Coagulation management in major trauma

H. Schoechl
Department of Anaesthesia and Intensive Care Medicine, AUVA Trauma Hospital, Salzburg, Austria

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Summary
Bleeding is a common problem in major trauma. Coagulopathy could be detected in approximately 25% of all trauma patients on arrival in the emergency room. The reasons for that are blood loss, dilution of the remaining coagulation factors by fluids not containing coagulation factors, consumption of coagulation factors and hyperfibrinolysis. Hyperthermia and acidosis are also well described contributors of coagulopathy. Diagnosis of coagulation abnormalities should be based on clinical judgement. Standard coagulation tests are universally available, but there is some evidence, that those tests are not predictive for transfusion requirement. Thrombelastography/metry is a promising technology which not only shows the initiation of the coagulation process but also the dynamic of clot formation and the clot firmness. It is the golden standard for the diagnosis of hyperfibrinolysis. To restore adequate haemostasis an aggressive treatment of hyperthermia and acidosis is essential. The concept of damage control surgery and permissive hypotension in server bleeding patients could reduce the whole amount of blood loss.

For coagulation factor replacement therapy fresh frozen plasma, PCC, fibrinogen concentrates and cryoprecipitate could be used. Haematocrit should be maintained in the range of 30% and platelet count should not drop below 50 000/µl. In some circumstances haemostatic agents such as DDAVP, antifibrinolytics and FVIIa could be helpful, especially if not treated adequately (4).

Pathophysiology of coagulopathy in trauma

Blood loss
Severe bleeding causes a concomitant loss of intravascular constituents and results in a major reduction of clotting factors. Fibrinogen seems to be the most vulnerable of the coagulation factors. It could be demonstrated in elective surgery as well as in trauma patients that an early depletion of fibrinogen occurs in the course of massive bleeding (17, 24).

The minimum amount of concentration of single clotting factors needed to assure efficacious coagulation in situations where loss of multiple clotting factors has occurred is not well defined and current models estimate a range of essential activity for single clotting factors between 25 and 30% (15).

Dilution
Dilutional coagulopathy is a consequence of volume replacement therapy in severe bleeding patients with fluids not containing adequate amounts of coagulation factors. The treatment sequence of fluid administration in massive trauma usually comprises application of crystalloids and colloids first, followed by packed red blood cells (PRC’s), which all are transfused to maintain adequate intravascular volume and to ensure sufficient tissue perfusion. This results in a dilution of the remaining coagulation factors and platelets.

Impaired fibrin polymerization is another well described consequence of colloidal volume replacement therapy. This by itself may aggravate the overall bleeding tendency (13, 15).

Thrombelastometric studies show that the maximum clot firmness (MCF) is reduced after volume replacement therapy with colloids, especially after administration of hydroxyethyl starches (HES). (13)

Dilutional thrombocytopenia occurs after transfusion of 15–20 PRCs (1). The total reduction in the number of platelets depends on the individual reaction of the patient and precise predictions of the resulting total platelet count are difficult (15).

After a single blood volume is lost, usually around 35–40% of the platelets remain within the intravascular compartment. If this is exceeded and the blood loss comprises 2.5-fold of the whole blood volume of the patient, a clinically relevant thrombocytopenia with platelet numbers of less than 50000/µl is commonly observed (17).

Concentration
In massive trauma, multiple injury sites exist with multiple exposition of tissue factor at the sites of injury. This may cause extensive activation of the coagulation cascade with consumption of clotting factors and, as a consequence, platelets. If so, the result is a depletion of clotting factors and platelets due to the body’s attempts to form multiple clots.

Hyperfibrinolysis
Under normal haemostatic conditions tissue plasminogen activator (t-PA) is secreted by endothelial cells. If clotting took place, t-PA binds to the clot-bound fibrin and causes local fibrinolysis via conversion of plasminogen to plasmin. The local control mechanisms during generation of plasmin are an essential requirement to ensure the lysis of the local thrombus only and to avoid systemic reactions.
In trauma, these local control mechanisms are usually no longer effective, resulting in systemic fibrinolysis and degradation of fibrin polymers and circulating fibrinogen (25).

