CRITICAL CARE

COMMENTARY

Is fibrinogen the answer to coagulopathy after massive transfusions?

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See related research by Grottke *et al.*, http://ccforum.com/content/14/2/R62

Abstract

Coagulopathy is a major cause of morbidity and mortality in patients who have suffered severe hemorrhage and received massive transfusions. Administration of a fibrinogen concentrate along with red blood cells can quickly restore hemostasis in a clinically relevant animal model.

Severe traumatic injury is frequently associated with hemorrhagic shock necessitating massive transfusions. Patients frequently become coagulopathic because of the combination of dilution of platelets and clotting factors, metabolic acidosis, hypothermia, and consumption of clotting factors. Although replacement of blood loss with fresh whole blood would be ideal, this is not possible in civilian situations under current blood-banking practices. Standard therapy involves the administration of packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate. The last of these is administered primarily to replete fibrinogen, which is commonly decreased by dilution as well as consumption. In the previous issue of *Critical Care*, Grottke and colleagues [1] explored the potential use of a fibrinogen concentrate instead.

Although these blood products are life-saving, they do have risks. In general, the more blood products administered, particularly PRBCs and FFP, the greater the risk for multiple organ system dysfunction and mortality [2-4]. Immunologic responses appear to play a major role.

In contrast, recent studies have suggested a beneficial effect of cryoprecipitate administration. In a military population of patients receiving massive transfusions, the ratio of fibrinogen (from all blood products) to PRBCs transfused was associated with reduced mortality [5]. Similarly, in a large database of civilians, administration of cryoprecipitate was associated with a decreased risk of multiple organ dysfunction [2].

Fibrinogen plays a critical role in hemostasis as it promotes platelet aggregation and, when activated to form fibrin, provides the substrate for red blood cells and platelets to form strong clots. In theory, administration of exogenous fibrinogen when the endogenous levels are low could bypass missing components of the clotting cascade.

Grottke and colleagues [1] have explored the use of different doses of a fibrinogen concentrate to correct the coagulopathy caused by hemodilution and to decrease bleeding in a clinically relevant animal model of trauma and hemorrhagic shock. This work builds upon the work of Fries and colleagues [6], which used a larger dose of fibrinogen. Fries and colleagues found a dose-dependent improvement in standard clotting studies and thromboelastograms (TEGs). Even with a relatively low dose, the authors found decreased bleeding and improved survival compared with controls. They also found no evidence of harm from the fibrinogen administration.

The model used in the study by Grottke and colleagues seems to be well designed to explore questions related to trauma and coagulopathy. The liver injury simulates severe trauma with active bleeding, which can be quantified. Coagulopathy is induced by hemodilution in a way that may be typical of the clinical situation of massive transfusion and fluid resuscitation without replacement of plasma, fibrinogen, or platelets. The use of the Cell Saver® (Haemonetics, Braintree, MA, USA), which might be used clinically to salvage and re-infuse the animals' red blood cells, further simulates clinical situations. The only aspect of the model that is not clinically relevant is timing since the coagulopathy and fibrinogen concentrate administration precede hemorrhage. This limitation does not detract from the utility of the model or the importance of the findings.

The results of this study [1] suggest that replacement of fibrinogen to a certain threshold level, perhaps as low as 70 mg/dL, is sufficient to provide hemostasis. Since fibrinogen needs to be activated to have an effect, it is intriguing and important to recognize that, even with

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this dilutional coagulopathy, sufficient activators seem to be present. Because of the question of activators, the authors see fibrinogen administration as adjunctive therapy to be used concomitantly with replacement of other coagulation factors.

Though not discussed much in the current paper, significant clinical experience with the fibrinogen concentrate used in this study has been reported. The product is clinically approved for use in patients with congenital fibrinogen deficiency and seems to have a good safety profile [7]. As a result, off-label use has already been reported. Fenger-Eriksen and colleagues [8] found that use of the fibrinogen concentrate improved standard clotting studies, increased fibrinogen levels, and decreased bleeding in patients with massive hemorrhage and decreased fibrinogen levels. Others have shown improved coagulation studies and decreased bleeding after cardiac [9], urologic [10], and orthopedic [11] surgery.

