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

Running head: Response of thromboelastometry profiles to therapy.

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Essentials

- The response of thromboelastometry (ROTEM) parameters to therapy is unknown.
- Prospectively recruited haemorrhaging trauma patients in 6 level-1 trauma centres in Europe.
- Blood products and pro-coagulants prevent further derangement of ROTEM results, although effects are small.
- ROTEM algorithms can be used to treat and monitor trauma induced coagulopathy.

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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: Prospective multicentre study in bleeding trauma patients (receiving ≥ 4 red blood cell units). Blood was drawn on the emergency department, after administration of 4, 8 and 12 RBCs and 24 hours 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: 309 bleeding and shocked patients were included. A mean dose of 3.8 grams of fibrinogen increased FIBTEMCA5 with 5.2 mm (4.1–6.3). 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 EXTEMCA5 values was more pronounced in patients with a ROTEM value indicative of TIC compared to the whole cohort. Plasma transfusion decreased EXTEM CT with 3.1 sec (-10–3.9) in the whole cohort and with 10.6 sec (-45–24) in the subgroup of patients with a ROTEM value indicative of TIC.

Conclusion: Effects of therapy on ROTEM values were small, but prevented further derangement of test results. In patients with ROTEM values corresponding to TIC, efficacy of PLT and plasma to correct deranged ROTEM parameters is possibly more robust.

Keywords: ROTEM, haemorrhage, transfusion, trauma, viscoelastic haemostatic assay

Introduction

Trauma-induced coagulopathy (TIC) develops in up to 25% of severely injured trauma patients, which 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, plasma and platelets in a 1:1:1 ratio [3-5]. While this non-specific 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 outcome, including infections [11], and organ failure [12-15], the outcome of traumatic bleeding is probably optimal with a targeted, precision-medicine approach to manage TIC, leading to improved outcomes while avoiding unnecessary transfusion.

This precision approach requires monitoring of effects of therapy. Clotting tests, like prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count have limited usefulness in guiding resuscitation strategy [16-18]. Viscoelastic Haemostatic Assays (VHA) such as thrombelastography (TEG®) or Rotational Thromboelastometry (ROTEM®) are rapid tests which can identify TIC in trauma patients [19-21]. A trial in which trauma patients were randomized to either TEG or conventional tests to guide lab-based transfusion therapy, showed a survival benefit for the TEG guided arm, while the amount of blood products that was needed was decreased [22]. These results are promising, although effects need to be validated in larger multicentre trials. Also, the response of VHA parameters to therapy given during bleeding is not known. Thereby, 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 multicentre observational study, termed the Activation of Coagulation and Inflammation in Trauma (ACIT) study (United Kingdom Clinical Research Network Study Portfolio, ID: 5637), this study was performed in 6 European level-1 trauma centres; London, Oslo, Copenhagen, Oxford, Cologne and Amsterdam, which are members of the International Trauma Research Network (INTRN). All adult trauma patients (age ≥18 years) who required a full trauma team activation, who received at least 4 units of RBCs within 24 hours and who were still alive after 24 hours, were recruited between January 2008 and April 2015. Patients who received >2 L intravenous fluids pre-hospital, who arrived >2 hours after injury in the Emergency Department (ED), who were transferred from other hospitals and patients who had burns covering more than 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 (<650mg/day), 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 hours 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 performed after approval by the local ethics committees.

The following data were collected prospectively to a centralized database: data on patient demographics, time of injury, trauma mechanism, vital signs and laboratory tests up to 24 hours' post-injury, Injury Severity Score (ISS), Abbreviated Injury Scale Score (AIS), 24-hours and 28-day mortality, total fluids (crystalloids, colloids, hypertonic saline), amount of red blood cell units (RBCs), plasma and platelet units (PLTs), anti-fibrinolytic (TXA) and pro-coagulant agents (fibrinogen concentrates, cryoprecipitate).

Blood sampling and ROTEM® assays

Blood was drawn and collected in citrated tubes immediately on arrival in the ED and at 24 hours post injury. Additionally, during resuscitation with blood component therapy, blood samples were drawn after administration of 4, 8 and 12 RBCs. The dose of plasma and platelets 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 based on our previous results in determining threshold values for TIC [26]. Within each assay, 6 ROTEM parameters were analysed; the clotting time (CT), the clot amplitude after 5 minutes (CA5), the clot amplitude after 10 minutes (CA10), the angle of tangent at 20 mm amplitude (alpha angle), the maximum clot firmness (MCF) and the lysis index of the clot after 30 minutes (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 to detect a low fibrinogen level (< 2.0 g/dl), with a cut-off value of < 10 mm. EXTEM-FIBTEM CA5 had the highest diagnostic performance to detect low platelet count (< 100 $x10^9$/L), with a threshold of 30 mm. EXTEM LY30 below 85% was associated with a sudden increase in red blood cell requirements and mortality. EXTEM CA5 had the highest diagnostic performance to detect coagulopathy as defined by an INR >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 centres.

