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WORD COUNT	4677	TIME SUBMITTED	06-FEB-2023 11:23AM
		PAPER ID	96293325

Name of Journal: *World Journal of Gastroenterology*
Manuscript NO: 80874
Manuscript Type: MINIREVIEWS

Approach to thromboelastography based transfusion in cirrhosis: An alternative perspective of coagulation disorders

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Abstract

Viscoelastic tests, specifically thromboelastography and rotational thromboelastometry are increasingly being used in the management of post-operative bleeding in surgical intensive care units (ICUs). However, life-threatening bleeds may complicate the clinical course of many patients admitted to medical ICUs, especially those with underlying liver dysfunction. Patients with liver cirrhosis have multiple coagulation abnormalities, which can lead to bleeding or thrombotic complications. Compared to conventional coagulation tests, a comprehensive depiction of the coagulation process and point-of-care availability are advantages favouring these devices, which may aid physicians in making a rapid diagnosis and instituting early interventions. These tests may help predict bleeding and rationalize the use of blood and blood products in these patients.

Key Words: Bleeding; Chronic liver disease; Liver cirrhosis; Thromboelastography; Viscoelastic tests

Kataria S, Juneja D, Singh O. Approach to thromboelastography based transfusion in cirrhosis: An alternative perspective of coagulation disorders. *World J Gastroenterol* 2023; In press

Core Tip: Viscoelastic haemostatic assays are increasingly used as "point-of-care" tests, providing a real-time, dynamic decisiveness of complex coagulation aberrations in cirrhotic patients. In cirrhosis, all patients undergoing a high-risk invasive procedure or actively bleeding should undergo thromboelastography (TEG) on evaluation, if available. Any reasonable TEG-based strategy will likely represent an improvement over strategies using traditional coagulation tests. The best approach will be to use the TEG supplemented by platelet count and fibrinogen. TEG is a promising diagnostic modality and may help in predicting bleeding and rationalizing the use of blood and blood products in these patients.

INTRODUCTION

The liver is essential to maintaining haemostasis[1]. Patients with cirrhosis may demonstrate altered coagulation and be traditionally considered "auto-anticoagulated"[2]. However, the current understanding of coagulopathy states that patients with cirrhosis have a re-balanced coagulation state[3]. This balance is precarious due to alterations in the hepatic synthesis of pro-and anticoagulant factors. The resiliency of the haemostatic system can be further decreased in cirrhotic patients by acute clinical conditions like systemic infection, altered volume status and renal function.

Given our current acquaintance with coagulation status in cirrhosis patients, there is considerable inquisitiveness in tests of coagulation that could provide a truly global view of the coagulation system. Conventional coagulation tests (CCTs) like prothrombin time (PT) and activated partial thromboplastin time (aPTT) are indicators of general liver dysfunction. They fail to seize the totality of *in vivo* coagulation dysfunction, such as the effect of blood flow, endothelial tissue factor (TF), platelet function, and use of plasma rather than whole blood[4,5]. Despite such concerns, these CCTs are commonly used to drive clinical decisions.

Thromboelastography (TEG) provides a more physiologically accurate assessment of the coagulation system. TEG has been used effectively as a rapid, point-of-care test to assess hypercoagulable, hypocoagulable, and re-balanced coagulation status to evaluate blood transfusion requirement, selection of an anticoagulant and suggest whether anticoagulation is, if at all required[6].

However, the precise strategy for TEG to guide blood product transfusion is unclear. Although the literature is repleted with prospective data demonstrating the superiority of TEG over CCTs for non-surgical patients in terms of the requirement of blood transfusion, mortality benefit, if any, has never been established[7-9]. The present article aims to review TEG's current evidence and clinical significance in guiding blood transfusion in cirrhosis patients.

