Form "EAST Multicenter Study Proposal"
Details #22 (submitted 09/29/2023)

Please indicate if this is a...	New MCT proposal submission
If a revised proposal summarize the changes made to this proposal based on the feedback received:	
Study Title	Standard Thromboelastography Protocols May Fail to Identify Coagulopathy in Hypothermic Trauma Patients – An EAST Multicenter Study
Primary Investigator:	Joseph Margolick, MD
Institution that will be the primary site for the study:	University of Arkansas for Medical Sciences
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Co-PI/second point of contact for the study:	Maraya Camazine, MD
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Are you a current member of EAST?	Yes
If you selected "No" above please identify a Sponsor that is an active EAST member:	

Background: Trauma remains the leading cause of death in individuals younger than 40, with hemorrhage being the primary preventable cause.1-4 Hemorrhage from trauma is frequently exacerbated by coagulopathy, which is a multifactorial process that can have devastating consequences irrespective of injury severity. Hypothermia is also a known component of the lethal triad and can worsen coagulopathy, and is highly pertinent to the trauma population as an estimated >20% of trauma patients will be hypothermic on arrival to treatment center.5 Extensive research has focused on optimal resuscitative strategies in patients with trauma-induced coagulopathy (TIC); however, the impact of hypothermia on the viscoelastic properties of blood clots remain unknown.6-8

Massive transfusion protocols and blood management programs must balance the risk of unnecessary exposure to blood products with the need for adequate treatment of severe bleeding. As a result, Rotational Thromboelastometry (ROTEM) and Thromboelastography (TEG) are commonly used blood tests that evaluate the viscoelastic properties of blood clot formation. ROTEM or TEG are utilized, depending on institutional preferences, in bleeding trauma patients to guide appropriate utilization of blood products and reverse coagulopathy.9-12 The impact of hypothermia on ROTEM samples remains unknown, with current literature on hypothermic viscoelastic properties being conducted utilizing TEG in animal studies or healthy volunteers.

Use this area to briefly outline the burden of the problem to be examined.

Significance: Given the frequent utilization of viscoelastic testing and the critical condition of the patients for whom ROTEM or TEG is intended, comprehending mechanical aspects of these tests is important. As previously indicated, bleeding trauma patients confront a multifaceted ailment of hypothermia, coagulation and acidosis, that synergistically leads to catastrophic outcomes if not rapidly addressed. Coagulopathy manifests early in trauma cases, often culminating in death within six hours of the onset of bleeding.13 Swift identification and rectification of coagulopathy, along with hemorrhage control, remain the cornerstone of treatment for these individuals.14-18

ROTEM and TEG studies typically adhere to a standardized testing temperature of 37°Celsius, regardless of the patient's core temperature.19 Whether the 37°C sample accurately represents the viscoelastic clotting properties of a hypothermic patient remains unanswered. Our hypothesis posits that warming the blood sample to 37°C may artificially normalize ROTEM and TEG values, thereby downplaying true coagulopathy in bleeding trauma patients. We postulate that ROTEMs and TEGs conducted at the true core body temperature of hypothermic patients more accurately reflect a patient’s impairment in blood clotting, as evidenced by more severe coagulopathy than their 37°C counterparts.

The objective of this study is to establish a high-quality, multi-center, prospective observational study of hypothermic trauma patients requiring viscoelastic monitoring. This study will compare viscoelastic tests conducted at the core temperature of hypothermic patients to their standard warmed samples. Our aim is to determine if ROTEM and TEGs conducted at a patient's core temperature provide better indications for resuscitation products and best practices for future hypothermic trauma patients. Data generated from this

prospective study will facilitate the exploration of various hypothesis-generating questions and may ultimately inform the development of new temperature specific algorithms. This initial study may guide efforts to secure funding for, and inform, randomized controlled trials evaluating patient outcomes when treated according to ROTEM or TEG samples run at patients' actual body temperature.

Briefly review what major published studies exist on the topic of the proposed project.

