DATA-DRIVEN DEVELOPMENT OF ROTEM AND TEG ALGORITHMS FOR THE MANAGEMENT OF TRAUMA HEMORRHAGE - A PROSPECTIVE OBSERVATIONAL MULTICENTER STUDY

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REPRINT REQUEST:

Same as corresponding author.

CONFLICT OF INTERESTS:

The authors declare that they have no conflict of interests.

FUNDING STATEMENT

This study is part-funded by the European Commission under the FP-7 HEALTH-Contract No. F3-2013-602771, entitled “Targeted Action for Curing Trauma Induced Coagulopathy” (TACTIC).

Website European Commission FP-7 HEALTH-Contract No. F3-2013-602771: http://cordis.europa.eu/project/rcn/110071_en.html

Both TEM® International GmbH and Haemonetics® are equal partners in the TACTIC program, and have been providing VHA devices and reagents for all participating institutions. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

SHORT RUNNING HEAD: VHA algorithms for trauma hemorrhage.

ABSTRACT:

Objective: Developing pragmatic data-driven algorithms for management of trauma induced coagulopathy (TIC) during trauma hemorrhage for viscoelastic hemostatic assays (VHAs).

Summary Background Data: Admission data from conventional coagulation tests (CCT), rotational thrombelastometry (ROTEM) and thrombelastography (TEG) were collected prospectively at 6 European trauma centers during 2008-2013.

Methods: To identify significant VHA parameters capable of detecting TIC (defined as INR > 1.2), hypofibrinogenemia (< 2.0g/L) and thrombocytopenia (< 100 $x10^9$/L), univariate regression models were constructed. Area under the curve (AUC) was calculated, and threshold values for TEG and ROTEM parameters with 70% sensitivity were included in the algorithms.

Results: 2287 adult trauma patients (ROTEM: 2019 and TEG: 968) were enrolled. FIBTEM clot amplitude at 5 minutes (CA5) had the largest AUC and 10mm detected hypofibrinogenemia with 70% sensitivity. The corresponding value for Functional Fibrinogen (FF) TEG Maximum Amplitude (MA) was 19mm. Thrombocytopenia was similarly detected using the calculated threshold EXTEM-FIBTEM CA5 30mm. The corresponding rTEG-FF TEG MA was 46mm. TIC was identified by EXTEM CA5 41mm, rTEG MA 64mm (80% sensitivity). For hyperfibrinolysis, we examined the relationship between viscoelastic lysis parameters and clinical outcomes, with resulting threshold values of 85% for EXTEM Li30 and 10% for rTEG Ly30.

Based on these analyses we constructed algorithms for ROTEM, TEG and CCTs to be used in addition to ratio driven transfusion and tranexamic acid.

Conclusion: We describe a systematic approach to define threshold parameters for ROTEM and TEG. These parameters were incorporated into algorithms to support data-driven

adjustments of resuscitation with therapeutics, to optimize damage control resuscitation practice in trauma.

MINI-ABSTRACT:

This large cohort study defines threshold parameters for the treatment of trauma-induced coagulopathy with ROTEM and TEG in trauma. We derived new precision algorithms for the use of ROTEM and TEG to individualize care and optimize standard empiric hemostatic resuscitation practice.

INTRODUCTION

Trauma remains one of the world's leading causes of death [1] with upwards of 2 million people dying from trauma hemorrhage each year [1,2]. Advances in our understanding of trauma-induced coagulopathy (TIC) and new approaches to resuscitation have led to large improvements in outcomes [3]. However even in the best centers, one in four trauma patients with severe bleeding die, and overall mortality may approach 50% [4]. Current resuscitation often manages coagulopathy empirically, is non-specific and does not correct a pre-existing coagulopathy [5,6]. A targeted, precision medicine approach to the treatment of TIC may lead to improved outcomes while reducing overall requirements for red cells and component therapies.