A secondary finding in this study is that standard clotting studies may not represent clinical hemostatic function as these normalized while the TEG remained abnormal. This finding is in agreement with others [12,13] and demonstrates the complexities in objectively monitoring coagulation with severe hemorrhage, hemodilution, and massive transfusions.

So where do we go from here? Grottke and colleagues [1] give us some guidance in this regard, recommending clinical studies of optimum level, need for combination therapy, timing, and patient selection. As far as the use of fibrinogen concentrates for patients with massive hemorrhage is concerned, there seem to be sufficient preclinical and preliminary clinical data to warrant a pivotal clinical trial in patients with massive hemorrhage. The work by Grottke and colleagues [1], as well as by others, gives us good data for dosing of fibrinogen concentrate and for minimal fibrinogen levels to be achieved. Trauma patients in hemorrhagic shock would be an appropriate target population. It may be that focused restitution of fibrinogen levels with a fibrinogen concentrate is more efficient and efficacious than the use of cryoprecipitate or other blood products. Although it is unlikely that fibrinogen will be a magic bullet, it may be an excellent adjunct to blood component replacement.

Abbreviations

FFP, fresh frozen plasma; PRBC, packed red blood cell; TEG, thromboelastogram.

Competing interests

SAT is a co-holder of a patent on the "Emergency Preservation and Resuscitation Method".

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Role of fibrinogen in trauma-induced coagulopathy

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Key points

- Fibrinogen levels decrease at an early stage in severe haemorrhage.
- Low fibrinogen levels are associated with increased perioperative bleeding.
- The threshold level for fibrinogen is not defined clearly.
- Early correction using fibrinogen concentrate can improve outcome.

Summary. Coagulation defects related to severe trauma, trauma-induced coagulopathy (TIC), have a number of causal factors including: major blood loss with consumption of clotting factors and platelets, and dilutional coagulopathy after administration of crystalloids and colloids to maintain blood pressure. In addition, activation of the fibrinolytic system or hyperfibrinolysis, hypothermia, acidosis, and metabolic changes can also affect the coagulation system. All of these directly affect fibrinogen polymerization and metabolism. Other bleeding-related deficiencies usually develop later in massive bleeding related to severe multiple trauma. In major blood loss, fibrinogen reaches a critical value earlier than other procoagulatory factors, or platelets. The question of the critical threshold value is presently the subject of heated debate. A threshold of 100 mg dl^{-1} has been recommended, but recent clinical data have shown that at a fibrinogen level of $<150–200$ mg dl^{-1}, there is already an increased tendency to peri- and postoperative bleeding. A high fibrinogen count exerts a protective effect with regard to the amount of blood loss. In multiple trauma patients, priority must be given to early and effective correction of impaired fibrin polymerization by administering fibrinogen concentrate.

Keywords: coagulation; transfusion; trauma

Coagulation defects related to severe trauma have a number of causal factors including: major blood loss with consumption of clotting factors and platelets, and dilutional coagulopathy after administration of crystalloids and colloids to maintain blood pressure. In addition, activation of the fibrinolytic system or hyperfibrinolysis, hypothermia, acidosis, and metabolic changes also affect the coagulation system. All of these directly affect fibrinogen polymerization and metabolism, whereas other bleeding-related deficiencies usually develop later in the course of massive bleeding related to severe multiple traumatized patients. In major blood loss, fibrinogen reaches a critical value earlier than other procoagulatory factors, or platelets. The question of the critical threshold value is presently the subject of heated debate. A threshold of 100 mg dl^{-1} has been recommended, but recent clinical data have shown that at a fibrinogen level of $<150–200$ mg dl^{-1}, there is already an increased tendency to peri- and postoperative bleeding. Thus, a high fibrinogen count may exert a protective effect with regard to the amount of blood loss.

