Original Article

Correlation between thromboelastography and rotational thromboelastometry values in adult liver transplant recipients

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ABSTRACT

Background and Aims: Viscoelastic haemostatic assays (VHA) namely Thromboelastogram (TEG) and Rotational thromboelastometry (ROTEM) are used for global assessment of coagulopathy and guiding transfusion during living donor liver transplant (LDLT).We conducted a study to compare the interchangeability of the values obtained from these devices in patients with End stage liver disease (ESLD) undergoing LDLT. **Methods:** In 76 patients undergoing LDLT, ROTEM and TEG were performed and assessed for interchangeability using Spearman Correlation. The direction and strength of correlation between equivalent parameters was calculated using Inter Class Correlation (ICC) and Bland Altman analysis. **Results:** The correlation ρ between CT (clotting time) of ROTEM and R of TEG was 0.16 ($P = 0.19$).The ICC was 0.15, with 95% confidence interval (CI) of -0.38-0.48 ($P = 0.25$).The ρ of CFT (ROTEM) with K (TEG) was 0.425 (P=<0.001). The ICC was0.49 with 95% CI of 0.17-0.69, $P = 0.003$.Alpha of ROTEM correlated with Angle of TEG with ρ of 0.475 (P=<0.001). The ICC was 0.61, with 95% CI of 0.36-0.76, P=<0.001.Maximum Clot firmness (MCF) correlated with maximum amplitude (MA) with ρ=0.76 (P=<0.001).The ICC was 0.86, with 95% CI of 0.77-0.92, P=<0.001. Lysis index (L30) of ROTEM correlated clot lysis (CL30) of TEG with ρ of 0.16 ($P = 0.18$).However, the ICC was 0.45, with 95% CI of 0.11-0.66, $P = 0.08$. The correlation between CT of ROTEM and R of TEG as well as L30 of ROTEM and CL30 of TEG was not significant.The strongest correlation was found between MCF and MA ($P < 0.001$). However the MCF/MA showed an agreement of only 86% (ICC = 0.86). **Conclusion:** Values from ROTEM and TEG were not found to be interchangeable.

Key words: Rotational thromboelastometry, thromboelastography, viscoelastic haemostatic assays

INTRODUCTION

Patients with ESLD are known to have a rebalanced coagulation system. The balance of both pro and anticoagulants together is responsible for the state of haemostasis. The standard laboratory tests which reflect one aspect of the coagulation cascade may not be accurate alone in reflecting the true state of haemostasis in patients with ESLD.[1] Viscoelastic haemostatic assays (VHA) are used for global assessment of coagulopathy and guiding transfusion during LDLT surgery.[2,3]

The VHAs assess the kinetics of clot formation and clot strength in whole blood, right from clot initiation through propogation and lysis simulating *in vivo* coagulation closely under low shear conditions.[4,5]

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Thromboelastogram (TEG) and Rotational thromboelastometry (ROTEM) are two different VHAs which are used as point of care devices to assess clot formation in a sample of whole blood. TEG has been used more in North America and ROTEM in Europe. Depending on availability different transplant centers have used either of the VHAs[6] and have reported a marked reduction in total transfusions during LDLT.[7-11] Although their graphs look similar, the activators used, the nomenclature, the reference ranges and their interpretation algorithms are dissimilar as has been shown in patients with early trauma coagulopathy. However the dynamics of haemostasis in patients with liver disease are altered. At our center, where TEG is used traditionally, we compared the values obtained from both these devices in patients with ESLD to see whether they were comparable and their values interchangeable before introducing it into our clinical practice.[12]

METHODS

This is a prospective observational study registered with CTRI no. -CTRI/2019/11/022179 after Institutional Review Board and Ethics Committee approvalRS/MSSH/MHIL/SKT-1/MHEC/ANAES_CLBS/18-10on 13th March 2018.The procedure follows the guidelines laid down in Declaration of Helsinki 2013.After informed written consent, 76consecutive adult patients with ESLD undergoing LDLT surgery were included in this study. None of the patients had any bleeding disorders. Anaesthetic and fluid management as well as transfusion decisions were as per usual departmental protocol. Baseline ROTEM and TEG were performed simultaneously with single blood sample drawn from patients once before the start of surgery as per usual protocol. The tests were done conventionally, according to the manufacturer's instructions. For ROTEM, the blood sample was collected in a BD Vacutainer Sodium Citrate 1.8 mL tube, and processed in the operation theatre by trained technologists. For TEG, samples was collected in a MONOJECT™ Sodium Citrate 2.7 ml tube and processed by trained technologist in the operation theatre. ROTEM delta system (TEM Systems, Inc., Durham, NC) used tissue factor (conventional) for the EXTEM assay, added cytochalasin D as aplatelet inhibitor for its FIBTEM assay. TEG 5000 Analyzer (HaemoscopeCorporation, Niles, IL, USA) used kaolin activation. The reports generated were used by the anaesthesiologist conducting the case for interpretation and case management.

