Original Article

Correlation of early ROTEM parameters with conventional coagulation tests in patients with chronic liver disease undergoing liver transplant

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ABSTRACT

Background and Aims: Viscoelastic tests such as rotational thromboelastometry (ROTEM) provide a quick and holistic assessment of coagulation status to guide transfusion during liver transplant (LT). Conventional coagulation tests (CCTs) measure single parameters in isolation, and also the results are delayed hampering management of patients during surgery. We evaluated the correlation of early ROTEM-derived parameters with CCTs and also assessed the ability of ROTEM-derived parameters to predict thrombocytopaenia and hypofibrinogenaemia during LT in patients with end-stage liver disease (ESLD). **Methods:** This retrospective study was carried out in 100 patients with decompensated ESLD undergoing LT. Correlation between CCTs and ROTEM parameters was analyzed. Receiver operating characteristic curves with area under the curve were used to determine the cut-off values of A5 andA10 on EXTEM and FIBTEM. **Results:** The values of $A5_{EXTEM}$ and $A10_{EXTEM}$ highly correlated with fibrinogen levels and platelet count, whereas $A5_{FIBTEM}$ and $A10_{FIBTEM}$ correlated well with fibrinogen levels. $A5_{EXTEM}$ <21 mm and $A10_{EXTEM}$ <28 mm correlated with a platelet count <75,000 mm^{-3}, whereas $A5_{EXTEM}$ <18 mm and $A10_{EXTEM}$ <25 mm correlated with a platelet count <50,000 mm^{-3}. Fibrinogen levels <100 mg/dL better correlated with $A5_{FIBTEM}$ <5 mm, $A10_{FIBTEM}$ <6 mm, $A5_{EXTEM}$ <21 mm and $A10_{EXTEM}$ <30 mm. **Conclusion:** Early ROTEM parameters A5 and A10 of both EXTEM and FIBTEM had an excellent correlation with thrombocytopaenia and hypofibrinogenaemia and may potentially guide early transfusion of relevant blood products during LT.

Key words: Coagulopathy, EXTEM, FIBTEM, liver transplantation, thromboelastometry

INTRODUCTION

Patients with chronic liver disease (CLD) are known to have an abnormal haemostatic potential which makes them more prone to major blood loss during surgery.[1] Liver transplant (LT) is associated with major bleeding and haemodilution which can change the coagulation status of patients dynamically. Hence, real-time monitoring of coagulation status is mandatory at different phases of LT, to guide transfusion of blood products. In contrast to conventional coagulation tests (CCTs) such as platelet count, fibrinogen levels and prothrombin time,[2] viscoelastic tests (VETs) such as rotational thromboelastometry (ROTEM) provide us a holistic assessment of coagulation status within 10–20 minutes thereby enabling prompt diagnosis and helping us provide timely necessary intervention.

Various stages of VETs correspond to the initiation, formation and stability of clot formation which involves interaction between coagulation factors and cellular components. ROTEM basically has four changes: EXTEM analyses the extrinsic pathway of coagulation; INTEM analyses the intrinsic pathway; FIBTEM analyses the contribution of fibrinogen to coagulation

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and APTEM detects degree of fibrinolysis.[3] ROTEM is found to be useful in predicting coagulation status in massive trauma, obstetric haemorrhage and cardiac surgery. Only few studies have are available which assessed the correlation of early ROTEM parameters and laboratory parameters.[4-6] Previous studies have used more than two components of ROTEM, which makes ROTEM a costly intervention. We intended to study whether only two components, EXTEM and FIBTEM, can adequately assess thrombocytopaenia and hypofibrinogenaemia.

