Journal of Thrombosis and Haemostasis, **17**: 441–448 DOI: 10.1111/jth.14378

ORIGINAL ARTICLE

Towards patient-specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry

NICOLE P. JUFFERMANS,* MATHIJS R. WIRTZ,* KIRSTEN BALVERS,*† KJERSTI BAKSAAS-AASEN,‡§ SUSAN VAN DIEREN,* CHRISTINE GAARDER,‡ PAUL A. NAESS,‡ SIMON STANWORTH,¶** PÄR I. JOHANSSON,†† JAKOB STENSBALLE,†† MARC MAEGELE,‡‡ J. C. GOSLINGS† and KARIM BROHI§§ FOR THE TACTIC PARTNERS[1]

**Department of Intensive Care Medicine, Amsterdam UMC, Academic Medical Center; †Trauma Unit, Department of Surgery, Academic Medical Center, Amsterdam, the Netherlands; ‡Department of Traumatology, Oslo University Hospital; §Department of Anesthesiology, Oslo University Hospital, Oslo, Norway; ¶NHS Blood and Transplant/Oxford University Hospitals NHS Trust, John Radcliffe Hospital; **Radcliffe Department of Medicine, University of Oxford, Oxford, UK; ††Department of Anesthesiology and Trauma Center, Center for Head and Orthopedics, and Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; ‡‡Department for Traumatology and Orthopedic Surgery, Cologne-Merheim Medical Center, University of Witten/Herdecke, Cologne, Germany; and §§Trauma Sciences, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK*

To cite this article: Juffermans NP, Wirtz MR, Balvers K, Baksaas-Aasen K, van Dieren S, Gaarder C, Naess PA, Stanworth S, Johansson PI, Stensballe J, Maegele M, Goslings JC, Brohi K for the TACTIC partners. Towards patient-specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry. *J Thromb Haemost* 2019; **17**: 441–8.

Essentials

- The response of thromboelastometry (ROTEM) parameters to therapy is unknown.
- We prospectively recruited hemorrhaging trauma patients in six level-1 trauma centres in Europe.
- Blood products and pro-coagulants prevent further derangement of ROTEM results.
- ROTEM algorithms can be used to treat and monitor trauma induced coagulopathy.

Summary. *Background:* Rotational thromboelastometry (ROTEM) can detect trauma-induced coagulopathy (TIC) and is used in transfusion algorithms. The response of ROTEM to transfusion therapy is unknown. *Objectives:* To determine the response of ROTEM profiles to therapy in bleeding trauma patients. *Patients/Methods:* A prospective multicenter study in bleeding trauma patients (receiving ≥ 4 red blood cell [RBC] units) was performed. Blood was drawn in the emergency department, after administration of 4, 8 and 12 RBC units and 24 h post-injury. The response of ROTEM to plasma, platelets (PLTs), tranexamic acid (TXA) and fibrinogen products was evaluated in the whole cohort as well as in the subgroup of patients with ROTEM values indicative of TIC. *Results:* Three hundred and nine bleeding and shocked patients were included. A mean dose of 3.8 g of fibrinogen increased FIBTEM CA5 by 5.2 mm (IQR: 4.1–6.3 mm). TXA administration decreased lysis by 5.4% (4.3–6.5%). PLT transfusion prevented further derangement of parameters of clot formation. The effect of PLTs on EXTEM ca5 values was more pronounced in patients with a ROTEM value indicative of TIC than in the whole cohort. Plasma transfusion decreased EXTEM clotting time by 3.1 s (− 10 s to 3.9 s) in the whole cohort and by 10.6 s (− 45 s to 24 s) in the subgroup of patients with a ROTEM value indicative of TIC. *Conclusion:* The effects of therapy on ROTEM values were small, but prevented further derangement of test results. In patients with ROTEM values indicative of TIC, the efficacy of PLTs and plasma in correcting deranged ROTEM parameters is possibly more robust.

Keywords: hemorrhage; ROTEM; transfusion; trauma; viscoelastic hemostatic assay.

Correspondence: Nicole Juffermans, Department of Intensive Care, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
Tel.: +31 20 566 8090
E-mail: n.p.juffermans@amc.uva.nl

[1]See Appendix for full list of contributors.

