ORIGINAL RESEARCH

A prospective evaluation of thromboelastometry (ROTEM) to identify acute traumatic coagulopathy and predict massive transfusion in military trauma patients in Afghanistan

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BACKGROUND: Hemorrhage is the leading cause of preventable trauma-related mortality and is frequently aggravated by acute traumatic coagulopathy (ATC). Viscoelastic tests such as rotational thromboelastometry (ROTEM) may improve identification and management of ATC. This study aimed to prospectively evaluate changes in ROTEM among combat casualties during the first 24 hours and compare the capabilities of our conventional clotting assay (international normalized ratio [INR], >1.2) to a proposed integrated ROTEM model (INR >1.2 with the addition of tissue factor pathway activation thromboelastometry [EXTEM] A5 ≤35 mm and/or EXTEM LI30 <97% on admission) to identify ATC and predict massive transfusion (MT).

STUDY DESIGN AND METHODS: This was a prospective observational study of trauma patients treated in NATO hospitals in Afghanistan between January 2012 and June 2013. ROTEM (EXTEM, functional fibrinogen thromboelastometry, APTEM, EXTEM with the addition of a fibrinolysis inhibitor) was performed on admission and at 6 and 24 hours by a designated research team. Treatment teams did not have access to the ROTEM results.

RESULTS: ROTEM values were available for 40 male casualties. The integrated ROTEM model classified 15% more patients with ATC than with INR alone and increased the detection of those that required MT by 22%. The sensitivity of the integrated ROTEM model to predict MT was higher than with INR greater than 1.2 (86% vs. 64%); however, specificity with both definitions for predicting MT was poor (38% vs. 50%, respectively).

CONCLUSION: These observations support the importance of early identification of and intervention in ATC. Integrating ROTEM into the definition of ATC would increase detection of those requiring MT arguing for its use as an adjunct to clinical presentation in the ultimate decision to initiate MT.

Hemorrhage is a leading cause of trauma mortality. Recent reports from the conflicts in Iraq and Afghanistan document that up to a quarter of total combat deaths are due to hemorrhage and are potentially preventable.[1,2] Acute traumatic coagulopathy (ATC) is frequently associated with major hemorrhage during the acute stage of trauma and is present in up to

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ABBREVIATIONS: ATC = acute traumatic coagulopathy; CRYO = cryoprecipitate; DCR = damage control resuscitation; EXTEM = tissue factor pathway activation thromboelastometry; APTEM = EXTEM in presence of a fibrinolysis inhibitor; FFP = fresh frozen plasma; INR = international normalized ratio; ISS = Injury Severity Score; MT = massive transfusion; PLT = platelets; ROTEM = rotational thromboelastometry.

38% of transfused combat casualties.[3] ATC is conventionally defined as a presenting international normalized ratio (INR) greater than 1.2 or 1.5 times normal, and those presenting with INR greater than 1.5 have a fivefold increase in mortality compared to those with INR less than 1.5.[3–6] Therefore, early detection and management of ATC is critical in the treatment of combat-related injury. Hemorrhage combined with hypotension, hypothermia, and acidosis results in dysregulation of hemostasis in ATC.[7,8] Previous studies of ATC have implicated activated protein C, dysregulated thrombin generation, clotting factor consumption, platelet dysfunction, dysfibrinogenemia, fibrinolysis, and endothelial dysfunction in the pathophysiologic changes leading to bleeding.[9–14]

Conventional coagulation screening tests such as prothrombin time, INR, activated partial thromboplastin time, and fibrinogen are of limited utility in guiding resuscitation of acute hemorrhage. They are poor predictors of massive transfusion and are crude instruments to guide specific blood component therapy.[15–17] Performed on platelet-poor plasma, these tests have turnaround times of at least 30 minutes, hindering rapid identification and ongoing management of ATC.[16–18] INR fails to identify specific underlying coagulopathic phenotypes, namely, deficient procoagulant versus excessive anticoagulant activity and quantifies clotting only during the initiation phase.[19,20] Platelet enumeration and fibrinogen tests fail to describe functional activity of thrombocytes and factor XIII–mediated fibrin cross-linking, respectively.