HAEMOSTATIC SYSTEM IN LIVER DISEASE

As per the cell-based model of haemostasis, coagulation occurs not as a "cascade" but in three overlapping stages: (1) The initiation phase ensues on TF carrying cells. If the procoagulant stimulus is sufficiently strong, factors Xa, IXa, and thrombin are formed in adequate levels to initiate the coagulation process successfully; (2) The amplification phase occurs as the activity moves from the TF-carrying cell to the platelet surface. The procoagulant stimulus is intensified in which platelets attach, are activated, and hoard activated cofactors on their surfaces; and (3) The propagation phase in which the "tenase" and "prothrombinase" complexes gathered on the platelet surface generate large amounts of thrombin, necessary to form a haemostatic fibrin clot[10].

In cirrhosis, all these three phases are affected by hepatic synthetic dysfunction and portal hypertension, resulting in a delicate state of 'new equilibrium' as depicted in Figure 1[11]. However, this balance can be altered by concomitant conditions such as sepsis or acute kidney injury (AKI) due to the interaction of platelets and released inflammatory mediators, as shown in Figure 2. Thus, the coagulation profile in cirrhotic patients is dynamic, with the resolution of global deficiencies once the critical illness resolves. This cell-based model also explains why regional haemostatic changes at the injury site do not override the systemic haemostatic equilibrium. Consequently, CCTs may remain unchanged in patients with a liver disorder with clinically evident bleeding.

According to Hoffman's concept of the cell-based model, bleeding can arise from disorders of primary haemostasis (abnormal platelet plug formation) or secondary haemostasis (reduced thrombin generation and subsequent fibrin clot formation). The liver plays a crucial role in maintaining primary and secondary haemostasis[11]. In fact, the liver is the site of synthesis of most coagulation factors except for von Willebrand factor (vWF), factor VIII (partly synthesized in the liver) and calcium[12].

Bleeding complications in cirrhotic patients may occur due to haemostatic failure or non-haemostatic causes. Spontaneous haemostasis-related bleeding' has recently been introduced to distinguish bleeding due to haemostatic anomalies from bleeding related to portal hypertension, traumatic or peptic ulcers. It is described as an unprovoked haemorrhagic of an unexplained cause. However, it should be emphasized that

spontaneous bleeding is uncommon in patients with cirrhosis, and bleeding is primarily related to portal hypertension caused by increased portal pressure rather than haemostatic failure. This was conclusively demonstrated by the inability of recombinant factor VII to achieve better control of variceal rebleeding[13,14]. Notably, a bleed not primarily caused by haemostatic failure can evolve into a haemostatic bleed due to severe blood loss and consumptive coagulopathy. Bleeding (tertiary haemostasis disorder) can also be due to premature platelet or fibrin clot dissolution or excessive fibrinolysis, which in cirrhotic patients has been anointed as "accelerated intravascular coagulation and fibrinolysis" (AICF). AICF is evident as mucosal or puncture wound bleeding, and the pathophysiology of AICF is not entirely understood. Hyperfibrinolysis parallels the severity of liver disease; mild systemic fibrinolysis is encountered in 30%-45% of cirrhotic patients, and clinically detectable fibrinolysis is witnessed in 5%-10% of the patients. AICF can be distinguished from disseminated intravascular coagulation by increased factor VIII levels (Figure 1)[15,16]. The three phases of coagulation in liver disease resulting in a "rebalancing" of haemostasis are given in Table 1[17,18].

Bleeding has been the primary prevailing concern for a considerable time in cirrhotic patients. However, thrombotic complications are recently being increasingly acknowledged and are attributed to shifts in the haemostatic balance. The relative risk of venous thromboembolism (VTE) in patients with cirrhosis was 1.74 (95% CI: 1.54-1.95) *vs* patients without non-cirrhotic liver in a case-control study[19]. These conclusions were mirrored by Wu *et al*[20], which showed an increased likelihood of VTE in cirrhosis [odds ratio (OR) 1.23 in compensated cirrhotic patients; OR 1.39 in decompensated cirrhotic patients]. Dysfibrinogenemia (*i.e.*, altered fibrinogen) may render decreased permeability of the formed clot apart from other factors. It may even confer hypercoagulable features, manifesting as macro and micro-thrombotic complications. The hypercoagulable state frequently occurs in cirrhosis due to primary biliary cholangitis, non-alcoholic fatty liver disease, and primary sclerosing cholangitis[21].

