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Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy:

A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays

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Abstract

Background—Massive transfusion protocols (MTPs) have become standard of care in the management of bleeding injured patients, yet strategies to guide them vary widely. We conducted a pragmatic, randomized clinical trial (RCT) to test the hypothesis that an MTP goal directed by the viscoelastic assay thrombelastography (TEG) improves survival compared with an MTP guided by conventional coagulation assays (CCA).

Methods—This RCT enrolled injured patients from an academic level-1 trauma center meeting criteria for MTP activation. Upon MTP activation, patients were randomized to be managed either by an MTP goal directed by TEG or by CCA (ie, international normalized ratio, fibrinogen, platelet count). Primary outcome was 28-day survival.

Results—One hundred eleven patients were included in an intent-to-treat analysis (TEG = 56, CCA = 55). Survival in the TEG group was significantly higher than the CCA group (log-rank P = 0.032, Wilcoxon P = 0.027); 20 deaths in the CCA group (36.4%) compared with 11 in the TEG

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group (19.6%) ($P = 0.049$). Most deaths occurred within the first 6 hours from arrival (21.8% CCA group vs 7.1% TEG group) ($P = 0.032$). CCA patients required similar number of red blood cell units as the TEG patients [CCA: 5.0 (2–11), TEG: 4.5 (2–8)] ($P = 0.317$), but more plasma units [CCA: 2.0 (0–4), TEG: 0.0 (0–3)] ($P = 0.022$), and more platelets units [CCA: 0.0 (0–1), TEG: 0.0 (0–0)] ($P = 0.041$) in the first 2 hours of resuscitation.

Conclusions—Utilization of a goal-directed, TEG-guided MTP to resuscitate severely injured patients improves survival compared with an MTP guided by CCA and utilizes less plasma and platelet transfusions during the early phase of resuscitation.

Keywords

coagulopathy; fibrinolysis; goal-directed; resuscitation; thrombelastography; transfusion

Injury is the second leading cause of death worldwide and the most common for individuals 15 to 49 years of age.[1–3] The burden of injuries has decreased due to strategies such as injury prevention, advanced prehospital care, regionalized trauma systems, damage control operative techniques, advances in critical care medicine, and rehabilitation with reintegration into society.[4,5] However, in both civilian and military trauma, uncontrolled bleeding remains the leading preventable cause of death, with as much as 40% of injury-related mortality due to hemorrhage.[6–9] This is largely attributed to the exacerbation of bleeding by dysfunctional hemostasis. In 25 to 35% of patients with severe injury, this trauma-induced coagulopathy is already present upon arrival to the emergency department (ED).[10,11]

Traditionally, assessment of hemostasis in the injured has been made with conventional coagulation assays (CCA) such as the international normalized ratio (INR) of prothrombin time, partial thromboplastin time (PTT), platelet count, and fibrinogen concentration. Viscoelastic assays of hemostasis (VHA) such as thrombe-lastography (TEG) (Haemonetics Corp, Niles, IN) and rotational thrombelastometry (ROTEM) (TEM International, GmbH, Munich, Germany) have been introduced into trauma care as a single assay that characterizes the life-span of a clot; from time to initial fibrin cross-linking, maximal clot strength incorporating platelets and red blood cells (RBC), to clot breakdown by fibrinolysis.[12]

To prioritize correction of coagulopathy, institutional massive transfusion protocols (MTPs) have been developed to systematically deliver blood products to the patient's bedside.[13] MTPs rely on abnormal values of CCA as triggers for transfusion of plasma, cryoprecipitate, and platelet units.[14] An alternative approach incorporates a VHA into MTPs to assess each stage of hemostasis, allowing for goal-directed treatment with blood products.

Methods of guiding MTPs vary widely among institutions,[14,15] and an optimal approach to the hemostatic resuscitation of the severely injured patient has yet to be defined. Thus, we designed a randomized trial to compare the effect of an MTP goal directed by TEG to a standard MTP guided by CCA on the primary outcome of survival after injury.

METHODS

Study Design

This investigator-initiated, single center, pragmatic, randomized trial was performed at Denver Health Medical Center, an academic level-1 trauma center. Given the pragmatic character of the trial, rapid enrollment and randomization upon MTP activation required exception from informed consent for emergency research,[16,17] which was approved by the local institutional review board as part of this study's protocol (COMIRB #10-0477). Patients or their next of kin were informed about enrollment at the earliest feasible opportunity and could discontinue their participation at any time. An independent data and safety monitoring board oversaw the trial conduct and reviewed any suspected adverse events, but no interim analyses were planned.

Study Participants

Injured patients at least18 years of age that met criteria for MTP activation upon ED arrival during a 3-year period ending July 30, 2014, were enrolled in the study. MTP activation was based on the Resuscitation Outcome Consortium criteria[18] [systolic blood pressure (SBP) <70 mm Hg or SBP 70–90 mm Hg with heart rate (HR) ≥108 beats/min], in addition to any of the following injury patterns: penetrating torso wound, unstable pelvic fracture, or abdominal ultrasound suspicious of bleeding in more than one region. Patients were not eligible if they were prisoners or pregnant; patients were removed from the study if these criteria became known after activation of the MTP.

Randomization

Using a traditional random-sequence system for each patient at the time of MTP activation could potentially delay care and lead to confusion because of the multidisciplinary personnel required to execute an MTP. In addition, several severely injured patients can present at the same time and are managed by the same clinicians. Thus, individual randomization was considered unsafe for this trial, and a process of randomization by weekly alternation of the 2 treatment modalities was devised. For example, patients enrolled during weeks 1 and 3 were in the CCA group, and those enrolled during weeks 2 and 4 in the TEG group. This predefined alternate week schedule continued until complete accrual and was not modified during the entire study period. Although unconventional, this randomization scheme has been used successfully in previous emergency research trials,[19] when enrollment is time-sensitive and the interventions must be made available without any delay. This randomization approach is recognized as appropriate in emergency research because it affords each patient an equal chance of being given each experimental group, and the assignment cannot be predicted for injured patients.[20,21]

One of the major problems of sophisticated randomization schemes, especially in emergency research, is adherence to protocol. In this pragmatic trial, our goal was to evaluate how massive transfusion of injured patients is practiced in generalizable clinical scenarios. Thus, the study followed guidelines for emergency research to make the intervention simple, time-sensitive, and pragmatic for the clinician.[22,23] No source of bias associated with this randomization method was identified.

