PRIMARY RESEARCH ARTICLE

A Comparative Analysis of Functional Fibrinogen Assays using TEG and ROTEM in Trauma Patients Enrolled in the FiiRST Trial

[1]Henry T Peng, [2]Barto Nascimento, [3]Homer Tien, [4]Jeannie Callum, [5]Sandro Rizoli, [6]Shawn G Rhind, [7]Andrew Beckett

ABSTRACT

Introduction: Given the growing use of both thrombelastography (TEG) and rotational thromboelastometry (ROTEM) in trauma and surgery, it is important to determine whether the two are interchangeable, and how comparable they are to Clauss fibrinogen assay and for clinical use. We recently completed a randomized control trial on early fibrinogen in trauma (the FiiRST trial). The object of this analysis was to evaluate the interchangeability and correlations between TEG and ROTEM functional fibrinogen assays in injured trauma patients. Also, we evaluated their correlation with Clauss fibrinogen and compared their potentials for diagnosis of coagulopathy and use in guided fibrinogen administration.

Materials and Methods: The Post-hoc analysis of the coagulation data collected as part of the FiiRST trial. It was a comparative analysis of functional fibrinogen assays using TEG and ROTEM in trauma patients screened for hypotension and need for blood transfusion. TEG and ROTEM tests were also compared with Clauss fibrinogen assay and INR as additional analyses of their clinical use.

Results: TEG and ROTEM parameter values were correlated but were significantly different, and their agreement fell outside acceptable limits and thus were not interchangeable. TEG maximum amplitude (MA) and ROTEM maximum clot firmness (MCF) showed closest correlations with Clauss fibrinogen concentration, particularly with ROTEM FIBTEM MCF (r = 0.84; p < 0.001). There were discrepancies between TEG and ROTEM in their detection of coagulation abnormalities, hypofibrinogenemia, and hyperfibrinolysis.

Conclusion: TEG and ROTEM fibrinogen assay parameters were associated, especially between TEG MA and ROTEM MCF, showing the strongest correlation, but the parameters were not interchangeable. TEG and ROTEM showed varying extents of correlations with Clauss fibrinogen. Overall, ROTEM parameters exhibited better correlations with Clauss fibrinogen than TEG. Different algorithms for TEG and ROTEM need to be developed for diagnosis of coagulopathy and guided fibrinogen administration in trauma.

Keywords: Coagulation tests, Fibrinogen concentrate, Functional fibrinogen, Thrombelastography, Thromboelastometry, Trauma

[1,6]Defence Scientist, [2–5,7] Medical Doctor and Professor

[1,6]Defence Research and Development Canada, Toronto Research Center, Toronto, Ontario, Canada

[2,3]Sunnybrook Health Sciences Centre, Department of Surgery, University of Toronto, Toronto, Canada

[4]Sunnybrook Health Sciences Centre, Department of Laboratory Medicine and Molecular Diagnostics; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

[5]St Michael's Hospital, Department of Surgery & Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

[7]Royal Canadian Medical Services, Ottawa, Ontario, and McGill University, Montreal, Quebec, Canada

Corresponding Author: Henry T Peng, Defence Scientist, Defence Research and Development Canada, Toronto Research Center, Toronto, Ontario, Canada, Phone: 1-4166352129, E-mail: henry.peng@drdc-rddc.gc.ca

INTRODUCTION

Viscoelastic hemostatic assays (VHAs)–Thrombelastography (TEG; Haemonetics Corporation, Haemoscope Division, Nile, Illinois, United States of America) and rotational thromboelastometry (ROTEM; Tem Innovations GmbH, Munich, Germany) are two point-of-care whole blood coagulation testing systems increasingly used to guide transfusion and hemostatic therapy in trauma.[1-4] They have been particularly useful in guiding fibrinogen replacement therapy.[5] VHA-guided fibrinogen therapy has been associated with reduced red blood cell (RBC), plasma and platelets (PLT) transfusion requirements and prediction of transfusion.[6,7] Furthermore, a recent randomized clinical trial demonstrated that TEG-guided massive transfusion protocol for severe trauma improved survival compared with that guided by conventional coagulation tests (CCTs) (prothrombin time (PT)/international normalized ratio (INR), fibrinogen and D-dimer).[8] Finally, TEG and ROTEM are the only hemostatic tests for rapid and accurate detection of systemic fibrinolysis in severe trauma.[9,10]

The two systems are based on similar technologies, both recording the viscoelastic changes that occur during the entire coagulation process, and commonly

believed to provide comparable results.[11] However, there is a primary hardware difference. ROTEM has an immobile cup, wherein the pin/wire transduction system slowly oscillates an arc of 4°45'. In addition, each ROTEM system has four channels with an integrated computer to operate as opposed to two channels in the TEG system that requires a separate computer to operate. It has been suggested that the ROTEM system uses a ball-bearing system for power transduction, which makes it less susceptible to movement and vibration.[12] In addition, different assays using a variety of reagents have been developed for each system, which may activate or inhibit specific coagulation pathways and provide different results.[13] For example, the functional fibrinogen reagent for TEG is composed of lyophilized tissue factor and a platelet inhibitor (abciximab) that binds to glycoprotein-IIb/IIIa receptors to inhibit platelet aggregation and exclude the platelet contribution to clot strength.[14] ROTEM fibrinogen assay uses extem and fibtem solutions. The extem solution contains a combination of recombinant tissue factor and phospholipids that activates the extrinsic pathway of the coagulation system, while the fibtem solution contains $CaCl_2$ as recalcification reagent and a platelet inhibitor (cytochalasin D) that inhibits platelet actin/myosin-system or cytoskeletal reorganization.[14]

Studies have shown that TEG and ROTEM provided different results when applied for diagnosing coagulopathy and guiding transfusion.[3] On the other hand, some comparative studies indicate correlations between the two systems depending on the measurement parameters,[15,16] activation reagents,[17] blood samples,[16,18] and specific assays.[14,19] The blood components (e.g., whole blood vs. plasma) and the type and concentration of activators could also influence the interpretation of coagulation profiles measured by each test.[20]

Both TEG and ROTEM functional fibrinogen assays have been used to diagnose fibrinogen deficiency and guide fibrinogen replacement in trauma where fibrinogen is believed to play a critical role.[21, 22] We have recently completed a randomised controlled pilot trial evaluating the administration of fibrinogen concentrate (FC) in the initial resuscitation of severe trauma (the FiiRST trial).[23] As part of a secondary coagulation study, we performed TEG and ROTEM fibrinogen assays and Clauss plasma fibrinogen measurements in all patients screened for enrollment in the trial. Although TEG and ROTEM have previously been compared to determine specific cut-offs of TEG maximum amplitude and ROTEM maximum clot firmness for an increased risk of receiving a transfusion,[24] this is the first comparative analysis of the two systems for fibrinogen assays and INR in trauma. In addition, a crossover analysis where ROTEM FIBTEM reagents (extem and fibtem) were used on TEG was also conducted to confirm whether the assay reagents or the device could contribute to the observed differences. We hypothesized that although the results may not be strictly interchangeable, both viscoelastic tests should correlate well, especially when the same reagents are used, and both tests would provide a good prediction for blood transfusion requirement, diagnosis of coagulopathy, and measure of coagulation in trauma. This paper focuses on the interchangeability between the two systems for functional fibrinogen assays and their correlations with Clauss fibrinogen assay, utility to detect coagulopathy including hypofibrinogenemia and hyperfibrinolysis in trauma at hospital admission. A following paper will be focused on comparing the TEG and ROTEM functional fibrinogen assays and CCTs for monitoring the effects of fibrinogen administration on coagulation profiles and predicting transfusion requirements.

