

Goal-directed Coagulation Management in Major Trauma

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Introduction

Severe tissue trauma is frequently associated with hemorrhagic shock and subsequent pronounced coagulopathy [1]. Uncontrolled bleeding is the second most common cause of death, and hemorrhage is directly responsible for 40 % of all trauma-related deaths [2]. Coagulopathy can be detected with standard coagulation tests immediately after arrival in the emergency room (ER) in approximately 25–35 % of all trauma patients [1, 2]. Moreover, early trauma-induced coagulopathy is associated with a 4-fold increase in mortality [1]. Blood coagulation monitoring is essential in order to assess the underlying coagulation disorder and to tailor hemostatic treatment. Thromboelastometry (TEM) and thrombelastography (TEG) are promising point-of-care technologies providing rapid information on the initiation process of clot formation, clot quality, and stability of the clot [3].

The primary aims in the treatment of hemorrhagic shock patients are control of ongoing bleeding, restoration of intravascular volume, and early, aggressive therapy of underlying coagulopathy. Experiences mainly derived from military trauma care (Table 1) suggest a high fresh frozen plasma (FFP) to red blood cell (RBC) ratio as treatment strategy in major bleeding patients. Such a strategy can be employed in combination with the administration of coagulation factor concentrates if these products are available to physicians. This combined coagulation therapy can be guided by TEM and TEG test results, allowing the optimization of hemostasis in trauma cases on an individualized basis [4]. These strategies focus on the same therapeutic goal: A quick and substantial increase in coagulation factors to fight coagulopathy, to reduce blood loss, and to improve survival.

Table 1. Studies describing the administered ratios of fresh frozen plasma: red blood cell (FFP:RBC) in trauma-related bleeding. This list is not intended to be exhaustive.

Author, year [ref]	Type of study	Country	Patient numbers
Borgman, 2007 [73]	Retrospective chart review	USA (Military)	246
Gunter, 2008 [74]	Retrospective	USA (Civilian)	259
Maegele, 2008 [75]	Retrospective trauma registry	Germany (Civilian)	713
Spinella, 2008 [76]	Retrospective	USA (Military)	708
Teixeira, 2009 [77]	Retrospective trauma registry	USA (Civilian)	383
Zink, 2009 [78]	Retrospective	USA (Civilian)	466
Kashuk, 2008 [79]	Retrospective	USA (Civilian)	133
Sperry, 2008 [80]	Prospective cohort study	USA (Civilian)	415

Pathophysiology of Coagulopathy in Trauma

In hemorrhagic shock caused by tissue trauma and vascular injury, an “endogenous” anticoagulant pathway is activated [5]. In shock, high amounts of tissue plasminogen activator (tPA) are released from endothelial cells and thrombomodulin is expressed on their surface. Thrombomodulin binds thrombin and subsequently activates the protein C pathway. Protein C together with its cofactor, protein S, slows down the accelerators of the coagulation process by inactivating FVIIIa and FVa. Furthermore, high amounts of protein C consume plasminogen activator inhibitor 1 (PAI-1), the major antagonist of t-PA. As a consequence, overwhelming amounts of t-PA are available, creating a profibrinolytic state [5]. The overall incidence of hyperfibrinolysis is still unclear. Fibrinolysis, according to TEM/TEG test results in two small studies, was observed in 2.5 % and 8.7 %, respectively, of all trauma patients [6, 7]. However, in major trauma the incidence seems to be higher. This is especially true in patients with severe shock who require catecholamines or vasopressin for blood pressure stabilization and are prone to hyperfibrinolysis. In summary, hyperfibrinolysis is more common than previously assumed and associated with a poor outcome [8].

Volume therapy plays an essential role in restoring intravascular fluid deficit. It is undisputed that dilution of the remaining coagulation factors is an inevitable consequence when intravascular volume is restored. Data from the German trauma registry revealed that 34 % of trauma patients suffer from severe coagulopathy on arrival in the emergency room [9]. This is in part related to aggressive pre-hospital volume replacement. Patients from this study received a mean of 2200 ml of fluid, but 50 % of patients received more than 3000 ml [9]. Whereas volume resuscitation using crystalloids may result in dilutional coagulopathy, *in vitro* studies revealed that colloids impair the fibrin polymerization process to an extent which is greater than the dilutional effect alone [10, 11].

Major trauma results in substantial tissue factor (TF) exposure with subsequent early fibrin formation. Consequently, consumption of coagulation factors primarily affects fibrinogen. Fibrinogen is not only the precursor of fibrin but also an important ligand between activated platelets and of paramount importance for the whole coagulation process [12]. In elective surgery, it was demonstrated that fibrinogen was the first coagulation factor reaching critical levels [13]. In severe trauma patients with a mean injury severity score (ISS) of 35, fibrinogen concentration decreased from 1.6 g in the field to 0.95 g on admission to the emergency room [14]. In an observational study (n = 161), Carroll and colleagues reported that 11 % of patients had a fibrinogen concentration of less than 1.0 g on admission to the ER, but contributed 31 % of all fatalities [6]. Since fibrinogen plays a central role in hemostasis it is obvious that a decrease in fibrinogen concentrations results in decreased clot stability and increased bleeding [15].

