The role of fibrinogen in trauma-induced coagulopathy*

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Summary
Fibrinogen plays an essential role in clot formation and stability. Importantly it seems to be the most vulnerable coagulation factor, reaching critical levels earlier than the others during the course of severe injury. A variety of causes of fibrinogen depletion in major trauma have been identified, such as blood loss, dilution, consumption, hyperfibrinolysis, hypothermia and acidosis. Low concentrations of fibrinogen are associated with an increased risk of diffuse microvascular bleeding. Therefore, repeated measurements of plasma fibrinogen concentration are strongly recommended in trauma patients with major bleeding. Recent guidelines recommend maintaining plasma fibrinogen concentration at 1.5–2 g/l in coagulopathic patients. It has been shown that early fibrinogen substitution is associated with improved outcome.

Zusammenfassung

Coagulopathy in trauma is a consequence of multiple mechanisms. These include (39)

• substantial blood loss,
• consumption of coagulation factors,
• dilution of the remaining coagulation proteins due to crystalloid and colloid fluid administration,
• profibrinolytic activation,
• acidosis and
• hypothermia.

Fibrinogen plays a central role in clot formation. Therefore, low fibrinogen concentrations are associated with an increased risk of bleeding due to impaired primary and secondary haemostasis (13, 17).

However, the threshold at which the plasma concentration of fibrinogen may be considered as critically low in trauma is not well established. Earlier guidelines suggested fibrinogen levels of 0.8–1 g/l as sufficient (69). The recent updates of the European Trauma Guidelines, the perioperative bleeding Guidelines of the European Society of Anaesthesiologists and the Canadian National Advisory Committee on Blood and Blood Products recommend that plasma fibrinogen concentration in bleeding trauma patients should be not lower than 1.5–2 g/l (24, 50, 92). However, until now no randomized controlled studies are available to support these suggested values (64), and data from cardiac surgery and postpartum haemorrhage indicate that threshold values should be higher (11, 46, 73, 74).

Experimental and initial clinical studies have reported promising outcomes in response to replacement of fibrinogen as the initial step in managing trauma-induced coagulopathy (TIC) (35, 82, 83, 93, 102). There are three treatment options for fibrinogen replacement:

• fresh frozen plasma (FFP),
• cryoprecipitate and
• fibrinogen concentrate (FC).

This review summarizes the role of fibrinogen in trauma related bleeding and covers diagnostic options to measure fibrinogen. Furthermore, therapeutic alternatives to increase plasma fibrinogen concentration are described.
Fibrinogen

Fibrinogen is a glycoprotein synthesized solely in the liver. Its typical molecular weight is approximately 340,000 Dalton and it consists of three polypeptide chains (alpha, beta, and gamma-), linked by disulphide bridges (55). It plays a central role in primary and secondary haemostasis and is the precursor of fibrin, which is essential for coagulation. Therefore, fibrinogen can be considered as the primary substance of the coagulation process (66).

Thrombin cleaves the fibrinogen molecule, and the resulting fibrin monomers are polymerised to form a fibrin clot. This matrix is stabilized by activated coagulation factor XIII (49, 55, 63). Fibrinogen plays an important role in the aggregation and linking of platelets (14).

Activated platelets express glycoprotein IIb/IIIa receptors on their surface with a high affinity to fibrinogen (101). Small quantities of fibrinogen are stored in the alpha-granules of platelets, and these are released following platelet activation (63, 66).

A healthy adult has approximately 10 g of fibrinogen (38) with the plasma concentration ranging between 2 and 4 g/l (64).

In clinical scenarios such as pregnancy, the plasma fibrinogen concentration is substantially higher. Fibrinogen is an acute phase reaction protein, so the level also increases significantly in response to trauma and inflammation (70, 77).

What reduces fibrinogen concentration in trauma?