Procedures

The coagulation assays, INR, PTT, fibrinogen, and D-dimer (Diagnostica Stago Inc, Parsippany, NJ) were performed on platelet poor plasma collected in citrated vacuum tubes, per routine clinical laboratory protocols. Platelet counts were available to both groups as part of the complete blood cell count. TEG (TEG-5000 Analyzer; Haemonetics Corp, Stoughton, MA) was performed on whole blood collected in vacuum tubes with no anticoagulant, and executed within 5 minutes from collection. This assay incorporates tissue factor to the whole blood sample immediately before test initiation to expedite results, also known as Rapid-TEG.

TEG yields the following variables: activated clotting time (ACT; the time to beginning of clot formation, seconds), angle (rate of clot strength increase, degrees), maximum amplitude (MA; maximal clot strength achieved, millimeters), and percent clot lysis 30 minutes after reaching MA (LY30, %). Studies have correlated ACT with coagulation factor activity and thrombin generation, angle with fibrinogen concentration and function, MA with platelet—fibrin interactions, and LY30 with fibrinolysis.[12]

Both groups had all tests performed (INR, PTT, fibrinogen, D-dimer, and TEG); however, managing clinicians only had access to the test(s) assigned to the study group and were blinded to the other tests. For example, during week 1, patients were enrolled in the CCA group; thus, the electronic medical record only reported the results of the CCA tests (INR, PTT, fibrinogen, D-dimer), blinding the managing clinicians to TEG results. Conversely, in week 2, patients were enrolled in the TEG group; the electronic medical record only reported TEG results, blinding the managing clinicians to CCA results. In order for each study group to reflect the clinicians' best practice, they could override the blinding scheme at any time if they deemed the other tests necessary for patient care, in which case, all tests were made available. The research team, who had no input into patient care, collected all test results regardless of study group.

Upon activation of the MTP the blood bank delivered 4 units of type-O, Rh-negative, RBC units and 2 of type-A plasma units (fresh frozen plasma, plasma frozen in 24 h, or thawed plasma) to the patient's bedside. This occurred regardless of randomization group, and these first units were administered according to the treating clinicians' criteria while awaiting results of coagulation tests (CCA or TEG). Thus, the first units of RBC and plasma were administered according to the clinician's practice regardless of randomization group.

In the CCA group, the following parameters triggered the following transfusions: INR equal or greater than 1.5 = 2 units of plasma; fibrinogen less than 150 mg/dL = 10-pack of cryoprecipitate; platelet count less than 100,000/μL = 1 unit of apheresis platelets. Antifibrinolytic medication (tranexamic acid, 1 g, intravenous) was administered in the setting of suspicion of fibrinolysis with an elevated D-dimer (>0.5 μg/mL). These thresholds for transfusion represent parameters that are considered standard of care based on published consensus guidelines.[24–29] In general, CCA results are available approximately 30 to 45 minutes from collection.

In the TEG group, the first variables of this assay become available within 5 minutes as point-of-care. The first TEG variable reported is ACT; an elevated ACT (≥140 s) has been shown to correlate not only with need for plasma transfusion, but also to be predictive of the TEG variables angle and MA being abnormal, which in turn trigger transfusion of cryoprecipitate and platelets, respectively.[30] Thus, those patients with a first measurement of ACT equal or greater than 140 seconds received 2 plasma units, 10-pack of cryoprecipitate, and 1 unit of apheresis platelets while awaiting results of angle and MA. If the ACT was 111 to 139, only 2 units of plasma were given. For subsequent TEGs, an ACT greater than 110 seconds triggered transfusion of 2 plasma units, angle less than 63 degrees a 10-pack of cryoprecipitate, MA less than 55 mm 1 apheresis platelet unit, and LY30 equal or greater than 7.5% administration of tranexamic acid (1 g, intravenous). Of note, after August 31, 2012 (61% of enrollment), the LY30 threshold for administration of tranexamic acid was lowered to equal or greater than 3% given emerging data demonstrating that this lower value correlated better with transfusion requirements and mortality.[31,32] Our institution's updated version (2015) of this MTP is provided as supplemental material, http://links.lww.com/SLA/A950.

For both treatment groups, tranexamic acid had to be administered within 3 hours from time of injury. RBC units were transfused in both groups to maintain a hemoglobin at least 10 g/dL while bleeding was ongoing. The MTP was stopped in both groups as clinically indicated, once control of bleeding was achieved and the patient was hemodynamically stable.

Outcomes

The primary outcome was 28-day survival. Preplanned analyses of secondary outcomes were blood product requirements in the first 2, 4, 6, 12, and 24 hours from time of injury, and mechanical ventilation time and intensive care unit (ICU) stay. The latter 2 were expressed as outcome-*free* days (ie, ventilator-*free* days and ICU-*free* days) to minimize survivor bias.[33] Sepsis, acute kidney injury (AKI), organ failure, deep vein thrombosis (DVT), and pulmonary embolism were defined in accordance to criteria of the National Trauma Data Bank.[34] Cause of death was ascribed by the attending physician based on clinical findings, and, when available, autopsy results.

Statistical Analysis

Power and sample size were calculated using PASS-11 software.[35] A 30% death rate was estimated in the control group[18]; thus, a sample size of 122 patients would have 80% power to detect a minimum of 20% points difference in survival rate between the 2 groups with 95% confidence.