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Hypothermia

Hypothermia is a common problem in trauma victims and correlates with a poor outcome. Wang and collaborators reported data from more than 38,000 trauma patients and found that admission hypothermia was independently associated with an increased odds of death in patients admitted with low core temperature

(odds ratio [OR] 3.03; 95 % confidence interval [CI] 2.62–3.51) [16]. An explanation for this finding could be that body temperature of less than 34 °C is associated with increased bleeding. Jurkovic et al. found that mortality of hypothermic patients was significantly higher than those who remained warm. In patients, who arrived in the ER with a core temperature of less than 32 °C 100 % mortality was observed [17]. Hypothermia compromises primary as well as secondary hemostasis and enhances clot lysis. However, these effects are of clinical relevance only at temperatures of less than 34 °C. At temperatures of 33 °C thrombin generation is markedly affected and platelet adhesion is diminished in the range of 33 % of normal [18].

Acidosis

Hypoperfusion and shock are further associated with increased base deficit, lactate concentration and acidosis. Several reports independently revealed that acidosis was related to poor outcome in trauma patients [19]. One reason for this finding is that acidosis affects the activity of coagulation factors, impairs thrombin generation and alters platelet function. Meng et al. showed in an *in vitro* model that the activity of the prothrombinase complex was reduced by approximately 70 % at pH 7.0 compared with pH 7.4 ($p < 0.05$) [20]. Martini reported that acidosis, induced by infusion of 0.2 M HCL accelerated fibrinogen degradation [21]. Platelet aggregation is also enhanced by acidosis [18].

Diagnosis

Due to the complex nature of acute trauma-induced coagulopathy, real time and reliable laboratory testing should be available in order to support a targeted therapeutic approach based on test results. The availability of such a ‘theranostic’ regime means that rapid diagnostic testing and drug therapy can be combined, with a real time feedback loop improving drug efficiency and minimizing side-effects. Theranostics will reach its full potential when drug discovery and development can be done on an individual basis, providing a truly personalized approach to treatment. The key questions that testing procedures should address when treating trauma victims with severe bleeding are: Why is the patient bleeding? and Is it due to surgical or coagulopathic bleeding?

When trying to answer these questions, the main hindrance is the time taken to receive test results from the clinical laboratories (29–295 minutes) [22, 23]. Although no single coagulation test can mirror the whole picture of coagulopathy, the standard coagulation tests, like prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen plasma concentration, are widely used in the perioperative setting. However, these tests were not developed to assess coagulation in acute bleeding situations [24] and the time needed to conduct these assays is incompatible with the prompt correction of coagulopathy which is required in the trauma setting [22]. Currently, point-of-care devices which are capable of monitoring PT and aPTT (CoaguChek® S and XS) have been employed in the emergency room and operating room (OR) [25]. However, measurements taken using these instruments have been shown to deviate from laboratory testing. The degree to which this variation has tangible clinical impact has

yet to be established [26]. However, irrespective of the need for faster testing procedures, these tests may have limited value for the assessment of coagulopathy and for guidance of hemostatic therapy. *In vivo* coagulation occurs primarily on the surface of platelets and TF-bearing cells [27]. Fibrinogen and platelets are tightly interwoven and RBCs also play a significant role in hemostasis [28]. However, these cells are removed by the centrifugation process. In addition, conventional tests stop with the formation of the first fibrin strands, when only approximately 5 % of thrombin has been generated [29]. These assays only provide information about the beginning of clotting and do not assess the quality and strength of the clot. Furthermore, the influence of (hyper)fibrinolysis on clot stability cannot be evaluated by routine coagulation tests [30]. Preoperative PT and aPTT testing has little predictive value for bleeding, while tests performed intraoperatively and postoperatively are of little value for identifying the cause of bleeding [24]. Obtaining test results, including fibrinogen concentration, is time consuming and of little use for the guidance of emergency hemostatic therapy. Furthermore, Fenger-Eriksen et al. demonstrated that different automated coagulation analyzers revealed significantly different levels of fibrinogen [31]. The presence of colloid plasma expander gave rise to erroneously high levels of fibrinogen recorded by some coagulation analyzers employing the Clauss method, overestimating levels by 80 % and 110 % in cases of 30 % and 50 % dilution, respectively (though in the absence of such confounders this method is reliable) [31, 32].

Taken together, standard coagulation tests do not offer useful information about the nature of the coagulopathy; their prognostic value for a potential bleeding tendency and transfusion of allogeneic blood products is poor. These limitations apply not only to preoperative testing, but also lead to limited usefulness of standard laboratory methods for the intraoperative and intensive care unit (ICU) periods in situations that are complicated by acute bleeding.

