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ORIGINAL RESEARCH ARTICLE

# TEG GUIDED PRE-PROCEDURE COAGULOPATHY SCREEN IN CIRRHOTICS

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## ABSTRACT

### Background and Aims

Hemostasis in cirrhotics exist in rebalance, defects in prohemostatic drivers are compensated by commensurate changes in antihemostatic drivers. Conventional coagulation tests (CCTs) in cirrhotics assess only procoagulant factors therefore poor predictors of bleeding risk. CCTs are routinely used before invasive procedures and attempts are made to correct these abnormalities before invasive procedures such practices are not evidence-based, and may even be harmful. Thromboelastography (TEG) hence is promising in evaluating the coagulation status of cirrhotics prior to procedures. TEG-guided transfusion can avoid unnecessary blood product transfusions.

### Methods

The prospective study included 133 cirrhotic patients undergoing central line placement, Conventional coagulation tests (CCTs), and Thromboelastography (TEG) were done in all patients and they were observed for postprocedural bleeding.

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**Results**
133 cirrhotic patients (mean age of 46 yrs, 90.9% males) with 90.9% and 9.1% patients in child t pugh (CTP) class B, C. All underwent central line placement. Bleeding time, clotting time were normal in all.PT/INR was prolonged in all. Comparison of TEG parameters (Rtime and MA) with INR and platelet counts showed a lower percentage of abnormal values of R time and MA value compared to INR and platelet count, with no post-procedural bleed. No correlation between CCTs and TEG variables and CTP score. None received blood transfusion pre-procedure.

**Conclusion**
Abnormal CCTS do not predict bleeding risk, TEG guided coagulopathy assessment is an important pre-invasive procedure evaluation for individuals with cirrhosis.

**Keywords:** Cirrhosis; Coaguloapthy; Teg; Preprocedure Evaluation

## INTRODUCTION

Hemostasis in patients with chronic liver disease exists in a state of rebalance, in which defects in hemostatic drivers are compensated for by commensurate changes in anti-hemostatic drivers.[1,2] Conventional tests of coagulation (CCTs) cannot evaluate this potential state of rebalance because they only assess components of clot formation and, therefore, may provide misleading information regarding the risk of bleeding, possibly leading clinicians to administer unneeded or even harmful hemostatic factors. Changes in the pro-hemostatic pathways are balanced by changes in the anti-hemostatic pathways in cirrhotics. This rebalanced homeostasis state is far more precarious and potentially unstable in cirrhotics as compared to healthy individuals, thus explaining the potential of bleeding and thrombotic complications in these patients. Therefore usefulness of CCTs in assessing the hemorrhagic risk and therapeutic strategies in patients with cirrhosis is debatable.[3,4] It is a common practice to prophylactically correct hemostatic abnormalities in patients with liver disease before invasive procedures by administration of blood products guided by the prothrombin time (PT) and the platelet count. Patients with liver disease have the greatest risk of transfusion-related lung injury as compared to other populations.[5]

Major procedures such as liver transplants have been performed without the administration of fresh frozen plasma despite the presence of an elevated international normalized ratio INR. With regards to this, Thromboelastography (TEG) is a commercially available, rapid, point-of-care assay that assesses clot formation in whole blood, including plasmatic and cellular components. It monitors hemostasis as a dynamic process in the whole blood as compared to CCTs.[6] Physical properties of the clot in whole blood via a pin suspended in a cup (heated to 37C) from a torsion wire connected with a mechanical-electrical transducer form the basis of TEG measurements. The elasticity and strength of the developing clot change

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the rotation of the pin, which is converted into electrical signals that a computer uses to create graphical and numerical output. TEG might be beneficial in evaluating the overall coagulopathy in a cirrhotic patient prior to invasive procedures and avoiding unnecessary transfusions.

**Aims & Objectives**

1. To Determine The Utility Of Thromboelastography (Teg) In Comparison To Conventional Coagulation Test In Cirrhotic Patients Undergoing Central Venous Cannulation.
2. The use of K time, Reaction time, and maximum amplitude of thromboelastogram to predict post central venous cannulation bleeding in patients with cirrhosis admitted to speciality medical ICU and gastroenterology ward of SMS hospital.
3. To correlate Thromboelastogram (TEG) parameters with the severity of liver disease (child status) and conventional coagulation parameters.