Recent findings suggest that fibrinogen availability may play an important role in the survival of trauma patients. The aim of this article is to summarize recent findings regarding changes in fibrinogen availability after traumatic injury. The effects of trauma and blood loss, haemodilution, hyperfibrinolysis, acidosis, and hypothermia are discussed in the context of fibrinogen availability and the potential benefit of fibrinogen supplementation.

Trauma-induced coagulopathy

The presence of TIC reflects the extent and severity of injury and correlates with mortality.[1 2] In spite of the rapid use of damage control surgery, the main cause of death in severe trauma, other than head injury, is bleeding, even at specialized centres.[3] In TIC, unlike what occurs in disseminated intravascular coagulopathy, there is no generalized intravascular microcoagulation with subsequent consumption. Instead, there is a bleeding-related loss of coagulation factors and platelets. Subsequently, the remaining procoagulant potential is diluted by the administration of crystalloids and, particularly, by colloids which may also directly affect fibrinogen polymerization.[4] Haemostasis is also fundamentally disturbed by increased fibrinolytic potential, hypothermia, acidosis, anaemia, and electrolyte disturbances, whereas hyperfibrinolysis, hypothermia, and acidosis directly disturb fibrinogen polymerization and metabolism.[5 6] There is a limited increase in fibrinogen synthesis during blood loss which cannot be compensated due to the concomitantly increased fibrinogen breakdown.[2 7] Fibrinogen is present at concentrations of grams per litre which is some 1000-fold higher than other coagulation factors, which are usually in milligrams per litre.

The aim of any haemostatic therapy is to minimize blood loss and transfusion requirements, and increased transfusion need is known to increase morbidity and mortality in trauma patients. In patients with similar Injury Severity Scores (ISS), mortality is virtually quadrupled as a result of coagulopathy.[1] Massive bleeding or massive transfusion in multiple trauma patients is necessarily associated with impaired coagulation. In simple terms, to achieve adequate haemostasis, sufficient thrombin and coagulable substrate are required. In addition to platelets, on whose surface most of the thrombin is formed, fibrinogen can be regarded as a primary substrate of coagulation.[8] If sufficient thrombin is formed, it converts fibrinogen to stable fibrin, which determines the firmness of the developing clot in the presence of factor XIII.[9]

Effect of volume replacement therapy on coagulation: dilutional coagulopathy

After trauma and massive bleeding, it is important to achieve normovolaemia to prevent the development of shock and acidosis, which are directly related to coagulopathy and worsen outcome.[10] In this setting, the optimal choice of volume expander remains controversial.

Crystalloids compromise the coagulation system chiefly through their diluting effect. Resuscitation with Ringer's lactate reduces tissue hypoxia indices but does not effect the changes in fibrinogen metabolism resulting from haemorrhage.[11]

Gelatin products also have a diluting effect and fibrin polymerization is impaired.[12] Decreased clot elasticity, decreased clot weight, and—compared with crystalloid solutions—an increased reduction in the von Willebrand factor have also been reported.

Hydroxyethyl starch (HES) solutions may increase haemorrhagic tendency, particularly solutions with a high molecular weight and high degree of substitution. HES causes hypocalcaemia, platelet coating, blockade of the fibrinogen receptor (GPIIb–IIIa), von Willebrand type 1-like syndrome, and a fibrin polymerization disturbance that might exceed the anticoagulant effect of gelatin.[13]

Hyperfibrinolysis

Hyperfibrinolysis in trauma patients cannot be predicted reliably, but appears to be linked to the severity of the trauma and the organ systems affected (e.g. head injury and urogenital tract injury).[14] Activation of the coagulation system, induced by tissue and endothelial damage, leads to simultaneous release of tissue plasminogen activator (t-PA) and its antagonist, plasminogen activator inhibitor type 1 (PAI-1). Initially, the increase in t-PA appears to outstrip that in PAI-1. In some studies, measurement of the molecular markers of fibrinolysis has shown an increase in fibrinolytic potential, whereas others have found lysis to be decreased as a consequence of trauma. In hyperfibrinolysis, the haemorrhagic tendency can only be treated by giving antifibrinolytics before giving fibrinogen concentrate or, if these are not available, cryoprecipitate. The efficacy of antifibrinolytics has been well described in cardiac, orthopaedic, and liver (transplant) surgery, but data on their use in severe trauma are lacking.[15]

