Injectable hemostatic adjuncts in trauma: Fibrinogen and the FlinTIC study

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For adequate hemostasis, sufficient amounts of thrombin and coagulable substrate are fundamental prerequisites. In addition to platelets, on whose surfaces most of the thrombin is generated, fibrinogen can be considered as the substrate of the coagulation process.[1–4] If sufficient thrombin is formed, it converts fibrinogen into stable fibrin, which determines the firmness of the developing clot in the presence of activated coagulation factor XIII[5,6] (Fig. 1).

Under physiologic conditions, fibrinogen availability is regulated through dynamic changes in synthesis and breakdown to preserve coagulation function. As a consequence of blood loss, consumption of coagulation factors, dilutional coagulopathy, hypothermia and acidosis, as well as profibrinolytic activation, fibrinogen may reach critical levels earlier than any other procoagulant factor and also platelets even before packed red blood cell concentrate administration becomes necessary.[7,8] Floccard et al.[9] have described even significant drops in fibrinogen levels to occur already during the ultra early prehospital phase of care when comparing blood samples obtained from bleeding trauma patients at the scene and at the time point of arrival to the trauma bay (fibrinogen median, 2.6 g/L; interquartile range [IQR], 2.3–3.1; 95% confidence interval [CI], 2.4–2.9 vs. 2.1 g/L; IQR, 1.4–2.5; 95% CI, 1.7–2.3) (changes, −0.6 g/L; IQR, −1.1 to −0.3; 95% CI, −0.9 to −0.3; $p < 0.001$). In this study, fibrinogen levels decreased substantially as a function of injury severity reflected by Injury Severity Scores (ISSs). Recently, Kimura et al.[10] have reported similar results when searching retrospectively for predictors of hypofibrinogenemia in 290 blunt trauma patients upon admission to a Level 1 trauma center during a 3-year period. Their multivariate regression analysis identified patient's age (odds ratio [OR], 0.97; $p < 0.001$), Triage Revised Trauma Score (T-RTS including Glasgow Coma Scale [GCS] score, respiratory rate, and systolic blood pressure; OR, 0.81; $p = 0.003$), and prehospital volume therapy (OR, 2.54; $p = 0.01$) as independent predictors for early hypofibrinogenemia.

In contrast to disseminated intravascular coagulopathy, there is no generalized intravascular microcoagulation with increased consumption in trauma-induced coagulopathy.[11] Instead, there is hemorrhage-related loss of coagulation factors and platelets with subsequent dilution of procoagulant factors due to (uncritical) volume resuscitation with direct effect on fibrinogen polymerization.[12] Dilution of fibrinogen by crystalloid fluids and additional reduced fibrin interlinkage by synthetic colloids has been discussed.[2]

Recently, experimental data confirmed significant fibrinogen breakdown by acidosis following hypoperfusion with no effect on fibrinogen synthesis,[13] while hypothermia decreased fibrinogen synthesis with no effect on fibrinogen degradation.[14] Furthermore, synthesis and degradation seem to be regulated through different mechanisms, and a potential deficit in fibrinogen availability during hypothermia has been suggested.[2]

Fibrinogen Levels During Trauma-Hemorrhage and Outcome

Low concentrations of fibrinogen on admission and during initial management are frequently observed in trauma patients and have strongly been associated with the severity of injury and the degree coagulopathy.[9,10,15,16] Coagulopathic civilian trauma patients had a median fibrinogen concentration of 0.9 g/L (IQR, 0.5–1.5) together with a maximum clot firmness (MCF) of 6 mm (IQR, 0–9), whereas only 2.5% of healthy volunteers had an MCF of 7 mm or less.[17] An MCF of 7 mm was associated with a fibrinogen level of approximately 2 g/L. Hagemo et al.[18] identified a fibrinogen concentration of 1.5 g/L or less in 8.2% (n = 93) and less than 2 g/L in 19.2% (n = 211) of their 1,133 patients derived from a multicenter trauma population. A nonlinear relationship between fibrinogen concentration and mortality was detected in the generalized additive and piecewise linear regression models. In the piecewise linear regression model, a breakpoint for optimal fibrinogen concentration at 2.3 g/L was identified (95% CI, 1.9–2.6). Less than this value, the odds of death by 28 days was reduced by factor 0.08 (95% CI, 0.03–0.20) for every unit increase in fibrinogen concentration.[18]

Rourke et al.[19] have characterized admission fibrinogen level, time course of fibrinogen depletion, and its correlation with factors associated with injury and outcomes in a prospective cohort of 517 trauma patients. In this study, low fibrinogen levels were independently associated with ISSs ($p < 0.01$), shock levels ($p < 0.001$), prehospital fluid volumes ($p < 0.001$) and an independent predictor for mortality at 24 hours and 28 days ($p < 0.001$).