Categorical variables were expressed as frequency (%) and compared using the χ^2 test, or the Fisher exact test for expected frequencies less than 5. Continuous variables were reported as median (interquartile range) and compared using the nonparametric Wilcoxon rank-sum test. Kaplan-Meyer curves were used to analyze survival, and compared using the log-rank test (privileges late survival) and the Wilcoxon test (privileges early survival). A Cox proportional hazards regression was conducted including hourly, cumulative

plasma:RBC unit ratios in the first 6 hours after ED arrival as a time-varying covariate, and a robust sandwich estimate to account for the repeated, correlated data. Violations to the proportionality assumption were checked and remediated by including an interaction of the variable with time. All tests were 2-tailed and significance set at $P < 0.05$.

Randomization effectiveness was assessed by comparing demographic characteristics, injury mechanisms, anatomic injury severity [Injury Severity Score (ISS), New ISS (NISS)], and physiologic derangement upon ED arrival [SBP, HR, base deficit (BD)]. In accordance to the CONSORT guidelines, no *P* values were reported for baseline comparisons.[36]

Outcome analyses were conducted as “intent-to-treat” (ITT) and “as treated” (AT). Four patients were incorrectly enrolled: 3 were later found to be under guardianship, and 1 was later found to have presented with hypotension due to medical reasons and not an injury (CONSORT Diagram Figure, http://links.lww.com/SLA/A950). The modified ITT excluded 7 patients who died within 30 minutes from arrival without receiving blood products or having any initial laboratory assessments, in accordance to the usual de-randomization process for emergency research[21] (CONSORT Diagram Figure, http://links.lww.com/SLA/A950). The AT analysis was performed considering patients reallocated to the TEG or CCA groups if the attending physician terminated blinding and had access to the test to which they were originally blinded to by the randomization schedule.

Coagulation assays were obtained at the earliest feasible opportunity upon ED arrival to define baseline characteristics, and from then on as dictated for treatment by the clinician and not at predetermined time points; thus, there were no “missing” data. The time points for analysis were artificially set from time of injury at 2 hours, 2.1 to 4.0, 4.1 to 6.0, 6.1 to 12.0, and 12.1 to 24.0 hours; test values within these test values within these time intervals were analyzed.

Analyses were conducted using SAS versus 9.3 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

Patient enrollment in this trial is depicted in the CONSORT Diagram Figure; http://links.lww.com/SLA/A950. Data were analyzed for 111 eligible, exposed patients: 55 in the CCA group and 56 in the TEG group. The study cohort had a median age of 39 years (28–53), ISS of 30 (24–43), NISS of 43 (29–57), arrival SBP of 92.0 mm Hg (78–110), arrival BD of 12.0 mEq/L (9–18), 67.6% had a blunt injury mechanism, and 18.9% presented with a severe traumatic brain injury (TBI) (defined as Glasgow Coma Scale <8 and head Abbreviated Injury Severity score >2). The median RBC transfusion requirement in the first 6 and 12 hours were 8 (5–16) and 10 (6–16) units, respectively. The overall mortality was 27.9%. The 2 groups were similar regarding demographics, injury severity (anatomic and physiologic), clinical, laboratory, and coagulation characteristics upon arrival to the ED, suggesting that randomization was effective (Table 1).

Twenty-eight-day survival in the TEG group was significantly higher than the CCA group (log-rank $P = 0.032$, Wilcoxon $P = 0.027$), as depicted in Figure 1. A Cox proportional hazards model demonstrated a statistically significant higher risk of death in the CCA group

than the TEG group [hazard ratio = 2.17 (95% confidence interval, 1.034–4.576); P = 0.043]. Table 2 depicts distribution and timing of deaths. In the CCA group, 20 deaths occurred (36.4%), compared with 11 deaths in the TEG group (19.6%) (P = 0.049). Most deaths occurred within the first 6 hours from ED arrival; 12 deaths in the CCA group (21.8%), compared with 4 deaths in the TEG group (7.1%) (P = 0.032). Median time to death from ED arrival was 4.2 hours (1.2–9.9) in the CCA group, compared with 10.4 hours (4.5–200.3) in the TEG group (P = 0.181). Hemorrhagic deaths occurred in 20% of patients in the CCA group compared with 8.9% of patients in the TEG group (P = 0.110).

In 8 CCA patients, the treating physician requested unblinding of TEG results to guide management. In this AT analysis (47 patients allocated to the CCA group and 64 to the TEG group), the survival difference widened, privileging TEG-managed patients (log-rank P = 0.003, Wilcoxon P = 0.002) (Fig. 2); 40.4% died in the CCA group, compared with 18.7% in the TEG group (P = 0.011) (Table 2). The difference in deaths due to hemorrhage, 23.4% in the CCA group compared with 7.8% in the TEG group, was significantly greater in this "as treated" analysis (P = 0.020) (Table 2).

Deaths due to TBI and organ failure did not differ significantly between the 2 groups, both in the ITT and AT analyses (Table 2). Baseline characteristics of demographics, injury severity, and coagulation assays (ED arrival) of nonsurvivors were similar between the 2 study groups (Table 3). No harmful or unintended effects resulting from the intervention were reported.

Table 4 depicts the amount of crystalloid and blood transfusions given by group. The amounts of administered crystalloid and RBC units at 2, 4, 6, 12, and 24 hours from time of injury were similar between the 2 groups. During the initial 2 hours of resuscitation, CCA patients required similar number of RBC units as the TEG patients [CCA: 5.0 (2–11), TEG: 4.5 (2–8); P = 0.317], but more plasma units [CCA: 2.0 (0–4), TEG: 0.0 (0–3); P = 0.022], and more platelets units [CCA: 0.0 (0–1), TEG: 0.0 (0–0); P = 0.041]. This resulted in a significantly higher plasma:RBC and platelet:RBC unit ratio among CCA membership patients than those in the TEG group for the corresponding time points (Table 4). More cryoprecipitate was used cumulatively at 24 hours in the CCA group [CCA: 1.0 (0–2), TEG: 0.0 (0–2); P = 0.040] (Table 4). The use of tranexamic acid did not differ significantly between the 2 groups (Table 4). Mortality of the 13 patients who received tranexamic acid was not significantly different when compared between the 2 groups (supplemental material, http://links.lww.com/SLA/A950).

