Coagulation defects in trauma patients: etiology, recognition, and therapy

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Hemostatic complications are common in trauma patients. These coagulation defects may be related to many processes, ranging from pre-existing disease to complications of therapy. This article reviews the causes of hemostasis defects, how to recognize them, and how to treat them.

Etiology

The coagulation defects that occur in trauma patients are complex in origin (Box 1). Often, these abnormalities are caused by many interrelated factors. The most common reasons for abnormal coagulation laboratory test results in these patients are dilution of hemostatic factors by fluid or blood resuscitation, severe hypothermia, tissue damage from trauma, and effects of underlying diseases.

Dilution

Simplistically, it seems obvious that if large amounts of fluid and packed red cells are given to patients, their plasma proteins (including coagulation factors) will be diluted [1]. In trauma patients, however, the situation is more complex. Fluid can shift to extravascular spaces; plasma proteins continue to be produced, and factors are being consumed. Studies have shown that dilution is often not an issue until over one blood volume (10 to 12 units of red cells) is given to a patient [2,3]. It is impossible to predict how an individual patient will respond to transfusions. Several studies have demonstrated poor correlation between the amount of blood products given and coagulation defects [4–7]. In Counts’ study [5], a very low correlation was seen with the amount of blood given and decreases in specific
factor levels, with the $r^2$ ranging from 0.02 to 0.17. Giving prophylactic platelets has been shown not to be an effective strategy for preventing defects [8]. Patients with disseminated intravascular coagulation caused by trauma may have severe coagulation defects even before the first transfusion. For these reasons, one needs to use specific monitoring of coagulation status and not rely on simplistic formulas for predicting factor deficiencies.

**Hypothermia**

Trauma patients are prone to hypothermia [9,10]. Patients may be out “in the field” for a prolonged period of time and be hypothermic on arrival [11]. Packed red cells are stored at 4°C, and the infusion of one unit can lower the body temperature by 0.25°C [12]. Infusion of fluids at room temperature can lower the temperature by 0.5°C for every liter infused. Exposure of viscera during surgery can result in profound cooling of the patient.

Hypothermia has profound effects on the coagulation system that are associated with clinical bleeding [9,13,14]. Coagulation occurs because of enzyme reactions that are temperature dependent. Even modest cooling slows these reactions, rendering the patient coagulopathic. For example, the Rohrer study showed that the activated partial thromboplastin time (aPTT) lengthened from 36 seconds at 37°C to 39 seconds at 34°C and to 46 seconds at 31°C [15]. In addition, all facets of platelet function decline with modest hypothermia [13,16]. Finally, hypothermia stimulates fibrinolysis, which can provoke more diffuse bleeding. Thus, even modest hypothermia can augment bleeding greatly.

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**Box 1. Coagulation defects: etiologies**

_Dilution of coagulation factors_

_Hypothermia_

Slowing down coagulation factor enzyme function
Platelet dysfunction
Enhanced Fibrinolysis

_Trauma_

Head trauma—disseminated intravascular coagulation

_Underlying disease_

Hemophilia
von Willebrand disease
Liver disease
Warfarin
Trauma

The key stimulus for coagulation is tissue trauma. The most profound example is head trauma [17,18]. Patients with severe brain injuries often have severe defibrination caused by exposure of the thromboplastin-rich brain tissue to flowing blood. These patients may present with severely deranged hemostasis characterized by fibrinogens below 50 mg/dL. They have severe consumptive coagulopathies and may require large amounts of blood products. Because the liver is the source of most coagulation proteins, severe liver injury or significant shock results in failure of the body to compensate for consumption of coagulation factors.

Although not as spectacular as brain injuries, any type of severe trauma that is associated with extensive tissue damage results in disseminated intravascular coagulation (DIC). There is also evidence that fibrinolysis may be activated in trauma patients, further amplifying the propensity for bleeding [19,20].

Underlying disease

Trauma is not restricted to previously healthy people. Patients with underlying coagulation defects often enter trauma systems and tend to do worse. Hemophiliacs may have impressive bleeding with their injuries. A rapidly emerging problem is the growing number of the population taking oral anticoagulants. The indications for long-term anticoagulation are increasing, and these patients are being seen more frequently in the trauma setting.

