CONTRACT REPORT

Project Title: A comparison of two viscoelastic testing systems for goal-guided administration of fibrinogen concentrate in severe trauma: TEG® and ROTEM®

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PWGSC's contract number: W7714-145967/A Task 5

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DRDC-RDDC-2016-C104

EXECTIVE SUMMARY - The following project was developed and funded in conjunction with DRDC and Canada. The funding was provided by Canada, to complete the study procedures: screening of patients and blood processing by the research assistants, data abstraction and interpretation by the DRDC scientific authority, coordination and organization of supplies (TEG® and ROTEM® reagents, office supplies, RA scheduling, report building).

Recruitment start date: 07-Oct-2014

Recruitment end date: 16-Nov-2015

28 day follow up end date for last randomized patient: 14-Dec-2015

Data un-blinded by group assignment on: 14-Dec-2015

Total patients screened: 1061

Total simultaneous tests that had TEG® and ROTEM® comparison: 380

ABSTRACT – Given the increased use of both thrombelastography (TEG®) and rotational thromboelastometry (ROTEM®) for hemorrhage control in trauma and surgery and similarities among various tests between the two, it is important to determine whether the two are interchangeable or one is superior to the other. We thus conducted a comparative study of functional fibrinogen assays using TEG® and ROTEM® in trauma to determine 1) their interchangeability for measuring coagulation profiles in all trauma patients screened at admission and randomized to receive fibrinogen concentrate and placebo, 2) capability to predict blood transfusion requirements, diagnose coagulopathy and detect coagulation effects of fibrinogen concentrate in the randomized controlled trial. Overall, TEG and ROTEM parameter values were correlated, but were significantly different, and their agreement fell outside acceptable limits and thus were not interchangeable, arguably due to differences in both devices and assay reagents used. Clinically, TEG Maximum Amplitude and ROTEM® Maximum Clot Firmness showed reasonable predictive accuracy for plasma transfusion and strong predictive accuracy for coagulopathy, but poor accuracy for any red blood cells and cryoprecipitate transfusion. Both TEG and ROTEM detected significant changes in maximum clot strength/firmness by fibrinogen treatment and over hospitalization time. In addition, ROTEM detected changes in coagulation time. Different algorithms for TEG and ROTEM need to be developed for diagnosis of coagulopathy and goal-guided administration of fibrinogen concentrate in trauma.

Study design and participants

This is a randomized-controlled, double-blinded feasibility trial conducted at the Sunnybrook Health Sciences Centre Level 1 Trauma Centre with accrual period between October 2014 and November 2015.

Adult (age>18 years) trauma patients were screened at admission and citrated whole blood was collected in a BD vacutainer containing 3.2% sodium citrate (Fisher Scientific, Nepean, ON, Canada). The patients were randomized to receive either 6 g fibrinogen concentrate (RiaSTAPTP) or placebo (normal saline) if they were identified as being at risk for significant hemorrhage as evidenced by: a) having a Systolic blood pressure (SBP) ≤ 100mmHg and b) requiring red blood cell (RBC) transfusion (ordered by treating physician – not necessarily administered) at any time from injury to 30 minutes after arrival to our trauma centre. Citrated whole blood was collected from the randomized trauma patients at 1-, 3-, 11-, 23- and 47-h post-infusion time as admission. It should be noted that the time points following

infusion are ±30 min, thus approximately 2, 4, 12, 24, and 48 h of hospital admission which were used for data analysis.

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 using the same reagents (ex-tem® and fib-tem®) and concentrations as used in ROTEM® FIBTEM for cross-over comparison. Key parameter values (e.g., coagulation time and maximum clot strength) were obtained. Plasma fibrinogen concentration was measured by Clauss method (27).

The study was approved by Sunnybrook Research Ethics Board and used waiver of consent, providing participants/Legal authorized representative with an information package about the study when capable to receive it.

Statistical analysis

Data were represented as mean ± standard deviation (SD) unless otherwise specified. Interchangeability was tested initially using the Spearman non-parametric analysis to evaluate the direction and strength of the correlation between equivalent ROTEM® and TEG® parameters (ROTEM® clotting time (CT) vs. TEG® reaction time (R); Alpha (ROTEM®) vs. Alpha (TEG®); clot formation time (CFT) vs. kinetics time (K); ROTEM® maximum clot firmness (MCF) vs. TEG® maximum amplitude (MA); ROTEM® lysis index at 30 min after CT (LI30) vs. TEG® lysis index at 30 min after MA (CL30). The larger the Spearman coefficient, stronger is the correlation between the two values. The agreement between ROTEM® and TEG® measurements was further evaluated using Bland-Altman difference mean plot (28). The mean values (M) of corresponding measurements for TEG® and ROTEM® variables were plotted against their differences (D). The limit of agreement (LoA) was defined as: $D \pm 1.96 * SD$ where D represents the mean difference and SD represents the standard deviation of the differences. The relationship between the differences and means of the results attained from the two tests was non-uniform. Initial tests indicated that a log transformation, which was recommended to address this issue (29), was insufficient. Therefore, we used a revised version of the Bland-Altman methodology (20, 28). If a significant linear association between the differences and means was found, then bivariate linear regression, defined as: $D = \alpha + \beta * M$, was used to calculate the estimated difference. This value was also used to calculate the corresponding LoA as proposed by Bland and Altman (29). Consequently, the LoA given in this situation was defined as: $(\alpha + \beta * A) \pm 1.96 * SD$, 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 (17, 20).

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

Linear regression for TEG FF MA, ROTEM FIBTEM MCF and TEG FIBTEM MA versus plasma fibrinogen concentration was performed.

The predictive power of each TEG and ROTEM test 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 mortality (N=3), we did not conduct the predictive analysis for mortality. Transfusion of red blood cells (RBC), fresh frozen plasma (FFP) and

cryoprecipitate within 24-h hospitalization was predicted using the TEG MA and ROTEM MCF at admission. Coagulopathy defined as an international normalized ratio (INR) ≥ 1.2 and plasma fibrinogen concentration < 1 g/L were predicted using the corresponding TEG MA and ROTEM MCF during 48-h hospitalization.