In an attempt to explain the effect of blood products on mortality, the effect of plasma:RBC unit ratio was studied as a time-varying covariate in the first 6 hours using Cox proportional hazards regression, adjusting for injury severity (NISS) and age. TEG group membership was shown to modify the effect of plasma:RBC ratio on mortality (interaction between study group and time-varying plasma:RBC unit ratio in the first 6 hours, P = 0.027). As illustrated in Figure 3, a higher plasma:RBC unit ratio was associated with lower predicted survival in the TEG group, whereas in the CCA group a trend was observed toward higher survival (interaction between group and plasma:RBC unit ratio P = 0.027). This suggests that TEG-

guided treatment allowed for more judicious use of blood products. In the AT analysis, similar results were observed (interaction $P = 0.046$).

There were no significant differences in INR, PTT, fibrinogen, platelet count, D-dimer, and viscoelastic TEG variables between the TEG and CCA groups at the time-intervals studied (Table 4).

Patients in the TEG group had more ICU-*free* days than those in the CCA group, with 16 days (0–22) in the TEG group compared with 8.5 days (0–19.5) in the CCA group ($P = 0.091$), and more ventilator-*free* days, with 18 days (0–25) in the TEG group compared with 13 days (0–22) in the CCA group ($P = 0.082$); these differences were not statistically significant. The groups had similar rates of sepsis (CCA 5.5% vs TEG 3.6%, $P = 0.688$), AKI (CCA 25.5% vs TEG 23.2%, $P = 0.823$), as well as DVT (CCA 10.9% vs TEG 14.3%, $P = 0.599$) and pulmonary embolism (CCA 0 vs TEG 1.8%, $P = 1.01$).

DISCUSSION

This study was conceived to trial a strategy that could further decrease the burden of injuries by targeting hemorrhage. The trial demonstrated that an MTP goal directed by TEG resulted in a survival benefit compared with guidance based on CCA (ie, INR, platelet count, fibrinogen concentration). This survival benefit resulted from less hemorrhagic deaths and less early deaths occurring in the TEG group compared with the CCA group (Table 2). An MTP based on CCA led to more plasma and platelets transfused in the early phase of resuscitation, and more cryoprecipitate overall, when compared with guidance with TEG; however, this did not result in improvement of coagulation assays in the CCA group compared with the TEG group for the corresponding time points (Table 4), suggesting more blood product utilization does not necessarily result in a hemostatic advantage. Although the survival benefit was attributable to the first 6 hours from ED arrival, survivors in the TEG-guided MTP group also benefited from more ICU-*free* and ventilator-*free* days.

These findings emerge as MTPs are now considered standard of care in trauma centers.[13,14] However, in the context of current evidence, disparate strategies to guide MTPs exist.[14,15] Although a retrospective study comparing a TEG-guided MTPs to a historic cohort supports the use of TEG to guide MTPs,[37] this has not been prospectively validated. Recently, the State of the Science in Transfusion Medicine Working Groups, sponsored by the National Heart, Lung, and Blood Institute, identified those research questions that could transform the clinical practice of transfusion medicine in the next 10 years.[38] One of these questions was whether use of a viscoelastic assay (ie, TEG and TEM) to guide transfusion improves outcomes when compared with traditional coagulation testing (ie, INR, PTT, platelet count, fibrinogen level).

In our current study, the TEG group had a significant improvement in survival at 28 days and at 6 hours from injury (Table 2) while using less plasma and platelets in the early phase of resuscitation compared with the CCA group (Table 4). A proposed alternative to goal-directed guidance of MTPs has been ratio-based transfusion.[39] When using such formulaic approach, it remains unclear at what point administration of higher plasma and platelet to

RBC ratios is no longer beneficial[40,41] and can lead to unnecessary use of blood products; particularly because the same ratio of blood products is given to every patient, at every time point in the MTP.[39,42] Recent characterization of 2 distinct phenotypes of trauma-induced coagulopathy by principal component analyses of coagulation proteins and viscoelastic TEG variables[43,44] has called for a more individualized approach.

In our study, the CCA group had more plasma and platelets transfused during the first 4 and 2 hours of resuscitation, respectively, resulting in a significantly higher plasma and platelet to RBC unit ratio than the TEG group (Table 4). Increasing the amount of plasma and platelet transfusion does not necessarily translate into a survival benefit, as demonstrated by a recent randomized trial in which more plasma and platelets were given to severely injured patients by increasing the ratio of plasma to platelet to RBC transfusion from 1:1:2 to 1:1:1, with no significant difference in the study's primary outcome of mortality.[42]

Although there were no major differences in the overall volume of blood products transfused at 24 hours (except for cryoprecipitate—more used in the CCA group), the 2 strategies trialled differed in the amount of plasma and platelet units delivered early in the resuscitation phase (Table 4), which is when the survival benefit occurred; in other words, administration of blood product when it was not needed or not administering it when it was. The effect of this trial may not be related to the amount of blood product given but to the importance of giving the appropriate treatment at the optimal time.

Despite this difference in the amount of hemostatic blood products delivered early in the resuscitation phase, the 2 groups were managed similarly regarding crystalloid administration and RBC transfusion at every time point (Table 4). This suggests 2 things: that the 2 groups were similar in terms of severity of injury and bleeding at baseline, and that the studied intervention only influenced the clinicians' care regarding hemostatic blood products and not other aspects of resuscitation.

Certainly, the implications of plasma and platelet transfusion on the development of organ dysfunction after trauma have been well documented,[45] and could explain the more ICU-*free* and ventilator-*free* days seen in the TEG group. Although the groups did not differ in the incidence of organ failure, a type-2 error is possible given the small subgroup sample.