In recent years, attention has focused upon viscoelastic methods as point-of-care tests for coagulation in massive blood loss [22, 33]. TEM measures the viscoelastic changes of clot formation in whole blood under low shear conditions. In contrast to standard coagulation tests, TEM/TEG provides information on the rapidity of coagulation initiation, kinetics of clot growth, clot strength and breakdown. ROTEM® (TEM International® GmbH, Munich, Germany) utilizes a newer and improved technique, using a plastic pin supported by a ball bearing, which rotates slowly backwards and forwards through an angle of 4.75°. This method is more stable and less sensitive to shock and vibration. The pin is vertically immersed into a cup containing the blood sample. In contrast, TEG® uses a torsion wire and the cup is rotating.

After re-calcification of the blood sample and addition of an activator, the coagulation process in the test cup starts. Following generation of the first fibrin filaments between the pin and the wall of the test cup, the rotation range of the pin is reduced. The movement of the pin is converted into an optical signal and transferred to a graphical display, which plots the changes in the viscoelastic properties of the clot over time. A set of standard reagents is used to discriminate between several potential causes of bleeding. Two basic tests that use intrinsic activation (INTEM) and extrinsic activation (EXTEM) provide information on the general coagulation status (impaired, normal, and hypercoagulable) through the following parameters: Clotting time (CT), clot formation time (CFT), alpha angle, maximum clot firmness (MCF) and clot lysis (CL) (Fig. 1).

In the FIBTEM test (Fig. 1), platelets are inhibited by cytochalasin D, therefore this test provides information on the fibrin component of the clot separately. In the APTEM assay, an antifibrinolytic (aprotinin) is added to the EXTEM assay. If this yields an improvement in all parameters (CT, CFT, α -angle, MCF) then this indicates hyperfibrinolysis, before there is any indicative breakdown in EXTEM (Fig. 2).

TEM and TEG can be carried out at the patient's bedside. The measurements are performed in whole blood, not in plasma. Also, without the need for centrifu-

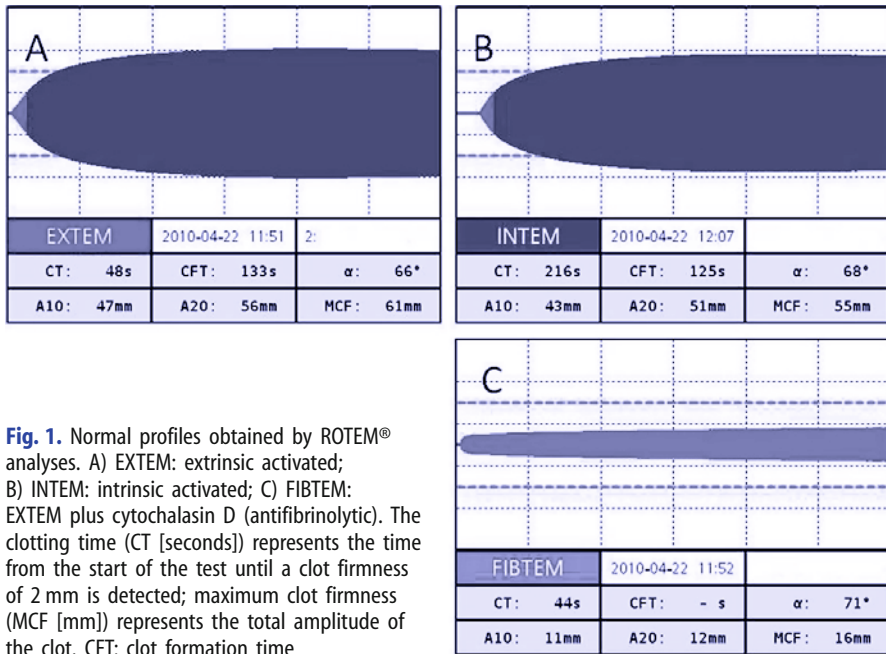


Fig. 1. Normal profiles obtained by ROTEM® analyses. A) EXTEM: extrinsic activated; B) INTEM: intrinsic activated; C) FIBTEM: EXTEM plus cytochalasin D (antifibrinolytic). The clotting time (CT [seconds]) represents the time from the start of the test until a clot firmness of 2 mm is detected; maximum clot firmness (MCF [mm]) represents the total amplitude of the clot. CFT: clot formation time