The primary objective of this study was to assess whether the early ROTEM parameters of EXTEM and FIBTEM correlated with CCTs. The secondary objective was to determine the cut-off values of ROTEM-derived parameters to predict thrombocytopaenia and hypofibrinogenaemia in our subset of patients. The primary outcome was to find a correlation of A5 andA10 values of both EXTEM and FIBTEM with platelet count, fibrinogen levels and prothrombin time. The secondary outcome was to determine the cut-off values of A5 and A10 of EXTEM and FIBTEM to predict thrombocytopaenia (platelet count <75000/mm^3) and hypofibrinogenaemia (fibrinogen levels <100 mg/dL)

METHODS

After institutional review board and ethical committee approval, data of patients who underwent orthotropic LT in our center between February 2017 and August 2017 were analyzed. All adult patients (18 years or more) who underwent LT during the study period were included in the study. Patients with other coagulation disorders, intake of antiplatelets and anticoagulants were excluded.

Data was obtained from anaesthesia record, electronic medical record and ROTEM machine database. The baseline characteristics of patients including age, gender, body mass index (BMI), etiology of liver disease, Model of End Stage Liver Disease (MELD) score, Child-Turcotte-Pugh (CTP) score and any associated bleeding disorders were noted. Anaesthesia protocol was similar in all patients. Samples for ROTEM analysis and CCTs including platelet count, prothrombin time and fibrinogen concentration were collected 30 min after induction of anaesthesia.

ROTEM tests were performed in the operating room according to the manufacturer's instruction using equipment and reagents provided by Tem International GmbH (Munich, Germany). Only EXTEM and FIBTEM analyses using appropriate reagents were performed simultaneously in all patients. 300 μL citrated whole blood was recalcified in a reaction cup with 20 μL star-TEM reagent, and was then activated with EXTEM reagent. In the EXTEM test, coagulation was activated extrinsically by tissue factor from rabbit brains. In the FIBTEM test, the contribution of platelets to whole blood coagulation was inhibited by the platelet-neutralising reagent cytochalasin D. The following ROTEM variables were recorded: Clotting time (CT), defined as the time in seconds from the start of measurement to the initiation of clotting (clot firmness of 2 mm); Clot formation time (CFT), defined as the time in seconds from initiation of clotting until a clot firmness of 20 mm; Maximum clot firmness (MCF), defined as the maximal amplitude (mm) of the graphical trace of clot firmness; Alpha-angle, defined as the tangent to the graphic trace at an amplitude of 2 mm; A5 (mm), the amplitude at 5 min after CT; A10 (mm), the amplitude 10 min after CT. Early ROTEM variables are CT, CFT, alpha-angle, A5 and A 10. CCTs were interpreted by the specialists in laboratory medicine, and the ROTEM findings were interpreted by the anaesthesiologist. The ROTEM machine normally requires 4 min for warm up, and placement of sample is usually complete within another 3–5 min. The rest of the analysis is usually completed in 20 min.

For the purpose of calculation of sample, the most important parameter is the correlation of platelet count with $A5_{EXTEM}$ and $A10_{EXTEM}$ values and fibrinogen with $A5_{FIBTEM}$ and $A10_{FIBTEM}$values. The study by Song *et al.* reported a correlation of 0.757 in patients with CLD. To be able to detect a correlation of at least 0.6 with 80% power and significance level 5%, the sample size computed was 92 using the formula [(Z $\alpha/2$ + Z β) 2 + 3], where Z $\alpha/2$ + 1.96 which corresponds to 95% level of confidence.

Continuous variables were expressed as median (interquartile range) or mean (standard deviation). Correlations between CCT results and those performed on ROTEM were analyzed using Spearman's rank correlation coefficient (*r*). Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to determine the optimal cut-off values of A5 andA10, and MCF on EXTEM and FIBTEM predicting platelet counts and fibrinogen concentrations.

RESULTS

In all, 100 patients with end-stage liver disease (ESLD), undergoing living donor liver transplantation, were enrolled for analysis. Eight patients were excluded in view of incomplete data. Hence, data from 92 patients were analyzed.

The baseline patient characteristics of patients including age, gender, BMI, etiology of liver disease, MELD score, CTP score and any associated bleeding disorders were noted [Table 1]. Most of our patients were males, with hepatitis-C-related CLD being the most common reason for LT.