Viscoelastic tests such as thromboelastography and rotational thromboelastometry (ROTEM) have played an increasingly important role in the identification and management of ATC.[14,16,21] Performed on whole blood samples, these tests allow for rapid identification of perturbations in the coagulation cascade and can evaluate the relative contribution of fibrinogen and platelets to clot strength. A recent study from Bagram Airfield, Afghanistan, demonstrated a significant improvement in adherence to damage control resuscitation (DCR) guidelines after the deployment of ROTEM in the field[22]; however, few studies overall have used ROTEM to evaluate the longitudinal effects of DCR on ATC in the combat setting.[23]

Recent data have established precedence for including EXTEM A5 35 mm or less and EXTEM LI30 less than 97% in the definition of ATC. For example, Chapman et al.[24] demonstrated an increased risk for MT and hemorrhage-related mortality in trauma patients who met criteria for MT and presented with evidence of fibrinolysis. Of the 73 patients included in that study, 91% versus 31% (p = 0.0008) required MT and 46% versus 5% (p = 0.0014) died of hemorrhage in the LY30 greater than 3% and LY30 3% or less cohorts, respectively. Building on the foundations of CRASH-2 and MATTERs, which focused worldwide attention on hyperfibrinolysis as a component of acute ATC, Chapman suggested LY30 greater than 3% as a clinically relevant marker of coagulopathy in trauma casualties.[24–26] Davenport et al.[16] established EXTEM

A5 35 mm or less as a marker of ATC. In their study of 300 trauma casualties, EXTEM A5 35 mm or less had a detection rate of 77% for ATC with a false-positive rate of 13%. These patients were more likely to receive RBC and plasma transfusions.

Small, single-center studies have supported the predictive value of several different ROTEM thresholds for MT. In a retrospective study of 323 patients admitted to a trauma center in Salzburg, Austria, Schöchl et al.[27] demonstrated significantly lower functional fibrinogen thromboelastometry (FIBTEM) maximum clot firmness in those requiring MT with a positive predictive value of 0.84. Davenport et al.[16] evaluated 300 adult patients who met the criteria for full trauma team activation and found EXTEM A5 35 mm or less had a 28% greater detection rate for those who would require MT compared to INR greater than 1.2. Similar attempts have been made to define specific viscoelastic test thresholds to guide transfusion of fresh frozen plasma (FFP)/plasma (EXTEM CT ≥80 s plus EXTEM A10 ≥40 mm or EXTEM maximum clot firmness ≥50 mm) and cryoprecipitate (FIBTEM maximum clot firmness ≤7–12 s).[28]

The primary aim of this study was to determine the relative capacities to identify coagulopathy and predict MT between 1) the established ATC definition using an INR cutoff of 1.2 and 2) an integrated ROTEM model that also includes EXTEM A5 35 mm or less and/or EXTEM LI30 less than 97%. Our secondary aim was to identify transfusion practices that failed to correct admission coagulopathy by 24 hours. A unique feature of this study is that ROTEM results were not available to treatment teams and therefore did not affect management.

METHODS

We conducted a prospective observational study of trauma patients treated at Craig Air Force Theater Hospital–Bagram, or Kandahar NATO Hospital in the Afghanistan Theater between January 2012 and June 2013. This study was approved by the US Army Medical Research and Materiel Command Institutional Review Board (HT-11-001 [M-10106]). We enrolled 88 US and Coalition military personnel identified as having injuries resulting in activation of DCR, which was decided by the treatment teams based on clinical status at presentation.

Only 40 of the 88 patients enrolled had ROTEM performed due to intermittent lack of reagent availability, not patient selection. These 40 were included in the final study analysis. Blood was obtained upon admission and at 6 and 24 hours after admission by a designated research team and analyzed by ROTEM with multiple assays (EXTEM, FIBTEM, APTEM); however, results were not made available to the treatment team. Upon arrival at the hospital, a sample of blood for ROTEM analysis was collected into a 2.7-mL citrate vacutainer (0.109 M buffered sodium citrate, 3.2%;

Becton Dickinson) and processed in the hospital laboratory according to manufacturer instructions. ROTEM was unavailable for 14 patients at 24 hours due to death or transfer.

