Rapid thrombelastography thresholds for goal-directed resuscitation of patients at risk for massive transfusion

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BACKGROUND: Uncontrolled hemorrhage is a leading cause of mortality after trauma accounting for up to 40% of deaths. Massive transfusion protocols offer a proven benefit in resuscitation of these patients. Recently, the superiority of thrombelastography (TEG)-guided resuscitation over strategies guided by conventional clotting assays has been established. We seek to determine optimal thresholds for rapid (r)-TEG driven resuscitation.

METHODS: The r-TEG data were reviewed for 190 patients presenting to our level 1 trauma center from 2010 to 2015. Criteria for inclusion were highest level trauma activation in patients 18 years or older with hypotension presumed due to acute blood loss. Exclusion criteria included isolated gunshot wound to the head, pregnancy, and chronic liver disease. Receiver operating characteristic (ROC) analysis was performed to test the predictive performance of r-TEG for massive transfusion requirement defined by need for (1) >10 units of RBCs total or death in the first 6 hours or (2) >4 units of RBCs in any hour within the first 6 hours. Cutpoint analysis was then performed to determine optimal thresholds for TEG-based resuscitation.

RESULTS: The ROC analysis of r-TEG yielded areas under the curve (AUC) greater than 70% for all outputs with respect to both transfusion thresholds considered, with exception of activated clotting time and lysis at 30 minutes for greater than 4 U RBC in any hour in the first 6 hours. Optimal cutpoint analysis of the resultant ROC curves was performed and for each value, the most sensitive cutpoint was identified, respectively activated clotting time of 128 seconds or longer, angle (α) of 65 degrees or less, maximum amplitude of 55 mm or less, and lysis at 30 minutes of 5% or greater.

CONCLUSIONS: Through ROC analysis of prospective TEG data, we have identified optimal thresholds to guide hemostatic resuscitation. These thresholds should be validated in a prospective multicenter trial. (*J Trauma Acute Care Surg.* 2017;82: 114–119.

LEVEL OF EVIDENCE: Therapeutic study, level V.

KEY WORDS: Injury; shock; coagulopathy; resuscitation; transfusion.

Uncontrolled hemorrhage is the leading cause of preventable trauma-related death accounting for up to 40% of deaths in severely injured hospitalized patients.[1] The underlying disturbances of the normal clotting system, broadly defined as trauma-induced coagulopathy (TIC), account for the majority of these hemorrhagic deaths.[2]

Survival curves in this population indicate that half of the deaths from exsanguination occur in the first 2 hours from injury, and furthermore, that hemorrhage accounts for the vast majority of deaths in the first 24 hours.[3] Specific injury patterns and other preinjury factors are often not evident at the time of initial presentation. Therefore, reliable objective means of early recognition and in turn, purposeful interventions are the keys to successfully managing these life-threatening coagulopathies.

Massive transfusion protocols (MTPs) offer a long-proven benefit in resuscitation of patients in hemorrhagic shock. With this concept established, much time and effort has been directed to identify the ideal ratio of products in resuscitation strategy and traditional intervention has been dictated by conventional coagulation assays (CCA), that is, international normalized ratio, partial thromboplastin time, fibrinogen, and platelet count.

A 2013 prospective study by Johansson et al.[4] attributed lower 28-day mortality (12%) and proportion of those deaths resulting from exsanguination (14%) to thrombelastography (TEG)-guided resuscitation. Our group has recently confirmed these results in a randomized control trial, showing that a goal-directed, TEG-guided MTP improves survival as compared with MTP guided by CCA based on its individualized, point-of-care, precision hemostatic approach. Furthermore, these results were achieved with less plasma and platelet transfusions during the early phases of resuscitation.[5] A crucial next step in optimizing this strategy is to establish a system of thresholds based on TEG outputs to guide intervention.