Effects of acidosis on fibrinogen metabolism

Acidosis can develop as a consequence of trauma and blood loss and is one of the most important predictors of coagulopathy in trauma patients, with the likelihood of death increasing as the severity of acidosis increases. The detrimental effects of acidosis on coagulation include impaired enzyme activity, depleted fibrinogen levels and platelet counts, prolonged clotting time, and increased bleeding time.[16 17]

The mechanisms contributing to the depletions of fibrinogen were studied recently in a swine model where acidosis of pH 7.1 was induced by an infusion of 0.2 N HCl in lactated Ringer's solution (LR).[18] When the target pH of 7.1 was achieved and Lactated Ringer's solution stabilized, stable 1-^{13}C-phenylalanine was infused for 6 h and d_5-phenylalanine was infused for 4 h. Blood samples were obtained hourly during the infusion and the isotopic labelling of fibrinogen was determined using gas chromatography and mass spectrometry analysis. This study showed that acidosis increased fibrinogen breakdown by 1.8-fold compared with control values, with no effects on fibrinogen synthesis.[18] Thus, it appears that acidosis had different effects on fibrinogen synthesis and breakdown and there was a potential depletion of fibrinogen availability after acidosis.

Effects of hypothermia on fibrinogen metabolism

Hypothermia, with a body temperature of $\leq$34°C, is commonly observed in severely injured patients. The relationship of hypothermia to abnormal coagulation and mortality has been well described. In a group of trauma patients with ISS $>$25, the mortality increased from 10 to 100% when body temperature declined from 35 to $<$32°C.[19] Around 80% of those who did not survive had a body temperature of $<$34°C at the time of death.[20] The known adverse effects of hypothermia on coagulation include prolonged prothrombin time and activated partial thromboplastin time in hypothermic patients and animal experiments, and in plasma samples cooled *in vitro*.[21 22]

The effects of hypothermia on fibrinogen metabolism and coagulation function were investigated in a normovolaemic swine model.[23] Hypothermia of 32°C was induced using a cold blanket with circulating water at 4°C. When the temperature was stabilized at 32°C, 1-^{13}C-phenylalanine and d_5-phenylalanine were infused to quantify fibrinogen metabolism.[23] Hypothermia of 32°C decreased fibrinogen synthesis, with no effects on fibrinogen degradation (Fig. 1). Fibrinogen synthesis and degradation are regulated via different mechanisms and there is also a potential deficit in fibrinogen availability after hypothermia.

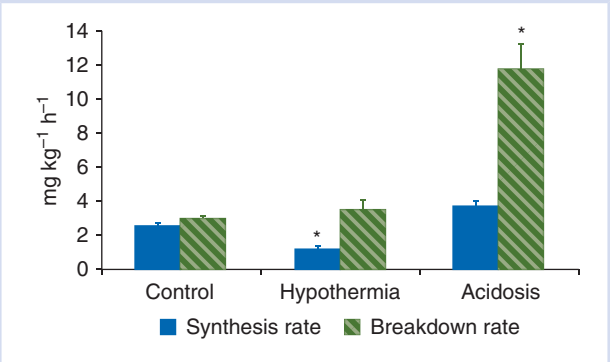

Fig 1 Changes in fibrinogen synthesis and breakdown in pigs after haemorrhage, hypothermia, and acidosis. Data from Martini and colleagues[17] and Martini and Holcomb.[18] *$P<0.05$ compared with control values.

Interaction of platelets with fibrinogen

International recommendations suggest replacement using platelet concentrates should be given for trauma- or surgery-related bleeding if the platelet count decreases below 50 000 μl^{-1}.[24] A lack of platelets primarily affects clot firmness, which is also influenced by fibrinogen plasma level. To assess an individual's need for replacement therapy, thrombelastographic (TEG®)/thrombelastometric (ROTEM®) measurements of clot firmness in relation to fibrinogen polymerization can provide valuable information, as strong fibrin polymerization can compensate for the decreased platelet contribution to clot firmness. Thrombocytopenic patients with inflammation-induced elevated fibrinogen values in TEG®/ROTEM® monitoring are often not transfused with platelet concentrates because the clot firmness is within the normal range.