Received: 16 October 2018
Manuscript handled by: M. Levi
Final decision: P. H. Reitsma, 19 December 2018

Introduction

Trauma-induced coagulopathy (TIC) develops in up to 25% of severely injured trauma patients, aggravates

massive hemorrhage, and is associated with increased mortality [1,2]. Current resuscitation practices often include an empirical balanced resuscitation approach with administration of red blood cells (RBCs), plasma and platelets (PLTs) in a 1 : 1 : 1 ratio [3–5]. Although this nonspecific strategy reduces the development of dilutional coagulopathy, it may not correct different pre-existing forms of coagulopathy that are present in individual patients [6,7]. Also, this empirical approach fails to correct TIC in recipients of large volumes of blood [8,9]. Implementation of the empirical 1 : 1 : 1 strategy, often as part of massive transfusion protocols, has increased the amount of blood products transfused [10]. As transfusion is also associated with adverse outcomes, including infections [11] and organ failure [12–15], the outcome of traumatic bleeding is probably optimal with a targeted, precision-medicine approach to the management of TIC, leading to improved outcomes while avoiding unnecessary transfusion.

This precision approach requires monitoring of the effects of therapy. Clotting tests, such as prothrombin time, activated partial thromboplastin time, and PLT count, have limited usefulness in guiding resuscitation strategy [16–18]. Viscoelastic hemostatic assays (VHAs), such as thrombelastography (TEG) and rotational thromboelastometry (ROTEM), are rapid tests that can identify TIC in trauma patients [19–21]. A trial in which trauma patients were randomized to either TEG or conventional tests to guide laboratory-based transfusion therapy showed a survival benefit for the TEG-guided arm, while the amount of blood products needed was decreased [22]. These results are promising, although the effects need to be validated in larger multicenter trials. Also, the response of VHA parameters to therapy given during bleeding is not known. Therefore, existing algorithms only provide threshold levels that trigger therapy [22–25]. In order to identify effective therapy for TIC, algorithms based on VHA parameters need to be refined. The aim of this study was to determine the response of ROTEM parameters to therapy in bleeding trauma patients.

Methods

As part of a prospective multicenter observational study, termed the Activation of Coagulation and Inflammation in Trauma study (United Kingdom Clinical Research Network Study Portfolio, ID: 5637), this study was performed in six European level 1 trauma centers, i.e. London, Oslo, Copenhagen, Oxford, Cologne, and Amsterdam, which are members of the International Trauma Research Network (INTRN). All adult trauma patients (aged $\geq$ 18 years) who required full trauma team activation, who received at least 4 units of RBCs within 24 h, and who were still alive after 24 h, were recruited between January 2008 and April 2015. Patients who received > 2 L of intravenous fluids prior to arrival at the hospital, who arrived in the emergency department (ED) > 2 h after injury, who were transferred from other hospitals and who had burns covering > 5% of the total body surface area were not eligible. Patients were retrospectively excluded if they declined to give informed consent, were taking anticoagulant medications other than aspirin (< 650 mg daily), had moderate or severe liver disease (Child's classification B or C3), had a known bleeding diathesis, had no ROTEM measurements available, or died within 24 h post-injury.

Written informed consent was obtained from each patient. When the patient was unconscious, written informed consent was obtained from a legal representative. This study was conducted according to the Statement of the Declaration of Helsinki, and was performed after approval by the local ethics committees.

The following data were collected prospectively and placed in a centralized database: data on patient demographics, time of injury, trauma mechanism, vital signs and laboratory test results up to 24 h post-injury, Injury Severity Score (ISS), Abbreviated Injury Scale score, 24-h and 28-day mortality, total fluids (crystalloids, colloids, and hypertonic saline), amount of RBC units, plasma and PLT units, and antifibrinolytic (tranexamic acid [TXA]) and procoagulant agents (fibrinogen concentrates and cryoprecipitate).

Blood sampling and ROTEM assays

Blood was drawn and collected in citrated tubes immediately on arrival at the ED and at 24 h post-injury. Additionally, during resuscitation with blood component therapy, blood samples were drawn after administration of 4, 8 and 12 RBC units. The dose of plasma and PLTs given in the intervals between blood draws was also prospectively collected. Two ROTEM assays (EXTEM and FIBTEM) were performed by trained personnel after blood samples were taken. These assays were chosen on the basis of our previous results obtained when we were determining threshold values for TIC [26]. Within each assay, six ROTEM parameters were analyzed: the clotting time (CT), the clot amplitude after 5 min (CA5), the clot amplitude after 10 min, the angle of tangent at 20-mm amplitude (α angle), the maximum clot firmness, and the lysis index of the clot after 30 min (LY30).