The Department of Defense Trauma Registry database provided clinical data such as Injury Severity Score (ISS), Glasgow Coma Scale, and vital signs as well as quantitative laboratory data including hematocrit, platelet count, base deficit, and INR upon admission. Data relating to prehospital treatment was not known; nor was INR at 6 hours and 24 hours. Additional data included the total amount of blood products (RBCs, cryoprecipitate, platelet [PLTs], and FFP units) administered within 24 hours from admission as well as age, sex, and mechanism of injury.

As in previous studies, we defined a massive transfusion as 10 or more RBC units given to one patient within 24 hours. For reporting purposes, apheresis PLT units were converted to whole blood–derived PLT units (1 apheresis PLT:6 U PLT) and cryoprecipitate 10-packs were converted to individual cryoprecipitate units. Reported outcomes for all patients in this study were the mean units of blood transfused and the ratios of products FFP:RBC, PLT:RBC, and cryoprecipitate (CRYO):RBC.

An integrated ROTEM model was used to define ATC, which included INR greater than 1.2, EXTEM A5 35 mm or less and/or EXTEM LI30 less than 97% on admission. Patients meeting at least one of these three criteria were included in the ATC cohort. We recognize that the standard ROTEM LI30 threshold for hyperfibrinolysis is less than 94%; however, to increase sensitivity, we decided on a higher target parameter of less than 97% for this study.

For continuous, normally distributed data, a Student's t test was performed for comparisons of means. For categorical data, the chi-square and Fischer exact tests were used. We compared the sensitivity, specificity, and positive and negative likelihood ratio of the established ATC definition using INR greater than 1.2 versus our integrated ROTEM model for predicting MT. We used a Pearson correlation coefficient (R^2) to determine the strengths of associations between 1) admission ISS, base deficit, platelet count, hemoglobin, or creatinine and degree of coagulopathy for any individual ROTEM parameter or INR, and 2) units of individual blood products transfused and Δ EXTEM A5 at 6 hours and 24 hours. Significance was set at p value less than 0.05. Statistical analysis was performed with computer software (JMP version 10, SAS Institute Inc.).

RESULTS

Description of subjects

ROTEM values were available for 40 males, predominantly from the US Army with smaller contributions from the US Air Force, Afghanistan National Army, and other non-US military. Median age was 26 years (95% confidence interval [CI], 17–35) (Table 1). Median ISS upon admission was 21.5 (95% CI, 14–27) overall with significantly higher scores for those who required MT (17 [95% CI, 10–21] vs. 27 [95% CI, 24–34]; p = 0.0002). Seventy percent of all patients met the criteria for severe trauma (ISS >15) as did 100% of those who required MT. Admission systolic blood pressure, heart rate, base deficit, and hemoglobin are reported in Table 1.

The most common injury mechanism was dismounted improvised explosive device (IED; 65%) followed by mounted IED (15%), gunshot wound (12.5%), and rocket-propelled grenade (7.5%). All patients who required MT

TABLE 1. Patient demographics			
Patient characteristics	All n = 40	No MT n = 25 (63%)	MT n = 15 (38%)
Age	26 (17–35)	26 (22–29)	24 (22–26)
Sex	100% Male	25 (100%)	15 (100%)
ISS	22 (14–27)	17 (10–21)	27 (24–34)
Glasgow Coma Score	15 (11.5–15)	15 (8–15)	15 (15–15)
ISS >15	28 (70%)	13 (52%)	15 (100%)*
Mechanism of injury			
Dismounted IED	26 (65%)	11 (44%)	15% (100%)†
Mounted IED	6 (15%)	6 (24%)	0
Rocket-propelled grenade	3 (7.5%)	3 (12%)	0
Gunshot wound	5 (12.5%)	5 (20%)	0
Admission physiology			
Systolic blood pressure (mm Hg)	119 (110–130)	121 (112–134)	113 (97–128)
Heart rate (bpm)	129 (103–144)	101 (95–108)	115 (98–130)
Base deficit	0.5 (−2.25–1.0)	1 (−3–1.6)	0 (−1.5–1.0)
Hemoglobin (g/L)	111 (101–120)	11 (10–13)	11 (10–11)
ATC (INR >1.2 alone)	22 (55%)	13 (52%)	9 (33%)
ATC (ROTEM and INR)*	28 (70%)	15 (60%)	13 (87%)
Mortality	2 (5%)	1 (4%)	1 (7%)