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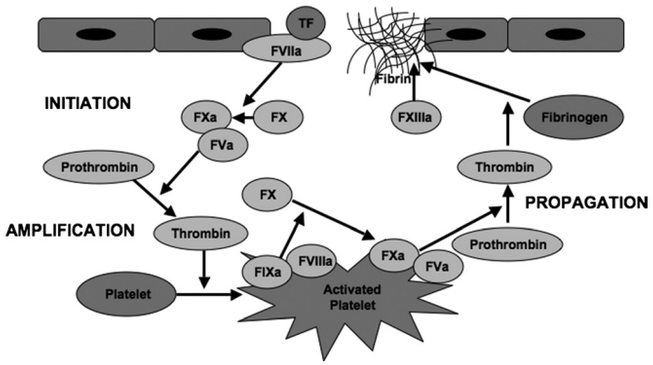

Figure 1. The three phases of hemostasis representing (*a*) initiation, (*b*) amplification, and (*c*) propagation. With injury to the vessel wall, TF is exposed and complexed to endogenous circulating FVII/FVIIa forming the TF/FVIIa complex initiating the coagulation process. TF/FVIIa complex converts FIX to FIXa and FX to FXa on TF-bearing cells (''INITIATION''). FXa/FVa complex converts prothrombin to thrombin with this little amount then activating FVIII, FV, FXI, and platelets (''AMPLIFICATION''). Activated platelets change shape and expose negatively charged phospholipids on their surface to which the FVIIIa/FIXa complex binds which, in turn, results in FX activation. The FXa/FVa complex activates prothrombin into thrombin, which then converts fibrinogen to fibrin (''PROPAGATION''). Fibrin cross-links with FXIII leading to stabilized clot formation. TF, tissue factor.

Similar results have been reported by a recent retrospective work.[10] Among injuries to different body regions, a strong contributor to low fibrinogen concentrations may be the occurrence of severe injuries to the extremities and the pelvic ring.[18]

In a similar approach, Inaba et al.[20] have retrospectively studied the impact of fibrinogen levels on mortality in a single-center cohort of 260 trauma patients undergoing a massive transfusion. The patients were stratified according to their admission fibrinogen levels as being normal (≥1.8 g/L), abnormal (≥1 to <1.8 g/L), and critical (<1 g/L). Ninety-two patients (35%) had normal admission fibrinogen levels, 114 (44%) had abnormal levels, and 54 (21%) had critical levels. Patients with critical fibrinogen levels had a significantly higher mortality at 24 hours compared with patients with abnormal (31.5% vs. 5.3%, adjusted $p < 0.001$) and normal fibrinogen levels (31.5% vs. 4.3%, adjusted $p < 0.001$). Patients with critical fibrinogen levels had significantly higher in-hospital mortality compared with patients with abnormal (51.9% vs. 25.4?%, adjusted $p = 0.013$) and normal fibrinogen levels (51.9% vs. 18.5%, adjusted $p < 0.001$). Also in this study, a critical fibrinogen level <1 g/L) was a strong independent predictor of mortality ($p = 0.012$).

Fibrinogen-Platelet Interactions

Both fibrinogen and platelets including their interactions are key to clot firmness and reductions in MCF (MCF in thromboelastometry/maximum amplitude [MA] in thrombelastography) and have frequently been associated with increased blood loss, blood transfusion requirement, and higher mortality.[21–26] Their level of contribution may vary, but it seems that strong fibrin polymerization can compensate for decreased platelet contribution to clot firmness[2,27–30] (Fig. 2). Harr et al.[29] have assessed the contribution of fibrinogen and platelets to clot strength by using a thrombelastography-based functional fibrinogen assay and reported a direct linear relationship with fibrinogen levels and percent fibrinogen contribution to clot strength ($R = 0.83$). Platelet counts, however, had only a moderate correlation to clot strength ($R = 0.51$). The addition of fibrinogen concentrate during in vitro studies increased clot strength (MA, 60.44 ± 1.48 to 68.12 ± 1.39) and percent fibrinogen contribution to clot strength (23.8% ± 1.8% to 37.7% ± 2.5%). The combination of fibrinogen and factor XIII was highly effective in raising FIBTEM MCF after dilution back to reference ranges in an in vitro model of dilutional coagulopathy.[30] Thrombocytopenic patients with