MATERIALS AND METHODS

Study Design and Participants

This study was conducted at the Sunnybrook Health Sciences Centre Level 1 Trauma Centre with accrual period between October 2014 and November 2015. The study details and primary outcomes have been published.[23] Briefly, adult (age >18 years) trauma (blunt or penetrating) patients were screened for study enrollment. Patients with hypotension (SBP <100 mm Hg) and need for RBC transfusion within 30 min of arrival were enrolled in the trial. All screened patients had blood samples collected in BD vacutainer containing 3.2% sodium citrate (Fisher Scientific, Nepean, ON, Canada) at admission and at predetermined time points throughout 48 hours of admission to the hospital. For this current study, we analyzed only data from admission samples for all screened patients and enrolled patients.

The blood was analyzed simultaneously by TEG functional fibrinogen (FF) and ROTEM® FIBTEM assays using standard reagents and procedures as recommended by each company and described below. In addition, TEG FIBTEM assay was performed on TEG using the same reagents (extem and fibtem) and concentrations as used in ROTEM FIBTEM for cross-over comparison. Key parameter values (e.g., coagulation time and maximum clot strength) were obtained. As part of standard of care all patients also had standard laboratory tests performed, including INR and fibrinogen level.

The study was approved by Sunnybrook Research Ethics Board and used exception from informed consent. All patients were informed of inclusion in the trial and had the ability to opt out any time during the trial.

## Principles of TEG and ROTEM Functional Fibrinogen Tests

Figures 1A and B show the testing principles of the two most used systems: TEG 5000 hemostasis analyzer (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA) and ROTEM delta system (Tem Innovations GmbH, Munich, Germany), respectively. Both systems measure the viscoelastic properties of blood as it clots under low shear stress, but there are primary hardware differences between the two.[25] For each TEG channel, a pin suspended by a torsion wire is immersed in 360 μL whole blood or plasma in a plastic cup made of acrylic polymer with a smooth interior surface. The cup transversely oscillates back and forth through an arc of 4.75° every 5 seconds while the pin is deflected by the torque pressure of the viscoelastic properties of blood during modifications of fibrin strands and platelet aggregates as coagulation and fibrinolysis proceed. Torque pressure is transmitted to the torsion wire, which is converted by a mechanical-electrical transducer to an electrical signal, monitored by computer.[26] For each ROTEM channel, a pin suspended on a ball bearing mechanism transversely oscillates back and forth through 4.75° every 6 seconds with a constant force in a fixed cup made of polymethylmethacrylate with a ridged interior surface into which a 340 μL sample of whole blood is electronically pipetted. As the blood clots, the impedance to pin rotation is transmitted via an optical detector system, and recorded by computer.[27] In addition, each ROTEM system has four channels and a built-in computer and automatic pipette to operate as opposed to two channels in the TEG system that requires a separate computer and manual pipette to operate. It is argued that the ROTEM system uses a ball-bearing system for power transduction, which makes it less susceptible to movement and vibration,[12] and that the automatic pipetting may ensure less variations among operations.[28]

The measurement of both instruments is graphically represented as a characteristic shape profile over time (Fig. 1c), from which the following parameters can be derived for TEG: (1) reaction time R, which is related to plasma clotting factors and circulating inhibitory activity; (2) coagulation time K, which is associated with the activity of the clotting factors, fibrinogen and platelets; (3) rate of clot polymerization, angle, which is a main function of platelets, fibrinogen and plasma components residing on the platelet surface; (4) maximum amplitude or maximum clot strength, MA, which is a direct function of the maximum dynamic properties of fibrin and platelet number and functions; and (5) fibrinolysis at 30 min LY30/CL30, which is related to plasma levels and activities of tissue plasminogen activator. Similar parameters to TEG as shown in Fig. 1c. (e.g., coagulation time (CT), clot formation time (CFT), angle, maximum clot firmness (MCF), clot lysis index LI30 and maximum lysis during measurement ML) can be derived from ROTEM which are commonly used in Europe.[29]

All the TEG and ROTEM parameters are derived in the same way for each assay, except the one for fibrinolysis. The TEG system provides LY30 and CL30. LY30 is computed as the percentage reduction of the area under a TEG tracing from the time MA is measured until 30 min after the MA. CL30 represents the value of the amplitude of a TEG tracing at 30 min after the MA relative to MA. The ROTEM system provides LI30 and ML as measures of fibrinolysis. LI30 is calculated as the ratio between clot firmness (in mm amplitude) at CT+30 min and maximum clot firmness (MCF) and ML is the percent of clot firmness lost after MCF during measurement. There are no same fibrinolytic parameters between TEG and ROTEM. CL30 is a fibrinolytic parameter in TEG most similar to LI30 in ROTEM.

