Viscoelastic Tissue Plasminogen Activator Challenge Predicts Massive Transfusion in 15 Minutes

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BACKGROUND: Coagulopathy is associated with massive transfusion in trauma, yet most clinical scores to predict this end point do not incorporate coagulation assays. Previous work has identified that shock increases circulating tissue plasminogen activator (tPA). When tPA levels saturate endogenous inhibitors, systemic hyperfibrinolysis can occur. Therefore, the addition of tPA to a patient's blood sample could stratify a patients underlying degree of shock and early coagulation changes to predict progression to massive transfusion. We hypothesized that a modified thrombelastography (TEG) assay with exogenous tPA would unmask patients' impending risk for massive transfusion.

STUDY DESIGN: Trauma activations were analyzed using rapid TEG and a modified TEG assay with a low and high dose of tPA. Clinical scores (shock index, assessment of blood consumption, and trauma-associated severe hemorrhage) were compared with TEG measurements to predict the need for massive transfusion using areas under the receiver operating characteristic curves.

RESULTS: Three hundred and twenty-four patients were analyzed, 17% required massive transfusion. Massive transfusion patients had a median shock index of 1.2, assessment of blood consumption score of 1, and trauma-associated severe hemorrhage score of 12. Rapid TEG and tPA TEG parameters were significantly different in all massive transfusion patients compared with non-massive transfusion patients (all $p < 0.02$). The low-dose tPA lysis at 30 minutes had the largest the area under the receiver operating characteristic curve (0.86; 95% CI 0.79 to 0.93) for prediction of massive transfusion, similar to international normalized ratio of prothrombin time of 0.86 (95% CI 0.81 to 0.91), followed by trauma-associated severe hemorrhage score (0.83; 95% CI 0.77 to 0.89). Combing trauma-associated severe hemorrhage and tPA-TEG variables results in a positive prediction of massive transfusion in 49% of patients with a 98% negative predictive value.

CONCLUSIONS: The tPA-TEG identifies trauma patients who require massive transfusion efficiently in a single assay that can be completed in a shorter time than other scoring systems, which has improved performance when combined with international normalized ratio. This new method is consistent with our understanding of the molecular events responsible for trauma-induced coagulopathy. (J Am Coll Surg 2017;225:138−147. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

ABC = assessment of blood consumption
AUROC = area under the receiver operating characteristic
Ht-TEG = high-dose tissue plasminogen activator thrombelastogram
INR = international normalized ratio
IQR = interquartile range
Lt-TEG = low-dose tissue plasminogen activator thrombelastogram
LY30 = lysis after 30 minutes
NPV = negative predictive value
POC = point of care
PPV = positive predictive value
r-TEG = rapid thrombelastography
TASH = trauma-associated severe hemorrhage
TEG = thrombelastography
TMA = time to maximum amplitude
tPA = tissue plasminogen activator

Early identification of patients who require a massive transfusion after injury remains a challenge. Current clinical tools to predict massive transfusion range from a simplified shock index based on heart rate and systolic blood pressure[1] to a more intensive calculation based on these variables in addition to injury mechanism, laboratory values, and imaging.[2] Newer prediction models include automated calculations made with phone-based algorithms using similar variables[3] and scores calculated on prehospital paramedic assessment.[4] The numerous scoring algorithms reflect the difficulty in correctly identifying patients who will require a massive transfusion and indicate a need to explore alternative methods, and many have been criticized for a poor positive predictive value (PPV).[5]

Coagulation abnormalities in trauma are associated with increased blood product use.[6-8] Endogenous traumatic coagulopathy[9] is common in patients with a high injury severity and advanced shock.[10] This trauma-induced coagulopathy, typically defined as an international normalized ratio (INR) of prothrombin time >1.5, is associated with increased mortality from hemorrhage.[11] Within trauma-induced coagulopathy, there are distinct mechanisms that drive impaired thrombin generation vs excessive fibrinolytic activity.[12,13] Clinical studies indicate that hypotension is the driver of hyperfibrinolysis.[14] In animals, tissue plasminogen activator (tPA) has been shown to rise during hemorrhagic shock, but not after tissue injury.[15] Therefore, as a trauma patient progresses toward decompensated hemorrhagic shock, systemic tPA levels are anticipated to increase.

Although elevated circulating tPA appears to drive this process, depletion of circulating inhibitors is necessary before an overt systemic hyperfibrinolytic phenotype develops. Whole blood of healthy individuals requires supraphysiologic concentrations of tPA to activate fibrinolysis in vitro due to the buffering capacity of plasma proteases.[16] Based on evidence that hemorrhagic shock releases tPA and increases circulating tPA activity due to persistent depletion of its inhibitors, resulting in hyperfibrinolysis, we developed an assay to predict massive transfusion. We hypothesize that modified thrombelastography (TEG) with the addition of exogenous tPA (tPA-TEG) predicts the patient's risk for requiring a massive transfusion more efficiently than current scoring systems.

METHODS

Patient characteristics

Consecutive adult trauma patients meeting criteria for the highest level of activation at our Level I trauma center (Denver Health Medical Center) from 2014 to 2016 were included in this analysis. All patients had samples collected under protocols approved by the Colorado Multiple IRB for prospective evaluation of coagulation in response to trauma. Patient demographics, injury mechanism, laboratory results, and transfusion requirements were recorded by professional research assistants who provide on-site, continuous coverage of the emergency department. Injury severity was measured by the maximum Abbreviated Injury Scale scores for the head/neck, chest, abdomen, and extremities; Injury Severity Score; and Glasgow Coma Scale.

Blood collection

Blood was collected in 3.5-mL tubes containing 3.2% citrate in the prehospital ambulance or on arrival to the emergency department. Prehospital or emergency department healthcare workers drew study-patient blood samples concurrently with the first set of blood samples used for in-hospital laboratory analysis. Professional research assistants performed TEG assays within 2 hours of blood draw. Additional assays were ordered at the discretion of the treating surgeon and performed by the hospital laboratory.

Viscoelastic assays

All viscoelastic assays were conducted by a team of trained professional research assistants with extensive experience in multiple types of TEG assays. Citrated blood samples were analyzed using the TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemonetics). The following indices were obtained from the tracings of the TEG: reaction time (minutes), angle (degree), maximum amplitude