Test results generated and patient data were tabulated by separate designated researcher who was blinded to the interpretation and case management. Statistical analysis was performed on tabulated data using SPSS version 18.Information regarding patients baseline demographic characteristics including age, gender, blood grouping and typing, etiology of liver disease, CTP (Child-Turcotte-Pugh) and MELD (Model of End-stage Liver Disease) scores, any medical comorbidities, all decompensations, baseline laboratory parameters were collected. Numerical data following normal distribution was expressed as mean ± S.D and those not following normal distribution were expressed as median ± interquartile range. ROTEM values include CT (Clotting time), CFT (Clot formation time), Alpha Angle(α), MCF (Maximum clot firmness) and ROTEM lysis index (L30) at 30 minutes after CTand TEG values include R (Reaction time), K (Kinetics of clot formation), Angle, MA (Maximum amplitude) and TEG lysis index at 30 minutes after MA (CL30).

Interchangeability between TEG and ROTEM was tested initially using the Spearman Correlation analysis to evaluate the direction and strength of correlation between equivalent parameters clotting time (CT) of ROTEM vs. reaction time (R) of TEG; Alpha of ROTEM vs. Angle of TEG; clot formation time (CFT) of ROTEM vs. kinetics time (K) of TEG; maximum clot firmness (MCF) of ROTEM vs. maximum amplitude (MA) of TEG as well as lysis index (L30) of ROTEM and (CL30) of TEG [Figure 1]. Further Intra Class Correlation (ICC) was estimated between the ROTEM and TEG parameters to find the accuracy and strength of association between POC coagulation techniques.

Following this, the Bland-Altman method was used to evaluate interchangeability. As shown in Figure 2, the difference of means of each set of values of TEG and ROTEM which were to be compared were plotted on the Y axis and the average of the means of the same set of values was plotted on the X axis.

RESULTS

From April 2018 to July 2018,76 consecutive adult patients with ESLD undergoing elective LDLT were enrolled and 76 ROTEM and TEG measurements were analyzed for correlation.The total blood products transfused during surgery were also correlated with

the baseline individual parameters of ROTEM and TEG to see for any association.

Mean age of the patients was 44.9 ± 12.8 years. 89% of the patients were males and the remaining were females. Mean CTP and MELD scores were 10.0 ± 2.3 and 20.2 ± 8.8 respectively as shown in Table 1. Predominant etiology was Viral (HBV + HCV) related Cirrhosis in 47%, followed by alcohol related cirrhosis in 22%.Incidence of NASH (Nonalcoholic steatohepatitis) related Cirrhosis was seen in 11%, with cryptogenic, NASH and Primary Sclerosing Cholangitis constituting the remaining 20%. Baseline laboratory parameters standard laboratory tests with mean and standard deviation/median are summarized in Table 2.

Interchangeability was tested using Spearman correlation coefficient calculated using a consistency definition. Two-way mixed effects model was used, while the estimator was the same whether the interaction effect is present or not. It was found that the correlation between CT of ROTEM and R of TEG was ρ(rho) = 0.16(P = 0.19) which was statistically not significant. The Spearman correlation and Intra Class Correlation (ICC) of ROTEM and TEG values are mentioned in Table 3. The ICC was only 0.15, with 95% confidence interval (CI) of -0.38-0.48 (P = 0.25) indicating lack of interchangeability.A decreasing pattern was observed in Bland-Altman graph [Figure 2a], with8% of values in disagreement.

CFT when correlated with K, the ρ was 0.425 (P = <0.001) which was statistically significant. However the ICC was only 0.49, with 95% CI of 0.17-0.69, P = 0.003; the Bland-Altman showed that 5%values were in disagreement [Figure 2b].

Alpha of ROTEM correlated with Angle of TEG with ρ of 0.475 (P = <0.001) which was statistically significant. However the ICC was 0.61, with 95% CI of 0.36-0.76, P = <0.001; and 8% values were in disagreement [Figure 2c].