Recent studies have demonstrated that fibrinogen is decreased to a higher extent than other coagulation factors in trauma or cardiac surgical patients (9, 29, 47, 88). Chambers et al. identified a fibrinogen level less than 1 g/l as the first laboratory indicator of coagulopathy (9). Low fibrinogen concentrations on admission to the emergency room (ER) or the intensive care unit are associated with high mortality and a high risk of massive transfusion (44, 84). Studies involving predominantly head trauma patients also demonstrated poorer outcome in patients with low fibrinogen levels on admission in the ER (33, 51, 85).

Blood loss and consumption

Blood loss is associated with a decrease in plasma fibrinogen concentration. Hiipponen et al. observed that in elective surgical patients deficiency of fibrinogen develops earlier than any other haemostatic abnormality when crystalloids, colloids or plasma-depleted red blood cell (RBC) concentrates are used to compensate bleeding (40). After a blood loss of 1.5 times the total calculated blood volume, plasma fibrinogen decreased to 1 g/l. Similar findings have been reported by McLouglin et al.: 75% blood volume exchange resulted in a fibrinogen concentration of 0.5 g/l (62).

Low fibrinogen concentrations on admission to the ER cannot be explained fully by blood loss and pre-hospital fluid resuscitation. Severe tissue trauma results in extensive exposure to tissue factor. Consequently, large amounts of fibrinogen are consumed at the side of injury. Davenport et al. reported a plasma fibrinogen concentration of 0.96 g/l among patients with TIC on admission to the ER. These patients received minimal pre-hospital fluid therapy (0–400 ml), meaning that low fibrinogen could not have been caused by dilution alone (20). It has recently been shown by our group that low fibrinogen concentrations on admission to the ER were closely linked to the severity of injury, signs of shock and blood loss (79) (Fig. 1).

Dilution and impaired fibrin polymerisation

In massive haemorrhage, fluid therapy plays an essential role in restoring intravascular volume. Importantly, the optimal fluid resuscitation strategy has not been yet determined (71, 104).
The main side-effect of volume resuscitation using crystalloids is dilutional coagulopathy. Artificial colloids such as starches and gelatines additionally impair fibrin polymerization (21, 26, 78).

In vitro dilution with starches and gelatines reduces maximum clot firmness, as measured using viscoelastic coagulation testing to a significant greater extent than crystalloids (78) (Fig. 2a, b).

Data from the German trauma registry revealed that 34% of trauma patients were coagulopathic according to standard coagulation test upon admission to the ER (54).

These findings are related to a strategy of aggressive pre-hospital volume replacement: The patients in this study received a median of 2200 ml until hospital admission. Flocard et al. took prehospital blood samples and observed a median fibrinogen concentration of 1.2 g/l among patients with an injury severity score (ISS) > 40, (29). Schöchl et al. reported similar findings in major trauma patients with a mean ISS of 38: mean plasma fibrinogen concentration on admission to the ER was 1.26 g/l (82).

Hyperfibrinolysis

Hyperfibrinolysis is defined as enhanced dissolution of the clot (86). It has been associated with pronounced bleeding, increased transfusion requirements and high mortality (8, 16, 47, 80, 94, 95). Cotton et al. reported an incidence of 2% in 1996 trauma patients according to thrombelastography (TEG) analyses on ER admission (16). Brohi et al. showed that hypoperfusion-induced activation of the protein C pathway is the main trigger of pro fibrinolytic activation (6).

In hypoperfusion associated with severe trauma and shock, high amounts of tPA (tissue plasminogen activator) are released from the endothelial cells. Additionally, thrombomodulin is expressed in the endothelium, and this binds thrombin. The resulting thrombin–thrombomodulin complex activates protein C, inactivating accelerators of coagulation (FVas and FVIIa) and also consuming plasminogen activator inhibitor type 1 (PAI-1) which is the major antagonist of tPA.

Consequently, tPA is inadequately antagonised by PAI-1. In turn, high concentrations of tPA convert plasminogen into plasmin resulting in a profibrinolytic state with subsequent cleavage of both fibrin and fibrinogen (6, 53). The resulting high quantities of fibrin/fibrinogen degradation products potentially inhibit fibrin polymerisation, resulting in poor clot quality (42).

