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A comparative study of viscoelastic hemostatic assays and conventional coagulation tests in trauma patients receiving fibrinogen concentrate

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ABSTRACT

Background: Both thrombelastography (TEG) and rotational thromboelastometry (ROTEM) have been investigated for diagnosis of coagulopathy and guidance of resuscitation in trauma and surgery. Given similarities between the two systems, it is important to determine whether one is superior to the other and how comparable they are to conventional coagulation tests (CCTs). Therefore, we conducted a comparative study of functional fibrinogen and coagulation assays using TEG and ROTEM and CCTs to determine their capability to monitor coagulation profiles, diagnose coagulopathy and predict blood transfusion requirements in trauma patients.

Methods: Blood samples were collected from 45 patients at admission and during 48-h hospitalization as part of a randomized control trial on early fibrinogen replacement in trauma. Functional fibrinogen (FF) TEG, ROTEM FIBTEM and EXTEM, and CCTs were performed and compared.

Results: We found significant differences between the placebo and fibrinogen groups over hospitalization time in FF TEG MA, ROTEM CT, MCF and LI30. FF TEG MA and ROTEM FIBTEM MCF mirrored plasma fibrinogen profiles, reached a maximum difference between the two groups 1–3 h after fibrinogen administration. In comparison, CCTs detected minimal hemostatic changes by fibrinogen treatment. TEG and ROTEM showed various degrees of correlations with CCTs. TEG MA and ROTEM MCF provided better predictions for plasma and RBC transfusions than CCTs, but poor accuracy for cryoprecipitate transfusion. Both TEG and ROTEM well predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L), but poorly detected coagulopathy (INR ≥ 1.2).

Conclusions: TEG and ROTEM detected increases in clot strength following early use of fibrinogen. ROTEM also detected changes in coagulation time and clot lysis. Both were better than CCTs for monitoring coagulation profiles and predicting transfusion requirements.

1. Introduction

Thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are two viscoelastic hemostatic assays in whole blood [1]. Both have been increasingly used to diagnose coagulopathy and guide hemostatic resuscitation in trauma [2]. TEG- and ROTEM-based algorithms have been widely used to direct fibrinogen administration in different settings leading to a reduction in blood product use, transfusion costs and even mortality [3,4]. A number of recent reviews and meta-analyses has found that TEG/ROTEM could reduce unnecessary blood transfusion in bleeding patients but not survival compared to conventional coagulation tests, primarily based on trials in cardiac surgery [5–8]. A recent retrospective observational study showed that incorporation of functional fibrinogen (FF) TEG into TEG-based

Abbreviations: CCT, conventional coagulation test; CRYO, cryoprecipitate; CT, coagulation time; CV, coefficients of variance; FC, fibrinogen concentrate; FF, functional fibrinogen; FFP, fresh frozen plasma; FiiRST, fibrinogen in the initial resuscitation of severe trauma; INR, international normalized ratio; MA, maximum amplitude; MCF, maximum clot firmness; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cells; ROC, receiver operating characteristic; ROTEM, rotational thromboelastometry; TEG, thrombelastography

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coagulation management and administration of fibrinogen concentrate reduced the need for transfusion in patients undergoing liver transplantation with no impact on survival [9]. A randomized clinical trial has concluded that TEG-guided massive transfusion protocol for severely trauma improved survival compared with that guided by CCTs (i.e., prothrombin time [PT]/international normalized ratio [INR], fibrinogen and D-dimer) and utilized less plasma and platelet transfusion during the early phase of resuscitation [10]. ROTEM-guided transfusion reduced intra-operative blood loss, fresh frozen plasma transfusion and direct cost during orthotopic liver transplantation compared to CCT-guided transfusion [11].

In addition to reducing the need for blood products, compared to CCTs (INR, partial thromboplastin time (PTT), fibrinogen, platelet count, D-dimer) TEG was better at identifying coagulopathy in patients with traumatic brain injury and predicting mortality in a retrospective study [12], as well as associated with improved functional outcomes after moderate-to-severe subarachnoid hemorrhage in a prospective observational study [13]. When compared to laboratory prothrombin time ratio, ROTEM clot amplitude at 5 min could identify acute traumatic coagulopathy and predict the need for massive transfusion faster and more accurately [14]. Furthermore, TEG and ROTEM can provide rapid and accurate detection of hyperfibrinolysis and prediction for mortality in trauma [15,16].

However, some studies have reported that TEG was less sensitive for diagnosis of traumatic coagulopathy than CCTs [17] and incorporation of TEG did not improve bleeding prediction in a retrospective study of cardiac surgery patients [18]. ROTEM was also found to be no better than CCTs for detecting differences between surviving and non-surviving critically ill patients [19] and was unable to predict postpartum hemorrhage and was not superior to CCTs in a prospective observational study of 217 healthy pregnant women [20].

On the other hand, studies have shown that TEG and ROTEM provide different results for diagnosing coagulopathy and guiding transfusion [21]. For example, ROTEM-guided transfusion tended to recommend fibrinogen replacement [22] while TEG-based algorithms appeared to recommend plasma transfusion [23]. The difference may be more due to ROTEM-guided transfusion utilizing FIBTEM which is a specifically designed ROTEM assay for fibrinogen level and function [24]. In contrast, FF TEG assay, equivalent to FIBTEM, was less recognized and barely included for TEG-guided blood product transfusions and fibrinogen administration [3,25].

A number of studies have been conducted to directly compare the two systems focusing on differences in parameter values [26], and inter- and intra-operator variabilities [27]. A few studies were focused on the correlations and interchangeability between the two systems in healthy population [28], cardiac surgical [29] and trauma patients [30]. There are also studies to compare their performance for evaluation of coagulation changes [31], platelet aggregation [32], fibrin-based maximum clot strength [33] and transfusion requirements in liver transplantation [23]. There are studies to compare TEG and ROTEM for detection of fibrinolysis, suggesting that tissue factor-activated ROTEM EXTEM and FIBTEM were more sensitive than kaolin-activated TEG for detection of hyperfibrinolysis during adult liver transplantation [34], but their functional fibrinogen assays were comparable [35].

We conducted a randomized control trial to investigate safety and feasibility of fibrinogen in the initial resuscitation of severe trauma (FiiRST) [36]. As part of a secondary coagulation study, TEG and ROTEM have been compared to determine the utility of each system in comparison with CCTs for monitoring any changes in coagulation profiles and predicting clinical outcomes in trauma patients randomized for pre-emptive treatment with fibrinogen concentrate (FC) or placebo within 60 min of arrival to the trauma room. In a previous paper we focused on the correlations and interchangeability between the two systems [37], and this paper focuses on their clinical performance for detection of hemostatic effects of fibrinogen administration, diagnosis of traumatic coagulopathy (INR ≥ 1.2), hypofibrinogenemia (fibrinogen level < 1 g/L) and prediction of blood transfusions in comparison with CCTs.

2. Materials and methods

2.1. 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 including inclusion and exclusion criteria and primary outcomes have been published [36]. Briefly, adult (age > 18 years) trauma patients were screened for eligibility if RBCs were ordered within 30 min of arrival. Patients with hypotension (systolic arterial pressure ≤ 100 mmHg) and need for RBC transfusion within 30 min of arrival were randomized to receive either 6 g FC (RiaSTAP™, CSL Behring) or placebo (normal saline). Blood was collected in BD vacutainer containing 3.2% sodium citrate (Fisher Scientific, Nepean, ON, Canada) at admission, 2, 4, 12, 24, and 48 h of hospital admission. The blood was analyzed simultaneously by TEG, ROTEM and CCTs as described below.