Patients with liver disease are particularly problematic and have a significantly higher mortality with trauma, in part because of their underlying hemostatic defects [21,22]. Patients with severe liver disease have multiple coagulation defects [23]. All major coagulation factors and inhibitors are synthesized solely in the liver, except factor VIII and von Willebrand factor. Patients with liver disease are thrombocytopenic and have evidence of platelet dysfunction. Liver disease is the most common cause of primary fibrinolysis because of a drop in plasma levels of fibrinolytic inhibitors and delayed clearance of plasmin. Evidence of fibrinolysis can be found in 30% of patients with end-stage liver disease.

As many as 1 in 100 patients have inherited coagulation defects. Most common is von Willebrand disease, which is associated with excessive persistent bleeding after trauma [24]. Most patients with von Willebrand disease have a history of excessive bleeding with minor procedures and a propensity for bruising. If not recognized, patients with von Willebrand disease can have on-going bleeding despite surgical management. One in 10,000 male patients has hemophilia [25]. These patients may exsanguinate with trauma unless specific factor replacement is provided.

Over 1% of the population takes warfarin. Several studies have shown that patients taking warfarin have higher morbidity and mortality when they present with intracranial hemorrhage [26,27]. It has been difficult to show that anticoagulated patients do worse with trauma, however, perhaps because these patients are identified early and receive plasma [28].
Recognition

Patients who bleed from coagulation defects have generalized bleeding from multiple sites. These patients have diffuse oozing in the surgical field, bleeding from intravenous (IV) sites, and ongoing blood loss into drains. A bleeding diathesis is confirmed by laboratory testing, but in emergency situations, therapy should be given while awaiting the results of testing.

Specific testing

The basic tests of coagulation are the platelet count, prothrombin time (PT–INR), the aPTT, and the fibrinogen level (Box 2).

Platelets are essential for initial hemostasis in that they form the platelet plug. Thrombocytopenia is the largest determinant of microvascular bleeding in massively transfused patients. In massively transfused patients, maintenance of the platelet count at 50,000/µL or higher results in less microvascular bleeding [5,19]. Platelet dysfunction also has been reported with trauma. There still is not a simple method for reliably measuring platelet function, however. Bleeding times are difficult to perform and not predictive of bleeding [29,30]. Recently, a rapid automatic test for platelet function, the PFA–100, was introduced [31]. It is unknown, however, whether measuring platelet function is helpful for the management of coagulation defects in trauma patients.

The PT–INR is a measure of the tissue factor VII pathway. It is sensitive to low levels of factor VII and is often mildly prolonged (1.3 to 2.0) in the trauma setting. Isolated elevations of the PT–INR reflect isolated factor VII deficiency and are not indicative of severe coagulation defects. It appears that INR elevations are not

Box 2. Specific testing

Key hemostatic tests

- Platelet count
- Hematocrit
- INR
- Activated partial thromboplastin time
- Fibrinogen
- Tests for more complex situations
- Thromboelastography
- Platelet function analysis
- Euglobulin clot lysis time
- Specific factor levels
indicative of the risk of generalized bleeding unless they are over 1.8 and are associated with an elevated aPTT [6].

The aPTT reflects multiple steps in the coagulation cascade. Elevated levels of the aPTT in the trauma setting indicate multiple and severe defects. aPTTs over 1.8 times controls have been associated with bleeding in several studies [5,6]. One common error is to draw coagulation laboratory tests through intravenous access lines. This commonly results in falsely elevated aPTT and can lead to therapeutic misadventures [32].

Fibrinogen is often the forgotten factor. Fibrinogen is important for forming the fibrin clot. Excessive bleeding has been reported with fibrinogen levels under 50 mg/dL [6]. Fibrinogen is also essential for the proper analysis of coagulation assays. The endpoints of both the PT-INR and aPTT are time to formation of the fibrin clot. When plasma levels of fibrinogen fall below 80 mg/dL, the clot may be small and undetectable. This results in a very prolonged PT–INR and aPTT.

Thromboelastogram (TEG) is a unique laboratory test that examines whole blood thrombus formation and lysis [33]. TEG is performed by placing 0.35mL of whole blood into an oscillating container with a pin that measures the force of thrombus formation. TEG measures five parameters:

1. r time: time from starting TEG until clot formation, correlated with coagulation factor activity
2. K time: time between tracing going from 2mm to 20 mm, correlated with speed of clot formation
3. alpha angle: slope of tracing between r and K time, correlated with fibrin formation
4. MA: greatest amplitude of TEG tracing, a marker of platelet function
5. Whole blood lysis index: amplitude of tracing 60 minutes after MA

Most modern TEG machines automatically calculate these parameters. TEG allows rapid point-of-care testing of coagulation, and it is particularly useful in assessing fibrinolysis. Research is underway to assess the role of TEG in the trauma setting.