Previous recommendations have been based on healthy individual criteria or associations with transfusion requirements (Johansson et al.,[4] Holcomb et al.,[6] Tapia et al.,[7] and Schochl et al.[8,9]). In this study, we propose optimal thresholds for rapid

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(r)-TEG driven resuscitation based on prospective data collected in severely injured patients at high risk for TIC.

PATIENTS AND METHODS

Our Denver Trauma Activation Protocol Database includes all trauma activation adult (>18 years of age) patients who sustained blunt or penetrating injuries, and had a citrated r-TEG performed by one of our onsite professional research assistants with blood collected in the field or at ED presentation, admitted from September 26, 2010, to June 30, 2015, to our level 1 trauma center. Clinicians were blinded to these research data, however, in most cases with evidence of bleeding, TEGs were also ordered by the care team and processed in the hospital clinical lab to guide resuscitation practice. The current study reports the results of the TEGs performed in our research laboratory, which are obtained for all patients enrolled in the database with an IRB-approved waiver of consent. The Denver Health Medical Center is an American College of Surgeons verified, state-designated level 1 trauma center. Criteria for inclusion were highest level trauma activation in patients 18 years or older with hypotension (defined as systolic blood pressure [SBP], ≤70 mm Hg or SBP ≤ 90 mm Hg plus heart rate, >108 bpm) presumed due to acute blood loss. 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 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.

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 r-TEG. Rapid TEG yields the following variables: activated clotting time (ACT) (the time to beginning of clot formation, seconds), angle (α; rate of clot strength increase, degrees), maximum amplitude (MA) (maximal clot strength achieved, millimeters), and percent clot lysis 30 minutes after MA is achieved (LY30). Studies have correlated ACT with coagulation factor activity and thrombin generation, angle with fibrinogen concentration and function, MA with platelet-fibrinogen interactions, and LY30 with fibrinolysis.[10]

The transfusion of products other than RBCs during this period was guided by r-TEG criteria proposed by the TEG manufacturers and widely accepted by blood banks as follows: ACT, greater than 110 seconds treated with plasma; angle, less than 66 degrees treated with cryoprecipitate; MA, less than 54 mm treated with platelets; and elevated LY30, greater than 3% treated with tranexamic acid.[11–13] The primary outcome was massive transfusion, defined as one of the following: (1) more than 4 units of RBCs in any 60-minute period in the first 6 hours from injury based on the threshold set forth by the PROMMTT. trial;[14] (2) greater than 10 units of RBCs or death in first 6 hours from injury based on findings previously published by our group.[15] Additional objective outcomes included mortality in first 24 hours, intensive care unit (ICU)-free days less than 14 and ventilator-free days less than 21.

TABLE 1. Patient Characteristics

	All Patients (n = 190)		No Massive Transfusion (n = 153)		Massive Transfusion (MTP) (n = 37)	
	N	Percent	N	Percent	N	Percent
Shock (SBP ≤ 90 mm Hg)	54	28.4%	30	32.1%	24	63.2%
Profound shock (SBP ≤ 70 mm Hg)	25	13.2%	11	7.1%	14	36.8%
Lactate > 5 mg/dL	35	35.7%	21	26.9%	14	63.6%
Base deficit > 8 mEq/L	53	43.1%	32	32.3%	21	80.8%
Traumatic brain injury	24	12.6%	11	7.1%	13	34.2%
ICU-free days < 14	42	22.1%	13	8.5%	29	78.4%
Ventilator-free days <21	51	26.8%	20	13.1%	31	83.8%
Mortality	25	13.2%	6	3.9%	19	51.4%
Massive transfusion rate	37	19.5%				
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age (n = 190), y	34	26–47	34	26–47	37	27–48
Time to ED (n = 190), min	25	20.3–32	25	21–31.5	24	20–39
ISS (n = 133)	22	10–34	14	9–29	38	29–43
New ISS (n = 133)	27	14–43	17	9–29	50	38–60.8
GCS (n = 190)	14.5	5.25–15	15	11.5–15	3	3–8
Temperature (n = 151), °C	36.45	36.3–36.8	36.55	36.3–36.8	36.3	35.7–36.9
Admission calcium (n = 168), mg/dL	8	7.6–8.5	8.1	7.7–8.5	7.7	7.2–8.4
Admission hemoglobin (n = 185), g/dL	13.9	12.5–15.3	14.1	13–15.4	12.3	9.9–14.0
Admission platelets (n = 184), 1,000/mL	254.5	204–310	263	213–317	176.5	116.5–276
Admission INR (n = 180)	1.1	1.04–1.3	1.1	1–1.2	1.55	1.3–2.08
Admission PTT (n = 180) units	27.75	24.7–33.1	26.85	23.8–29.8	42.9	32.6–74.0

