Haemostasis management of massive bleeding

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Keywords
Massive bleeding, trauma-induced coagulopathy, hyperfibrinolysis, transfusion trigger

Summary
Trauma-induced coagulopathy (TIC) is a frequent complication of severely injured patients. The etiology of TIC is complex. Contributing factors include overwhelming generation of thrombin and activated protein C, consumption of coagulation factors and platelets, hyperfibrinolysis, and dilution of clotting factors through administration of fluids. In addition, hypothermia and shock-associated metabolic acidosis augment the clotting dysfunctions. The occurrence of TIC has been shown to be an independent risk factor for death after trauma warranting aggressive treatment. On admission to the emergency room patients with massive blood loss should be employed on basis of clinical and diagnostic variables to identify patients at high risk of coagulopathy. Patients at high risk should be treated with tranexamic acid (1 g bolus followed by 1 g/h), and critical factor and platelet deficiencies should be corrected by transfusion of factor concentrates and platelet concentrates. In addition, plasma should be administered in a 1:1 ratio with red cells. The use of recombinant factor VIIa should be considered if major bleeding persists despite best-practice use of blood products.

Schlüsselwörter
Hämorrhagischer Schock, Trauma-induzierte Koagulopathie, Hyperfibrinolyse, Transfusionstrigger

Zusammenfassung

Massive bleeding is associated with an increased risk for the development of coagulopathy. The risk depends on the origin of bleeding, the degree of vascular disruption, and the extent of blood loss and is highest in patients with severe trauma injury who arrive in hemorrhagic shock (23). In a retrospective review including 1088 patients over a 5-year period, 24.4% of patients were coagulopathic on admission defined as prothrombin time, activated partial thromboplastin time, or thrombin time greater than 1.5 times normal (27). These data were confirmed by other retrospective studies indicating that 25% to 45% of trauma patients were coagulopathic on admission to the trauma unit (4, 18, 23). The occurrence of coagulopathy is associated with increased mortality and morbidity rates. MacLeod and colleagues showed that abnormal prothrombin time and activated partial thromboplastin time values on admission are independent predictors of mortality (18). They concluded that an abnormal admission prothrombin time increases the adjusted odds of dying by 35% and that an abnormal admission activated partial thromboplastin time increases the adjusted odds of dying by 326% (18). Given the worse outcome of patients with a coagulopathic condition than patients with the same injury severity without a clotting disturbance one could conclude that early and aggressive treatment of trauma-induced coagulopathy will reduce early in-hospital mortality rates and improve patients’ outcome. Evidence that support this assumption comes from previously published treatment studies showing that the use of antifibrinolytics and of blood products including plasma, fibrinogen, and platelet support significantly reduces mortality rates of severe trauma patients (6).

Also in major surgery massive bleeding is a frequent and serious complication. However, contrary to trauma injury the risk for coagulopathy is lower, because tis

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sue trauma is more controlled, tissue anoxia is better controlled, blood losses can be replaced in a timely manner, and coagulopathy can be treated at earlier stages.

**Acute coagulopathy after massive blood loss**

The mechanisms causing acute coagulopathy in trauma are multifunctional. The basic mechanisms are summarized in figure 1. Massive bleeding from the injured vessels leads to loss of coagulation factors and platelets (2, 14, 17). Simultaneously, trauma-induced exposure of tissue factor material that enter the circulation through the flowing blood induce a systemic thrombin burst leading to the consumption of clotting factors and platelets. Moreover, on the surface of endothelial cells thrombin bound to its endothelial cell receptor thrombomodulin converts protein C in its active form, activated protein C (APC).

With ongoing blood loss and the development of haemorrhagic shock the blood flow in the microcirculation continuously turns down resulting in hypoperfusion. This hypoperfusion leads to accumulation of APC, because activation of protein C through thrombin-thrombomodulin is an ongoing process. In addition, hypoperfusion-related anoxia stimulates endothelial cells to release plasminogen activators resulting in the generation of plasmin, the key fibrinolytic enzyme. Plasmin generation is further augmented by inactivation of plasminogen activator inhibitors through APC (Fig. 1).

