REVIEW ARTICLE

Coagulopathy and blood component transfusion in trauma

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Trauma is a serious global health problem, accounting for approximately one in 10 deaths worldwide. Uncontrollable bleeding accounts for 39% of trauma-related deaths and is the leading cause of potentially preventable death in patients with major trauma. While bleeding from vascular injury can usually be repaired surgically, coagulopathy-related bleeding is often more difficult to manage and may also mask the site of vascular injury. The causes of coagulopathy in patients with severe trauma are multifactorial, including consumption and dilution of platelets and coagulation factors, as well as dysfunction of platelets and the coagulation system. The interplay between hypothermia, acidosis and progressive coagulopathy, referred to as the 'lethal triad', often results in exsanguination. Current management of coagulopathy-related bleeding is based on blood component replacement therapy. However, there is a limit on the level of haemostasis that can be restored by replacement therapy. In addition, there is evidence that transfusion of red blood cells immediately after injury increases the incidence of post-injury infection and multiple organ failure. Strategies to prevent significant coagulopathy and to control critical bleeding effectively in the presence of coagulopathy may decrease the requirement for blood transfusion, thereby improving clinical outcome of patients with major trauma.

Trauma is a serious global health problem, accounting for approximately one in 10 deaths worldwide.[75 78] Trauma accounts for 5 million deaths per year, of which 1 million are in Europe.[78] It is estimated that by 2010 the annual trauma-related mortality worldwide will increase to 8.4 million.[74] Almost 50% of injury-related mortality is in young people between the ages of 15 and 44 yr.[78] Hence, the burden to society due to loss of productivity is enormous, amounting to a total of 182 million disability-adjusted life years lost annually.[78]

Resuscitation of trauma patients has improved significantly over the years. However, uncontrolled bleeding remains a major challenge, accounting for around 40% of trauma-related deaths,[46 47 91] and uncontrollable bleeding is the leading cause of potentially preventable and early in-hospital death.[46 91] Hence, effective control of bleeding may decrease mortality.

Life-threatening bleeding in trauma patients is usually caused by a combination of vascular injury and coagulopathy. Injury to major vessels often requires surgical intervention, but arterial embolization can be a useful approach to bleeding control, even in patients with multiple trauma.[35 76] Coagulopathy-related diffuse bleeding is difficult to manage. The causes of coagulopathy are multifactorial and interrelated, including consumption and dilution of coagulation factors and platelets, dysfunction of platelets and the coagulation system, increased fibrinolysis, compromise of the coagulation system by the infusion of colloid, hypocalcaemia, and disseminated intravascular coagulation-like syndrome.[29 30 36 52 71 86 87] Coagulopathy in conjunction with hypothermia and acidosis is often referred to as the 'lethal triad' because of the high mortality.[36 48 58]

Resuscitation of trauma patients with critical bleeding involves the infusion of large volumes of crystalloid and colloid followed by red blood cell (RBC) transfusion. However, RBC concentrates contain negligible amounts of platelets and coagulation factors. As a result, RBC transfusion, while improving oxygen transport, does not correct depletion of coagulation factors and platelets and can result in coagulopathy. Current management for coagulopathy-related bleeding is mainly based on transfusion of fresh frozen plasma (FFP), platelets, coagulation factor concentrates

(fibrinogen and prothrombin complex concentrates) and, where available, cryoprecipitate. When coagulopathy is accompanied by hypothermia and acidosis, even adequate replacement may not be able to control the bleeding, resulting in exsanguination.[28] Coagulopathy occurs early in the post-injury period,[61] and has been shown to be an independent predictor of mortality.[55 60 61] Therefore, correction of coagulopathy may potentially decrease mortality in patients with severe trauma.

Infection and multiple organ failure (MOF) are serious complications in patients who survive the initial insult from injury. Evidence has been accumulating that RBC transfusion may have negative effects on long-term outcome by increasing the incidence of post-injury infection and MOF.[15 22 73 92 107] A reduction in RBC transfusion may decrease these complications and improve outcome.

This article discusses the pathophysiology of coagulopathy in major trauma, the interrelationship between massive RBC transfusion and coagulation, unresolved issues in blood component replacement therapy, and the effect of allogeneic RBCs on outcome. In addition, it provides some guidance for the therapeutic use of blood components. Finally, the unmet need for effective haemostatic therapy is highlighted.