In addition to the differences in instrument, the two viscoelastic point-of-care systems used different reagents resulting in various tests with different normal values and therapeutic triggers and treatment options[1, 11, 25, 30,31] as summarized in Table 1. For example, the functional fibrinogen reagent for TEG is composed of lyophilized tissue factor and a platelet inhibitor (abciximab) that binds to glycoprotein IIb/IIIa receptors to inhibit platelet aggregation and exclude the platelet contribution to clot strength.[14] To perform TEG functional fibrinogen assay, 0.5 mL of citrated or native blood was activated with a mixture of tissue factor and the platelet inhibitor and then 340 μL of the activated blood was added to a TEG cup preloaded with 20 μL 0.2 M $CaCl_2$.[32] ROTEM fibrinogen assay was performed by directly mixing 20 μL extem, fibtem and 300 μL citrated blood in a ROTEM cup.[14] The extem solution contains a combination of recombinant tissue factor and phospholipids that activates the extrinsic pathway of the coagulation system, while the fibtem solution contains $CaCl_2$ as a recalcification reagent and a platelet inhibitor (cytochalasin D) that inhibits actin/myosin-system. A new reagent called fibtem plus contains 2 platelet inhibitors, cytochalasin D which inhibits platelet cytoskeletal reorganization, and tirofiban, a glycoprotein IIb/IIIa inhibitor similar to abciximab which prevents fibrinogen from binding to glycoprotein IIb/IIIa receptors on the surface of platelets and platelet aggregation.[33] A recent study showed that the addition of a synthetic IIb/IIIa receptor antagonist alone or in combination with acetylsalicylic acid could reduce platelet aggregation and its contribution to clot strength in both EXTEM and FIBTEM tests.[34]
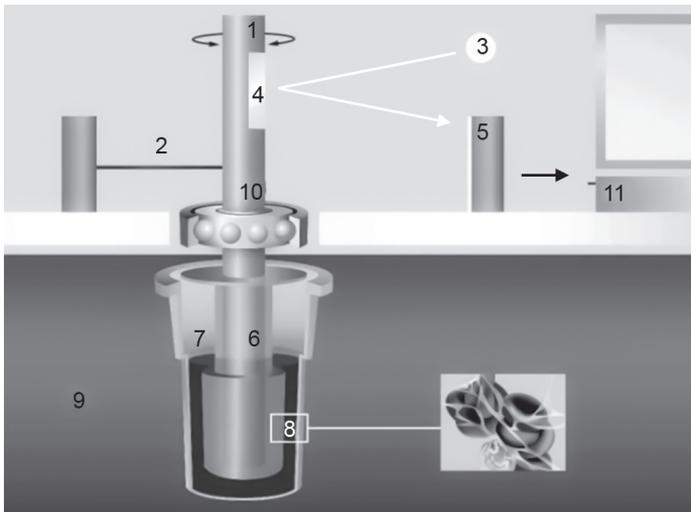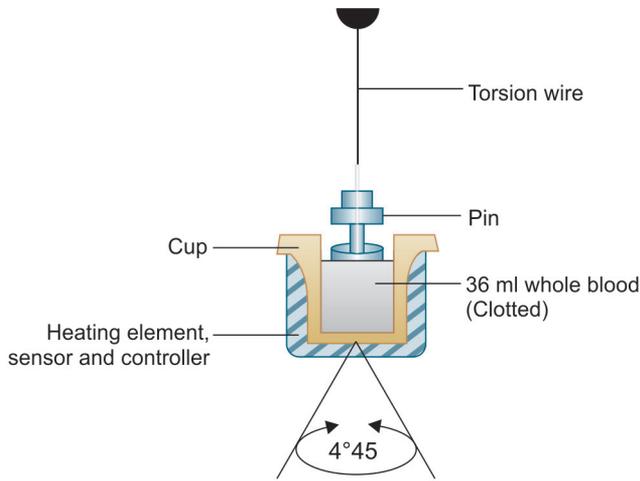
1. Oscillating axis (~4.75º)
2. Spring
3. Light source
4. Reflector
5. Detector (electric camera)
6. Sensor pin
7. Cup filled with blood
8. Fibrin thread and thrombocyte aggregate
9. Heated cup holder
10. Ball bearings
11. Data processing
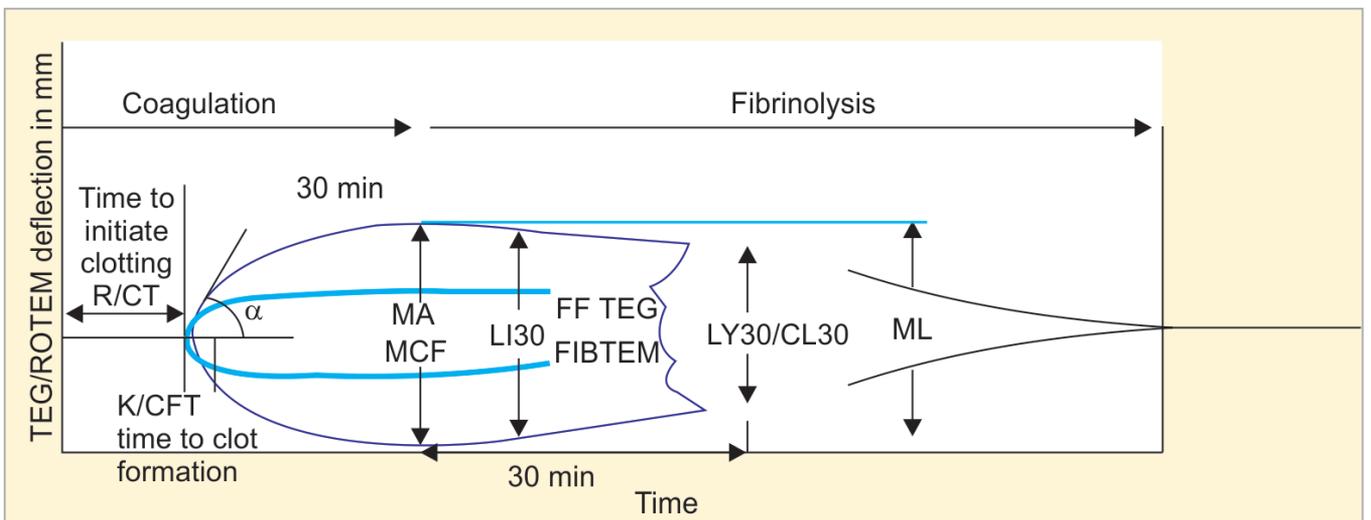
Figs 1 A to C: Schematic illustration of (A) TEG mechanism and machine, (B) ROTEM mechanism and machine, and (C) a representative TEG/ROTEM tracing showing the relationship between the qualitative tracing and the quantitative parameters. *Courtesy*: Haemonetics Corporation and TEM Systems, Inc.

Table 1: Normal and trigger values of commonly employed TEG and ROTEM assays for hemostatic therapy in bleeding patients.[1,11,25,30,31]

TEG reagents	TEG parameters	Reference ranges*	Patient values	ROTEM reagents	ROTEM parameters	References ranges*	Patient values	Coagulopathy	Therapy
Kaolin suspension in buffered stabilizers and a blend of phosphor-lipids	Kaolin TEG R	300-600 sec	≥ 600 sec	In-tem: ellagic acid and partial thrombo-plastin phosphor-lipid and preservatives in buffer	INTEM CT	122–208 sec	>200 sec	Coagulation factors deficiency	Fresh frozen plasma (FFP)
	Kaolin TEG Angle	53–72°	<52°		INTEM Angle	70–81°	Not available (N/A)	Fibrinogen deficiency	FFP, Cryo-precipitate or fibrinogen concentrate
	Kaolin TEG MA	50–70 mm	<45 mm		INTEM MCF	51–72 mm	N/A	Platelets deficiency if FF TEG MA normal	Platelets
	Kaolin TEG LY30	−2.3–5.77%	>4%		INTEM ML	0–12%[29]	>15%	Hyper-fibrinolysis	Tranexamic acid
Consisting of 8% kaolin, human recombinant tissue factor, phosphor-lipids, buffer and stabilizers	RapidTEG R	22–44 sec	>66 sec	Extem: a mixture of recombinant tissue factor and phosphor-lipids	EXTEM CT	43–82 sec	>80 sec	Coagulation factors deficiency	FFP
	RapidTEG K	30–118 sec	>150 sec		EXTEM CFT	48–127 sec	N/A	Fibrinogen deficiency	FFP, Cryo-precipitate or fibrinogen concentrate
	RapidTEG Angle	66–82°	<56°		EXTEM Angle	65–80	N/A	Fibrinogen deficiency	FFP, Cryo-precipitate or fibrinogen concentrate
	RapidTEG MA	52–71 mm	<55 mm		EXTEM MCF	52–70 mm	<50 mm	Platelets deficiency if FF TEG MA of FIBTEM normal	Platelets
	RapidTEG LY30	0.0–7.5%	>7.5%		EXTEM ML	0–18%[29]	>15%[10]	Hyper-fibrinolysis	Tranexamic acid
Lyophilized tissue factor and abciximab	TEG FF MA	11–24 mm	<14 mm	Fibtem: a combination of platelet inhibitor (cytochalasin D) and extem	FIBTEM MCF	7–24 mm	<9 mm	Fibrinogen deficiency	Cryo-precipitate or fibrinogen concentrate
Lyophilized heparinase in a TEG cup	Kaolin/ heparinase TEG R	300-600 sec	Delta+> 180 sec	hep-tem: lyophilized heprinase, and in-TEM	HEPTEM CT	122–208 sec	Ratio+>1.25	Heparini-zation	Protamine or FFP

*Unless specified, the reference ranges are according to the manufacturers of TEG and ROTEM for citrated and recalcified blood samples. +Difference in R between kaolin and heparinase TEG and kaolin TEG, and ratio between INTEM CT and HEPTEM CT. +Difference in R between kaolin/heparinase TEG and kaolin TEG, and ratio between INTEM CT and HEPTEM CT.

