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Original Article

Anaesthesia Section

Thromboelastography Parameters Suggestive of Hypercoagulability and its Correlation with Thrombotic Complications in Liver Transplantation- A Retrospective Study

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ABSTRACT

Introduction: Conventional coagulation parameters like, Prothrombin Time (PT), International Normalised Ratio (INR) reflects only the synthesis or status of procoagulant factor levels. Whereas, Thromboelastograph (TEG) reflects ongoing coagulation process and helps in identifying hypocoagulable or hypercoagulable status. The hypercoagulable TEG parameters in the perioperative period can guide the physicians to prevent adverse thrombotic complications, instead of depending on the Conventional Coagulation Tests (CCTs), which has the potential to mislead and may delay appropriate clinical interventions.

Aim: To establish, if correlation exists between TEG parameters suggestive of hypercoagulability and the occurrence of perioperative thrombotic complications and also to see if CCT correlates with hypercoagulable TEG parameters in liver transplantation.

Materials and Methods: This was a retrospective analysis which was done in 32 patients of Diseased Donor Liver Transplantion (DDLT), from August 2018 to September 2019 at tertiary care centre in Chennai, Tamil Nadu, India. Data were analysed for correlation with hypercoagulable TEG parameters and perioperative thrombotic events. Thromboelastograph parameters were also compared with CCT like INR, platelet count. The Mann-Whitney U-test was considered significant if p-value <0.05, at 95% confidence interval.

Results: Amongst the aetiology of the transplanted patients (32), the highest number of patients in the present study had alcoholic liver disease {n=11 (34.37%}. A comparison of paired G values with International Normalised Ratio (INR) showed that there was no significant correlation between G value and INR {r=-0.2, p-value=0.47 (Spearman's rank correlation)}. The G values were compared with platelet counts and a moderate correlation was found (r=0.62, p-value <0.001). The patients with high G traces had platelet counts of normal reference range. There was no correlation between the R time and INR (r-value=0.04), (p-value=0.32).

Conclusion: Thromboelastograph parameters suggestive of hypercoagulability can be useful to predict the occurrence of thrombotic complications in liver transplant surgery. The present study found a moderate correlation was seen between the G value in TEG and platelet counts. No correlation was present between r value and INR value. There is always a possibility of aggravating the thrombotic potential, if the management is solely based upon the PT, INR, platelet count values.

Keywords: International normalised ratio, Point of care coagulation tests, Prothrombin time, Thromboelastography, Thrombotic complications

INTRODUCTION

The widely believed concept of end stage liver disease, projects these patients are hypocoagulable in nature and are prone for complications arising due to bleeding tendencies. But new evidence suggests, cirrhosis patients have decreased synthesis of both procoagulant and anticoagulant factors, tilting the balance towards, rebalanced haemostasis [1]. Thrombocytopenia is partially compensated for by the high levels of von Willebrand Factor with reduced ADAMTS-13 (A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motifs- member 13) [2].

The hypercoagulable Thromboelastograph (TEG) parameters in the perioperative period can guide the physicians to prevent thrombotic complications, instead of depending solely on the Conventional Coagulation Tests (CCTs), which has the potential to mislead and delay appropriate clinical interventions.

Northup P infers that traditional testing like Prothrombin Time (PT)/ International Normalised Ratio (INR) reflects only the synthesis or status of procoagulant factors levels and thus does not correspond to bleeding or clotting risk in this population [2]. Whereas TEG reflects global ongoing coagulation process in-vivo and helps in identifying patients at higher risk of hypocoagulable or hypercoagulable complications in liver transplant [2]. Thromboelastograph is based on the principle that physical properties of a clot determine the patients haemostatic status. Thromboelastograph displays the viscoelastic properties of clot formation in whole blood, via a pin suspended in a cup from a torsion wire connected to a mechanical electrical transducer [3].

In the retrospective analysis of 124 liver transplants, by Krzanicki D et al., it was concluded that CCT have no ability to diagnose hypercoagulability [4]. These patients may end up with complications if hypercoagulability is unrecognised and therefore inappropriately managed [4]. Wesley B et al., state that Maximum Amplitude (MA), can be used to predict hypercoagulability, thereby the potential to develop venous thromboembolism after trauma and surgical intervention [5]. Conventional coagulation tests poorly reflect the whole coagulation system [6]. An important reason for this difference is because conventional tests are performed in plasma without platelets and the cellular component, whereas TEG is done in whole blood [7].