The study was approved by Sunnybrook Research Ethics Board and used exception from informed consent.

2.2. Principles of TEG and ROTEM analysis

Fig. 1(a, b) shows the testing principles of the two mostly used systems: TEG 5000 hemostasis analyzer (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA) and ROTEM delta system (Instrumentation Laboratory, Bedford, MA, USA), 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 [37]. For each TEG channel, a pin suspended by a torsion wire is immersed in 360-μL whole blood or plasma in a plastic cup. The cup transversely oscillates back and forth through an arc of 4.75° every 5 s while the pin is deflected by the torque pressure of the viscoelastic properties of blood 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. For each ROTEM channel, a pin suspended on a ball bearing mechanism transversely oscillates back and forth through 4.75° every 6 s with a constant force in a fixed cup into which a 300-μL sample of whole blood and 40-μL reagents are electronically pipetted. As the blood clots the impedance to pin rotation is transmitted via an optical detector system, and recorded by computer. 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 [38], and that the automatic pipetting may ensure less variations among operations [27].

The measurement of both instruments is graphically represented as a characteristic shape profile over time (Fig. 1(c)), 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, α 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 or the rate of amplitude reduction 30 min after MA, LY30/CL30, which is related to plasma levels and activities of tissue plasminogen activator. Similar parameters to TEG as shown in Fig. 1(c) [e.g., coagulation time (CT), clot formation time (CFT), α

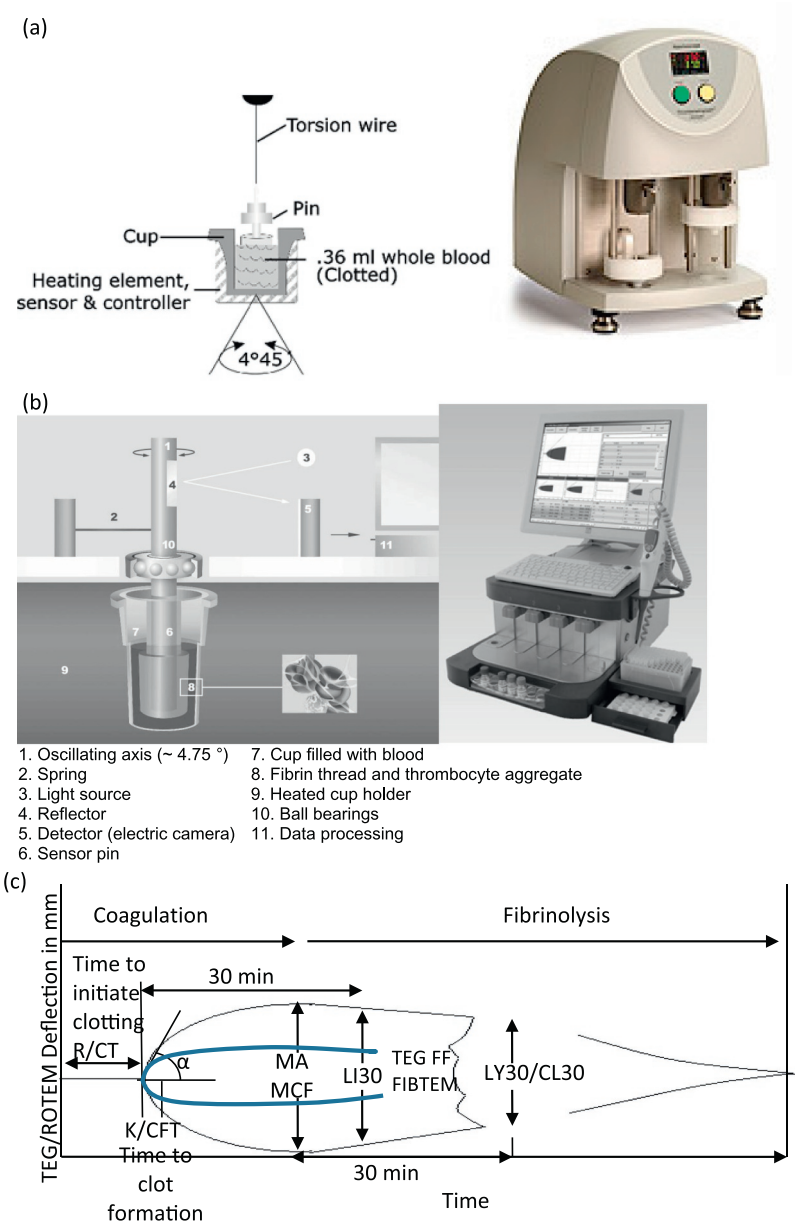

Fig. 1. Schematic illustration of (a) TEG mechanism and machine, (b) ROTEM mechanism and machine, and c) a representative TEG/ROTEM tracing showing the relationship between the qualitative tracing and the quantitative parameters. Courtesy of Haemonetics Corporation and TEM Systems, Inc.

angle, maximum clot firmness (MCF), clot lysis index LI30] can be derived from ROTEM which are commonly used in Europe [39]. In addition, the clot amplitude at 10 min after CT (CA10) has been reported as well.

2.3. TEG analysis

The citrated whole blood was analyzed using a computerized TEG Hemostasis System 5000 (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA). To perform a standard FF TEG test, 500 μL of the blood sample was pipetted into a FF vial which contains lyophilized tissue factor with platelet inhibitor (abciximab) (Haemoscope Corporation, Niles, IL), 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. The test is designated as FF TEG. To perform a crossover test using the ROTEM reagents on TEG with the same reagent:blood ratio as the ROTEM FIBTEM test, 21 μL ex-tem, 21 μL fib-tem 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 test is designated as TEG FIBTEM.

2.4. ROTEM analysis

The citrated whole blood was also analyzed simultaneously using a ROTEM delta (Instrumentation Laboratory, Bedford, MA, USA). ROTEM FIBTEM was performed using 300 μL of citrated whole blood and 20 μL of ex-tem together with 20 μL of fib-tem following the procedure as recommended by the company. ROTEM EXTEM was conducted in parallel using 300 μL of the same blood sample and 20 μL of start-tem together with 20 μL of ex-tem. The following parameters were recorded for both EXTEM and FIBTEM: clotting time CT, clot formation time CFT, Alpha angle, maximum clot firmness MCF and clot lysis LI30.

2.5. CCTs

Blood was processed and analyzed immediately for prothrombin time, activated partial thromboplastin time, fibrinogen concentration (Clauss assay), platelet count and hemoglobin according to clinical laboratory procedures. INR was calculated from prothrombin time in accordance with the specific reagents and device characteristics in the laboratory.

2.6. Comparison of TEG/ROTEM analysis and CCTs

We compared the corresponding three TEG/ROTEM functional fibrinogen tests (two standard tests: FF TEG and ROTEM FIBTEM as per manufacturer's reagents and procedures, and one crossover test: TEG FIBTEM using the same reagent and concentration as ROTEM FIBTEM. Additional ROTEM EXTEM was conducted to see if simultaneous assays using various reagents would correlate better with therapeutic outcomes. These tests and CCTs were compared for ability to detect the effects of fibrinogen concentrate on coagulation profiles, predict blood transfusion requirements, and detect coagulopathy and hypofibrinogenemia.