**METHODS**

Cirrhotic patients were classified into A, B, and C stages, depending on the Child- Turcotte-Pugh (CTP) score. In this longitudinal preliminary prospective pilot observational study, a total of 133 cirrhotic patients undergoing central venous line placement were included between June 2016 to June 2018. Adult patients diagnosed with Child B and C cirrhosis requiring elective central venous catheter (CVC) insertion were included in the study. Platelet count, INR, serum creatinine, TEG, and Child-Turcotte-Pugh (CTP) score were recorded before the procedure.

Right-sided internal jugular veins were cannulated. On the basis of presence or absence of post- procedural bleed, the CTP score, a component of TEG (R - reaction time, K - coagulation time, MA - maximum amplitude and α - angle) and laboratory parameters of both the groups were compared, data analysed and conclusions were drawn. Conventional coagulation tests (CCTs), especially platelet count was done by Automated Hematology Analyser SYSMEX XT 4000 i. PT INR was estimated by STAGO machine. Thromboelastography (TEG) was done in all patients by Multi- TEMA (Hemologix) and they were observed for post-procedural bleeding. None of the patients received prophylactic transfusion before the procedure. The study was approved by the ethical review committee of S.M.S Medical College and hospital, Jaipur Rajasthan India bearing no 3690/2018/17/2/18. Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori by the institution’s human research committee.

**Inclusion Criteria**

Adult patients diagnosed with Child B and C cirrhosis requiring elective central venous catheter (CVC) insertion in speciality medical ICU of SMS hospital.

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**Exclusion Criteria**

Patients with active bleeding, known local vascular abnormality, skeletal deformity or history of prior central vein cannulation and patients who did not consent to the procedure were excluded from the study.

**Study Parameters**

Baseline laboratory investigations including platelet count, INR, serum creatinine and TEG were recorded within six hours before the procedure. TEG® was performed using kaolin as the activator. Measurement of TEG consisted of the following four variables: (i) Reaction time (R): Time from the start of the recording until the amplitude reaches 2 mm; (ii) Coagulation time (K): Time from the end of the reaction time until the amplitude reaches 20 mm; (iii) Maximum amplitude (MA): Maximum width of the TEG trace represents the absolute strength of the clot; and (iv) Angle (α): Formed by the slope from the R value to the K value.

**Cannulation Technique**

Right-sided internal jugular vein (IJV) was cannulated using a landmark technique.[7]

**Assessment with Conventional Coagulation Tests, TEG and Data Collection**

Before IJV cannulation CCTs and TEG were performed and analyzed in the standard format. In summary, within 4 min of drawing the sample, 360 L (approx. 6 drops) of blood was pipetted out in a plastic cup of the TEG machine. Sample was processed for 60 min and following parameters were recorded: (1) reaction (r) time: defined as the time between the start of the test and the initial fibrin formation, (2) kinetic (k) time: defined as the time from initial fibrin formation to reach an amplitude of 20 mm, (3) alpha (a) angle: this measures the speed at which fibrin builds up and cross linking takes place, (d) maximum amplitude (MA): measures the ultimate strength of the fibrin clot, (e) lysis at 30 min (LY30): defined as the percentage decline in amplitude at 30 min post MA, this represents the degree of fibrinolysis (0-15%). Figure 1, 2, 3 and 4 are graphical and tabulated explanations of the physiological genesis, waveform plot, interpretation, and treatment accordingly.