The most common macro-thrombotic presentation in patients with liver disease is portal vein thrombosis (PVT), occurring in 8% to 18% of cirrhosis18. The incidence of PVT

increases with deteriorating liver dysfunction and decreased portal flow. Deep venous thrombosis and pulmonary embolism (PE) are other macro-thrombotic complications which have been reported in 5% of hospitalized patients with chronic liver disease (CLD)[17,22]. Micro-thrombotic complications include intrahepatic microthrombi ("parenchymal extinction"), resulting in nodules, porto-pulmonary hypertension, and cirrhosis as an ischemic/reinjury process. These often merit exigent considerations of anticoagulant usage.

TESTS OF COAGULATION IN CIRRHOSIS

Presently all available laboratory haemostasis measures have significant limitations in patients with liver disease. Paradigmatic is the case of cirrhotic patients in which PT or international normalized ratio (INR) was designed to manage warfarin-treated patients based on the activity of an added commercially available thromboplastin reagent. PT and aPTT only indicate the outset of thrombin generation; however, they do not allude to the state of enzymatic coagulation. PT/INR has been validated as a prognostic marker for mortality in liver disease but has never been validated to predict bleeding risk or guide transfusions, especially for pre-procedure risk measures[14]. Nonetheless, it has been used as a surrogate marker for estimating bleeding risk in cirrhosis, for many decades, on a routine basis due to lack of something better. The arbitrary 'cut-offs' used as clinical targets for preventing bleeding are not recommended or supported by scientific evidence. Furthermore, using fresh frozen plasma (FFP) to normalize a raised INR in cirrhosis does not alter thrombin production (factor II) but exacerbates portal hypertension[23-25].

Thrombocytopenia is the most commonly encountered haematological abnormality in patients with liver disease. Platelet count thresholds are often specified for invasive procedures in patients with severe cirrhosis-related thrombocytopenia. In vitro data suggests that a threshold of 50-55 × 10^9/L is vital for adequate platelet procoagulant activity, and levels below this range fail to promote thrombin generation[26]. However, the platelet function associated with primary haemostasis (*i.e.*, adhesiveness and aggregation) has not been evaluated. Current guidelines and expert opinion recommend

considering platelet-raising treatments before high-risk procedures or in patients with active bleeding with platelet counts < 50000 × 106/L. However, there is no firm evidence that prophylactic platelet transfusion to achieve this target enhances haemostasis[15,23].

As mentioned previously, platelet count does not account for other factors affecting platelet function in cirrhosis[27], which include:

Uremic platelet dysfunction (*e.g.*, hepatorenal syndrome): Diminished platelet activity with decreased serotonin in alpha granules and dysregulated metabolism of thromboxane A2.

Anaemia: With less than 25% haematocrit, erythrocyte concentration is inadequate to facilitate platelet margination, impairing the clotting process.

Sepsis and endotoxemia due to bacterial translocation.

Recently, fibrinogen levels have become more meaningful than INR to couple with platelet counts for evaluating the bleeding risk. The Clauss method for detecting fibrinogen is turbidimetric and relies on thrombin-induced fibrin formation. Nevertheless, fibrinogen levels do not account for the synthesis of abnormal fibrinogen in cirrhotic patients caused by hypersialylation of the fibrinogen, leading to impaired fibrinogen-to-fibrin conversion[28]. In the setting of trauma surgery in patients without the underlying liver disorder, administration of fibrinogen factor to accomplish levels of fibrinogen > 200 mg/dL is associated with better effectual haemostasis. However, in routine clinical practice, the most agreed-upon cut-off of fibrinogen in cirrhotic patients with active bleeding is > 120 mg/dL[29]. In cirrhotic patients, spontaneous or procedure-related bleeding is relatively common when plasma fibrinogen levels are less than 100 mg/dL. Whether this relationship is causal or reflects disease severity is unclear. As such, the available evidence suggests that tests measuring clot formation and strength (*i.e.*, fibrinogen) may have better predictive value for bleeding events than coagulation initiation tests[29,30].