Table 1: Demographic characteristics

Variable	Mean (range)
Age	46.44 (18 - 66)
Gender, male (%)	71%
BMI	26.77
Aetiology	
HCV	27%
Alcoholic	21%
HBV	16%
Cryptogenic	10%
Nash	10%
Others	17%
MELD	18.9 (8-40)
CTP	10.3 (5-14)
Haemoglobin	9.8 (6.2-15.5)
Platelet	131 (15-252)
Fibrinogen	168.9 (37-431)
INR	1.67 (1.08-10)

HBV – Hepatitis B Virus; HCV – Hepatitis C Virus; BMI – Body mass index; MELD – Model of End Stage Liver Disease score; CTP – Child Turcotte Pugh Score; INR – International Normalized Ratio

Spearman's rank correlation coefficient (r) was calculated for EXTEM A5 with EXTEM MCF, EXTEM A10 with EXTEM MCF, FIBTEM A5 with FIBTEM MCF and FIBTEM A10 with FIBTEM MCF. There was excellent correlation between all sets analyzed with $r > 0.95$ in all the analyses [Figure 1].

There was moderate but significant correlation between EXTEM A5 with platelet count ($r = 0.566$) and EXTEM A10 with platelet count ($r = 0.590$) as shown in Figure 2. A similar correlation was also sought between EXTEM A5 with fibrinogen and EXTEM A10 with fibrinogen; the Spearman's correlation coefficient was 0.745 and 0.759, suggesting a good correlation [Figure 3]. A similar correlation between FIBTEM A5 with fibrinogen and FIBTEM A10 with fibrinogen also showed a good correlation as depicted in Figure 4. There was no correlation of ROTEM variables with International Normalized Ratio INR values.

Youden'S index was done to calculate the optimal cut-off to define thrombocytopaenia (platelet $<75{,}000$ mm^{-3} and $<50{,}000$ mm$^{-3)}$ and hypofibrinogenaemia (fibrinogen <100 mg/dL). ROC analysis was done to determine the sensitivity, specificity and AUC, and they are as shown in Table 2.

DISCUSSION

LT is associated with major bleeding and requirement for massive transfusion. Patients with decompensated liver disease have a rebalanced coagulation system where coagulation factors and anticoagulants may both be are reduced in equal proportions.[7-9] Thrombin production