**Therapy**

Therapy of the bleeding trauma patient is directed at correcting the coagulation defects, treatment of related problems such as underlying coagulation defects, and therapy of complications such as hypothermia.

**Massive transfusion**

Trauma patients can require large amounts of transfusions. Early data showed high mortality rates with transfusion of over 20 units of blood [3], but with modern blood banking techniques and improved laboratory testing, this rate has decreased.
dramatically. Recent studies showed a survival rate of 43% to 70% in patients transfused with over 50 units of blood [34–36].

The approach to massive transfusion involves measuring five laboratory tests that reflect the basic parameters essential for both blood volume and hemostasis. The tests are: hematocrit, platelet count, INR, activated partial thromboplastin time, and fibrinogen level.

The clinical laboratory should be able to perform these tests rapidly and report them to the trauma team. Replacement therapy is based on the results of these laboratories.

Hematocrit goals vary with the clinical situation. For the rapidly bleeding patient, blood is given until the patient is stable. For patients who are suffering mainly from derangements in coagulation, a lower hematocrit goal may be more appropriate.

For a platelet count less than 50 to 75,000/μL, a plateletpheresis concentrate or 6–8 pack of single-donor platelet concentrate is given to the patient. Because the platelets are suspended in plasma, this transfusion also provides plasma to the patient. As a key determinant of primary hemostasis, platelets should be monitored aggressively and replaced.

For a fibrinogen level less than 100 mg/dL, 10 units of cryoprecipitate should be given. This should raise the fibrinogen by 100 mg/dL. In certain clinical situations, such as brain injuries, hepatic trauma, or limb reperfusion, severe fibrinolysis may occur, and large amounts of cryoprecipitate may be required.

For INR over 2.0 with an abnormal aPTT, two to four units of FFP are given. As noted previously, isolated elevation of the INR does not require replacement therapy.

For an aPTT greater than 1.5 times normal, two to four units of plasma are given. If the aPTT is markedly elevated (> 80 seconds) one should make sure the sample is not contaminated by heparin. If both the PT–INR and aPTT are increased, then the fibrinogen may be low.

One should repeat the basic five laboratory tests after administering the blood products. This allows one to ensure adequate replacement therapy was given for the abnormal laboratories. Frequent checks of the coagulation laboratories also allow rapid identification and therapy of new coagulation defects before they become severe. A flow chart of the laboratories and the blood products administered also should be kept. Best results for massive transfusions are obtained when a multidisciplinary approach is used that involves the trauma team, transfusion medicine, anesthesia, and hematology.

Occasionally, empiric therapy of the severely bleeding patient is required. One should start with platelet products, since they also provide plasma. In patients likely to have DIC also (ie, head trauma patients), empiric administration of 10 units of cryoprecipitate is indicated.

There are many reports on the use of recombinant activated factor VIIa (rVIIa) for the massively bleeding trauma patient [37–39]. rVIIa binds to the tissue factor exposed at the site of injury and stimulates coagulation. Dosing has ranged from 90 to 270 μg/kg. Definite recommendations on use await completion of clinical
trials. The use of rVIIa, however, may be reasonable in a patient who continues to have diffuse bleeding despite maximal replacement of blood products or in trauma patients on warfarin.

Complications of transfusions

One of the major complications of transfusing the trauma patient is hypothermia. This can be prevented by several measures. One is to transfuse the blood through blood warmers. Devices are available that can warm a unit of blood in 1 minute. An increasingly popular technique is to perform damage control surgery. Patients initially are stabilized with control of damaged vessels and packing of oozing sites [40]. Then the patient is taken to the ICU to be warmed and have coagulation defects corrected. This is discussed extensively in another article in this issue.

Although much feared, electrolyte abnormalities are unusual even in the massively transfused patient [41]. Platelet and plasma contain citrate, which can chelate calcium. However, the citrate is metabolized rapidly, however, and it is rare to see clinically significant hypocalcemia. Although empiric calcium replacement often is recommended, one study suggests this is associated with a worse outcome and should not be done [42]. If hypocalcemia is a clinical concern, levels should be drawn to guide therapy.

Although potassium leaks out of stored red cells, even old units of blood only contain a total of 8 mEq, so hyperkalemia is usually not a concern. There are rare reports of sodium bicarbonate or other incompatible fluids being added to cell saver blood, leading to massive hemolysis and fatal hyperkalemia. It is important to remember that fluids such as Ringer’s lactate and glucose solutions cannot be given with blood.