Pathophysiology of coagulopathy in trauma

Haemostasis process

Haemostatic response to vascular injury consists of a series of interactions between the subendothelial matrix, platelets and coagulation proteins[12 44 45 56 103] (Fig. 1). Normally, the endothelial cells lining the inner wall of blood vessels prevent the subendothelial matrix and tissue factor from coming int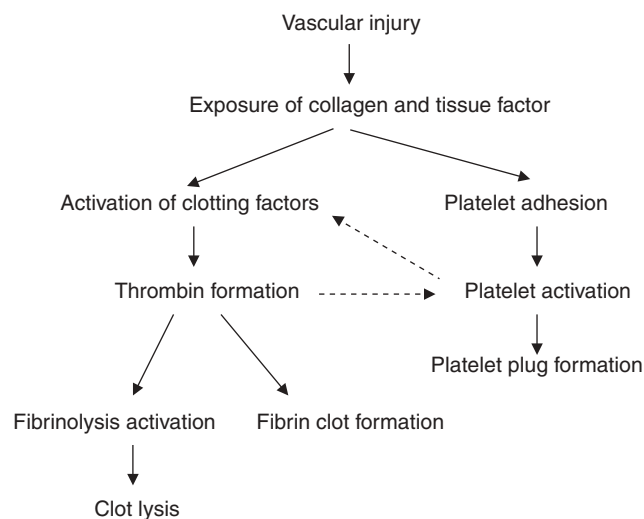o direct contact with circulating platelets and coagulation proteins. Vascular injury disrupts the integrity of the endothelial lining, exposing the subendothelial matrix. The adherence of platelets to the subendothelial matrix leads to platelet activation and platelet plug formation. The platelet plug acts as a catalytic surface for the recruitment and activation of coagulation proteins, optimizing the coagulation process.

The coagulation process (Fig. 2) is initiated by the binding of activated factor VII (which normally circulates in minute quantities) to the exposed tissue factor, which initiates coagulation by activating factors IX and X. Activated factor IX also activates factor X. Activated factor X, in turn, rapidly converts prothrombin to thrombin, generating small amounts of thrombin which are insufficient to convert fibrinogen to fibrin. The generation of thrombin is amplified by several feedback mechanisms. First, the generation of activated factor VII is increased by activation of factor VII bound to tissue factor by activated factors VII, IX and X. Second, the thrombin generated activates factors V and VIII, the cofactors which accelerate the activation of prothrombin and factor X, respectively. Thrombin increases the generation of activated factor IX by converting factor XI to an activated form. The generation of large amounts of activated factor X by activated factors IX and FVIII ensures that sufficient amounts of thrombin are continuously generated to convert fibrinogen to fibrin, hence forming a clot. In the final step of coagulation, thrombin activates factor XIII to activated factor XIII, which then cross-links the soluble fibrin monomers to form a stable fibrin clot. In addition, thrombin activates the thrombin-activatable-fibrinolysis inhibitor which protects the clot from premature fibrinolysis.[12 44 45 56 88 103]

The haemostatic system is regulated by several anticoagulant proteins and inhibitors, as well as by the fibrinolytic process. When operating in balance, these interdependent processes ensure that the formed fibrin clot stops the bleeding, and subsequently revascularization occurs to maintain the blood flow. Massive bleeding in patients with major trauma can stretch the capacity of the coagulation process to the limit, resulting in coagulopathy, uncontrollable bleeding and exsanguination, even in patients with previously normal haemostasis.

Vascular injury

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Exposure of collagen and tissue factor

Activation of clotting factors   Platelet adhesion

↓   ↓

Thrombin formation - - - - -> Platelet activation

↓   ↓

Fibrinolysis activation   Fibrin clot formation   Platelet plug formation

↓

Clot lysis

Fig 1 Simplified diagram showing the key steps of the haemostasis process.