All values reported as median (95% CI).
ATC = acute traumatic coagulopathy; IED = improvised explosive device; INR = international normalized ratio; ISS = Injury Severity Score; MT = massive transfusion; ROTEM = rotational thromboelastometry
* p = 0.0015
† p < 0.0001
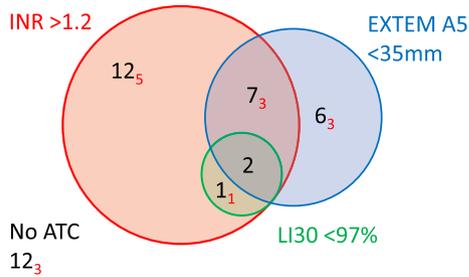
Fig. 1. ATC and MT by type of coagulation disturbance N = total with abnormality (40), Nx = number receiving MT (15).

Fig. 2. Progression of EXTEM A5 through 24 hours in those presenting with EXTEM A5 less than 35 mm.

suffered attack by a dismounted IED, and two of these patients died after suffering severe trauma (ISS scores of 38 and 24, respectively) and ATC (patient A presented with an INR of 1.3 and an EXTEM A5 of 30 mm; patient B presented with an INR of 1.6 and an EXTEM LI30 of 25%).

A total of 28 patients (70%) presented with ATC as defined by our integrated ROTEM model. Twelve (30%) showed isolated INR abnormality, six (15%) showed isolated EXTEM A5 abnormality, and no patients presented with isolated hyperfibrinolysis. Concomitant abnormalities were observed in eight patients—seven (18%) with INR and EXTEM A5, and one (3%) with INR and EXTEM LI30 (Fig. 1). Two patients (5%) had abnormalities in all three parameters at admission. We found no significant correlations between admission ISS, base deficit, platelet count, hemoglobin, or creatinine and degree of coagulopathy for any individual ROTEM parameter or INR (data not shown).

Fifteen patients required MT, of whom five had isolated INR greater than 1.2 and three had isolated EXTEM A5 35 mm or less. Three additional patients presented with concomitant INR and EXTEM A5 abnormalities, and one presented with both INR and EXTEM LI30 abnormalities. Only three patients who required MT failed to meet ATC criteria at admission as defined by our study (Fig. 1).

Transfusion and ROTEM characteristics over 24 hours

ATC not present at admission

Of the 12 patients who did not have ATC at admission, 4 exhibited a drop in EXTEM A5 to 35 mm or less within the first 6 hours. One received MT but did not have 24-hour ROTEM data available to assess its impact. Two additional patients received sub-MT in a 1:1:1 ratio of RBC:PLT:FFP without CRYO and demonstrated a continued decline in EXTEM A5 between 6 hours and 24 hours. Another patient received a balanced transfusion using all four components, with stabilization of EXTEM A5 at 24 hours. No patients developed de novo EXTEM A5 abnormalities between 6 hours and 24 hours, and no deaths were observed in this subgroup of delayed-onset ATC. Due to our study limitations, we could not determine when during transfusion these coagulopathies
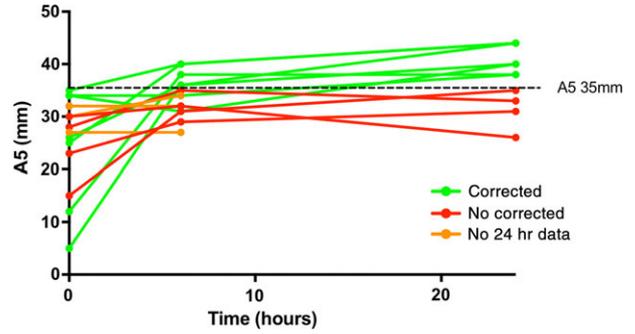
occurred. The development of hyperfibrinolysis was not observed within the first 24 hours for any patient with normal EXTEM LI30 at admission.