Thromboelastograph parameters correlate with Conventional Coagulation Parameters (CCT) parameters. The TEG r time has been found to correlate with PT, INR, activated Partial Thromboplastin Time (aPTT), TEG k time has been found to correlate with fibrinogen and platelet count, TEG MA value and alpha angle both correlate with platelet count and fibrinogen values, and LY30 values correlate with fibrin degradation products [8]. Another measurement of clot strength, as the end result of the interaction of platelets and fibrin,

is the shear elastic modulus strength or G [9]. G is a computer-generated value, that reflect the strength of the clot from the initial fibrin burst through fibrinolysis G=(5000×amplitude)/(100-amplitude) normal=5.3-12.4 dynes/cm^2. Lesley DP et al., found that, among 530 liver transplantations, baseline and 120 minute postreperfusion G value (increased net clot strength) and LY60 measured at 120 minute postreperfusion time, were predictors of early hepatic artery thrombosis and portal venous thrombosis [10].

The present study aimed to establish if correlation exists between TEG parameters suggestive of hypercoagulability and the occurrence of perioperative thrombotic complications and also to see if CCT correlated with hypercoagulable TEG parameters in liver transplantation.

MATERIALS AND METHODS

This was a record-based retrospective study, conducted in a public sector tertiary care centre at Stanley Medical College, Chennai, Tamil Nadu, India, from August 2018 to September 2019. Institute Ethics Committee approval was obtained (SMC/IEC 22- 2/4/2018).

Inclusion criteria: All the 32 consecutive patients who underwent DDLT from August 2018 to September 2019 were included in the study.

Exclusion criteria: Re-exploration surgeries were excluded from the retrospective analysis.

Parameters:

- The R time represents period of time of latency from start to initial fibrin formation due to effects of Factor VIIa and Tissue Factor that is equated with PT, INR which reads the coagulation the initial stage of fibrin formation.
- Maximum Amplitude (MA) represents the strongest point of fibrin clot and correlates to platelet function. So R time and MA data was used in the inclusion criteria to analyse the coagulation at its initial and final stage. The K time, alpha angle, LY30 were excluded since they interpret amplification of clotting and clot stability respectively.
- The cut-off values for the TEG parameters, suggestive of hypercoagulability, were R time <12 minutes and G value (G>7100 dyne/cm^2) [3].

Data Collection

The TEG analyser haemoscope employing kaolin kit was used in all the DDLT patients as per institutional protocol. Normal reference range of the TEG parameters was R time: 12-26 minutes, k time 3-13 minutes, MA 42-62, G value 3200-7100 dyne/cm^2. The MA data from TEG are a reflection of platelet function, fibrinogen levels, and the interaction between platelets and the coagulation system. All TEG Maximum amplitude data were converted to their respective G values before the analysis (a mathematical formula i.e., G=5000×MA/100 - MA, which is inbuilt in the software) [7].

Data was analysed for correlation with perioperative thrombotic events and hypercoagulable TEG parameters. Thromboelastograph parameters were also compared with CCT. Data from TEG and CCTs (PT, INR, platelet count) were collected at the baseline, during the dissection, anhepatic, and reperfusion stages, when clinical scenario mandated (like excess blood loss and response to product transfusion) 1st postoperative day and 3rd postoperative day. When more than one TEG was performed during a particular stage, the first panel from that stage was used for the analysis. Standard postoperative thromboprophylaxis involved low-molecular-weight heparin administration once the INR was <2.

As per the Institutional criteria, Frozen Fresh Plasma (FFP) was transfused when R time>10 mins, fibrinogen was transfused, if alpha angle <45 degrees, single donor platelets administered when MA <45 mm. Clinical correlation was also taken into account. Packed red cell transfusions were given at a haemoglobin level of 9 gm/dL or less.

The G value is an indicator of clot strength. We identified all patients who met the high G value criteria (G>7100 dyne/cm^2) and had shortened R times (<12 minutes). The TEG data were compared to the results of conventional clotting tests. The authors reviewed medical records for the detection of thrombotic phenomenon like deep venous thrombosis, pulmonary embolism, hepatic/portal arterial and venous thrombosis, cerebral thrombosis in the intraoperative period and first 30 days following transplantation. Intraoperative transfusion data were available for all patients.

STATISTICAL ANALYSIS

After collecting data, it was compiled and entered in Microsoft Excel Sheet. Analysis was done using statistical software, Statistical Package for the Social Sciences (SPSS) version 16.0. All continuous variables were expressed as mean and standard deviation. All categorical variables were expressed as percentages and proportions. The Mann-Whitney U-test was considered significant if p-value <0.05, at 95% confidence interval.