An animal study found that the administration of fibrinogen concentrate significantly improved clot firmness in comparison with the transfusion of 3-day-old aphaeresis concentrates or placebo.[25] In uncontrolled bleeding, the fibrinogen-treated animals had significantly lower blood loss and longer survival times than animals given platelet concentrate and placebo.

Fibrinogen replacement in TIC

It may be thought that coagulation disturbances should not be treated until the source of the bleeding has been surgically dealt with. A strong counterargument to this is that this delay reduces the haemostatic potential to such a degree that surgery becomes much more difficult and microvascular bleeding in non-injured organ systems can occur. The resulting deficit can be so pronounced that conventional coagulation therapies will fail.

As a consequence of blood lost, dilutional coagulopathy, hypothermia, and acidosis, fibrinogen may reach critical levels at an early stage in multiple trauma patients with massive bleeding. Even small quantities of colloids (>1000 ml) can impair fibrin polymerization.[13] Normovolaemic dilution can cause the critical fibrinogen concentration to be reached even before administration of red blood cells becomes necessary.[26] As discussed above, the critical fibrinogen value is unclear with some recommending 100 mg dl^{-1} [27] or even 50 mg dl^{-1} [28] adequate. These recommendations also do not take account of the fact that plasma fibrinogen measurements, both in the high and the very low range, are not readily standardized. They can be distorted upwards by the use of colloids and, particularly, HES[29 30] and do not agree with functional measurements.[13]

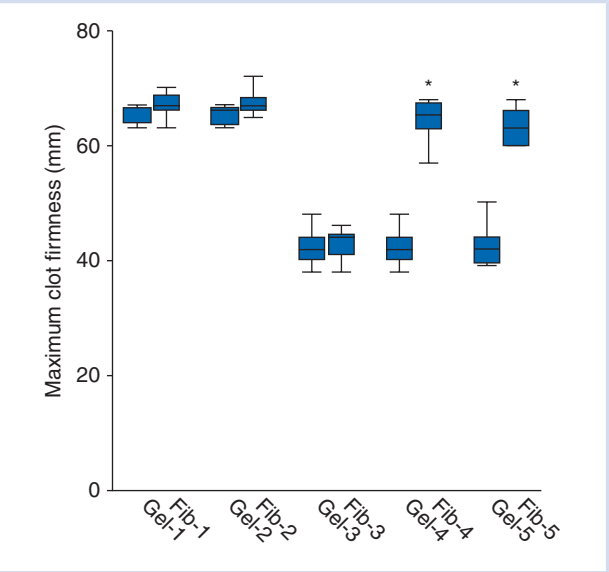

Fig 2 Clot firmness measured with the ROTEM system in an animal model of controlled and uncontrolled haemorrhage: MCF (in mm) at baseline (1), after removal of 65% of the estimated blood volume (2), after colloid administration (3), after substitution of fibrinogen concentrate (Fib) or placebo (Gel) (4), and after an observation period of 2 h (5).[31]

The influence of fibrinogen concentrate has been examined in several animal models of uncontrolled bleeding. In one model, 65% of the estimated total blood volume was withdrawn from pigs and compensated with gelatin to induce severe dilutional coagulopathy. Fibrinogen concentration or a placebo was subsequently administered. The compensation with fibrinogen concentrate normalized the impaired clot strength (Figs 2 and 3). The animals who received fibrinogen concentrate showed statistically significantly less blood loss after a stab incision to the liver.[31]

Clinical data from gynaecological, neurosurgery, and cardiac surgery show that perioperative and postoperative haemorrhagic tendency is increased when fibrinogen levels are below 150–200 mg dl^{-1}.[32–37] Data on the efficacy of fibrinogen concentrates in acquired fibrinogen deficiency are limited. Observational reports from clinical use and retrospective data analyses have shown that fibrinogen concentrate is able to stabilize reduced clot strength.[38–40] During spinal or large craniofacial operations, reduced clot strength

