Admission rapid thrombelastography delivers real-time “actionable” data in pediatric trauma

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Abstract
Purpose: Admission rapid thrombelastography (rTEG) is a “real-time” clinical tool used to evaluate trauma-induced coagulopathy and direct hemostatic resuscitation. The relationship of rTEG to conventional coagulation tests (CCT) and early lifesaving interventions (LSI) in pediatric trauma is unknown.

Methods: Severely injured patients (age ≤ 14 years) with an rTEG were retrospectively reviewed (8/1/2009–8/31/2011). Demographic and clinical information was collected. Spearman’s correlation and regression models were used to evaluate rTEG with respect to CCT, early transfusion, LSI, and mortality.

Results: Eighty-six patients were identified. The median age was 8 years, and the median injury severity score (ISS) was 21. Activated clotting time (r = 0.68), k-time (r = 0.77), and α-angle (r = −0.75) showed strong correlation to PTT, and maximum amplitude (MA) (r = 0.46) showed good correlation to platelet count (all p < 0.001). When controlling for age, gender, and ISS, regression analysis showed that ACT, r-value, k-time, α-angle, and MA predicted red blood cell and plasma transfusion within 6 h. MA (OR 0.82, 95% CI 0.70–0.96; p = 0.018) was predictive of LSI. All rTEG values, except for LY30, predicted mortality.

Conclusion: Admission rTEG correlates with CCT and predicts early transfusion, early LSI, and outcome in pediatric trauma. rTEG provides valuable data for goal-directed hemostatic resuscitation of critically injured children.

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1. Purpose

Trauma is a leading cause of morbidity and mortality in children [1,2]. Acute coagulopathy of trauma is an ill-defined but well-described phenomenon of multifactorial etiology that is common in severely injured patients [3]. In children, this coagulopathy is strongly associated with increased morbidity and mortality [4,5]. Therefore, rapid identification and management of this coagulopathy is a critical component of the trauma resuscitation.

Conventional coagulations tests (CCT) such as the prothrombin time (PT), international normalized ratio (INR), and activated prothrombin time (aPTT) evaluate components of the traditional, “cascade” model of hemostasis characterized by the classic extrinsic and intrinsic pathways and are widely used in trauma patients. Originally designed for the management of certain disease states or to guide anticoagulation therapy, CCT incompletely characterize the
coagulopathy associated with severe trauma [6–9]. Additionally, there is often a significant delay in obtaining results from even emergent CCT that is suboptimal in the management of critically ill trauma patients [3,10–12]. In contrast, thrombelastography (TEG) is a point-of-care measure of hemostasis that evaluates the global viscoelastic mechanical properties of whole blood [13]. TEG generates a graphical tracing and multiple data points that may more accurately reflect the in vivo interactions of all the components of coagulation and fibrinolysis [10,13]. TEG has been shown to reflect acute coagulopathy of trauma and predicts morbidity and mortality [11,14–16]. In adults, admission rapid TEG (rTEG— a TEG assay using kaolin and tissue factor as activating agents) has been shown to be quickly available (within minutes) and to correlate with CCT as well as predict early transfusion of red blood cells, plasma, and platelets [10]. In a large prospective series of adult trauma patients, rTEG was clinically superior to CCT for identifying patients at risk for acute coagulopathy of trauma [27]. These data can be used to guide hemostatic resuscitation of adult and pediatric patients [12,17,18,27].

The purpose of this study is to evaluate the use of admission rTEG in pediatric trauma patients for predicting the acute coagulopathy of trauma as well as the clinical trajectory as assessed by early blood product transfusion and early lifesaving interventions. We hypothesize that admission rTEG will correlate with CCT and predict outcome as well as the need for early blood product transfusion and early lifesaving interventions in children.

2. Methods

This research was approved by the IRB (HSC-MS-11-0403). The study center is an American College of Surgeons verified Level I pediatric trauma center. The trauma registry was retrospectively queried for consecutive pediatric patients (age less than 14 years) who were the institutions highest-level trauma activation from August 1, 2009 through August 31, 2011. Patients were excluded if they were discharged from the emergency center (EC) to home or were admitted to a non-intensive care setting. Demographic and clinical data were extracted from the registry database and medical record and included age, gender, weight, mechanism of injury, scene and EC vital signs, Glasgow coma score (GCS), abbreviated injury scale (AIS), injury severity score (ISS), initial laboratory data (rTEG, PT, PTT, INR, fibrinogen, hemoglobin, platelet, and base deficit), 6-h transfusion requirements (red blood cells, plasma, platelets and cryoprecipitate), lifesaving interventions (LSI) performed within 6 h, and 30-day mortality. An LSI was defined as emergent endotracheal intubation, emergent bedside surgical procedure (intracranial monitor placement, thoracotomy tube placement, emergent central venous access), or an emergent surgical procedure (craniotomy, thoracotomy, or laparotomy).