It is important to underscore the pragmatic character of this trial. It was not designed to test one coagulation assay against the other head-to-head; they are obviously different (eg, the time to delivery of results varies widely between assays). Rather, it was designed to represent how clinicians deliver care in 2 real-world clinical scenarios: a trauma center that only has CCA available to guide an MTP, and a trauma center that has TEG available to guide an MTP. There were no prespecified time points at which clinicians had to deliver transfusions or obtain an assay. The findings of this study reflect not a research protocol, rather the clinicians' best practice (including that of the multidisciplinary team of health care providers that execute an MTP) in a standard of care environment where only one thing was controlled—the results of the coagulation assay they could view. This pragmatic design makes the study's findings generalizable.[23,46]

Despite the similarity in demographics, injury severity, coagulopathy score, and coagulation assays upon ED arrival between the study groups, it is possible that the 2 groups differ regarding unmeasured variables and that the increased mortality seen in the CCA group could be explained by greater risk of death. Yet, the “as-treated” analysis confirmed the survival benefit detected in the ITT analysis, with less hemorrhagic deaths in those who were initially in the CCA group but crossed over to the TEG group (Table 2). Regarding the randomization scheme used, although unconventional, it has been used successfully in previous emergency research clinical trials[19]; nevertheless, randomization is deemed effective when the studied groups are similar at baseline, as shown in Table 1.

This trial demonstrates that a goal-directed, TEG-guided MTP improves survival after injury and promotes appropriate use of hemostatic blood products while favorably impacting ICU stay and mechanical ventilation time. These findings support individualized hemostatic resuscitation of trauma patients by tailoring of MTPs to the dynamic biology of hemostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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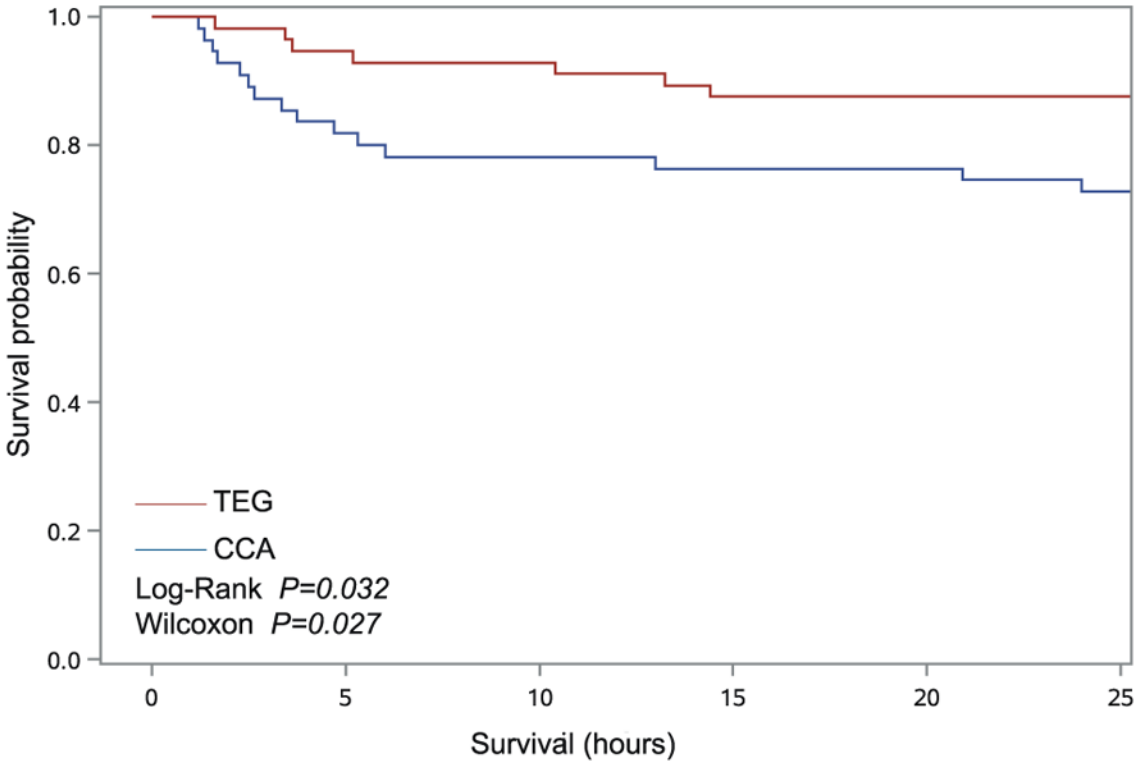

FIGURE 1.

Kaplan-Meier estimates of survival by randomization group for patients analyzed as intention-to-treat. Survival in the TEG group was significantly higher than the CCA group (log-rank $P = 0.0324$, Wilcoxon $P = 0.0275$).

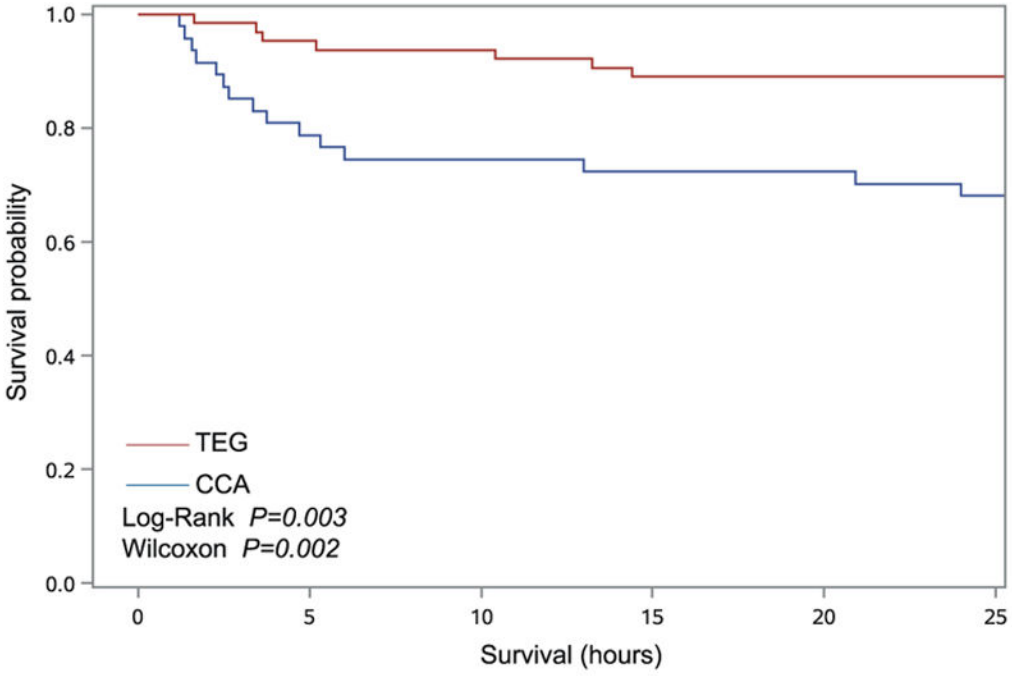

FIGURE 2.

