in 10^7 for Hepatitis C, and 0.83 in 10^7 for Hepatitis B).[14] Ideally, the blood group for FFP administration should match the patient's ABO group, but if this is unavailable, differently grouped FFP can be given if anti-A or anti-B titres are low. However, FFP from Group O donors should only be given to Group O recipients. In Rhesus D negative children and women of childbearing age, FFP from Rhesus D negative male donors should be used, although the risk of sensitization is very small because of the low levels of red cell stroma. Patients with thrombotic thrombocytopenia purpura should receive solvent/detergent pathogen-reduced plasma as this contains low levels of von Willebrand's Factor multimers that are intimately involved in the disease pathophysiology.

Cryoprecipitate

The main constituents of cryoprecipitate are Factors VIII and XIII, von Willebrand's Factor, fibronectin, and fibrinogen. Typical units contain 70 IU ml^{-1} Factor VIII and are rich in fibrinogen (140 mg). Cryoprecipitate is manufactured by thawing FFP at 4°C, removing the precipitated layer, which is then centrifuged and re-suspended in 20–40 ml plasma. It is indicated for bleeding associated with hypofibrinogenaemia (i.e. a fibrinogen level of <0.75 g $litre^{-1}$) with von Willebrand's disease and for patients with haemophilia, if Factor VIII is not available. In complex coagulopathy, giving FFP alone may result in adequate fibrinogen replacement and hence avoid the need for cryoprecipitate.

One unit of cryoprecipitate per 7–10 kg body mass raises the plasma fibrinogen level by at least 0.5 g $litre^{-1}$. Although ABO blood group compatibility is not essential for transfusion of cryoprecipitate, it is nevertheless preferred.

Fibrinogen

The fibrinogen level required for haemostasis is 0.75 g $litre^{-1}$. Fibrinogen is indicated for acquired hypofibrinogenaemia with massive bleeding, disseminated intravascular coagulation, or inherited hypofibrinogenaemia. Commercially prepared fibrinogen concentrates are available in countries other than the UK.

Cryosupernatant

This is the supernatant plasma removed during cryoprecipitate preparation. It contains von Willebrand's Factor, Factors XIII, and fibronectin. However, it is low in Factor VIII and fibrinogen (unlike cryoprecipitate).[14]

Platelets

Platelets are mainly indicated for thrombocytopenia or platelet function defects. Ideally, the platelet count should not be $<50 \times 10^9$ $litre^{-1}$.[17] However, a higher target level (100×10^9 $litre^{-1}$) may be appropriate for patients with multiple trauma or central nervous system injury.[18]

Platelets concentrates are produced by the buffy coat method or plateletpheresis. One adult-dose platelet preparation is obtained by pooling four to six buffy coat concentrates within 8 h and then re-suspending them in plasma or a platelet suspension medium. Alternatively, platelets can be obtained from a single donor by apheresis which involves a centrifuge removing the platelets and the remaining blood being re-transfused to the donor. This technique can provide up to three units (or three single adult doses) per donor and is useful when HLA matching is required. One adult dose of platelets can consist of a single donor platelet concentrate or 4–6 concentrates of pooled platelets. A typical volume from a single donor is 150–300 ml, whereas that from a pooled platelet dose is 150–450 ml. Platelets concentrates are slightly acidotic (pH 6.4–7.4).

One unit of platelets (pooled or single donor) should increase the platelet count by 20×10^9 $litre^{-1}$. However, the actual increase in platelet count also depends upon sequestration in the spleen and the rate of peripheral destruction or loss. The required dose may be calculated as the desired percentage increment × the blood volume × a correction factor (usually 0.33) to account for splenic sequestration. The usual dose in adults is 10–15 ml kg^{-1} (approximately two units).

Platelets are administered over 30 min via a standard giving set. The need for platelet transfusion depends upon many factors and not a single laboratory result. Considerations include type of blood loss, ability to control bleeding, consequences of uncontrolled bleeding, actual and anticipated rate of bleeding, and presence of factors affecting platelet function, for example, drugs, renal failure, extracorporeal circulation. Platelets are usually administered for bone marrow failure, prophylaxis for surgery or invasive procedures, platelet dysfunction in massive transfusion, and disseminated intravascular coagulation. The risks of platelet transfusion are alloimmunization (leading to difficulty matching platelets for future transfusion), infection, allergy, and TRALI.[17] Platelets are relatively contraindicated in thrombotic thrombocytopenic purpura (unless there is a life-threatening haemorrhage) and heparin-induced thrombocytopenia because of the risk of acute arterial thrombosis.

Although the platelet count should normally be checked approximately 1 h after a transfusion to ensure adequacy of therapy, transfused platelets take up to 4 h to become fully functional. An increase of $<20 \times 10^9$ $litre^{-1}$ may indicate the presence of HLA antibodies, which will render further non-HLA matched platelets ineffective. A refractory response to platelet infusion may also be caused by ABO incompatibility.

