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Rotational thromboelastometry thresholds for patients at risk for massive transfusion

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Abstract

Background—Goal-directed hemostatic resuscitation based on thrombelastography has a survival benefit compared to conventional coagulation assays. While thrombelastography transfusion thresholds for patients at risk for massive transfusion (MT) have been defined, similar cutoffs do not exist for the other commonly used viscoelastic assay, rotational thromboelastometry (ROTEM). The purpose of this study was to develop ROTEM blood product thresholds in patients at risk for MT.

Methods—ROTEM was assessed in trauma activation patients admitted from 2010 to 2016 (n = 222). Receiver operating characteristic curve analyses were performed to test the predictive performance of ROTEM measurements in patients requiring MT. The Youden Index defined optimal thresholds for ROTEM-based resuscitation.

Results—Patients who required MT (n = 37, 17%) were more severely injured. EXTEM clotting time (CT) was longer in patients with MT compared to non-MT (87 *versus* 64 s, P < 0.0001). EXTEM angle was shallower in MT patients compared to non-MT (54° *versus* 69°, P < 0.0001). Clot amplitude after 10 min (CA10) was less in MT compared to non-MT patients (30.5 *versus* 50)

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Disclosure

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mm, P < 0.0001). Clot lysis index 60 min (CLI60) was lower in patients who had MT than non-MT (47 *versus* 94%, P = 0.0006). EXTEM CT yielded an area under the receiver operating characteristic curve (AUROC) = 0.7116 and a cut point of >78.5 s. EXTEM angle had an AUROC = 0.865 and a cut point of <64.5°. EXTEM CA10 had an AUROC = 0.858, with a cut point of <40.5 mm. CLI60 had an AUROC = 0.6788 with a cut point at <74%.

Conclusions—We have identified ROTEM thresholds for transfusion of blood components in severely injured patients requiring an MT. Based on our analysis, we propose plasma transfusion for EXTEM CT > 78.5 s, fibrinogen for angle <64.5°, platelet transfusion for CA10 < 40.5 mm, and antifibrinolytics for CLI60 < 74%.

Keywords

Massive transfusion; TEG; ROTEM; Coagulopathy; Resuscitation

Introduction

Uncontrolled hemorrhage is the leading cause of preventable death following trauma, accounting for up to 40% of deaths.¹ An endogenous trauma-induced coagulopathy accounts for most of these hemorrhagic deaths and is a multifocal process attributed to reduced thrombin generation, fibrinogen depletion, platelet dysfunction, and systemic hyperfibrinolysis.^{2–5}

Half of deaths from acute blood loss occur within the first 2 h after injury, and hemorrhage accounts for the vast majority of deaths within the first 24 h.⁶ Reliable objective means of early recognition and targeted transfusion interventions are the key to successful management of life-threatening trauma-induced coagulopathy.

Massive transfusion protocols (MTPs) offer a proven benefit in resuscitation of patients in hemorrhagic shock. Much effort has been directed to identifying the ideal ratio of blood products in resuscitation strategies.^{6,7} Traditional interventions have been guided by conventional coagulation assays (CCAs), such as international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen level, and platelet count. Our group has shown that a goal-directed, thrombelastography (TEG)-guided MTP improves survival as compared with MTP guided by CCAs. Furthermore, these results were achieved with the transfusion of less plasma and platelets during the early phases of resuscitation.⁸

We have defined optimal transfusion thresholds using TEG for patients at risk for massive transfusion (MT) as an activated clotting time (ACT) < 128 s, angle <65°, a maximum amplitude (MA) < 55 mm, and lysis 30 min after achieving MA (LY30) >5%.⁷ However, these thresholds are not directly translatable for use in rotational thromboelastometry (ROTEM), another commonly used viscoelastic assay because of differences in instrumentation and reagents.⁹ Therefore, we hypothesize that we can identify ROTEM measurements that indicate the need for MT in injured patients using ROTEM and thresholds for specific blood component therapy in these high-risk patients.

Methods

Study design

This is an analysis of prospectively collected data from our Trauma Activation Protocol registry, which includes consecutive adult (age 18 y old) patients who met criteria for the highest level of trauma team activation at the Denver Health Medical Center, an American College of Surgeons-verified and state-certified level 1 trauma center affiliated with the University of Colorado Denver and were at risk for MT. Exclusion criteria were unsalvageable injuries (defined by patients in asystole at emergency department arrival), isolated gunshot wounds to the head, pregnancy, documented chronic liver disease, or a known coagulation disorder.