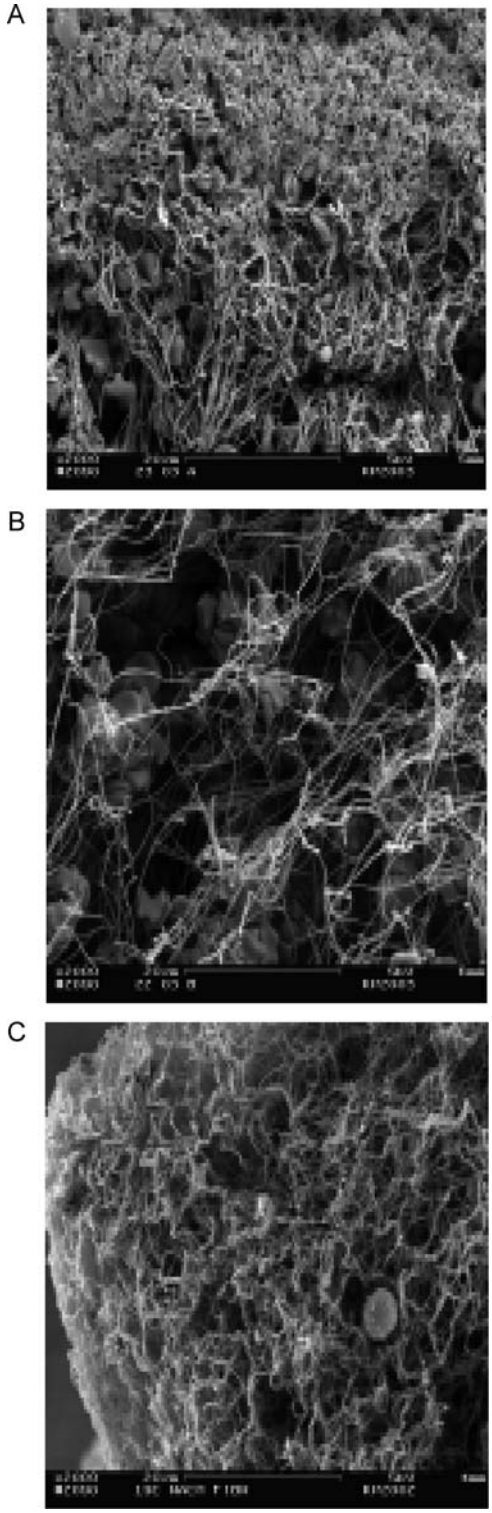

Fig 3 Electron microscopic scan of a ×2000 magnified blood clot in a non-diluted state (A), after 65% haemodilution with gelatin (B), and after administration of fibrinogen concentrate to compensate dilutional coagulopathy (C). The administration of fibrinogen was able to compact the rarefied fibrin network again.[31]

was improved by administering fibrinogen concentrate alone.[41] A retrospective study in 252 seriously injured soldiers who received massive transfusion correlated the amount of fibrinogen given (a combination of cryoprecipitate and fresh-frozen plasma) and survival.[42]

Four other small prospective clinical studies have examined the use of fibrinogen concentrate (ROTEM®-assisted in two studies). In all four studies, coagulation was optimized, perioperative bleeding was reduced by 32%,[43] and transfusion requirement was significantly reduced.[44–46]

In summary, a high circulating fibrinogen exerts a protective effect with regard to blood loss. In clinical practice, TEG® or ROTEM® monitoring simplifies and improves coagulation monitoring and management. In bleeding which requires transfusion, fibrinogen concentrate (or cryoprecipitate) should be administered if the maximum clot firmness (MCF) in the FIBTEM® analysis is below 10–12 mm, the 10 min value is below 7 mm (depending on the clinical situation), or both. If ROTEM® monitoring is not available, fibrinogen plasma levels should be maintained at a minimum of 150–200 mg dl^{-1}.

