The Use of Thromboelastography Guided Transfusion Therapy in Trauma: An Integrative Review

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**Introduction**

Trauma induced mortality can often be attributed to hemorrhage in the early phase of trauma.\(^1\) Up to one-half of trauma deaths are due to uncontrolled bleeding within the first few hours of injury.\(^1\) Patient survival following a traumatic injury is reliant upon the trauma team’s ability to gain early control of bleeding.\(^2\) Ways in which the trauma team can gain control of bleeding include rapid identification of the source of hemorrhage, applying direct pressure to the source of hemorrhage, and aggressive resuscitation. Resuscitation efforts are focused on restoring normal physiology and oxygen delivery to tissues.\(^1\) Resuscitation involves the use of transfusion therapy.

Transfusion therapy includes the administration of fluid, blood, blood products, and various medications. Administration of any of these things is not without significant risks to the patient. These risks are summarized in Table 1 (Appendix A).\(^{28}\) Inappropriate trauma resuscitation and/or transfusion reactions decrease the patient’s chance of survival, mainly due to inflammation and failure of organ systems.\(^{3-5}\) It is important that all members of the trauma team are aware of these potential pitfalls of transfusion therapy.

The challenge for the trauma team is determining minimum thresholds for transfusion. Current guidelines for trauma state that hemorrhaging trauma patients should first receive two liters of crystalloid fluid, followed by the administration of O negative blood, and then activation of the facility’s massive transfusion protocol.\(^6\) Once the massive transfusion protocol is activated, current trauma guidelines recommend transfusing Red Blood Cells (RBCs),
Platelets, and Plasma in a 1:1:1 ratio. One benefit to using the fixed ratio method for blood product administration is the products can be rapidly obtained and administered as this method does not require any laboratory testing be conducted on the patient prior to administration. In addition, this method has been accepted and implemented in many trauma centers throughout the world.

There are, however, disadvantages to using the fixed ratio method of blood product administration. One disadvantage of using this method is that it is not patient or situation specific. When using blanket guidelines such as these with trauma patients there is a potential for: 1) administration of inappropriate therapy; 2) unnecessary transfusion reactions; 3) excessive use of blood products; 4) increased costs; and/or 5) increased morbidity and mortality. For these reasons, use of this method in which RBCs, Platelets and Plasma are administered in a 1:1:1 ratio to hemorrhaging trauma patients remains a source of controversy. These concerns have led experts to seek out and evaluate alternative methods for determining transfusion needs in trauma patients. One such method is goal-directed therapy using thromboelastography (TEG). TEG can better assess a trauma patient’s coagulation status and allows for treatment that is tailored to the patient’s specific needs. This ultimately leads to decreased mortality, morbidity and improved outcomes overall.

Thromboelastography (TEG)

TEG is a whole blood coagulation analyzer that is representative of cell based coagulation. It is a point of care test that quickly measures the rate, strength, and stability of clotting. This assessment of hemostasis is more representative of in vivo hemostasis than traditional coagulation profiles. TEG has been found to be particularly useful with trauma
patients. Rapid interpretation of TEG in trauma patients can help practitioners identify coagulopathies sooner, guide transfusion therapy more accurately, and decrease blood product utilization.9,11,15-20 TEG machines have been available for more than 20 years. However, this technology has only recently begun to be utilized in the clinical setting.14,21 This is mainly because the old TEG machines are cumbersome, difficult to operate, and overall are not very practical for clinical use. These practical barriers have since been evaluated and removed from the original machines. Newer TEG machines are more portable, easier to operate, and can provide detailed information regarding coagulation status in as little as five minutes.14