Although multiple parameters can be measured for blood coagulation and fibrinolysis, maximum amplitude MA in TEG FF and maximum clot strength MCF in ROTEM FIBTEM have been mostly used as a direct measure of fibrinogen levels. According to each manufacturer, the normal range of MA as measured by TEG FF using citrated blood is 11–24 mm (Guide to functional fibrinogen) and the normal range of MCF as measured by ROTEM FIBTEM assay is 7–24 mm (Instructions for use of fibtem).

ROTEM Analysis

The citrated whole blood was analyzed using a ROTEM delta system (Tem Innovations GmbH, Munich, Germany). The instrument was periodically checked with ROTROL–N and ROTROL–P for quality controls. Analyses were performed using 300 µL of citrated whole blood and 20 µL of extem together with 20 µL of fibtem following the procedure as recommended by the company. The test is designated as ROTEM FIBTEM. In addition, ROTEM EXTEM was performed simultaneously using 300 µL of the same blood sample and 20 µL of start-tem (0.2 M calcium chloride) together with 20 L of extem.

The following parameters were recorded for the ROTEM tests: clotting time CT (sec), clot formation time CFT (sec), Alpha angle (°), maximum clot firmness MCF (mm), time to reach MCF and clot lysis LI30 (%).

TEG Analysis

The citrated whole blood was also analyzed in parallel using a computerized TEG hemostasis s ystem 5000 (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA). The system had to pass the electronics testing and quality control according to manufacturer's protocol prior to sample analysis. To perform a standard TEG functional fibrinogen (FF) test, 500 µL of the blood sample was pipetted into a FF vial which contains lyophilized tissue factor with platelet inhibitor (abciximab) (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA), and gently mixed by inversion five times, and then 340 µL of the mixture from the FF vial was added into a TEG cup pre-warmed to 37°C containing 20 µL of 0.2 M calcium chloride. Measurements of reaction time R (sec), kinetics time K (sec), Alpha angle (°), maximum amplitude MA (mm), time to MA TMA (sec) and clot lysis LY30/CL30 (%) were carried out and the test is designated as TEG FF. To perform a cross-over test using the ROTEM reagents on TEG with the same reagent:blood ratio as the ROTEM FIBTEM test, 21 µL of extem, 21 µL of fibtem and 318 µL of the citrated blood were pipetted into a TEG cup. The mixture with a total volume of 360 µL was withdrawn and pipetted back to the cup, and the cup was loaded onto the pin immediately to start the test. The measurement was run until all following interested parameter values were obtained as the TEG FF: R, K, Alpha, MA, TMA, and LY30/CL30. The test is designated as TEG FIBTEM.

Comparison of TEG and ROTEM Analysis

We compared the corresponding parameters between the three tests (two standard tests: TEG FF and ROTEM FIBTEM as per manufacturer's reagents and procedures, and one cross-over test: TEG FIBTEM using the same reagent and concentration as ROTEM FIBTEM). These tests were performed simultaneously to analyze the same blood sample collected from all trauma patients screened at hospital admission and randomized into the FC and placebo group. The fibrinogen levels could be different among the three groups which may lead to different correlations between TEG and ROTEM within each group.

All the TEG and ROTEM parameters are derived in the same way for each assay, except the one for fibrinolysis. The TEG system provides LY30 and CL30. LY30 is computed as the percentage reduction of the area under a TEG tracing from the time MA is measured until 30 min after the MA. CL30 represents the value of the amplitude of a TEG tracing at 30min after the MA relative to MA. The ROTEM system provides LI30 as a measure of fibrinolysis. It is calculated as the ratio between clot firmness (in mm amplitude) at CT + 30 min and MCF. There are no same fibrinolytic parameters between TEG and ROTEM. CL30 is a fibrinolytic parameter in TEG most similar to LI30 in ROTEM. Therefore, we compared TEG CL30 instead of LY30 with ROTEM LI30 for fibrinolysis.

We further compared TEG FF and ROTEM FIBTEM for detecting coagulopathy including hypofibrinogenemia and hyperfibrinolysis. Trauma-induced coagulopathy (TIC) was defined by an admission INR >1.3 or Clauss fibrinogen level < 1.5 g/L,[35] or TEG FF and ROTEM FIBTEM principle parameters (MA, CL30/LY30, MCF, LI30/ML) outside manufacturers' normal ranges (MA 11–24 mm, CL30 < 97.5, LY30 > 7.5, MCF 7-24 mm, LI30 < 94, ML > 15). Hypofibrinogenemia was defined by Clauss fibrinogen level < 1.5 g/L, or TEG FF MA and ROTEM FIBTEM MCF below the normal values. TEG FF CL30/LY30 and ROTEM FIBTEM LI30/ML were used to measure hyperfibrinolysis assuming the same prognostic values (97.5%, 7.5% and 94%, 15%) as RapidTEG LY30 and ROTEM EXTEM ML. Hyperfibrinolysis was defined as CL30 < 97.5% or LY30 > 7.5% and LI30 < 94% or ML > 15%, respectively.

Conventional Coagulation Tests

Blood was collected at admission was processed and analyzed immediately for fibrinogen concentration,

prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count and hemoglobin according to clinical laboratory procedures. Plasma fibrinogen concentration was measured by Clauss method.[36] PT was converted to INR according to the specific reagents and device characteristics in the lab.

Statistical Analysis

Data were represented as mean ± standard deviation (SD) unless otherwise specified. Spearman non-parametric analysis was performed to evaluate interchangeability between equivalent TEG and ROTEM parameters. The following criteria were used for the strength of the correlations: <0.3 (low), 0.3-0.7 (moderate), >0.7 (high).[37]

The agreement between TEG and ROTEM measurements was further evaluated using Bland-Altman difference mean plot.[38] The mean values (M) of corresponding measurements for TEG and ROTEM variables were plotted against their differences (D). If a significant linear association between the differences and means was found, then bivariate linear regression, defined as: $D = a + b * M$, was used to calculate the estimated difference. This value was used to calculate the corresponding limit of agreement (LoA) as proposed by Bland and Altman.[39] Consequently, the LoA given in this situation was defined as: $(a + b * M) ± 1.96 * SD$, where SD represents the estimated standard deviation of the residuals. Predefined clinically acceptable LoA has been defined in the literature as ± 10% of the average values between methods.[15, 18]

Paired *t*-test was used to compare the corresponding parameter values between the two systems obtained from the same blood sample collected from screened patients at admission.