Primary hyperfibrinolysis is an increasingly vital pathophysiological process in CLD, resulting in an increased risk of variceal bleeding. D-dimer is a nonspecific marker of fibrin degradation. While evidence suggests that elevated D-dimer indicates

hyperfibrinolysis and can predict gastrointestinal bleeding in this population, elevated D-dimer alone provides limited information regarding an individual's fibrinolytic state[31,32].

Thrombin generation assays (TGAs) evaluate the time of thrombin generation and its decline when plasma is triggered by TF and phospholipids. Thus, TGA can reflect the activity of both pro-and anticoagulant factors[33,34]. Nevertheless, clinical trials are needed to test this conjecture. Similarly to PT and aPTT, TGA is performed on plasma instead of whole blood. However, because of their method, TGA approximates the *in vivo* coagulation balance better than CCTs.

TEG quantitatively assesses the capability of whole blood to form a clot, providing a comprehensive picture of coagulation status compared to standard laboratory tests, which are confined to developing the first fibrin strands. However, TEG is insensitive to the platelet adhesive/aggregating activity of vWF and the anticoagulant action of the protein C and protein S system; it may lead to an underestimation of haemostatic capacity[17].

PRINCIPLES OF TEG

The principle of this *in vitro* test is to detect and quantify dynamic changes in the viscoelastic properties of a whole blood sample during clotting under low shear stress (Figure 3A). TEG results are depicted as 2-dimensional graphs, with time on the x-axis and amplitude (in millimeters) on the y-axis (Figure 3B). A normal TEG trace analogizes a cognac glass lying on the side (Figure 4)[17]. An evident prolongation of R is associated with clotting factor levels of 30% or less[35]. Different activators can be added to the blood to assess better various aspects of the clotting cascade (Table 4). Conventional TEG involves clot initiation by adding kaolin, simulating the intrinsic coagulation pathway. In contrast, rapid TEG involves the addition of kaolin and TF, causing massive thrombin burst and providing initial results (K time) within 6 min and alpha angle/MA within 15 min[36,37]. Thus, the results of rapid TEG can be achieved approximately 10 min earlier than the kaolin TEG and about 30 min earlier than CCTs[37]. This could guide critical

resuscitations more competently, enabling real-time monitoring and goal-directed therapy. Though the activators reduce the test turnaround time (*e.g.*, kaolin), the sensitivity of VETs could be blunted, and subtle changes in coagulation and clot lysis might not be detected[17].

Correlation of CCTs and VETs

A strong correlation between TEG measures of clot formation and clot strength and conventional fibrinogen level has been observed in CLD who are critically ill. Nevertheless, weak or unpredictable correlations exist between TEG and CCTs measuring coagulation initiation (*i.e.*, TEG R-time and PT/INR/aPTT), TEG and conventional platelet count and measures of fibrinolysis (TEG LY30 and traditional D-dimer)[38-40]. The absence of correlation between PT/INR and R may be explained by several elements, such as the use of different activators, the use of whole blood *vs* plasma, and the fact that R-time, unlike INR, reflects the balance of both pro- and anticoagulants. This supports the evidence that clotting initiation and speed measures are challenging to interpret in this cohort, while TEG MA and conventional fibrinogen may be more reliable. Nonetheless, the results of these tests should always be correlated with the clinical situations, bearing clearly in mind that numbers must always be interpreted.