Kashuk and colleagues reported TEG results from 61 trauma patients at risk of post-injury coagulopathy (47). The patients were stratified by transfusion requirements into three groups: minimal (0–5 U RBC), moderate (6–9 U RBC) and massive transfusion (>9 U RBC). Fibrinolysis was defined as >15% reduction from the maximum amplitude. The median fibrinogen concentration in patients with primary fibrinolysis within an hour of ER admission was 1.04 g/l. These patients had higher transfusion requirements and higher mortality. Levrat et al. reported no measurable fibrinogen concentration in five patients with thromboelastometrically observed complete breakdown of the clot (54). Recently, Theusinger et al. described 13 trauma patients with fibrinolysis ac-
cording to ROTEM test results. The median fibrinogen concentration on admission to the ER was 0.7 g/l compared with 1.6 g/l in a group of matched patients without hyperfibrinolysis (95). In another study, which included 33 trauma patients with ROTEM-diagnosed hyperfibrinolysis, mean fibrinogen concentration was 1.1 g/l among survivors and 0.75 g/l among non-survivors (80).

In summary, trauma patients with hyperfibrinolysis diagnosed by ROTEM/TEG have low fibrinogen concentrations on admission to the ER, and the hyperfibrinolytic state diminishes these levels further.

Acidosis and hypothermia affect fibrinogen metabolism

Acidosis and hypothermia have both been identified as potential contributors to coagulopathy (15). Decreased fibrinogen levels after the infusion of hydrochloric acid solution (HCl) were reported by Dunn et al. in dogs (23). Martini et al. measured the synthesis and breakdown of fibrinogen in a pig model after infusion of HCl (59). They found that fibrinogen consumption was accelerated, but synthesis remained unchanged, decreasing fibrinogen availability. In another swine study by Martini et al. fibrinogen concentration was decreased by acidosis but not by hypothermia (58).

The underlying mechanism of the observed fibrinogen depletion is speculative. It cannot be fully explained by a reduced synthesis rate, which is in pigs approximately 1–3% per hour. Altered sequestration or an increased degradation of fibrinogen is more likely. An important criticism of this study is that HCl was used to decrease pH which potentially could result in an additional degradation of fibrinogen. In a porcine model with acidosis and oxygen deficit caused by traumatic shock, White and co-workers observed a decrease in fibrinogen concentration as an early marker of haemostatic dysfunction, with reduced clot strength – maximum amplitude (MA) – in TEG analyses (103). Darlington et al. also observed in a swine study that acidosis, induced by shock and hyperventilation, reduced fibrinogen concentration by 14.5% (18).

A reduction in body temperature is a common problem among major trauma patients, and it is well established that hypothermia contributes to coagulopathy (15).

Hypothermia of 32°C not only prolongs standard coagulation tests but also decreases fibrinogen synthesis by about 50% (60). However, fibrinogen breakdown was not altered – in contrast to acidosis.

Fibrinogen measurement

Our group and others reported that trauma patients with high ISS are prone to hypofibrinogenaemia (20, 29, 47, 79, 83). Therefore, measurement of fibrinogen concentration is highly recommended in major trauma patients when they are admitted to the ER. In emergency situations, a rapid, simple and reliable method for quantifying clottable fibrinogen is needed. The two most common laboratory methods are
• Clauss and
• prothrombin time (PT)-derived.

In total, there are more than 60 different ways of measuring fibrinogen concentration including numerous variations of the Clauss method (89). This introduces many factors that may affect the measured fibrinogen concentration, including the type of device, software, readout method, activators or calibration.

PT-derived fibrinogen is based on the fact that the difference between baseline and maximum turbidity during PT measurement is proportional to the fibrinogen concentration between 0.5 and 16 g/l (2). In contrast, the Clauss method is based on the addition of concentrated thrombin to diluted plasma, which converts fibrinogen to fibrin. The clotting time is inversely proportional to the amount of fibrinogen in the sample.