Linear regression for TEG FF MA, ROTEM FIBTEM MCF and TEG FIBTEM MA versus plasma fibrinogen concentration was performed. We focused on the TEG and ROTEM measurement on maximum clot strength (i.e., TEG maximum amplitude MA and ROTEM maximum clot firmness MCF) as they are mostly used parameters to detect fibrinogen levels and guide fibrinogen administration in trauma.[20,40]

Chi-square test or Fisher's exact test was used when appropriate to compare proportions of patients with different coagulation profiles (hypercoagulability, normal coagulability, and hypercoagulability), hypofibrinogenemia and hyperfibrinolysis according to TEG FF and ROTEM FIBTEM.

All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corporation, Armonk, New York, USA) with a significant level of p<0.05.

RESULTS

A total of 172 patients screened for the trial had TEG FF, TEG FIBTEM and ROTEM FIBTEM tests simultaneously performed at admission. In addition, the following numbers of CCTs have been completed for 45 included patients during hospital admission and 48-h hospitalization: 233 of PT, 209 of aPTT, 218 of Clauss assays (plasma fibrinogen levels), 245 of platelet count and 246 of hemoglobin tests.

Table 2 summarizes the correlations between all key TEG and ROTEM parameters values. Significant correlations were found for all corresponding parameters between TEG and ROTEM (p≤0.002) except TEG FIBTEM CL30 and ROTEM FIBTEM LI30 (p = 0.078). The strongest correlation was found between MA and MCF (r = 0.75/0.82) while the weakest is seen between CL30 and LI30 (r = 0.22/0.10). There were also significant correlations between TEG FF R and ROTEM FIBTEM CT (r = 0.26, p <0.001) and between TEG FIBTEM R and ROTEM FIBTEM CT (r = 0.41, p <0.001). Generally, higher correlations were seen when the same ROTEM FIBTEM reagents (extem and fibtem) were used on both TEG and ROTEM, which is consistent with our previous comparative study on other TEG and ROTEM assays.[41]

Next, we used the Bland-Altman difference mean plots to determine the agreement between the TEG and ROTEM parameters. Table 3 shows the limits of agreement (LoA) calculated from the results as described in Methods. None of the LoA for any of the parameters except TEG FIBTEM CL30 and ROTEM FIBTEM LI30 fell within the clinically acceptable range defined as ±10% threshold of the mean values.

As summarized in Table 4, on average TEG FF assay had a longer R (132.1 ± 58.3 sec), smaller Alpha (58.4 ± 12.4°), larger MA (22.4 ± 7.5 mm), smaller CL30 (98.8 ± 8.9%) and shorter time to MA (TMA: 845.0 ± 209.3 sec) compared to

Table 2: Correlations between TEG and ROTEM values for functional fibrinogen assays in screened patients

Variables	Spearman coefficients	p-values
R vs. CT	0.26[a]/0.41[b]	<0.001[a]/<0.001[b]
K vs. CFT	0.39[a]/0.31[b]	<0.001[a]/0.002[b]
Alpha vs. Alpha	0.46[a]/0.66[b]	<0.001[a]/<0.001[b]
MA vs. MCF	0.75[a]/0.82[b]	<0.001[a]/<0.001[b]
CL30 vs. LI30	0.22[a]/0.10[b]	<0.001[a]/0.078[b]

[a]TEG FF vs. ROTEM FIBTEM; [b]TEG FIBTEM vs. ROTEM FIBTEM

Table 3: Limits of Agreement (LoA) between TEG and ROTEM values for functional fibrinogen assays in screened patients

TEG/ROTEM variables	α	β	LoA	Clinically acceptable LoA
R vs. CT	68.2/32.7	−1.4[a]/-0.2	± 58.0/± 36.4	± 9.8/± 5.3
K vs. CFT	-316.5/-186.6	1.8[a]/1.9	± 516.0/± 396.3	± 33.0/± 30.3
Alpha vs. Alpha	42.0/-27.5	−0.5[a]/0.3	± 21.6/± 12.5	± 6.5/± 7.2
MA vs. MCF	-7.6/-3.2	0.1[a]/0.01	± 10.6/± 10.1	± 2.0/± 1.9
CL30 vs. LI30	30.5/6.1	−0.3[a]/−0.06	± 10.9/± 6.7	± 9.9/± 9.9

Data represent TEG FF vs. ROTEM FIBTEM/TEG FIBTEM vs. ROTEM FIBTEM

Table 4: Comparison between TEG and ROTEM values for functional fibrinogen assays in screened patients

Variables	TEG FF	ROTEM FIBTEM	TEG FIBTEM	p values
R and CT (sec)	132.1 ± 58.3	63.3 ± 17.7	41.8 ± 21.2	<0.001[a]/<0.001[b]
K vs. CFT (sec)	190.0 ± 136.4	466.3 ± 800.7	108.3 + 102.9	0.17[a]/0.34[b]
Alpha vs. Alpha	58.4 ± 12.4	67.7 ± 16.9	73.7 ± 7.1	<0.001[a]/<0.001[b]
MA vs. MCF	22.4 ± 7.5	17.1 ± 8.0	20.3 ± 8.1	<0.001[a]/<0.001[b]
TMA vs. Time to MCF (sec)	845.0 ± 209.3	1309.2 ± 517.6	436.0 ± 172.5	<0.001[a]/<0.001[b]
CL30 vs. LI30 (%)	98.8 ± 8.9	99.1 ± 6.8	99.4±6.7	<0.001[a]/<0.001[b]

Data are expressed as mean ± standard deviation; [a]TEG FF vs. ROTEM FIBTEM; [b]TEG FIBTEM vs. ROTEM FIBTEM.

ROTEM FIBTEM CT (63.3 ± 17.7 sec), Alpha (67.7 ± 16.9°), MCF (17.1 ± 8.0 mm), LI30 (99.1±6.8%) and time to MCF (1309.2 ± 517.6) (p < 0.001). In contrast, TEG FIBTEM assay had a shorter R (41.8 ± 21.2 sec), larger Alpha (73.7 ± 7.1°), MA (20.3 ± 8.1 mm), larger CL30 (99.4 ± 6.7%) and shorter TMA (436.0 ± 172.5) than the corresponding ROTEM FIBTEM parameters (p < 0.001). No significant difference was found between TEG K and ROTEM CFT.

There was a significant correlation between plasma fibrinogen concentration and MA or MCF as measured by each of TEG and ROTEM fibrinogen assays, with a largest correlation coefficient for ROTEM FIBTEM (r = 0.84, p < 0.001) followed by TEG FF (r = 0.64, p < 0.001) and TEG FIBTEM (r = 0.62, p < 0.001) (Fig. 2).