RESULTS

Amongst the aetiology of the transplanted patients, the highest number of patients in the present study had alcoholic liver disease [Table/Fig-1].

Aetiology	Frequency, n (%)
Alcoholic liver disease	11 (34.37%)
Hepatitis B virus related	5 (15.63%)
Hepatitis C virus related	4 (12.50%)
Wilson's disease	4 (12.50%)
Budd chiari syndrome	2 (6.25%)
Autoimmune hepatitis	2 (6.25%)
Hepatocellular carcinoma	4 (12.50%)
Total	32

[Table/Fig-1]: Aetiologies of the end stage liver disease in the study population.

Perioperative thrombotic events: Among the 32 transplant recipients, none of the patients had intraoperative thrombotic events, while five patients had thrombotic complications in the postoperative period. Two patients suffered portal vein thrombosis on the 5th postoperative day, and their INR values were more than 2.5 throughout the postoperative period. These two cases had received 4 units of FFPs on day 3, and were managed by re-exploration and portal vein thrombectomy and heparinisation. These two portal vein thrombosis cases had shortened R time (less than 3.5 minutes) during the intraoperative period, both in the dissection phase. But the G values were normal in the TEG samples.

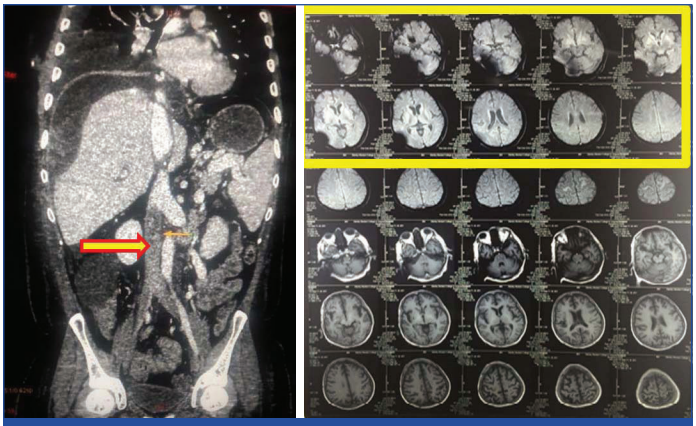
One patient had IVC thrombosis [Table/Fig-2], in the whole infra hepatic region, who had a high G value 17000 dyne/cm^2 on the postoperative day 3, but R time was normal in all TEG. This patient was managed with oral anticoagulant, Dabigatran.

One liver transplant recipient had Osmotic Demyelination Syndrome (ODS) with cerebral embolic infarct in the frontal region [Table/Fig-3]. But none of the TEG samples showed shortened R or high G value.

In one patient, there was sluggish flow in the portal vein, which had high g value with normal r value in the intraoperative TEG. This patient had preoperative portal vein thrombosis for whom intraoperative portal vein thrombectomy was done. Flow patterns normalised in two days after escalating low molecular weight heparin.

None of the patients had hepatic artery thrombosis, DVT or pulmonary emboli.

Analysis of TEG parameters: An 11.2% of the study population had short baseline r time and 10.25% of the study population had high baseline G value [Table/Fig-4]. An 11.2% had shortened R Times and were below the lower reference range for R times



[Table/Fig-2]: Inferior venacava Thrombosis. **[Table/Fig-3]:** Magnetic resonance imaging showing Osmotic Demyelination Syndrome (ODS)/cerebral emboli. (Images from left to right)

(12 minutes) at some stage of the perioperative period. Total 49.1% of the patients had a normal R time on atleast one TEG trace, suggesting these patients are not entirely hypocoagulable.

High percentage of short R time was seen in the dissection phase (50%) in the intraoperative period. In short R time category, 75% of the TEG samples were in 3rd POD. An 18.2% had shortened R Times and were below the lower reference range for R times (12 minutes) at some stage of the perioperative period. Total 49% of the patients had a shortened R time on at least one TEG trace [Table/Fig-4,5].

Parameter	Frequency (n,%)	Median (dynes/cm²)	Range (dynes/cm²)
R time			
Short R time	4 (11.2%)	8.2	7.5-10.2
Normal R time	15 (49.1%)	11.2	10.4-14.5
Long R time	13 (39.7%)	19.2	15.7-22.5
G value			
High G value	3 (10.25%)	9226	8062-14012
Normal G value	12 (38.62%)	6227	5226-7641
Low G value	17 (51.13%)	3126	1021-4126

[Table/Fig-4]: Proportion of baseline r-times and G values (n=32).