PT-derived fibrinogen measurement is commonly used in some countries such as the UK, but it is not recommended by guidelines on fibrinogen assays because of the potential for discrepancies versus the Clauss method (56). With the Clauss method, numerous variations are possible with respect to the read-out method (photo-optical, mechanical or electromechanical), type of calibrator, analyser platform and assay brand. All of these variations have the potential to influence the result, especially in trauma where further clinical variables – e.g. haemodilution with hydroxyethyl starch (HES) or the presence of fibrin/fibrinogen degradation products or lipids – may amplify any differences between measurement methods.

A variety of shortcomings have been reported with both PT-derived and Clauss methods. Perhaps the most important consideration in trauma is the turnaround time, because laboratory test results are typically not available for 60 minutes or more after sending the blood sample. Dav enport and co-workers reported a median turnaround time for standard coagulation assessment of 78 minutes (interquartile range: 62–103 minutes) (20). This is in line with a French survey which reported a corresponding median time of 88 minutes (range: 29–295 minutes) (97). This significantly limits the clinical value of PT-derived and Clauss measurements of fibrinogen.

A much reduced turnaround time (14 minutes) has been reported for laboratory coagulation testing (10). This was achieved by
• rapid centrifugation,
• swift sample transport,
• optimal communications and
• an extended calibration range.

However, in most centres it is doubtful whether this would be feasible in daily clinical practice. Also, with regard to the absolute differences observed with various dilution fluids, fibrinogen measurements must sometimes be interpreted with caution. When using the PT-derived and Clauss methods, it has been observed that the presence of artificial colloids (e.g. dextran or HES) significantly raises measured
fibrinogen concentration above that predicted by the dilutional effect (41).

Thus, when high volumes of synthetic colloids are used during massive transfusion, hypofibrinogenemia may potentially be overlooked.

This possibility has been confirmed by Adam et al., who reported that photo-optical methods significantly overestimate the fibrinogen concentration in blood diluted with HES (1, 2). Fibrinogen concentration was overestimated by >80% and >110% with 30% and 50% dilution, respectively. Photo-optical Clauss methods have also been shown by Fenger-Eriksen et al. to overestimate fibrinogen concentration in samples diluted with HES (28).

Viscoelastic tests

Modern viscoelastic methods such as thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) or thrombelastography (TEG®, Haemonetics Corp., Braintree, MA, USA) provide information on the

• speed of initiation of coagulation,
• kinetics of clot growth,
• clot strength and
• potential breakdown of the clot.

These coagulation assessment methods offer interesting alternatives for trauma care providers to standard laboratory tests in the management of trauma patients (45, 47, 82, 85). Specific ROTEM and TEG assays – FIBTEM and Functional Fibrinogen (FF), respectively – are designed to assess the functional capacity of fibrinogen. This is achieved by assessing clotting in the presence of a platelet inhibitor: Cytochalasin D for the FIBTEM assay and abciximab for the FF assay. It allows specific evaluation of the fibrin component of the clot. Because fibrin clot strength is principally (though not exclusively) dependent on fibrinogen, any functional impairment of fibrinogen (e.g. by colloids) will be reflected in the test results.

Recent data suggest that differences between FF and FIBTEM test results may be encountered, for example in the presence of heparin (90). Interestingly, it has also been shown that the FIBTEM assay may have potential for early prediction of massive transfusion (84). An important advantage of both the FIBTEM and FF assays is a short turnaround time. ROTEM and TEG analyses are performed in whole blood, avoiding the need for centrifugation. For ROTEM, a mean manipulation (set-up) time of 2 minutes 51 seconds has been reported for trained physicians (76), meaning that the first test results (clot amplitude at 5 minutes, A5) can be expected in around 8 minutes. Turnaround times for the FF assay have not been reported. Rapid availability of test results can be valuable in facilitating early decision making (84).

Rationale for fibrinogen replacement

The consequences of low plasma fibrinogen concentration are not fully acknowledged by trauma care providers. Therefore, in many trauma centers fibrinogen is not measured on a regular basis when patients with major trauma are admitted to the ER. There is no universally accepted critical fibrinogen concentration in trauma.