Monitoring a patient’s coagulation status has traditionally involved the use of plasma based laboratory tests including prothrombin time (PT), activated partial thromboplastin time (PTT), and international normalized ratio (INR). While these tests are useful in determining a patient’s etiology of bleeding, their use in the critically ill trauma patient is very limited for several reasons. Obtaining the results of traditional laboratory testing can take up to 90 minutes or more.17 TEG on the other hand, is a point of care test that can produce results rapidly. PT, PTT, and INR are plasma based tests, whereas TEG utilizes whole blood.9,14 This difference between using plasma based laboratory testing and whole blood analysis using TEG, plays an important role because of the information that can be derived from the results of the tests. While PT, PTT, and INR test results give information on a patient’s coagulation profile, they cannot identify factor deficiencies, whereas TEG results provide this information and more.8 TEG results provide information on the patient’s ability to form a clot, stabilize the clot, and lyse the clot.14 Thus, a key difference between traditional laboratory testing and TEG is that TEG provides real-time information on the functionality of the entire clotting system.22
With the increased use of TEG in the clinical setting it is important that trauma team members receive education and training regarding the use of TEG guided transfusion therapy in hemorrhaging trauma patients. To understand how TEG works and to be able to interpret the results of the TEG test, one must have a basic understanding of the clotting cascade, otherwise known as coagulation.

The Clotting Cascade

Biologically, the clotting cascade is simply the body’s attempt to stop bleeding once an injury or insult has occurred. The internal wall of a blood vessel (in both arteries and veins) is comprised of a layer of endothelial cells. The disruption of this layer of endothelial cells, due to an injury or insult, initiates the clotting cascade. Once disrupted, the endothelial cells release vasoactive substances that cause the injured vessel to constrict which minimizes blood loss from the area of injury. At the same time platelets are activated causing them to congregate at the area of injury and become sticky. This stickiness allows the platelets to adhere to other platelets, as well as, the injured area on the vessel and form a plug that fills the wound. This platelet plug is the initial clot and plays a vital role in emergently putting a stop to bleeding. However, the clot is very weak at this point and will only decrease blood loss at the injury site temporarily. Without further stabilization through cementation, the platelet plug will be washed away by blood flowing through the vessel. Cementation of the platelet plug requires that the following steps occur in sequence:

1. First, a series of chemical reactions leads to the production of prothrombin activator.
2. This prothrombin activator then works by converting prothrombin (a protein in blood) into thrombin.

3. Thrombin then converts fibrinogen into fibrin (an insoluble protein).

4. These fibrin fibers now form a tight mesh over the wound and throughout the platelet plug. This mesh works by trapping platelets and other blood cells, holding them tightly in place.

5. A stable clot has now been formed.

Prothrombin and fibrinogen are always present in our circulating blood in an inactive form. They are activated only when the prothrombin activator is produced in response to injury. See Figure 1 (Appendix 2),\textsuperscript{23} for a summary of this process. Having prothrombin and fibrinogen normally circulating in inactive form is an important part of regulating the clotting cascade.

It is important that the human body is able to form a blood clot in response to injury, yet have regulatory mechanisms in place to prevent the formation of excessive or unwarranted blood clots.\textsuperscript{23} Following a vessel injury, there is first formation of a clot, then cementation of the clot. The combination of these two things is known as hemostasis.\textsuperscript{23} Once the area of injury has healed and the clot is no longer needed, it is important that the body is able to breakdown the clot. This is important because without removal, the clot could lead to stricture or complete occlusion of the vessel over time. To remove the cemented clot, it is broken down through a process known as fibrinolysis. Fibrinolysis is the body’s way of breaking down the fibrin that is cementing the clot. Fibrinolysis occurs through the following steps:\textsuperscript{24}
1. Fibrinolysis starts with Plasminogen. Plasminogen is a glycoprotein found in our circulating blood. It is incorporated into the blood clot when the clot is formed.

2. Tissue plasminogen activator (tPA), is a substance released by the endothelial cells lining the vessel in response to thrombin.

3. When released, tPA acts on plasminogen and converts it to plasmin.

4. It is the plasmin that then degrades the fibrin cementing the clot. Once broken down into smaller fragments, these fibrin degradation products are cleared from the body through the monocyte-macrophage system.