In this same patient cohort, we recently determined ROTEM thresholds with a high detection rate for TIC, as measured on ED arrival [26]. FIBTEM CA5 had the highest diagnostic performance in detecting a low fibrinogen level (< 2.0 g dL^{-1}), with a cut-off value of < 10 mm. EXTEM-FIBTEM CA5 had the highest diagnostic performance in detecting a low PLT count (< 100×10^9 L^{-1}), with a threshold of 30 mm. EXTEM LY30 below 85% was associated with sudden increases in RBC requirements and mortality. EXTEM ca5 had the highest diagnostic performance in detecting coagulopathy, as defined by an International Normalized Ratio (INR) of > 1.2, with a CA5 threshold of 40 mm. The response of ROTEM parameters

to treatment was investigated in all bleeding patients, as well as in those patients with a ROTEM profile corresponding to TIC upon ED arrival. The number of PLT units was corrected for the number of pooled donors, as this differs between centers.

The effect of plasma and PLT therapy on ROTEM parameters was analyzed by relating the therapy given within a time interval to changes in ROTEM results in the following measurement. These intervals are the baseline to 4 RBC units time point, the 4 RBC units to 8 RBC units time point, and the 8 RBC units to 12 RBC units time point. This approach was chosen because VHA parameters change rapidly in response to blood products. To describe the effects of TXA and fibrinogen products on ROTEM VHA profiles, the change between baseline and 24-h measurements was used. Intervals in which a ROTEM value was missing, and the change for ROTEM values could therefore not be calculated, were left out. This resulted in a variable amount of intervals that could be evaluated. There was no loss of data regarding the 28 day mortality. Other outcome data were not gathered, as the denominator of measurements comprises intervals and not patients.

Transfusion strategy

In all trauma centers, issuing of blood products, antifibrinolytic agents and procoagulant agents by the blood bank was performed through locally implemented massive transfusion protocols (MTPs). In most centers, the MTP was activated for patients with a systolic blood pressure of < 90 mmHg and with an inadequate response to fluid administration, and for whom there was a suspicion of ongoing bleeding. Centers empirically applied blood products in a fixed ratio. Administration of TXA, followed by continuous infusion for a period of 8 h, was used as a principal component of the MTP in all centers. Cryoprecipitate was used in London, Oxford, and Copenhagen, and fibrinogen concentrates were used in Oslo, Cologne, and Amsterdam. The trigger for use of these concentrated fibrinogen products differed between centers, from a fibrinogen level of ≤ 1.0 g L^{-1} to a fibrinogen level of ≤ 2.0 g L^{-1}. Centers had a restrictive approach to the use of fluids, but there was no shared protocol on fluid management. Differences in protocols have been described previously [27].

Statistics

Sample size was not prespecified in this exploratory study, as ROTEM responses to therapy have not been described before. Patient characteristics and ROTEM values are given in the tables, and expressed as mean and standard deviation (SD) if normally distributed; non-normally distributed data are expressed as median and interquartile ranges. Categorical data are presented as frequencies and percentages. To test for differences in patient characteristics and ROTEM profiles, Student's *t*-test and Mann–Whitney *U*-tests were used. Categorical variables were compared by use of the chi-square test. For multiple comparisons, a one-way ANOVA was used. A *P*-value of < 0.05 was considered to be statistically significant.

Results

In total, 309 patients for whom ROTEM profiles were available were transfused with ≥ 4 RBC units (their characteristics are shown in Table 1). Most patients had sustained a blunt trauma, were in shock, and were coagulopathic, as reflected by a prolonged mean INR and decreased levels of fibrinogen. The mean baseline ROTEM variables were mostly within the reference values as provided by the manufacturer (Table 2). All measurements together yielded 426 time intervals in which the effect of transfusion strategy on the ROTEM profiles could be determined, although the amount of intervals available for analysis varied per treatment and per test.

ROTEM response to treatment with fibrinogen

Of the 309 patients, 119 (39%) received fibrinogen products, containing a mean of 3.8 g (SD 1.2 g) of fibrinogen. Patients given fibrinogen products were more severely injured, as reflected by a higher ISS, and more acidotic than those not receiving fibrinogen (Table S1). Also, baseline fibrinogen levels were lower in patients receiving fibrinogen. Despite this, in the whole group of patients receiving fibrinogen, administration of fibrinogen products resulted in a greater increase in FIBTEM parameters than in patients not receiving fibrinogen (Table 3). In patients with a ROTEM profile known to correspond with a low fibrinogen level (FIBTEM CA5 < 10 mm) [26], the response to therapy was the same as in the whole cohort receiving fibrinogen.

