Thromboelastography-Guided Transfusion Therapy in the Trauma Patient

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This article presents thromboelastography (TEG) as an important assay to incorporate into anesthesia practice for development of evidence-based therapy of trauma patients receiving blood transfusions. The leading cause of death worldwide results from trauma. Hemorrhage is responsible for 30% to 40% of trauma mortality and accounts for almost 50% of the deaths occurring in the initial 24 hours following the traumatic incident. On admission, 25% to 35% of trauma patients present with coagulopathy, which is associated with a sevenfold increase in morbidity and mortality. The literature supports that routine plasma-based routine coagulation tests, such as prothrombin time, activated partial thromboplastin time, and international normalized ratio, are inadequate for monitoring coagulopathy and guided transfusion therapy in trauma patients.

A potential solution is incorporating the use of the TEG assay into the care of trauma patients to render evidence-based therapy for patients requiring massive blood transfusions. Analysis with TEG provides a complete picture of hemostasis, which is far superior to isolated, static conventional tests. The result is a fast, well-designed, and precise diagnosis enabling more cost-effective treatment, improved clinical outcome, accurate use of blood products, and pharmaceutical therapies at the point of care.

Keywords: Coagulopathy, thromboelastography, transfusion therapy, trauma.

The trauma patient presents special conditions and problems for anesthesia providers. The trauma triad of death is a medical term that is often used to describe the conditions of hypothermia, acidosis, and coagulopathy. This triad is seen in patients who have severe traumatic injuries and is the cause of a major rise in the mortality rate because of continual microvascular bleeding. The leading cause of death worldwide results from trauma, with hemorrhage being responsible for 30% to 40% of trauma mortality and accounting for almost 50% of the deaths occurring in the initial 24 hours following the traumatic incident. On admission, 25% to 35% of trauma patients present with coagulopathy, which is associated with a sevenfold increase in morbidity and mortality.

There is emerging consensus that routine plasma-based tests (RCoT), such as prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR), may be inadequate for monitoring coagulopathy and guiding transfusion therapy in trauma patients. A correct diagnosis is critical for patient survival. Applying the thromboelastography (TEG) assay to transfusion therapy for the trauma patient can help guide the anesthesia provider to correctly diagnose and properly treat the hemorrhaging patient. Closing the gap between coagulopathic hemorrhage and death will require a change in current clinical practice to modify and update transfusion regimens.

The purpose of this article is multifaceted. The author outlines the importance of addressing coagulopathic conditions that can be experienced in trauma patients and relates contributing factors to the development of this derangement. A comprehensive history and review of the literature are presented to demonstrate a thorough assessment of the problem relating to coagulopathy. An explanation is provided to the reader why RCoT may be inadequate to guide transfusion therapy in trauma anesthesia and why TEG may serve as a more preferable diagnostic assay. The pathways of coagulation are discussed, and finally, the author offers recommendations for future practice.

History and Review of Literature

Evidence from the relevant literature suggests it is important to address coagulopathy in trauma patients. Results of a study between cohorts presenting with similar injury severity scores determined that the patient cohort presenting with coagulopathy experienced 2 to 3 times greater mortality rate. The prevention of coagulopathy is superior to treatment, yet most protocols are designed to treat preexisting and/or ongoing coagulopathy. Uncontrolled coagulopathic hemorrhage is now seen as the major cause of preventable death in trauma patients. There are 3 phases of hemorrhagic shock due to coagulopathy. These phases are compensated, uncompensated but reversible, and irreversible hemorrhagic shock. Once the irreversible hemorrhagic shock phase has been entered, blood pressure, tissue oxygenation, and perfusion do not improve with either fluid replacement therapy or the use of inotropic agents. The goal of
resuscitative care is to delay or prevent the transition to irreversible hemorrhagic shock.