We focused on those parameters that provide the greatest diagnostic and therapeutic discrimination. They include R, MA, LY30 for TEG, and CT, MCF and LI30 for ROTEM as listed in Table 1. Their reference values are according to the manufacturers of TEG and ROTEM or literature reports [37,39]. However, LY30 and LI30 are derived differently. There are no similar fibrinolytic parameters between TEG and ROTEM. TEG CL30 computed as the value of the amplitude of a TEG tracing at 30 min after the MA relative to MA is most similar to ROTEM LI30 calculated as the ratio between clot firmness at CT + 30 min and MCF. We thus chose to compare these two fibrinolytic parameters.

2.7. Statistical analysis

Data were represented as mean ± standard deviation (SD) unless otherwise specified. Linear mixed model with random patient effects and Bonferroni post hoc tests were used to test the main effects of fibrinogen treatment and hospitalization time on TEG/ROTEM and CCTs measurements, respectively. Independent *t*-test was used to compare measurements between the placebo and fibrinogen groups. Spearman non-parametric analysis was performed to evaluate the direction and strength of the correlations between TEG/ROTEM parameters and CCTs.

The predictive power of each TEG/ROTEM test and CCT for each clinical outcome (e.g., coagulopathy, blood transfusion) was examined by comparing the area under the receiver operating characteristic curves (AUC ROC) using C-statistic and 95% confidence interval, while controlling for treatment effects between the placebo and fibrinogen groups. Given small 28-d mortality and number of patients receiving ≥10 RBC units within 24-h hospitalization ($n = 3$), we did not conduct the predictive analysis for mortality and massive transfusion. Transfusion of red blood cells (RBC), fresh frozen plasma (FFP) and cryoprecipitate (CRYO) within 24-h hospitalization was predicted using the TEG MA and ROTEM MCF at admission. Coagulopathy defined as an INR ≥ 1.2 and hypofibrinogenemia defined as plasma fibrinogen concentration < 1 g/L were predicted using the corresponding TEG MA and ROTEM MCF during 48-h hospitalization.

All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corporation, Armonk, New York, USA) with a significant level of $p < .05$.

Table 1
Commonly employed parameters and their reference values in TEG and ROTEM assays.

TEG/ROTEM parameters	Reference values[a]		
	FF TEG	ROTEM FIBTEM	ROTEM EXTEM
R/CT (sec)	Not available	43–69 [39]	43–82
MA/MCF (mm)	11–24	7–24	52–70
LY30/LI30 (%)	0–7.5 [37]	94–100 [37]	94–100 [37]

[a] Unless specified, the reference ranges are according to the manufacturers of

3. Results

A total of 45 patients were randomized to receive either placebo saline or FC infusion, having respective TEG FF/FIBTEM, ROTEM FIBTEM/EXTEM tests and CCTs simultaneously performed during hospital admission and 48-h hospitalization. The main findings of the trial including the demographics and clinical outcomes of the patients have been published [36].

3.1. Comparison of TEG/ROTEM and CCTs for coagulation profiles

As summarized in Table 2, ROTEM FIBTEM indicated significant changes in coagulation time CT by both treatment ($F_{1,228} = 17.13$, $p < .001$) and hospitalization time ($F_{5,228} = 3.90$, $p = .002$). TEG FIBTEM showed only changes in R time by treatment ($F_{1,228} = 4.92$, $p = .028$), but no effects of hospitalization time ($F_{5,228} = 0.77$, $p = .58$), and FF TEG was unable to detect any changes in R time by either treatment ($F_{1,218} = 1.45$, $p = .23$) or hospitalization time ($F_{1,218} = 1.68$, $p = .14$). ROTEM EXTEM only showed the between-group differences in CT ($F_{1,\ 234} = 27.02$, $p < .001$), but no change in CT over time ($F_{5,\ 234} = 0.99$, $p = .42$). On the other hand, all TEG and ROTEM tests detected significant changes in MA and MCF by treatment and hospitalization time ($p < .001$). Interestingly, TEG FIBTEM showed significantly different CL30 between the placebo and FC groups ($F_{1,\ 222} = 5.04$, $p = .026$) as well as over hospitalization time ($F_{5,222} = 3.90$, $p = .002$), while ROTEM FIBTEM showed only changes in LI30 over time ($F_{5,230} = 3.30$, $p = .007$), and FF TEG and ROTEM EXTEM indicated no changes in CL30 and LI30, respectively.

When compared at the same time point between the two groups, FF TEG MA for the placebo patients was significantly lower than that for the FC patients at all time points ($p \leq .019$) during the 48-h hospitalization except at admission ($p = .11$). ROTEM FIBTEM CT and MCF showed the between-group differences in the period 2–24 h after admission ($p \leq .028$ for CT and $p \leq .002$ for MCF). TEG FIBTEM R differed between the two groups only at 4 h ($p = .012$) and TEG FIBTEM MA differed in the same period 2–24 h ($p \leq .009$) as ROTEM FIBTEM MCF. Similar to ROTEM FIBTEM, ROTEM EXTEM CT and MCF showed the between-group differences in the period 2–24 h ($p \leq .013$ for CT and $p \leq .004$ for MCF). Only ROTEM FIBTEM detected a decrease in fibrinolysis by LI30 in the FC group at 2 h after admission ($p = .02$).

Further analyses of the between-group differences as measured at time points revealed that FF TEG detected a maximum increase in MA by 9.7 mm at 2 h, while ROTEM FIBTEM showed a maximum increase in MCF by 10.6 mm at 4 h. The corresponding values at 2 and 4 h are 12.1 and 12.2 mm for TEG FIBTEM MA, and 7.3 and 7.8 mm for ROTEM EXTEM.

The time courses of CCT parameters with significance differences between the placebo and FC groups during the 48 h after admission are also shown in Table 2. Significant effects of the FC treatment and hospitalization time on fibrinogen concentration and platelet count were observed, while there was a change in hemoglobin over time. Specifically, there were differences in fibrinogen concentration at 2, 4 and 12 h, reaching a maximum at 2–4 h (1.6–1.8 vs. 2.9 g/L, $p < .001$). Platelet count and hemoglobin showed a between-group difference in 24 h ($p = .035$) and 2 h ($p = .028$), respectively. There were no differences in INR and PTT between the two groups and across the hospitalization time.

CCTs demonstrated less pronounced between-group differences over

Table 2
Significant TEG, ROTEM and CCT parameters measured in severe trauma patients randomized for placebo and fibrinogen treatment during 48-h hospitalization.