The means by which rTEG specimens are processed and the results are reported have been previously described in detail elsewhere [10]. Briefly, blood was collected in a citrated tube and transported to the laboratory where reversal with calcium chloride was performed. Standard tissue factor and kaolin-activated rTEG was performed according to manufacturer’s instructions on a TEG thrombelastograph 5000 (Hemoscope Corporation, Niles, IL) in the EC Stat Lab that is in close proximity to the trauma resuscitation area. The rTEG tracing is displayed real time in the trauma resuscitation bay with well-defined components (Fig. 1). The r-value or ACT (activated clotting time) is defined as the time between the initiation of the test and fibrin formation and is representative of clotting factors (normal range, 0–118 s). The k-time is the time needed for the tracing to reach 20 mm from 2 mm and is increased with hypofibrinogenemia or platelet deficiency (normal range, 1–2 min). The α-angle is the rate of clot formation and decreases with hypofibrinogenemia or platelet deficiency (normal range, 66°–82°). The maximal amplitude (MA) is the greatest amplitude of the tracing and represents the platelet contribution to clot strength (normal range, 54–72 mm). Finally, LY30 is the percent amplitude reduction at 30 min after achievement of MA and represents fibrinolysis (normal range, 0.0%–7.5%). The rTEG tracing and parameters (including normal ranges) are automatically generated and are displayed on monitors in the trauma bay. A computer record in the electronic medical record was also available for review. The rTEG was interpreted by the treating trauma team.

Continuous data are presented as medians with the 25th and 75th interquartile range (IQR) with comparisons between groups performed using the Wilcoxon rank-sum test or Mann–Whitney U test. Categorical data are reported...
as proportions and were tested for significance using the χ² or Fisher’s exact tests. Correlation of rTEG values with CCT was assessed with Spearman’s correlation coefficients and simple linear regression. ACT, r-value, k-time, and α-angle were correlated with PT, aPTT, and INR. α-angle and MA were correlated with platelet count.

Multivariate linear regression analyses were performed controlling a priori for age, gender, and ISS to evaluate the relationship between all rTEG and CCTs and transfusion. Controlling for these same variables, a logistic model was created to determine if these values could predict the need for early LSIs (within the first 6 h) and then for 30-day mortality.

All statistical tests were two-tailed with p < 0.05 set as significant. Correlation coefficient ranges were defined as follows: r < 0.3, weak; 0.3 > r > 0.7, moderate, r > 0.7, strong correlation. Results are presented as odds ratios, 95% confidence intervals (CI), and p-values. STATA Statistical software (version 10.0; College Station, TX) was used for analysis.

3. Results

Eighty-six patients met the inclusion criteria. Patient demographic information can be found in Table 1. The median age was 8 years and 67% were male. Eighty-eight percent of patients sustained a blunt mechanism of injury. The median scene GCS was 9 and the median ED GCS was 3. Traumatic brain injury, as defined by head AIS ≥ 3, was present in 55% of patients. This population was severely injured with a median injury severity score of 21 (9, 33). There were 76 survivors (88%) and 10 non-survivors (12%).

Clinically relevant correlations between rTEG values and CCT can be found in Table 2. Overall, ACT (r = 0.68), k-time (r = 0.77), and α-angle (r = -0.75) showed strong correlation to PTT and MA (r = 0.46) showed good correlation to platelet count (all p < 0.001).

Multivariate linear regression was then carried out to evaluate the prediction of early blood product transfusion (0–6 h) (Table 3). With the exception of LY30 and fibrinogen levels, all the CCTs and rTEG values predicted
Conclusion

Cryoprecipitate transfusion volumes were only predicted by hemoglobin level and aPTT. However, only INR and CCTs and rTEG values predicted transfusion volumes. With respect to plasma, all the red cell transfusion volumes. With respect to plasma, all the CCTs and rTEG values predicted transfusion volumes except hemoglobin and aPTT. However, only INR and hemoglobin level predicted platelet transfusion volumes. Cryoprecipitate transfusion volumes were only predicted by k-time (coef. −0.73, 95% CI −1.227 to −0.236 with \( p = 0.004 \)) and \( \alpha \)-angle (coef. 0.07, 95% CI. 0.0147–0.126, \( p = 0.014 \)) (data not shown).