Consumption coagulopathy

The pathogenesis of coagulopathy in trauma patients is complex. The precise cause is difficult to identify and is likely to be multifactorial (Table 1). Tissue damage, anoxia and shock activate the coagulation system, which in turn activates fibrinolysis.[29 30 36 52 87] The occurrence of multiple intravascular thrombi associated with areas of focal necrosis in various vital organs is similar to the findings in patients with disseminated intravascular coagulation.[36] Whether these changes represent a true disseminated intravascular coagulation remains unclear.[65] However, normal activation of the coagulation and fibrinolytic systems results in the consumption of platelets and coagulation factors, and
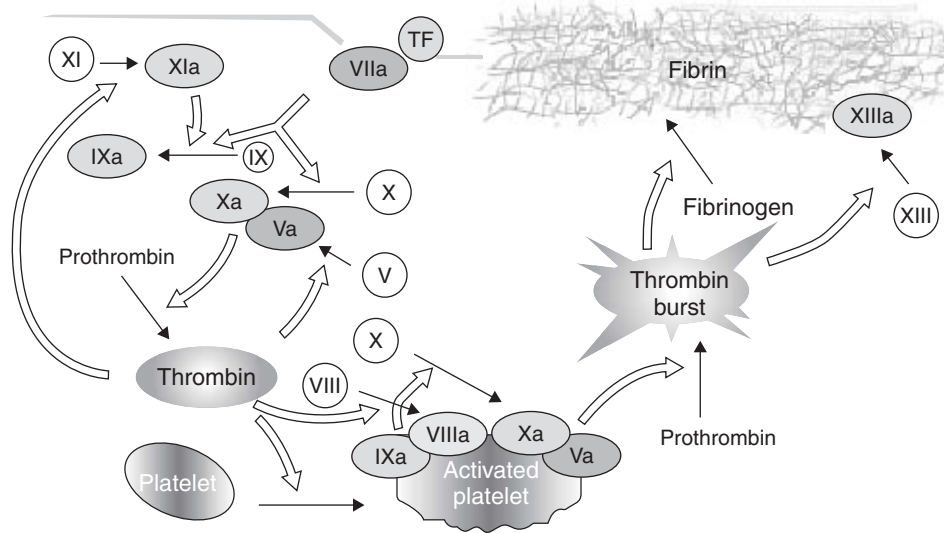
Fig 2 The coagulation process. For explanation see text.

Table 1 The major causes of coagulopathy in trauma patients

Blood loss
Consumption of platelets and coagulation factors
Dilution of coagulation factors and platelets
Increased fibrinolysis
Impaired functions of platelets and coagulation factors
Coagulation-compromising effect of colloids
Hypothermia
Hypocalcaemia

continuing bleeding causes further depletion of these haemostatic constituents from the circulation.

Increased fibrinolysis

Laboratory evidence has demonstrated both hypofibrinolytic and hyperfibrinolytic states in trauma patients.[23 24 87] The fibrinolytic status of trauma patients will vary with the severity of injury and the time from injury to the assessment of fibrinolytic activity. Simmons and colleagues have shown that immediately following trauma fibrinolytic activity increases. It returns to normal after the first 24 h in patients with mild to moderate injury, but remains elevated in those with major injuries.[97] In the presence of hypothermia, fibrinolytic activity is increased.[106] However, it should be noted that studies showing increased fibrinolysis in trauma patients were mainly published before 1990. It is conceivable that advances in emergency care, changes in fluid resuscitation policy, and improved quality of blood components might produce different results if such studies were performed today.

Hypothermia-induced coagulopathy

In trauma patients without pre-existing disease or massive head injury, the following conditions have been identified as significant risk factors for life-threatening coagulopathy: injury severity score >25, systolic blood pressure <70 mmHg, acidosis with pH <7.10 and hypothermia with a body temperature <34°C.[16] The interrelationship between hypothermia, metabolic acidosis and progressive coagulopathy is referred to as the 'lethal triad'; each factor exacerbates the others, leading to life-threatening bleeding or exsanguination (Fig. 3).[16 28 48 58 72] The causes of hypothermia are multifactorial and interdependent, including altered central thermoregulation, decreased heat production due to tissue hypoperfusion in haemorrhagic shock, exposure to low ambient temperature, and infusion of inadequately warmed resuscitation fluids and blood components.[79]

The coagulation process consists of multiple enzymatic reactions, which are temperature-dependent and function optimally at 37°C. The deleterious effect of hypothermia on coagulopathy in trauma patients has been well documented,[28 54 77 104] and when occurring in conjunction with metabolic acidosis, can result in a mortality rate as high as 90%.[28 54] The effect of hypothermia on coagulopathy is difficult to identify by routine coagulation screening tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), because these tests are routinely carried out at 37°C. Nevertheless, when PT and aPTT tests are carried out at low temperatures, as seen in hypothermic patients, both are significantly prolonged.[34 90 105] In addition, both *in vitro* and *in vivo* studies have shown that hypothermia significantly impairs platelet function and the formation of a platelet plug[70 100 104 105] and activates fibrinolysis.[106]