		Admission	2 h	4 h	12 h
FF TEG	MA (mm)	18.6 ± 6.6[a]/23.1 ± 11.0[b] $p = .11$	15.5 ± 4.6[a]/25.2 ± 7.4[b] $\mathbf{p < .001}$	17.3 ± 3.1[a]/26.3 ± 5.1[b] $\mathbf{p < .001}$	20.4 ± 4.7[a]/26.5 ± 6.2[b] $\mathbf{p = .001}$
ROTEM FIBTEM	CT (sec)	71.3 ± 19.5[a]/70.4 ± 37.3[b] $p = .93$	66.0 ± 16.9[a]/54.9 ± 11.2[b] $\mathbf{p = .020}$	66.2 ± 13.4[a]/52.4 ± 7.0[b] $\mathbf{p < .001}$	62.7 ± 10.7[a]/54.4 ± 7.7[b] $\mathbf{p = .007}$
	MCF (mm)	13.0 ± 6.6[a]/14.6 ± 8.6[b] $p = .49$	9.5 ± 4.2[a]/19.8 ± 6.9[b] $\mathbf{p < .001}$	9.1 ± 2.8[a]/19.7 ± 5.4[b] $\mathbf{p < .001}$	13.7 ± 6.7[a]/20.4 ± 6.3[b] $\mathbf{p = .002}$
	LI30 (%)	93.7 ± 22.5[a]/94.9 ± 15.6[b] $p = .84$	99.5 ± 1.0[a]/100.0 ± 0.0[b] $\mathbf{p = .02}$	99.8 ± 0.7[a]/99.9 ± 0.2[b] $p = .35$	99.9 ± 0.6[a]/99.9 ± 0.5[b] $p = .91$
TEG FIBTEM	R	50.9 ± 47.2[a]/49.6 ± 41.3[b] $p = .93$	49.4 ± 34.1[a]/37.3 ± 10.8[b] $p = .16$	50.4 ± 26.1[a]/33.2 ± 11.7[b] $\mathbf{p = .012}$	46.1 ± 19.2[a]/39.0 ± 10.5[b] $p = .19$
	MA	15.6 ± 7.3[a]/16.5 ± 8.3[b] $p = .73$	12.0 ± 4.4[a]/24.1 ± 7.5[b] $\mathbf{p < .001}$	13.7 ± 6.0[a]/25.9 ± 13.1[b] $\mathbf{p = .001}$	17.9 ± 7.8[a]/25.0 ± 7.5[b] $\mathbf{p = .009}$
ROTEM EXTEM	CT	76.1 ± 32.7[a]/62.0 ± 12.7[b] $p = .092$	74.7 ± 24.0[a]/57.2 ± 9.5[b] $\mathbf{p = .005}$	68.3 ± 11.2[a]/57.1 ± 14.9[b] $\mathbf{p = .008}$	67.6 ± 11.5[a]/55.8 ± 12.3[b] $\mathbf{p = .002}$
	MCF	57.9 ± 11.1[a]/62.3 ± 8.5[b] $p = .17$	55.2 ± 5.8[a]/62.5 ± 7.5[b] $\mathbf{p = .001}$	56.6 ± 5.8[a]/64.4 ± 6.8[b] $\mathbf{p < .001}$	59.9 ± 4.1[a]/65.5 ± 5.8[b] $\mathbf{p = .001}$
Fibrinogen concentration (g/L)		2.1 ± 0.6[a]/2.0 ± 0.7[b] $p = .75$	1.6 ± 0.5[a]/2.9 ± 0.7[b] $\mathbf{p < .001}$	1.8 ± 0.6[a]/2.9 ± 0.7[b] $\mathbf{p < .001}$	2.3 ± 0.6[a]/3.0 ± 0.6[b] $\mathbf{p = .002}$
Platelet count ($\times 10^9$/L)		238.1 ± 66.1[a]/271.0 ± 73.5[b] $p = .14$	166.4 ± 46.4[a]/176.9 ± 56.4[b] $p = .53$	163.5 ± 46.8[a]/171.4 ± 60.0[b] $p = .64$	145.8 ± 47.2[a]/163.4 ± 45.6[b] $p = .22$
Hemoglobin (g/L)		125.7 ± 20.0[a]/116.0 ± 14.6[b] $p = .080$	118.6 ± 21.0[a]/104.8 ± 16.3[b] $\mathbf{p = .028}$	114.1 ± 18.7[a]/109.6 ± 14.4[b] $p = .41$	100.8 ± 25.5[a]/108.8 ± 12.9[b] $p = .22$

	24 h	48 h	Treatment effects	Time effects
FF TEG	21.2 ± 6.0[a]/27.8 ± 7.6[b] $\mathbf{p = .006}$	26.7 ± 6.8[a]/31.7 ± 5.0[b] $\mathbf{p = .019}$	$F(1,218) = 64.71$, $\mathbf{p < .001}$	$F(5,218) = 9.20$, $\mathbf{p < .001}$
ROTEM FIBTEM	63.6 ± 10.1[a]/56.5 ± 10.2[b] $\mathbf{p = .028}$	66.1 ± 31.0[a]/62.2 ± 12.6[b] $p = .64$	$F(1,228) = 17.13$, $\mathbf{p < .001}$	$F(5,228) = 3.90$, $\mathbf{p = .002}$
	17.6 ± 5.3[a]/24.1 ± 6.2[b] $\mathbf{p = 0.001}$	25.1 ± 8.8[a]/29.9 ± 6.7[b] $p = .088$	$F(1,231) = 69.17$, $\mathbf{p < .001}$	$F(5,231) = 25.71$, $\mathbf{p < .001}$
	99.9 ± 0.4[a]/99.9 ± 0.7[b] $p = .73$	100.0 ± 0.0[a]/99.8 ± 1.0[b] $p = .33$	$F(1,230) = 1.85$, $p = .18$	$F(5,230) = 3.30$, $\mathbf{p = .007}$
TEG FIBTEM	43.1 ± 9.0[a]/36.9 ± 15.4[b] $p = .13$	45.5 ± 24.7[a]/44.1 ± 10.8[b] $p = .83$	$F(1,222) = 4.92$, $\mathbf{p = .028}$	$F(5,222) = 0.77$, $p = .58$
	19.8 ± 4.5[a]/25.4 ± 5.7[b] $\mathbf{p = .001}$	26.7 ± 8.9[a]/28.0 ± 4.5[b] $p = .61$	$F(1,221) = 44.29$, $\mathbf{p < .001}$	$F(5,221) = 10.47$, $\mathbf{p < .001}$
ROTEM EXTEM	67.3 ± 14.9[a]/57.6 ± 7.7[b] $\mathbf{p = .013}$	67.2 ± 9.3[a]/64.8 ± 13.3[b] $p = .54$	$F(1,234) = 27.02$, $\mathbf{p < .001}$	$F(5,234) = 0.99$, $p = .42$
	62.3 ± 4.2[a]/66.8 ± 5.3[b] $\mathbf{p = .004}$	66.3 ± 4.9[a]/68.9 ± 4.7[b] $p = .12$	$F(1,232) = 37.33$, $\mathbf{p < .001}$	$F(5,232) = 7.98$, $\mathbf{p < .001}$
Fibrinogen concentration (g/L)	3.4 ± 0.9[a]/4.0 ± 1.0[b] $\mathbf{p = .073}$	5.3 ± 1.8[a]/6.0 ± 1.6[b] $p = .32$	$F(1, 206) = 32.48$, $\mathbf{p < .001}$	$F(5, 206) = 74.58$, $\mathbf{p < .001}$
Platelet count ($\times 10^9$/L)	129.5 ± 29.1[a]/158.1 ± 50.6[b] $\mathbf{p = .035}$	119.5 ± 29.3[a]/139.5 ± 45.9[b] $p = 0.12$	$F(1, 233) = 8.91$, $\mathbf{p = .003}$	$F(5, 233) = 30.56$, $\mathbf{p < .001}$
Hemoglobin (g/L)	95.0 ± 15.2[a]/97.4 ± 14.6[b] $p = .61$	83.5 ± 17.1[a]/85.6 ± 11.3[b] $p = .66$	$F(1, 233) = 1.32$, $p = .25$	$F(5, 233) = 21.20$, $\mathbf{p < .001}$

The bold p values are statistically significant ($p < .05$). Data represent mean ± standard deviation.
[a] Placebo.
[b] Fibrinogen concentrate.