Table 1 Baseline characteristics and outcome of patients receiving ≥ 4 red blood cell units

	N = 309 (SD)
Age (years)	44.8 (1.1)
Male gender (%)	73
Trauma mechanism, blunt (%)	83
ISS	29.1 (0.7)
SBP (mmHg)	106.2 (1.9)
Heart rate (beats min^{-1})	110.2 (1.7)
Lactate (mmol L^{-1})	5.1 (4.4)
GCS	10.8 (0.3)
Hb (g dL^{-1})	12.5 (0.1)
Platelet count ($\times 10^9$ L^{-1})	214.2 (4.1)
INR	1.22 (0.1)
Fibrinogen (g L^{-1})	1.9 (0.1)
Base excess (mEq L^{-1})	− 7.5 (0.4)
28-day mortality (%)	22.9

GCS, Glasgow Coma Score; Hb, hemoglobin; INR, International Normalized Ratio; ISS, Injury Severity Score; SBP, systolic blood pressure.

ROTEM response to treatment with platelets

Of the 309 patients, 212 (69%) received PLTs. Patients given PLTs had lower baseline platelet counts than those not receiving PLTs, although the PLT count was normal in most patients (Table S2). In all patients, EXTEM parameters of clot formation worsened during the course of bleeding and treatment (Table 4). In the whole group of patients receiving PLTs, EXTEM values were higher during management than in those not receiving PLTs, although the difference did not reach statistical significance. In patients with a ROTEM profile known to correspond to low PLT levels [26], the decrease in EXTEM ca5 was significantly less than in those not receiving therapy.

ROTEM response to treatment with plasma

Of the 309 patients, 280 (91%) received plasma. The patients receiving plasma were more shocked, as reflected by a higher heart rate and lower base excess (Table S3). In the whole group of patients receiving plasma, plasma transfusion significantly reduced EXTEM CT, with a mean of 3.1 s, as compared with patients not receiving plasma (Table 5), in whom EXTEM CT was prolonged during bleeding and management. In those patients with an EXTEM CT known to correspond to coagulopathy, ROTEM responses to therapy were more pronounced, with an EXTEM CT reduction of 10.6 s, although statistical significance was not reached, owing to a wide confidence interval. It is of note that the amount of intervals was small.

Table 2 Baseline rotational thromboelastometry variables of patients receiving ≥ 4 red blood cell units

	N = 309
EXTEM CT (s)	70.3 (2.0)
EXTEM CA5 (mm)	39.7 (0.6)
EXTEM CA10 (mm)	49.6 (0.7)
EXTEM MCF (mm)	58.5 (0.6)
EXTEM α angle (°)	67.9 (0.6)
EXTEM LY30 (%)	96.9 (1.0)
EXTEM CFT (s)	136.4 (10.9)
FIBTEM CA5 (mm)	10.0 (0.3)
FIBTEM CA10 (mm)	10.9 (0.3)
FIBTEM MCF (mm)	12.7 (0.4)
FIBTEM α angle (°)	61.7 (0.5)
FIBTEM LY30 (%)	94.9 (1.0)

CA5, clot amplitude after 5 min; CA10, clot amplitude after 10 min; CFT, clot formation time; CT, clotting time; LY30, lysis index of the clot after 30 min; MCF, maximum clot firmness. Data are mean and standard error of the mean.

ROTEM response to treatment with TXA

Use of TXA was not registered in 19 patients. Of the remaining 290 patients, 112 (39%) received TXA. Patients given TXA were more severely injured, as reflected by a higher ISS, and were more shocked and more acidotic than those not receiving TXA (Table S4). In the whole group of patients receiving TXA, administration of TXA resulted in greater improvements in lysis and FIBTEM parameters than in patients not receiving TXA (Table 6). In those patients with a LY30 suggestive of hyperfibrinolysis [26], the response to therapy was the same as in the whole cohort receiving TXA.