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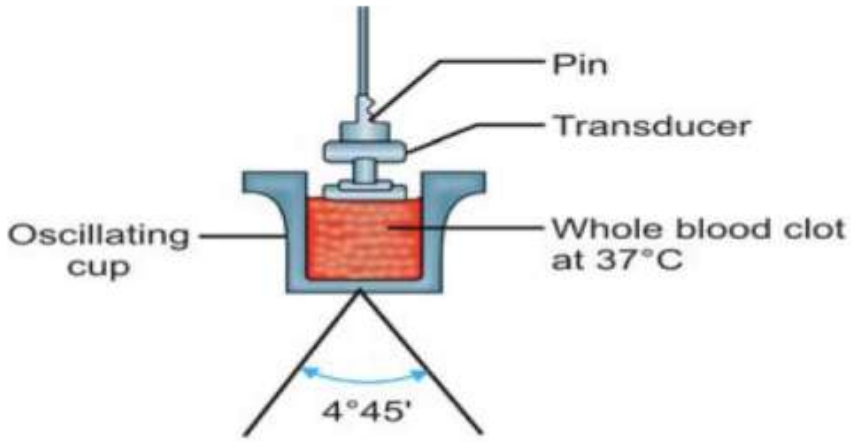


***Figure 1. Demonstrates principles of TEG: Rotation of the pin in the cup containing blood sample and the angle of rotation it makes depends on the viscosity of blood, which is fed to a computer and processed to form a waveform graph***

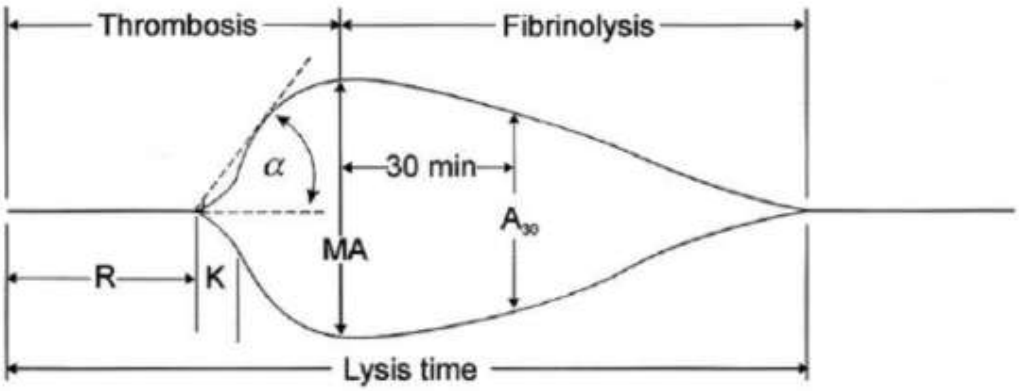


***Figure 2: Characteristics of computer generated TEG waveform graph showing R,K time, angle, MA mean amplitude and Lysis 30***

| TEG Value | Normal* | Description | Measures |
|---|---|---|---|
| TEG-ACT (rapid) | 80 - 140 sec | "Activated clotting time" to initial fibrin formation | clotting factors (extrinsic/intrinsic pathways) |
| R time (conventional) | 5.0 - 10.0 min | "Reaction time" to initial fibrin formation | clotting factors (intrinsic pathway) |
| K time | 1.0 - 3.0 min | "Kinetic time" for fibrin cross linkage to reach 20 mm clot strength | fibrinogen, platelet number |
| α angle | 53.0 - 72.0 degrees | Angle from baseline to slop of tracing that represents clot formation | fibrinogen, platelet number |
| MA | 50.0 - 70.0 mm | Maximum amplitude of tracing | platelet number and function |
| G value | 5.3 - 12.4 dynes/cm$^2$ | Calculated value of clot strength | entire coagulation cascade |
| LY 30 | 0 - 3% | Clot lysis at 30 minutes following MA | fibrinolysis |

***Figure 3: Interpretation of TEG variables***

| TEG Value | Transfuse |
|---|---|
| TEG-ACT > 140 | FFP |
| R time > 10 | FFP |
| K time > 3 | cryoprecipitate |
| α angle < 53 | cryoprecipitate +/- platelets |
| MA < 50 | platelets |
| LY30 > 3% | tranexamic acid |

***Figure 4: Recommended Transfusion strategies depending on TEG values***

**RESULT**

In this prospective pilot observational study, a total of 133 cirrhotic patients undergoing central venous line placement were included (Mean age of 46 years, 90.9% males, ethanol 88.8% was the most common etiology of cirrhosis followed by acute on chronic liver failure (ACLF) HBV related (9%) ACLF ethanol related (6.1%).Table No1.