In summary, hypothermia impairs thrombin generation[69] and the formation of platelet plugs and fibrin clots, and at the same time increases clot lysis, resulting in coagulopathy and uncontrollable bleeding. Routine coagulation tests usually underestimate the degree of coagulopathy in a hypothermic patient and this should be taken into consideration when interpreting the results and correcting the coagulopathy.
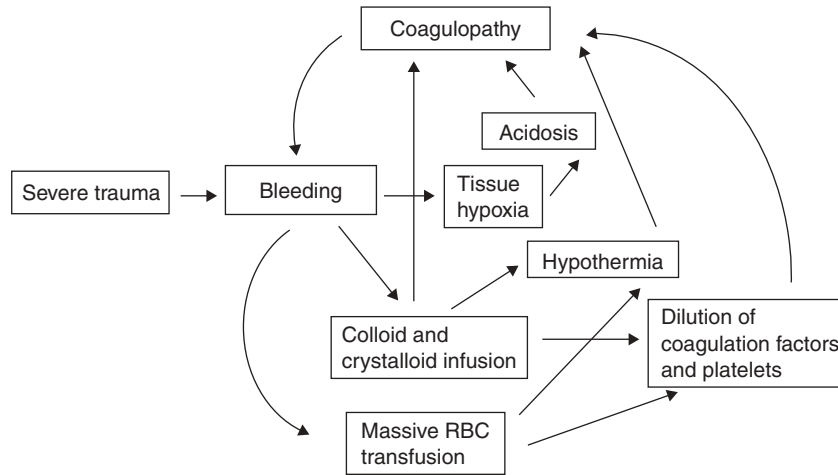
Fig 3 The interplay between metabolic acidosis, hypothermia and progressive coagulopathy in trauma (modified from reference 72, with permission from Excerpta Medica Inc.).

Decreased levels of coagulation factors and platelets

Infusion of large volumes of crystalloid and colloid during resuscitation reduces the concentrations of platelets and coagulation factors. In addition, thrombocytopenia is seen commonly in patients who have received massive blood transfusion, and has been thought to be a major cause of coagulopathy.[14 17 71 86 97] Although platelets are present in whole blood, storage at 4°C severely damages them and the remaining platelets disappear from the circulation almost immediately after transfusion.[8 71] In current practice, RBCs in additive solution rather than whole blood are widely used.[27] Consequently, RBC units contain negligible amounts of coagulation factors and platelets, and thrombocytopenia and subnormal levels of coagulation factors often occur at an early stage during massive RBC transfusion.

The effect of acute RBC loss on coagulation

The specific effect of RBCs on coagulation is unclear. *In vitro* experiments have shown that RBC membranes contain the enzyme elastase, which can activate factor IX and may serve as a triggering mechanism for blood coagulation.[50 51] In normal volunteers, an acute reduction in haematocrit results in reversible platelet dysfunction.[99] In contrast, using thromboelastography, Iselin and colleagues have found that an isolated reduction in haematocrit does not compromise coagulation.[49] As no data from trauma patients are available, the effect of acute RBC loss on coagulation in this group of patients is unknown.

Effect of massive RBC transfusion on coagulation

Blood transfusion in the past was largely dependent on the use of whole blood, whereas modern practice is based on the concept of specific component therapy. In developed countries, most whole blood units are separated within 18–24 h into RBCs, platelets and plasma, and, in some blood centres, cryoprecipitate is prepared after thawing FFP at 2–4°C. Blood component therapy optimizes the use of resources by allowing components to be used in different patients. It avoids the potentially harmful effects caused by the transfusion of surplus constituents.[4] For example, transfusion of whole blood instead of RBCs in additive solution to an anaemic patient increases the risk of plasma-associated transfusion reactions such as TRALI (transfusion-related acute lung injury), which is related to the presence of antibodies to HLA or leucocytes in the donor's plasma.[84]

While specific component therapy provides both logistic and economic benefits,[4] in massive RBC transfusion, coagulopathy due to low levels of platelets and clotting factors occurs at an earlier stage compared with the use of whole blood. A unit of whole blood contains approximately 200 ml of plasma with sufficient amounts of stable clotting factors, especially fibrinogen. In contrast, only a negligible amount of plasma—and therefore coagulation factors and platelets—remains in an RBC unit, and a plasma-free additive solution is added to the unit to provide nutrients and energy to RBCs, as well as pH buffering during storage.[24] During the Vietnam war, when stored whole blood was used, it was found that the platelet count did not fall below 100×10^9 litre^{-1} even after transfusion of 6 litres.[97] Nowadays, in contrast, 85% of patients receiving at least 10 units of RBCs in additive solution develop thrombocytopenia.[27]

The relationships between volume of blood loss, replacement volume and the reduction in coagulation factor and platelet levels are difficult to establish. This is due to several factors including the dynamics of blood loss, the difficulties in estimating true blood loss, the interindividual variations in clotting factor levels and the functionality of organ systems involved in haemostasis, i.e. the liver, spleen, and bone marrow. Martinowitz and colleagues found that in 36 patients with severe trauma, after massive RBC transfusion with a median of 21 units, the median fibrinogen level

was 1.5 g litre^{-1} (interquartile range 1.1–2.6 g litre^{-1}).[66] A similar finding was reported by Hiippala and colleagues, who found fibrinogen levels <1.0 g litre^{-1} after replacement of approximately 1.5 blood volumes in 60 major surgery patients.[42] However, McLoughlin and colleagues found that fibrinogen levels below 1.0 g litre^{-1} occurred after replacement of only 0.5 blood volume.[68] Nevertheless, this study was carried out in eight patients who had unusually low baseline levels of fibrinogen (around 1.6 g litre^{-1}).