The normal down-regulation of fibrinolysis by plasminogen activator inhibitor 1 (PAI 1) is also reduced due to the widespread endothelial damage. PAI-1 has been characterized as a potent inhibitor of t-PA. PAI-1 is normally synthesized and secreted from endothelial cells. During endothelial cell stimulation this process is reduced leading initially to a loss of local antifibrinolytic activity.

Hypofibrinolysis, as a general phenomenon during serious medical conditions, is much more common than previously assumed. It occurs in major trauma, hepatic trauma, severe pelvic- and brain injury. The current diagnostic deficiency to early identify hypofibrinolysis can be explained by the absence of routine laboratory tests for fibrinolysis. The most efficient diagnostic tool to detect hypofibrinolysis is thrombelastography/metrit (TEG/TEM). Recently, rotational thrombelastometric studies have shown that approximately 15–20% of major trauma patients suffering from massive bleeding also present with pronounced hypofibrinolysis. This could support the hypothesis that early administration of antifibrinolytic agents may be beneficial during hemorrhage control in the treatment of trauma patients (28).

### Hypothermia

Hypothermia is a major contributor towards coagulopathy in trauma. The coagulation process consists of multiple temperature-dependent enzymatic reactions. The optimal temperature to ensure an adequate function of coagulation factors is around 37°C. For every decrease in temperature comprising a step of 10°C, enzymatic activity is reduced by approximately 50% (32).

Not only coagulation factors are affected in hypothermia, but also platelet function, which decreases if temperature is reduced. Aggregation and adhesion of platelets are significantly reduced at temperatures of 33°C compared to temperatures of 37°C (39). Valeri et al. demonstrated that production of thromboxane B2 by platelets in baboons was reduced during hypothermia, correlating with an increase in bleeding time (37).

There is some evidence that hypothermia increases clot lysis (40). Using routine laboratory coagulation parameters like e.g. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) to identify clotting changes caused by hypothermia usually is without success as laboratory standard procedures require measuring of PT and aPTT at standard temperatures of 37°C, therefore correcting hypothermia-induced changes (32).

### Acidosis

Acidosis has a detrimental effect on coagulation. Meng et al. demonstrated in an in vitro experiment that the activity of the FXa/FVa prothrombinase complex was decreased by 70% at pH 7.0; Fig. 1 (29).

Induction of acidosis in animal studies leads to a decrease in fibrinogen of approximately 20% (27). Recombinant factor VIIa (rFVIIa) is also less effective under conditions of acidosis (29). Acidosis also adversely affects platelet function, particularly activation and aggregation (34). In major trauma patients, low pH on admission to the hospital was highly predictive of the development of a bleeding coagulopathy (7).

### Clinical bleeding

One important aspect in the diagnosis of a tendency towards increased bleeding is the „clinical impression”. Diffuse microvascular bleeding from cut surfaces, bleeding from intravascular catheter insertion sites or diffuse mucosal bleeding are predictive for an ongoing coagulopathy.

### Standard coagulation tests

In most hospitals the standard coagulation tests PT and aPTT are performed. PT and aPTT are expected to become elevated when levels of factor V, VII and IX are below 50% (10). If fibrinogen levels fall to 40mg/dl or lower, PT and PTT can be affected, even if the concentration of the remaining coagulation factors stays in the normal range. It is assumed that coagulopathy effects PT and aPTT by prolonging normal values by the factor of 1.5 to 1.8 (14).

The use of standard coagulation assays to monitor bleeding is associated with technique-inherent deficiencies, as these assays were developed to monitor anticoagulation and not to predict clinical course of bleeding (10, 23). Therefore routine coagulation parameters fail to accurately monitor the state of coagulopathy due to several reasons: Firstly, in vivo coagulation occurs primarily on the cell surfaces of platelets and tissue factor-bearing cells. (28) Secondly, the important role of erythrocytes in hemostasis needs to be considered as well. Thirdly, laboratory analysis of PT and aPTT is performed on platelet-poor plasma and therefore does not consider nor measures the complex
in-vivo cellular interactions, which occur during clotting. Therefore, and as a consequence, the prognostic value of the standard clotting assays PT and aPTT regarding the prediction/monitoring of bleeding tendency and PRC-transfusion is regarded to be poor (38).