Several studies evaluating TEG and ROTEM show the benefit of viscoelastic guided resuscitation including: quick identification of patients at risk of bleeding, more precise and rapid reversal of coagulopathy, reduced mortality, decreased blood product administration, decreased ventilator days and shorter intensive care unit stays.17,20 Previous works evaluating these modalities in the hypothermic setting predominately utilize TEG as the test device; however, data is conflicting. Within these studies, researchers typically enrolled healthy individuals where samples are collected, cooled to test temperature and analyzed without warming. Cundrle et al. conducted a TEG study in patients requiring therapeutic hypothermia post cardiopulmonary resuscitation with minimal differences in in-vivo values at hypothermic vs. normothermic temperatures.21 Conversely, Forman et al. conducted TEG testing in encephalopathic neonates undergoing therapeutic hypothermia.22 They found TEG results differed significantly by temperature protocol with clinical risk for bleeding more frequently seen in the hypothermic assays. Additional studies have been conducted in hypothermic animals with varying levels of impact observed.23,24 There is limited data evaluating hypothermic ROTEM samples, and no large scale studies specifically evaluating viscoelastic monitoring at native temperatures in hypothermic trauma patients exist.

Local data: We conducted a pilot study at our institution evaluating the viscoelastic properties of ROTEM samples from hypothermic, bleeding trauma patients. We compared ROTEMs analyzed at patients' hypothermic core body temperature to standard 37°C samples obtained from the same patient. Twenty-four paired ROTEMs from 12 patients were analyzed. Median age was 48 (38-59), and 50% were male. The average temperature of hypothermic ROTEM assay was 34.2°C. Clot Formation Times (CFT) were prolonged within the hypothermic assay by an average of 45.4 seconds (EXTEM) and 51.3 seconds (INTEM), $p<0.01$ for both (Figure 1). Maximum Clot Firmness (MCF) was decreased by an average 3.0 mm (EXTEM, $p=0.01$) and 3.3 mm (INTEM, $p<0.01$). EXTEM and INTEM A10 and A20 values additionally showed decreased amplitude using the hypothermic protocol (all $p<0.01$). Using local ROTEM-directed transfusion guidelines, 25% of patients who did not meet platelet transfusion criteria based on standard protocol results, met transfusion criteria based on hypothermic protocol results.

Use this area to briefly outline how this idea is innovative and it's anticipated impact.

Data evaluating viscoelastic testing using hypothermic protocols is limited, with data predominately describing TEG use. Trauma patients in particular are at risk for coagulopathy from multiple etiologies, with early and efficient hemostatic resuscitation being one of the few interventions associated with positive mortality benefits. Expectedly, tests guiding transfusion and resuscitation need to be as accurate as possible. Our study is innovative because, other than our pilot study, this type of analysis has not been performed before. Our initial data is reassuring and indicates that statistically and clinically significant differences exist when comparing hypothermic assays to warm assays. Understanding the difference between hypothermic and warm assays is imperative to optimal resuscitation.

Describe what & how the proposed MCT will add to the existing body of knowledge & literature.

This MCT is needed to further quantify and expand upon our site's early data comparing hypothermic and standard ROTEM assay results. To date, no trials evaluating in-vivo hypothermic TEG or ROTEM assays exist in hypothermic trauma patients. Our aim is to fill the knowledge gap pertaining to the clinical impact of hypothermic testing, further identify and quantify blood product administration using hypothermic guided resuscitation practices, and ultimately compare hypothermic to standard protocols in a randomized controlled trial with intent to amend transfusion guidelines as indicated. Implementation and completion of this prospective multi-center trial is the first step towards these goals.

Primary aim

Determine if hypothermic testing protocols for ROTEM are associated with clinically significant differences in coagulation parameters compared to standard warm protocol testing. Our primary hypothesis is that results from hypothermic ROTEM assays will reflect more significant coagulopathy when compared to warmed samples. Our objective is to determine if hypothermic ROTEM samples will indicate a need for more plasma, cryoprecipitate and/or platelets for coagulopathy reversal compared to warmed samples.

Secondary aims

To test the primary hypothesis, hypothermic ROTEMs parameters will be compared against standard warmed ROTEM samples. Two ROTEM samples will be drawn from each hypothermic trauma patient. The warmed 37°C sample will be compared to the sample analyzed at patients' core body temperature.

Our secondary aim will be to evaluate if the coagulation parameter differences in hypothermic samples are replicated with TEG. Hypothermic TEG parameters will be compared against standard warmed TEG samples. Data for both TEG and ROTEM will be analyzed through our transfusion algorithm to determine if indicated blood products vary between hypothermic and warmed samples. We hypothesize that hypothermic TEG samples will demonstrate worse coagulopathy than warmed samples.

Tertiary aim

Determine if tranexamic acid (TXA) administration has an impact on fibrinolysis parameters in hypothermic patient samples. To assess TXA efficacy in hypothermic patients, a subset analysis in patients who receive TXA will be conducted. Hypothermic and standard assay results pertaining to fibrinolysis will be compared and will determine if a difference exists between samples.