MCF correlated with MA with ρ = 0.76 (P = <0.001) which was also statistically significant.However, the ICC was 0.86, with 95% CI of 0.77-0.92, P = <0.001; and in Figure 2 it was seen that 7% values were found in disagreement [Figure 2d].

L30 of ROTEM correlated with CL30 of TEG with ρ of 0.16 (P = 0.18).However the ICC was 0.45, with 95% CI of 0.11-0.66, P = 0.08; which was not significant.

Table 1: Demographics and descriptive statistics of the patients included in study

	Mean±SD	Median (Range)
Demographics		
Age	44.9±12.8	47.0 (37.0-54.0)
Height	164.5±15.8	168.0 (160.0-172.0)
Weight	74.2±20.4	74.0 (63.8-83.0)
BMI	26.9±5.0	26.4 (23.3-29.5)
CTP	10.0±2.3	10.0 (8.0-12.0)
MELD/PELD	20.2±8.8	18.0 (13.0-27.0)
Transfusion data		
PRBC	4.438±3.9823	4.000 (1.000-7.000)
FFP	2.5±3.4	1.0 (0.0-5.0)
CRYO	3.2±4.0	0.0 (0.0-6.0)
RDPC	0.5±1.6	0.0 (0.0-0.0)
SDPC	0.0±0.2	0.0 (0.0-0.0)
TEG Values		
R (mins)	9.4±5.0	8.4 (7.1-10.7)
K (mins)	4.2±3.2	3.5 (2.2-4.7)
ANGLE	52.8±17.1	54.0 (43.0-67.0)
MA (mm)	48.7±13.4	47.8 (39.7-56.5)
CL30 (%)	97.9±4.5	100.0 (97.2-100.0)
ROTEM Values		
CT (seconds)	150.2±227.9	96.0 (71.0-142.0)
CFT (seconds)	371.9±542.9	211.0 (151.0-368.0)
Alpha	51.4±14.9	50.4 (43.0-67.0)
MCF (mm)	40.94±11.841	43.00 (32.00-50.00)
L30 (%)	97.6±10.1	100.0 (100.0-100.0)

Table 2: Baseline Laboratory Values

Variable	Value
Haemoglobin (g/dl)	10.03±2.17
Platelets (Cells ×10^3/mm^3)	117±37
INR	1.88±0.97
Fibrinogen (g/dl)	173±84
Bilirubin (mg/dl)	2.7 (0.8-37.9)
Albumin (g/dl)	2.5±0.6
Creatinine (mg/dl)	0.8 (0.4-4.2)

Table 3: Spearman and Intraclass Correlation Coefficients between TEG and ROTEM Parameters

Parameters	Spearman Correlation		ICC	
	ρ	*P*	95% confidence interval	*P*
R vs CT	0.16	0.19	0.15(-0.38-0.48)	0.25
K vs CFT	0.425	<0.001	0.49 (0.17-0.69)	0.003
Angle vs Alpha	0.475	<0.001	0.61 (0.36-0.76)	<0.001
MA vs MCF	0.76	<0.001	0.86 (0.77-0.92)	<0.001
CL30 vs L30	0.16	0.18	0.45 (0.11-0.66)	0.08

All parameters except CT/R *(P* = 0.19) and L30/CL30 (P = 0.18) on analysis showed a statistically significant correlation *(P* < 0.001). The scatter plots in Figure 1 show that the correlation between CT of ROTEM and R of TEG as well as L30 of ROTEM and CL30 of TEG was not