The studies contributing to this database were approved by the Colorado Multiple Institution Review Board and performed under a waiver of consent. Trained research professional assistants performed all viscoelastic assays within 1-h post-injury. Clinicians were blinded to these research data. TEGs were ordered at the discretion of the care team and processed in the hospital clinical laboratory to guide resuscitation in injured patients.

The transfusion of products other than red blood cells during this period was guided by rapid thrombelastography (rTEG) criteria, as previously described.^{8,10} The primary endpoint of this study was MT, defined as >10 units of red blood cells or death in first 6 h from injury based on findings previously published by our group.¹¹

TEG is used at our institution and more commonly in the United States, while ROTEM is used widely in European centers.⁹ Although the technologies and reagents are somewhat similar, the measurements reported are not the same and cannot be generalized from one instrument to the other.¹²

Rotational thromboelastometry

ROTEM was performed on whole blood collected in vacuum tubes with citrate added to prevent clotting before the analysis. The specific ROTEM assays used were EXTEM (activated with tissue factor), FIBTEM (activated similar to EXTEM but with cytochalasin D to inhibit the contribution of platelets to the clot),¹³ and APTEM, which is a modified EXTEM, in which aprotinin inhibits plasmin *in vitro* if systemic fibrinolysis is present.¹⁴ ROTEM tests yield the following variables that were used to assess the dynamic process of clot formation and breakdown in this study: time to clot initiation (clotting time [CT, s]), dynamics of clot formation (angle [degrees] and clot formation time [CFT, s]), clot strength (maximum clot formation [MCF, mm] and clot amplitude after 10 min [CA10, mm]), and fibrinolysis (clot lysis index at 30 min [CLI30, %] and 60 min after CT [CLI60, %]).¹⁴ Prolonged clot initiation is an indication for plasma and reflected by EXTEM CT. Abnormal dynamics of clot formation is an indication for fibrinogen products and reflected by EXTEM CFT, EXTEM angle, FIBTEM angle, FIBTEM MCF, and FIBTEM CA10. Low clot strength is an indication for platelets and reflected by EXTEM CA10 and EXTEM MCF. Increased fibrinolysis is an indication for antifibrinolytics and reflected by EXTEM CLI30 and CLI60. Clinicians based blood product transfusions on clinical rapid TEG and were blinded to ROTEM values.

Rapid thrombelastography

Thrombelastography (TEG-5000 analyzer; Haemonetics Corp, Stoughton, MA) was performed on whole blood collected in vacuum tubes with citrate added to prevent clotting before analysis. This assay incorporates tissue factor to the whole blood sample immediately before test initiation to expedite results, also known as rTEG. rTEG yields the following variables: ACT (the time to beginning of clot formation, s), angle (α ; rate of clot strength increase, degrees), MA (maximal clot strength achieved, millimeters), and percent clot LY30. Thresholds for determination of predictive capacity have previously been defined as an ACT < 128 s, angle <65°, a MA < 55 mm, and LY30 >5%.⁷

Conventional coagulation assays

Samples were collected during trauma activations upon arrival to the emergency department in tubes containing 3.2% citrate and 4 mL of heparin (19 units/mL). Values for CCAs (INR and aPTT) were determined by the clinical laboratory at Denver Health Medical Center by a standard protocol. Abnormal values for CCAs were set as INR>1.3 and aPTT>34 as previously published.^{15–17}

Statistical analysis

GraphPad Prism version 7.0a (GraphPad Software, Inc; La Jolla, CA) and Excel version 12.2.5 (Microsoft Corporation; Redmond, WA) were used for statistical analysis. For nonnormally distributed variables, data were expressed as median and interquartile range using a two-tailed Mann–Whitney test. Area under the receiver operating characteristic (AUROC) curve analysis was performed for each ROTEM measurement to assess its predictive performance for MT. For each of the ROTEM measurements, we selected the thresholds with the strongest differentiation of the outcome (MT) as identified by the maximum Youden Index (J = sensitivity + specificity – 1). The maximum Youden's Index is the value closest to one.¹⁸ The sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) correspondent to the chosen cutoff were determined for the ROTEM indices for clot initiation, dynamics of clot formation, clot strength, and fibrinolysis. The sensitivity, specificity, PPVs, and NPVs were also determined for rapid TEG variables, INR, and aPTT.