Kaplan-Meier estimates of survival by randomization group for patients analyzed as treated. Survival in the TEG group was significantly higher than the CCA group (log-rank $P = 0.0039$, Wilcoxon $P = 0.0029$).

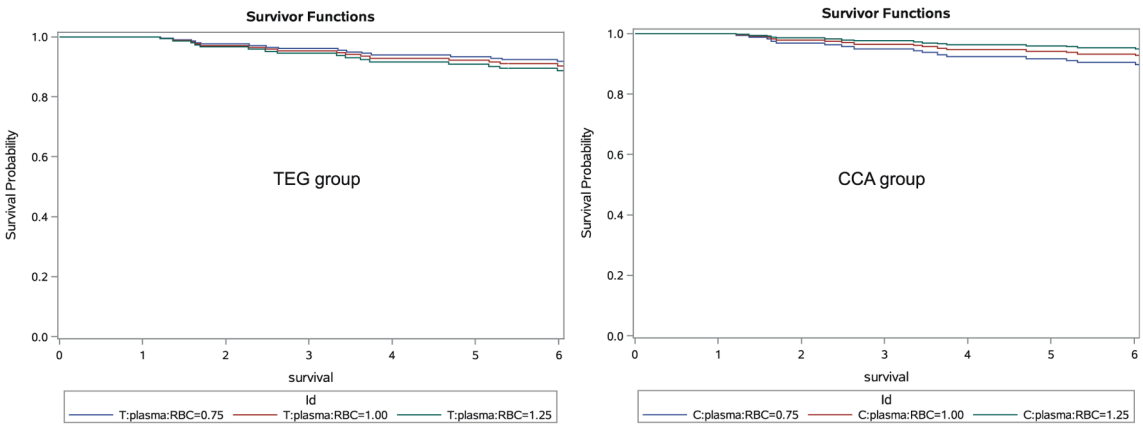

FIGURE 3.

Survival curves for different plasma:RBC ratios in the TEG and CCA groups, controlling for injury severity and age (median NISS = 43; age = 38 yrs).

TABLE 1

Baseline Patient Characteristics of Intention-to-treat Population—Vital Signs, Laboratory, and Coagulation assays Collected Upon ED Arrival

	CCA Group (N = 55)		TEG Group (N = 56)	
Characteristic	**Median**	**IQR**	**Median**	**IQR**
Demographic data				
Age, yrs	38.0	25–53	41.0	28–54
Male sex, no. (%)	41 (74.5)		37 (66.0)	
BMI, kg/m^2	25.5	23–30	25.9	23–31
Time from injury to ED, min	29.0	21–72	35.5	23–94
Injury severity (anatomic)				
ISS	33.0	25–43	29.5	23–41
NISS	43.0	34–57	41.0	29–50
Blunt mechanism, no. (%)	36 (65.4)		39 (69.6)	
Severe TBI (AIS head >2 and GCS <8), no. (%)	12 (21.8)		9 (16.0)	
Injury severity (physiologic) (characteristics on ED arrival)				
ABC score	2.0	1–3	2.0	1–2
TASH score	12.0	9–17	13.0	9–15
GCS	14.0	3–15	14.5	6–15
SBP, mm Hg	90.0	76–110	97.0	78–120
HR, beats/min	112.5	94–134	107.5	90–123
Temperature, °C	36.2	35–37	36.5	35–37
pH	7.20	7.0–7.3	7.21	7.1–7.2
Base deficit, mEq/L	13.7	9–18	11.0	9–16
Lactate, mmol/L	5.4	3.9–7.9	6.9	3.8–7.6
Hemoglobin, g/dL	11.8	9.6–13.3	12.3	10.5–13.6
Platelet count/mm^3	214.5	165–279	214.5	145–318
Creatinine, mg/dL	1.2	0.9–1.5	1.1	1.0–1.3
Calcium, mg/dL	6.9	6.3–8.1	7.0	6.4–7.8
Initial coagulation assessments upon ED arrival				
TEG-ACT, s	130.0	113–178	128.0	113–140
TEG-angle, degrees	50.9	28–69	52.3	30–70
TEG-MA, mm	47.5	34–53	53.9	28–63
TEG-LY30, % of clot lysis	0.5	0–4.4	1.2	0.1–20
INR	1.46	1.2–2.3	1.45	1.2–1.7
PTT, s	38.5	27–52	32.1	27–39
Fibrinogen, g/dL	113.0	68–139	132.1	94–220
D-dimer, g/dL	12.9	6–20	10.3	2–20

Continuous values expressed in median (interquartile range, IQR), categorical characteristics expressed in number (no.) and percent (%).

ABC score indicates assessment of blood consumption score; ACT, activated clotting time; BMI, body mass index (expressed in kg/m^2); ED, emergency department; GCS, Glasgow coma scale; HR, heart rate; INR, international normalized ratio; ISS, injury severity score; LY30, % clot lysis 30 minutes after reaching MA; MA, maximum amplitude; NISS, new injury severity score; PTT, partial thromboplastin time; SBP, systolic blood pressure; TASH score, trauma-associated severe hemorrhage score; TBI, traumatic brain injury; TEG, thrombelastography.