As fibrinogen is the most important coagulation factor and decreases early in the course of severe trauma, there is an utmost need and importance to determine plasma fibrinogen levels as soon as possible once the patient has arrived at the emergency room. (26) The initial determination of fibrinogen has to be followed by regular controls during the initial and ongoing treatment of the patient. Hematocrit and platelets have to be evaluated immediately after arrival of the patient in the ER, too.

**Thrombelastography/-metry**

TEG is a device that measures the viscoelastic properties of the clot during its formation and subsequent lysis. TEG seems to be helpful in coagulation management during treatment of severe trauma (12, 22). To perform TEG, a blood specimen of the patient is added to the test cell. After re-calification of the blood sample and the addition of an activator like e.g. thromboplastin (extrinsic pathway) or caolin (intrinsic pathway), the coagulation process in the test cell starts (Fig. 2).

Measuring of coagulation in TEG is performed by the insertion of a vertically immersed plastic pin that rotates slowly to the left and the right side within a range of an angle of 4.75° into the sample specimen in the test cell. With the generation of the first fibrin filaments between the pin and the wall of the test cell, the rotation range of the pin gets reduced. The increasing forces exerting their adhesive influences on the range of movement of the pin are converted and transferred to a graphical recorder, which plots the changes of viscoelastic properties on the clot over time. TEG provides information on how fast the clot forms, the speed of clot growth, clot strength and a breakdown of the clot.

Rotational thrombelastometry analyser (ROTEM®) is a four channel system where a set of standardized reagents are utilized to enable the physician to discriminate between several potential causes of bleeding. Two basic tests using intrinsic contact activation by ellagic acid and extrinsic activation by tissue factor provide first information on the general coagulation status (impaired, normal, and exceeding).

The so called FIBTEM assay is a test where the platelets are inhibited by cytochalasin resulting in the possibility to evaluate the fibrin component of the clot separately. The Aprotinin thrombelastometry (APTEM)-test is used for confirmation of a state of hyperfibrinolysis. In this test, coagulation is activated similar to Extrinsic Thrombelastometry (EXTEM) by tissue factor but differs to EXTEM as aprotinin is added to the blood specimen in order to inhibit the fibrinolysis in vitro. If hyperfibrinolysis is active in the sample, the clot lysis seen in the INTEM and EXTEM tests (maximum lysis >15%/h) is corrected in the APTEM (Fig. 2 and Fig. 3b).

**Treatment of coagulation disorders**

**Basic steps**

**Management of temperature**

Hypothermia is a common problem in trauma victims and correlates with a significantly worse prognosis (7, 21). As hypothermia compromises primary- as well as secondary hemostasis and enhances clot lysis, all efforts should be initiated 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 essential. Intraoperative use of patient warming devices is strongly recommended (1, 7, 12, 21). As coagulation test are performed at a standard temperature of 37°C, this usually leads to an underestimation of the degree of the in vivo existing coagulopathy.

**Damage control**

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 to reduce bleeding tendencies. Abdominal packing as well as external fixation of extremity fractures shortens operation time and 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 mortality in major trauma patients (20).

**Permissive hypotension**

A permissive reduction of the blood pressure by reduced fluid administration in the prehospital setting and the initial hospital phase may reduce the amount of blood loss. Dutton et al. showed in severely injured patients that an intraoperative reduction of the systolic blood pressure down to 70 millimeter of mercury (mmHg) reduced the time of active bleeding compared with a systolic blood pressure (RR) around 100 mmHg. (2.4 h vs. 2.9 h) Mortality was not altered (11).

**Coagulation factors**

**Fresh frozen Plasma (FFP)**

In current clinical practice FFP is most frequently used to replace lost coagulation factors. Guidelines regarding its use have been published. However, appropriate use of FFP continues to be a topic of controversy (5, 8, 11, 30).

According to the current guidelines FFP should be transfused if PT/aPPT are prolonged above 1.5-times of the normal value, if fibrinogen plasma level is less than 0.8 g/l and if the plasma levels of coagulation factors are less than 30% (1). Furthermore, the optimal ratio of PRC/FFP has not been clarified yet (1, 14, 18, 19).