In principle, the timely measurement of haemostatic competence should provide guidance for the management of individual patients. Unfortunately, the commonly used tests, PT and aPTT, are global tests which were originally developed to monitor anticoagulant therapy and their predictive value in trauma or surgical settings has never been validated.[21] Repeated measurement of fibrinogen concentration can help determine when fibrinogen replacement therapy is required in an individual patient. Thromboelastograph® data provide a qualitative and dynamic assessment of coagulation process from clot formation to clot lysis and use of the Thromboelastograph® may be useful in trauma patients.[18]

The increased acid load from RBC units may also contribute to coagulopathy. The pH of an RBC unit is low, and decreases progressively during storage, due to the production of lactic acid by RBCs, from around 7.0 initially to around 6.3 at the end of its shelf-life.[53] Because of the high buffering capacity of plasma in the circulation, transfusion of RBCs with such low pH does not usually cause acid–base disturbance. However, in the case of trauma patients who are already acidotic, massive transfusion of RBCs further increases the acid load,[7] which may in turn exacerbate the ongoing coagulopathy.

RBC transfusion is certainly life-saving in trauma patients with haemorrhagic shock. However, with the modern RBC components, which do not contain platelets and coagulation factors, coagulopathy occurs at an early stage during massive RBC transfusion.

Excess amounts of citrate anticoagulant are present in FFP. Trauma patients, particularly those with hypovolaemic shock or hypothermia, who have received large volumes of FFP may develop hypocalcaemia through citrate binding to circulating ionized calcium.[3 19 81] Because ionized calcium is one of the essential elements in coagulation, hypocalcaemia may contribute to coagulopathy.

Unresolved issues regarding blood transfusion in trauma

Optimal replacement therapy for FFP and platelets

It is well recognized that patients receiving massive RBC transfusion should also be given FFP, platelets, fibrinogen concentrate or cryoprecipitate. However, there are no universally accepted guidelines for the replacement of these haemostatic components. Current recommendations are usually based on experts' opinions or personal experience rather than evidence from randomized controlled trials.

Two different approaches to blood component replacement have been recommended and each has advantages and disadvantages. The first approach is to transfuse FFP and platelets prophylactically after a certain number of units of RBCs have been transfused.[27 42] However, there is no consensus on the optimal ratios; these vary widely, ranging from 1:10 to 2:3 for FFP:RBCs and from 6:10 to 12:10 for platelets:RBCs.[27 42 43] More importantly, there is no conclusive evidence that such a practice prevents the development of coagulopathy or improves bleeding.[64 82] There is no apparent relationship between bleeding and the total volume of plasma transfused.[82] The benefit of prophylactic platelet transfusion is also inconclusive, despite the fact that thrombocytopenia is commonly seen in patients who have received massive RBC transfusion.[38 40 85] Many studies have shown that thrombocytopenia does not always correlate with abnormal bleeding.[17 39 82] It is plausible that both platelet function and platelet count are fundamental for effective haemostasis.

The second approach is to transfuse FFP, platelets or cryoprecipitate only when there is clinical or laboratory evidence of coagulopathy.[25 37 42 86 98] For instance, when there is microvascular bleeding, a PT or aPTT >1.5 times normal value, thrombocytopenia with a platelet count <50–100×10^9 litre^{-1} or fibrinogen concentration <1 g litre^{-1} (Fig. 4).[1 14 25 27 64] The guidelines for blood component therapy recommended by the American Society of Anesthesiology Task Force on Blood Component Therapy are summarized in Table 2.[1] This approach also has its shortcomings. Clinical evidence of coagulopathy such as microvascular bleeding at an occult site can be difficult to
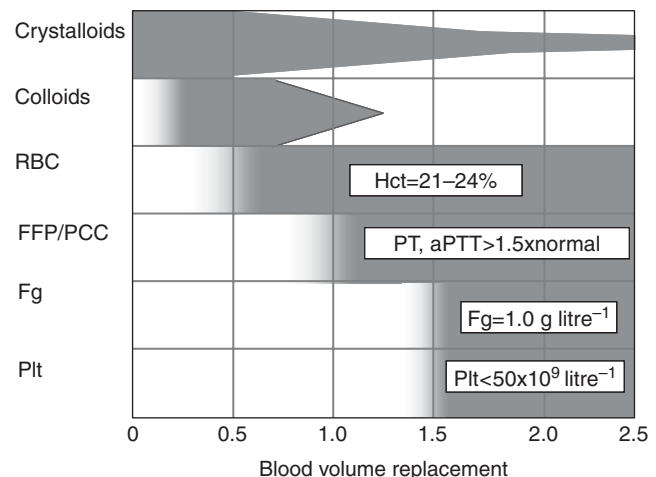