Design

Prospective (observational with or without consent requirement)

Inclusion Criteria

Age: >18 years

Trauma patient

Core body temperature below 35C

Requires ROTEM or TEG testing as part of workup

Patients taking anticoagulants will be included as part of this study

Exclusion Criteria

Patients who are normothermic or hyperthermic at time of admission

Known pre-existing coagulopathy

Patients less than 18 years of age

Pregnant patients

Please describe, completely but succinctly, how the project will be conducted.	The Principal Investigator will carefully monitor study procedures to protect the quality of the data and the integrity of the study. This will be a prospective multi-center observational study of trauma patients evaluated in the emergency department. Blood samples collected for routine ROTEM and TEG testing will use excess blood to run a secondary sample at the reported hypothermic patient temperature. To do this block (ROTEM) or cup (TEG) heaters will be used in the standard fashion for the 37° Celsius sample; the second block or cup will be analyzed at the patients core body temperature. In addition to general viscoelastic monitoring results, we will also be accessing patient records for information regarding injury pattern, clinical parameters on ED admission, comorbid medical conditions, treatment, and outcomes.
Primary Outcome	Primary outcome: Numeric difference in hypothermic vs. warmed ROTEM and TEG samples.
Secondary Outcome(s)	Secondary Outcome: Theoretical difference in indicated blood products based on hypothermic vs. warmed assay results for both TEG and ROTEM samples.
Select the variables to be collected & analyzed:	Baseline Participating Institution Information,Demographics,Baseline Clinical Characteristics,Hospital Course,Treatments & Interventions,Outcomes of Interest
Additional variables:	Full data collection below

Outline the data collection plan/tool succinctly

All data collected will be stored in REDCap and de-identified prior to sharing with research team members or participating sites. REDCap-stored data will include and be categorized in the following manner: demographics, patient clinical background, pre-intake data, laboratory data, admission clinical or hemodynamic data, TEG- or ROTEM-indicated intervention, post-admission interventions used, and patient outcomes.

Demographics: age, gender, weight, height, ethnic group, race, blood type, anticoagulant usage

Transfer data as applicable: EMS/flight transfer time, blood product and pre-hospital interventions

Laboratory data: hematocrit, hemoglobin, lactate, platelet count, base deficit, fibrinogen, INR, PT, PTT, thromboelastography (TEG) or (rapid TEG) or ROTEM

oTEG, rTEG, ROTEM data to include hypothermic data and standard protocol data

Admission clinical or hemodynamic measures: Glasgow Coma Scale, systolic BP, mean arterial pressure, heart rate, respiratory rate, tissue oxygen saturation, arterial saturation, temperature, mechanism of injury, Injury Severity Score (ISS) and Abbreviated Injury Score (AIS) information when applicable, Arterial pH, Lactate

Blood product or hemostatic adjuncts administered: RBC, plasma, platelet, cryoprecipitate, tranexamic acid, aminocaproic acid, recombinant activated factor VII, fibrinogen, prothrombin complex concentrates

oIncludes field, referring hospital, inter-hospital transport, tertiary hospital, trauma bay, OR, and ICU product utilization

Patient outcome data: 28 day mortality and cause of mortality, ICU LOS, ventilator days, hospital LOS, total blood product utilization

oCause of death will be categorized into hemorrhage, CNS injury, multiple organ failure, or other

Has IRB approval been obtained at the primary site?	Yes
Is DUA required for participation in the study?	Yes
If applicable, list the primary contact (name/email) to contact to initiate & execute DUA:	Hanna K Jensen - HKJensen@uams.edu
Identify the individuals that will primarily be responsible for data collection process:	All HIPAA compliant IRB approved personnel are eligible to assist with data collection to include: medical students, research team members, residents, fellows, and PIs
Is there a primary statistician assigned to assist the PI w/design & data analysis?	Yes
If no, how was study design/power analysis determined/who will handle analysis once complete?	

Effects of Interest. This is a single group study design intended to evaluate the potential need for modifications to current standard of viscoelastic monitoring in trauma patients. This study is strictly observational and no changes will be made to a patient's care as part of this study. The overarching research question: Should transfusion and resuscitation protocols that depend on viscoelastic monitoring parameters be modified to account for the coagulation metrics of hypothermic blood? To answer this, we must first identify whether treatment indications are dependent on the temperature of the blood sample being analyzed.