Table 3
Correlations between TEG/ROTEM assays and CCTs.

Variables	INR	PTT	Fibrinogen concentration	Platelet count	Hemoglobin concentration
R/CT	ρ = 0.13, p = .069[a]	ρ = **0.31, p < .001**[a]	ρ = −0.10, p = .15[a]	ρ = −0.058, p = .39[a]	ρ = 0.050, p = .46[a]
	ρ = **0.21, p = .001**[b]	ρ = **0.22, p = .002**[b]	ρ = **−0.29, p < .001**[b]	ρ = **−0.19, p = .004**[b]	ρ = 0.068, p = .30[b]
	ρ = **0.24, p = .001**[c]	ρ = **0.19, p = .008**[c]	ρ = **−0.17, p = .017**[c]	ρ = **−0.20, p = .003**[c]	ρ = −0.049, p = .47[c]
	ρ = **0.21, p = .001**[d]	ρ = **0.27, p < .001**[d]	ρ = **−0.32, p < .001**[d]	ρ = **−0.25, p = .001**[d]	ρ = **0.064, p = .33**[d]
K/CFT	ρ = 0.042, p = .62[a]	ρ = −0.022, p = .81[a]	ρ = **−0.46, p < .001**[a]	ρ = 0.068, p = .41[a]	ρ = **0.25, p = .002**[a]
	ρ = **0.35, p = .001**[b]	ρ = 0.11, p = .32[b]	ρ = **−0.41, p < .001**[b]	ρ = **−0.34, p = .001**[b]	ρ = 0.16, p = .12[b]
	ρ = 0.16, p = .11[c]	ρ = −0.025, p = .80[c]	ρ = **−0.31, p = .002**[c]	ρ = −0.17, p = .08[c]	ρ = −0.059, p = .54[c]
	ρ = **0.25, p < .001**[d]	ρ = **0.19, p = .008**[d]	ρ = **−0.63, p < .001**[d]	ρ = **−0.42, p < .001**[d]	ρ = **0.15, p = .025**[d]
Alpha/Alpha	ρ = −0.072, p = .29[a]	ρ = −0.099, p = .16[a]	ρ = **0.40, p < .001**[a]	ρ = 0.10, p = .13[a]	ρ = **−0.19, p = .004**[a]
	ρ = −0.08, p = .29[b]	ρ = 0.04, p = .62[b]	ρ = **0.54, p < .001**[b]	ρ = 0.089, p = .22[b]	ρ = **−0.23, p = .001**[b]
	ρ = −0.12, p = .066[c]	ρ = −0.028, p = .70[c]	ρ = **0.65, p < .001**[c]	ρ = 0.11, p = .10[c]	ρ = **−0.26, p < .001**[c]
	ρ = **−0.26, p < .001**[d]	ρ = **−0.17, p = .019**[d]	ρ = **0.70, p < .001**[d]	ρ = **0.34, p < .001**[d]	ρ = **−0.20, p = .002**[d]
MA/MCF	ρ = **−0.14, p = .036**[a]	ρ = **−0.28, p < .001**[a]	ρ = **0.75, p < .001**[a]	ρ = **0.14, p = .044**[a]	ρ = **−0.31, p < .001**[a]
	ρ = **−0.14, p = .046**[b]	ρ = **−0.23, p = .001**[b]	ρ = **0.87, p < .001**[b]	ρ = 0.097, p = .14[b]	ρ = **−0.29, p < .001**[b]
	ρ = −0.11, p = .12[c]	ρ = **−0.25, p = .001**[c]	ρ = **0.78, p < .001**[c]	ρ = 0.020, p = .77[c]	ρ = **−0.35, p < .001**[c]
	ρ = **−0.25, p < .001**[d]	ρ = **−0.14, p = .044**[d]	ρ = **0.70, p < .001**[d]	ρ = **0.32, p < .001**[d]	ρ = **−0.18, p = .005**[d]
CL30/LI30	ρ = −0.032, p = .65[a]	ρ = −0.041, p = .58[a]	ρ = **0.21, p = .004**[a]	ρ = **−0.22, p = .001**[a]	ρ = **−0.18, p = .007**[a]
	ρ = **0.14, p = .038**[b]	ρ = **0.18, p = .01**[b]	ρ = **0.20, p = .003**[b]	ρ = **−0.36, p < .001**[b]	ρ = **−0.15, p < .026**[b]
	ρ = 0.052, p = .45[c]	ρ = −0.092, p = .20[c]	ρ = 0.13, p = .064[c]	ρ = **−0.14, p = .036**[c]	ρ = 0.032, p = .63[c]
	ρ = **0.22, p = .001**[d]	ρ = 0.018, p = .80[d]	ρ = **−0.20, p = .003**[d]	ρ = **−0.18, p = .005**[d]	ρ = 0.13, p = .052[d]

The bold p values are statistically significant (p < .05).
[a] FF TEG.
[b] ROTEM FIBTEM.
[c] TEG FIBTEM.
[d] ROTEM EXTEM.

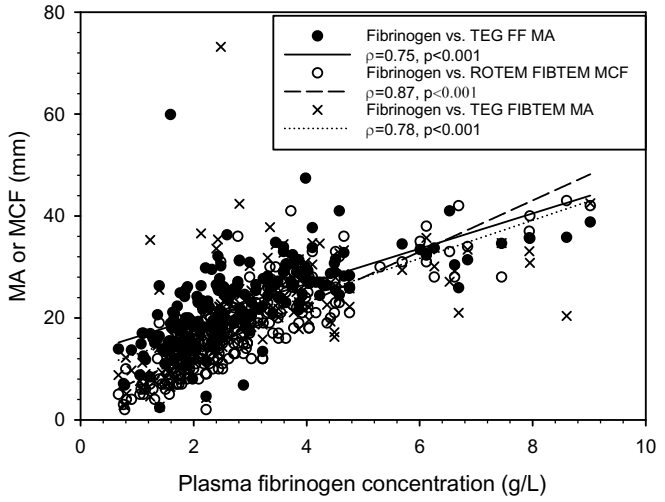

Fig. 2. Correlations between plasma fibrinogen concentration and fibrinogen clot strength as assessed by FF TEG MA, ROTEM FIBTEM MCF and TEG FIBTEM MA.

the hospitalization time than TEG and ROTEM. ROTEM was more sensitive to fibrinogen treatment than TEG. When the ROTEM reagents were used on TEG more changes were detected.