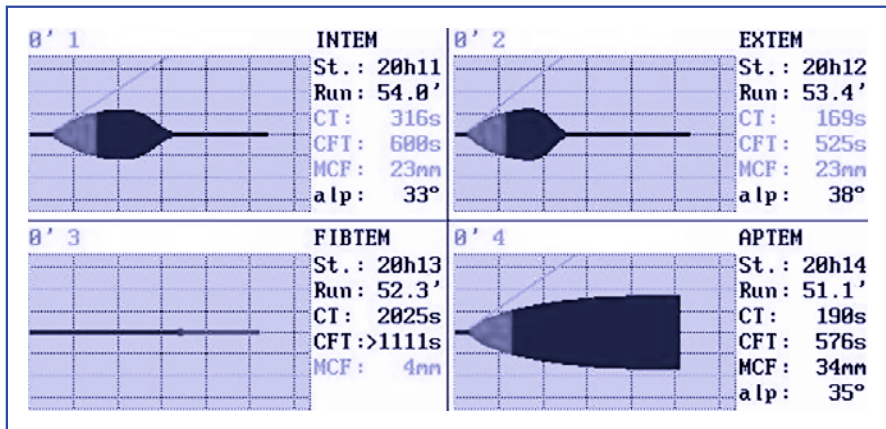


Fig. 2. Hyperfibrinolysis in ROTEM®. Clot breakdown is seen using INTEM and EXTEM, no clot formation is observed in FIBTEM, stable clots are seen in APTEM.

gation, the time taken to receive test results is much shorter (approximately 10 minutes) compared with conventional laboratory testing (mean 88 minutes, 29–295 minutes) [23]. Recent data suggest that viscoelastic devices are superior to routine coagulation tests in detecting trauma-induced coagulopathy [3, 33]. Kashuk et al. showed that FFP would have been administered to significantly more patients based on conventional transfusion triggers compared to TEG® test results (61.5 % by international normalized ratio [INR] versus 26.9 % by TEG p = 0.003), suggesting that TEG® might be useful in guiding transfusion therapy and reducing FFP transfusion [3].

In a study that included 69 trauma patients, Kaufmann et al. showed that only the ISS and TEG® results were predictive of early transfusion requirements [34]. Plotkin et al. reported that only the maximum amplitude and not standard coagulation tests, like PT and aPTT, was predictive for blood product transfusions [35]. In addition, hyperfibrinolysis may influence the coagulation process in major trauma and is associated with high mortality [8]. The ROTEM remains the only tool for detecting hyperfibrinolysis in acutely bleeding patients, since all laboratory based techniques used to detect hyperfibrinolysis (e.g., euglobulin lysis time [ELT], plasmin-antiplasmin, PAI-1) are complex and too time-consuming [7].

Treatment of Coagulation Disorders

Hypothermia is a common problem in trauma victims and correlates with a significantly worse prognosis [19]. Thus, no efforts should be spared to maintain adequate body temperature. During the initial evaluation phase in the ER the patient should be kept dry and covered. Consequent warming of fluids and blood components prior to infusion is mandatory. Intraoperative use of patient warming devices is strongly recommended [36]. In bleeding patients it is important to fight against the vicious cycle of hypothermia, acidosis and coagulopathy.

The concept of ‘damage-control surgery’ is an accepted and well proven strategy in the treatment of exsanguinating trauma patients and is adopted worldwide. Abdominal packing as well as external fixation of extremity fractures shortens operation time and minimizes exposure of the patient to a cold environment. It has been demonstrated that the concept of ‘damage-control surgery’ reduces the total amount of blood loss and improves survival in major trauma patients [37].

In pre-hospital care, identification of bleeding trauma patients and rapid transport to a definitive care facility is of paramount importance. In the pre-hospital phase, fluid resuscitation should be minimized to what is necessary to maintain adequate vital signs and avoid hypovolemic cardiac arrest. The concept of deliberate hypotension is well accepted although the scientific basis is poor and only very limited data are available in the literature. Fluid resuscitation should preserve vital functions without increasing the risk of further rebleeding. Experimental studies employing an uncontrolled bleeding model revealed improved survival in animals that were fluid resuscitated to low blood pressure thresholds [38]. In a pig study of uncontrolled bleeding, an aortotomy of 2 mm was performed in the infrarenal aorta. With a drop in blood pressure, initial hemorrhage stopped spontaneously. Fluid resuscitation resulted in rebleeding with an increase

in blood pressure (average systolic pressure of 94 ± 3 mmHg) [39]. In one pre-hospital study, restrictive fluid replacement in patients with penetrating trauma resulted in improved outcome [40]. Dutton et al. reported that an intra-operative targeted systolic blood pressure as low as 70 mmHg reduced the time of active bleeding compared with a systolic blood pressure around 100 mmHg (2.4 h vs. 2.9 h, respectively) in severely injured patients. However, mortality rates were comparable in both groups [41]. In summary, the lowest acceptable blood pressure level and how long such a targeted low blood pressure can be tolerated are still unknown. This level is also influenced by pre-existing conditions, like coronary artery disease or stroke, which have to be taken into account.