The primary effect of interest: Is there a statistical difference in coagulation metrics between hypothermic blood compared to warmed (current standard of care) blood in trauma patients? If so, what is the magnitude of difference between these testing methodologies?

Include detailed description of the data analysis plan:

The secondary effect of interest: Is there a statistical difference between hypothermic and standard viscoelastic tests that translates to clinically relevant changes regarding coagulopathy reversal? We plan to determine if using hypothermic TEG or ROTEM to guide resuscitation would result in a theoretically increased use of plasma, cryoprecipitate, platelets and TXA. To do this, we would determine the resuscitation strategy for each viscoelastic sample and – based on established transfusion thresholds – determine if hypothermic viscoelastic properties are different enough to result in a change in resuscitation approach (i.e., actual transfusion). Results of this study may inform future randomized controlled trials comparing the clinical effects of hypothermic patients treated with a resuscitation algorithm based on hypothermic ROTEM or TEG to those treated with standard ROTEM or TEG.

General Statistical Approach. Exploratory data analysis of all data collected will include the following overall summary measures for numerical variables: mean, standard deviation, minimum, maximum, and quartiles. For categorical data, we will construct frequency tables for each level within each variable. Bar charts, contingency tables, scatterplots and boxplots will be constructed to visualize associations as needed. Generalized linear models will be employed to evaluate relationships between variables, with random effect site (hospital), covariate effects for patient demographic and clinical characteristics, blood product and other intervention administration, TEG/ROTEM parameters by assay and temperature (hypothermic and warmed), and post-intervention clinical outcomes. Distributional, independence and homogeneity of variance assumptions will be investigated for each model evaluated and, if violated, transformations and/or nonparametric methods will be employed. Outliers will be identified

In a pilot study, we found that hypothermic samples, as compared to warmed samples, yielded effect sizes (mean difference divided by standard deviation of differences) from 0.94 to 1.85 for ROTEM parameters A10, A20, alpha and MCF for both the intrinsic and extrinsic assays. For a sample size of 15 (paired) samples and Type I error rate of 0.05, an effect size of 0.8 will provide 82.1% power to detect a significant difference between the paired samples (2-sided test).

Include Power Analysis:

In the same pilot study, ROTEM-indicated standard of care intervention protocol was as follows: warmed – Plasma: 3/12 = 25%, Cryoprecipitate: 6/12 = 50%, Platelets: 0 / 12 = 0%; hypothermic – Plasma: 2/12 = 16.7%, Cryoprecipitate: 6/12 = 50%, Platelets: 3/12 = 25%. In all, 5/12 = 41.7% had a different ROTEM-derived treatment indication based on the warmed sample compared to the results from the hypothermic sample. Given a trauma patient from this population with an assumed probability of needing a blood product treatment of 0.25, collecting 50 paired samples will provide 81.1% power to detect a 20% difference in treatment indications for a 2-sided test given a = 0.05, based on a normal approximation to a paired 2-sample proportion testing design. To replicate this in both ROTEM and TEG and account for incomplete data entries, we aim to collect 150 paired samples (75 ROTEM and 75 TEG) for the study. We believe this would be possible to obtain with 7-10 ROTEM and 7-10 TEG sites (14-20 sites total).

Please note what your enrollment procedure for this study entails:

To permit a consecutive sample of patients at clinical sites and avoid sampling bias, we request a waiver of consent to collect data via medical record review. This study is minimal risk, observational, and involves no additional interventional procedures. Laboratory specimens collected as part of this study will be obtained as routine standard of care with small aliquots of excess blood used for hypothermic testing. Additional vials of blood are not required to conduct this study. Hypothermic results will not be entered into the patient chart or used to direct patient care. Discussion and study buy-in with laboratory personnel will be required as part of this study. Enrolled patients will have a ROTEM or TEG performed according to standard site protocol, and then an additional sample run at their hypothermic temperature.

Outline consent procedures here, if applicable:

A consent waiver is required as many participants will be in critical condition requiring emergent testing, transfusion, intubation and surgery. Since our study procedure will use excess blood collected from a patient during standard course of their care, there is minimal additional risk. There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future. The primary benefits of this study would be guiding clinical practice for future use of ROTEM and TEG results in hypothermic patients.

Please indicate what resources are available at the primary study institution:

Presence of a dedicated statistician,Research personnel

Include a brief listing of key references:

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13.Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers. Apr 29 2021;7(1):30. doi:10.1038/s41572-021-00264-3

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