Discussion

The results indicate that, during management of patients with traumatic bleeding, almost all of the ROTEM profiles show further deterioration. This study suggests that the effect of treatment with transfusion products and procoagulant therapy with the aim of improving deranged ROTEM parameters can be monitored during traumatic hemorrhage. Fibrinogen, plasma, PLTs and TXA improve ROTEM parameters of clot formation and firmness, and decrease clot lysis. Although the effects can be described as modest, it must be noted that these improvements were detected during ongoing resuscitation of patients who were actively bleeding. In the subgroup of patients with ROTEM threshold values that were previously identified to correspond to coagulopathy (i.e. low fibrinogen levels, thrombocytopenia, increased fibrinolysis, and/or an INR of > 1.2), the efficacy of plasma and PLTs in correcting ROTEM parameters was possibly more robust than in the whole bleeding population receiving treatment.

We previously showed that, in the same cohort of patients, administration of fibrinogen did not result in

Table 3 Rotational thromboelastometry (ROTEM) response to fibrinogen

	All patients receiving fibrinogen *N* = 119 intervals	Patients with FIBTEM CA5 < 10 receiving fibrinogen *N* = 82 intervals	Patients not receiving fibrinogen *N* = 190 intervals
FIBTEM CA5 (mm)	5.0 (3.9–6.1)*	5.1 (3.8–6.4)*	2.4 (1.5–3.3)
FIBTEM CA10 (mm)	5.5 (4.2–6.8)*	5.5 (4.1–7.0)*	2.8 (1.8–3.7)
FIBTEM MCF (mm)	5.8 (4.1–7.4)*	5.8 (3.8–7.9)*	2.1 (0.8–3.6)
FIBTEM α angle (°)	8.4 (5.3–11.6)*	8.4 (5.4–11.4)*	3.2 (1.0–5.5)

CA5, clot amplitude after 5 min; CA10, clot amplitude after 10 min; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving fibrinogen. ROTEM response was determined in the interval between baseline and $t = 24$ h.

Table 4 Rotational thromboelastometry (ROTEM) response to platelets

	All patients receiving platelets $N = 137$ intervals	Patients with EXTEM ca5 – FIBTEM CA5 < 30 receiving platelets $N = 25$ intervals	Patients not receiving platelets $N = 103$ intervals
EXTEM ca5 (mm)	− 1.55 (− 4.48 to 1.37)	0.74 (− 4.77 to 6.25)*	− 4.39 (− 6.06 to − 2.72)
EXTEM CA10 (mm)	− 1.14 (− 4.24 to 1.95)	0.53 (− 5.6 to 6.66)	− 4.13 (− 5.96 to − 2.3)
EXTEM MCF (mm)	− 0.11 (− 2.77 to 2.55)	1.45 (− 3.92 to 6.81)	− 2.67 (− 4.58 to − 0.75)
EXTEM α angle (°)	0.43 (− 2.96 to 3.82)	1.18 (− 5.8 to 8.16)	− 3.34 (− 5.07 to − 1.62)

CA5, clot amplitude after 5 min; CA10, clot amplitude after 10 min; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving platelets. ROTEM response was determined in intervals during resuscitation therapy.

Table 5 Rotational thromboelastometry (ROTEM) response to plasma

	All patients receiving plasma $N = 117$ intervals	Patients with EXTEM CT > 80 and CA5 > 40 receiving plasma $N = 17$ intervals	Patients not receiving plasma $N = 42$ intervals
EXTEM CT (s)	− 3.1 (− 10.0 to 3.9)*	− 10.6 (− 45.7 to 24.2)	10.8 (− 0.8 to 22.3)
EXTEM MCF (mm)	− 1.7 (− 3.3 to − 0.1)	− 5.2 (− 12.1 to 1.7)	− 4.1 (− 7.9 to − 0.4)
EXTEM CFT (s)	19.5 (4.7–34.3)	30.31 (1.2–59.4)	37.4 (5.4–69.4)

CT, clotting time; CFT, clot formation time; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving plasma. ROTEM response was determined in intervals during resuscitation therapy.