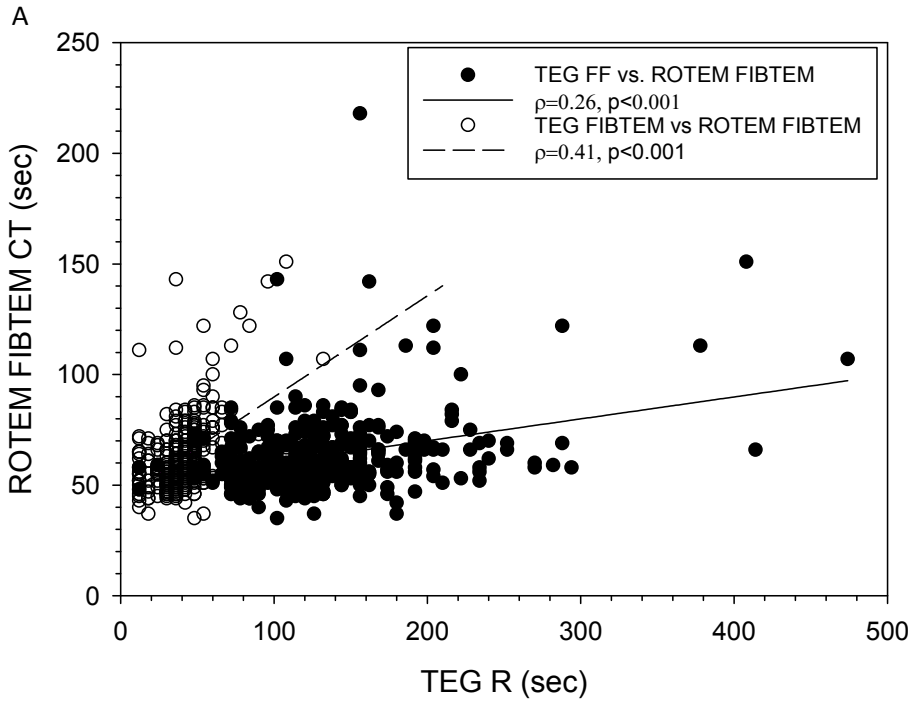
Linear mixed model with random patient effects and Bonferroni post hoc tests was used to test the main effects of fibrinogen treatment and hospitalization time on TEG and ROTEM measurements, respectively.

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 1061 patients were screened and 45 patients were enrolled into the trial between October 2014 and November 2015, having 380 respective TEG® FF, TEG FIBTEM and ROTEM® FIBTEM tests simultaneously performed during hospital admission and 48-h hospitalization.

Fig. 1A shows 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 ($r=0.41$, $p<0.001$). Fig. 1B shows significant correlations between TEG FF MA and ROTEM FIBTEM MCF ($r=0.75$, $p<0.001$) and between TEG FIBTEM MA and ROTEM FIBTEM MCF ($r=0.82$, $p<0.001$). When the same reagents were used in both systems stronger associations were observed between TEG FIBTEM and ROTEM FIBTEM than between TEG FF and ROTEM FIBTEM.



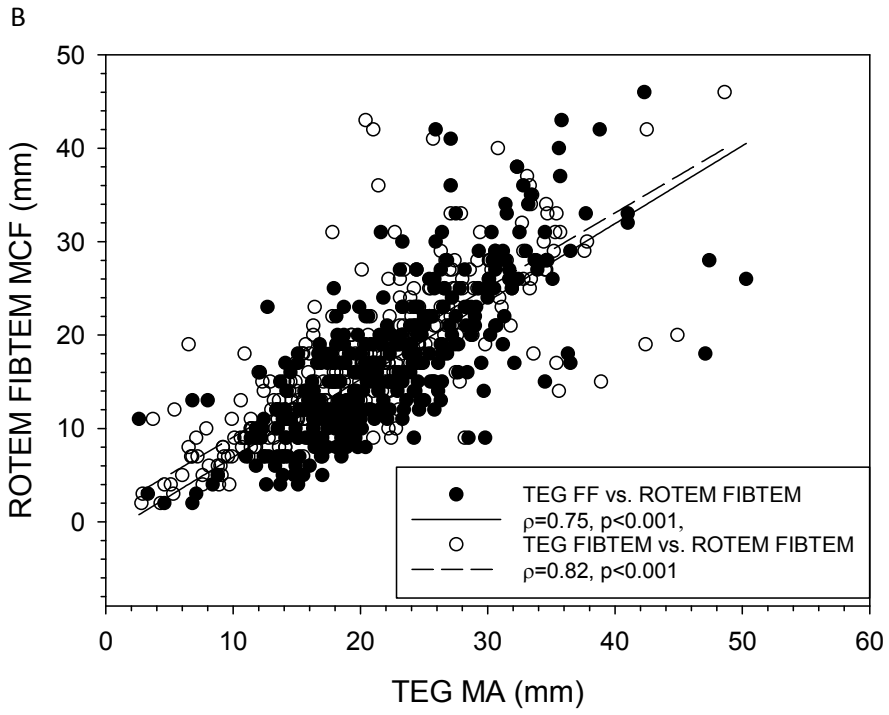


FIG. 1. Correlations between TEG Functional Fibrinogen (FF), TEG FIBTEM and ROTEM FIBTEM. A: R vs CT; B: MA vs MCF.