We also compared TEG and ROTEM correlations with CCTs as summarized in Table 3. ROTEM FIBTEM showed more correlations between their parameter values and different conventional coagulation measures than FF TEG and TEG FIBTEM. Specifically, ROTEM FIBTEM CTs correlated weakly with all CCTs (INR, PTT, fibrinogen concentration, platelet count) except hemoglobin, while FF TEG R only showed a moderate correlation with PTT (ρ = 0.31, p < .001). On the other hand, FF TEG Alpha, ROTM FIBTEM Alpha and TEG FIBTEM Alpha all showed moderate correlations with fibrinogen concentration and weak correlations with hemoglobin concentration. FF TEG MA and ROTEM FIBTEM MCF showed similar correlations with INR, PTT, hemoglobin and fibrinogen concentration, but FF TEG MA showed a weak correlation with platelet count (ρ = 0.14, p = .044) while ROTEM FIBTEM MCF and TEG FIBTEM MA showed no correlations with platelet count. In addition, ROTEM FIBTEM LI30 showed weak to moderate correlations with all CCTs, while FF TEG CL30 only showed week correlations with fibrinogen concentration, platelet count and hemoglobin concentration, and TEG FIBTEM CL30 only showed a weak correlation with platelet count (ρ = 0.14, p = .036). Overall, ROTEM EXTEM showed similar or stronger correlations with CCTs compared to ROTEM FIBTEM except no correlations between LI30 and PTT/hemoglobin concentration. In addition, ROTEM EXTEM LI30 had negative correlations with fibrinogen concentration (ρ = −0.20, p = .003), while FF TEG CL30 and ROTEM FIBTEM LI30 showed positive correlations (ρ = 0.21, p = .004 and ρ = 0.20, p = .003).

3.2. Detection of hypofibrinogenemia, coagulopathy, and blood transfusion

In addition to analysing the ability of the ROTEM and TEG parameters to monitoring coagulation effects of fibrinogen treatment, we also studied their clinical applicability for measuring coagulopathy and fibrinogen levels, and predicting blood transfusions in the trial. Given the small sample size for mortality and massive transfusion, we did not include these in the analysis. We focused on the TEG and ROTEM measurement on maximum clot strength (i.e., TEG MA and ROTEM MCF) as they are mostly used parameters to detect fibrinogen levels and guide fibrinogen administration in trauma [22,40], related to mortality, coagulopathy and transfusion requirements for blood products in trauma [41].

As shown in Fig. 2, fibrinogen levels ranged from 0.22 to 9.02 g/L for all patients during 48-h hospitalization, with 2.8% below 1 g/L, 10.1% of measures below 1.5 g/L and 28.6% below normal level of 2 g/L. FF TEG MA ranged 2.4–59.9 mm with 3.5% below the manufacturer's normal value of 11 mm [42], ROTEM FIBTEM MCF 2–43 mm with 5.8% below the manufacturer's normal value of 7 mm [39], and TEG FIBTEM MCF 2.6–73.2 mm. There were significant correlations 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 (0.87) followed by TEG FIBTEM (0.78) and FF TEG (0.75).

Table 4
Area under the ROC curve for TEG and ROTEM parameters as predictors of hypofibrinogenemia, coagulopathy and blood transfusions.

Outcome	TEG/ROTEM variables	Area under the ROC curve (95% CI)	*p* Values
48-h Fibrinogen < 1 g/L	TEG FF MA	0.948 (0.886–1.000)	**.002**
	ROTEM FIBTEM MCF	0.962 (0.900–1.000)	**< .001**
	TEG FIBTEM MA	0.945 (0.893–0.997)	**< .001**
	ROTEM EXTEM MCF	0.920 (0.833–1.000)	**< .001**
INR ≥1.2 within 48-h hospitalization	FF TEG MA	0.557 (0.480–0.634)	.15
	ROTEM FIBTEM MCF	0.564 (0.488–0.640)	.10
	TEG FIBTEM MA	0.533 (0.455–0.611)	.41
	ROTEM EXTEM MCF	0.609 (0.535–0.683)	**.005**
24-h RBC	FF TEG MA	0.669 (0.498–0.839)	.27
	ROTEM FIBTEM MCF	0.799 (0.624–0.974)	.053
	TEG FIBTEM MA	0.668 (0.401–0.934)	.28
	ROTEM EXTEM MCF	0.691 (0.516–0.866)	**.046**
24-h plasma	FF TEG MA	0.696 (0.514–0.877)	**.042**
	ROTEM FIBTEM MCF	0.720 (0.548–0.891)	**.023**
	TEG FIBTEM MA	0.712 (0.546–0.877)	**.027**
	ROTEM EXTEM MCF	0.717 (0.548–0.887)	**.023**
24-h cryoprecipitate	FF TEG MA	0.653 (0.455–0.851)	.14
	ROTEM FIBTEM MCF	0.660 (0.492–0.828)	.13
	TEG FIBTEM MA	0.685 (0.522–0.847)	.072
	ROTEM EXTEM MCF	0.499 (0.309–0.688)	.99

The bold *p* values are statistically significant ($p < .05$).

As shown in Table 4, all TEG MA and ROTEM MCF predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) with high accuracies (c-statistic ≥0.92, $p \leq .002$), which is consistent with the prediction in cardiac surgery [43].

For the diagnosis of coagulopathy, only EXTEM MCF performed reasonably well for INR ≥ 1.2 (c-statistic: 0.609, $p = .005$). There appears to be no significant difference in the predictive value of TEG MA or ROTEM MCF for either INR or fibrinogen.

For predicting the need for blood transfusions, ROTEM FIBTEM MCF (c-statistic: 0.799, $p = .053$) and ROTEM EXTEM MCF ((c-statistic: 0.691, $p = .046$) appear to have better predictive accuracy compared to FF TEG MA (c-statistic: 0.669, $p = .27$) and TEG FIBTEM MA (c-statistic: 0.668, $p = .28$) for predicting 24-h RBC transfusion. All variables, FF TEG MA (c-statistic: 0.696, $p = .042$), ROTEM FIBTEM MCF (c-statistic: 0.720, $p = .023$), TEG FIBTEM MA (c-statistic: 0.712, $p = .027$), and ROTEM EXTEM MCF (c-statistic: 0.717, $p = .023$) have reasonable predictive accuracy for 24-h plasma transfusion. No TEG and ROTEM measurements were found to be significantly associated with 24-h CRYO transfusion. In contrast, none of the CCTs predicted the transfusion requirements except that fibrinogen concentration provided significantly prediction for 24-h CRYO transfusion (c-statistic: 0.761, $p = .011$).

Overall, TEG MA and ROTEM MCF provided better predictions than CCTs for RBC and plasma transfusions, while fibrinogen concentration showed better prediction for CRYO since it was used to guide CRYO administration.

4. Discussion

There are studies involving ROTEM tests especially ROTEM FIBTEM to assess hemostatic effects of fibrinogen administration in major trauma [22,44–46], cardiovascular surgery [47,48], liver transplantation [49] and postpartum hemorrhage [50]. Some of these studies also used ROTEM to guide administration of FC [22] and examined predictive values of ROTEM FIBTEM MCF for severe bleeding [48] and fibrinogen concentration [46]. In contrast, no study on the effects of fibrinogen administration on FF TEG has been reported. As far as we know our study is the first one to compare the clinical performance between TEG and ROTEM functional assays for monitoring the hemostatic effects of fibrinogen treatment and their predictive accuracies for coagulopathy and blood transfusions in trauma, taking into account of the effects of reagents by a crossover comparison. We also compared the clinical performance of TEG and ROTEM fibrinogen assays with CCTs.