TIC has multiple phenotypes and individual patients may present with different forms of coagulopathy at different times in their clinical course [7,8]. Contemporary resuscitation of bleeding trauma patients delivers volume resuscitation through an empiric, balanced transfusion of red blood cells, plasma and platelets in proportions approximating that of whole blood [9]. While this approach reduces the development of dilutional coagulopathy, it does not treat any underlying coagulopathy and does not fully support hemostasis in patients who require large volumes of transfusion [5,6]. The targeted correction of underlying coagulopathy using conventional coagulation tests (CCTs) is attractive in principle and supported by small trials [10,11]. However, the logistics of providing laboratory results in a suitable timeframe are challenging [11,12]. This has led to the suggestion of a hybrid approach, starting with empiric therapy and switching to an individualized, precision approach as soon as coagulation assessments are available [13-15]. This approach ideally requires rapidly available point of care assessments of coagulopathy and has resulted in renewed interest in viscoelastic hemostatic assays (VHAs) to diagnose the underlying

hemostatic deficiencies and to guide coagulation support. However, there is currently insufficient data to support the use of VHAs in trauma hemorrhage [16-20]. While a number of small studies shows VHA results can predict transfusion requirements or guide therapy, there is minimal evidence for parameters to guide the administration of coagulation therapeutics during active trauma hemorrhage [21-23].

The overall objective of this study was to develop pragmatic data-driven algorithms for the VHAs in the management of TIC during trauma hemorrhage. Our first aim was to determine, for both thromboelastometry (ROTEM®) and thromboelastography (TEG®), parameters and thresholds with high detection rate for TIC. We then aimed to determine the optimum parameters to guide therapy – specifically thresholds to guide the treatment of hypofibrinogenemia, thrombocytopenia, coagulation factor deficiency and hyperfibrinolysis. Finally, we wished to synthesize these findings into pragmatic algorithms for clinical practice.

METHODS

Study design

This study was part of the TACTIC (Targeted Action for Curing Trauma Induced Coagulopathy) program [24] of the International Trauma Research Network (INTRN) [25]. The prospective multinational observational study ACIT (Activation of Coagulation and Inflammation in Trauma) was the research platform for the study. Patients were recruited prospectively at six major trauma centers in five different countries - the UK, Denmark, Germany, the Netherlands and Norway.

Participants

Adult trauma patients who met the local criteria for full trauma team activation were eligible for inclusion. Patients who received more than 2000 mL of fluids before arrival in the

emergency department (ED) or who arrived more than 2 hours from time of injury were excluded, as were patients who were pregnant, had known liver failure, pre-existing bleeding disorders or were taking oral anticoagulants other than aspirin. Patients who had received blood products or Tranexamic Acid (TXA) before admission were not excluded. Initial consent was provided by a physician independent of the study. Written informed consent was obtained as soon as possible from the patients or their next of kin. The study was approved by local ethical authorities and performed in accordance with local ethical regulations and the Declaration of Helsinki.

Data collection

Patient demographics, time and mechanism of injury, pre-hospital fluid administration, vital signs on admission, total amount of fluids and blood products administered within the first 12 hours, and CCTs on admission were collected prospectively. Injury severity was scored when relevant information was available. TEG and ROTEM values were recorded electronically and later transferred manually to the case report form (CRF).

Sampling techniques and measurements

ACIT first began recruiting patients in 2008 with ROTEM, and TEG analyses were added in parallel from 2013. Blood samples were collected within 20 minutes of arrival in the ED. Samples for TEG, ROTEM and CCTs were collected in citrated tubes. Samples for blood gas analyses were collected in heparinized syringes in accordance with local routines. TEG and ROTEM were performed within one hour, at 37°C by dedicated study personnel using the TEG 5000® Thrombelastograph Hemostasis Analyzer (Haemonetics Corp., Braintree, MA, US) and the ROTEM Delta® (TEM international GmbH, Munich, Germany). The methodology and the parameters of TEG and ROTEM have been described previously [26,27].

ROTEM, TEG and CCT analyses

The ROTEM assays used in this study were the EXTEM and FIBTEM, both activated by tissue factor derived from rabbit brain, with cytochalasin D added to the FIBTEM sample for platelet inhibition [27]. TEG assays were standard TEG, where the sample is activated by Kaolin, Rapid TEG (rTEG) where the sample is activated by both Kaolin and tissue factor, and Functional Fibrinogen TEG (FF TEG) where lyophilized tissue factor with a platelet inhibitor Abciximab (a glycoprotein IIb/IIIa-inhibitor) is added for platelet inhibition to isolate the fibrin component of the clot [27]. The CCTs were Prothrombin Time (PT), fibrinogen concentration and platelet count (PLT). PT was converted to international normalized ratio (INR) in accordance with the specific reagents and device characteristics in the respective laboratories. Fibrinogen was measured by the Clauss method [28].