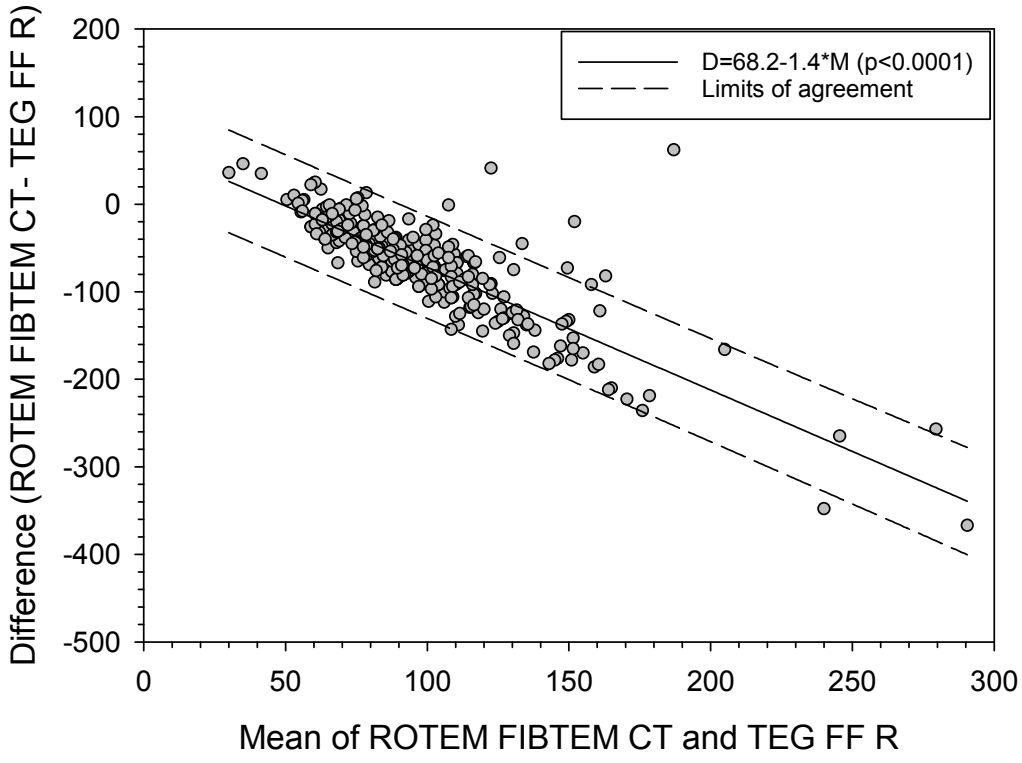
Table 1 summarizes their correlations between all key TEG and ROTEM parameters values. Significant correlations were found for all corresponding parameters between TEG and ROTEM ($p \leq 0.002$) except TEG FIBTEM CL30 and ROTEM FIBTEM LI30 ($p=0.078$). The strongest correlation was found between MA and MCF ($\rho=0.75/0.82$) while the weakest is seen between CL30 and LI30 ($\rho= 0.22/0.10$). Generally, higher correlations were seen when the same ROTEM FIBTEM reagents (ex-tem and fib-tem) were used on both TEG and ROTEM, which is consistent with our previous comparative study on other TEG and ROTEM assays [5].

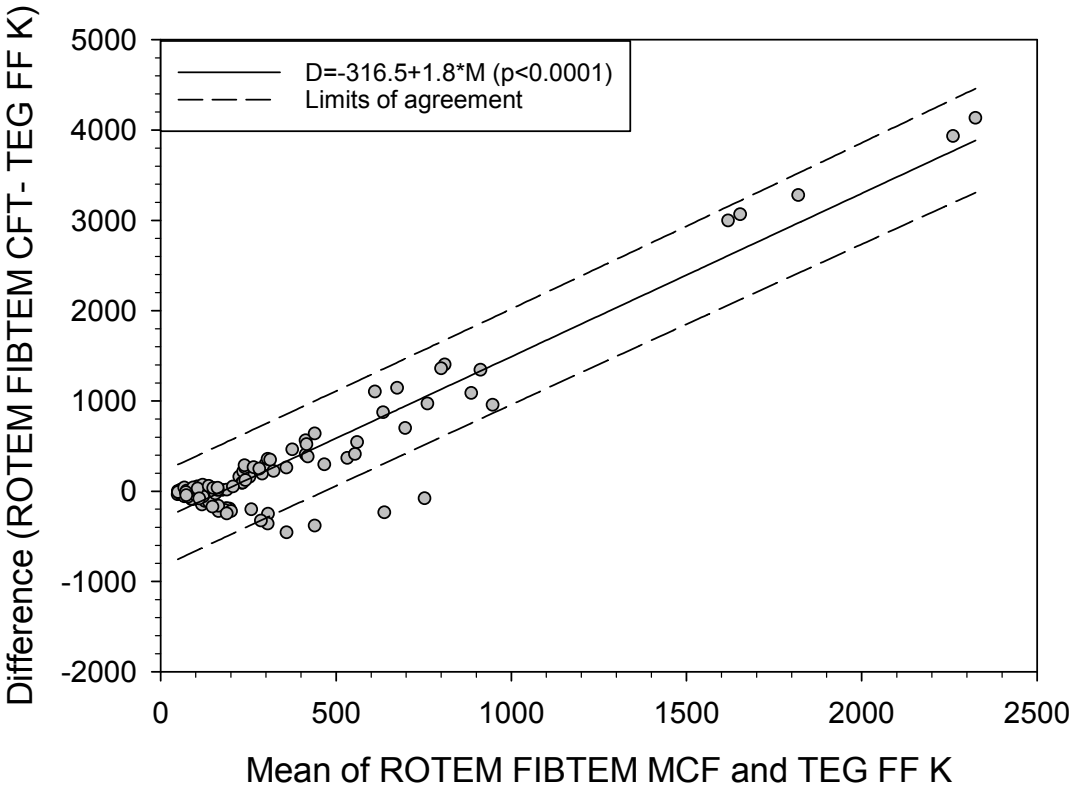
TABLE 1. **Correlations between TEG and ROTEM values for functional fibrinogen assays**

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

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

Next we used the Bland-Altman difference mean plots to determine the agreement between the TEG® and ROTEM® parameters (Fig. 2). A significant linear association was found between the difference (D) and mean (M) for all investigated parameters. Table 2 shows the limits of agreement (LoA) calculated from the results as described in Methods. None of the limits of agreement 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.