A logistic regression model was developed evaluating the need for early LSIs (Table 4). In this model, only the MA (OR 0.82, 95% CI 0.70–0.96; \( p = 0.018 \)) was predictive of LSIs. With respect to the different types of LSI, there were 56 endotracheal intubations, 18 central line placements, 18 emergent laparotomies or thoracotomies, 7 tube thoracostomy placements, 5 intracranial pressure monitor placements, and 4 craniotomies. Of note, 50% (\( n = 23 \)) of the endotracheal intubations were performed in patients with an AIS head score ≤ 2.

There was no difference between survivors and non-survivors with respect to age, gender, or race. Non-survivors had a lower median EC systolic blood pressure, higher median head AIS, lower GCS, and higher median ISS. Of the 10 deaths, 7 had a head AIS ≥ 2. Non-survivors were also more coagulopathic with a prolonged median INR, aPTT, ACT, r-value, k-time, and a lower angle, and MA (all \( p < 0.05 \)). There was no significant difference between median hemoglobin and platelet count. Multivariate logistic regression showed that all rTEG values (except for LY30) predicted mortality; aPTT and platelet count were associated with a significant increase in the odds of mortality.

4. Conclusion

This analysis of 86 severely injured pediatric patients shows that admission rTEG correlates with CCT and, more importantly, is predictive of the need for early blood product transfusion and LSI. Furthermore, a coagulopathic rTEG profile is associated with increased odds of mortality. These results are not surprising—critically ill, traumatically injured patients are more coagulopathic. These patients would be expected to receive blood products, require emergent LSIs, and have a higher mortality.

Coagulopathy is known to be associated with worse morbidity and mortality in severely injured pediatric trauma patients. In a series of 102 traumatically injured children coagulopathy was associated with increased odds of death [5]. A large retrospective review of 744 pediatric patients in the Joint Theater Trauma Registry from US support combat hospitals in Iraq confirmed these findings [4].

There exist very few practical tools to assist in the rapid identification and management of the coagulopathic trauma patient. CCT reflects the linear enzymatic reactions of the classic intrinsic and extrinsic pathways that describe conventional hemostasis. These tests were originally intended to follow the effect (and effectiveness) of oral and intravenous anti-coagulants and were not developed for quantifying or describing defects in coagulation following surgery, trauma or resuscitation. Not surprisingly, this model grossly underestimates the complexity of coagulation in the acutely injured patient. These diagnostic tests provide little insight into the functional nature of the multitude of cell-based, complex interactions that occur between the endothelium, coagulation proteins, and cells [19]. Additionally, with respect to the management of the critically ill trauma patient, these tests take an inappropriately long time to generate results [3,10–12,17]. These factors make CCT suboptimal for management of trauma resuscitation.

However, thrombelastography provides a global assessment of a patient’s current hemostatic function and may be the best way of evaluating the coagulopathy of trauma [13]. There are multiple assays and instruments currently available to generate tracings and data from the mechanical properties of clotting blood. The two most commonly utilized are TEG (thrombelastography) and ROTEM (rotational thromboelastometry). In traditional thrombelastography (TEG), a small sample of uncitrated whole blood (about 0.3 ml) is pipetted into a cuvette and activated with a reagent (kaolin). The sample is placed into the thrombelastograph machine where the cuvette oscillates and a pin suspended in the blood by a torsion wire transduces the viscoelastic mechanical properties of the blood into a graphical tracing. Computational algorithms generate the individual data points (r-time, MA, etc.). In ROTEM, the pin oscillates instead of the cup. Despite the variations, each technique has reliable internal validity and reference ranges of multiple assays have been describes for children of all ages [20–25]. TEG needs to be performed rapidly on whole blood (usually within 5 min) before the blood starts clotting. In our institution, rTEG is performed using the reverse citrate method (citrated blood from a blue top tube is reversed with calcium chloride) to prevent prematurely clotting. These center-specific

<table>
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<th>Multivariate linear regression model predicting early lifesaving interventions.</th>
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<td>Odds ratio</td>
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<tr>
<td>ACT</td>
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<td>r-Value</td>
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<td>k-Time</td>
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<td>( \alpha )-Angle</td>
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<td>MA</td>
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<td>LY30</td>
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<tr>
<td>PTT</td>
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<td>INR</td>
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<td>Hemoglobin</td>
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<td>Fibrinogen</td>
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Only MA was predictive of LSI. Coef.: coefficient of correlation; 95% CI: 95% confidence interval; aPTT: activated partial thromboplastin time; INR: international normalized ratio; ACT: activated clotting time; MA: maximal amplitude.
alterations to the rTEG assay highlight the need for individual institutions to identify their specific resources and capabilities for optimal utilization of rTEG.