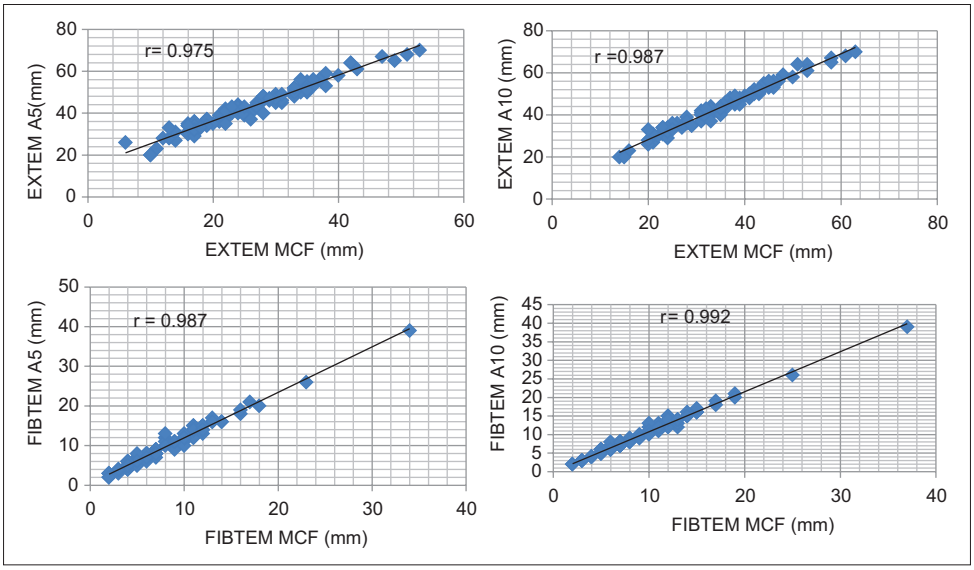

Figure 1: Correlation of A5 and A10 of EXTEM and FIBTEM with MCF

Table 2: Cut-off points to predict thrombocytopaenia and hypofibrinogenaemia

Problem	CCT value	ROTEM value	Sensitivity	Specificity	AUC
Thrombocytopaenia	Platelets <75,000/mm^3	A5EXTEM ≤21	85.7%	74.1%	0.866
	Platelets <50,000/mm^3	A5EXTEM ≤18	79%	80%	0.915
Hypofibrinogenaemia	Fibrinogen <100 mg%	A5FIBTEM ≤5	88.9%	77%	0.857
		A10FIBTEM ≤6	94.4%	75.7%	0.870
		A5 EXTEM ≤21	82.4%	84%	0.871
		A10EXTEM ≤30	82.4%	89%	0.876

ROTEM – Rotational thromboelastometry; CCT – Conventional coagulation test; AUC – Area under curve

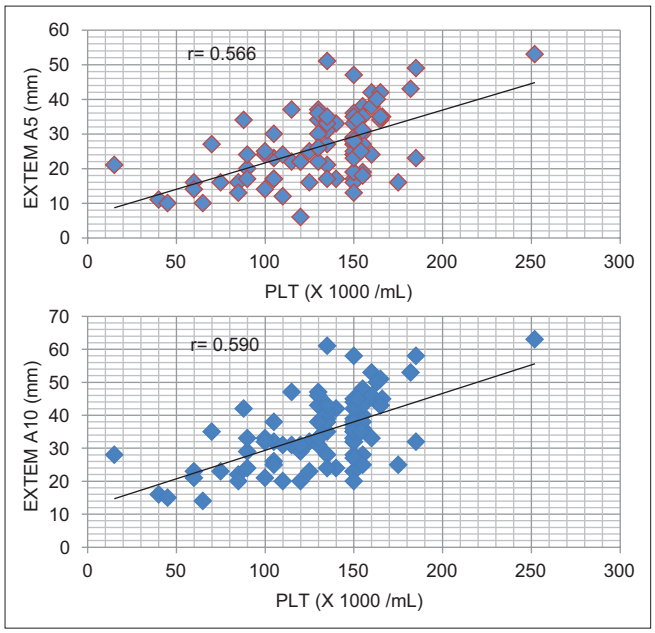

Figure 2: Correlation of EXTEM A5 and A10 values with platelet count

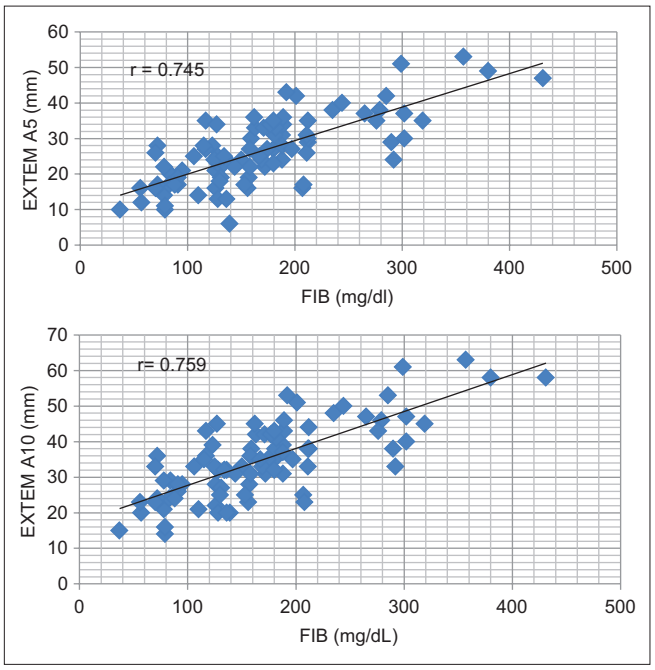

Figure 3: Correlation of EXTEM A5 and A10 values with fibrinogen

was found to be unaffected despite high INR values in cirrhotic patients. These patients are very prone to bleeding and thrombosis, and such tipping of balance to either side can occur any time during the course of surgery. Therefore, timely and judicious replacement of blood products or antifibrinolytics is essential during the surgery to prevent such complication.