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

Transfusion strategy

In all trauma centres, issuing of blood products, anti-fibrinolytic and pro-coagulant agents by the blood bank was performed through locally implemented massive transfusion protocols

(MTP). In most centres, the MTP was activated for patients with a systolic blood pressure <90 mmHg with inadequate response to fluid administration and suspicion of ongoing bleeding. Centres empirically applied blood products in a fixed ratio. Administration of tranexamic acid (TXA), followed by a continuous infusion over 8 hours, was used as a principle component of the MTP in all centres. Cryoprecipitate was used in London, Oxford and Copenhagen, whereas Oslo, Cologne and Amsterdam used fibrinogen concentrates. The trigger for these concentrated fibrinogen products differed between centres from a fibrinogen level ≤1.0 g/L to ≤2.0 g/L. Centres were restrictive in the use of fluids, but there was no shared protocol on fluid management. Differences in protocols have been described before [27].

Statistics

Sample size was not prespecified in this exploratory study, as ROTEM responses to therapy have not been described before. Descriptives of the groups are given in tables and expressed as mean and standard deviation if normally distributed, whereas not normally distributed data are expressed as median and interquartile ranges. Categorical data were presented as frequencies and percentages. To test for differences in patient characteristics and ROTEM profiles, the Student`s T-test and the Mann-Whitney U tests were used. Categorical variables were compared using the Chi-square test. For multiple comparisons, a one way ANOVA was used. A p-value <0.05 was considered to be statistically significant.

Results

In total, 309 patients were transfused with ≥4 RBCs for whom ROTEM profiles were available (characteristics 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 patients (39%) received fibrinogen products, containing a mean of 3.8 (SD 1.2) grams of fibrinogen. Patients administered fibrinogen products were more severely injured as reflected by a higher ISS and they were more acidotic compared to those not receiving fibrinogen (Sup Table 1). 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 when compared to patients not receiving fibrinogen (Table 3). In patients with a ROTEM profile known to correspond with low fibrinogen (FIBTEM CA5<10 mm) [26], the response to therapy was the same as in the whole cohort receiving fibrinogen.

ROTEM response to treatment with platelets

Of the 309 patients, 212 (69%) received PLTs. Patient administered PLTs had lower baseline platelet counts then those not receiving PLTs, although platelet count was normal in most patients (Sup Table 2). 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 when compared to those not receiving PLTs, although not reaching statistical significance. In patients with a ROTEM profile known to correspond to low platelet levels [26], the decrease in EXTEM CA5 was significantly less when compared to those not receiving therapy.

ROTEM response to treatment with plasma

Of the 309 patients, 280 (91%) patients received plasma. The patients receiving plasma were more shocked, as reflected by a higher heart rate and lower base excess (Sup Table 3). In the whole group of patients receiving plasma, plasma transfusion significantly reduced EXTEM CT with a mean of 3.1 sec compared to patients not receiving plasma (Table 5), in whom EXTEM CT 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 EXTEM CT reduction of 10.6 sec, although statistical significance was not reached due to a wide confidence interval. Of note, the amount of intervals was small.

ROTEM response to treatment with tranexamic acid

Use of TXA was not registered in 19 patients. Of the remaining 290 patients, 112 patients (39%) received TXA. Patients administered TXA were more severely injured as reflected by a higher ISS and were more shocked and more acidotic compared to those not receiving TXA (Sup Table 4). In the whole group of patients receiving TXA, administration of TXA resulted in a greater improvement of lysis and FIBTEM parameters when compared to patients not receiving TXA (Table 6). In those patients with a LY30 suggestive of hyper fibrinolysis [26], the response to therapy was the same as in the whole cohort receiving TXA.

Discussion

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 pro-coagulant therapy with the aim to improve 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 effects can be described as modest, it must be noted that these improvements were detected during ongoing resuscitation of hemorrhage. 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>1.2), the efficacy of plasma and PLTs to correct ROTEM parameters was possibly more robust when compared to the whole bleeding population receiving treatment.

We previously showed that in the same cohort of patients, administration of fibrinogen did not result in correction of low fibrinogen levels in patients who are actively bleeding [28]. Here, we show that a mean dose of fibrinogen of 3.8 grams improves EXTEM CA5 levels with 5 mm. Thereby, this ROTEM marker may guide fibrinogen dosing in traumatic bleeding. Of note, it was shown before that low fibrinogen levels are associated with adverse outcome in traumatic hemorrhage [29-31]. Unfortunately, we cannot provide further analysis of the effect of fibrinogen dose on correction of ROTEM, 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 gram of TXA improved all early markers of clot formation and decreased markers of lysis. It was shown before that TXA administration is associated with good outcome [28]. Taken together, results indicate that monitoring of the effect of pro-coagulant therapy on TIC is possible during management of bleeding trauma patients.