It is of utmost importance that both coagulation and fibrinolysis occur in harmony. In addition to this, it is crucial that both coagulation and fibrinolysis processes are activated in response to an appropriate stimulus, have adequate factors available, and that the system is not overwhelmed by injuries too extensive to manage all at once. If any of these things is disrupted, homeostasis is no longer maintained and the patient’s mortality risk increases.\(^1\) This is especially important to consider in patients with traumatic injuries. In addition to severe bleeding, coagulopathy in trauma is associated with high mortality.\(^8\)

The etiology of the coagulopathy seen in trauma patients is not completely understood. It is, however, known to be complex and multifactorial. At the cellular level, traumatically injured patients appear to have an increased blood sugar, increased cellular oxygen extraction, increased procoagulant tendency with mobilization of clotting factors and platelet reserves.\(^1\) In addition to this, severe trauma has been shown to increase levels of proinflammatory cytokines, cause loss of tissue factor and thrombin regulation, and increase procoagulant phospholipids, as well as, tissue-factor bearing microparticles.\(^20\) Even though
science and research support the above mentioned dyscrasias in trauma, individual trauma patients present with a wide range of coagulopathies.25

While coagulopathy varies from patient to patient, even among those with similar injuries, there are a few commonalities. One commonality is that an increased injury severity score has been associated with more pronounced coagulopathy.25 Another commonality is that acute traumatic coagulopathy has been found to be an important prognostic indicator.10 In addition to these commonalities, hemorrhage and thromboembolic disease have been found to be the two leading causes of preventable death in trauma.20 Thus, successful management of the severely injured trauma patient requires trauma team members to have knowledge of both hemorrhage and coagulation.18 This includes being able to rapidly and accurately identify and treat both hemorrhage and coagulation simultaneously. Hence, TEG can be an invaluable tool in the management of trauma patients.

**Understanding TEG**

TEG can be used to perform several different tests that assess various aspects of coagulation. These tests include functional fibrinogen which evaluates fibrin, multiplate which evaluates platelets, native whole blood analysis which assesses coagulation without the use of any activating agents, heparinase which assesses the impact of heparin, RapidTEG and standard TEG. Standard TEG is the point of care coagulation test most frequently used and researched. While the process of TEG is the same with each of these tests, the difference between them is the chemical reagents in which the patient’s blood sample is mixed with.26 For purposes of this article, when mentioning TEG the author is referring to the standard TEG test.
TEG is a point of care test that is relatively simple. First, a small sample of blood is retrieved from the patient and mixed with citrate. Citrate is used as an anticoagulant at this point to avoid clot formation before the start of the test. This sample is then placed in a small cylindrical cup that has been heated to 37°C. The cup is heated to 37°C to resemble the normal temperature of a human body. The cup also contains the activating agent kaolin as well as calcium. Kaolin is a type of clay powder that is very sensitive to clotting, factor deficiency and anticoagulants. Kaolin is the reagent mixed with the patient’s blood sample when using TEG to activate clotting and accelerate clot formation. Calcium is added to the sample to overcome the citrate that was initially mixed with the patient’s blood as citrate is known to cause hypocalcemia which could impact the TEG test results. A thin torsion wire connected to both a stationary pin and to the computer, is inserted into this cup containing the blood sample. The cup then gently oscillates around the submerged torsion wire in a limited arc, six times a minute. This movement imitates sluggish venous flow which further activates the coagulation process. The blood clot begins to form between the torsion wire and the wall of the cup, see Figure 2 (Appendix C).