EXTEM A5 35 mm or less on admission

Seven (47%) of the 15 patients who presented with EXTEM A5 35 mm or less on admission demonstrated correction to EXTEM A5 greater than 35 mm at 24 hours. Three required MT and two autocorrected without any transfusion. The remaining two required sub-MTs—one received a 1:1 ratio of RBC:FFP without PLTs or CRYO, and the other received a 1:2:1:1 ratio of RBC:PLT:CRYO:FFP (Fig. 2, Table 2).

Seven (47%) of the patients presenting with EXTEM A5 abnormality failed to correct at 24 hours. Two received MT, one of whom died. Unbalanced transfusion ratios were observed in both cases (Table 2). Two additional patients who failed to correct were not transfused. Both presented with elevated INR and one presented with clinical signs of shock, including tachycardia, diastolic hypotension, and anemia. Although our study design limited our understanding as to why they were not transfused despite these signs and symptoms, both patients ultimately survived. One patient (6%) with EXTEM A5 35 mm or less did not have any subsequent data collected and was excluded from analysis. Concomitant INR or LI30 abnormalities did not affect EXTEM A5 correction success at 24 hours (odds ratio, 1.0; 95% CI, 0.13–7.57; p = 1.00). The use of any single blood component correlated poorly with ΔEXTEM A5 at 6 and 24 hours (data not shown); however, the average units of all blood components transfused were higher for those who corrected and transfusion ratios more closely approximated 1:1:1:1 RBC:PLT:CRYO:FFP (1:0.8:0.9:0.9 vs 1:0.6:0.4:0.8 [Table 3]).

EXTEM LI30 less than 97% on admission

Only one patient presenting with LI30 less than 97% had both 6-hour and 24-hour LI30 data available for analysis. After receiving a balanced MT with 26 U RBC, 24 U PLT, 30 U of CRYO, and 29 U FFP, his LI30 corrected from 25% to 100% at

TABLE 2. Patients with EXTEM 35 mm or less on admission; blood components transfused, INR, and EXTEM A5 values at 0, 6, and 24 hours

Patient ID	RBC	PLT	CRYO	FFP	INR	EXTEM 0 hours	EXTEM 6 hours	EXTEM 24 hours
EXTEM A5 not corrected to >35 mm at 24 hours								
1	9	6	10	6	1.02	23	**29**	**31**
2	18	12	10	18	1.3	30	**32**	**26**
3	4	0	0	0	1.22	15	**31**	**35**
4	0	0	0	0	1.37	27	**27**	
5	5	0	0	4	1.6	30	**34**	
6	0	0	0	0	1.44	32	**32**	
7	12	12	0	10	1.3	28	**35**	33
EXTEM A5 corrected to >35 mm 24 hours								
8	8	18	10	9	1.61	34	**34**	38
9	12	12	20	7	1.16	12	38	38
10	8	0	0	10		34	**31**	40
11	22	12	10	18		25	40	44
12	0	0	0	0	1.6	35	40	44
13	0	0	0	0	1.2	5	36	40
14	16	12	20	15	1.2	26	36	44

CRYO = cryoprecipitate; EXTEM = tissue factor pathway activation thromboelastometry; FFP = fresh frozen plasma; INR = international normalized ratio; PLT = platelets

6 hours and remained there after 24 hours. This patient died, although the exact mechanism of death was not provided.

Due to study limitations, we were unable to assess longitudinal changes in INR for coagulopathic patients requiring transfusion.

Identification of MT by INR and ROTEM predictors

We directly compared the performance of the established definition of ATC using INR greater than 1.2 against our integrated ROTEM model for detecting MT and observed increased sensitivity (64% vs. 86%), positive likelihood ratio (1.3 vs. 1.4), and negative likelihood ratio (0.7 vs. 0.4) in the latter. Specificity was greater using INR greater than 1.2 but was poor in both cases (50% vs. 38%).