Coagulation Therapy

Ratio driven 'damage-control resuscitation'

In current clinical practice, FFP is most frequently used to replace lost coagulation factors. However, the appropriate use of FFP continues to be a controversial topic [42]. The 'damage-control resuscitation' concept proposes early and aggressive strategies with a predetermined fixed ratio of blood components for treatment of trauma-induced coagulopathy [43]. Recent studies suggest that use of a ratio driven concept of FFP:RBC in a 1:1 ratio improves survival in severe bleeding in military and civilian trauma (Table 1). The results of these studies are conflicting and most of the trials are retrospective.

Recently, Murad et al. published a meta-analysis of 10 observational studies in order to assess the effects of high volume plasma transfusion on outcome and adverse effects in trauma and surgical patients (Table 2) [44]. The majority of bleeding patients suffered from penetrating trauma. All except two studies demonstrated improved survival. Five studies demonstrated that a higher ratio of FFP:RBC was associated with increased survival. A dose-response relationship was observed, although the relationship was not linear. A significant reduction in mortality was revealed in patients receiving FFP:RBC in ratios greater than 1:3. (OR 0.38; 95 % CI 0.24–0.60; $I^2 = 85$ %; p value for Q test = 0.01). However, a dose dependent relationship could not be observed in other studies.

Table 2. Mortality in patients undergoing massive transfusion. (Adapted from [44])

Author, year [ref]	Odds ratio	Lower limit	Upper limit	Plasma (events/total)	Control (events/total)
Borgman, 2007 [73]	0.29	0.16	0.51	31/162	38/84
Cotton, 2009 [81]	0.46	0.28	0.75	54/125	88/141
Holcomb, 2008 [82]	0.58	0.40	0.84	87/252	102/214
Kashuk, 2008 [79]	0.44	0.22	0.88	23/59	44/74
Maegele, 2008 [75]	0.59	0.42	0.81	76/229	222/484
Teixeira, 2009 [77]	0.18	0.12	0.28	58/226	103/157
Scalea, 2006 [48]	1.49	0.63	3.53		
Snyder, 2009 [49]	0.84	0.47	1.50		
Duchesne, 2008 [83]	0.05	0.02	0.13	19/71	56/64
Dente, 2009 [84]	0.12	0.02	0.67	7/50	4/7
	0.38	0.24	0.60		

Heterogeneity: $p = 0.01$; $I^2 = 85$ %

Limitations of the ratio driven concept

It has been shown that large amounts of FFP are needed in order to sufficiently increase coagulation factor activity [45]. This strategy requires immediate access to large volumes of thawed universal donor FFP. Prior to infusion, FFP has to be thawed, which takes at least 30 minutes. To negate this time delay, pre-thawing of FFP could be carried out. However, this is unfeasible anywhere other than busy trauma centers because of the likely waste and potential overuse that would occur [46]. In the future, lyophilized plasma, immediately available in the ER could solve these logistic problems [47].

Most of the studies addressing an early formula-driven hemostatic resuscitation with different FFP:RBC ratios are retrospective (**Table 1**).

Survivor bias

The evidence for a beneficial effect of ratio driven plasma transfusion on the survival of trauma patients undergoing massive transfusion is of very low quality and at high risk of bias as patients with the highest survival chance were treated with the maximum of resources. Additionally a survivor bias must be considered. Patients with massive, uncontrollable bleeding died before large amounts of FFP could be infused. Therefore, non-survivors received a lower FFP:RBC. In the only prospective study, Scalea et al, reported no survival benefit for higher FFP:RBC ratios when early deaths were excluded [48]. In another study, Snyder et al. [49] calculated regression models to correct survivorship bias. Mortality in the group with high FFP:RBC ratios (> 1:2) was compared with that in the group with low ratios (< 1:2). The high ratio resulted in better survival at 24 hours when a fixed FFP:RBC ratio was given. This survival advantage disappeared when the ratio was treated as a time-dependent variable (relative risk = 0.84, 95 % CI = 0.47 to 1.5) (**Table 2**). These studies highlight a problem regarding how the length of time taken to administer RBC or FFP affects the real ratios of transfused products. It is incumbent upon the scientific community to define a period of time in which it is acceptable to assume a ratio of 1:1 RBC:FFP administration. The authors believe that for units of these products to be considered equal they must be transfused within 30 minutes of each other.

Potential harms

Although the incidences of transfusion-related acute lung injury (TRALI) are typically reported, of more clinical significance is acute lung injury (ALI), which occurs more often in those patients receiving allogeneic products. There is growing evidence that large amounts of FFP transfusion are associated with an increased risk of ALI and acute respiratory distress syndrome (ARDS) [50, 51]. In the meta-analysis by Murad and collaborators, there was a threefold increase in ALI in patients receiving high volume FFP therapy (OR 2.92; 95 % CI 1.99–4.29) (**Table 3**) [44]. Chaiwat et al. also reported a dose dependent increase in ARDS following FFP transfusion [50]. Transfusion of more than 5 units of FFP was identified as an independent predictor of ARDS. In critically ill patients, a multivariate analysis revealed that transfusion of FFP was associated with an increase in infectious complications or of infection per unit of FFP transfused (OR 1.039, CI 1.013–1.067) [51].