Definitions

We defined the presence of TIC as INR > 1.2 [12]; hypofibrinogenemia was defined as fibrinogen concentration < 2.0 g/L [9]; and thrombocytopenia as a platelet count below 100 x 10^9 /L [9,19]. In the absence of an accepted laboratory definition of hyperfibrinolysis in trauma patients we aimed to determine threshold values for treatment through their relationship with mortality and transfusion requirements.

Statistical analyses

Multiple imputations were performed on all TEG and ROTEM data, to deal with the missing data. Predictive mean matching was performed and 10 imputation sets were constructed. The imputations were tested using graphical density plots where the imputed data was plotted separately from the original data and convergence was checked. The outcomes from the analyses were pooled using Rubin's rule [29]. Statistical analyses were also performed with non-imputed data, to confirm that multiple imputations had not introduced unacceptable bias.

To identify significant VHA parameters capable of identifying TIC, hypofibrinogenemia and thrombocytopenia univariate regression models were constructed for these outcomes and areas under the curves (AUCs) were calculated. The platelet component was examined by subtracting the FIBTEM clot amplitude at 5 minutes (CA5) from the EXTEM CA5 and the FF TEG maximum amplitude (MA) from the rTEG MA. Threshold values for TEG and ROTEM parameters with sensitivities approaching 60%, 70%, 80% and 90% were calculated with corresponding specificities, Negative Predictive Values (NPVs) and Positive Predictive Values (PPVs).

The multiple imputations and the univariate analyses were performed with R version 3.1.2. All other analyses were performed with SPSS version 23 (IBM Corporation, United States).

Algorithm development

All centers in the TACTIC program have empiric replacement therapy of high-dose plasma and platelet transfusions given alongside red blood cell transfusions as the basis of their major hemorrhage protocol [3,19,30]. All centers also empirically give tranexamic acid to all patients activating the major hemorrhage protocol [31,32]. This concept of personalized hemostasis control augmenting baseline empiric therapy has been previously described as the 'Copenhagen Concept' [13-15].

Algorithms were based on the principles that they should be able to guide hemostatic therapy, namely fibrinogen replacement, platelet transfusions, plasma procoagulant supplementation and antifibrinolytic therapy. Algorithms were also to be as pragmatic and easy to follow as possible, using parameters that were not only strongly associated with underlying coagulopathy states, but also had face validity to clinicians. The key outputs of this study are the trigger thresholds for administration of coagulation therapies. We selected the earliest

available parameter that provided the required information and threshold levels that were at least 70% sensitive despite potentially low specificity, as the interventions are known to carry generally acceptable risk in a life-threatening setting. Threshold values were also selected to be easier to recall if small changes (e.g. rounding up or down) would not significantly alter the performance of individual parameters. For the therapies and doses associated with these thresholds we chose best practice levels from current guidelines and evidence.

RESULTS

From August 2008 to December 2014, a total of 2287 patients were recruited to ACIT across 6 sites. ROTEM was performed in 2019 patients, while 968 patients had TEG assessments on admission. Patient demographics, injury characteristics, admission parameters and outcomes were similar in both cohorts (Table 1). Overall approximately 6.5% of the cohort was coagulopathic by INR on admission and 15% required at least 4 units of red cell transfusions in the first 12 hours.

Detection of Hypofibrinogenemia

For ROTEM, the FIBTEM CA5 reported the highest AUC for hypofibrinogenemia (0.80) (Figure 1) (see Table, Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95% CI). As expected, FIBTEM maximum clot firmness (MCF) also performed well with an AUC of 0.78 (Figure 1) (see Table, Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95% CI). A FIBTEM CA5 threshold of 10mm had a sensitivity of 70%, specificity of 76% and NPV of 88% for the detection of hypofibrinogenemia (Table 2).

For TEG the rTEG MA was the best performing variable with an AUC of 0.76 (Figure 1) (see Table, Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95% CI). Both FF TEG MA and Kaolin-TEG MA had AUCs of 0.72 (Figure 1) (see Table,

Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95% CI). An FF-TEG MA of 19 mm had a sensitivity of 70% and specificity of 59% for the detection of hypofibrinogenemia, with an NPV of 89% (Table 2).

Detection of Thrombocytopenia

Only 44 (2%) ROTEM patients and 17 (1,5%) TEG patients presented with low platelet counts. The EXTEM-FIBTEM CA5 had an AUC of 0.75 for identifying patients with low platelet counts and EXTEM-FIBTEM MCF performed similarly with an AUC of 0.70 (see Table, Supplemental Digital Content 2: Detection of low platelets; AUCs and 95% CI) (see Figure, Supplemental Digital Content 3: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG, thrombocytopenia). An EXTEM-FIBTEM CA5 threshold of 30 mm had a sensitivity of 74% with a specificity of 63% and a NPV of 99% (Table 3).