D=-316.5+1.8*M (p<0.0001)
Limits of agreement
Difference (ROTEM FIBTEM CFT- TEG FF K)
Mean of ROTEM FIBTEM MCF and TEG FF K
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4000
3000
2000
1000
0
-1000
-2000
0
500
1000
1500
2000
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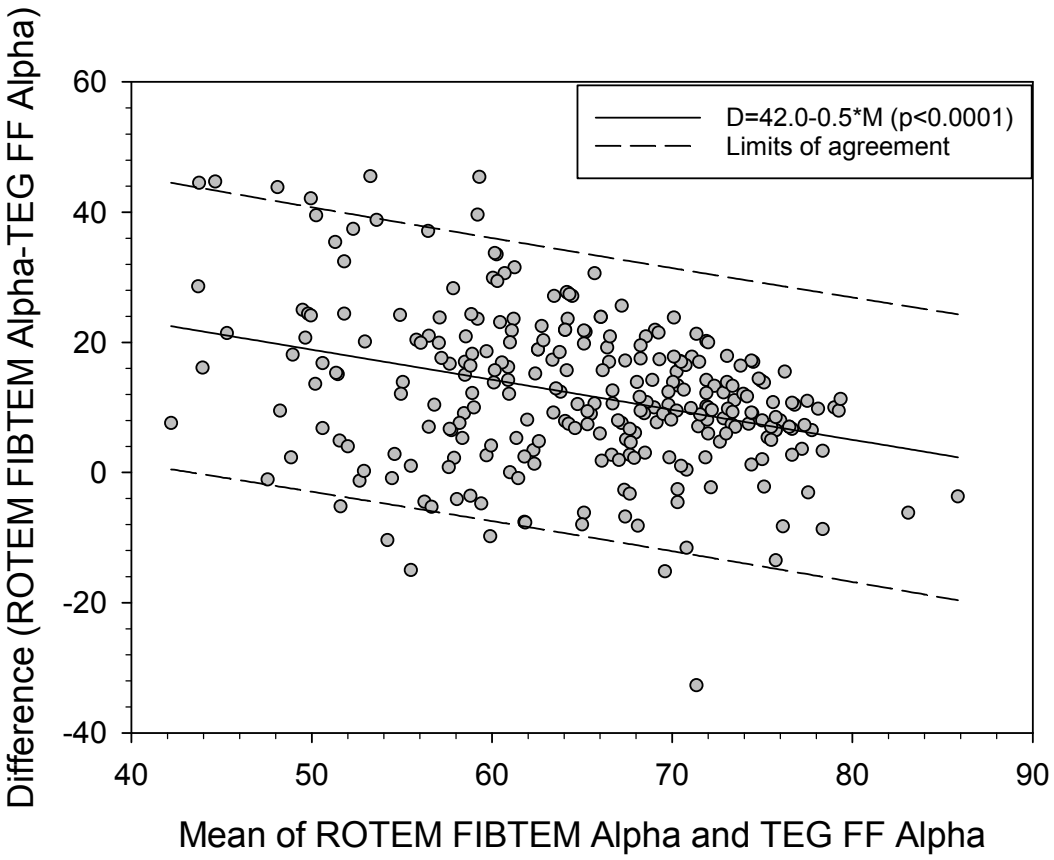
D=42.0-0.5*M (p<0.0001)
Limits of agreement
Difference (ROTEM FIBTEM Alpha-TEG FF Alpha)
Mean of ROTEM FIBTEM Alpha and TEG FF Alpha
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50
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70
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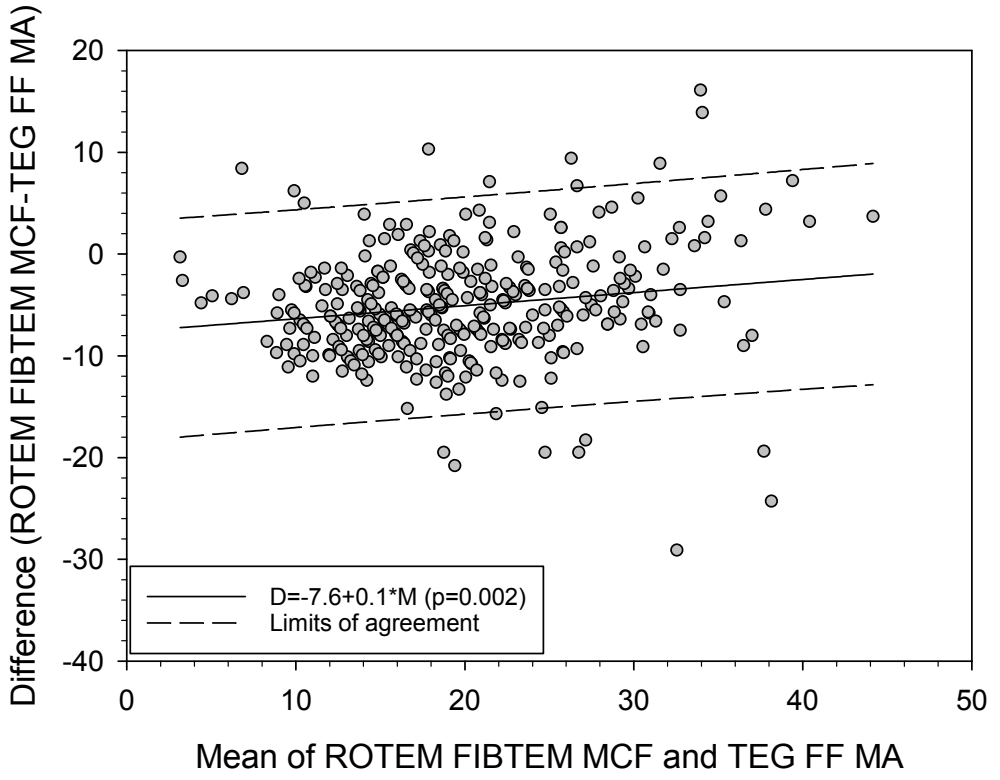
90