The recognition of coagulopathy at the time of admission is crucial. Hess et al.\(^5\) asserted that several factors contribute to the development of coagulopathy: blood loss, hemodilution by physiologic vascular refill, consumption of platelets, hypothermic platelet dysfunction, reduction of enzyme activity, acidosis-induced reduction in coagulation factor activity, and unopposed fibrinolysis. Customarily, volume resuscitation starts with a combination of crystalloids, colloids, and uncrossmatched packed red blood cells (RBC) because of ease of availability. Uncrossmatched packed RBC are readily available but are generally used only in cases of dire emergency. These products may further dilute coagulation factors contributing to a negative spiral effect of dilutional coagulopathy.\(^9\) ABO typing of blood and thawing of component replacement factors requires time during the initial phase of the resuscitation. By the time that type-specific fresh frozen plasma, platelets, and cryoprecipitate are added to the regimen, they generally fail to correct the coagulopathy because of hemodilution.\(^10\) Thromboelastography can enable the anesthetists to minimize hemodilution and possibly prevent exacerbation of coagulopathies by transfusing the correct blood product when the patient needs it.

There has been growing consensus that RCoT are ill suited for monitoring coagulopathy and guiding transfusion therapy in hemorrhaging patients.\(^3,11\) These assay tests were developed more than 50 years ago for treatment of patients with hemophilia and have never been validated for the prediction of uncontrolled hemorrhage in trauma patients. Even though abnormal PT, APTT, and INR results are consistent with increased mortality in the trauma patient, these plasma-based tests communicate only the small amount of thrombin formed during the initial phases of coagulation and have little predictive value (≤ 50\%) with respect to hemorrhage.\(^12\)

A new understanding of the classic coagulation cascade was put forth in 1994 by the introduction of a cell-based model.\(^13\) The cell-based model emphasizes the importance of tissue factor as the initiator of the coagulation cascade and the pivotal role of platelets for intact hemostasis. This new understanding explains the poor correlation between RCoT and clinical bleeding and provides a more accurate picture of why use of these laboratory studies is insufficient in trauma resuscitation.\(^13\) Correct detection of coagulopathy is crucial for survival, and interest has renewed in viscoelastic assay studies to guide transfusion therapy in trauma patients.

Thromboelastography is a real-time viscoelastic assay that measures the strength of fibrin-platelet bonds in whole blood. The result of this process is a functional hemostatic plug. Historically, TEG analysis has been used extensively in the disciplines of cardiovascular surgery, liver transplantation, and obstetrics.\(^14\)

The TEG assay is a relatively simple process. A small sample of whole blood (0.36 mL) is placed into a cup heated to 37°C. The cup is gently rotated back and forth constantly, at a set speed, through an arc (cycle time, 6/ min). This sluggish flow mimics the venous circulation and activates the coagulation process. A stationary pin attached to a torsion wire is inserted into the sample cup, and fibrin begins to form between the torsion wire and the wall of the cup. This fibrin-platelet binding links the cup and pin together (Figure 1). The speed and strength of clot formation are converted by a mechanical-electrical transducer to an electrical signal that is computer analyzed. These data are converted to a numeric value and graphic representation of the plasmatic coagulation system, platelet function, and fibrinolysis (Figure 2).

There are 4 main values of interest expressed in this assay: the R value (start of clot or fibrin formation), K value (fibrin kinetics or speed of clot formation), \(\alpha\) angle (fibrin cross-linking), and the MA (width of tracing representing clot strength). These values expose the precise mechanism contributing to the coagulopathy, as depicted...
in Table 1. The differential diagnosis can be deduced whether the dysfunction is a result of hemodilution, loss of coagulation proteins, or platelet dysfunction. The R value represents the reaction time for initial fibrin formation (normal, 7.5-15 minutes). The prolongation of this value can represent a deficiency in coagulation factors, effects of endogenous heparin released in trauma, and/or hemodilution. The treatment with fresh frozen plasma or no treatment would depend on the clinical picture of the patient. Conversely, a shortening in the R value (less than 3 minutes) would indicate a state of hypercoagulability, and treatment with an anticoagulant of choice may prove beneficial. The K value (normal, 3-6 minutes) and α angle (normal, 45° to 55°) depicts the speed at which the clot strengthens. A low value may indicate the need for fibrinogen administration, and a high value may indicate hypercoagulability for which the patient may benefit from anticoagulant therapy. Last, the MA, or maximum amplitude (normal, 50-60 mm), represents the overall maximum attainable clot strength. A decreased value can result from hypofibrinogenemia, decreased platelet function, or quantity. Transfusing platelet pools in patients who present a decreased MA may improve hemostatic conditions. An MA result greater than 75 mm is evidence of a prothrombotic state, and an anticoagulant of choice may be clinically indicated. The qualitative analysis that TEG provides can facilitate administration of the right blood product or anticoagulant, in correct amounts, at just the right time.