| **Age (mean +-SD), years** | **46 years** |
|---|---|
| Male, n (%) | 90.9% males |
| Etiology, n (%)of cirrhosis | |
| ethanol | 88.8% |
| ACLF HBV related | 9% |

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| | |
|---|---|
| ACLF ethanol related | 6.1% |
| Child class B | 121 |
| Child class C | 12 |
| Mean APTT | 35+- 3s |
| Mean INR | 3.4 +-2.4 |
| Mean platelet count | 66091 +-17748/cu mm |
| R time | 6.4 +-4.8 min |
| MA value | 55.4 +-16.6 mm |

***Table 1: Salient parameters of the study, including TEG variables***

Patients in Child Turgot Pugh class B & C were 121 and 12 respectively. None of the patients developed clinically significant bleeding requiring transfusion post-procedural (internal jugular venous catheter insertion. None of the patients had any evidence of hypercoagulability.

Bleeding time (BT) and clotting time (CT) were normal in all patients. All parameters on TEG tracing were within normal limits.

The mean activated partial thromboplastin time (APTT) was 35+- 3s (control 28 s), the Mean International normalized ratio. (INR) was 3.4 +-2.4, Mean platelet count was 66091 +-17748/cu mm. Statistical analysis of the data was done to look for associations between different variables especially platelet count and INR and TEG parameters and the presence of post-procedural bleeding. TEG values R time (6.4 +- 4.8 min) and MA value (55.4 +-16.6 mm) were normal in all patients while INR and platelet count were abnormal in all patients. Table no: 2

| **Indicators** | **Mean** | **Deviation** |
|---|---|---|
| INR | 3.4 | 2.4 |
| CHILD Score | 6.667 | 0.8 |
| PLT | 66091 | 17748.9 |
| APTT | 35 | 3.0 |
| TT | 12.273 | 0.6 |
| R | 6.4 | 4.8 |
| K | 3.052 | 1.3 |
| Angle | 48.179 | 16.7 |
| MA | 55.297 | 16.6 |
| LY30 | 0.255 | 1.2 |

***Table 2: TEG variables, with platelet count, INR APTT,CTP variables of severity of cirrhotic patients***

**Correlation between TEG Parameters and CCTs (Conventional Coagulation Parameters)**

Considering the platelet count weak correlations were found with MA ($r=0.150$) ($p>0.05$), and weak correlations were found with angle ($r=0.04$) ($p>0.05$). However the correlations of PT, and INR were weak with R ($r=0.350$) ($p<0.05$) and weak with K ($r=0.122$) ($p>0.05$) and were inverse

with angle (r= -0.43) (p<0.05), MA (r= -0.51) (p<0.05). Thus to summarize, there was no significant correlations between TEG parameters and conventional test of coagulation.

**Correlation between TEG Parameters and CLD Severity**

All TEG parameters in our study except the R-value did not show a significant correlation with the CTP score. Table no: 3

| | **INR** | | **Platelet** | | **CTP score** | |
|---|---|---|---|---|---|---|
| | | | | | | |
| | **co p value** | | **co p value** | | **co p value** | |
| R (min) | 0.370 | <0.05(0.034) | 0.084 | 0.643 | 0.404 | <0.05(0.020) |
| k (min) | 0.121 | 0.501 | 0.062 | 0.733 | -0.513 | 0.757 |
| ά, Angle (degree) | -.429 | <0.05 (0.013) | 0.058 | 0.747 | 0.105 | 0.562 |
| MA (min) | -0.513 | <0.05 | 0.150 | 0.405 | -0.110 | 0.541 |
| | | (0.02) | | | | |

***Table 3: CO: denotes correlation coefficient, table shows statistical correlation between INR, Platelet count and CTP scores with various TEG variables***

All statistical analysis was done using SPSS16 software.

**DISCUSSION**

Hemostatic changes associated with liver disease result in net rebalance of the coagulation system with the reduction of pro-coagulants and fibrinolytic factors (rebalanced hemostasis) rather than true coagulopathy. TEG can more accurately reflect the dynamic effects of pro-coagulants, natural anticoagulants, platelets, and the fibrinolytic pathway and as such may provide a more accurate estimate of underlying coagulopathy.[8,9,10,11] In this study TEG was performed by citrated whole blood without anticoagulation with kaolin activation.