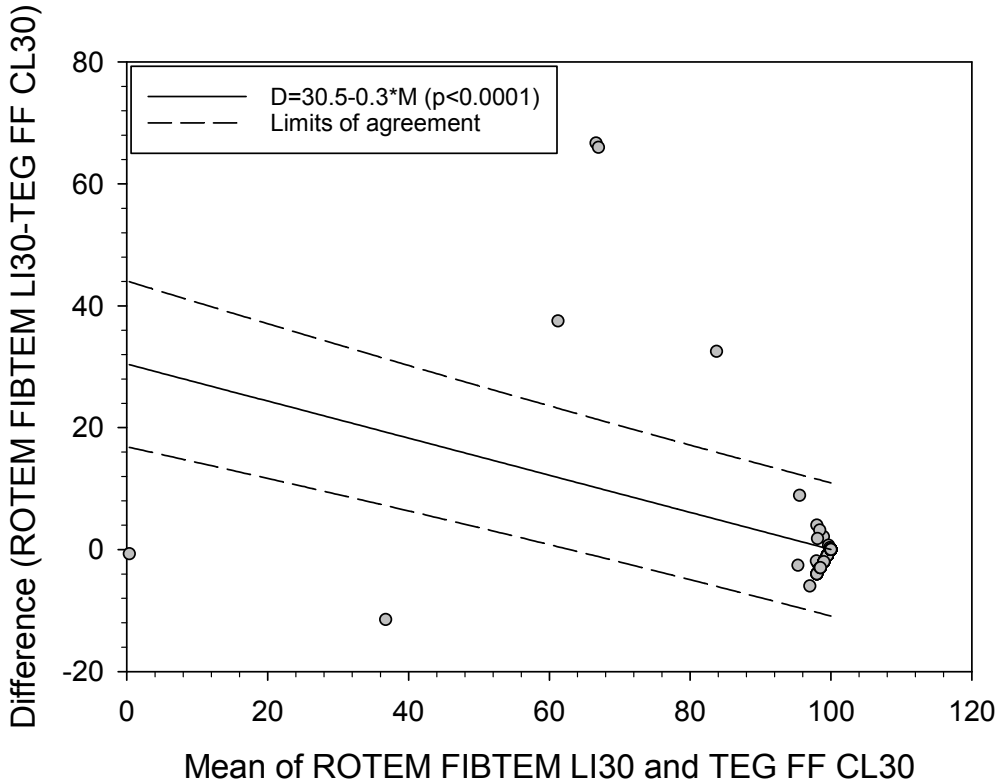


FIG. 2. Bland-Altman plots mean plots of TEG vs. ROTEM parameters for their standard functional fibrinogen assays (R/CT, CFT/K, Alpha (TEG®)/Angle (ROTEM®), MA/MCF, CL30/LI30).

TABLE 2. **Limits of Agreement (LoA) between TEG and ROTEM values for functional fibrinogen assays**

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

As summarized in Table 3, 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) and smaller CL30 (98.8±8.9%) compared to ROTEM FIBTEM CT (63.3±17.7 sec), Alpha (67.7±16.9°), MCF (17.1±8.0 mm) and LI30 (99.1±6.8%) ($p<0.001$). 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) and larger CL30 (99.4±6.7%) than the corresponding ROTEM FIBTEM parameters ($p<0.001$). No significant difference was found between TEG K and ROTEM CFT.

TABLE 3. **Comparison between TEG and ROTEM values for functional fibrinogen assays**

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	0.17/0.34
Alpha vs. Alpha	58.4±12.4	67.7±16.9	73.7±7.1	<0.001/<0.001
MA vs. MCF	22.4±7.5	17.1±8.0	20.3±8.1	<0.001/<0.001
CL30 vs. LI30 (%)	98.8±8.9	99.1±6.8	99.4±6.7	<0.001/<0.001

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

In addition to analysing the interchangeability of the ROTEM® and TEG® parameters, we also studied their clinical applicability for measuring fibrinogen levels, predicting the need for blood transfusion and the diagnosis of coagulopathy, and monitoring coagulation effects of fibrinogen treatment in the

randomized trial. Given the small sample size for mortality, we did not include it in the analysis. 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 (12, 30), related to mortality, coagulopathy and transfusion requirements for blood products in trauma (25, 31).

Table 4 details the demographics and clinical outcomes of the two groups of patients included in this study. For the demographics, except for a difference in median age, there were no significant differences in gender, trauma type, time from injury to hospital and injury severity score between the placebo and fibrinogen groups. With respect to the clinical outcomes, only significant difference in plasma fibrinogen concentration was observed between the two groups (2.6 vs. 3.3 g/L, $p<0.001$).

TABLE 4. **Demographics and clinical outcomes of the patients enrolled in the trial**

	Treatment groups	
	Placebo (N=24)	Fibrinogen (N=21)
Age (years)	28 (24-41)	48 (30-58)
Gender (% male)	87	77
Penetrating type of trauma (%)	54	52
Time from injury to hospital (mm)	43 (33-55)	44 (30-59)
Injury Severity Score	23 (18-29)	25 (19-29)
RBC within 24 h (unit)	3 (2-4)	3 (2-5)
Plasma with 24 h (unit)	0 (0-2)	0 (0-2.5)
Cryoprecipitate with 24 h (unit)	0 (0-10)	0 (0-0)
Fibrinogen concentration over 48 h (g/L)	2.6±1.4	3.3±1.5
International Normalized Ratio over 48 h	1.2±0.2	1.2±0.2
Mortality	1	2

Data are presented as median (interquartile range), mean ± standard deviation or percentage

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 (0.84) followed by TEG FF (0.64) and TEG FIBTEM (0.62) (Fig. 3).