Both TEG and ROTEM detected significant effects of treatment and hospitalization time on their maximum clot strength/firmness in consistent with the evolution of fibrinogen levels with a maximum treatment effect in the period 2–4 h after admission (1–3 h after fibrinogen administration). This is in agreement with the reported increase in ROTEM FIBTEM MCF and maximum fibrinogen concentration at 1 h after infusion of FC in patients with afibrinogenemia [51]. However, FF TEG MA showed the treatment effect for up to 48 h, while ROTEM FIBTEM and EXTEM MCF and TEG FIBTEM MA showed the effect for 24 h which is more consistent with the between-group difference in fibrinogen levels. ROTEM also showed the effect on its coagulation time CT. Similar effects on ROTEM CT and MCF have been observed in other studies investigating the changes to ROTEM parameters before and after fibrinogen administration and between control and fibrinogen groups over time for 24 h in major trauma [44,45] and between placebo and fibrinogen treatment groups over time for 11 days in cardiovascular surgery [47]. The FIBTEM-detected effect of fibrinogen treatment on fibrinolysis is consistent with another study where fibrinolysis as measured by ROTEM FIBTEM was reduced after fibrinogen administration in major trauma [44]. In contrast, this effect was not detected by FF TEG and ROTEM EXTEM.

The difference in TEG and ROTEM response to fibrinogen treatment may come from both the use of different assay reagents and instrument itself. It has been speculated that ROTEM FIBTEM reagents might contain stabilizing agents (e.g., dimethyl sulfoxide) and more tissue factor than FF TEG reagent [52]. The platelet inhibitor in TEG (abciximab) is less effective in eliminating platelet contribution to clot strength than that in ROTEM (cytochalasin D) [53], affecting their correlations and changes with fibrinogen concentration. On the other hand, the different response to fibrinogen treatment between TEG FIBTEM MA and ROTEM FIBTEM MCF measured using the same reagents implies that the device itself may be also a contributing factor. The hardware differences between the two systems include the mechanisms for cup/pin rotation, detection of the rotation, cup materials and interior surface properties [26].

Another possible explanation for the different sensitivity might be their differences in coefficients of variance (CV) which range from 7.06 to 59.98% for TEG and 3.12 to 39.07% for ROTEM when measuring platelet rich plasma [54]. This wide variability may affect the mean

parameter values of each test and consequently compromise the evaluation of fibrinogen treatment especially by TEG given its larger CV compared to ROTEM. The within-subject CV was reported as 5–8% for FF TEG MA and 3–5% for ROTEM FIBTEM MCF [33]. A recent study showed that inter- and intra-operator CVs were significantly lower for ROTEM MCF compared with TEG MA (8.3 and 6.9% vs. 12.2 and 12.1%) [27].

Although fibrinogen replacement would have a direct effect on plasma (Clauss) fibrinogen level other CCTs (e.g., INR and PTT) are commonly used to measure the hemostatic effects of fibrinogen [45,47]. These tests are influenced by fibrinogen but not independently, thus they are not useful to discriminate fibrinogen deficiency from other coagulation problems.

Similar effects of fibrinogen treatment on CCTs observed in our study have been reported. Specifically, there were few differences in the values of CCTs except fibrinogen concentration between propensity score-matched patients receiving fresh frozen plasma or fibrinogen concentrate/prothrombin complex concentrate from admission to 24 h in trauma [45] and between control (fresh frozen plasma and placebo) and fibrinogen groups from pre-surgery up to postoperative day 11 in cardiovascular surgery [47]. No changes in INR, PTT and minor changes in platelet count and hemoglobin were detected. The fibrinogen concentration profile observed in our study is generally consistent with the literature showing an immediate increase after the fibrinogen administration, a period of higher fibrinogen concentrations for 1–2 days in the fibrinogen group, followed by comparable fibrinogen concentrations between the control and treatment groups in trauma [45] and cardiac surgery [47].

The correlations between different TEG or ROTEM parameters and CCTs have been reported with mixed results. However, there are only few studies on the correlations between TEG or ROTEM fibrinogen assays and CCTs specifically focusing on the correlations between FF TEG MA/ROTEM FIBTEM MCF and fibrinogen concentration [41]. Correlation analysis was carried out for values between TEG or ROTEM and CCTs that measure similar aspects of the coagulation cascade. Surprisingly FF TEG R showed no correlations with INR and fibrinogen concentration although there was also no association of FF TEG R with Clauss fibrinogen concentration as reported in another study by Harr et al. [40]. In addition, we did not see expected stronger correlations with INR than PTT as INR measures extrinsic pathway as TEG and ROTEM fibrinogen assays (tissue factor activation with platelet inhibition). On the other hand, the correlations between FF TEG and CCTs are generally consistent with no or weak correlations ($\rho < 0.5$) found between kaolin-activated TEG (R, K, Alpha, MA, LY30) and CCTs (e.g., INR, PTT, fibrinogen concentration, platelet count) in healthy women during normal pregnancy [55] and aged fracture patients [56], but are in contrast with weak ($\rho < 0.3$) to strong ($\rho > 0.7$) correlations reported between kaolin-activated TEG parameters (R, Angle, MA) and CCTs (INR, PTT, fibrinogen concentration and platelet count) in patients undergoing elective surgery [57] and significant correlations found between all rapid TEG parameters (R, K, Alpha, MA) and CCTs (INR, PTT, fibrinogen concentration and platelet count) in trauma patients at admission [58]. Specifically, the correlations between FF TEG and CCTs found in our study are in agreement with another study reporting comparable correlations between kaolin-TEG R and PTT ($r = 0.33$, $p = .036$), K and fibrinogen concentration ($r = -0.56$, $p = .0002$), Angle and fibrinogen concentration ($r = 0.42$, $p = .0063$), but a weaker correlation between MA and fibrinogen concentration ($r = 0.39$, $p = .013$), and a stronger correlation between MA and platelet count ($r = 0.41$, $p = .009$) [56] likely due to the inhibition of platelet functions in our FF TEG assay. In the same study, authors also found no correlations between R and INR, K/Angle and platelet count as in our study.

With regard to the correlations between ROTEM and CCTs, our findings are consistent with those found between ROTEM FIBTEM MCF and CCTs in liver transplantation patients [59] except we did not observe a correlation with platelet count. Similarly, except for MCF our ROTEM FIBTEM parameters showed weaker correlations with CCTs than those measured by ROTEM EXTEM and INTEM [60]. Specifically, significant correlations were reported between ROTEM EXTEM CT and prothrombin time ($r = 0.53$, $p < .001$) or fibrinogen concentration ($r = 0.40$, $p < .001$), between EXTEM CFT and platelet count ($r = 0.33$, $p < .001$), INTEM CT and PTT ($r = 0.47$, $p < .001$), in trauma patients sampled at admission and at 6-, 12-, and 24-h after admission [60]. The same study also reported similar correlations when only samples taken at admission were analyzed. On the other hand, no correlations were reported between ROTEM EXTEM/FIBTEM CT/MCF and INR/PTT in critically ill patients sampled at 0–10 days after admission to ICU, while the correlations between EXTEM MCF and platelet count ($r = 0.76$, $p < .01$), and between FIBTEM MCF and fibrinogen concentration ($r = 0.75$, $p < .01$) were significant [19].