GCS, Glasgow Coma Score; INR, international normalized ratio; PTT, partial thromboplastin time.

TABLE 2. Rapid Citrated TEG

Output	Median	Interquartile Range
ACT, s	121	113–136
Angle (α), degrees	70	64.4–74.1
MA, mm	61.5	54.5–65.5
LY30, %	1.9	1.0–3.6

Covariates: Shock was defined as admission SBP of 90 mm Hg or less and profound shock as SBP of 70 mm Hg or less. Admission lactate greater than 5 mg/dL and admission base deficit greater than 8 mEq/L were used as determinants of critically impaired tissue perfusion. Traumatic brain injury was defined as Glasgow Coma Scale score less than 8 and head Abbreviated Injury Scale score greater than 2.

Statistical Analysis

Receiver operating characteristic (ROC) curve analyses were performed to test the predictive performance of citrated r-TEG values ACT, angle, MA, and LY30 with respect to the stated outcomes. For each of these parameters, we selected the thresholds with the strongest differentiation of the outcome (i.e., massive transfusion) via optimal ROC curve cutpoint analysis to identify ideal thresholds for TEG-guided resuscitation. Three methods of cutpoint analysis were used: (1) maximum Youden's Index (J); (2) shortest distance to (0,1); and (3) sensitivity, specificity equality. We then calculated the mean of these three values to determine the final threshold for each r-TEG output.

Youden's Index (J) is calculated as: J = Sensitivity + Specificity − 1, with a value of 1 representing a perfect test with no false positives or false negatives. The maximum Youden's Index is the point on the ROC curve where resultant J value is closest to 1.[16]

Shortest distance to (0,1) is a similar concept that aims to identify the optimal cutpoint by isolating the point on the ROC curve closest to the upper left-hand corner. Depending on shape of the curve, this value will either prioritize sensitivity or specificity indiscriminately.[17]

Sensitivity, specificity equality identifies the optimal cutpoint where these two values are nearest to equilibrium. In a perfectly symmetric curve, this point would also equal the shortest distance to (0,1).[18]

RESULTS

Overall, 190 patients met inclusion criteria (Table 1), of whom 81% were men, and 59% sustained blunt trauma. Age ranged from 18 to 93 years (median, 34; interquartile range [IQR], 26–47). Median injury severity score (ISS) was 22 (IQR, 10–34) and median new ISS (NISS) was 27 (IQR, 14–43). Median time from injury to ED arrival was 25 (IQR, 20.3–32) minutes. Overall, 28.4% of these patients were in shock and 13.2% were in profound shock, whereas 12.6% sustained traumatic brain injury. With respect to ICU course, 22.1% had less than 14 ICU-free days and 26.8% had less than 21 ventilator-free days. The mortality rate was 13.2% (Table 1).