The application of TEG technology has been well described in the acute trauma setting. A series of 69 patients showed that TEG was cheaper and superior to CCT [26]. A series of 300 adult trauma patients found that conventional coagulations tests (aPTT specifically) were not available within clinically useful timeframes (median of 78 min). In this study, a ROTEM thromboelastometry curve showed within 5 min that a reduction in clot strength identified patients more likely to receive massive transfusion [3]. In a prospective study of 69 adult patients with traumatic brain injury, patients with a prolonged r-value had an increased incidence of neurosurgical intervention and an increased mortality [16]. A retrospective analysis of 89 patients showed that clot strength (MA) was found to correlate with packed red cell, plasma, and platelet transfusions in the first 24 h. When controlling for age and ISS, MA was a significant predictor of mortality [14]. In a series of 80 patients, rTEG G-value (an exponential value derived from the linear MA) was shown to be the best predictor of massive transfusion and death in massively transfused resuscitated trauma patients [15]. In this series, rTEG results were generally available within 15 min while CCT resulted in 30 min or more. rTEG has also been compared to standard (kaolin-only) TEG as well as conventional coagulation tests where the authors concluded that rTEG is the most rapid test available for providing reliable information of coagulopathy in patients with multiple injuries [11].

A large retrospective review of a prospectively maintained trauma database of 272 adult trauma patients from our institution found that rTEG results were available within 5 to 15 min while CCT results took approximately 48 min ($p < 0.001$) [10]. The initial resuscitation response and procedures for obtaining laboratory data are identical for adult and pediatric trauma activations and these data reflect the relevant turnaround times for rTEG and CCT in our pediatric patients. In a larger series from the same center of 1974 adult trauma patients, ACT was shown to correlate moderately with INR and PTT, $k$-time showed a moderate correlation with PTT, and MA demonstrated moderate correlation with both platelet count and fibrinogen [27]. These correlations became stronger in patients presenting with shock and isolated traumatic brain injury. Regression analysis showed that all rTEG values were predictive of early red blood cell transfusion, and all but LY30 and fibrinogen predicted early plasma and platelet transfusion. rTEG values were also useful in predicting substantial bleeding, the need for massive transfusion, and were independent predictors of 24 mortality. The authors concluded that rTEG data are clinically superior to CCT and identifies patients at risk of early blood product transfusion. These data and others have been used to generate rTEG guided protocols for goal-directed hemostatic resuscitation in adults [17,27,28].

The relationship of rTEG to the performance of LSI is not surprising; coagulopathic traumatically injured patients would be expected to require LSIs. This study adopted a broad definition of LSI to include interventions not typically associated with complications of coagulopathy but that are common in severely injured children. A limitation of our study is that the indications for the specific interventions were not recorded. Therefore, for example, it is difficult to know if endotracheal intubation was required for hemorrhagic shock or progressive traumatic brain injury. Although coagulopathy certainly plays a role in the evolution of injury in trauma, the need to perform LSI would be apparent on physical examination. In this context, rTEG may be valuable for managing traumatic coagulopathy in preparation for performing a LSI. In actuality, rTEG may be a confounding variable in its relationship to LSI and could be a marker for injury severity and these relationships would be better assessed in a large prospective trial.

There are several additional limitations to the present analysis. This is a retrospective study from a single center with a very small number of patients and the results need to be carefully evaluated. The time period of this study encompasses the period when rTEG was being incorporated into the management of adult and pediatric trauma. rTEG and CCT data were available to the treating trauma team and it is uncertain which test played a more significant role in directing the transfusion. It is unclear, how rTEG data impacted the care of our patient population and it is difficult to make definitive statements on the ability of rTEG to impact clinical outcomes.

This is the first study describing the use of rTEG in pediatric trauma. Our findings parallel the results of the adult studies in that admission rTEG values correlate with CCT—the current yet flawed “gold standard” for evaluating coagulation abnormalities in trauma patients. We similarly found that rTEG values also predict early transfusion requirements, specifically packed red cells and plasma. We also showed that abnormalities in the rTEG coagulation profile increase the odds of patients receiving an early LSI. The true benefit of rTEG may be its point-of-care availability and the ability to receive rapid, reliable, actionable data in the trauma bay and enables traumatologists to incorporate a rapid assessment of coagulopathy in clinical management. A protocol-driven prospective trial of goal-directed hemostatic resuscitation algorithms using rTEG parameters is a natural extension of this concept that has the potential to improve the resuscitation of severely injured children.

References


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