Our previous study has shown the strongest correlations between TEG MA and ROTEM MCF among all measured parameters as reported in various studies comparing TEG and ROTEM tests [30,61]. In addition, these two parameters had most associations with CCTs and the strongest correlations with fibrinogen concentration, suggesting they are most useful for monitoring hemostatic status in trauma patients. The strong correlations between TEG MA/ROTEM MCF and fibrinogen concentration are consistent with their changes in response to the fibrinogen treatment. It is interesting to note that the stronger associations of ROTEM parameters with fibrinogen concentration may contribute to more changes in hemostasis as measured by ROTEM FIBTEM than FF TEG. We thus further compared the clinical performance for detection of hypofibrinogenemia, coagulopathy and prediction of blood transfusions based on TEG MA and ROTEM MCF.

Clinically, the trigger levels of fibrinogen administration have been reviewed [4] and historically, fibrinogen supplementation has been recommended for plasma fibrinogen levels below 1 g/L [4] which approximately corresponds to FF TEG MA of 16 mm and ROTEM FIBTEM MCF of 8 based on the correlations obtained in our study. The respective value is higher than the lower threshold of the normal range for FF TEG (11–24 mm) [42], but slightly lower than that of the reference range for ROTEM FIBTEM (9–25 mm) [39]. This is in agreement with the report that the threshold for fibrinogen substitution of 9 mm MCF in ROTEM FIBTEM does not march the threshold of ≤1.0 g/L fibrinogen plasma concentration measured by Clauss method [62].

In addition, different cut-off values of fibrinogen concentrations ranging from 1 to 1.8 g/L were used to define hypofibrinogenemia and a range of fibrinogen levels from 0.8 to 2.0 g/L have been recommended as transfusion triggers in trauma and massive hemorrhage [4,20], with 1 g/L in most guidelines [63]. As a result, a range of thresholds in ROTEM FIBTEM have been used to trigger fibrinogen replacement [3], e.g., CA10 < 7 mm or MCF < 7 mm in trauma, CA10 ≤ 10 mm in cardiac surgery and MCF ≤ 6 mm in liver transplantation. These discrepancies should be considered carefully when developing goal-guided administration of FC using TEG and ROTEM functional fibrinogen assays. Future studies comparing different intervention thresholds of ROTEM FIBTEM MCF have been suggested [3]. Clinical data comparing the effect of predefined thresholds for fibrinogen augmentation are required to optimize fibrinogen substitution regarding efficacy, patient safety and costs.

Compared to ROTEM MCF, TEG α-angle has been mostly used as the parameter to guide fibrinogen replacement (mostly by CRYO) and may be not appropriate [64]. FF TEG has been less employed to measure fibrinogen levels and guide its administration with FF TEG MA < 14 mm to trigger fibrinogen substitution in patients with massive hemorrhage [65], and MA ≤ 7 mm in liver transplantation [9].

All TEG and ROTEM parameters performed similarly well in diagnosing hyperfibrinogenemia defined by a fibrinogen level < 1 g/L, but poorly in detecting coagulopathy when defined by INR ≥1.2. None of the measurements performed statistically better than the others except ROTEM EXTEM. It is expected that as the specific tests for functional

fibrinogen FF TEG and ROTEM FIBTEM may not be accurate for coagulopathy defined by CCTs other than fibrinogen level, e.g., INR.

However, these is no sound evidence to support the usefulness of INR, PTT for diagnosis of coagulopathy or to guide haemostatic therapy [66]. The use of CCTs such as INR in trauma has been severely criticized due to the lack of association with bleeding and blood transfusion. It has been reported that INR overestimated coagulopathy and should not be used to guide blood transfusion in stable trauma and surgical patients [67].

Concerning blood transfusions, early identification of the patents that are coagulopathic and require massive transfusion at hospital would minimize treatment time delays and have a significant impact on patient outcomes. The measurements of clot strength and firmness (FF TEG MA and ROTEM FIBTEM MCF) at hospital admission were good indicators for the need of plasma transfusion during the 24-h hospitalization. Currently, FF TEG MA and ROTEM FIBTEM MCF have been incorporated into transfusion algorithms for blood products including fibrinogen replacement therapy. For example, FF TEG has been used together with kaolin TEG for goal-directed resuscitation of patients with massive hemorrhage [65]. Below a cut-off value of 14 mm for FF TEG MA fibrinogen supplementation by fresh frozen plasma (20–30 mL/kg), CRYO pool (3–5 mL/kg) or fibrinogen concentrate (adults 1–2 g) has been recommended. Alternatively, ROTEM FIBTEM has been used with ROTEM EXTEM [22,45] providing different cut-off ROTEM values for administration of fibrinogen concentrate at various doses. ROTEM FIBTEM MCF has been used to calculate fibrinogen dose in cardiac surgery [48]. However, none of the parameters was clearly superior to others in these determinations for any blood transfusion except that the prediction of 24-h RBC transfusion was significant by ROTEM EXTEM MCF ($p = .046$) and close to significance by FIBTEM MCF ($p = .053$). The association between abnormal clot strength and firmness with the need for blood transfusion has been consistently reported by recent studies [2,10]. These studies did not investigate the functional fibrinogen tests using TEG and ROTEM to predict the need for blood transfusions.

Studies have shown lower FF TEG MA and ROTEM FIBTEM MCF in transfused patients receiving ≥10 RBC units than non-transfused patients [41] and in trauma patients requiring plasma transfusion [25]. Among other ROTEM tests (e.g., EXTEM, INTEM), FIBTEM MCF provided a high predictive value of 0.84 for massive transfusion in trauma [68]. It is believed that TEG and ROTEM can assist the clinician in determining whether the injured patient needs transfusion, which hemostatic product to use and even the amount. Optimal cut-off FF TEG MA of 14.9 mm, FIBTEM MCF of 10 mm for transfusions of red blood cells, and FF TEG MA of 16.9 mm and FIBTEM MCF of 14 mm for fresh frozen plasma and platelets have been reported [61]. These observations formed the basis for the argument on using TEG and ROTEM for trauma resuscitation and led to the development of goal-directed trauma transfusion guidelines [24].

Our study has limitations. This is a single centre pilot study with a small number of patients. Only three out of 45 patients required massive transfusion and died. As a result, the prediction for massive transfusion and mortality cannot be adequately analyzed. We were unable to evaluate the effects of crystalloids on TEG/ROTEM assays and fibrinogen concentration measurement since the hemodilution could decrease ROTEM FIBTEM and EXTEM MCF [69].

5. Conclusion

Both TEG MA and ROTEM MCF can be used to measure hemostatic effects of fibrinogen concentrate in the early resuscitation of severe trauma and may be more reflective of changes in hemostasis following fibrinogen treatment than CCTs. In addition, ROTEM CT and LI30 may be also used to monitor the changes in coagulation time and fibrinolysis by fibrinogen administration. The different detection ability between TEG and ROTEM may result from both the instrument itself and the activation reagents used to perform the assays. Both systems appear to have a similar, but better clinical performance than CCTs in predicting the need for plasma transfusion and monitoring fibrinogen functions. Further comparison of clinical performance between these two systems and CCTs with a larger sample size is warranted in trauma care.

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Declaration of interest

The authors have no conflicts to declare.

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