Table 6 Rotational thromboelastometry (ROTEM) response to tranexamic acid (TXA)

	All patients receiving TXA $N = 76$ intervals	Patients with EXTEM LY30 < 85% receiving TXA $N = 34$ intervals	Patients not receiving TXA $N = 170$ intervals
EXTEM LY30 (%)	5.4 (4.3–6.5)*	5.4 (4.1–6.7)*	3.0 (2.1–3.9)
FIBTEM CA5 (mm)	6.0 (4.8–7.3)*	6.1 (4.6–7.5)*	3.6 (2.6–4.5)
FIBTEM CA10 (mm)	6.1 (4.4–7.9)*	6.1 (3.6–8.6)*	3.2 (1.7–4.6)
FIBTEM MCF (mm)	8.1 (5.3–10.9)*	8.1 (5.0–11.2)*	3.3 (0.8–5.8)
FIBTEM α angle (°)	5.4 (4.4–6.5)*	5.4 (4.1–6.7)*	3.0 (2.1–3.9)
FIBTEM LY30 (%)	6.0 (4.8–7.3)*	6.0 (4.5–7.5)*	3.6 (2.6–4.5)

CA5, clot amplitude after 5 min; CA10, clot amplitude after 10 min; LY30, lysis index of the clot after 30 min; Data are median and interquartile range (IQR); MCF, maximum clot firmness. *$P < 0.05$ versus not receiving TXA. ROTEM response was determined in the interval between baseline and $t = 24$ h.

correction of low fibrinogen levels in patients who are actively bleeding [28]. Here, we show that a mean dose of fibrinogen of 3.8 g improves EXTEM ca5 levels by 5 mm. Therefore, this ROTEM marker may guide fibrinogen dosing in patients with traumatic bleeding. Notably, it was shown previously that low fibrinogen levels are associated with adverse outcomes in patients with traumatic hemorrhage [29–31]. Unfortunately, we cannot provide further analysis of the effect of fibrinogen dose on correction of ROTEM parameters, because the exact timing of fibrinogen administration was not noted.

For monitoring of the effect of TXA, there are currently no conventional clotting tests available at the bedside. In this study, 1 g of TXA improved all early markers of clot formation, and decreased markers of lysis. It was shown previously that TXA administration is associated with a good outcome [28]. Taken together, the results indicate that monitoring of the effect of procoagulant therapy on TIC is possible during the management of bleeding trauma patients.

Plasma transfusion reduced EXTEM CT, whereas, in patients not receiving plasma, EXTEM CT was further prolonged during bleeding. As EXTEM CT is a marker of TIC that occurs very early during ROTEM testing, the results suggest that EXTEM CT may guide the specific need for an increased dose of plasma. Note that, as low fibrinogen levels affect the whole coagulation process, and fibrinogen will also reduce EXTEM CT, one may first consider correcting a fibrinogen deficiency with fibrinogen concentrates prior to considering additional plasma.

In severe injury, a drop in the PLT count occurs late [32]. Therefore, the PLT count as such may not be a

useful transfusion trigger. In this study, in which most patients had normal PLT counts, the derangement of EXTEM parameters of clot formation was less pronounced in patients receiving PLT transfusion, which may suggest that EXTEM parameters are more useful then PLT counts in monitoring effects of therapy.

Previously, in the same cohort of patients, threshold ROTEM values corresponding to TIC and adverse outcomes were identified [26]. With these values, algorithms for guidance of the management of patients with TIC were constructed. The aim of this study was to provide follow-up data. Here, we show that, in bleeding patients, transfusion of plasma and PLTs in those patients with ROTEM levels that would trigger therapy according to threshold values corresponding to TIC [26] resulted in more improvement of ROTEM values than in the whole group of bleeding patients. However, the effect of plasma did not reach statistical significance, probably because of a loss of data points. Whether use of the algorithm to guide therapy results in better outcomes while reducing unnecessary transfusion is currently under investigation in a randomized controlled trial [33].

Limitations of this study should be acknowledged. Studies were performed in patients with ongoing bleeding, in whom the rate of bleeding most likely affected ROTEM results, but this is impossible to account for. Another issue is that blood products were administered together, making it impossible to attribute an effect on ROTEM values to a specific therapy. However, these issues reflects real-life clinical practice. Another important limitation is that we were not able to report on ROTEM changes in response to different doses of fibrinogen and TXA. This remains an area that needs to be explored. Also, exsanguinating patients were excluded, in order to provide for follow-up samples. Therefore, the results may not apply to the most severely bleeding patients. Also, as most patients in this study had sustained blunt injuries, it remains to be determined whether the response to therapy is the same in patients with penetrating injury. Finally, transfusion protocols differ between centers, which is a limitation of this observational study.

Conclusion

VHAs such as ROTEM can be used for monitoring of treatment for TIC during ongoing traumatic hemorrhage. In patients with ROTEM threshold values known to correspond to coagulopathy, the efficacy of plasma and PLTs was possibly clearer than in the whole bleeding population, suggesting that ROTEM-based algorithms can be used to treat and monitor TIC.