The r-TEG outputs are depicted in Table 2 and ROC analysis assessing the predictive value of the r-TEG variables for massive transfusion in Table 3. For transfusion threshold greater than 4 U RBC in any hour in the first 6 hours postinjury, the areas under the ROC curve (AUC) were 0.69 seconds for ACT, 0.84 for angle, 0.83 for MA, and 0.69 for LY30. Activated

TABLE 3. ROC AUC With 95% Confidence Intervals and Optimal Cutpoints

MTP Defined		ACT	LY30	Angle	MA
>10 U RBC or death in 6 h (n = 30)	AUC (95% CI)	0.72 (0.61–0.82)	0.72 (0.59–0.84)	0.80 (0.70–0.90)	0.81 (0.72–0.90)
>4 U RBC/h in the first 6 h (n = 30)	AUC (95% CI)	0.68 (0.58–0.80)	0.69 (0.56–0.81)	0.84 (0.76–0.91)	0.83 (0.75–0.91)
Death within 24 h postinjury	AUC (95% CI)	0.77 (0.65–0.89)	0.70 (0.51–0.88)	0.73 (0.58–0.89)	0.71 (0.56–0.86)
<14 ICU-free days	AUC (95% CI)	0.67 (0.58–0.76)	0.60 (0.48–0.72)	0.74 (0.66–0.83)	0.77 (0.69–0.85)
<21 ventilator-free days	AUC (95% CI)	0.64 (0.54–0.74)	0.54 (0.42–0.66)	0.73 (0.64–0.82)	0.75 (0.67–0.84)
Optimal cutpoints	**Method**	**ACT, s**	**LY30, %**	**Angle, degrees**	**MA, mm**
>10 U RBC or DEATH in 6 h	Youden index (J)	128	7.7	62.3	54
	Distance to (0,1)	128	3.4	62.3	55.5
	Sen = Spec	128	2.8	66.9	57.5
>4 U RBC/h in the first 6 hours	Youden index (J)	139	7.7	62.3	54
	Distance to (0,1)	128	2.6	65.0	55.5
	Sen = Spec	128	2.7	66.5	57.5
Death within 24 h postinjury	Youden index (J)	128	9.5	65.3	47.5
	Distance to (0,1)	136	3.8	65.3	55.5
	Sen = Spec	136	2.7	66.5	60
<14 ICU-free days	Youden index (J)	128	3.8	71	55.5
	Distance to (0,1)	128	2.8	66.9	55.5
	Sen = Spec	128	2.2	68.6	59.5
<21 ventilator-free days	Youden index (J)	144	7.7	65	55.5
	Distance to (0,1)	128	3.8	65.3	55.5
	Sen = Spec	128	2.1	68.8	60

CI, confidence interval; Sen, sensitivity; Spec, specificity.

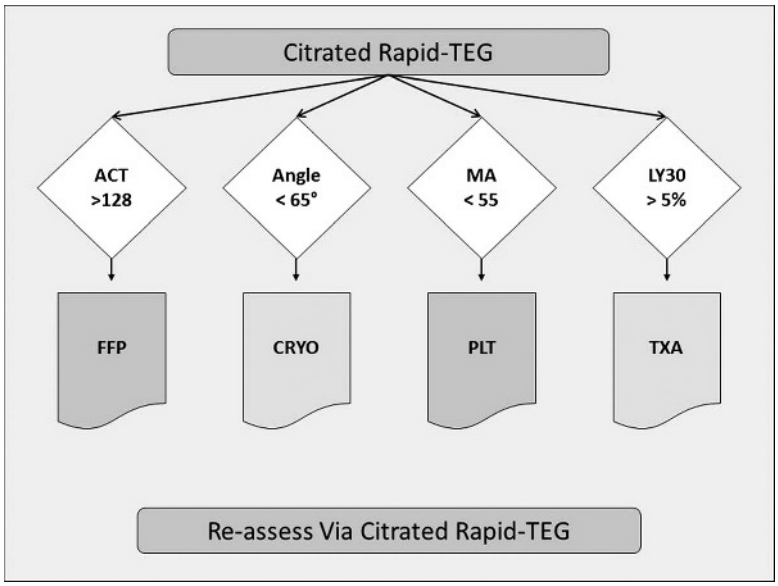

Figure 1. TEG-guided resuscitation thresholds—a schematic representation of the appropriate use of the thresholds in a TEG-guided MTP.

clotting time and LY30 were the only AUCs in this analysis slightly below the 0.70 threshold, suggesting only fair predictive capacity. For massive transfusion defined as need for greater than 10 U or death within 6 hours postinjury, the AUCs were 0.72 seconds for ACT, 0.80 for angle, 0.81 for MA, and 0.72 for LY30 (Table 3).