• British and American guidelines recommend administering fibrinogen if the concentration falls below 1 g/l (69, 72). However, this threshold applies to patients with non-surgical bleeding and not necessarily to those with active blood loss.

• In contrast, current European Trauma Guidelines, the Guidelines from the European Society of Anaesthesiology and the Canadian National Advisory Committee on Blood and Blood Products recommend a plasma fibrinogen concentration in trauma patients not lower than 1.5–2.0 g/l (24, 50, 92).

Fibrinogen levels below 1 g/l are generally insufficient to curtail blood loss in massive haemorrhage (13).

• In massively transfused patients, levels below 0.5 g/l are associated with a risk of diffuse microvascular bleeding.
• Platelet transfusion is also less effective with low fibrinogen concentrations (17).

Moreover, the efficacy of recombinant factor VIIa is limited in patients with low fibrinogen concentrations (61).

To optimize the activity of locally produced thrombin, fibrinogen replacement should be considered as first-line therapy in patients with substantial dilutional coagulopathy (3, 31, 32, 35).

Bolliger and co-workers studied the effects of 80% haemodilution with crystalloids, using thrombin generation and ROTEM assays (3). Peak thrombin generation decreased by 56% and clot formation time was prolonged. In vitro administration of fibrinogen concentrate to achieve levels ≥2 g/l normalised the speed of clot formation, while levels above 2.5 g/l fully optimized all ROTEM coagulation parameters. Maximum clot firmness, reduced by in vitro dilution with either colloids or crystalloids, may be increased by fibrinogen concentrate (21, 25, 30, 36, 78). Reversal of the dilutional effect is, however, more likely with crystalloid dilution. For example, fibrinogen failed to completely reverse the effects of dilution with 6% HES (21, 78). This suggests that artificial colloids, particularly starches, have additional negative effect on fibrin polymerisation (37).

Potential compensatory effect of fibrinogen on low platelet count

Severe ongoing blood loss results not only in depletion of coagulation proteins but also a critical drop in platelet count. The availability of platelet concentrate (PC) is limited due to a short storage life (5 days), and PC shortages can be common in busy trauma centres.

Platelets play an important role in the whole coagulation process, including thrombin generation and clot firmness. Data from animal and human studies have shown that fibrinogen may potentially compensate for low platelet counts, by increasing overall clot firmness (52, 98). Velik-Salcher et al. investigated the effect of fibrinogen concentrate (FC) transfusion on blood loss in a thrombocytopenic swine model (target platelet count < 30000/µl). Transfusion of FC (250 mg/kg bodyweight)
results in lower blood loss and improved survival rate compared to the transfusion of 2 units of platelet concentrate (98). However, these data have to be interpreted with caution as the corresponding fibrinogen dose used in this study equals 17.5 g in a 70 kg person – a single dose rarely used in clinical practice.

However, in situations where PC is not available and the platelet count is low, fibrinogen supplementation could potentially be considered as a treatment option.

Clinical trials investigating the use of FC in trauma patients with either low platelet count or platelet inhibition therapy, e.g. clopidogrel and aspirin (81), would be valuable.

### Fibrinogen supplementation

Data showing that fibrinogen supplementation improves survival in trauma patients are limited (5, 82, 83, 93, 102). In a retrospective study of 252 massively transfused casualties, Stinger et al. found an association between the fibrinogen:RBC ratio and survival. Patients receiving 0.48 g fibrinogen per unit of RBC had improved survival compared to patients treated with 0.1 g fibrinogen per unit of RBC (93). However, patients in the high-ratio group showed also higher platelet counts.

### FFP

In current clinical practice, FFP is most frequently used to replace coagulation factors (4, 19). FFP is usually donated by healthy volunteers, so it contains only low concentrations of fibrinogen, and there is considerable variation between donors. Mean fibrinogen concentrations between 2 and 2.9 g/l have been reported in FFP and solvent-detergent (SD) plasma (69, 96, 99), and Theusinger et al. reported concentrations below 1 g/l (96).