Results

There were 222 nonconsecutive patients with ROTEM completed. All patients had EXTEM performed, while due to technical difficulties, only 212 patients also had FIBTEM performed and 128 APTEM. Table 1 illustrates the demographic characteristics of patients who required MT (17%) and those who did not. Patients who had an MT were more severely injured, had signs of more pronounced shock, and more abnormal ROTEM indices compared to those who did not require an MT (Table 2).

The AUROC for ROTEM measurements are shown in Table 3. Of all ROTEM variables that measured dynamics of clot formation, EXTEM angle was the best predictor of MT (AUROC = $0.865\ 95\%$ confidence interval [CI] 0.7961-0.934, P < 0.0001). CA10 was the best predictor of MT of the ROTEM indices measuring clot strength (AUROC = 0.8580, 95% CI

0.7884–0.9275, P < 0.0001). CLI60 was the best predictor of MT for ROTEM parameters assessing fibrinolysis (AUROC = 0.6788, 95% CI 0.5565–0.8010, P = 0.0007).

The ROTEM predicted thresholds for the ROTEM-guided MT based on the Youden Index are shown in Table 4. CLI60 of <74% had a much greater specificity and PPV while sensitivity and NPV were better with CT and MCF EXTEM/APTEM. The predictive capacity of rapid TEG and CCA (INR and aPTT) are shown in Table 5. The predictive capacity is similar between both ROTEM and TEG for clot initiation, dynamics of clot formation, and clot strength. However, the PPV of LY30 is better than CLI60 but still remains fairly low at 58%.

Discussion

In this study, we determined the degree of discrimination offered by ROTEM output values with respect to the need for MT. Based on the ROTEM parameters evaluated, thresholds were identified that could be used to guide hemostatic resuscitation for injured patients who require MT. We would therefore propose plasma transfusion for EXTEM CT > 78.5 s, fibrinogen products for EXTEM angle <64.5°, platelet transfusion for EXTEM CA10 < 40.5 mm, and antifibrinolytics for EXTEM CLI60 < 74% (Figure).

The purpose of goal-directed therapy is to optimize a normal hemostatic competence until surgical hemostasis is obtained, which has been shown to improve mortality.¹⁹ Our primary aim was to determine optimal thresholds for blood component therapy in patients at risk for MT. Viscoelastic assays illustrate multiple, different hemostatic indices but not all are used clinically. Prolonged clot initiation is an indication for plasma, abnormal dynamics of clot formation is a signifier for fibrinogen products, low clot strength is an indication for platelets, and increased fibrinolysis is an implication for antifibrinolytics.⁸ Therefore, we used ROTEM measurements that focus on these aspects of clot formation and breakdown to develop a proposal for ROTEM-guided resuscitation. Studies have correlated EXTEM CT with coagulation factor activity; EXTEM Angle, EXTEM CFT, FIBTEM CA10, FIBTEM Angle, and FIBTEM MCF with fibrinogen level and function; EXTEM CL10, and EXTEM MCF with platelet-fibrinogen interactions; EXTEM CL130, EXTEM CL160, and EXTEM CT > APTEM CT or EXTEM MCF < APTEM MCF as evidence for fibrinolysis.^{14,20–24}

In this study, we found that the ROTEM measurements that yielded the greatest AUROC curves were EXTEM angle (AUROC = 0.865) and EXTEM CA10 (AUROC = 0.858). This would correspond to deficiencies in dynamics of clot formation and clot strength, respectively. EXTEM CT yielded a weaker but fair AUROC curve of 0.7116. EXTEM CLI60 yielded a suboptimal AUROC curve of $0.6788.^{25}$ Extent of fibrinolysis, measured by TEG, and early mortality exhibit a quadratic relationship.²⁶ This observation may be responsible for the diminished ability of viscoelastic measurement of fibrinolysis to predict MT. Furthermore, because of the suboptimal AUROC for CLI60, the predictive performance was compared to EXTEM CT > APTEM CT and EXTEM MCF < APTEM MCF. The addition of APTEM permits the quantitative assessment of fibrinolysis and thus an estimate of therapeutic benefit from response to an anti-fibrinolytic agent, specifically, tranexamic acid. An improvement in CT or MCF on APTEM compared to EXTEM unmasks a