Table 5 compares the two assays for detection of coagulation abnormalities, hypofibrinogenemia, and hyperfibrinolysis. Among screened patients, TEG FF indicated normal coagulation profile in a smaller percentage and hypercoagulable profile in a larger proportion at admission than ROTEM FIBTEM (67.1% vs. 83.4% and 25.5% vs. 8.9%). With regard to hypercoagulability, 8.4% were observed for TEG FF, while 7.7% and 15.4% were observed for ROTEM FIBTEM depending on the parameters (LI30 vs. ML) used for the diagnosis. Similar divergent results were observed in enrolled patients, with two to three times increases in coagulation abnormalities, more than that identified by INR and fibrinogen level (19.5%). The detection rate for hypofibrinogenemia was higher as measured by TEG FF MA < 11 mm than that by FIBTEM MCF < 7 mm among both screened (3.9% vs. 6.5%) and enrolled patients (7.3% vs. 17.1%) and was significantly different from 14.6% among enrolled patients defined by Clauss fibrinogen level < 1.5 g/L. ROTEM FIBTEM showed less hyperfibrinolysis with 2.4% according to LI30<94%, but more hyperfibrinolysis with 13.7% according to ML > 15% than FF TEG CL30 < 97.5% and LY30 > 7.5% with 4.7% and 4.2%, respectively. Similar divergent results were observed in enrolled patients, with two to three times increases in hyperfibrinolysis.

Table 5: Diagnostic characteristics of TEG and ROTEM functional fibrinogen assays for coagulation, hypofibrinogenemia and hyperfibrinolysis

Coagulopathy	Population	According to TEG FF MA <11 mm or >24 mm or CL30 < 97.5%	According to TEG FF MA<11 mm or >24 mm or LY30 >7.5%	According to FIBTEM MCF<7 mm or >24 mm or LI30<94%	According to FIBTEM MCF <7 mm or >24 mm or ML>15%	According to INR >1.3 or fibrinogen level <1.5 g/L
Hypocoagulability/ Normalcoagulability/hypercoagulability	Screened patients	8.4%/67.1%/25.5%	8.4%/ 67.1/25.5%	7.7%/83.4%/8.9%	15.4%/75.7%/8.9%	N/A
	Enrolled patients	24.4%/41.5%/34.1%	19.5%/46.4%/34.1%	24.4%/68.3%/7.3%	31.7%/61.0/7.3%	19.5%
Hypofibrinogenemia	Screened patients	3.9%		6.5%		N/A
	Enrolled patients	7.3%		17.1%		14.6%
Hyperfibrinolysis	Screened patients	4.7%	4.2%	2.4%	13.7%	N/A
	Enrolled patients	17.9%	12.2%	9.8%	26.8%	

Manufacturer reference ranges: TEG FF MA 11-24 mm, CL30 97.5-100%, LY30 0-7.5%; ROTEM FIBTEM MCF 7–24 mm, LI30 94–100%, ML 0–15%.
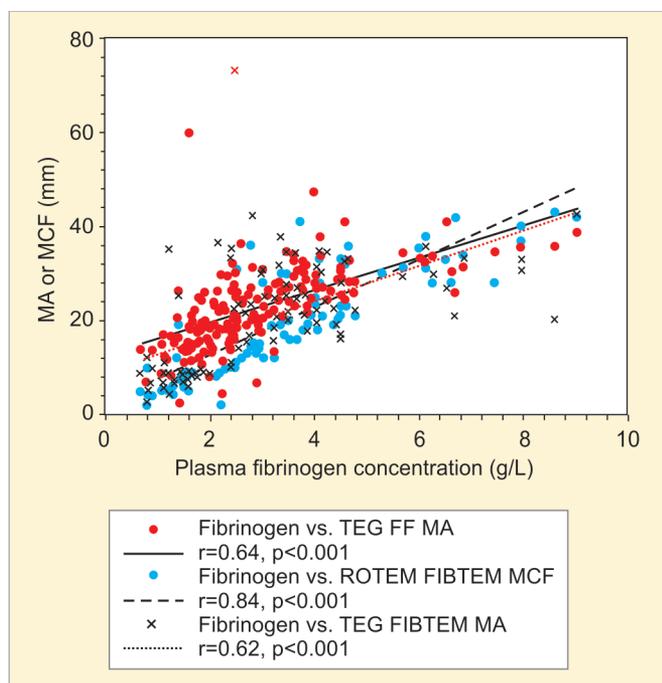
Fig. 2. Correlations between plasma fibrinogen concentration and fibrinogen clot strength as assessed by TEG FF MA, ROTEM FIBTEM MCF and TEG FIBTEM MA.

DISCUSSION

There are studies assessing the interchangeability of ROTEM and TEG for different coagulation assays in cardiac surgical[15] and trauma patients.[18] In our study, we compared TEG and ROTEM for fibrinogen assays, taking into account of the effects of reagents by a cross-over comparison, in trauma patients initially screened for hypotension and need for transfusion at hospital admission in a setting of a clinical trial.

The strongest correlations between TEG MA and ROTEM MCF among all measured parameters are consistent with other studies comparing TEG and ROTEM tests using no activators[16] or activators (e.g., kaolin-activated TEG vs. extem and in-tem activated ROTEM).[15, 18, 41] Furthermore, our study showed a similar correlation coefficient between the standard TEG FF MA and ROTEM FIBTEM MCF to another study comparing the two functional fibrinogen assays (0.75 vs. 0.71).[24] In addition, we found significant correlations among other corresponding parameters (e.g., between K and CFT, and between TEG Alpha and ROTEM Alpha) although they were not well reported and compared in TEG and ROTEM fibrinogen assays.[14]

Despite the strength of the correlation of most parameters, the results of our study indicate that when TEG and ROTEM were performed using either their own standard or the same reagents, the equivalent measurements were not interchangeable (TEG R vs. ROTEM CT; K time vs. CFT; Alpha (TEG) vs. Alpha (ROTEM); MA vs. MCF; CL30 vs. LI30). Except for lysis indicators when the same reagents were used (i.e., ROTEM FIBTEM LI30 and TEG FIBTEM CL30), all other parameters fell markedly outside the predefined clinically acceptable LoA. These results are similar to those reported recently by Hagemo et al.[18] and our previous study comparing standard TEG with kaolin as an activator and ROTEM with tissue factor-based extem as the activating agent in severe bleeding trauma patients.[42]

The lack of interchangeability is consistent with other studies comparing TEG and ROTEM for different coagulation assays in cardiac surgical[15] and trauma patients,[18] and may come from both the use of different assay reagents and instrument itself.[40, 43] The shorter TEG FIBTEM R compared to TEG FF R indicates that the reagent for ROTEM FIBTEM (extem) is stronger activator than that used in TEG FF. It has been speculated that ROTEM FIBTEM reagents might contain stabilizing agents (e.g., DMSO) and more tissue factor than TEG FF reagent.[44] The larger TEG MA compared to ROTEM FIBTEM MCF is consistent with other studies comparing these two functional fibrinogen assays for whole blood from surgical patients[33, 45] and healthy volunteers.[46, 47] This is likely due to different effectiveness of the platelet inhibitors in TEG (i.e., abciximab) and ROTEM (i.e., cytochalasin D) in eliminating platelet contribution to clot strength.[47] The correlation between TEG FF MA and platelet count implies the platelet contribution still existed in comparison with no correlation between ROTEM FIBTEM and TEG FIBTEM where cytochalasin D was used as the platelet inhibitor. On the other hand, the larger TEG FIBTEM MA than ROTEM MCF obtained using the same reagent at the same concentration implies that TEG system itself may also give a larger value of clot strength. The shorter time to reach maximum clot strength in both TEG FF and FIBTEM is likely due to the hardware differences between the two systems which include the mechanisms for cup/pin rotation, detection of the rotation, cup materials and interior surface properties.[16, 17] Clot firmness at 5 and 10 minutes after CT has been validated to surrogate MCF in ROTEM to shorten the timeline for goal-directed transfusion for trauma patients.[48]