TABLE 2

Outcome of Mortality Stratified by Study Group

	Intention to Treat		
	CCA (N = 55)	**TEG (N = 56)**	***P***
Deaths, no. (% within group)	20 (36.4)	11 (19.6)	0.049
Time to death in hours from ED arrival, median (IQR)	4.2 (2.4–9.9)	10.4 (4.5–200.3)	0.181
Deaths occurring in the first 6 hours from ED arrival, no. (% within group)	12 (21.8)	4 (7.1)	0.032
Deaths occurring >6 h from ED arrival, no. (% within group)	8 (14.5)	7 (12.5)	0.785
Hemorrhagic deaths, no. (% within group)	11 (20.0)	5 (8.9)	0.110
TBI deaths, no. (% within group)	6 (10.9)	4 (7.1)	0.537
Organ failure, no. (% within group)	3 (5.5)	2 (3.6)	0.675
	As Treated		
	CCA (N = 47)	**TEG (N = 64)**	***P***
Deaths, no. (% within group)	19 (40.4)	12 (18.7)	0.011
Time to death in hours, median (IQR)	3.5 (2.2–8.3)	11.5 (4.9–211.0)	0.073
Deaths occurring in the first 6 hours from ED arrival, no. (% within group)	11 (23.4)	4 (6.2)	0.010
Deaths occurring >6 h from ED arrival, no. (% within group)	8 (17.0)	8 (12.5)	0.589
Hemorrhagic deaths, no. (% within group)	11 (23.4)	5 (7.8)	0.020
TBI deaths, no. (% within group)	6 (12.8)	4 (6.3)	0.321
Organ failure, no. (% within group)	2 (4.3)	3 (4.7)	1.00

ED indicates emergency department; IQR, interquartile range; TBI, traumatic brain injury.

TABLE 3

Baseline Characteristics of Nonsurvivors Stratified by Study Group—Vital Signs, Laboratory, and Coagulation Assays Collected Upon ED arrival

	CCA (N = 20)		TEG (N = 11)		
Characteristic	**Median**	**IQR**	**Median**	**IQR**	***P***
Demographic data					
Age, yrs	40.3	32–57	56.8	38–63	0.172
Male sex, no. (%)	13 (65.0)		9 (81.8)		0.420
BMI, kg/m^2	26.5	24–34	29.5	22–36	0.837
Time from injury to ED, min	28.0	21–77	26.1	20–70	0.829
Injury severity (anatomic)					
ISS	37.5	33–45	47.5	22–59	0.314
NISS	45.5	39–57	54.5	29–66	0.354
Blunt mechanism, no. (%)	15 (75.0)		9 (81.2)		1.00
Severe TBI (AIS head >2 and GCS <8), no. (%)	5 (25.0)		4 (36.4)		0.687
Injury severity (physiologic) (characteristics on ED arrival)					
ABC score	2.0	1–3	2.0	1–3	1.00
TASH score	14.0	8–17	15.0	9–17	0.917
GCS	7.0	3–14	6.5	3–13	0.703
SBP, mm Hg	89.0	40–100	90.0	38–102	0.949
HR, beats/min	112.5	75–133	109.0	71–130	0.843
Temperature, °C	36.1	35.0–37.1	36.0	35.0–36.8	0.899
pH	7.19	6.9–7.3	7.11	6.9–7.2	0.419
Base deficit, mEq/L	17.5	9–20	15.0	8–19	0.323
Lactate, mmol/L	8.8	2–14	8.2	2–12	0.679
Hemoglobin, g/dL	11.3	8–12	12.7	6–13	0.744
Platelet count/mm^3	200.5	120–240	144.0	117–157	0.099
Creatinine, mg/dL	1.2	0.9–1.4	1.3	1.0–1.5	0.662
Calcium, mg/dL	6.8	5.8–7.9	6.9	5.7–8.7	0.801
Initial coagulation assessments (characteristics on ED arrival)					
TEG-ACT, s	202.5	140–220	220.0	160–240	0.271
TEG-angle, degrees	49.0	30–59	44.0	30–53	0.784

	CCA (N = 20)		TEG (N = 11)		
Characteristic	**Median**	**IQR**	**Median**	**IQR**	***P***
TEG-MA, mm	47.1	31–49	41.7	26–47	0.596
TEG-LY30, % of clot lysis	4.1	2.9–7.7	4.5	2.8–12.8	0.794
INR	2.1	1.3–3.0	2.0	1.2–2.5	0.495
PTT, s	49.4	39–70	44.2	38–60	0.284
Fibrinogen, g/dL	84.5	69–147	94.7	75–151	0.951
D-dimer, g/dL	14.7	9–25	19.0	11–31	0.355

ABC score indicates assessment of blood consumption score; ACT, activated clotting time; BMI, body mass index (expressed in kg/m^2); ED, emergency department; GCS, Glasgow coma scale; HR, heart rate; ISS, injury severity score; LY30, % clot lysis 30 minutes after reaching MA; MA, maximum amplitude; NISS, new injury severity score; SBP, systolic blood pressure; TASH score, trauma-associated severe hemorrhage score; TBI, traumatic brain injury; TEG, thrombelastography.

TABLE 4

Blood Product Use and Coagulation Assessments Stratified by Study Group and Time—Time Points Calculated Form Time of Injury

	CCA Group (N = 55)			TEG Group (N = 56)			
Cumulative Requirements	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***P***
RBC (units)							
At 2 h	55	5.0	2–11	56	4.5	2–8	0.317
At 4 h	48	8.0	4–14	55	6.0	4–13	0.434
At 6 h	45	8.0	5–15	53	8.0	4–14	0.716
At 12 h	42	10.5	6–15	50	9.5	5–16	0.496
At 24 h	40	11.0	6–16	48	9.5	5–16	0.413
Plasma (units)							
At 2 h	55	2.0	0–4	56	0.0	0–3	0.022
At 4 h	48	4.0	0–6	55	2.0	0–5	0.044
At 6 h	45	5.0	2–8	53	4.0	2–6	0.305
At 12 h	42	6.0	4–8	50	5.0	3–8	0.533
At 24 h	40	6.0	4–9	48	5.0	3–9	0.509
Cryoprecipitate (10-pack = 1 unit)							
At 2 h	55	0.0	0–0	56	0.0	0–0	0.533
At 4 h	48	0.0	0–1	55	0.0	0–0	0.841
At 6 h	45	0.0	0–2	53	0.0	0–2	0.473
At 12 h	42	1.0	0–2	50	0.0	0–2	0.121
At 24 h	40	1.0	0–2	48	0.0	0–2	0.040
Platelets (units)							
At 2 h	55	0.0	0–1	56	0.0	0–0	0.041
At 4 h	48	0.0	0–1	55	0.0	0–1	0.981
At 6 h	45	1.0	0–1	53	1.0	0–2	0.925
At 12 h	42	1.0	0–2	50	1.0	0–2	0.539
At 24 h	40	1.0	0–2	48	1.0	0–2	0.934
Plasma:RBC ratio (units)							
At 2 h	55	0.3	0–0.5	56	0	0–0.3	0.022
At 4 h	48	0.4	0–0.5	55	0.2	0–0.4	0.025