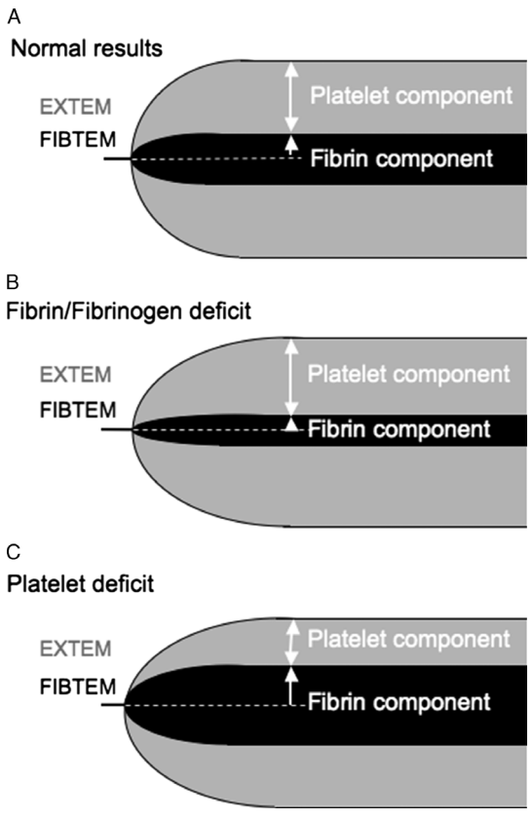

Figure 2. Diagnosis of fibrin(ogen) deficit as compared with platelet deficit based on thromboelastometry. Fibrinogen and platelets both contribute to clot firmness (*A*). However, with the activation assay only, fibrin(ogen) deficit (*B*) and platelet deficit (*C*) cannot be distinguished. With the supplementary platelet inhibition assay, the two coagulopathic conditions can be separated. Furthermore, a strong fibrin polymerization can compensate for decreased platelet contribution to clot firmness (*C*). The EXTEM test activates hemostasis via the physiologic activator TF. The result is influenced by extrinsic coagulation factors, platelets, and fibrinogen. The FIBTEM test is an EXTEM-based assay for the fibrin part of the clot. FIBTEM eliminates the platelet contribution of clot formation by inhibiting the platelets irreversibly with cytochalasin D. FIBTEM allows for the detection of fibrinogen deficiency or fibrin polymerization disorders and may identify rapidly the need to substitute fibrinogen. TF, tissue factor.

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inflammation-induced elevated fibrinogen levels in viscoelastic tests are often not transfused with platelet concentrates because of their clot firmness being in reference ranges. According to our own clinical experience, fibrinogen concentrate may even be effective in improving hemostasis in patients with very low platelet counts besides additionally being on antiplatelet drug therapy.[31] In an animal setting of uncontrolled bleeding, the administration of fibrinogen concentrate substantially improved clot firmness compared with the transfusion of 3-day-old apharesis concentrates or placebo.[32] This translated also into increased survival times and reduced blood loss.

Early Fibrinogen Concentrate Supplementation

While hemostatic therapy in surgical and/or massively injured trauma patients typically involves the transfusion of fresh frozen plasma (FFP), a systematic review including 91 eligible studies (70 on FFP and 21 on fibrinogen concentrate supplementation) published between 1995 and 2010 suggests purified human fibrinogen concentrate to offer an alternative to FFP in some instances.[33] Five studies have reported the outcome of fibrinogen concentrate versus a comparator. The evidence was consistently positive (70% of all outcomes), with no negative effects reported (0% of all outcomes). Fibrinogen concentrate was compared directly with FFP in three high-quality studies and was found to be superior for more than 50% of outcomes in terms of reducing blood loss, allogeneic transfusion requirements, length of stays on intensive care units and in the hospital, and increasing plasma fibrinogen levels. However, there was no fibrinogen concentrate comparator study in patients with hemorrhage caused by massive trauma, although efficacy across all assessed outcomes was reported in a number of noncomparator trauma studies. A more recent systematic review by Aubron et al.[34] with particular focus on evaluating the use of fibrinogen concentrate in severe trauma provided a similar signal but simultaneously called for additional studies because of methodological flaws in the existing literature.