Large quantities of FFP are often required for a sufficient increase in plasma fibrinogen levels. If the target plasma fibrinogen level is above the fibrinogen concentration in FFP, sufficient increase would not be feasible even with high-volume transfusion. Chowdhury et al. assessed the effects of FFP on coagulation factors in patients either scheduled to undergo invasive procedures or with active bleeding. Two doses of FFP were investigated: 12.2 and 33.5 ml/kg bodyweight. A sufficient increase in fibrinogen concentration (1 g/l) was observed only in patients receiving the high dose; the increase was 0.4 g/l with the low dose (12).

Another disadvantage of FFP is that it requires 20–30 minutes of thawing before administration, resulting in substantial time delay. To overcome this problem, FFP is stored as pre-thawed plasma in some trauma centres (67). However, this can result in waste and potential overuse. An interesting alternative is to use lyophilized plasma, which is immediately available in the ER (43). Rourke et al. reported recently that FFP and PC were insufficient to maintain fibrinogen concentration albeit RBCs to FFP were transfused in 1:2 ratios. Only supplementation of cryoprecipitate resulted in a maintenance of an adequate fibrinogen content (75).

### Cryoprecipitate

Cryoprecipitate is another potential source of fibrinogen, with higher fibrinogen concentration than FFP. However, it suffers from several important drawbacks. The fibrinogen content of cryoprecipitate is not well standardized and may vary widely (120–796 mg per single unit) (7). Cryoprecipitate is generally used as a pooled product comprising single units from 6–10 donors, and this increases recipients’ donor exposure. It is stored frozen at −30°C and has to be thawed prior to administration (91).

Moreover, cryoprecipitate is not usually subjected to viral inactivation, and it has been withdrawn from most of European countries due to safety concerns.

However, it is still available in the UK and the USA (91). British and American guidelines for the use of cryoprecipitate in massive haemorrhage suggest transfusion when the plasma fibrinogen level is below 1.0 g/l (69, 72). The recommended dose for an adult trauma patient is one single unit per 5–10 kg bodyweight (48) or, according to recent European Trauma Guidelines, 15–20 single units in a 70 kg adult (92). Nascimento et al. found that infusion of one unit of cryoprecipitate increased plasma fibrinogen concentration by approximately 0.06 g/l (68).

In trauma patients, data showing improved survival following transfusion of cryoprecipitate are still limited (68, 75, 100). In a retrospective observational study comparing the mortality of 4 groups (tranexamic acid only, cryoprecipitate only, tranexamic acid and cryoprecipitate, and neither tranexamic acid nor cryoprecipitate) Morrison et al. reported that cryoprecipitate independently add to the survival benefit of tranexamic acid in seriously injured patients requiring transfusion (65).

### Fibrinogen concentrate

Highly purified and lyophilized fibrinogen concentrate (FC) is licensed throughout Europe and the USA for congenital deficiency (27). In some countries it is also licensed for acquired hypofibrinogenaemia (e.g. trauma). FC
- is easily and quickly reconstituted using water, and
- can be administered without thawing or cross-matching (73).

FC may also be infused rapidly: administration of 6 g fibrinogen in 1–2 minutes has been reported in the context of severe bleeding (87).

FC contains a defined concentration of fibrinogen, with a much higher consistency than indicated by the labelled range (the package insert indicates a possible range of 0.9–1.3 g per vial, but actual quantities are close to labelled quantity of 1 g) (87).

Fibrinogen levels are much less predictable with cryoprecipitate due to donor dependency, and the unpredictability is increased with FFP where each unit is from an individual donor (73). FC undergoes numerous purification and viral inactivation steps during manufacture, including pasteurisation and filtration (34). FC has been reported to be generally well tolerated (22, 27).