Cutpoint analysis on each of these curves yielded a range of optimum thresholds for TEG parameters for the massive transfusion outcome. As shown in Table 4, most of the cutoffs for the TEG parameters were consistent across the optimality criteria (Youden Index, Sen = spec, distance [0,1]), with the exception of LY30, for which we noted a difference between the Youden Index and the other two optimality criteria. The TEG cutoffs for massive transfusion were also remarkably consistent with the cutoffs determined for the three objective outcomes (death, ICU-free, and ventilator-free days).

DISCUSSION

In this study, we determined the degree of discrimination offered by r-TEG output values ACT, angle, MA, and LY30 with respect to massive transfusion need. Based on these data, the optimal thresholds for TEG-guided resuscitation are as follows: ACT, 128 seconds or longer; angle, 65 degrees or less; MA, 55 mm or less; and LY30, 5% or greater (Fig. 1) with predictive accuracy of these values for massive transfusion need depicted in Table 5. We considered two definitions of massive transfusion based on the literature. The greater than 10 U RBC in the first 6 hours threshold originated from work of our group first published in 2008 that challenged the historical definition greater than 10 U RBC in first 24 hours. This modification was based on the fact that 80% of RBC transfusions were completed in the first 6 hours and that transfusion need in this 6-hour window was among the most significant determinants of mortality. The greater than 4 U RBC given in any hour in the first six hours threshold was suggested by the multicenter, prospective PROMMT trial in the recent publication by Moren et al.[14] demonstrating a significant mortality difference in patients who receive greater than 4 U per any hour within the first 6 hours.

In our study, we found that AUCs were consistent for each r-TEG value considered across the range of transfusion requirements as were the thresholds determined from optimal cut point analysis of the ROC curves. Of the r-TEG outputs considered, angle and MA consistently yielded the strongest ROC signals for all definitions of massive transfusion considered. AUC was 80% or greater for both of these outputs with respect to both transfusion requirements representing good to excellent discrimination. It is logical that these values would provide crucial

TABLE 4. Mean Optimal TEG Cutpoint Values for Each of the Outcomes

Mean Cutpoint	ACT, s	LY30, %	Angle, Degrees	MA, mm
>10 U RBC or DEATH in 6 h	128 (0.72)	5 (0.72)	64 (0.80)	55 (0.81)
>4 U RBC/hour within 6 h postinjury	139 (0.69)	4 (0.69)	65 (0.84)	55 (0.83)
Death within 24 h postinjury	133 (0.68)	5 (0.72)	66 (.071)	54 (0.64)
<14 ICU-free days	128 (0.61)	3 (0.64)	69 (0.68)	57 (0.69)
<21 Ventilator-free days	133 (0.61)	5 (0.63)	66 (0.66)	57 (0.69)

TABLE 5. Predictive Accuracy (%) of TEG Output Mean Thresholds for Massive Transfusion

TEG Output	Sensitivity	Specificity	Predictive Value of a Positive	Predictive Value of a Negative
ACT > 128 s	64	67	66	65
LY30 > 5%	54	91	86	66
Angle < 65 degrees	70	81	79	73
MA < 55 mm	70	82	79	73

insight to transfusion need as they serve as surrogates for clot strength. It is also noteworthy that angle provides a comparably strong signal to that yielded by MA for eventual transfusion need because the angle value is available significantly earlier in the real-time output of the r-TEG tracing allowing for earlier clinical intervention.