**Discussion**

**Coagulation Pathways.** The PT and INR depict the extrinsic pathway of the coagulation cascade. Tissue factor is exposed from the injured endothelium and combines with factor VII to produce factor VIIa. Factor VIIa will subsequently bind with tissue thromboplastin to convert factor X to Xa. When factor X is activated, it signals the beginning of the final common pathway. Therefore, only 2 coagulation proteins are represented in the extrinsic pathway, or less than 3% of the overall clot strength. This condition omits information on approximately 97% of the hemostatic process. Confounding the problem with RCoT is the fact that platelets are responsible for approximately 80% of total clot strength. Platelets are an important variable in the hemostatic process and are immediately lost during the centrifuge process. When RCoT assays are analyzed, the plasma and the contribution of platelets in their role to clot strength are gone.

Analysis of the intrinsic pathway offers double the amount of information about the coagulation pathway compared with the extrinsic pathway. The factors represented are XII, XI, IX, and VIII and 3 natural anticoagulant proteins, C, S, and Z. Although there is twice the amount of information, less than 10% of the overall clot strength is represented in this APTT assay. When the final common pathway is reached by either intrinsic or extrinsic mechanisms, factor X is activated and the conversion of prothrombin to thrombin results. The conversion of prothrombin to thrombin is where the serious affair of the hemostatic process truly begins. Thrombin will activate factor V to factor Va and factor VIII to factor VIIIa and will serve as a positive feedback loop. This positive feedback mechanism greatly increases the production of thrombin. Information on these important feedback loops are lost because only isolated pieces of the pathway are examined in RCoT because of whole blood is not being analyzed. Thrombin cleaves fibrinogen to fibrin monomers, to form fibrin polymers. Formation of fibrin polymers serves as the first mechanical evidence of a clot. It is at this point where all RCoT assays stop analysis. Routine coagulation tests stop where two coagulation proteins are represented in the extrinsic pathway, or less than 3% of the overall clot strength. This condition omits information on approximately 97% of the hemostatic process. Confounding the problem with RCoT is the fact that platelets are responsible for approximately 80% of total clot strength. Platelets are an important variable in the hemostatic process and are immediately lost during the centrifuge process. When RCoT assays are analyzed, the plasma and the contribution of platelets in their role to clot strength are gone.
Abbreviations: FFP, fresh frozen plasma; RBC, red blood cells; RCoT, routine coagulation test; TEG, thromboelastography.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of surgery</th>
<th>No. of patients</th>
<th>Major conclusions</th>
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<tr>
<td>Shore-Lesserson et al24 (1999)</td>
<td>Cardiac surgery</td>
<td>105</td>
<td>Patients who underwent TEG received less FFP and platelet transfusions postoperatively than did RCoT-treated patients</td>
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<tr>
<td>Manikappa et al11 (2001)</td>
<td>Cardiac surgery</td>
<td>150</td>
<td>TEG demonstrated greater accuracy than RCoT in predicting significant postoperative hemorrhage and significantly decreased the need for transfusion of RBC, FFP, and platelets</td>
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**Table 2. Comparison Studies of Routine Coagulation Tests and Thromboelastography**

Abbreviations: FFP, fresh frozen plasma; RBC, red blood cells; RCoT, routine coagulation test; TEG, thromboelastography.

is that of platelet activation. Thrombin is the most potent platelet activator in the body and serves as the catalyst for the hemostatic process.