hyperfibrinolytic state.^{27,28} CLI60 of <74% had a much greater specificity and PPV while sensitivity and NPV were better with CT and MCF EXTEM/APTEM comparison (Table 4). This indicates fibrinolysis is driven by mechanisms beyond tissue plasminogen activator; for example, poor clot structure that may not be inhibited by tranexamic acid. EXTEM CT > APTEM CT and EXTEM MCF < APTEM MCF are determined more rapidly than EXTEM CLI60 based on the time for results. However, if the amount of blood obtained is limited, EXTEM CLI60 should be used to determine fibrinolysis as all aspects of proposed ROTEM thresholds can be determined from the EXTEM test alone.

The test with the greatest PPV was the EXTEM angle (Table 4). None of the parameters evaluated had a PPV that was greater than 53%. However, one could argue that there is greater harm in not identifying the need for MT than overestimating a need for MT. Furthermore, the value of ROTEM and TEG is in identifying which blood component is required.

A comparison of predictive capacity can be made between ROTEM, TEG, and CCAs (Tables 4 and 5). Rapid TEG had a similar PPV as EXTEM with regard to clot initiation (ACT), dynamics of clot formation (angle), and clot strength (MA). The PPV was better with rTEG LY30 compared to EXTEM CLI60 but was still only 58%. From this comparison of viscoelastic assays, it remains difficult to determine which, if either, assay is better. Furthermore, this study was not specifically designed to compare ROTEM *versus* TEG because it is not the same patient population as the previous study,⁷ so these comparisons must be taken cautiously. We have previously shown that a TEG-guided MTP improves survival as compared with those guided by CCA. These results were achieved with the use of less plasma and platelet transfusions during the early phases of resuscitation.⁸ Based on this, we would argue that either viscoelastic assay, ROTEM, or TEG, should be used instead of CCAs to guide resuscitation in injured patients. This is further illustrated by the fact that the PPV for aPTT and INR are no greater than 46.2% for either test.

There are several limitations to this study. These data reflect a single time point of a dynamic process and do not take into account the temporal changes of the coagulation process throughout the acute phase of resuscitation. Transfusion of blood products was based on goal-directed resuscitation based on TEG. These ROTEM values are then predictive of a MT that is already guided by viscoelastic testing. Because the measurements are analyzed for MT and not for individual components, they should be used cautiously. However, at this time, these measurements provide the best guidelines for specific component therapy. Finally, the sample size limits the ability to analyze subgroups.

In conclusion, these thresholds provide an important point in the evolution of viscoelasticbased resuscitation strategies. They may act as a guide to further evaluate ideal thresholds for the transfusion of specific blood products These observations should serve as a building block for a multicenter trial that should validate or refine these recommendations. Furthermore, refinement of the ROTEM-based resuscitation strategies should include optimizing the respective clinical interventions for each given ROTEM output.

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Fig 1.

Proposed resuscitation thresholds based on ROTEM parameters implicating need for MT. A schematic representation of the proposed thresholds in a ROTEM-guided MTP for injured patients. Cryo = cryoprecipitate; PLTs = platelets; TXA = tranexamic acid. (Color version of figure is available online.)

Demographic characteristics of patients.

Variable	Massive transfusion	No massive transfusion	P value
Age (y)	36 (27–48)	36 (26–49)	0.9749
NISS	46.5 (38–57)	17 (4–28)	< 0.0001
ED SBP (mmHg)	60 (0-100)	112 (92–138)	< 0.0001
ED heart rate (BPM)	95 (0–128)	100.5 (85–116)	0.2381
ED GCS	3 (3–13)	15 (9–15)	< 0.0001
ED temp (celsius)	36.3 (35.65–36.95)	36.6 (36.3–36.8)	0.3059
Calcium (mg/dL)	7.65 (6.8-8.65)	8 (7.5–8.5)	0.201
Lactate (mg/dL)	8.1 (4.7–14.55)	3.35 (2.1–5.0)	< 0.0001
Base deficit	14 (8.5–20.5)	6.5 (3–9.25)	< 0.0001
Hgb (g/dL)	11.6 (9.7–13.95)	13.9 (12.6–15.3)	0.0001
Platelet count (1000/mL)	176.5 (112–244)	258 (213–311)	< 0.0001
INR	1.72 (1.33–2.07)	1.1 (1.04–1.23)	< 0.0001
PTT (s)	43.4 (33.7-80.5)	27.4 (24.1–31.2)	< 0.0001
Fibrinogen (mg/dL)	122 (68.75–237.5)	208 (170-265)	0.0243
D-Dimer (ng/mL)	19.86 (8.82–20.01)	2.145 (0.405-7.615)	0.0018

Data are presented as median and interquartile range.