Activated clotting time and LY30 yielded weaker, but still significant ROC signals of AUC 0.72 for both with respect to the need for greater than 10 U RBC or death in the first 6 hours representing good discrimination, but fell just below this threshold for ACT and LY30 with respect to the need for greater than 4 U RBC in any hour in the first six hours (0.69 for both). Receiver operating characteristic analysis proved a suboptimal method for establishing cutpoints for these two TEG outputs. This is likely explained by the more complex and nonlinear relationship these outputs have with the outcomes considered. For example, our group has previously demonstrated the quadratic relationship between LY30 and early mortality.[2]

Potential thresholds were considered using the three most commonly used methods of cutpoint analysis including the maximum Youden's index, shortest distance to (0,1) and sensitivity, specificity equality. The range of optimal cut points yielded by these methods (ACT of 128–139 seconds, angle of 62.3–66.9°, MA of 54–57.5 mm, and LY30 of 2.6–7.7%) was consistent with our group's prior clinical experience.

The next objective was to move from a recommended range to distinct thresholds. We determined that our strongest recommendations could be made from the strongest ROC curves regardless of which definition of massive transfusion generated the curve. Thus, we elected to use the ROC curve yielded greater than 10 U RBC or death in the first 6 hours to derive our recommendations for ACT and LY30 based on the stronger AUCs (0.72 vs. 0.68 and 0.72 vs. 0.68, respectively). And conversely, we used the ROC curves produced by the greater than 4 U RBC in any hour in the first six to determine the optimal threshold for angle and MA again based on the relative strength of these curves (0.84 vs. 0.80 and 0.83 vs. 0.81, respectively).

In comparison, Holcomb et al.'s[6] 2012 study of consecutive trauma admissions, which concluded that r-TEG could replace CCA, used both correlation and multivariate regression analysis to validate predetermined cutoffs for TEG values based on associations with transfusion requirements. For instance, they assessed an ACT greater than 128 seconds, the same cutpoint arrived at through our analysis because of its historical association with international normalized ratio greater than 1.5. In their cohort, an ACT greater than 128 seconds was associated with an odds ratio of 1.7 for prediction of early blood requirement and an odds ratio of 1.95 for prediction of massive transfusion. Holcomb and colleagues also used the same threshold recommendation for MA (<55) but differed with respect to angle (<56 vs. ≤ 65 in our analysis) and LY30 (>3% vs. ≥ 5% in our analysis). Other key differences between these studies include: (1) We used massive transfusion as our primary outcome rather than need for early transfusion. (2) By selecting for patients with hypotension presumed due to acute blood loss, we assessed a cohort with more severe injuries as evidenced by increased ISS (median, 22; IQR, 10–34 vs. IQR, 17; IQR, 9–26), increased base deficit greater than 8 mEq/L (43% > 8 vs. 25% > 5), and increased massive transfusion rate (19.5% vs. 5%).

In conclusion, these thresholds, to our knowledge, represent the first based on an analysis of severely injured patients at high risk for TIC and provide an important standard in the evolution of TEG-guided resuscitation. Our experience can serve as a building block for a multicenter trial, which should aim to refine these recommendations for specific patient subgroups and to account for the diversity of interventions used by different trauma centers. Furthermore, refinement of the TEG-guided resuscitation strategy should include optimizing the respective clinical interventions for each given r-TEG output.

AUTHORSHIP

P.M.E. was primary author responsible for statistical analysis and direct preparation of the article and figures. E.E.M. was the lead principal investigator on this project and provided direct input to the direction of the analysis of the data and writing of the article. A.S. contributed in the preparation of the article. M.P.C., H.B.M., and E.G. contributed significantly to study design and preparation of the article. C.C.S. and A.B. provided oversight to the strategic aims of the article and preparation of the article.

DISCLOSURE

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