When fluid resuscitation is achieved by administration of crystalloids and colloids, plasmin and APC are washed out from the microcirculation resulting in an immediate

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**Fig. 1** Mechanisms of trauma-induced coagulopathy: The coagulopathic cascade in severe trauma is initiated through massive blood loss combined with excessive activation of the coagulation cascade at the injury site resulting in the loss and consumption of clotting factors. Depending on the severity of the injury tissue factor bearing material and thrombin are released into the circulation resulting in a systemic activation of the coagulation cascade. Bound to its endothelial cell receptor thrombomodulin, thrombin induces the formation of activated protein C (APC). Simultaneously, the ongoing blood loss induces a hypoperfusion of the microvasculature resulting in the accumulation of APC in this compartment. Furthermore, anoxia induces the release of plasminogen activators (PA) from endothelial cells (EC) inducing hyperfibrinolysis through generation of plasmin. The development of hyperfibrinolysis is augmented by the proteolytic degradation of plasminogen activator inhibitors (PAI) through APC. When reperfusion of the microvasculature is achieved through administration of fluids, APC and plasmin are washed out and induce a systemic anticoagulant and hyperfibrinolytic response.
systemic anticoagulant response and systemic hyperfibrinolysis (5). Moreover, the use of plasma expanders leads to dilutional coagulopathy and colloids, such as hydroxylethyl starch, interfere with the function of several clotting factors (24).

Through loss, consumption, and dilution plasma levels of several clotting factors become critical low. The first protein reaching critical low concentrations is fibrinogen (11). This can be explained by the complex synthesis of fibrinogen in the liver and by the proteolysis of fibrinogen through plasmin. In an animal model Hiippala analysed the loss of clotting factors with extensive blood loss (Tab. 1). At present it has been not systematically analysed whether low levels of factor XIII (FXIII) also contribute to the occurrence of trauma-induced coagulopathy. One should expect low levels of FXIII in trauma patients since the initial thrombin burst activates and depletes FXIII and the synthesis capacity of the organisms seems to be too low for rapid correction of plasma levels of FXIII (13, 30).

Further factors that contribute to the development of TIC are acidosis and hypothermia. Acidosis lowers the activity of procoagulant clotting factors and down-regulates the inactivation of plasminogen activators through plasminogen activator inhibitors. Hypothermia decreases the activity of the coagulation cascade, since the activity of enzyme-catalyzed reactions is decreased by about 50% for every 10°C drop in temperature.

### Initial assessment of the patient’s coagulopathic risk

The risk of patients with massive blood loss to develop TIC is influenced by various factors including the amount of blood loss, the type of injury, the development of a haemorrhagic shock, and the presence of comorbidities. Based on clinical and laboratory variables that are immediately available on admission of the patient to the trauma unit the ‘Deutsche Gesellschaft für Unfallchirurgie’ has developed a scoring system to predict the probability for life-threatening haemorrhage after severe injury (19). The probability index of this trauma associated severe haemorrhage (TASH)-score was validated on 5,834 datasets of trauma patients. Using variables of the TASH-score patients at high risk for the development of trauma-induced coagulopathy can be identified immediately after admission to the trauma unit. Clinical and laboratory variables derived from the TASH-Score that identify high risk patients are summarized in Table 2. The early identification of high risk patients will guide initial treatment decisions and will help to activate logistics in acute trauma care, for example blood bank resources.

### Assessment of critical factor deficiencies

Loss and consumption of clotting factors and platelets is of critical importance for the development of TIC. Routine laboratory assays such as the prothrombin time, the activated partial thromboplastin time, and single factor testing are highly standardized laboratory assays that accurately measure plasma levels of activable clotting factors (4, 14). In turn, the presence of TIC can be confirmed using these tests (2, 18, 23). However, in most hospitals these coagulation tests are performed at the central laboratory requiring transportation of blood samples. Due to this logistic problem results of these coagulation assays are frequently only available with a delay of more than 15 min.