Addendum

N. P. Juffermans, C. Gaarder, S. Stanworth, P. I. Johansson, M. Maegele, J. C. Goslings, and K. Brohi study concept and design. N. P. Juffermans, M. R. Wirtz, K. Balvers, K. Baksaas-Aasen, S. van Dieren, C. Gaarder, P. A. Naess, S. Stanworth, P. I. Johansson, J. Stensballe, M. Maegele, J. C. Goslings, and K. Brohi acquisition, analysis or interpretation of data. N. P. Juffermans, K. Balvers, and M. R. Wirtz drafting of the manuscript. N. P. Juffermans, M. R. Wirtz, K. Balvers, K. Baksaas-Aasen, S. van Dieren, C. Gaarder, P. A. Naess, S. Stanworth, P. I. Johansson, J. Stensballe, M. Maegele, J. C. Goslings, and K. Brohi critical revision of the manuscript for important intellectual content. N. P. Juffermans, S. van Dieren, and K. Baksaas-Aasen: statistical analysis. N. P. Juffermans, C. Gaarder, S. Stanworth, P. I. Johansson, M. Maegele, J. C. Goslings, and K. Brohi study supervision.

Acknowledgements

All author institutes are affiliated members of the INTRN, and as such this work represents a combined output resulting from this Network. Funding: The research leading to these results has received funding from the European Commission under FP7 HEALTH-Contract No. F3-2013-602771 and from TEM international GmbH.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

TACTIC partners

R. Bergman, K. M. Kolstadbråten, C. Rourke, L. Gall, N. Curry, E. K. Stürmer, N. Schäfer, A. Driessen, A. Schubert, K. Görlinger, M. Harrison, J. Buchanan, J. D. Dias, S. Neble, and H. Sayel.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Baseline patient characteristics stratified by fibrinogen treatment.
Table S2. Baseline characteristics of patients stratified by platelet transfusion therapy.
Table S3. Baseline characteristics of patients stratified by plasma transfusion therapy.
Table S4. Baseline characteristics of patients stratified by TXA treatment.

References

1 Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma* 2003; **54**: 1127–30.

2 MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma* 2003; **55**: 39–44.

3 Johansson PI, Oliveri RS, Ostrowski SR. Hemostatic resuscitation with plasma and platelets in trauma. *J Emerg Trauma Shock* 2012; **5**: 120–5.

4 Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013; **148**: 127–36.

5 Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BR, Scalea TM, *et al*. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015; **313**: 471–82.

6 Stensballe J, Ostrowski SR, Johansson PI. Haemostatic resuscitation in trauma: the next generation. *Curr Opin Crit Care* 2016; **22**: 591–7.

7 Meledeo MA, Herzig MC, Bynum JA, Wu X, Ramasubramanian AK, Darlington DN, Reddoch KM, Cap AP. Acute traumatic coagulopathy: the elephant in a room of blind scientists. *J Trauma Acute Care Surg* 2017; **82**: S33–40.

8 Khan S, Brohi K, Chana M, Raza I, Stanworth S, Gaarder C, Davenport R. Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. *J Trauma Acute Care Surg* 2014; **76**: 561–7; discussion 7–8.

9 Khan S, Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, Curry N, Stanworth S, Gaarder C, Brohi K. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. *Intensive Care Med* 2015; **41**: 239–47.

10 Balvers K, Coppens M, van Dieren S, van Rooyen-Schreurs IH, Klinkspoor HJ, Zeerleder SS, Baumann HM, Goslings JC, Juffermans NP. Effects of a hospital-wide introduction of a massive transfusion protocol on blood product ratio and blood product waste. *J Emerg Trauma Shock* 2015; **8**: 199–204.

11 Juffermans NP, Vlaar AP, Prins DJ, Goslings JC, Binnekade JM. The age of red blood cells is associated with bacterial infections in critically ill trauma patients. *Blood Transfus* 2012; **10**: 290–5.

12 Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Arch Surg* 2005; **140**: 432–8.

13 Johnson JL, Moore EE, Kashuk JL, Banerjee A, Cothren CC, Biffl WL, Sauaia A. Effect of blood products transfusion on the development of postinjury multiple organ failure. *Arch Surg* 2010; **145**: 973–7.

14 Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg* 1997; **132**: 620–4.