Table 3. Incidence of ALL in patients receiving high volumes of fresh frozen plasma (FFP). Adapted from [44]

Author name, year [ref]	Odds ratio	Lower limit	Upper limit	Plasma (events/total)	Control (events/total)
Leese, 1987 [85]	0.78	0.30	2.07	8/99	10/99
Leese, 1991 [86]	0.97	0.22	4.23	4/35	4/34
van der Werff, 1997 [87]	4.30	1.29	14.30		
Martin, 2003 [88]	4.10	1.55	10.85	12/83	7/177
Gajic, 2004 [89]	2.28	1.15	4.54		
Dara, 2005 [90]	5.04	1.26	20.16	8/44	3/71
Khan, 2007 [91]	2.48	1.29	4.75		
	2.32	1.46	3.71		

Heterogeneity: $p = 0.14$; $I^2 = 38\%$

Timing of Coagulation Therapy

A key element in the sufficient treatment of trauma-induced coagulopathy is the early administration of coagulation factors. Snyder et al. reported that the first unit of FFP was administered in trauma patients a mean of 93 min after admission, while the first unit of RBCs was administered after 18 min (mean) [49]. A massive time delay in FFP transfusion was also reported by Riskin and colleagues [53]. These authors reviewed data on trauma patients requiring 10 or more RBC units during the first 24 hours of admission for a period of two years before and after the establishment of a massive transfusion protocol. The FFP:RBC ratios were identical in the two phases (1:1.8 and 1:1.8, $p = 0.97$). Despite the similar FFP:RBC ratios and overall mean numbers of transfusions, mortality decreased from 45 % to 19 % ($p = 0.02$). A significant finding in this study was that the mean time to the administration of the first FFP was decreased from 254 to 169 minutes ($p = 0.04$) in the second part of the study. This study highlighted a significant reduction in mortality despite unchanged FFP:RBC ratios and equivalent overall mean numbers of transfusions, which underscores the importance of timely substitution of coagulation factors. The low volume of clotting factor concentrates offers the benefit of significant time savings when supplementing clotting factors. For example, fibrinogen concentrates are able to provide up to 6 g of fibrinogen in 1–2 minutes [54], which would be impossible to achieve using FFP.

Individualized Goal-directed Coagulation Therapy

During the past few years, new insights into the pathophysiology of trauma-induced coagulopathy and the widespread use of viscoelastic coagulation monitoring has boosted the development of alternative treatment strategies. The basic concept of individualized goal-directed coagulation therapy is based on a quick and reliable diagnostic tool for assessment of the patient's current coagulation status. For this approach, point-of-care diagnostic tools like TEM or TEG are essential. Coagulation therapy can be tailored to the actual patients needs according to the test results [55].

The concept of goal-directed coagulation therapy primarily focuses on improvement of clot strength. Data from combat trauma revealed that a low max-

imum amplitude in TEG was predictive for blood product requirements, suggesting that clot quality is an important determinate of bleeding tendency [35]. Fibrinogen, platelets and FXIII are the major components of clot firmness. Thus, fibrinogen concentration appears to be a determining factor to guarantee the quality of blood clots in normal individuals and in trauma patients [56, 57]. Evaluation of fibrinogen should be a cornerstone in all transfusion algorithms, especially if used in patients with excessive bleeding. Regular monitoring of fibrinogen levels is strongly recommended.

The optimal level of fibrinogen that should be administered to trauma patients with life-threatening bleeding is still unknown. Plasma fibrinogen concentrations of less than 1 g/l, which are proposed in older guidelines are considered insufficient to prevent significant blood loss. Current recommendations suggest the critical fibrinogen concentration in the range of 1.5–2 g/l [36]. The total amount of fibrinogen administered seems to correlate with outcome. Stinger et al. reported in combat trauma patients receiving massive transfusions, that the amount of fibrinogen (calculated from all blood products) infused correlated with survival. Patients receiving a RBC:fibrinogen ratio > 0.2 g were more likely to survive when compared with the lower ratio groups [58].

Improvement in clot quality

The first step in goal-directed coagulation therapy is to improve clot quality by increasing the fibrinogen concentration. This can be achieved by either administering large volumes of FFP [45] or *via* the infusion of cryoprecipitate or fibrinogen concentrate. Cryoprecipitate is used as a therapeutic option in congenital fibrinogen deficiency; however, it was withdrawn from most European countries some years ago on the basis of safety concerns, though it remains available in the UK and the USA [57]. Fibrinogen concentrate (trade name: RiaSTAP®) is licensed in all European countries and the USA, but only for congenital fibrinogen deficiency. For acquired bleeding, a pasteurized fibrinogen concentrate (trade name: Haemocomplettan P/HS®) is licensed in Austria, Brazil, Bulgaria, Germany, the Czech Republic, Hungary, Kuwait, the Netherlands, Portugal, Romania, Switzerland, Taiwan and Turkey [56]. Recently a triple virus-inactivated fibrinogen concentrate (trade name: Clottafact®) received a national license in France for use in acquired bleeding.