Fig 4 Fluid and blood component treatment in major bleeding (modified from reference 25, with permission from European Society of Haemapheresis). Values of various parameters represent trigger points at which relevant blood components should be transfused. RBC, red blood cells; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; Fg, fibrinogen; Plt, platelets; Hct, haematocrit; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Table 2 Guidelines for replacement therapy in patients with coagulopathy

Coagulation parameter	Recommended therapy
Prothrombin time >1.5 times normal	Fresh frozen plasma, prothrombin complex concentrate
Activated partial thromboplastin time >1.5 times normal	Fresh frozen plasma
Fibrinogen <1.0 g litre^{-1}	Fibrinogen concentrate, cryoprecipitate
Platelets <50×10^9 litre^{-1}	Platelets

observe.[27] In addition, laboratory tests may take 30–60 min from blood sampling to availability of results. The haemostatic status of trauma patients with massive bleeding can change rapidly, and hence the results might not reflect the patient's current status. Moreover, as discussed earlier, tests which are carried out at a standard temperature of 37°C, may not detect hypothermia-related coagulopathy. There may be a further delay between receiving the clinical or laboratory evidence and the required blood components being available, during which the coagulation status may have changed again.

Limitations on restoration of haemostasis

Both FFP and cryoprecipitate contain coagulation factors only in their physiological, low concentrations, which vary between donors. During the preparation of FFP, the levels of coagulation factors are diluted by approximately 15% in the first step as a result of the added anticoagulant solution. Further losses might also occur during the freezing–thawing process. Consequently, large volumes of FFP are needed to correct coagulation factor deficiency.[13]

The loss of platelets during the preparation process is more substantial: around 50% of the original number present in whole blood.[7] During storage, platelets undergo changes which result in the loss of their functional activity.[95] Hence, even transfusion of RBCs, FFP and platelets in a 1:1:1 ratio will not necessarily reconstitute the levels and functions of coagulation factors and platelets to the levels seen in normal whole blood.

The use of fresh whole blood

The use of 'fresh' (<24 h old) unrefrigerated whole blood instead of RBCs in trauma patients requiring massive transfusion has been proposed as means of overcoming coagulopathy.[26 33] This approach poses major logistic problems. Most blood banks process almost all whole blood units into blood components, and in an emergency situation fresh whole blood, especially in large amounts, is therefore not readily available. Moreover, as several countries have implemented universal leucodepletion, i.e. all blood units are leucodepleted before storage, whole blood which is leucodepleted is not really 'whole' as almost all platelets and some clotting factors are removed during the leucocyte filtration process.[59] Hence, the use of fresh whole blood may

not correct massive transfusion-related coagulopathy and is a rather impractical option. Moreover, the use of fresh whole blood would preclude adequate screening testing, which would dramatically decrease the safety of blood transfusion.

Clearly, the current practice of component replacement therapy in trauma patients with life-threatening bleeding is not ideal. Evidence from randomized controlled trials for a conclusive, optimal strategy is still lacking. Nevertheless, it may not be feasible to carry out such trials for ethical and logistic reasons. There is a limit on what can be achieved by blood component replacement therapy in trauma patients with uncontrollable bleeding.

Effect of RBC transfusion on longer-term outcome in trauma

Over the years, the risk of transfusion-transmitted infections caused by known pathogens, such as hepatitis B, hepatitis C and human immunodeficiency virus (HIV), has been significantly decreased.[6] However, there remains a residual risk of infection caused by these pathogens. There is increasing concern over infection caused by emerging pathogens, such as the agent of variant Creutzfeldt–Jacob disease (vCJD), hepatitis G virus, and West Nile virus.[6 83] In addition, blood transfusion is associated with a number of acute and delayed non-infectious complications (Table 3).[3]

In patients with major trauma, there appears to be a relationship between RBC transfusion and poorer outcome, in particular the development of post-injury multiple organ failure and infection, which will be discussed in more detail.