CLINICAL APPLICATIONS OF TEG IN LIVER DISEASE

TEG and invasive procedures in patients with cirrhosis

Bleeding complications after the invasive procedure are foreknowing in cirrhotic patients, though the incidence varies widely[41]. Although the risk of bleeding after the procedure is related to alterations in clotting factors, the risk is also inherent to a given procedure (Table 4) and the clinical situation[41]. In cirrhotic patients with acute illness or ACLF, the association between clotting tests and bleeding events may not be as apparent/evident as in stable patients. Moreover, managing complications, such as sepsis or AKI, instead of correcting haemostatic abnormality may result in improved outcomes. A retrospective study revealed that AKI was the only independent risk factor

for post-paracentesis hemoperitoneum. In contrast, no significant difference was observed with CCTs (platelet count and INR levels) between patients with or without this complication[42].

Three recent randomized trials conducted in cirrhotic patients undergoing invasive procedures demonstrated a decreased requirement for prophylactic blood product transfusions using TEG-guided transfusions compared to standard test-based protocols[7-9]. However, they could not demonstrate any relationship between abnormal TEG tracing and bleeding, primarily due to the scarcity of documented bleeding events. Similarly, TEG did not help to predict the inability to control bleeding or prevent rebleeding. Also, no impact on other clinically relevant outcomes was observed. Moreover, each study used various transfusion protocols, making comparisons difficult and challenging for physicians to decide whether the lower cut-off for transfusion would have been more beneficial. In another study on cirrhotic patients undergoing various invasive procedures without prophylactic administration of blood products, even with abnormal CCT and TEG R-time and maximum amplitude (MA), one patient experienced bleeding (0.7%)[43]. Also, a recent study in 90 patients with cirrhosis undergoing central venous cannulation demonstrated that a prolonged TEG K-time (≥ 3.05) minutes could not predict bleeding complications (accuracy 69.4%, P = 0.047)[44]. Thus, it indicates that post-procedural bleeding events are rare and indirectly implies that uncorrected coagulopathy does not modify the post-procedural outcome. Nevertheless, coagulation tests can be utilized to evaluate the severity of liver disease or the patient's baseline haemostatic function and to provide an initial benchmark to guide management in the case of post-procedural bleeding.

Most of the latest guidelines recommend against using CCTs and correction of coagulopathy before undergoing common gastrointestinal procedures in patients with stable cirrhosis. Also, there are no recommendations for or against using TEG in such patient populations (Table 5)[15,23,45,46]. However, in patients with severe abnormal coagulation parameters or thrombocytopenia undergoing a moderate to high-risk

procedure, clinical judgment about prophylactic blood transfusions should comprise discussions about possible benefits and risks[7,15], as depicted in Figure 5.

Use of TEG in cirrhosis with active bleeding

Bleeding related to portal hypertension, variceal and non-variceal, is primarily managed with local measures such as endoscopic band ligation, laser or injection therapy, and by lowering portal pressure using vasoactive drugs than pro-haemostatic therapy. The observation that variceal bleeding in patients on anticoagulants was not severe or associated with worse outcomes compared to patients who are not on anticoagulants confirms that the role of the haemostatic system in variceal bleeding, if present, is minor[47]. Randomized controlled studies have shown that in cirrhotic patients with variceal and non-variceal bleeding, using VETs to guide blood product transfusion requirements did not result in superior control of bleeding, morbidity or mortality benefit compared to CCTs to guide transfusion[48-50]. However, the transfusion requirement was significantly lower in the VET group. Although the study by Kumar *et al*[51] demonstrated significantly lower intensive care unit (ICU) stay using TEG-guided resuscitation, there was no difference in the hospital stay or other outcomes. Nevertheless, it is questionable whether, in active variceal bleeding, VETs-guided pro-haemostatic therapy is beneficial and contributes to the control of bleed when the standard treatment with vasoactive drugs and endoscopic therapy is provided.