Parameters	Dissection N (%)	Anhepatic N (%)	Reperfusion N (%)	1st POD N (%)	3rd POD N (%)
R time					
Short R time (n=4)	2 (50%)	1 (25%)	1 (25%)	1 (25%)	3 (75%)
Normal R time (n=15)	6 (40%)	6 (40%)	3 (20%)	7 (46.7%)	8 (53.3%)
Long R time (n=13)	1 (10%)	3 (20%)	10 (70%)	4 (30.7%)	9 (69.3%)
G value					
High G value (n=3)	1 (33%)	1 (33%)	1 (34%)	1 (34%)	2 (66%)
Normal G value (n=12)	4 (33%)	6 (50%)	2 (17%)	7 (58.3%)	5 (41.7%)
Low G value (n=17)	3 (20%)	3 (20%)	11 (60%)	8 (47%)	9 (53%)

[Table/Fig-5]: R time and G time in different phases.

[Table/Fig-6] gives the number of blood products given and the corresponding G values. The median haemoglobin for the whole study population was 8.7 gm. Among the patients who had normal or low G value the median Hb was 9. Study population who had high G value had a median Hb value of 9.2. Median platelets were 112×10³ cells/dL in patients who had high G value.

A comparison of paired G values with point-of-care INR tests showed that there was no significant correlation between the two parameters {r=-0.2, p-value=0.47 (Spearman's rank correlation)}. G values were compared with platelet counts, and a high correlation was found {r=0.62, p-value <0.001 (Spearman's rank correlation)}. The patients with high G traces had platelet counts within the normal reference range [Table/Fig-7]. No correlation was found between the R time and INR (r=0.04, p-value=0.32).

Variables	Study population Median (IQR)	Normal or low G value Median (IQR)	High G value Median (IQR)	p-value
Laboratory tests				
Haemoglobin (gm/dL)	8.7 (7.8-10.4)	9 (8.2-10.7)	9.2 (8.9-10.9)	0.03
Platelets (10³/µL)	79 (35-114.4)	89 (49.2-118.2)	112 (89.1-130.2)	0.002
International normalised ratio	1.86 (1.5-2.8)	2.10 (1.8-2.5)	1.7 (1.3-2.2)	0.47
Fibrinogen (g/L)	2 (1-2.5)	1.8 (1.2-2.8)	2.9 (2.1-3.82)	0.006
Products				
Packed cells (units)	3 (0-8)	3 (1-6)	3 (0-6)	0.7
Frozen fresh plasma (units)	4 (0-10)	4 (2-6)	1 (0-4)	0.03
Platelets (units)	2 (1-2.5)	1 (0-2)	0 (0-2)	0.21

[Table/Fig-6]: Association between various laboratory parameters and G value.

Laboratory tests	Normal or low G value Median (IQR)	High G value Median (IQR)	r-value	p-value
International normalised ratio	2.10 (1.8-2.5)	1.7 (1.3-2.2)	-0.2	0.47
Platelet count (10³/µL)	89 (49.2-118.2)	112 (89.1-130.2)	0.62	<0.001

[Table/Fig-7]: Correlation between various laboratory parameters and G value.

DISCUSSION

Hypercoagulability can lead to serious thromboembolic complications within the liver transplant graft vessels, which is life-threatening. Most often thrombotic complications were overlooked, because of anticipation of bleeding tendencies and probable overcorrection. The present retrospective study was designed to analyse if thrombotic complications had occurred in patients whose TEG parameters had suggested hypercoagulability. There was moderate correlation between the G value in TEG and platelet counts. No correlation was present between r value and INR value.

Five out 32 patients had thrombotic complications, out of which 2 cases of portal vein thrombosis had prolonged INR (>2), for which 4 units of FFPs were given postoperatively. It would have been useful if a modification in the thromboprophylactic strategy using both TEG parameters and CCT was employed before clinical interventions.

Krzanicki D et al., were able to demonstrate significant intraoperative TEG evidence of hypercoagulability and reported that it is common (16-86%) in liver transplantation [3]. The CCT have a limited ability to diagnose hypercoagulability because PT/INR and activated Partial Thromboplastin Time (aPTT) are sensitive to deficiencies of procoagulant factors, but not the concomitant reduction of anticoagulant factors found in liver disease [1]. High INR does not exclude the possibility that a patient has a thrombotic tendency and TEG evidence of enhanced coagulability [5,6]. Another problem is that the INR value varies between laboratories in patients with liver disease [7,8]. So, interventions done based on the raised INR value, might pose thrombotic risk to the patient.