The early administration of fibrinogen concentrate in bleeding trauma patients maintains fibrinogen concentration and clot firmness as reflected by thromboelastometry during the initial phase of care,[19,35] and for patients undergoing a massive transfusion after injury, as the fibrinogen level increased, a stepwise improvement in survival was reported.[20] Fenger-Eriksen et al.[36] have observed that the use of fibrinogen concentrate may improve standard coagulation parameters (e.g., prothrombin time and activated partial thromboplastin time), increase fibrinogen levels, and decrease bleeding in patients with massive hemorrhage and lower fibrinogen levels.

In the study by Rourke et al.,[19] the early administration of cryoprecipitate, which contains unstandardized combinations of fibrinogen, factor VIII, von Willebrand factor, and factor XIII, was associated with improved survival, and ex vivo fibrinogen administration reversed coagulopathic thromboelastometric parameters. In several retrospective studies of single-center experiences managing massive blood loss in trauma, the use of thromboelastometry-guided fibrinogen supplementation together with other blood products reduced mortality when compared with expected mortality,[37] reduced the exposure to allogeneic blood products,[38,39] and increased 30-day survival.[40] A matched-pairs analysis based on data captured into the German Trauma Register DGU revealed that the early use of fibrinogen concentrate may be associated with a lower 6-hour mortality and an increased time to death in exsanguinating trauma patients.[41] Similar results were obtained from an early observational study in combat-related trauma.[42]

Fibrinogen-Containing Agents and Tranexamic Acid

The MATTERs II study retrospectively assessed the impact of fibrinogen-containing cryoprecipitate in addition to the antifibrinolytic tranexamic acid (TXA) on survival in 1,332 combat injured.[43] Despite greater magnitude of injuries as reflected by ISS and packed red blood cell requirements, mortality was lowest in the cryoprecipitate/TXA (11.6%) and TXA groups (18.2%) compared with the cryoprecipitate (21.4%) and no cryoprecipitate/TXA (23.9%) groups. Cryoprecipitate and TXA were independently associated with a similarly reduced mortality (OR, 0.61; 95% CI, 0.40–0.94; $p = 0.02$ and OR, 0.61; 95% CI, 0.42–0.89; $p = 0.01$). Thus, fibrinogen-containing cryoprecipitate may independently add to the survival benefit of TXA in the seriously injured requiring transfusion.

Measurement of Plasma Fibrinogen

Several laboratory methods for measuring plasma fibrinogen concentrations are available, but results may vary depending on the type of method and the use of artificial colloid plasma expanders.[6] To date, the Clauss method is the most commonly used method to assess plasma fibrinogen concentrations in daily clinical practice. Solomon et al.[44] have evaluated the performance and repeatability of the Clauss method by testing plasma samples from patients undergoing cardiopulmonary bypass surgery in six different quality-controlled and specialized laboratories according to accredited standard operating procedures. Regarding within-center agreement for Clauss measurements, mean differences between duplicate measurements were between 0.00 g/L and 0.15 g/L, with intervals for 95% limits of agreement for mean Bland-Altman differences of up to 1.3 g/L. Regarding between-center agreement, some mean differences between pairs of centers were greater than 0.5 g/L. Differences of up to 2 g/L were observed with individual samples. Furthermore, adopting only the Clauss method in daily clinical practice can provide erroneously high levels if applied in patients who have received colloid plasma expanders. This may result in the hazardous delay or complete absence of treatment with fibrinogen.[6]

Modeling of Fibrinogen Supplementation With Fibrinogen Concentrate, Plasma, and Cryoprecipitate

Collins et al.[45] have created a theoretical tool to model the effect of fibrinogen concentrate, cryoprecipitate, and therapeutic plasma on the individual's plasma fibrinogen level. A fibrinogen concentration simulator (FCS_{amount}) was developed in which the amount of hemostatic agent was calculated from the patient characteristics, agent characteristics, and target plasma fibrinogen level (Fig. 3). The authors, however, acknowledge that the current tools may be intended for educational purposes rather than for clinical application.