Another possible explanation for the lack of interchangeability might be their wide coefficients of variance (CV) which range from 7.06 to 59.98% for TEG and 3.12 to 39.07% for ROTEM with the lowest CV seen for Alpha/Alpha and the highest CV for K/CFT when measuring platelet-rich plasma.[49] This wide variability may affect the calculation of the tests mean values and differences and consequently the evaluation of the closeness between TEG and ROTEM variables. The within-subject coefficient of variability was reported as 5 to 8% for TEG FF MA and 3 to 5% for ROTEM FIBTEM

MCF.[14] A recent study showed that inter/intra-operator CVs were significantly lower for ROTEM MCF compared with TEG MA (8.3 and 6.9% vs. 12.2 and 12.1%).[28]

The correlations between different TEG or ROTEM tests and Clauss fibrinogen assay have been reported. However, there are only few studies on the correlations between TEG or ROTEM fibrinogen assays specifically focusing on the correlations between TEG FF or ROTEM FIBTEM MCF and fibrinogen concentration.[48, 50] Correlation analysis was carried out for values between TEG or ROTEM that correlate with fibrinogen (MA/MCF).[51] No correlation was demonstrated when other VHA parameters were used.[32]

Most importantly, our study showed that fibrinogen concentration was correlated with almost all TEG and ROTEM parameters, implying fibrinogen contributes to all aspects of clot formation and stability from the initiation and progression of blood coagulation to the end of fibrinolysis. The strongest correlations were between TEG MA or ROTEM MCF and fibrinogen concentration, suggesting these parameters are most useful for monitoring hemostasis status in trauma patients.

TEG MA and ROTEM MCF reflect the maximum strength of a blood clot. The stronger correlation for ROTEM FIBTEM is likely due to more effectiveness at inhibiting the platelet contribution to clot strength than TEG FF as reported in the literature.[47] The correlation coefficients between plasma fibrinogen concentration and TEG MA, ROTEM MCF found in our study are slightly higher than the range as reported in the literature (0.56 for TEG FF, 0.66 for ROTEM FIBTEM in cardiac surgery patients;[33] 0.64 for TEG FF, 0.68 for ROTEM FIBTEM in trauma.[24,48]

Although TEG and ROTEM were correlated for functional fibrinogen assays their parameter values were significantly different and not clinically interchangeable. Therefore, guidelines developed for one instrument should not be used for the other. The difference may result from both the instrument itself and the activation reagents used to perform the assays. Both systems showed varying degrees of associations with CTTs, with ROTEM exhibiting stronger associations than TEG, and fibrinogen concentration being principally correlated with each system. Further comparisons between these two systems for diagnosis of coagulation abnormalities, hypofibrinogenemia and hyperfibrinolysis were discussed below.

The hypercoagulable state detected by TEG FF and ROTEM FIBTEM in our study (19.5-31.7%) is close to the range of 25–33% of severe trauma patients present with a laboratory-defined coagulopathy.[52] TEG and ROTEM could detect a hypercoagulable state and were better tests than prothrombin time or activated partial thromboplastin time.[53, 54] The coagulation abnormalities classified with TEG FF in our enrolled patients are slightly higher than those based on kaolin TEG in a similar trauma population on admission (17.8% hypercoagulable and 26.3% hypercoagulable).[53] The hypercoagulability according to our ROTEM FIBTEM test is lower than that reported using ROTEM EXTEM in combat casualties, while the hypercoagulability is comparable.[55] These disparities may be explained at least in part by different tests and reference values of TEG and ROTEM used to define hypo- and hypercoagulability in these studies. It should be noted that TEG FF and ROTEM FIBTEM are mainly used for diagnosis of fibrinogen deficiency and guidance of fibrinogen administration according to their MA and MCF values instead of diagnosis of TIC through other TEG (kaolin and Rapid) and ROTEM tests (EXTEM).[56, 57]

Divergent cut-off values of TEG and ROTEM have been used in algorithm-based fibrinogen replacement therapy in trauma[58] and bleeding patients.[59, 60] We chose the manufacturer suggested normal ranges for MA and MCF for comparison purpose, which indicated different numbers of hypofibrinogenemia patients as diagnosed by each test. The prevalence of hypofibrinogenemia in our enrolled patients is higher than that reported in the literature using the same definition at the fibrinogen level of 1.5g/L (14.6 vs. 8.2%). This is likely due to higher injury severity in our study population (injury severity score of 24 vs. 16). The fibrinogen level of 1.5 g/L approximately corresponds to TEG FF MA of 18 mm and ROTEM FIBTEM MCF of 10mm based on the correlations obtained in our study (Fig. 2). The respective value is 7 mm higher than the lower threshold of the normal ranges for TEG FF (11–24 mm) and 3 mm higher than that of ROTEM FIBTEM (7–24 mm) as recommended by each manufacturer. These discrepancies may explain the difference between TEG FF MA and ROTEM FIBTEM MCF for the diagnosis of hypofibrinogenemia and should be considered carefully when developing goal-guided administration of fibrinogen concentrate using TEG and ROTEM functional fibrinogen assays. Future studies comparing different intervention thresholds of ROTEM FIBTEM MCF have been suggested.[5]

More hyperfibrinolysis as indicated by ROTEM FIBTEM ML than FF TEG LY30 is consistent with the literature showing ROTEM FIBTEM and EXTEM ML was more sensitive than contact-activated kaolin TEG LY30 in identifying hyperfibrinolysis in patients undergoing liver transplantation.[61] Different TEG and ROTEM parameters and values have been used to define hyperfibrinolysis and treatment in trauma.[62] As ML is not calculated at a fixed time point but is defined as % lysis at the end of the measurement, it may vary with the total runtime and the

time after maximum clot formation. As ML was obtained at a longer time than LI30 in our study, it captured the immediate and late-stage hyperfibrinolysis[10] and thus detected more hyperfibrinolysis than LI30. Compared to other TEG (kaolin and Rapid) and ROTEM tests (EXTEM and INTEM), TEG FF and ROTEM FIBREM provided more rapid detection of fibrinolysis.[63]

The increases in coagulation abnormalities, hypofibrinogenemia, and hyperfibrinolysis in enrolled patients compared to screened patients are due to higher injury severity. This is in agreement with the literature that showed increased TIC including hypofibrinogenemia and hyperfibrinolysis with injury severity.[64]

CONCLUSION

Although TEG and ROTEM were correlated for functional fibrinogen assays their parameter values were significantly different and not clinically interchangeable. Therefore, guidelines developed for one instrument should not be used for the other. The difference may result from both the instrument itself and the activation reagents used to perform the assays. Both systems showed various degrees of associations with Clauss fibrinogen, with ROTEM exhibiting better associations than TEG. Further comparison of clinical performance between these two systems for diagnosis of coagulopathy and guided fibrinogen administration is warranted.