The major inherent disadvantage associated with the use of FFP is reflected by the difficulty to standardize the content of coagulation factors in FFP. The concentration of the clotting factors is donor-dependent. Prior to infusion, FFP has to be thawed, which takes at least 30 minutes time. There is also a risk for Transfusion-Induced-Lung-Injury (TRALI), which is related to the presence of antibodies to human leukocyte antigen (HLA) or to the presence of leukocytes in the donor’s plasma (8, 35). Finally, FFP contains a huge volume of citrate, which binds calcium (11).

**Prothrombin complex concentrate (PCC)**

Prothrombin complex concentrates are virtually-inactivated plasma products that contain the vitamin K-dependent coagulation factors (II, VII, IX, X) and the inhibitors antithrombin (AT), Protein S, -C, and -Z. To prevent activation of the coagulation factors, most PCCs contain heparin. As PCCs include heparin, their use is contraindicated in patients with a known heparin-induced thrombocytopenia (HIT).

PCCs may be beneficial in patients with massive bleeding where an immediate therapy of the coagulation defect is indicated. In situations of known deficiency of prothrombin complex factors, such as in vitamin K-deficiency or if an immediate reversal of coumarin therapy is necessary, PCCs constitute an useful therapeutic option. The products are well standardized and immediately available. One unit of PCC/kg body weight (b.w.) increases the PT by approximately 1% (11). There is only limited in vivo data on the use of modern PCC-preparations in trauma patients suffering from acquired coagulation factor deficiencies caused by massive blood loss (12).

**Fibrinogen**

Evaluation of fibrinogen should constitute a component of all transfusion algorithms, especially if used in patients with excessive bleeding. Regular monitoring of the fibrinogen levels is therefore recommended. Ensuring adequate levels of fibrinogen is crucial in management of massive hemorrhage. Fibrinogen concentration of less than 1 g/l is generally insufficient to prevent significant blood loss in severe bleeding. Most transfusion guidelines recommend treatment if fibrinogen falls to below 1 g/dl. However, starting fibrinogen substitution therapy at such low levels is not without problems as it may be quite difficult to be successful in reversing the already existing and negative effects of hypofibrinogenemia.

**Corpuscular blood components**

**Hematocrit**

A sufficient amount of red blood cells is required for adequate hemostasis. There is evidence that clot formation is impaired if hematocrit is low. Red blood cells apply a rheological effect on the margination of platelets against the vessel wall. This provides an optimal interaction between platelets and the injured vessel wall (15). Furthermore, red blood cells seem to be able to directly activate platelets. Red blood cells contain adenosine diphosphat (ADP), which has a direct stimulating effect on platelets (31). Valeri et al. demonstrated that a reduction in hematocrit of 15% causes a much
more pronounced prolongation of bleeding time than a reduction in platelet count of up to 34% (36). The optimal, precise range of the hematocrit in the bleeding patient is still unclear but recommendations state to keep the hematocrit in the range of at least 30–35% (15).

Platelets

The platelet count in trauma patients should be kept above 50,000/µl (1, 12). However, there is a highly variable relationship between platelet counts and efficacy of platelets. Refrigeration of platelets, even for a short period of time, results in an irreversible loss of platelet function and therefore platelets have to be stored at 22°C. Studies of chilled platelets have shown that this irreversibly alters their morphology as well as the expression of GPIb receptors on the platelet, causing rapid clearance of transfused platelets from the circulation (34). After room temperature storage of up to 5 days, the risk of bacterial contamination becomes significantly increased. Platelets are available as whole-blood-derived single units and as apheresis units. The transfusion of one whole-blood-derived platelet concentrate will increase the platelet count by approximately 5 × 10^10/l. Single donor platelets obtained by apheresis are equivalent to approximately six platelet concentrates (6).