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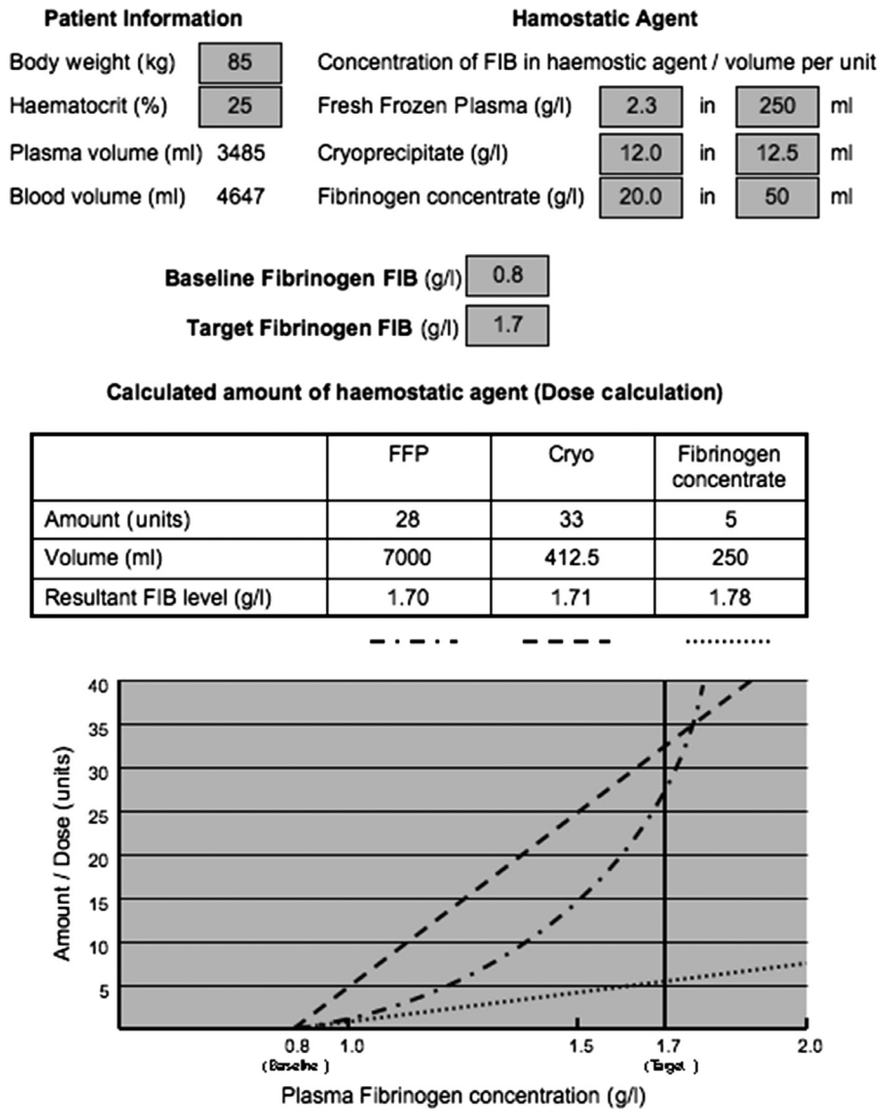

Figure 3. Fibrinogen concentration/dose simulation according to Görlinger (personal communication) and Collins et al.[45] To increase the plasma fibrinogen concentration from 0.8 g/L (baseline) to the target level of 1.7 (g/L), 28 U of FFP (7,000 mL) or 33 U of cryoprecipitate (412.5 mL) or 5 U of fibrinogen concentrate (250 mL) is necessary. Cryo, cryoprecipitate; FIB, fibrinogen.

Current Recommendations

The 2013 updated European guideline for the management of bleeding and coagulopathy following major trauma recommends the treatment with fibrinogen concentrate or cryoprecipitate in the continuing management of the patient if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 g/L to 2.0 g/L.[46] The initial fibrinogen concentrate dose of 3-g to 4-g or 50-mg/kg cryoprecipitate is suggested and repeated doses may be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. The evidence supporting this practice is limited and largely derived from elective surgery and postpartum hemorrhage. Hagemo et al.[18] have reported a breakpoint for initial fibrinogen concentration around 2.29 g/L, below which the odds of death within 28 days is reduced by factor 0.08 for every unit increase in fibrinogen concentration. This finding may indicate that the negative impact of low fibrinogen concentrations may still be underestimated in daily trauma care.

Risks Associated With Early Fibrinogen Supplementation

Fibrinogen supplementation can be achieved by using plasma, cryoprecipitate, or fibrinogen concentrate. However, there are a number of safety concerns associated with the first two allogeneic blood products, and there is a lack of high-quality evidence to support their use.[8] In addition, there is sometimes a substantial delay associated with the preparation of frozen products for infusion. In contrast, fibrinogen concentrate provides a promising alternative to allogeneic blood products and has a number of advantages. For example, (i) it allows a standardized dose of fibrinogen to be rapidly administered in a small

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Figure 4. Study team at the Cologne-Merheim Medical Center's (CMMC) rescue helicopter based currently at Cologne-Bonn Airport (''Christoph 3,'' Cologne, Germany).

volume, (ii) it has a very good safety profile, and (iii) it is virally inactivated as standard.[8] Beyerle et al.[47] have recently confirmed the good safety profile of human fibrinogen concentrate in a range of nonclinical investigations using different animal models.