	CCA Group (N = 55)			TEG Group (N = 56)			
Cumulative Requirements	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***P***
At 6 h	45	0.5	0.3–0.6	53	0.4	0.2–0.8	0.871
At 12 h	42	0.5	0.3–0.7	50	0.5	0.3–0.9	0.568
Platelet:RBC ratio (units)							
At 2 h	55	0	0–0.1	56	0	0–0	0.026
At 4 h	48	0	0–0.1	55	0	0–0.1	0.783
At 6 h	45	0.1	0–0.1	53	0.1	0–0.1	0.984
At 12 h	42	0.1	0–0.1	50	0.1	0–0.2	0.225
Intravenous crystalloids (mL)							
At 2 h	55	3800	3000–5100	56	3750	1000–10,000	0.596
At 4 h	50	6700	4750–8500	53	6000	2000–23,000	0.914
At 6 h	50	8000	5000–9683	52	8000	3000–29,000	0.506
At 12 h	42	11,738	8900–14,100	50	11,026	5300–31,600	0.197
At 24 h	40	14,239	10,533–17,613	48	13,420	6363–33,000	0.208
Antifibrinolytic used, no. (% within group)	111		9 (16.4)			4 (7.1)	0.154
Coagulation assessment							
TEG-ACT							
At 2 h	40	134.0	130–233	36	128.0	112–199	0.523
2.1–4 h	45	120.0	130–169	41	128.0	121–171	0.755
4.1–6 h	39	124.0	113–142	52	121.0	117–144	0.948
6.1–12 h	42	128.0	121–144	52	121.0	113–140	0.593
12.1–24 h	41	128.0	121–128	51	128.0	121–136	0.931
TEG-angle							
At 2 h	40	63.9	37–68	36	66.1	46–74	0.343
2.1–4 h	45	57.5	44–68	41	64.9	53–69	0.637
4.1–6 h	39	70.8	64–72	52	68.2	60–73	0.901
6.1–12 h	43	68.5	60–70	52	65.5	57–73	0.451
12.1–24 h	42	69.1	61–71	51	71.3	64–74	0.109
TEG-MA							
At 2 h	40	46.2	32–57	36	49.1	38–56	0.294

	CCA Group (N = 55)			TEG Group (N = 56)			
Cumulative Requirements	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***P***
2.1–4 h	45	40.1	29–54	41	45.3	42–55	0.972
4.1–6 h	39	53.8	49–59	52	51.0	46–57	0.858
6.1–12 h	43	55.0	52–57	52	56.9	49–58	0.598
12.1–24 h	42	56.5	46–61	51	56.9	54–61	0.605
TEG-LY30							
At 2 h	46	0.9	0–1.3	46	0.6	0–9	0.449
2.1–4 h	45	0.4	0.1–1.2	41	0.1	0–5	0.313
4.1–6 h	39	0.0	0–0	52	0.0	0–1.5	0.852
6.1–12 h	43	0.3	0–0.5	52	0.1	0.1–1.5	0.303
12.1–24 h	42	0.7	0.2–1.5	51	0.7	0.7–1.7	0.737
INR							
At 2 h	51	2.1	1.6–3.9	51	1.8	1.5–2.3	0.082
2.1–4 h	50	2.8	1.5–4.2	46	1.9	1.7–3.0	0.811
4.1–6 h	43	1.5	1.3–2.2	47	1.8	1.3–2.1	0.580
6.1–12 h	44	1.4	1.2–1.6	50	1.4	1.3–1.9	0.627
12.1–24 h	43	1.5	1.4–1.7	51	1.4	1.3–2.0	0.554
Fibrinogen							
At 2 h	36	109.0	62–164	33	114.0	82–139	0.278
2.1–4 h	42	101.4	62–159	43	102.0	67–129	0.782
4.1–6 h	39	161.5	112–175	45	153.0	111–180	0.918
6.1–12 h	44	185.5	159–232	48	159.0	111–214	0.717
12.1–24 h	43	233.0	218–256	49	203.0	150–266	0.714
Platelet count							
At 2 h	54	139.0	72–218	56	160.0	81–249	0.324
2.1–4 h	51	96.0	61–145	48	99.0	70–143	0.978
4.1–6 h	43	90.0	60–144	52	100.0	89–140	0.295
6.1–12 h	39	116.0	75–157	47	110.0	90–139	0.342
12.1–24 h	39	96.5	72–128	46	109.0	91–130	0.168
D-dimer							
At 2 h	35	5.6	1–18	33	6.9	2–15	0.155

	CCA Group (N = 55)			TEG Group (N = 56)			
Cumulative Requirements	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***P***
2.1–4 h	39	8.2	1–19	40	7.4	2–15	0.261
4.1–6 h	33	8.3	1–15	42	8.7	2–13	0.938
6.1–12 h	42	8.0	2–13	48	6.4	3–13	0.752
12.1–24 h	42	5.4	2–13	48	5.0	3–13	0.707

ACT indicates activated clotting time; INR, international normalized ratio; IQR, interquartile range; LY30, % clot lysis 30 minutes after reaching MA; MA, maximum amplitude; PTT, partial thromboplastin time; RBC, red blood cells; TEG, thrombelastography.

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