For TEG the subtracting amplitude of FF TEG MA from the rTEG MA had an AUC of 0.54 (See Table, Supplemental Digital Content 2: Detection of low platelets; AUCs and 95% CI) (See Figure, Supplemental Digital Content 3: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG, thrombocytopenia). A rTEG – FF TEG MA threshold of 45 mm had a sensitivity of 65% with a specificity of 32% and NPV of 98% (Table 3).

Detection of Hyperfibrinolysis

To identify thresholds for the detection of hyperfibrinolysis we examined the relationship between viscoelastic lysis parameters and clinical outcomes. For ROTEM maximum lysis (ML) there was a step-change in mortality in patients with a ML above 20% (ML %: $\leq$ 20% vs > 20% - 9.5% vs 50.0%, $p < 0.001$). At 30 minutes, the ROTEM Lysis Index (LI30) parameter showed a similar mortality outcome threshold at 85% (LI30: < 85% vs $\geq$ 85% - 76.2% vs 10.8%, $p < 0.001$). Only 3.5% of those with an LI30 above 85 % subsequently

developed an ML > 20%, of which 4 patients died (10.5% mortality - not significantly different from LI30 ≥ 85% or ML < 20% groups). Mean 24-hour packed red blood cell (PRBC) requirements also increased markedly at LI30 levels below 85% (LI30: < 85% vs ≥ 85% - 14 vs 7 units, $p < 0.001$).

For TEG detection of hyperfibrinolysis, there was an increase in mortality at rTEG clot lysis at 30 minutes (LY30) values above 10% (LY30: ≤ 10% vs > 10% - 8.8% vs 60.0%, $p < 0.001$). There was an associated increase in PRBC requirements at this threshold: (LY30: ≤ 10% vs >10% - 2 vs 10 units, $p < 0.001$).

Detection of Coagulopathy

For ROTEM, EXTEM CA5 had the greatest AUC (0.78) for identification of INR >1.2 which was closely followed by the MCF, clot formation time (CFT), α-angle and clotting time (CT) (0.76, 0.76, 0.75 and 0.72, respectively) (Figure 2) (See Table, Supplemental Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). A CA5 threshold of 41 mm had a sensitivity of 73% for the detection of coagulopathy with a specificity of 70%, and a NPV of 97% (Table 4).

For detection of coagulopathy with TEG the highest AUC was with the FF TEG reaction time (r), α-angle and MA parameters, all with an AUC of 0.73 (Figure 2) (See Table, Supplemental Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). The rTEG r performed similarly with an AUC of 0.71, with rTEG activated clotting time (ACT) and MA at 0.69 and 0.67 respectively (Figure 2) (See Table, Supplemental Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). The best performing Kaolin-TEG variable was the MA with an AUC of 0.71. The Kaolin-TEG r had a much lower AUC at 0.58 (See Table, Supplemental Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). An rTEG

ACT of 121 had a sensitivity of 63 % for detection of coagulopathy with a specificity of 68% and a NPV of 96% (Table 4).

Algorithm Development

Based on the analyses above we constructed management algorithms for ROTEM, TEG and CCTs (Fig 3a, b and c respectively) to be used in addition to baseline damage control resuscitation (empiric high-dose plasma and platelets and baseline administration of tranexamic acid).

ROTEM

Given the principles of timely availability, adequate performance and pragmatic triggers, we defined a FIBTEM CA5 threshold of 10 mm for the dosing of additional fibrinogen (Table 2). For administering additional platelets transfusions, we used the EXTEM CA5 – FIBTEM CA5 threshold of < 30 mm. To identify those patients who may require additional plasma despite sufficient replacement of fibrinogen and platelets we selected a standard EXTEM CT value of > 80 seconds in the presence of a non-coagulopathic EXTEM CA5 (> 40 mm). Additional TXA would be administered when EXTEM LI30 < 85%.