Stored blood is acidic, with a pH of 6.5 to 6.9. Acidosis attributed solely to transfused blood is rare, however. Empirical bicarbonate replacement has been associated with severe alkalosis and is not recommended [43,44].

Blood salvage is used frequently in trauma patients to help lessen red cell transfusions. With blood washing, reports of coagulopathies have lessened [45]. Coagulopathy can occur, however, both due to dilution and infusion of thrombogenic substances [45,46]. Patients receiving large amounts of cell saver blood (>10 to 15 units) should have their coagulation status carefully monitored.

Adjunctive therapy

Trauma patients with liver disease require very close monitoring. These patients may develop dramatic coagulation defects with only minor trauma. For a summary of adjunctive therapy, see Box 3.

Abnormal fibrinolysis is an often overlooked cause of bleeding in patients with liver disease. Bleeding in these patients tends to be characterized by diffuse oozing from sites of minor trauma. Often these patients are treated futilely with massive amounts of fresh frozen plasma before the fibrinolytic defect is discovered.
### Box 3. Adjunctive therapy

**Liver disease: fibrinolysis**
- Amicar 5 grams bolus then 1 g/h for 8 hours

**Hemophilia**
- Factor VIII deficiency: 50 µg/kg of factor VIII concentrate
- Factor IX deficiency: 120 units/kg of factor IX concentrate

**von Willebrand disease**
- Humate–P 3000 factor VIII units

**Warfarin**

| INR 1.5–3.0 | Fresh plasma, 7.5mg/kg | Vitamin K, 1 mg IV or by mouth |
| INR 3.0–4.5 | Fresh plasma, 15 mg/kg | Vitamin K, 2.5 mg IV or by mouth |
| INR 4.5–10 | Fresh plasma, 15 mg/kg | Vitamin K, 5 mg IV or by mouth |
| INR > 10 | Fresh plasma, 15 mg/kg | Vitamin K, 10 mg IV or by mouth |

Diagnosis is made either clinically or, if available, by demonstrating a shortened euglobulin clot lysis time in the setting of excessive bleeding.

In the patient who is bleeding from fibrinolysis, a trial of antifibrinolytic therapy is warranted. The patient should be screened for DIC and significant urinary tract bleeding. The dose of epsilon–aminocaproic acid is a bolus of 4 to 5 g given over 1 hour, followed by a continuous infusion of 1 g per hour for 8 hours [47–49].

Patients with inherited coagulation defects should receive specific therapy. Severely injured patients with von Willebrand disease should receive Humate–P to replace missing factor. If the injuries are modest, desmopressin (0.3 µg/kg) can be given to the patients instead of Humate–P. Because 20% of patients with von Willebrand disease do not respond to desmopressin, however, this should never be given empirically to patients, unless their disease type is known. Hemophiliacs...
should receive doses of concentrate to raise their levels to over 100%. Arrangements should be made to monitor factor levels to guide therapy precisely.

Trauma patients on warfarin require immediate reversal. The short-term risk of thrombosis is outweighed by the need to control hemostasis. Patients should receive vitamin K to reverse the warfarin with dosing guided by the INR. This should be supplemented by plasma at 15 mL/kg. Patients with intracranial hemorrhage also should receive either prothrombin complex concentrates 50 to 75 units/kg or rVIIa 40 μg/kg.

Correcting coagulation defects before procedures

Procedures such as central venous line placement very frequently are performed successfully on patients with coagulopathies (Box 4) [50–53]. One study found the risk was not related to the degree of hemostatic defects [54]. In this study, the risk of hemorrhage was higher when inexperienced operators attempted line placement. For urgent line placement, experience of the operator is more important than waiting for transfusion therapy [54]. In a nonurgent situation, raising the platelet count to 30 to 50,000/μL and attempting to lower the aPTT to less than 1.5 times normal may be reasonable goals, but one should not delay a necessary procedure by trying to achieve arbitrary targets for laboratory values.

Summary

Trauma patients have many reasons to have defects in coagulation. These can be caused by the trauma or because of pre-existing disorders. Trauma patients who are at risk for coagulation defects should be screened with the basic tests (aPTT, INR/PT, platelet counts, hematocrit, and fibrinogen), with therapy based on the results. Attention also should be paid to any other correctable factors such as hypothermia. Finally, pre-existing disorders can influence the patient’s hemostasis greatly and may require specific therapies.

References