The speed at which the clot forms and strength of the clot is converted by a mechanical-electrical transducer into an electrical signal which is then analyzed by a computer. This data is then converted to numeric values and a graphic representation of the plasmatic coagulation system, platelet function, and fibrinolysis is provided see Figure 3 (Appendix D). It is important to note that the coagulation process can be affected by several factors including the patient’s genetics, acute and chronic illness, environment, and various medications. These factors must be taken into consideration when interpreting TEG results.
**TEG Results**

Coagulation starts with the formation of a clot. The clot is initially weak until it is stabilized by fibrin through a cementing type process. This formation and stabilization of the clot is represented by four values on the TEG tracing. These are the R value, K value, alpha angle and maximum amplitude (MA). The R value represents initiation of a clot and is the time it takes for the blood to start to form a clot. R is the time from the start of the test until the first evidence of a clot is detected. The K value represents the speed at which the clot is forming. K is the time from the end of R until the clot reaches 20mm. The alpha angle is similar to K in that it represents the speed of clot formation. It is the angle that is formed by the slope of the R value to the K value on the TEG tracing. The MA represents the ultimate strength and overall stability of the clot. The MA measures the width of the TEG tracing. The normal numerical ranges for these four values are as follows:

- **R value (s):** 180-480
- **K value (s):** 60-180
- **Alpha angle (°):** 55-78
- **MA (mm):** 51-69

Next, the clot is broken down through fibrinolysis. Fibrinolysis is represented on the TEG tracing as LY30. LY30 is the amount (recorded in percentage) of the clot that is lysed 30 minutes after the MA. Reference ranges for what is considered to be a normal value for LY30 is a source of controversy. Some studies have suggested that the risk of hemorrhage is increased for trauma patients with an LY30 of greater than 3%.27
TEG in Trauma

With TEG, a sample of whole blood is rapidly analyzed. This expeditious turn-around time provides information on the patient’s coagulation profile in real time. This can be extremely beneficial in trauma patients. Successful management of a trauma patient requires that they are rapidly evaluated, diagnosed and treated. TEG awards the trauma team the ability quickly formulate a diagnosis then provide treatment that is goal-directed and specific to the individual needs of each patient. Use of viscoelastic monitoring, such as TEG, has been shown to aid in producing a favorable survival rate when used in the management of major trauma patients.

Even though the etiology is not completely understood, it is not uncommon for trauma patients to present with a wide-range of coagulopathies. In fact, approximately 25% of severely injured trauma patients are found to have a coagulopathy on admission to the emergency department. Figure 4 (Appendix E) provides examples of coagulopathies that could be seen either as a result of trauma or secondary to other factors or co-morbid conditions.

Utilizing TEG in the treatment of trauma patients has been shown to rapidly provide highly specific results that depict underlying coagulopathies. This allows for earlier identification of coagulopathies and more accurately guided transfusion therapy. Ultimately this leads to less blood product utilization, improved patient outcomes, and decreased overall surgical costs. Once a coagulopathy diagnosis is made in the trauma patient, a treatment plan must quickly be put into place. While TEG is currently being used as a template for treatment of trauma patients there is a lack of consistency in the interpretation of TEG, formulation of goals, and treatment methods based on TEG results. There is a need for further
research in order to develop guidelines that address these issues. Until then, individual trauma facilities will likely continue to create and implement their own guidelines. The following is an example of such guidelines for using TEG as a guide to transfusion in trauma:

- Increased R time => Administer Fresh Frozen Plasma (FFP)
- Decreased alpha angle => Administer Cryoprecipitate
- Decreased MA => Administer Platelets (consider Desmopressin (DDAVP))
- Hyperfibrinolysis => Administer Tranexamic Acid (or Aminocaproic Acid)

Conclusion

Further research needs to be done regarding the use of TEG in trauma, particularly regarding treatment of the patient based on TEG results. However, many facilities throughout the nation are currently utilizing TEG routinely in trauma, have devised their own treatment guidelines, and are seeing favorable outcomes. At this point it appears that the advantages of TEG significantly outweigh any of its potential disadvantages. This coupled with its ability to be used universally throughout the facility means most facilities would likely benefit from purchasing and implementing TEG for both patient care and research. For these reasons, the use of TEG in trauma will likely increase throughout the nation over the next few years. One of the current limitations to TEG is not having enough appropriately trained staff to perform and interpret TEG. Therefore, institutions providing care to trauma patients should strongly consider providing proper education and training to trauma team members on the use of TEG.
References


8. Wikkelsø A, Wetterslev J, Møller AM, & Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding (review). *Cochrane Database of Systematic Reviews*. 2016; 8:1-146.