Fibrinogen concentrates are immediately available, contain a defined amount of fibrinogen, and enjoy a favorable safety profile with respect to transmission of infectious diseases or TRALI [59]. In order to increase the fibrinogen concentration by approximately 1 g/l in a patient with a body weight of 70 kg, the administration of approximately 3 g of fibrinogen concentrate is necessary. It is possible to utilize both EXTEM and FIBTEM to monitor improvements in clot quality after fibrinogen concentrate administration (Fig. 3), and thus guide dosing. Fibrinogen concentrates have been used with success as standard replacement therapy in major surgery and trauma patients [4, 60, 61]. However, more trials of this kind need to be undertaken to firmly establish treatment protocols in which fibrinogen concentrate is used as primary hemostatic therapy in cases of bleeding trauma patients.

As platelets are important determinates of clot quality and serve as a matrix for coagulation factors, the platelet count in trauma patients should be kept above 50,000/ μ l [36]. Notably, the platelet count provides no information about possible platelet dysfunction. In trauma patients, recent intake of aspirin and to

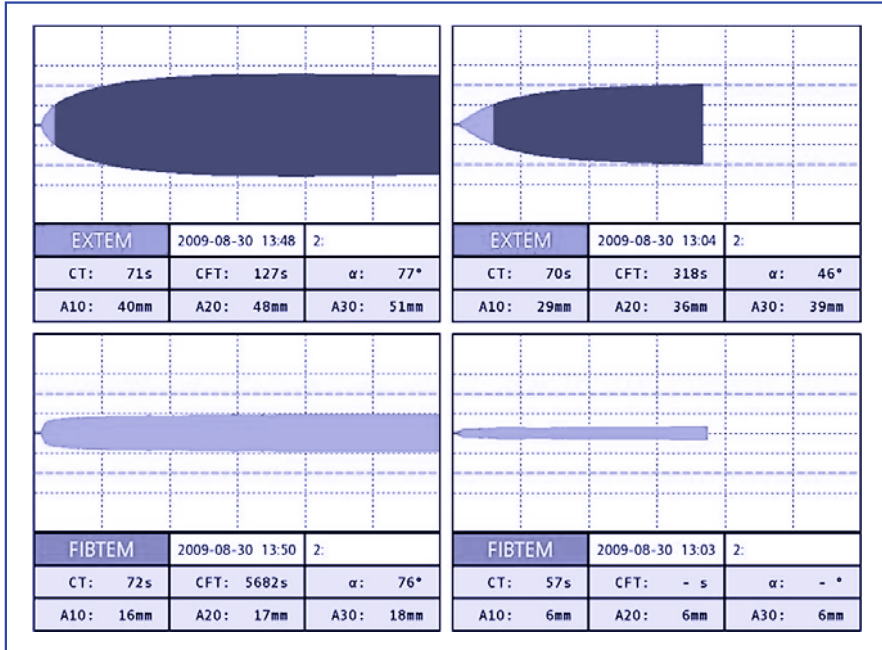


Fig. 3. Increase in maximum clot firmness can be observed using EXTEM and FIBTEM. Measurements recorded before and after the administration of 8 g fibrinogen concentrate are shown.

a greater extent adenosine diphosphate (ADP) receptor antagonists can create severe bleeding tendency. The potential compensatory role of high dose fibrinogen in thrombocytopenia and platelet dysfunction requires further investigation [28, 62, 63].

Improvement of thrombin generation

Measurement of endogenous thrombin potential showed that thrombin generation was markedly increased following trauma, even in patients with prolonged standard coagulation tests [64]. Accordingly thrombin generation *per se* is not an initial problem at the early stage of injury but later on in the course of trauma management [65]. An improvement in thrombin generation can be achieved by administration of FFP, rFVIIa and prothrombin complex concentrates (PCCs). PCC is a virally-inactivated plasma product containing the vitamin K-dependent coagulation factors (II, VII, IX, X), the inhibitor proteins, C, S and Z, and small amounts of antithrombin. To prevent activation of the coagulation factors, most PCCs contain heparin as well. PCCs may be beneficial in patients with massive bleeding who require immediate therapy of the coagulation defect. In situations where prothrombin complex factors are deficient, such as patients receiving vitamin K antagonist therapy, PCCs should be administered in line with current guidelines [66, 67]. The products are well standardized and are licensed in Europe for use in the reversal of vitamin K antagonist therapy, the treatment of acquired bleeding and as prophylactic therapy for perioperative bleeding. Although this broad range of indications can be treated with PCCs, only a small number of

studies have been carried out to establish their efficacy outside of anticoagulation reversal [4, 68, 69]. To date there is no PCC in the USA licensed for vitamin K antagonist reversal; all available PCCs are only 3-factor concentrates and are only indicated for treatment of hemophilia B.