Very small amounts of thrombin are required to cleave fibrinogen and activate platelets; however, a much larger amount of thrombin is necessary to produce a stable network of platelet-fibrin polymers. This fundamental principle further explains why RCoT do not agree with actual clinical bleeding observed in vivo.12,18 Thromboelastography evaluates the mechanical properties of the hemostatic process, including time to initial fibrin formation, the kinetics of initial fibrin clot formation, and length of time to achieve maximum strength, and the final strength and stability of the fibrin clot. The resulting strength of the fibrin clot formation determines how well the clot can prevent hemorrhage without permitting inappropriate thrombosis formation. Each variable communicable by TEG assay expresses a unique component or relationship within the delicately balanced coagulation cascade process and benefits the practitioner by early detection of coagulopathic derangements. Randomized controlled trials comparing RCoT and viscoelastic assay are described in Table 2.

- **Benefits of TEG.** The TEG assay produces a rapid, low-cost method for differential diagnosis regarding the need for surgical reexploration in patients with continued microvascular oozing.19 This translates to the potential for enormous savings in healthcare costs, decreasing the demand on our blood bank reserves and improving the quality of patient care.20-22

The medical literature is replete with hazards associated with transfusion of allogeneic blood products. Small shifts in pH has a much greater effect on the coagulation process than small changes in temperature. Stored blood has lower levels of 2,3-diphosphoglycerate, lower pH, and increased levels of supernatant potassium. These changes can exacerbate the conditions of the trauma patient because a normal serum pH does not consistently reflect the pH in hypoxic tissue.23 The TEG assay has been demonstrated to significantly decrease the requirement for perioperative allogeneic transfusion.14 A landmark study conducted by Shore-Lesserson et al24 compared the effect of TEG-guided transfusion algorithm against routine transfusion therapy in patients undergoing complex cardiac surgery. The result produced a 75% reduction in the number of patients receiving fresh frozen plasma and more than a 50% reduction in the transfusion of platelets.

Current studies advocate equal transfusion ratios of packed RBC, fresh frozen plasma, and platelets (1:1:1) to improve survival rates in trauma patients rather than early and substantial use of crystalloids and/or colloids.6,10,25-27 This approach to trauma resuscitation has been widely studied in severely injured patients and has become a commonplace practice to minimize dilutional coagulopathy. The ongoing conflict in the United States Theater of Operations in the Middle East has produced retrospective data suggesting that whole blood is superior to component replacement therapy in the massively transfused trauma patient.28-33 However, treating these patients indiscriminately with fresh frozen plasma, platelets and cryoprecipitate is not only uneconomical, Hess et al3 reported that this practice is “dangerous.” Perkins et al34 reported improved 30-day survival rates associated with the increased use of platelets in massive transfusion. The optimal ratio of packed RBC to platelets is not clearly understood and warrants more investigation because although increased platelet ratios increase survival rates in massively transfused patients, they also are associated with multiple organ failure.35

Acute lung injury is a syndrome of acute hypoxemic respiratory failure, noncardiogenic in origin, with the presence of bilateral pulmonary infiltrates. Acute lung injury has a 33% rate of incidence among the critically injured trauma population. A recent study published by Edens et al36 suggested that there might be an independent relationship between the amount of fresh frozen plasma transfused and the development of early acute lung injury. Because of the current shifts in transfusion practice leaning toward infusion ratios of packed RBC to fresh frozen plasma approaching 1:1, mortality rates have improved. However, evidence also suggests that
this transfusion strategy may be associated with a higher incidence of acute lung injury, and the patient implications related to this finding are unknown at this time. Khan et al demonstrated that the development of acute lung injury was dose dependent on the actual numbers of fresh frozen plasma transfused. Thromboelastography can provide anesthetists with information on which blood products would prove most efficacious to the hemorrhaging trauma patient and guide transfusion therapy in appropriate quantities.