Hemostatic agents

Desmopressin (DDAVP)

DDAVP is a vasopressin analogue, which has fewer vasoactive side effects but still antidiuretic properties. DDAVP releases von-Willebrand factor and factor VIII (FVIII) from endothelial cells, resulting in a 200–300% increase of these factors in the plasma. There is a release of t-PA too, resulting in a small increase in general fibrinolysis. The net effect, however, is a significant improvement in primary hemostasis (26). In patients with impaired platelet function such as in aspirin-associated bleeding, uremia, liver cirrhosis and type 1 von-Willebrand disease, DDAVP should be considered. The recommended dosage is 0.3 µg/kg b.w. within a time frame of 30 minutes. Unfortunately and until now, there are no randomized, controlled clinical studies available showing a benefit of DDAVP administration in trauma patients suffering from coagulopathy.

Antifibrinolics

Antifibrinolytic agents are routinely used in cardio-surgery and in liver transplantation. There are no data available in trauma patients from randomized, controlled clinical studies investigating the potential important role of antifibrinolytic drugs. In severe trauma, hyperfibrinolysis seems to be underestimated, mainly because of a lack in the availability of routine laboratory tests (28).

Aprotinin is a polypeptide derived from bovine lungs. Aprotinin is able to inhibit quite a number of different serine proteases, including plasmin. It is recommended to administer first a bolus of 10 000 KIU/kg b.w. followed by continuous infusion of 100 000/h. As rare adverse drug reactions, life-threatening anaphylactic reactions have been reported while aprotinin was administered (26).

Tranexamic acid competitively inhibits the lysine-binding sites of fibrin for plasminogen. The result is the inhibition of the conversion of plasminogen to plasmin. The recommended dose is 10–15 mg/kg b.w. An infusion of 1 mg/kg b.w./hour may follow.

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) is an analogue to the naturally occurring serine protease factor VIIa, which reflects approximately 1% of the total circulation factor VII usually present in plasma. rFVIIa exerts its function by binding to exposed tissue factor at the site of injury. This results in a massive increase in thrombin generation. Thrombin production is further accelerated on the surface of activated platelets by rFVIIa (Thrombin burst). In large doses, rFVIIa requires only fibrinogen, factor II (FII) and platelets to stimulate coagulation.

rFVIIa is currently licensed for the management of patients with hemophilia A and B who develop inhibitors, for deficiencies of FVII and Glanzmann’s thrombasthenia (2, 24).

Up to now, there is only one randomized controlled clinical study in trauma patients available. In this study, patients with blunt and penetrating trauma were treated either with rFVIIa or placebo. In patients suffering from blunt trauma, a reduction of 2.6 PRC transfusions was demonstrated due to the use of rFVIIa. In penetrating trauma, application of rFVIIa resulted only in reduction of 1 PRC transfusion. However, the cumulative dosage of rFVIIa in this study was quite high (400 µg/kg b.w.) (3).

The recommended dose in severe bleeding is 90–120 µg/kg b.w. (2). Because of the short half-life of rFVIIa of around 2.6h, a second dose could be administered after 120 minutes (2, 28). It is important to note that it is imperative to optimize the hemostatic preconditions of the bleeding trauma patient prior to the administration of rFVIIa. Fibrinogen concentration should be at least in the range of 0.5–1 g/dl, the pH-value should exceed 7.2, the platelet count should be approximately in the range of 50 000/µl and hyperfibrinolysis should have been corrected as well (28).

Conclusion

Coagulopathy following severe trauma is a common problem and associated with a high mortality. Hypothermia and acidosis are impotent contributors to coagulation disturbances. Thrombelastometry/graphy offers an interesting tool in the diagnosis of severe bleeding patients. The main treatment options are damage-control-surgery, permissive hypotension in uncontrolled bleeding and consequent rewarming of hypothermic patients. Fibrinogen is the most vulnerable coagulation factor and it should be replaced early in the course of bleeding. Prohemostatic agents such as DDAVP, antifibrinolytics and recombinant FVIIa could be helpful treatment options under some circumstances.
References


Correspondence to:
Herbert Schoechl, MD
Department of Anaesthesiology and Intensive Care Medicine
AUVA Trauma Hospital Salzburg
Franz Rehrl Platz 5
5020 Salzburg, Austria
E-mail: herbert.schoechl@auva.at