Plasma transfusion reduced the EXTEM CT, whereas in patients not receiving plasma, EXTEM CT further prolonged during bleeding. As EXTEM CT is a marker of TIC that occurs very early during ROTEM testing, results suggest that EXTEM CT may guide the specific need for increased dose of plasma. Of note, as low fibrinogen levels affect the whole coagulation 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 platelet count occurs late [32]. Thereby, the platelet count per se 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 in patients receiving PLT transfusion, which may suggest that EXTEM parameters are more useful then platelet counts in monitoring effects of therapy.

Previously, in the same cohort of patients, threshold ROTEM values corresponding to TIC and adverse outcome were identified [26]. With these values, algorithms for guidance of management of TIC were constructed. This study aims 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], show more improvement of ROTEM values then in the whole group of bleeding patients. However, the effect of plasma did not reach statistical significance, likely due to a loss of data points. Whether use of the algorithm to guide therapy results in better outcome while reducing unnecessary transfusion, is currently under investigation in a randomized controlled trial [33].

Limitations to this study should be acknowledged. Studies were performed in patients with ongoing bleeding, in which the rate of bleeding most likely affected ROTEM results, but which is impossible to account for. Another issue is that blood products were administered together, rendering it impossible to attribute an effect on ROTEM value 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 which needs to be explored. Also, exsanguinating patients were excluded in order to provide for follow-up samples. Thereby, results may not apply to the most severely bleeding patients. Also, as most patients in this study had sustained blunt injury, it remains to be determined whether response to therapy is the same in patients with penetrating injury. Lastly, transfusion protocols differ between centers, which is a limitation to this observational study.

Conclusion

Viscoelastic haemostatic assays 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.

Authorship Contribution

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Table 1. Baseline characteristics and outcome of patients receiving ≥ 4 RBCs

	N=309
Age, years	44.8 (1.1)
Gender, male	73%
Trauma mechanism, blunt	83%
ISS	29.1 (0.7)
SBP, mmHg	106.2 (1.9)
Heart rate, bpm	110.2 (1.7)
Lactate, mmol/L	5.1 (4.4)
GCS	10.8 (0.3)
Hb, g/dL	12.5 (0.1)
Platelet count, x10^9/L	214.2 (4.1)
INR	1.22 (0.1)
Fibrinogen, g/L	1.9 (0.1)
Base Excess, mEqL	-7.5 (0.4)
28 day mortality	22.9 %

Table 2. Baseline ROTEM variables of patients receiving ≥ 4 RBCs

	N=309
EXTEM CT (sec)	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 (sec)	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)

Data are mean and SE of the mean or % of total

Table 3. ROTEM response to fibrinogen

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

*=P<0.05 versus not receiving fibrinogen. Response of ROTEM was determined in the interval between baseline and t=24 hours.

Table 4. ROTEM response to platelets

	All patients receiving platelets	**Patients with EXTEM CA5 – FIBTEM CA5 < 30 receiving platelets**	**Patients not receiving platelets**
	N=137 intervals	**N=25 intervals**	**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)

*=P<0.05 versus not receiving platelets. Response of ROTEM was determined in intervals during resuscitation therapy.

Table 5. ROTEM response to plasma

	All patients receiving plasma	**Patients with EXTEM CT>80 while CA5>40 receiving plasma**	**Patients not receiving plasma**
	N=117 intervals	**N=17 intervals**	**N=42 intervals**
EXTEM CT (sec)	-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 (sec)	19.5 (4.7 to 34.3)	30.31 (1.2 to 59.4)	37.4 (5.4 to 69.4)

*=P<0.05 versus not receiving plasma. Response of ROTEM was determined in intervals during resuscitation therapy.

Table 6. ROTEM response to TXA

	All patients receiving TXA	**Patients with EXTEMLY30<85% receiving TXA**	**Patients not receiving TXA**
	N=76 intervals	**N=34 intervals**	**N=170 intervals**
EXTEM LY30 (%)	5.4 (4.3 to 6.5)*	5.4 (4.1 to 6.7)*	3.0 (2.1 to 3.9)
FIBTEM CA5 (mm)	6.0 (4.8 to 7.3)*	6.1 (4.6 to 7.5)*	3.6 (2.6 to 4.5)
FIBTEM CA10 (mm)	6.1 (4.4 to 7.9)*	6.1 (3.6 to 8.6)*	3.2 (1.7 to 4.6)
FIBTEM MCF (mm)	8.1 (5.3 to 10.9)*	8.1 (5.0 to 11.2)*	3.3 (0.8 to 5.8)
FIBTEM α angle (°)	5.4 (4.4 to 6.5)*	5.4 (4.1 to 6.7)*	3.0 (2.1 to 3.9)
FIBTEM LY30 (%)	6.0 (4.8 to 7.3)*	6.0 (4.5 to 7.5)*	3.6 (2.6 to 4.5)

*=P<0.05 versus not receiving TXA. Response of ROTEM was determined in the interval between baseline and t=24 hours.

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