The issue as to whether the administration of fibrinogen via factor concentrate, cryoprecipitate, or FFP may be associated with an increased risk for posttraumatic venous thromboembolism has not been addressed yet, and a causative relationship between high fibrinogen levels and thromboembolic events in the further sequalae after trauma is not established. In patients undergoing cardiac surgery or cystectomy, intraoperative administration of fibrinogen concentrate resulted in higher early postoperative fibrinogen levels, but already at 24 hours after surgical intervention, fibrinogen levels were identical in patients with and without intraoperative fibrinogen administration.[48,49] A similar observation was recently reported from a cohort of severely injured and bleeding trauma patients.[50] Experimental data reported by Zentai et al.[51] demonstrate that human fibrinogen concentrate does not suppress endogenous fibrinogen synthesis. Furthermore, fibrinogen provides also some antibacterial properties as recently identified by Pahlman et al.[52] The peptide fragment GHR28 released from the β-chain of fibrinogen has been demonstrated to have antimicrobial activity against bacteria. Thus, fibrinogen seems to be involved in the early innate immune system to quickly wall off and neutralize invading pathogens.

Prophylactic infusion of 2-g fibrinogen concentrate in patients undergoing cardiac surgery in a randomized study by Karlsson et al. has not been shown to trigger any postoperative thromboembolic events.[49] Despite a transient increase in fibrinogen concentration after infusion and a subsequent reduction in blood loss, hemostatic parameters did not differ significantly between the groups in the later sequalae. The currently still recruiting Phase III REPLACE study (Study of Fibrinogen Concentrate (Human; FCH) to Control Bleeding During Complex Cardiovascular Surgery) titrates the amount of human fibrinogen concentrate (FCH) based on the measured MCF and body weight to high MCF targets of 22 mm.[53] This study aims to demonstrate that FCH can reduce the amount of donor blood products needed during complex cardiovascular surgery including safety. In an experimental model of dilutional coagulopathy combined with liver trauma, even doses of up to 600-mg/kg fibrinogen to correct coagulation profiles and blood loss were not associated with signs of thromboembolism as detected via organ histology.[54] Similar results have previously been reported by the same group and by Grottke et al. using fibrinogen doses of up to 200 mg/kg.[55,56] The role of hyperfibrinogenemia as a potential factor for heparin resistance in the context of heparin-based venous thromboembolism prophylaxis remains to be elucidated.[57] Our own preliminary results, however, indicate that heparin resistance may rather be related to ultra-high levels of factor FVIII (>400%) and not fibrinogen.

Fibrinogen in Trauma-Induced Coagulopathy (FlinTIC) Study

As the current literature demonstrates, there are no adequately powered and designed prospective clinical studies yet available to show the risk-benefit analysis of using a source of supplemental fibrinogen for the management of the bleeding trauma patient, and well-designed prospective randomized controlled studies evaluating the effect of fibrinogen supplementation in trauma are urgently needed.[33,34,58–60] In this context, the FIinTIC study is the first of its kind to prospectively assess the effect of early treatment with fibrinogen concentrate in the trauma population presumed to bleed.[61] Severe traumatized patients with visible significant bleeding and/or with clinical signs of internal significant bleeding in shock treated by an emergency physician of the helicopter service or the ground team will be enrolled in the study at the scene. Thirty patients are scheduled to be randomized to receive 50-mg/kg fibrinogen concentrate (FGTW fibrinogen concentrate, 1.5 g in 100 mL; LFB France), while the other 30 patients receive placebo. The primary outcome includes changes in plasma coagulation as reflected by fibrinogen polymerization with the FIBTEM MCF, and secondary outcomes are transfusion requirement/blood loss, thromboembolic complications, and clinical end points such as morbidity and length of stays on intensive care units and overall in the hospital. The FIinTIC study is a multicenter double-blind, placebo-controlled, randomized pilot trial conducted in the difficult environment of the prehospital setting currently involving different helicopter and ground emergency medical service stations across Austria, Germany, and the Czech Republic (Fig. 4). The recruitment will be finished by next year.

AUTHORSHIP

M.M. wrote the manuscript, C.S., H.S., and D.F. contributed to the manuscript with data from their work. M.Z. critically reviewed the manuscript. All authors have approved the manuscript.

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