Schöchl et al reported recently that TEM-guided goal-directed coagulation therapy using coagulation factor concentrate (PCC and fibrinogen concentrate) was associated with increased survival rates compared to those predicted by the trauma injury severity score (TRISS 32.4 %) and by the revised injury severity classification (RISC) score of the German trauma registry [4].

Recombinant activated factor VII (rFVIIa) is an analog to the naturally occurring serine protease factor VIIa, which reflects approximately 1 % of the total circulating factor VII usually present in plasma [27]. rFVIIa exerts its function by binding to exposed tissue factor at the site of injury, thus causing a massive increase in thrombin generation. Thrombin production can be further accelerated on the surface of activated platelets by rFVIIa. However, in cases of depleted levels of factor II (FII), such as dilutional coagulopathy, the substrate required for thrombin generation is lacking and a beneficial effect of rFVIIa administration is mitigated. rFVIIa initially requires available FII and subsequently fibrinogen and platelets to stimulate coagulation. rFVIIa is currently licensed for the management of patients with hemophilia A and B who develop inhibitors to exogenously administered factor concentrates, and in some countries for deficiencies of FVII and Glanzmanns thrombasthenia. The results of two randomized controlled trials in bleeding trauma patients treated with rFVIIa are available. In the first study a reduction of 2.6 RBC transfusions was observed when rFVIIa had been administered [70]. In penetrating trauma patients, rFVIIa resulted only in a reduction of 1 RBC transfusion [70]. The second study was terminated after inclusion of 573 of 1502 planned patients because of unexpected low mortality in the placebo group and difficulties in the enrolment of patients [71]. The data collected to this point showed a mortality of 11.0 % (rFVIIa group) versus 10.7 % (placebo group) ($p = 0.93$) in blunt trauma and 18.2 % (rFVIIa group) versus 13.2 % (placebo group) ($p = 0.40$) after penetrating injuries. rFVIIa patients with blunt trauma received a mean of 7.8 ± 10.6 RBC units and 19.0 ± 27.1 total allogeneic units through 48 hours, whereas placebo patients received 9.1 ± 11.3 RBC units ($p = 0.04$) and 23.5 ± 28.0 total allogeneic units ($p = 0.04$). Thrombotic adverse events were similar across study cohorts [71]. In both studies, the cumulative dosage of rFVIIa was high (400 $\mu\text{g}/\text{kg}$)

XIV

Improvement in clot stability

Hyperfibrinolysis contributes to a coagulopathy to an unknown degree. According to the studies of Brohi and co-workers, a profibrinolytic state can be triggered by severe tissue trauma and hypovolemic shock [1]. When clot stability is impaired by premature breakdown, antifibrinolytics may be indicated [8]. Data from the recently published Crash-2 trial, where early use of tranexamic acid (1g over 10 min followed by an infusion of 1 g over 8 h) was tested against placebo, a survival benefit of 1.5 % was shown (relative risk 0.91, 95 % CI 0.85–0.97, $p = 0.0035$) in the tranexamic acid group. Thromboembolic side effects were similar in both groups. Surprisingly, blood product transfusion was not different between the groups ($p = 0.21$) [72].

Conclusion

Coagulopathy following severe trauma is a common problem and associated with high mortality. TEM/TEG are promising diagnostic tools in the management of severely bleeding patients. The main therapeutic options in the treatment of coagulopathic patients are damage-control-surgery, permissive hypotension in uncontrolled bleeding and consequent maintenance of normal body temperature. Ratio driven resuscitation protocols with a high ratio of FFP:RBC revealed improved survival in military and civilian trauma care. In contrast, goal-directed coagulation therapy focuses on the actual demand of the patient and individualizes coagulation therapy. A modern monitoring device delivering prompt and reliable data about the actual coagulation status of the patient is essential for this approach. Hence, it follows that the most modern therapeutics available, coagulation factor concentrates, would be used predominantly. Fibrinogen is the most vulnerable coagulation factor and should be replaced early in the course of bleeding. An improvement in thrombin generation can be achieved by PCC, FFP and rFVIIa.

In the case of tranexamic acid, a large randomly controlled trial revealed improved survival rates and this drug should be considered as a therapeutic option. No data from large prospective randomized studies are currently available regarding ratio driven standard therapy using FFP and platelet concentrates. Growing evidence suggests that early aggressive supplementation of coagulation factors is crucial. If this is confirmed in future randomly controlled trials, coagulation factor concentrates would be faster and more effective than allogeneic products to increase the coagulation potential and could become the standard for point-of-care-guided, targeted treatment for trauma-induced coagulopathy.

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