DISCUSSION

Defined by INR greater than 1.2, the prevalence of ATC was 55%, higher than other published studies of military combat casualties.[3] Additionally, ISS scores were high, with 70% of patients presenting with severe injury. The injury mechanisms and patterns in this cohort provided a unique

TABLE 3. Comparison of mean (SD) units and ratios of individual blood components transfused for those with and without correction within 24 hours

Blood product	Correction	No Correction	p
RBC	9.4 ± 8.0	6.8 ± 6.6	0.52
Platelet	7.7 ± 7.5	4.3 ± 5.7	0.2
Cryoprecipitate	8.5 ± 9.0	2.9 ± 4.9	0.16
FFP	8.4 ± 6.9	5.4 ± 6.7	0.42
Ratio* (RBC:PLT:CRYPO:FFP)	1:0.8:0.9:0.9	1:0.6:0.4:0.8	…

* Comparison of mean values.

opportunity to evaluate ATC in critically injured but otherwise young and healthy individuals. That ROTEM was an investigational tool to which providers did not have access provided an opportunity to evaluate DCR practices as they are currently applied in theater.

Our integrated ROTEM model of ATC identified an additional 15% of patients presenting with coagulopathy who otherwise would have gone undetected using INR alone, accounting for 20% of all MTs. Compared with the established INR definition of ATC, the integrated ROTEM model improved sensitivity and both positive and negative likelihood ratios for predicting MT, capturing 86% of all MT patients. Notably, both models demonstrated poor specificity, supporting the notion that not all coagulopathic patients experience significant hemorrhage, and underscoring the importance of relying on these tests only in a larger clinical context. Nevertheless, our observations support earlier studies that advocate for integrating ROTEM in the identification of ATC and the need for MT.[24–26]

Overall, DCR practiced in this study successfully mitigated ATC development in those who presented noncoagulopathic and corrected coagulopathy in those with ATC at admission. One-half of all patients who presented with EXTEM A5 abnormalities at admission corrected by 24 hours and only one patient who failed to do so died. Repeat INR was not recorded, so it is not known if more patients (than 47% of EXTEM A5 ≤35 mm on admission) remained coagulopathic within the definition of the integrated ATC model. Despite the high prevalence of ATC and severe trauma in this cohort, mortality was only 5%. EXTEM LI30 was 25% at admission in one of these two patients, suggesting early severe hyperfibrinolysis, which has been demonstrated to portend high mortality.[29,30]

In the cases of where EXTEM A5 remained 35 mm or less at 24 hours, we observed an overall trend toward fewer

blood products transfused, and specifically an underutilization of CRYO and FFP leading to unbalanced transfusion ratios. This observation highlights the importance of early identification and intervention with ATC and the benefit of balanced transfusion using a 1:1:1:1 ratio. It is possible that use of ROTEM to guide DCR, rather than reliance on ratio-based transfusion might have resulted in more efficient correction of ATC, but we were unable to evaluate this possibility due to study design. A prior study of ROTEM use to guide DCR in combat casualties suggest that ROTEM results led clinical teams to transfusion ratios that closely resembled 1:1:1:1.[22]

Our cohort was small and homogenous with a large predominance of severe trauma requiring MT and large-volume sub-MT. A high percentage (90%) of hemorrhagic deaths occur prehospital; this cohort included only patients surviving transfer to hospital. No data were available on pre-hospital management of patients, including blood products or tranexamic acid administered, which is noted as a limitation of the study.

CONCLUSION

Our integrated ROTEM model of ATC demonstrated a 15% increased burden of coagulopathy above those captured by INR alone and increased the detection of those that required MT by 22%. The specificity, however, was poor, arguing for its use as an adjunct to clinical presentation in the ultimate decision to initiate MT in the combat setting. DCR protocols, as they are currently practiced in theater, limited the development of ATC after presentation and in many cases resulted in the reversal of coagulopathy as demonstrated by longitudinal EXTEM A5 values over 24 hours and were associated with low overall mortality. In cases where coagulopathy either developed after admission and/or failed to be corrected at 24 hours we observed a decreased use of blood products overall and specifically of cryoprecipitate and FFP. These observations support the importance of early identification of and intervention for ATC patients with an adherence to balanced transfusion. Further studies on the use of ROTEM in the combat trauma setting are needed to develop future goal-directed resuscitation protocols.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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