### Table 1. Acute transfusion reactions: frequencies, associated symptoms, etiology, management, and prevention

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Frequency estimates</th>
<th>Etiology</th>
<th>Symptoms/Signs</th>
<th>Management (level of evidence)</th>
<th>Prevention (level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor allergic</td>
<td>11.463</td>
<td>Allergy to transfused donor antigens (protein or carbohydrate)</td>
<td>Urticaria, pruritus</td>
<td>Temporarily stop the transfusion and administer antihistamines (A) and/or steroids (C).</td>
<td>Premedication with antihistamine and/or steroids (C).</td>
</tr>
<tr>
<td>TACO</td>
<td>1.808</td>
<td>Volume overload due to underlying cardiac disease and/or too rapid infusion rate</td>
<td>Dyspnea, orthopnea, cough</td>
<td>Temporarily stop the transfusion and administer diuretics (B).</td>
<td>Use of pre-pooling products for plasma exchange (B).</td>
</tr>
<tr>
<td>FNHTR</td>
<td>1.141</td>
<td>Predominant cause: cytokine accumulation during product storage. Minor cause: leukocyte antibody reacting with transfused leukocytes</td>
<td>Fever, chills</td>
<td>Temporarily stop the transfusion and administer antihistamines (C).</td>
<td>Premedication (antipyretic)</td>
</tr>
<tr>
<td>TRALI</td>
<td>1.619</td>
<td>ll. Leukocyte priming substances</td>
<td>Dyspnea, fever, hypotension</td>
<td>Stop transfusion and manage symptoms (A).</td>
<td>Transfusion-related acute lung injury (B).</td>
</tr>
<tr>
<td>Severe allergy/anaphylaxis</td>
<td>1.16256</td>
<td>Allergy to transfused donor antigens</td>
<td>Rash, wheeze, stridor, dyspnea, angioedema, hypotension</td>
<td>Stop transfusion and administer intramuscular epinephrine (A).</td>
<td>For minor allergic plus supportive care including vasopressors.</td>
</tr>
<tr>
<td>TAD</td>
<td>1.58055</td>
<td>Unknown</td>
<td>Dyspnea</td>
<td>Suspend transfusion and assess severity. Resume transfusion if symptoms subside and no other pulmonary transfusion reaction is suspected.</td>
<td>Switch from ACE inhibitors to alternative antihypertensive.</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BCSH, British Committee for Standards in Haematology; BP, blood pressure; TACO, transfusion-associated circulatory overload; CXR, chest radiograph; FNHTR, febrile non-hemolytic transfusion reaction; TRALI, transfusion-related acute lung injury; HLA, human leukocyte antigen; AHTR, acute hemolytic transfusion reaction; TAD, transfusion-associated dyspnea; TTISS, Transfusion Transmitted Injury Surveillance System.[^28] (Reprinted with permission from Dovepress, 2016.)[^28]
Appendix B

Figure 1. Cementation of a Clot

A prothrombin activator converts prothrombin into thrombin. Thrombin is an enzyme that converts fibrinogen into fibrin. Prothrombin and fibrinogen are proteins that are always present in our blood.23 (Reprinted with permission from Crampton.)23
Figure 2. Thromboelastograph Components

(Reprinted with permission from AANA, 2013.)\textsuperscript{15}
Appendix D

Figure 3. TEG Tracing

Measure all phases of hemostasis in whole blood.

The TEG® hemostasis system continuously measures all phases of hemostasis as a net product of whole blood components

(Reprinted from Haemonetics, 2017.)}^{14}
Appendix E

Figure 4. TEG Tracing Examples

Abbreviations: UK, urokinase; SK, streptokinase; t-PA, tissue plasminogen activator; D.I.C, disseminated intravascular coagulation.

(Reprinted from Life in the Fastlane, 2014.)

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