Despite the use of FC for routine trauma therapy in some countries for decades, few reports of FC as a haemostatic agent in this setting have been published. A
Tab. 1 Attributes of different sources of fibrinogen concentrate available for the management of perioperative bleeding, modified according to Soerensen B et al. (91)

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>cryoprecipitate</th>
<th>fibrinogen concentrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>content of fibrinogen</td>
<td>inconsistent and donor dependent</td>
<td>variable fibrinogen content</td>
<td>constant amount of fibrinogen in each vial</td>
</tr>
</tbody>
</table>
| side effects, risk of immunological reactions | • ABO group matching required  
• transfusion related lung injury  
• acute lung injury  
• transfusion related cardiac overload  
• sepsis  
• multi organ failure | • ABO group matching required  
• low risk (because resuspended in small volume of plasma) of  
— transfusion related lung injury  
— severe anaphylactic reactions | negligible risk of immunological reactions (because purification steps during preparation and removal of donor antibodies) |
| risk of viral / pathogen transmission | low risk for quarantined plasma and SD plasma | potential risk of pathogen transmission — not virally inactivated | pasteurization and filtration steps minimize the risk of pathogen transmission |
| number of Units / vials required to provide a 4 g dose | 6–8 Units | 29 Units (based on 140 mg/U) | 4 vials |
| time to administration | has to be thawed prior to use | immediately available |                                                                 |

retrospective study included 131 major trauma patients (median ISS of 38) who received > 5 units of RBC in 24 hours (82). Haemostatic therapy was guided by ROTEM test results; 128 patients received FC and 101 received PCC. Only 12 patients were treated with FFP. ROTEM-guided based hemostatic therapy using coagulation factor concentrates significantly reduced mortality compared with estimations based on trauma injury severity score (TRISS) or revised injury severity classification (RISC) methodology (82). In another study, 80 major trauma patients receiving ROTEM-guided therapy based on coagulation factor concentrates (FC and PCC) were compared with controls from the German Trauma Registry, treated with FFP according to standard clinical practice (mostly without guidance from viscoelastic coagulation testing) (83). RBC and PC transfusions were avoided in significantly higher proportions of patients in the coagulation factor concentrate group. Weiss et al. recently studied 223 patients (62 trauma patients) with major bleeding, treated with a combination of FFP and FC (102). Fibrinogen substitution was initiated at a median blood loss of 2 l and plasma fibrinogen concentration of 1.45 g/l. A median dose of 12 g fibrinogen (4 g in fibrinogen concentrate and 8 g in FFP) was transfused. Plasma fibrinogen concentration at the end of surgery was 2.19 g/l. Interestingly, only 6% of patients had supra-physiological fibrinogen levels (>4.0 g/l) at the end of the operation.

In addition to these three studies, three case reports of ROTEM-guided FC therapy in major trauma patients have been published (5, 81, 105). Transfusion of FFP and PC was avoided in all three cases, and the patients went on to make a full recovery. Post-treatment improvements in clot formation and clot strength can be monitored using viscoelastic coagulation tests, particularly the FIBTEM assay or the FF assay (73, 82, 89, 90). Such improvements are shown (Fig. 2c, d). Depending on the baseline concentration and blood volume, administration of 3 g fibrinogen via FC transfusion may be expected to increase the plasma fibrinogen concentration by approximately 1 g/l in a 70 kg adult patient. The advantages and disadvantages of different sources of fibrinogen are summarized (Tab. 1).

**Conclusion**

Many patients with severe trauma have low fibrinogen levels on admission to the emergency room, and this may be attributable to a variety of reasons.

In many trauma centres, fibrinogen is not routinely measured upon admission to the ER. Thus, hypofibrinogenaemia in trauma can easily be overlooked.

Because of their short turnaround times, either the FIBTEM or the FF assay should be used in preference to laboratory fibrinogen concentration measurement to estimate the functional capacity of fibrinogen within the coagulation process.

There are three potential sources of fibrinogen: FFP, cryoprecipitate and FC. When using FFP, high-volume transfusion is necessary to provide sufficient increase in plasma fibrinogen levels. Larger and more rapid increases can be achieved using either cryoprecipitate or FC. However, cryoprecipitate contains variable quantities of fibrinogen, it must be thawed before use, and there have been significant safety concerns regarding the use of this product mainly relating to a lack of viral inactivation. In contrast, FC is rapidly available, contains a high and standardised amount of fibrinogen, and is virally inactivated.

**Conflicts of interest**

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