Multiple organ failure

Multiple organ failure is a serious post-injury complication resulting in prolonged intensive care unit (ICU) stay, requirement for mechanical ventilation for a longer period, and high mortality. Once MOF has developed, the mortality rate can be as high as 36%.[73] RBC transfusion has been shown to be an independent risk factor for post-injury MOF[73 92] and there is a strong dose–response relationship between early RBC transfusion and the development of MOF.[73] Analysis of a database consisting of 513 patients with major trauma, severe bleeding and haemorrhagic shock indicated that patients who developed MOF received an average of 13 units of RBCs in the first 12 h after injury compared with 3.8 units in patients who did not develop MOF.[73] Moreover, the age of transfused RBC has been shown to be an independent risk factor for post-injury MOF.[107] A decrease in the volume of RBCs transfused may decrease the risk and severity of MOF.

The precise mechanism of RBC transfusion-related MOF is yet to be established. Nevertheless, recent evidence supports the hypothesis that, during storage, bioreactive lipids, which have polymorphonuclear cell priming activity, are generated from RBCs.[96] While the initial insult caused by tissue damage and hypoxia primes the inflammatory system,

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Table 3 Transfusion-associated non-infectious complications of massive transfusion

Acute (within 24 h of transfusion)
    Haemolytic reactions
    Febrile non-haemolytic reactions
    Allergic reactions
    Transfusion-related acute lung injury
    Hypothermia
    Hypocalcaemia
    Metabolic acidosis
Delayed (>24 h after transfusion)
    Alloimmunization
    Immunosuppression
    Post-transfusion purpura
    Graft-*vs*-host disease

subsequent transfusion of stored RBCs containing these bioreactive lipids activates a systemic inflammatory response resulting in MOF.[73]

Post-injury infection

Infection is a common complication in trauma patients. RBC transfusion has been shown to be an independent risk factor for the development of post-injury infection,[15 22] and several mechanisms have been proposed. The exposure of patients to large amounts of foreign antigens may lead to down-regulation of the immune system.[101] The presence of leucocytes in RBC units has been thought to be a major contributory factor to the immunosuppressive effect of allogeneic blood transfusion.[9 10] Nevertheless, results from clinical trials are inconclusive as to whether leucodepletion eliminates the immunosuppressive effect of allogeneic blood.[80 101] An alternative non-immune-mediated mechanism of post-injury infection has been proposed. Stored RBCs are less deformable and more rigid, and once transfused they may obstruct capillary blood flow, predisposing tissue to ischaemia and infection as well as poor delivery of prophylactic antibiotics.[63 80 101]

A prospective observational study by Claridge and colleagues[15] revealed that the infection rate in trauma patients receiving at least one unit of RBCs during the first 48 h of hospital admission was significantly higher than that in the patients receiving none (33.0 *vs* 7.6%, $P<0.0001$), and there was a strong dose-dependent correlation between the amount transfused and the development of infection. However, the odds ratio of RBC transfusion as a risk factor for the development of post-injury infection was only 1.084 (95% confidence interval 1.028–1.142, $P=0.0028$).

In a prospective observational study, Malone and colleagues[62] analysed data from 15 534 trauma patients, of whom 1703 received RBC transfusion with a mean of 6.8±6.7 units. The results showed that, after controlling for severity of shock, RBC transfusion within the first 24 h was associated with increased mortality, admission to the ICU and lengths of ICU and hospital stays, which may be related to an increased risk of nosocomial infection. Nonetheless, there was no supportive evidence for a cause–effect relationship.

The development of infection might be associated with the length of storage of transfused RBCs. Based on 269 patients undergoing coronary artery bypass graft surgery, Vamvakas and Carven[102] found that the risk of post-operative pneumonia increased by 1% per day of increase in the mean storage time of the transfused RBC. In addition, a similar finding was observed by Leal-Noval and colleagues,[57] who conducted a study in 897 patients undergoing cardiac surgery. The results showed that each day of storage of the oldest unit increased the risk of pneumonia by 6% and transfusion of RBC units that were stored for >28 days could be a risk factor for nosocomial pneumonia.