Correlation between platelet count, MA, and angle was found to be weak in our study, however, Agarwal et al, and Kyung Hwa shin et al reported the correlation to be moderate to strong.[12] The difference may be attributable to the small number of patients, the operator-dependent nature of the procedure, and the dynamic nature of the coagulation process in the pathophysiological milieu of the patient at the time of sampling.

The R time correlated with the CTP score in our study, Tripodi et al, reported some parameters of ROTEM were significantly correlated with CTP or MELD score.[13] TEG parameters and severity markers (CTP score, Model for end-stage disease (MELD) weakly correlated in the study by Kyung-Hwa Shin et al. This discrepancy might be due to a weak correlation between PT, INR, and TEG parameters. This probably explains the fact that the PT and INR were significantly abnormal. The TEG parameters (R time, MA, angle) showed a comparatively lesser degree of abnormality explaining the lack of significant post-procedural bleeding despite the deranged INR & platelet count, besides the fact that the physiological

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genesis of PT, INR, and TEG variables are different just hence, comparing them would akin to comparing apples and oranges.

Furthermore, VETs (Viscoelastic tests) suffer from a unique set of pre-analytic and analytic variables that impact test reliability and reproducibility. It is essential that the personnel running the tests are adequately trained and that the equipment is subject to standard quality management procedures for VETs.

Our observations, even though limited to a single experience and small sample size, support to the use of TEG analysis to evaluate the coagulopathy of cirrhotic patients. In many studies, there is a heterogenous population of cirrhotic patients with variations in the stable and unstable CTP score B and C, different etiologies of cirrhosis coexisting comorbidities thus causing alterations in the pathophysiological milieu of the patient during the sampling leading to variations in correlation between TEG and conventional tests of coagulation. When using Viscoelastic tests (VETs) like TEG and ROTEM, some drawbacks have to be considered. First, these tests are generally poorly sensitive to platelet function and mild fibrinolysis disorders,[14] and their sensitivity to fibrinogen levels is quite variable depending on the test methodology.[15] Second, even if considered as being global tests, they do not evaluate the contribution of the endothelium, whose dysfunction likely contributes to hemostasis disturbances.[16] Moreover, similarly to D-dimers and SFC, a correlation between methods is moderate, and inter-laboratory variation is high,[17] but probably improving with the introduction of new methods (ROTEM Sigma®, TEG6S®, and Quantra®). Regarding preanalytical conditions, the time interval between blood collection and VET,[18] anticoagulants and/or additives used in sample tubes, over or under filling of blood tubes, hemolysis and hematocrit can influence the test results. Pneumatic tube transport systems (PTS) may also exert little influence on test results, depending on the acceleration forces of the local system. Therefore, this effect should be evaluated locally when utilization of PTS is considered for blood sampled for VETs. Finally, the accuracy of these tests for bleeding management or thrombotic risk stratification has not been validated in any hyperinflammatory context. It is essential that the personnel running the tests are adequately trained and that the equipment is subject to standard quality management procedures for VETs. Besides, information on the association between bleeding risk and TEG parameters is limited. Therefore large randomized prospective studies should be designed to organize and standardize all available data in this field. To summarize, TEG-guided preprocedural assessment in cirrhotics avoids unnecessary blood transfusions.

Limitations in this study include small sample size, non-estimation of coagulation factors, proteins C and S, antithrombin III, and fibrin degradation products, so we are unable to assess the exact roles of these factors in coagulation dysfunction in ACLF patients. Fibrinogen and platelets both contribute to clot strength. We did not assess fibrinogen levels, and thus cannot comment on the interplay between fibrinogen and platelets in the assessment of clot strength.

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## Conclusion

Our study showed no significant correlation between INR, platelet count (CCTs) compared to TEG parameters in cirrhotic patients and a weak correlation between CTP scores and TEG parameters, however, TEG-guided transfusions represent rationale transfusion practices in cirrhotic patients prior to invasive procedures like central venous line placements as it avoids unnecessary transfusions.

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