Antifibrinolytic agents

Abnormal fibrinolysis activity may be an overlooked cause of bleeding, particularly in patients with liver disease. If bleeding continues despite FFP and platelet administration, the use of antifibrinolytics should be considered. Thromboelastography may be helpful in differentiating between hyperfibrinolysis and hypocoagulation.[19] Antifibrinolytic agents act by inhibiting serine proteases such as plasmin by decreasing conversion of plasminogen to plasmin, preventing plasmin/fibrin binding, and displacing plasmin from the developing clot.

Aprotinin is a single-chain polypeptide of 58 amino acid residues cross-linked by three disulphide bridges. It inhibits human trypsin, plasmin, plasma, and tissue kallikrein by complexing at the serine site of the enzyme. These enzyme interactions have differing dissociation constants. The aprotinin/trypsin complex is the most stable, whereas the aprotinin/plasmin is a relatively weak association. As aprotinin is quickly eliminated (after about 1 h), it should ideally be given by infusion to maintain its effect. The recommended dose in bleeding caused by hyperfibrinolysis is 500 000 KIU h^{-1} (KIU, kallikrein inactivating units); this dose is

equivalent to 14 mg of pure polypeptide.[20] Aprotinin is more efficacious when used prophylactically and can decrease the blood loss during major procedures associated with massive haemorrhage, especially in cardiac surgery.[12] Anaphylactic reactions and acute renal failure are recognized complications.

Lysine analogues

Plasminogen has five lysine binding sites, one of high and four of low affinity for fibrin. These sites are completely blocked by the synthetic antifibrinolytic amino acids and saturation with lysine analogues displaces plasminogen from the fibrin surface.

Aminocaproic acid has a similar effect to aprotinin, but is less expensive and has a lower risk of anaphylaxis. Its elimination half-life is 1–2 h, being primarily excreted unchanged in the urine. For bleeding, the loading dose is 5 g i.v. over 1 h and then 1–2 g h^{-1}.[20] However, aminocaproic acid does not have a licence in the UK.

Tranexamic acid is the trans-stereoisomer of 4-aminomethylcyclohexane carboxylic acid and has a molecular weight of 157. It is very weakly protein bound (only 3%) but is exclusively bound to plasminogen. A dose of 10 mg kg^{-1} gives satisfactory inhibition of fibrinolysis (more sustained than aminocaproic acid) and has been used to prevent/reduce bleeding after tonsillectomy, prostatic surgery, cervical conisation, and severe menorrhagia.[20] Antifibrinolytics have been used successfully in cardiac surgery to reduce mortality, re-thoracotomy, and transfusion requirements.[12]

Coagulation factor concentrates

Coagulation factor concentrates, which include prothrombin complexes, Factor XIII, and Factor VIIa, are most commonly indicated in trauma, liver disease, and oral anticoagulant toxicity. They offer a rapid and relatively easy method of improving coagulation stability without the risks of FFP transfusion, volume load, or infectious complications.

Prothrombin complex concentrates (Factors II, VII, IX, and X) are recommended for the rapid correction of acquired coagulation factor disturbance (i.e. warfarin overdose).[21] At a dose of 30 IU kg^{-1} i.v., prothrombin complex concentrate (Beriplex, Centeon, Marburg, Germany) satisfactorily reversed coagulation deficiencies in 16 critically ill patients.[22] The effectiveness is monitored by the PT and further doses can be given at 8–12 h intervals as required. Although there is little evidence to suggest increased risk of disseminated intravascular coagulation or widespread thrombosis, it should be noted that patients on warfarin tend to have an underlying hypercoagulable state.[22]

Factor XIII stabilizes clot formation by binding fibrin molecules. The A chain of Factor XIIIa is a transglutaminase which catalyses the cross-linking of epsilon lysine bonds between the fibrin molecules, hence increasing mechanical clot strength and resistance to plasmin proteolysis.[23] The platelet count and Factor XIII levels are functionally interdependent (platelets also stabilize the clot and are an alternative source of Factor XIIIa). Although Factor XIII is available as a single recombinant concentrate (initial dose 2500 IU i.v. for an adult patient), its use in the UK is restricted to patients with congenital Factor XIII deficiency.

A cell-based model of coagulation, comprising three overlapping phases, has recently been described.[24,25] In the initiation phase, Factor VII forms complexes with tissue factor exposed at the sites of injury. On the surface of the tissue factor-bearing cell, Factors V, IX, and X are activated and a small amount of thrombin is produced (Fig. 2). This thrombin activates platelets producing inversion of their cell membranes to expose phospholipids on the cell surface, allowing activated factors (Va, VIIIa, Ixa, and XIa) to accumulate on the platelet surface (Fig. 3). Activated Factor VIII and Va on the platelet surface catalyse the large-scale platelet thrombin generation by further activation of Factor IX, X, and XI (Fig. 4).