In conclusion, fibrinogen availability is regulated through dynamic changes of synthesis and breakdown to maintain coagulation function. Recent studies have shown the role of fibrinogen availability in TIC. Haemodilution, hyperfibrinolysis, acidosis, and hypothermia all depleted fibrinogen availability and consequently impair coagulation process. Recent retrospective studies in trauma patients and animal models suggest that fibrinogen supplementation may be beneficial. Further prospective clinical trials to confirm the benefits of fibrinogen supplementation in trauma patients with TIC are warranted.

Conflict of interest

D. Fries received an honorarium for consulting from LFB and a fee for lectures from CSL Behring.

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EDITORIAL

Towards early individual goal-directed coagulation management in trauma patients

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Major trauma is associated with significant blood loss due to both the severity of injuries and trauma-related coagulopathy. Acute coagulopathy in trauma patients is frequent and has been associated with a worse clinical outcome.[1 2] In this issue of the *British Journal of Anaesthesia*, Fries and Martini[3] review the mechanisms of trauma-related coagulopathy and the central role of fibrinogen in its treatment. This is a very timely issue since the understanding of the coagulopathy of trauma and shock has indeed increased tremendously in recent years. In addition, fibrinogen is increasingly viewed as the coagulation factor that is the first to become critically low in cases of major haemorrhage.[1]

Acute traumatic coagulopathy has traditionally been explained as an acquired disorder in the coagulation system which occurs through loss or impaired function of coagulation proteases and platelets. However, severe trauma leads to massive haemorrhage with activation and subsequent exhaustion of the coagulation system. Dilution from fluid resuscitation results in an additional relative deficiency of coagulation factors and platelets. Finally, physical factors such as acidaemia and hypothermia further compromise coagulation proteases and platelet function, worsening the evolving coagulopathy.

Recent studies have shown that nearly 25% of trauma patients present with a clinically significant coagulopathy upon arrival in the emergency department which affects their overall outcome.[4] Interestingly, this early coagulopathy occurred before any significant consumption or fluid administration and in the absence of a relevant acidaemia or hypothermia. Therefore, it has been postulated that the early coagulopathy after trauma be physiologically and mechanically distinct. This acute coagulopathy of trauma, which has also been called endogenous acute coagulopathy[5] or acute coagulopathy of trauma and shock,[6] is driven by a combination of tissue trauma and shock with systemic hypoperfusion. Thus, the anticoagulant thrombomodulin protein C pathway is overtly activated, resulting in reduced pro-coagulatory potential and increased fibrinolytic activity.[7 8] Once protein C is activated through a thrombin–thrombomodulin-dependent reaction, activated protein C (aPC) exerts its profound anticoagulant effects by irreversibly inactivating factors Va and VIIIa. In addition to its direct inhibition of fibrin formation, aPC causes resolution of formed clots by stopping the inhibition of fibrinolysis by direct inhibition of plasminogen activator inhibitor 1.[9 10]

After major trauma, surgeons and anaesthetists are faced with a dual problem of physical damage, including vascular injury, with 'surgical' haemorrhage and a component of coagulopathy with 'coagulopathic' bleeding (and any combination thereof). The first requires surgical control, and the second requires treatment with pro-coagulatory substances such as labile/allogeneic blood products, coagulation factor concentrate, and, potentially, anti-fibrinolytics. In this situation, the physician must first immediately analyse the situation to establish whether coagulopathy is present and subsequently decide what should be used for treatment, given the hazards, unknowns, and costs of allogeneic blood products, factor concentrates, and anti-fibrinolytics.