TEG

We constructed a TEG algorithm using the same principles. We selected a FF TEG < 20 mm as a threshold value for additional fibrinogen (Table 2). For other parameters, rTEG parameters were used rather than Kaolin TEG for their timeliness [33], given there was no significant loss of sensitivity or specificity across these tests. We chose a rTEG – FF TEG MA below 45mm as a threshold for giving additional platelet transfusions (Table 3). For additional plasma, we again used a standard rTEG ACT > 120 seconds' threshold provided

there was no indication for fibrinogen or platelets (i.e. rapid TEG MA > 65 mm (Table 4)). A Rapid TEG LY30 > 10% was used as a threshold value for additional TXA.

For both ROTEM and TEG algorithms the suggested therapeutic interventions are the same and based on current best practice guidance or evidence. For fibrinogen supplementation, we suggest a replacement dose of 4g (usually as cryoprecipitate or fibrinogen concentrate) [34]; for low platelet levels, we suggest 1 pool of platelet transfusions; for evidence of low procoagulant activity we suggest additional plasma as an extra 4 units of FFP [6]; and for evidence of hyperfibrinolysis we suggest an additional 1g bolus of tranexamic acid [35,36].

DISCUSSION

We have defined accurate, rapidly available parameters that identify the key coagulation derangements that are corrected by available therapeutics, together with threshold values for their administration. With this large prospective cohort study across five countries we have developed data-driven algorithms for individualized hemostasis management of trauma patients. We adopted a pragmatic approach focusing on available hemostatic therapies as an addition to a baseline damage control resuscitation. The empiric ratio MTP continues until hemostasis, adding the available hemostatic therapies as guided by TEG/ROTEM or CCT as soon as the test results are available. In studying ROTEM and TEG devices in parallel we have produced algorithms applicable to all centers regardless of which device is available. This study therefore fills a considerable evidence gap in the role of viscoelastic hemostatic assays in the management of bleeding trauma patients [16-18,20,21].

The parameters proposed in this study will need further validation in subsequent studies. For internal validation, the ACIT study continues to run across the INTRN sites. External

validation will be needed from other centers and networks, especially those in other countries and healthcare systems. Although the parameters and thresholds used in our algorithms were data driven, there was limited evidence for the choice or dose of therapeutic agents. We used a combination of available evidence, guidelines and intrinsic expertise alongside the desire for the algorithms to be broadly applicable at an international level. Each individual agent and dose is worthy of further study. As a whole, the algorithms are being taken forward by the TACTIC partners into a randomized controlled trial (RCT) of viscoelastic assays versus conventional coagulation therapy (the iTACTIC trial, ClinicalTrials.gov Identifier: NCT02593877). This should provide evidence for the whole algorithm approach, which can be refined and updated with future investigations.

There are several limitations to our study in addition to the lack of a separate validation set. Despite the large cohorts and high injury severity scores, the number of coagulopathic and massively bleeding patients was around 15%. Some specific derangements, such as low platelet counts, were very rare, especially as we focused on the first sample drawn after admission. This will lead to bias to the negative predictive value of a parameter and potentially under-represent their positive predictive value and overall accuracy. Thresholds for hyperfibrinolysis had to be determined from clinical correlates in the absence of a definitive laboratory comparator test. The prehospital use of tranexamic acid will have contributed to the relatively low observed rates of admission hyperfibrinolysis, but should not have affected the actual threshold levels we calculated. Further external validation studies should be performed to confirm the applicability of these criteria for antifibrinolytic administration.

Some of the differences in performance between ROTEM and TEG parameters are also likely to be due to the difference in sample sizes between the two cohorts. As we aimed to develop

internationally relevant algorithms, we did not explore between-center variations in prehospital or in-hospital practices. However, overall the clinical and transfusion practices at the centers are more similar than they are different, and all adhere to modern practices of damage control resuscitation [30]. We therefore believe the study findings represent the real-world situation and are thus broadly applicable across similar healthcare systems.

CONCLUSION

In this large prospective cohort study, we have determined the clinically optimal tests, parameters and thresholds to guide hemostatic therapies in trauma patients. We present algorithms for a precision approach to TIC, augmenting standard damage control resuscitation practice. These algorithms are being taken forward for evaluation in the iTACTIC multicenter randomized controlled trial of viscoelastic assays versus CCTs on clinical outcomes in trauma hemorrhage.

ACKNOWLEDGMENTS

TACTIC/ INTRN collaborators: R. Bergman, H. Campbell, N. Curry, E.K. Stürmer, N. Schäfer, A. Driessen, A. Orr, K. Görlinger, N. Flåten, K.M. Kolstadbraaten

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TABLES:

FIGURES:

SUPPLEMENTAL DIGITAL CONTENT