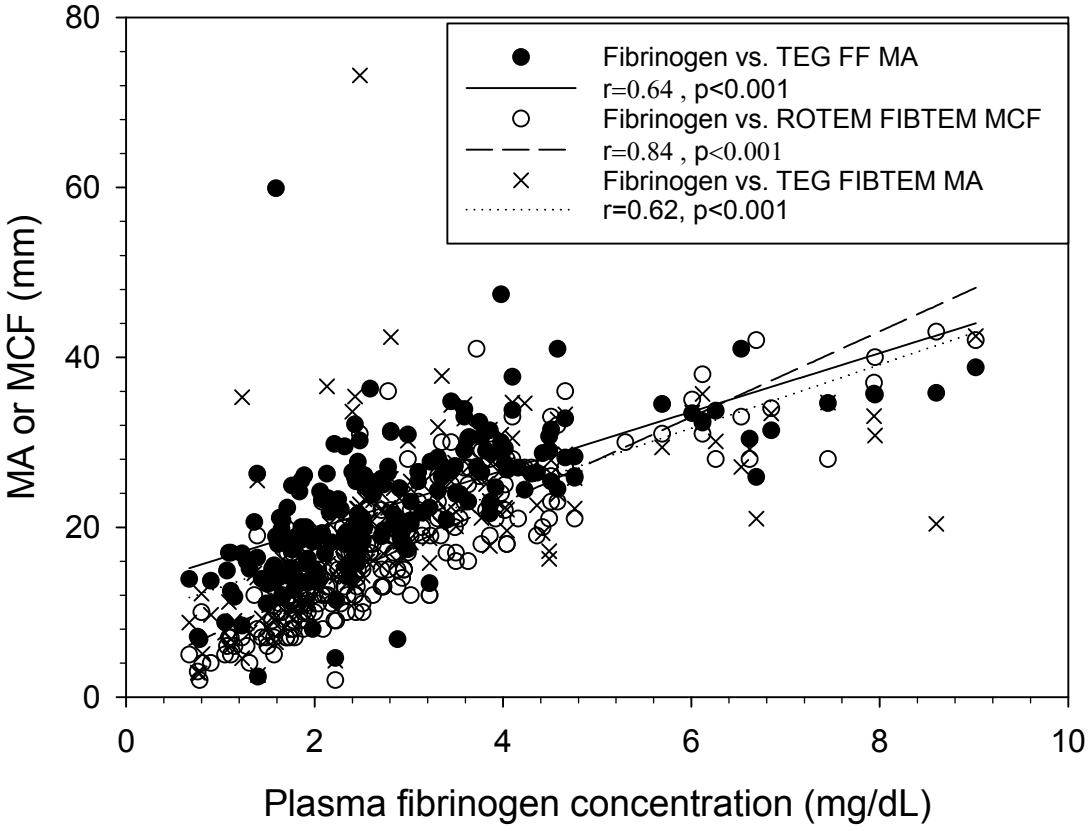
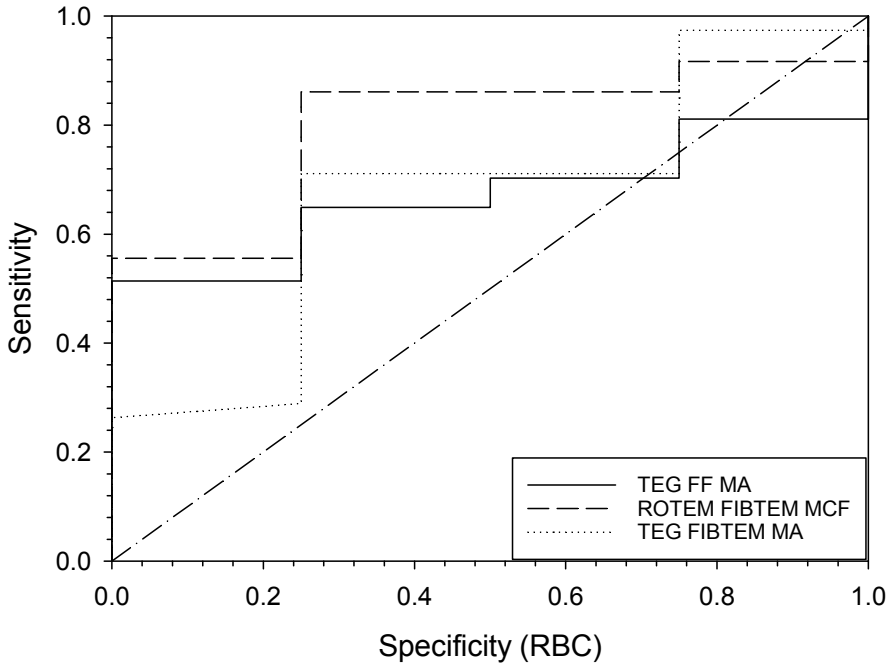


FIG. 3. Correlations between plasma fibrinogen concentration and fibrinogen clot strength as assessed by TEG FF MA, ROTEM FIBTEM MCF and TEG FIBTEM MA.

Fig. 4 displays the ROC curves comparing the predictive accuracy of TEG FF MA, ROTEM® FIBTEM MCF, and TEG® FIBTEM MA for the predetermined clinical outcomes (blood transfusion). Table 5 summarizes the C-statistics and the 95% confidence intervals and includes a p-value for each prediction. For predicting the need for blood transfusions, all variables, TEG FF MA (c-statistic: 0.696, p=0.042), ROTEM FIBTEM MCF (c-statistic: 0.720, p=0.023), and TEG FIBTEM MA (c-statistic: 0.709, p=0.027), have reasonable predictive accuracy for 24-h plasma transfusion. ROTEM FIBTEM MCF (c-statistic: 0.799, p=0.053) appears to have better predictive accuracy compared to TEG FF MA (c-statistic: 0.669, p=0.27) and TEG FIBTEM MA (c-statistic: 0.668, p=0.28) for predicting 24-h RBC transfusion. All measurements had poor performance accuracy for predicting 24-h cryoprecipitate transfusion with no statistical significance.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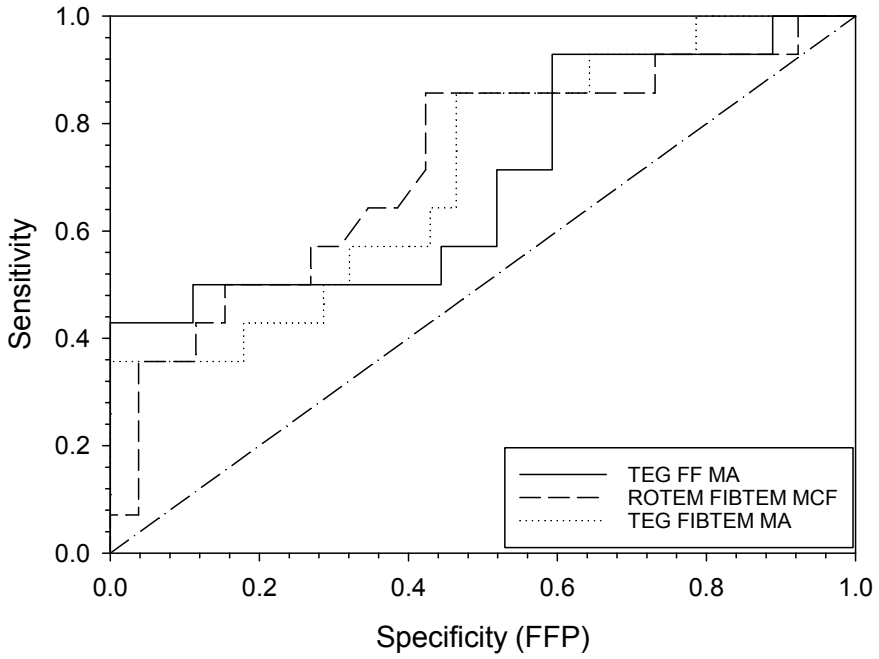
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ROTEM FIBTEM MCF
TEG FIBTEM MA