Possible alternatives are point-of-care assays such as the thrombelastography (2, 20, 25). Thrombelastography is performed with whole blood and measures the viscoelastic properties of the growing thromb-
Thrombelastography measurements with tissue factor bus after induction of clotting under low shear conditions (20). Thrombelastography identifies critical low fibrinogen levels, identifies platelet dysfunction in patients suspected to be on antithrombin agent treatment, identifies hyperfibrinolysis, modifies treatment with antifibrinolytic agents. Platelet function analyser or whole blood aggregometry identifies platelet dysfunctions in patients presenting with massive blood loss.

PT: prothrombin time; aPTT: activated partial thromboplastin time

**Assessment of systemic endogenous anticoagulation**

There is growing evidence that thrombin triggered formation of APC augments the bleeding tendency in trauma patients. At present, however, no routinely usable assay system is available allowing the measurement of plasma levels of APC. Plasma levels of APC-protein C inhibitor complexes are indirect measures that indicate the formation of APC. Testing for this biomarker is time consumptive and not applicable in the bleeding patient.

**Assessment of hyperfibrinolysis**

The release of plasminogen activators from hypoxic endothelial cells and the inactivation of plasminogen activator inhibitors through proteolysis by APC contribute to the development of hyperfibrinolysis in trauma patients. The euglobulin lysis time or the detection of plasmin-antiplasmin-complexes is referred to be the gold standard tests for the diagnosis of hyperfibrinolysis (28). However, both tests are complex and time consuming procedures that can take more than 180 min making them not feasible for the diagnosis of hyperfibrinolysis in bleeding patients, although they are sensitive measures for the detection of hyperfibrinolysis in vivo.

Thrombelastography is a practicable but less sensitive alternative method to both assays for the detection of hyperfibrinolysis (22). By analyzing blood samples in the presence and absence of the plasmin inhibitor aprotinin a lysis ratio can be calculated by dividing the maximal clot firmness measured in the presence of aprotinin through the value measured in the absence of the plasmin inhibitor aprotinin. Using such an aprotinin-based approach Levrat and colleagues were able to detect 5 patients with hyperfibrinolysis in a group of 23 trauma patients. Euglobulin lysis time detection confirmed the presence of hyperfibrinolysis in these 5 patients, whereas the remaining 18 patients were tested negative for the presence of hyperfibrinolysis (15).

This indicates the ability of aprotinin-modified thrombelastography to detect hyperfibrinolysis in the bleeding patient.

**Management of trauma-induced coagulopathies**

Options to prevent or treat coagulopathies associated with massive blood loss include treatment with the antifibrinolytic agent tranexamic acid, the transfusion of blood products such as plasma and platelets, factor concentrates, and the use of recombinant activated factor VII (rFVIIa).

**Treatment of hyperfibrinolysis**

Antifibrinolytic agents are successfully used to decrease bleeding and transfusion requirements in surgical patients. Based on these data the authors of the European Guideline 2010 on the ‘Management of bleeding following major trauma’ suggested the use of antifibrinolytics such as tranexamic acid and ε-aminocaproic acid to the treatment of trauma patients (23).

Tranexamic acid is a synthetic lysine analogue that inhibits plasmin generation. Tranexamic acid is distributed throughout all tissues and the plasma half-life is 120 min. In-vitro studies have suggested that a dose of 10 μg/ml is required to inhibit fibrinolysis (1). Evidence that the use of tranexamic acid improves the outcome of trauma patients comes from the recently published CRASH-2 trial (6). This study includes 20,211 trauma patients with or at risk for substantial bleeding who were randomly assigned to a tranexamic acid treatment group or to placebo. Tranexamic acid was administered as a bolus of 1 g followed by another 1 g over 8 h. In-hospital mortality within 4 weeks of injury was the primary outcome, while thromboembolic events, transfusions, or surgical interventions were secondary outcomes. All-cause mortality was 14.5% in the tranexamic acid group (1436/10060) compared with 16.0% with placebo (1613/10067); relative risk 0.91, (95% CI 0.85–0.97; p = 0.0035). Bleeding-related mortality was also reduced (4.9% vs 5.7%), without an increase in fatal or non-fatal vascular occlusive events.