Patients receiving long-term thrombolytic therapy can be assessed preoperatively with precision and accuracy to determine the potential for perioperative hemorrhage. A preoperative platelet count provides information only on how many platelets are present and does not analyze functionality. Functional, not quantitative, measurements are necessary to make evidence-based decisions on whether to proceed with surgical intervention. The platelet system has 2 components: (1) activation and (2) aggregation. Once the coagulation cascade has been activated, the question remains whether the platelets are functionally capable of aggregating to form a platelet plug. Thrombolytic drugs such as clopidogrel, prasugrel, and abciximab act to prevent platelet aggregation in contrast to aspirin and nonsteroidal drugs, which alter platelet adhesion and anchoring. The TEG assay can be used for preoperative risk stratification based on individual hemostatic conditions. Platelet mapping depicts whether a delay in surgery is necessary or, may possibly proceed earlier than anticipated. The return of platelet function can be followed with serial studies, and the need for platelet availability can be correctly anticipated.

Thromboelastography offers point-of-care testing, which produces the advantage of convenient and rapid results when decisions need to be made. Currently, no published data exist quantifying how many hospitals use TEG analysis nationwide; however, hemorrhage and thrombotic issues are a shared concern across hospital specialties. Viscoelastic assays are currently endorsed by several international guidelines and textbooks concerning massive transfusion in trauma.38-40

A classic work by Ammar advances the use of TEG analysis for aiding early extubation. Early extubation is often prevented by excessive bleeding. This condition renders the patient hemodynamically unstable and may require surgical reexploration to determine the cause of the bleeding. The process of coagulation is dynamic; however, TEG allows the practitioner to quantify and qualify 85% to 90% of this system.19 In a comparison of TEG with RCoT profiles, traditional RCoT results will provide at best a 51% predictive value for perioperative bleeding. This would be analogous to flipping a coin to determine results. Pinpointing the dysfunction and formulating evidence-based therapy to address specific coagulopathies become a reality, allowing the practitioner to minimize complications and deliver specific treatment to the patient. The intraoperative use of TEG analysis can identify the reason for the bleeding and guide therapy during the postoperative course, which will facilitate earlier extubation and may decrease length of stay in the intensive care unit.

• Practice Implications. The TEG assay presents new challenges and practice implications to anesthesia providers. Further nursing research incorporating the TEG assay into the anesthesia preoperative screening phase can expand on the body of knowledge and possibly improve patient care. Strategies must be developed to assist the anesthetists to correctly interpret the results of TEG analysis, formulate therapeutic goals, and develop appropriate transfusion guidelines. Accomplishing this objective will require the development of multidisciplinary teams to implement comprehensive strategies addressing policy and procedure development, promote cooperative collaboration, and implement education and training among multiple hospital departments that would be affected by the practice change. A paradigm shift in evidence-based practice is called for to embrace the TEG assay into patient care. These evidence-based practice changes can serve to decrease mortality rates in the trauma population and possibly other medical disciplines, rendering a more cost-effective hospitalization course.

Summary

The purpose of this article has been to outline the importance of addressing coagulopathic conditions experienced in trauma patients and relate contributing factors to the development of coagulopathy. An in-depth history and review of the literature has been presented to demonstrate a thorough assessment of the problem. Explanation has been given to the reader why RCoT assays may be inadequate to guide transfusion therapy in trauma anesthesia. A brief outline of the coagulation pathway has been presented along with a discussion detailing the advantages that the TEG assay can offer compared to RCoT, which can benefit the patient, anesthetist, and hospitals. Potential practice implications have been put forth to challenge anesthesia providers to adopt current evidence-based practice changes.

Evidence-based transfusion therapy could offer mutual benefit to trauma patients and hospitals. Incorporating the TEG assay into transfusion practice offers many distinct advantages. Prior studies have shown that the TEG assay allows for point-of-care testing that produces convenient, rapid results in situations when decisions need to be made quickly without undue strain on blood bank resources. The potential positive results could promise better health outcomes for trauma patients, including earlier extubation, reduced medical costs without a decrease in patient care, as well as decreased chance of future need for transfusions or additional surgery, and less
recovery time in critical care units. Thromboelastography has the potential to prevent coagulopathy and promote effective control of bleeding in the presence of coagulopathy. These are all noteworthy points of service to our patients. Prior studies suggest that TEG could be a productive compliment to current methods, and in some cases, a superior method altogether. Further nursing research using the TEG assay in other disciplines needs to be developed in order to expand on this beneficial body of knowledge and improve patient care.

REFERENCES
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