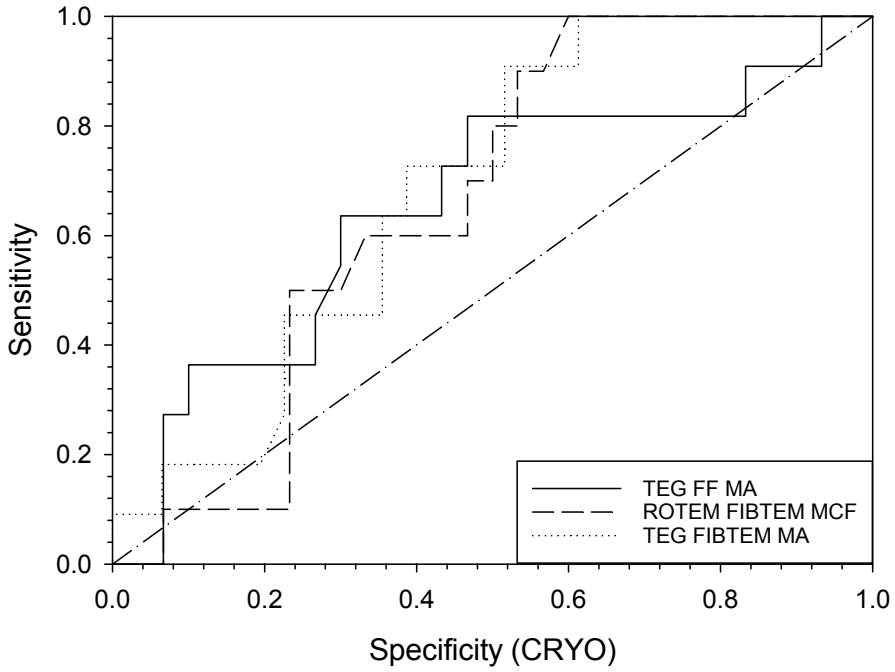

FIG. 4. TEG FF MA, ROTEM FIBTEM MCF and TEG FIBTEM MA ROC curves for transfusion within 24-h hospitalization (RBC, FFP, CRYO).

For the diagnosis of coagulopathy, defined in this study by conventional lab tests, all variables performed reasonably well for INR≥1.2 (c-statistic>0.7, $p<0.05$) and very well for fibrinogen <1 g/L (c-statistic>0.9, $p<0.05$). There appears to be no significant difference in the predictive value of TEG MA or ROTEM MCF for either INR or fibrinogen.

TABLE 5. **Area under the ROC curve for TEG and ROTEM parameters as predictors of blood transfusion and coagulopathy**

Outcome	TEG/ROTEM variables	Area under the ROC curve (95% CI)	P values
24-h RBC	TEG FF MA	0.669 (0.498-0.839)	0.27
	ROTEM FIBTEM MCF	0.799 (0.624-0.974)	0.053
	TEG FIBTEM MA	0.668 (0.401-0.934)	0.28
24-h plasma	TEG FF MA	0.696 (0.514-0.877)	0.042
	ROTEM FIBTEM MCF	0.720 (0.548-0.891)	0.023
	TEG FIBTEM MA	0.712 (0.546-0.877)	0.027
24-h cryoprecipitate	TEG FF MA	0.653 (0.455 to 0.851)	0.14
	ROTEM FIBTEM MCF	0.660 (0.492 to 0.828)	0.13
	TEG FIBTEM MA	0.685 (0.522-0.847)	0.072
INR ≥ 1.2 within 48-h hospitalization	TEG FF MA	0.716 (0.546-0.886)	0.033
	ROTEM FIBTEM MCF	0.787 (0.644-0.930)	0.005
	TEG FIBTEM MA	0.798 (0.660-0.936)	0.003
48-h Fibrinogen < 1 g/L	TEG FF MA	0.986 (0.948-1.000)	0.022
	ROTEM FIBTEM MCF	1.000 (1.000-1.000)	0.019
	TEG FIBTEM MA	0.973 (0.915-1.000)	0.026

Fig. 5A shows TEG FF R, ROTEM FIBTEM CT and TEG FIBTEM R over hospitalization time for the two treatment groups combined. Fig. 5B depicts corresponding maximum clot strength/firmness as measured by each test. As summarized in Table 6, ROTEM FIBTEM indicated significant changes in coagulation time CT by both treatment ($F_{1,228}$=17.13, p<0.001) and hospitalization time ($F_{5,228}$=3.90, p=0.002). TEG FIBTEM showed only changes in R time by treatment ($F_{1,228}$=4.92, p=0.028), but no effects of hospitalization time ($F_{5,228}$=0.77, p=0.58), and TEG FF was unable to detect significant changes in R time by either treatment ($F_{1,218}$=1.45, p=0.23) or hospitalization time ($F_{1,218}$=1.68, p=0.14). On the other hand, all TEG and ROTEM tests detected significant changes in MA and MCF by treatment and over hospitalization time.