<table>
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Tab. 3 Initial haemostasis screen of patients presenting with massive blood loss

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requirements showed no statistically significant difference between both groups (6, 16).

It is recommended that patients presenting with a high risk of TIC should receive a bolus of 1 g tranexamic acid upon admission to the trauma unit followed by continuous infusion of 1 g over 8 h. In patients showing laboratory evidence of hyperfibrinolysis the continuous infusion of tranexamic acid should be increased to 20 mg/kg b.w./h. Tranexamic acid treatment should be continued once bleeding has been adequately controlled.

Treatment of factor deficiencies and of low platelet counts

There is growing evidence that the early and aggressive correction of clotting factor deficiencies improves the outcome of trauma patients (21, 10, 9). Transfusion of blood products such as fresh frozen plasma, clotting factor concentrates, and platelet concentrates can be used to prevent and treat clinically relevant coagulation factor deficiencies in patients with massive blood loss.

Early use of fresh frozen plasma at a 1:1 ratio to packed red blood cells has been shown to effectively avoid dilutional coagulopathy (7, 12, 23, 31). However, in patients presented with clinically relevant factor deficiencies at admission to the trauma unit the administration of fresh frozen plasma is not sufficient to restore critical coagulation factor deficiencies. In this situation the use of specific factor concentrates such as fibrinogen concentrate, FXIII concentrate, and prothrombin complex concentrate is recommended (23). Fibrinogen concentrate should be administered if plasma fibrinogen levels of less than 100 mg/dl are accompanied by ongoing bleeding. The optimal initial dose has not been defined but from practical reasons an initial dosage of 3 g of fibrinogen is recommended since administration of 3 g fibrinogen will raise plasma fibrinogen levels above 100 mg/dl even in the presence of severe fibrinogen deficiency (7, 8, 22, 26). Transfusion triggers for the use of FXIII concentrate have not been established so far, but from a pathophysiologic point of view it seems reasonable to recommend that plasma levels of FXIII less than 50% should be corrected by the use of FXIII concentrate at an initial dosage of 25 IU/kg b.w.. Platelet concentrates should be administered if platelet counts fall below 50 000/μl at an initial dosage of two platelet concentrates either prepared by single-donor apheresis or by pooling of platelet concentrates obtained from whole blood units.

Treatment of systemic endogenous anticoagulation

The activity of APC is controlled by inactivation through the protein-C-inhibitor. In the absence of a pharmacological agent that specifically inhibits APC, substitution of protein-C-inhibitor through transfusion of plasma is the only way to correct increased plasma levels of APC.

Treatment of patients pretreated with antithrombotic agents

There is an ongoing number of patients treated with antiplatelet agents and oral anticoagulants. Trauma patients on antiplatelet agents and orals should be transfused with platelet concentrates as soon as possible. The recommended initial dosage is 2 platelet concentrates. Patients taking oral anticoagulants of the vitamin-K-antagonistic type should be treated with 50 U/kg b.w. of prothrombin complex concentrate. In addition 10 mg vitamin K should be administered through the intravenous route (29).

Since patients taking antithrombotics are at an increased risk for the development of thromboembolic complications, intravenous anticoagulation should be initiated once bleeding has been stopped.

Treatment with recombinant activated factor VII

The use of rFVIIa as an initial adjunctive treatment in patients with severe trauma has been investigated in a randomized clinical study including patients with blunt and penetrating trauma patients (3). In blunt trauma patients the use of rFVIIa significantly reduced the need for transfusion requirements and the incidence of acute respiratory distress syndrome but showed no effect on the overall mortality rates in blunt and penetrating trauma patients. Therefore, rFVIIa should be not considered as a first-line treatment in TIC. It should be considered if major bleeding persists despite correction of coagulation factor deficiencies and critically low platelet counts by the use of blood products. In addition, severe acidosis should be corrected before rFVIIa will be used. Recombinant FVIIa should be administered at an initial dose of 100 μg (5 KIE)/kg b.w. followed by a second and third dose 1 and 3 hours later.

References

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