It is noteworthy that studies on the effect of RBC transfusion on post-injury infection are mainly observational studies and should be interpreted with caution. Such studies cannot clearly define whether RBC transfusion causes post-injury complications or whether trauma patients who require RBC transfusion have had more severe illnesses, and, therefore, are more likely to develop complications. Only randomized prospective trials will provide a definitive answer. However, conducting such trials in severe trauma patients is extremely difficult, if not impossible, as exemplified by Schulman and colleagues.[93 94] They conducted a randomized prospective trial to establish the effect of varying age of RBCs on clinical outcome in trauma patients. Patients were only to be randomized if there were at least 15 units of 'young' (<11 days old) and 15 units of 'old' (>20 days old) type-specific leucodepleted RBCs available at the time. Despite 8000 injuries being evaluated, of which 3600 were severe, only 24 patients could be randomized and included in the trial, due to the limitation of blood bank inventory. On average, patients included in the trial received 10 units of RBCs. There were no statistically significant differences in post-injury complications between the two groups, which could be due, at least partly, to the limited number of patients studied. However, it is also possible that not only the age of RBCs, but also other factors, contribute to transfusion-associated post-injury infection.

RBC units have a limited shelf-life of around 42 days. Blood banks usually issue the oldest units of RBCs to avoid wastage from expired units. It may seem logical to suggest that fresher RBC units be used for resuscitation of trauma patients with massive blood loss. However, this approach might not be practical in terms of inventory management. A more practical strategy would be to attempt to reduce the amount of RBCs transfused. A prospective randomized controlled trial in critically ill trauma patients (Transfusion Requirements in Critical Care Trial, TRICC) has shown that a restrictive RBC transfusion strategy (haemoglobin concentration 70 g litre^{-1}) appears to be safe.[41 67]

The need for haemostatic agents

Despite significant improvements in resuscitation of trauma patients with haemorrhagic shock, coagulopathy-related bleeding remains a major challenge. The mainstay of

coagulopathy management is transfusion of FFP, platelets, fibrinogen and cryoprecipitate where available. During the preparation and storage of blood components, platelets undergo changes which result in progressive loss of their viability and function. Although some of the changes are reversible, there is little evidence that transfused platelets resume their normal function immediately, and the functional activities of coagulation factors in FFP are also decreased from their original level. Despite these storage changes, FFP, platelets and cryoprecipitate provide sufficient haemostasis in most patients. However, in certain cases, such as when coagulopathy is present in conjunction with hypothermia and acidosis, there is a limit on the level of haemostasis that can be restored by replacement therapy. In some cases, even adequate replacement fails to control the life-threatening bleeding resulting in exsanguination. Alternative haemostatic treatments, which are efficacious in such a setting, might be life-saving, and the use of haemostatic treatments that reduce RBC transfusion requirement might decrease post-injury complications such as MOF and infection, and eventually improve outcome.

The precise cause of coagulopathy-related bleeding can be difficult to identify and is usually multifactorial. An ideal haemostatic agent should therefore be efficacious in a wide range of haemostatic dysfunctions, simple to store and use, and have a rapid action. In addition, as the haemostatic status of patients with severe trauma may quickly swing from bleeding to thrombosis,[31 56 97] a relatively short half-life is necessary to minimize thromboembolic complications.

Activated recombinant coagulation factor VII (rFVIIa) is a potential candidate. A recent review by Goodnough and colleagues[32] has shown that rFVIIa may provide effective haemostasis in a wide range of bleeding conditions. In trauma patients with coagulopathic bleeding, Dutton and colleagues[20] used rFVIIa as the last resort and found that the bleeding decreased in most cases. A randomized controlled trial showed that rFVIIa significantly decreased the RBC transfusion requirement in patients with major trauma, and there were trends towards the reduction of MOF and acute respiratory distress syndrome.[11] Detailed results are yet to be published. Nonetheless, based on the results from 36 patients with severe trauma, the Israeli Multidisciplinary rFVIIa Task Force issued guidelines for the use of rFVIIa in uncontrolled bleeding,[66] which recommended that optimal preconditions (fibrinogen concentration $\geqslant 0.5$ g litre^{-1}, platelet count $\geqslant 50$ litre^{-1}, pH $\geqslant 7.2$) should be achieved before the administration of rFVIIa. As with any haemostatic agent, there are concerns over the potential thrombogenicity of rFVIIa.[5] Nevertheless, there are some clinical data showing a favourable safety and efficacy profile.[89]

Conclusions

Over recent years, the resuscitation of trauma patients with haemorrhagic shock has improved progressively.

Nevertheless, non-surgically correctable bleeding remains a major challenge. Currently, blood component replacement therapy remains the mainstay of coagulopathy-related bleeding. In certain cases, this might fail to control the bleeding resulting in exsanguination. Although RBC transfusion can be life-saving, its negative effects on post-injury outcome have been well documented. Haemostatic agents, which can effectively control bleeding and reduce the amount of RBCs required, may decrease mortality and morbidity in trauma patients but are unlikely to replace blood transfusion completely.

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