The turnaround time of CCTs is more and it may not fairly reflect the *in vivo* coagulation status in patients with CLD. VETs are a point of care (POC) test that provide a holistic assessment of the coagulation system and the results can be obtained in a much shorter time.

The final strength of the clot is assessed by MCF, and this takes 30–40 min to derive on an average after CT. Our results show that A5 and A10 of both EXTEM and FIBTEM have excellent correlation with MCF values. Hence, MCF can reliably be predicted at 5–10 min after CT from A5 and A10 values of EXTEM and FIBTEM. This is in concordance with the results of Song *et al.* and Roullet *et al.*[4,10]

The correlation coefficient of EXTEM A5 and EXTEM A10 corresponds better with fibrinogen values ($r = 0.745$) compared with platelet values ($r = 0.566$). This is in contradiction to the previous studies done in this aspect.[4,10,11] This could be due to the fact that platelet function and platelet numbers do not always match in CLD due to rebalancing of haemostasis.

Our results also show that INR values have no correlation with ROTEM-derived parameters. This again reinforces the fact that INR is a poor predictor of bleeding in patients with CLD because it assays only the procoagulants and does not study the effect of anticoagulants.[12]

In our study, we could predict the critical platelet and fibrinogen values from early ROTEM variables reliably. In a previous study in patients with CLD, the cut-off values for predicting a platelet count <50,000 mm^{-3} were an EXTEM A5 of 19mm and an A10 of 27 mm.[10] Our results showed that EXTEM of A5 of 18mm and A10

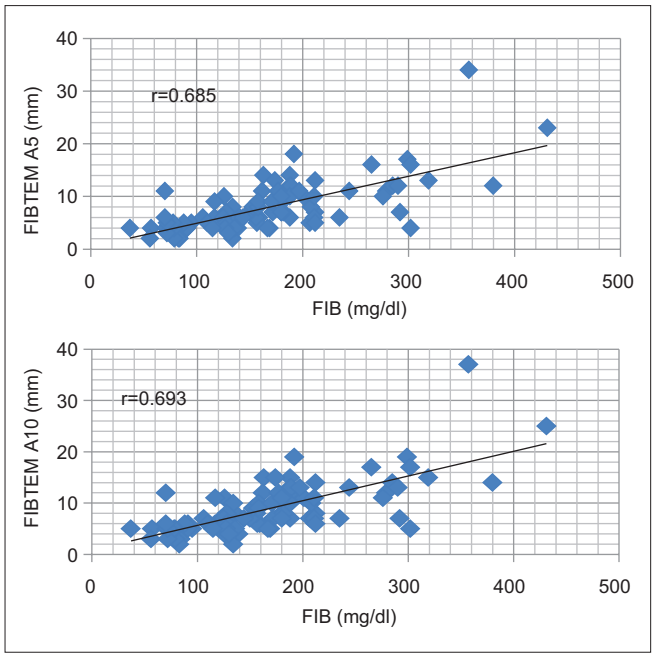

Figure 4: Correlation of FIBTEM A5 and A10 values with fibrinogen values

of 25 mm predicted a platelet count of <50,000 mm^{-3} with good sensitivity and specificity.

Additionally, we found an EXTEM cut-off value to predict fibrinogen values <100 mg/dL as our EXTEM values showed better correlation with fibrinogen than platelet values. An EXTEM A5 of 21 mm and A10 of 30 mm predicted a fibrinogen level <100 mg/dL with fair sensitivity and specificity.

A limitation of our study is that the data are retrospective in nature and there may be chances of selection bias. We did not correlate the early ROTEM variables with the transfusion requirements, and further prospective studies are required to analyze this aspect. Future prospective trials comparing ROTEM and CCT repeated intraoperatively at various time points may improve our knowledge and understanding further.

CONCLUSION

In conclusion, early ROTEM variables such asA5 and A10 values ofEXTEM and FIBTEM A5 and A10 can effectively predict thrombocytopaenia and hypofibrinogenaemia within 5–10 min after CT of ROTEM.

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Conflicts of interest

There are no conflicts of interest.

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