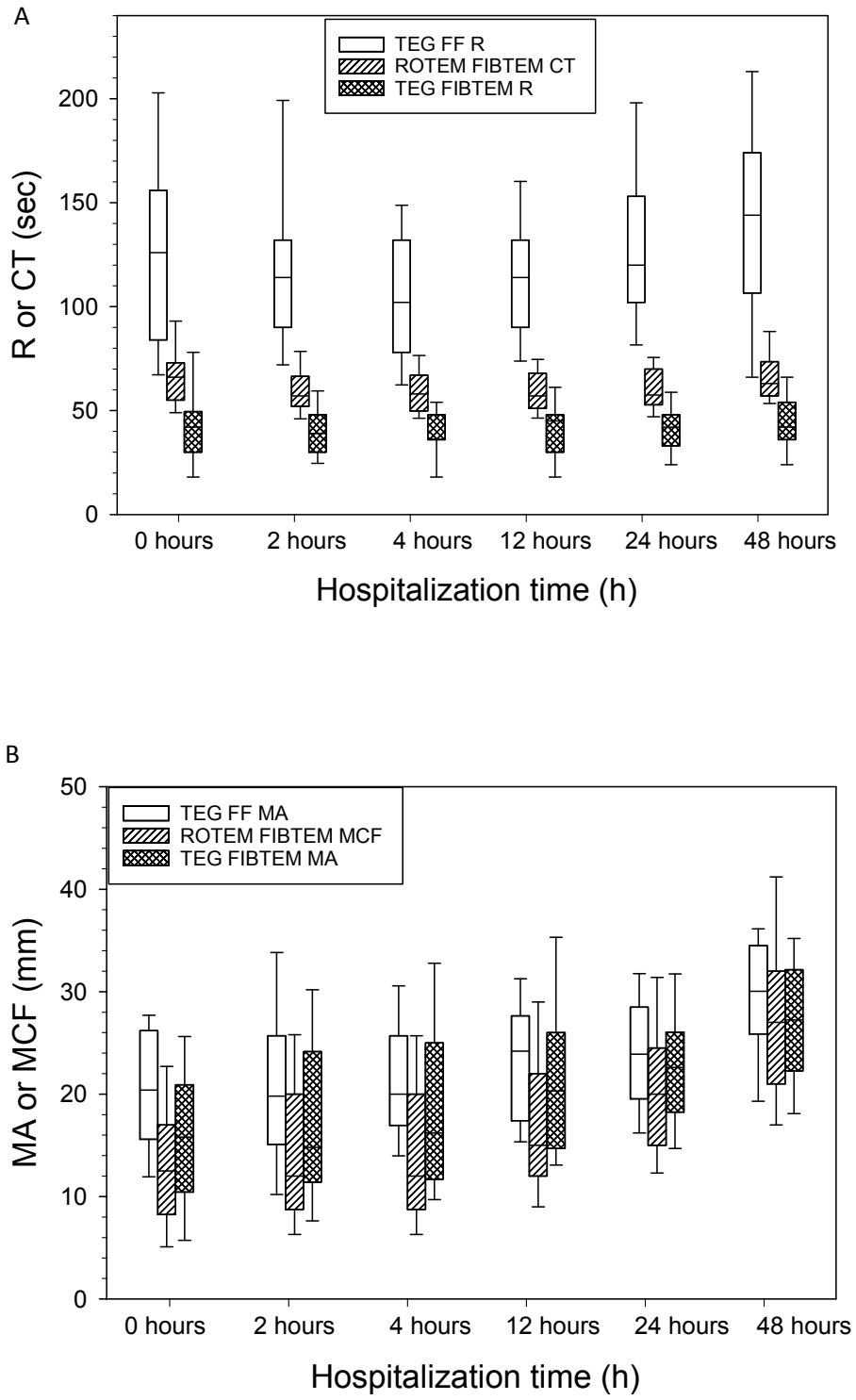

FIG. 5. Comparison of coagulation profiles as a function of hospitalization time in trauma patients receiving fibrinogen concentrate or placebo as measured by TEG Functional Fibrinogen (FF), ROTEM FIBTEM and TEG FIBTEM. The boxplots represent median values, interquartile ranges, and 5th and 95th percentiles.

TABLE 6. **Relationships between TEG and ROTEM parameters, fibrinogen treatment and hospitalization time**

TEG/ROTEM variable	Fixed effects	DF	F values	P values
TEG FF R	Fibrinogen treatment	1, 218	1.45	0.23
	Hospitalization time	5, 218	1.68	0.14
TEG FF MA	Fibrinogen treatment	1, 218	64.71	<0.001
	Hospitalization time	5, 218	9.20	<0.001
ROTEM FIBTEM CT	Fibrinogen treatment	1, 228	17.13	<0.001
	Hospitalization time	5, 228	3.90	0.002
ROTEM FIBTEM MCF	Fibrinogen treatment	1, 231	69.17	<0.001
	Hospitalization time	5, 231	25.71	0.002
TEG FIBTEM R	Fibrinogen treatment	1, 222	4.92	0.028
	Hospitalization time	5, 222	0.77	0.58
TEG FIBTEM MA	Fibrinogen treatment	1, 221	44.29	<0.001
	Hospitalization time	5, 221	10.47	<0.001

Comparing the parameter values at specific hospitalization time indicated a longer TEG® FF R ($p<0.001$) and a larger TEG® FF MA at all hospitalization time points ($p<0.001$) except at 48 h ($p=0.20$) than corresponding ROTEM FIBTEM CT and MCF, respectively. Crossover comparison where the ROTEM reagents were used on TEG, showed a shorter R at all hospitalization time ($p<0.001$), and a larger MA at all hospitalization time points ($p<0.05$) except at 48 h ($p=0.95$) in the TEG® FIBTEM assay than in the ROTEM® FIBTEM assay. These results are consistent with the results presented in Table 3.

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 appear to have a similar clinical performance in predicting the need for plasma transfusion, diagnosing trauma coagulopathy, and

monitoring fibrinogen functions. However, ROTEM may provide more information about the need for RBC transfusion and the change in coagulation time by fibrinogen treatment. Further comparison of clinical performance between these two systems with a larger sample size is warranted in trauma care.

References

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