ACKNOWLEDGEMENTS

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INVITED COMMENTARY

Viscoelastic Coagulation Technology: Comparing Apples to Apples, Apples to Oranges, or Fruits to Vegetables?

Coagulation is a complex process representing a continuous balance of thrombotic and fibrinolytic chemistry and mechanics aimed at keeping our vasculature from completely clotting while at the same time limiting hemorrhage in the setting of a vascular injury. Perhaps there is no entity where coagulation and its management is more complex than in the setting of trauma shock where blood with its distinct cell types (red cells, white cells, platelets) and noncellular components (plasma) are constantly bathing the 7000 m^2 of vascular endothelium.[1] Together this blood-endothelial unit (blood) is the largest organ of the body. With the ischemia, oxygen debt, tissue injury, cellular injury, adrenergic activation, inflammation and other processes caused by traumatic shock it not surprising that it may be prone to failure.[2] Trauma included coagulopathy (TIC) is manifestation of this failure. Increasing recognition of this complex life-threatening state is driving many aspects of resuscitation techniques such as damage control surgery and its transfusion practices. It makes sense given the heterogeneity in patient demographics, injury patterns, and timing of resuscitation, that developing precision vital signs for blood to guide transfusion would be attractive.

Common plasma-based laboratory methods used for detection of coagulopathy after trauma such as the pro-thrombin time and activated partial thromboplastic time have been and continue to be used as the default coagulation monitoring technologies in most centers initially encountering and resuscitating victims of trauma. Given their plasma-based nature, they have limited ability to detect early coagulation changes in traumatic shock or to give insight into what types of blood management are required to restore hemostasis while surgical hemostasis is underway. However, what is really surprising is that we even assumed they would be helpful given they were never designed to be used in the management of trauma but instead to monitor and manage anticoagulation therapy using vitamin K antagonists (PT) and unfractionated heparin (aPTT).

Described by Hertert in 1948, viscoelastic hemostatis assays (VHA) thromboelastrography (TEG) and its close relative rotational throboelastometry (ROTEM) examine the evolving viscoelastic properties of whole blood as it is exposed to a low shear rotational.[3] These changes provide rich insight into clotting onset times, rate of clot production, clot strength and even clot lysis. An increasing number of studies and literature are evolving now examining the ability of these two commercialized technologies to affect the management and outcome of patients with traumatic shock.[4,5] Of interest is if the values provided by these two similar technologies can be used interchangeably.

In this issue, Peng and colleagues report on the comparison of serial TEG and ROTEM functional fibrinogen assays in patients who were enrolled in a feasibility trial of randomized administration of fibrinogen concentrate after trauma (FiiRST trial).[6] While not used to implement or guide fibrinogen therapy, the goal was to compare and understanding their potential for diagnosis of coagulopathy and use in guided fibrinogen administration. In addition to comparing each technology to each other they carried out cross over design where reagents from each device's assays were used to run thee assay on the other device. Appropriately using the Bland-Altman technique, the authors clearly demonstrate that most if not all of the various assays are not interchangeable between TEG and ROTEM. The authors demonstrate that there are moderate to good correlations between the TEG and ROTEM functional fibrinogen assays and fibrinogen levels (r = 0.64 and 0.84 respectively).

While Peng and colleagues are not the first to demonstrate that the raw values of these two similar approaches are not interchangeable, their study does seem, however, to be the first to examine performance in a cross over design concentrating on fibrinogen and comparing to conventional coagulation testing and fibrinogen level testing. However, one would not anticipate that they should be given the mechanical approach to the measure, the various reagents are not identical, and the reported co-efficient of variations which are somewhat wide.

More importantly, the authors used data to group patients as hypo, normo, and hypercoagulable as well as having hypofibrinogenemia and hyperfibrinolysis based on the respective manufacturers' range of normal values finding a wide range of performance. This data is interesting if not a bit disturbing given the some of the different ranges. However, what is missing from this study as well as others making comparison of TEG and ROTEM (especially in observational studies where values are not used to guide management) is that the values are not matched to clinical phenotypes and actions taken based on the phenotypes. The data and study design do not allow us to know if in fact that patients assigned hypo, normo and hypercoagulable, or as having hyperfibrinolysis actually acted as if they were and if they did, what actions were taken. While the population studied in the FiiRST trial is small, there is an opportunity to match TEG and ROTEM values to actionable phenotypes in an unbiassed manner since treatments

were not based TEG or ROTEM values. Good correlations of TEG and ROTEM functional fibrinogen assays with fibrinogen levels is nice but did either match patient hemostatic behavior? Since patients were randomized to receive fibrinogen concentrate, the opportunity to observe the transition of phenotypes based on TEG and ROTEM also exists and if additional transfusion of blood products affected these. This data is not reported but could be in the future.

If VHA techniques are to be widely embraced for goal directed diagnosis and management of TIC, each technology should be specifically studied in the setting of traumatic shock and diagnostic values of various VHA parameters such as maximum amplitude (or maximum clot firmness) be determined that are matched to a TIC phenotype and that are in turn can be altered with guided treatment. Studies such as those reported by Steller and colleagues are beginning to do this for example by using ROTEM to develop clinical thresholds for transfusion and comparing these to previously developed thresholds using TEG.[7] The data in that study do not demonstrate clear superiority of one technology over the other.

This emphasizes the need for more studies to match values of the respective technologies to TIC phenotypes in real time. The more valuable question to ask from a performance comparison is what values in each group would have impacted treatment decisions based on the phenotype. This replaces statistically significant differences with what is clinically significant. Adding to this will be the requirement to compare the values serially as the dynamic human physiologic system undergoes additional treatment and hemorrhage. Good agreement at one stage of TIC does not guarantee good agreement at latter stages.

This approach will be challenging if it is not done before wider spread adoption of these technologies and we may miss our opportunity to create threshold values that are unbiassed by treatment. Further challenges are on the horizon as new VHA based technologies are created which use TEG and ROTEM as predicate technologies or as new generation TEG and ROTEM devices which replace the original pin/cup configuration are developed and adopted. We are in effect comparing devices to each other instead of developing them specifically for the disease of interest and how the use of the specific technology impacts treatment and outcome.

Is the Peng study an apples to apples comparison between TEG and ROTEM? Maybe, or it may be closer to apples versus oranges (comparing fruit to fruit). However, until the data is matched to a true actionable phenotype, such studies will be a fruit to vegetable comparison since the technologies were not specifically designed with the complexities of traumatic shock and its management in mind.

References

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Kevin R. Ward
Departments of Emergency Medicine and Biomedical Engineering
Michigan Center for Integrative Research in Critical Care
University of Michigan