NISS = new injury severity score; ED = emergency department; SBP = systolic blood pressure; Hgb = hemoglobin; PTT = partial thromboplastin time; GCS = glasgow coma scale; BPM = beats per minute.

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ROTEM indices by massive transfusion status.

	Massive transfusion	No massive transfusion	P value
EXTEM			
CT (s)	87 (67.25–118.3)	64 (56–75)	< 0.0001
CFT (s)	160 (107.8–281.5)	106 (87–131.8)	< 0.0001
Angle (degrees)	54 (40.5–64)	69 (65–72)	< 0.0001
CA10 (mm)	30.5 (21.5–42)	50 (44–56)	< 0.0001
MCF (mm)	42 (24.75–52.75)	59 (54–64)	< 0.0001
CLI30 (%)	100 (22.75–100)	100 (100–100)	0.0003
CLI60 (%)	47 (1.25–96.75)	94 (91.5–97)	0.0006
FIBTEM			
Angle (degrees)	55 (0-68)	66 (60–71.25)	0.0211
CA10 (mm)	5 (3–9)	12 (9–15)	< 0.0001
MCF (mm)	5 (3–9)	13 (10–16)	< 0.0001
APTEM			
CT (s)	86.5 (63.75–126)	61.5 (51.75–149)	< 0.0001
MCF (mm)	47 (39–55.5)	60 (54–63.25)	< 0.0001

Data are presented as median and interquartile range.

Area under the receiver operating characteristic curve for all ROTEM measurements.

Clot initiation	AUROC	95% confidence interval	P value
EXTEM CT	0.7116	0.6003-0.8229	< 0.0001
Dynamics of clot formation			
EXTEM CFT	0.7315	0.6173-0.8458	< 0.0001
EXTEM angle	0.8650	0.7961-0.9340	< 0.0001
FIBTEM angle	0.7084	0.4987-0.9181	0.0225
FIBTEM CA10	0.8492	0.7773-0.9212	< 0.0001
FIBTEM MCF	0.8515	0.7803-0.9226	< 0.0001
Clot strength			
EXTEM CA10	0.8580	0.7884-0.9275	< 0.0001
EXTEM MCF	0.8499	0.7775-0.9224	< 0.0001
Fibrinolysis			
EXTEM CLI30	0.6116	0.4987-0.7245	0.0343
EXTEM CLI60	0.6788	0.5565-0.8010	0.0007

Table illustrates the AUROC with 95% confidence intervals of multiple ROTEM parameters for each aspect of clot formation and breakdown (clot initiation, dynamics of clot formation, clot strength, and fibrinolysis or clot breakdown).

Predictive performance of ROTEM variables for MT.

ROTEM variables	Sensitivity	Specificity	PPV	NPV
EXTEM CT > 78.5 s	58.33%	81.62%	42.98%	57.74%
EXTEM angle <64.5°	80.56%	77.72%	52.02%	48.62%
EXTEM CA10 < 40.5 mm	77.22%	89.19%	46.24%	54.38%
EXTEM CLI60 < 74%	52.78%	96.76%	37.68%	63.01%
EXTEM CT > APTEM CT	65.00%	33.33%	20.00%	80.95%
EXTEM MCF < APTEM MCF	76.90%	58.82%	32.25%	90.90%

Predictive performance of rapid TEG variables for MT.

rTEG variables	Sensitivity	Specificity	PPV	NPV
ACT >128 s	58.33%	74.32%	30.88%	90.07%
Angle <65°	75.00%	81.97%	49.09%	94.34%
MA <55 mm	72.22%	83.61%	46.43%	93.87%
LY30 > 5%	41.67%	93.99%	58%	89.12%
INR >1.3	66.67%	88.20%	46.15%	94.58%
aPTT >34 s	69.23%	86.36%	42.86%	93.83%