Five patients in the present study had thrombotic complications. But statistical significance could not be arrived since the sample size was small. And also, as per the institutional protocol both CCTs and TEG were done in the first three perioperative days only and not beyond. In the postoperative period, the time at which coagulation pathophysiology stabilises in a liver transplant recipient,

is uncertain. Interventions done based on the CCTs might pose thrombotic risk to the patient. Importantly, in the postoperative period (at 5 and 10 days after surgery), in-vitro thrombin generation tests showed an increased rate and total amount of thrombin generation. Decreased levels of protein C and S and persistently high levels of factors VIII are likely related to this hypercoagulable status [12,13]. Whether this in vitro hypercoagulable status has a direct link to thrombotic complications has not yet been studied and requires further research.

The R time represents the time to initial fibrin formation, and a short R time indicates an accelerated rate of fibrin formation. G value is an indicator of clot strength. A clot with a high tensile strength, i.e., high G value is more resistant to both mechanical and enzymatic degradation. Therefore, R time and G value can predict the risk of thrombosis [8].

Conventional coagulation tests are still measured along with TEG, because its role in monitoring coagulation is not totally debatable. Prothrombin time does not consider thrombomodulin, a transmembrane protein on vascular endothelial cells that down regulates thrombin generation. This is the main physiological activator of protein C. By failing to measure the anticoagulant factors effect on thrombin generation, the balance of coagulation is inaccurately measured by PT, so there are chances of misrepresenting the risk of haemorrhage [5].

The use of perioperative coagulation monitoring using TEG/ROTEM for targeted management of coagulopathy in OLT now forms part of the European Society of Anaesthesia (ESA) guidelines for the management of massive bleeding [11-13].

Major surgery itself can induce a hypercoagulable state and this hypercoagulability has been implicated previously in the pathogenesis of postoperative thrombotic complications. The PT and aPTT are misleading in this subset of population as they measure only the decreased synthesis of procoagulant factors [2,4]. Furthermore, these tests are performed on plasma rather than whole blood and thus do not reflect endothelial tissue factor, blood flow, platelet function, and other factors that contribute to clot formation in-vivo.

The G values and point-of-care INR tests showed that there was no significant correlation between the two parameters in the present study. A recent systematic review and meta-analysis of 8939 postsurgical patients, in whom 717 thrombotic events occurred, suggests that elevated MA was a statistically significant indicator for hypercoagulability [5].

Other limitations of PT/INR are that it is not possible to estimate the overall strength and stability of the clot because these tests are read at the initiation of fibrin polymerisation. This initial fibrin polymerisation can happen at very low levels of thrombin generation of approximately 10 to 20 nM i.e., <5% of the total thrombin that can be generated [9]. Wide derangements in INR may not represent a defect in coagulation [10].

Though TEG is a good test to monitor bed side coagulation status, but it is necessary to use standard coagulation tests to identify coagulation abnormalities with a good statistical significance. TEG may give an overall representation of haemostasis; however, it cannot replace the CCT [14,15].

Recipients are susceptible to life threatening thrombotic complications if hypercoagulability is undiagnosed and inadequately treated, particularly in the immediate postoperative period. When there is evidence of an excessively shortened R time and a normal or high MA or G value, then it may be reasonable to give a small intravenous dose (3000-5000 U) of heparin [16,17]. It is advisable to avoid prohaemostatic agents, including FFP, platelets, and antifibrinolytics, when there is TEG evidence of hypercoagulability. Although antithrombotic regimens carry the risk of bleeding complications, these may be justified by the severity of the thrombotic syndromes [18,19].

Limitation(s)

The limitations of the present study are its retrospective design and the sample size was only 32. All the consecutive liver transplant surgeries were included, irrespective of the aetiology of the liver dysfunction including patients with thrombotic aetiology. Only kaolin TEG parameters were used, since heparinase TEG was used only in selective patients in the study centre.

CONCLUSION(S)

Hypercoagulable TEG parameters can point toward the occurrence of thrombotic complications in liver transplant surgery. The present study found a moderate correlation between the G value in TEG and platelet counts. No correlation was present between r value and INR value. In in this study, even though there is lack of correlation between the TEG and CCT parameters which were studied, it is safer to use both the tests before, clinical interventions. The potential of TEG in identifying patients at risk of thromboembolism and improving the quality of thromboprophylaxis is a promising avenue for clinical research.

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