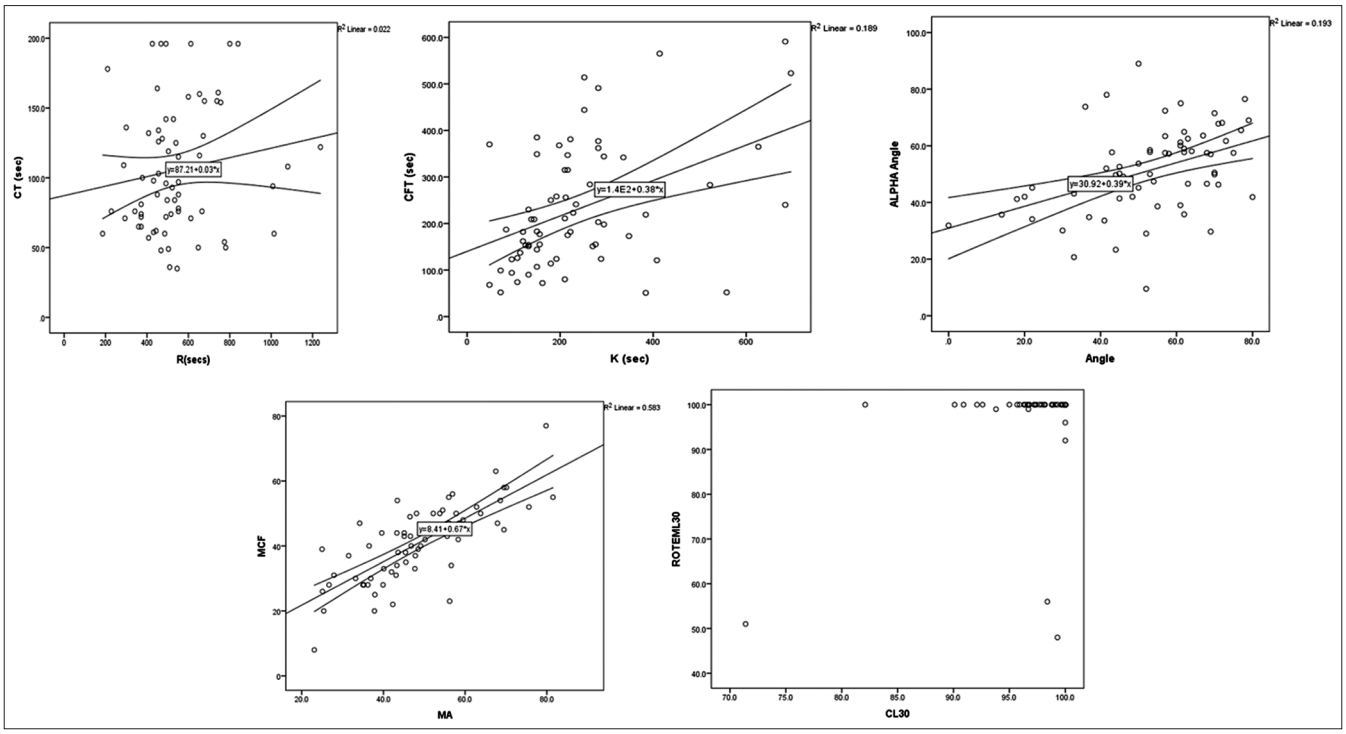

Figure 1: Scatter plots of ROTEM vs. TEG parameters (CT/R, CFT/K, Alpha (Rotem)/Angle (TEG), MCF/MA, L30/CL30)