15 Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. *Arch Surg* 1994; **129**: 39–45.

16 Holcomb JB, Minei KM, Scerbo ML, Radwan ZA, Wade CE, Kozar RA, Gill BS, Albarado R, McNutt MK, Khan S, Adams PR, McCarthy JJ, Cotton BA. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. *Ann Surg* 2012; **256**: 476–86.

17 Dzik WH. Predicting hemorrhage using preoperative coagulation screening assays. *Curr Hematol Rep* 2004; **3**: 324–30.

18 Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, Pusateri AE, Vos JA, Guymon CH, Wolf SE, Mann KG, Holcomb JB. Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. *J Trauma* 2009; **67**: 266–75. Discussion 75–6.

19 Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, Stanworth S, Brohi K. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011; **39**: 2652–8.

20 Woolley T, Midwinter M, Spencer P, Watts S, Doran C, Kirkman E. Utility of interim ROTEM((R)) values of clot strength, A5 and A10, in predicting final assessment of coagulation status in severely injured battle patients. *Injury* 2013; **44**: 593–9.

21 Rugeri L, Levrat A, David JS, Delecroix E, Floccard B, Gros A, Allaouchiche B, Negrier C. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* 2007; **5**: 289–95.

22 Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, Wohlauer MV, Barnett CC, Bensard DD, Biffl WL, Burlew CC, Johnson JL, Pieracci FM, Jurkovich GJ, Banerjee A, Silliman CC, Sauaia A. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Ann Surg* 2016; **263**: 1051–9.

23 Maegele M, Nardi G, Schochl H. Hemotherapy algorithm for the management of trauma-induced coagulopathy: the German and European perspective. *Curr Opin Anaesthesiol* 2017; **30**: 257–64.

24 Schochl H, Maegele M, Solomon C, Gorlinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. *Scand J Trauma Resusc Emerg Med* 2012; **20**: 15.

25 Stettler GR, Moore EE, Nunns GR, Chandler J, Peltz E, Silliman CC, Banerjee A, Sauaia A. Rotational thromboelastometry thresholds for patients at risk for massive transfusion. *J Surg Res* 2018; **228**: 154–9.

26 Baksaas-Aasen K, Van Dieren S, Balvers K, Juffermans NP, Naess PA, Rourke C, Eaglestone S, Ostrowski SR, Stensballe J, Stanworth S, Maegele M, Goslings C, Johansson PI, Brohi K, Gaarder C. Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage: a prospective observational multicenter study. *Ann Surg* 2018. https://doi.org/10.1097/SLA.0000000000002825

27 Schafer N, Driessen A, Frohlich M, Sturmer EK, Maegele M. Diversity in clinical management and protocols for the treatment of major bleeding trauma patients across European level I Trauma Centres. *Scand J Trauma Resusc Emerg Med* 2015; **23**: 74.

28 Balvers K, van Dieren S, Baksaas-Aasen K, Gaarder C, Brohi K, Eaglestone S, Stanworth S, Johansson PI, Ostrowski SR, Stensballe J, Maegele M, Goslings JC, Juffermans NP. Combined effect of therapeutic strategies for bleeding injury on early survival, transfusion needs and correction of coagulopathy. *Br J Surg* 2017; **104**: 222–9.

29 Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012; **10**: 1342–51.

30 Inaba K, Karamanos E, Lustenberger T, Schochl H, Shulman I, Nelson J, Rhee P, Talving P, Lam L, Demetriades D. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg* 2013; **216**: 290–7.

31 Hagemo JS, Stanworth S, Juffermans NP, Brohi K, Cohen M, Johansson PI, Roislien J, Eken T, Naess PA, Gaarder C.

Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. *Crit Care* 2014; **18**: R52.

32 Stansbury LG, Hess AS, Thompson K, Kramer B, Scalea TM, Hess JR. The clinical significance of platelet counts in the first 24 hours after severe injury. *Transfusion* 2013; **53**: 783–9.

33 Baksaas-Aasen K, Gall L, Eaglestone S, Rourke C, Juffermans NP, Goslings JC, Naess PA, van Dieren S, Ostrowski SR, Stensballe J, Maegele M, Stanworth SJ, Gaarder C, Brohi K, Johansson PI. iTACTIC – implementing treatment algorithms for the correction of trauma-induced coagulopathy: study protocol for a multicentre, randomised controlled trial. *Trials* 2017; **18**: 486.