Factor VII circulates as a single chain of 406 amino acids and is activated to two active enzyme chains by the cleavage at arginine 152. Activated Factor VII plays a key role in initiating coagulation at the site of injury by complexing with tissue factor in addition to activating platelets and promoting thrombin generation (amplification). It also stimulates clot stabilization via enhanced Factor VIIIa and IXa activation catalysing Factor Xa production (propagation).

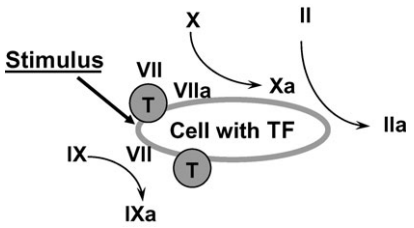

Fig. 2 Initiation and initial generation of thrombin. Coagulation will be initiated within the vasculature on a tissue factor-bearing cell (mononuclear cells, endothelial cells, and stromal fibroblasts) after stimulation (reproduced with permission from de Moerloose[25]).

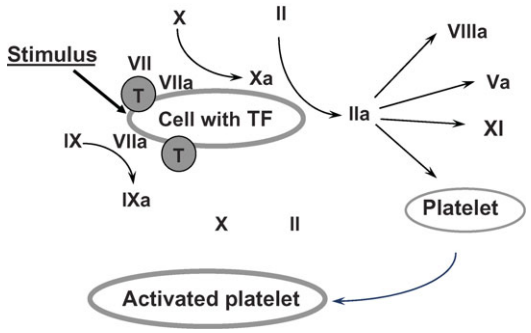

Fig. 3 Amplification. The first thrombin generated will activate platelets, Factors VIII, V, and XI. This will lead to a burst of thrombin generation, which occurs on activated platelets (reproduced with permission from de Moerloose[25]).

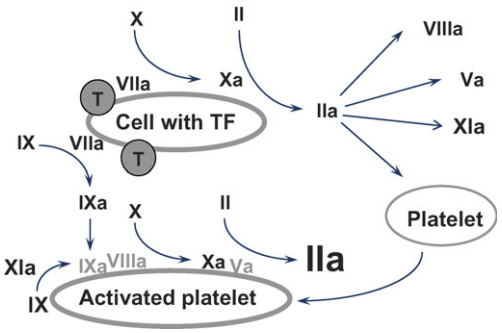

Fig. 4 Propagation. Propagation occurs on the surface of platelets, and results in the production of large amounts of thrombin (reproduced with permission from de Moerloose[25]).

Recombinant Factor VIIa is almost identical to circulating Factor VIIa and supranormal doses (i.e. 10 × normal levels) can compensate for lack of Factors VIII or IX. Recombinant Factor VIIa is licensed for the treatment of bleeding with inhibitors to factors VIII or IX, but has been shown to be effective in patients with trauma, thrombocytopenia, and oral anticoagulation overdose.[26–28] A review of off-label use of recombinant Factor VIIa considered seven studies examining its use for reversing anticoagulant therapy, 18 reports in perioperative or traumatic blood loss and 13 in patients with hepatic dysfunction.[29] The authors concluded that the use of recombinant Factor VIIa was appropriate in the following limited circumstances:

(i) cardiac, thoracic, aortic, or spinal surgery, hepatic resection, hysterectomy, or post-partum bleeding (when significant clotting factor replacement had failed);
(ii) for severe multiple trauma (only if surgery and substantial blood loss replacement are unsuccessful); and
(iii) for non-traumatic intracranial bleeding (only if less than 4 h has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and haematoma expansion).

The timing of the decision to administer recombinant Factor VIIa remains uncertain as the success or failure of clotting factor replacement, surgery, or other interventions has to be assessed clinically on a patient-by-patient basis. However, in severe bleeding, the Israeli Multidisciplinary rFVIIa Task Force recommends that it should only be given when the fibrinogen levels are >0.5 g litre^{-1}, platelet count $>50 \times 10^9$ litre^{-1}, and the pH > 7.2.[30] The recommended dose is 50–100 μg kg^{-1} i.v. A second dose can be given but, thereafter, further administration may be ineffective, suggesting that the source of bleeding is uncontrolled.

Conclusion

The conservative management of bleeding in critically ill patients should be considered as part of a process that enhances haemostatic control by surgical or radiological intervention as appropriate. General measures to improve coagulation (i.e. correcting anaemia, avoiding hypothermia, and acidaemia) should be simultaneously applied with other specific therapeutic options. These may include pharmaceutical agents such as desmopressin and antifibrinolytic drugs, blood products, such as FFP, cryoprecipitate, fibrinogen, platelets, and coagulation factors (e.g. prothrombin complex concentrates, Factor VIII, and recombinant Factor VIIa).

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Please see multiple choice questions 8–10