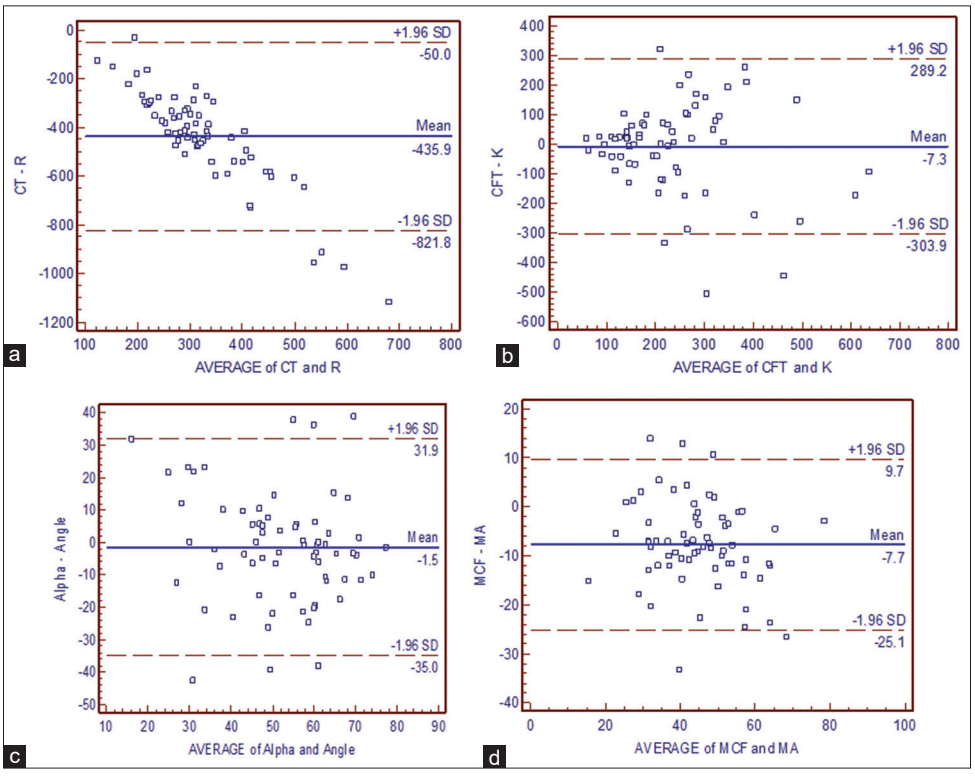

Figure 2: Bland-Altman plots of difference of means and average of ROTEM vs. TEG parameters((a) CT/R, (b) CFT/K, (c) Alpha (Rotem)/Angle (TEG), (d) MCF/MA)

significant.The strongest correlation was found between MCF/MA (*P* = <0.001).However, the ICC was weak.The MCF/MA showed an agreement of 86% (ICC = 0.86).The other set of values ROTEM Angle/Alpha of TEG were found to be in agreement in 61% cases and K/CFT even lesser (in 49%). None of the compared set of values of the VHAs were found to be 100 percent interchangeable.

DISCUSSION

ESLD patients are known to be in a rebalanced state of coagulation and usually present with deranged standard laboratory tests.[1] Reports of standard laboratory tests have a long turnover time, which delays the management of coagulopathy in the intraoperative period.[13] Hence VHAs are routinely used intraoperatively to guide blood product transfusion for optimal management of coagulopathy during LDLT.[2,14] A few studies have compared both these VHAs in the normal population who suffered trauma,[15-17] but none in patients with ESLD undergoing LDLT. Since the graph of these two assays looks similar and both record the graph created by the torque between the cup and the pin, it has been assumed that results from both the devices are interchangeable but in reality that may not be true. We conducted an observational study to see if the values generated by the two VHAs are interchangeable.

Our study has found that values from ROTEM and TEG are not interchangeable even though they both seem to share a common functional mechanism. Although a significant linear association with strong correlation was seen for some of the parameters like CFT with K and MA with MCF, rest of the parameters showed either moderate or poor correlation. This could be due to different coagulation activators which the devices use.[18] ROTEM uses tissue factor as activator whereas TEG uses kaolin as activator of coagulation.

Another reason for lack of correlation could be subtle differences in the technological principle, although both measure viscoelastic changes in blood as it clots under low shear conditions after adding a specific coagulation activator and the graph is plotted based upon impedence to rotation. In ROTEM, the cup containing the blood sample is static and the pin which is suspended continuously rotates back and forth through an angle of 4.75° in the center of the plastic cup. Whereas in TEG, suspended torsion wire is constant and the cup moves back and forth through an arc of 4.75° around the fixed plastic pin.[18]

The wide coefficient of variance of both ROTEM and TEG might be the third possible reason for lack for interchangeability. Reported coefficient of variance for these POC tests range between 7% to 83%.[19] If the coefficient of variance is more than 30%, the test is considered inaccurate and lacks repeatability.

Although we have compared the values of some parameters of both VHAs, there are some basic differences between them. Result parameters of ROTEM are achieved in seconds where as their comparable TEG counterparts take minutes to provide the corresponding value, due to use of different activators. Variables reflective of fibrinogen deficiency on ROTEM could not be compared with any value of TEG, due to lack of a corresponding value on TEG.In our study, we did not compare A5 or A10 of ROTEM which is used to decide between fibrinogen deficiency or need for platelet transfusion.[20] Certain values compared in our study were not necessarily the ones which we use for clinical decision making. For example decision to transfuse platelets can be made from the difference in A5 on FIBTEM and EXTEM on ROTEM and the same is decided from MA on TEG. Since A5 and MA are not comparable quantities we compared MCF of ROTEM with MA since both values are reflective of platelet function.

In conclusion, conventionally performed TEG and ROTEM failed to show strong correlation between its parameters and hence they lack interchangeability. Guidelines established for one device should not be extrapolated to the other. There is need for RCTs to show which device between ROTEM/TEG better predicts coagulopathy and helps reduce blood transfusion during LDLT.

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Conflicts of interest
There are no conflicts of interest.

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