A first option to boost blood coagulation after major trauma is to administer a 'massive transfusion package' with a fixed

ratio of fresh frozen plasma (FFP) to red blood cell (RBC), some with a high ratio and some even include platelets.[11] The apparent success of such algorithms in improving survival of US Army combat victims has been described.[1 12] However, there are also studies, in which a high FFP:RBC regimen has shown no benefit with regards to survival.[13 14] There is an important study showing that the introduction of 'massive transfusion packages' resulted in a significant reduction in mortality without a change in the FFP:RBC ratio given in the first 24 h.[15] Interestingly, in this study, FFP (169 *vs* 254 min) and platelets (241 *vs* 418 min) were administered much earlier after the introduction of 'massive transfusion packages'.[15] There are several important aspects to consider when interpreting results of studies showing a benefit of a high FFP:RBC ratio in trauma patients. The data are retrospective and primarily refer to young, previously healthy male patients with penetrating injuries. In addition, the FFP:RBC ratio usually is calculated for the first 24 h of treatment. Therefore, there may be a significant selection bias in that clinicians may have allocated most resources, including FFP, to those patients most likely to survive.[16] There may also be a survivor bias in that those with the worst injury and bleeding died too early to receive a large amount of FFP.[16 17] In addition, FFP transfusion is associated with adverse effects such as increased incidence of nosocomial infections,[18] multiple organ failure,[17] lung injury,[16 17] and possibly mortality.[16 19] Therefore, although the use of FFP is suggested in massive bleeding, the recently published AABB guidelines[12] and the updated European guideline on the management of bleeding after major trauma[1] do not recommend transfusion of plasma at a FFP:RBC ratio of 1:3 or more.

A second treatment option aimed at early, individual optimization of blood coagulation after major trauma is to assess each trauma patient's coagulation status on admission in the emergency room and throughout the surgery with point-of-care viscoelastic coagulation monitoring (thrombelastography, TEG®, Haemonetics Corp., formerly Haemoscope or rotational thromboelastometry, ROTEM®, tem innovations GmbH, formerly Pentapharm).[20 21] These bed-side devices allow analysis of the entire blood coagulation within 10–15 min[22] including the detection of (hyper)fibrinolysis.[7 8] With this information, coagulation can be readily and individually optimized, for example, with anti-fibrinolytics and blood coagulation factor concentrates and later, if necessary with labile blood products. With such an algorithm, the use of RBC, FFP, and platelets can be significantly reduced[23] and survival of trauma patients may be significantly improved.[24] In this study, the observed mortality was 24.4% which was significantly lower than the expected mortality based on the trauma injury severity score (TRISS) of 33.7%.[24]

Fibrinogen may be the key element of blood coagulation and is the first element to get critically low.[1] Fibrin polymerization can be compromised by colloids which are frequently used in the initial resuscitation of trauma victims. Interestingly, this form of blood coagulation compromise can be reversed by the administration of fibrinogen.[25] Therefore, aiming at functional fibrinogen levels as assessed by thromboelastometry[23 24] appears reasonable. This is also proposed in the updated European guidelines on the management of bleeding after major trauma.[1] If thrombelastometric monitoring is not available, serum fibrinogen levels of 1.5–2.0 g litre^{-1} should be targeted.[1] However, clinicians should be aware that in the presence of artificial colloids such as hydroxyethyl starch, gelatin, or dextran, the most often used fibrinogen measurement method, the Clauss method, significantly overestimates fibrinogen concentration.[26 27]

An additional benefit of bed-side coagulation monitoring is speed. If the coagulation status measured on arrival in the emergency department, the main coagulation problem is known within 15 min. The trauma patient can then immediately and specifically be treated according to an institutional transfusion algorithm. Importantly, guidelines aimed at optimizing the individual's coagulation status also avoid excessive pro-coagulatory potential with associated thrombotic complications. The time advantage of bed-side coagulation monitoring compares very favourably with the improved times of FFP administration described in the study of the introduction of a massive transfusion package.[15]

The review by Fries and Martini[3] explaining the mechanisms of coagulopathy of trauma and shock and the central role of fibrinogen is an important contribution towards a better understanding of this complex situation and a better treatment of trauma patients. Their recommendation to view fibrinogen as a central element of blood coagulation is in agreement with the updated European guideline on the management of bleeding after major trauma.[1] The first goal is that all hospitals treating trauma patients have an institutional algorithm for the management of a trauma patient with major bleeding. The ultimate goal is to establish algorithms allowing early individual goal-directed coagulation management in trauma patients. To introduce such concepts into general medicine, they need to be rigorously tested in large prospective randomized trials.

Conflict of interest

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