If local measures and portal pressure-lowering drugs cannot contain bleeding, the decision to correct coagulopathy by transfusing blood products should be viewed case-to-case basis[13]. Since VETs are quicker and more accurate than CCTs and provide a more practical understanding of fibrinolysis, which may indicate the need to start antifibrinolytic therapy, they have a theoretical advantage over CCTs in guiding active bleeding.

Unlike pressure-driven bleeding, AICF is basically due to disturbed haemostatic mechanisms[15]. Antifibrinolytic therapy, such as epsilon aminocaproic acid or tranexamic acid, is potentially effective, inhibiting the fibrin clot's dissolution. Neither

agent is thought to have inherent hypercoagulable risks except for a pre-existing pathological thrombus such as PVT. The 'native TEG' can detect this condition in liver disease patients by the presence of an increase in LY30[17].

TEG-based algorithms may allow targeted and specific blood product transfusions in patients with severe bleeding, such as FFP or cryoprecipitates[17]. However, the threshold values of various aspects of the VETs to trigger transfusion are yet to be validated in appropriate clinical studies.

Heparin-like effect in cirrhosis

A stressful condition such as surgery or sepsis can trigger the release of endogenous glycosaminoglycans (GAGs) (*e.g.* heparin sulphate and dermatan sulphate) from the endothelium glycocalyx layer or mast cell, which, when shed, retain their anticoagulant activity[52,53]. It is thought to be an adaptive reaction to maintain the patency of progressively procoagulant microvasculature through endogenous heparinization, thus preventing spontaneous thrombosis.

Endogenous GAGs may increase the bleeding risk in a few patients. This was illustrated by Senzolo *et al*[54], where GAGs affected haemostasis in cirrhotic patients with sepsis. Another prospective analysis further confirmed the presence of endogenous heparinoid in patients with cirrhosis and acute variceal bleeding and was found to be associated with bleeding-related mortality[55]. After appropriate therapy, endogenous heparinoids are cleared with normalization of the coagulation profile, thus emphasizing the association between the coagulation cascade and inflammatory pathways.

Although CCTs are insensitive to this effect, the native TEG is extremely sensitive to the presence of heparin and heparin-like substances, which is detectable by an increased R-time on TEG analysis[56]. Adding heparinase I, which cleaves heparin-like compounds, can demonstrate a heparin-like effect due to raised GAGs, correlating with an anti-Xa activity[57]. Therefore, heparinase TEG will normalize the prolongation of the R-value observed on native TEG. Thus, TEG helps differentiate between a coagulation factor

deficiency and heparin-produced coagulopathy using heparinase-modified TEG and the native TEG.

TEG in orthotopic liver transplant

Kang *et al*[58] at the University of Pittsburgh introduced TEG-based algorithms to guide blood product transfusion for correcting coagulopathy in OLT in the early 1980s. It was shown that TEG reduced transfusion requirements by 33% compared with a historical cohort. Secondary endpoints like re-intervention for bleeding, AKI, or hemodynamic instability were significantly lower in the VET group. Although numerous studies have described the usefulness of VET in lowering transfusion requirements in LT, most of these studies commonly compared the results with historical cohorts having a relatively high baseline transfusion rate[59,60]. A recent study of sixty LT patients showed no significant differences with and without VET monitoring though overall transfusion was low, with many patients receiving no transfusion[61]. As bleeding and transfusion management continues to evolve, the results of these earlier studies cannot be easily employed in the present era. Also, the thresholds described for VET for initiating transfusion are still to be established, and values may be substantially above the normal ranges before an intervention is advised.

A significant proportion of patients undergoing LT will inevitably have enormous blood loss, and VET can be helpful in such occasions to enable goal-targeted treatment and assess the effectiveness of any therapeutic intervention. The short turnaround times of VET (10-20 min) are vital for directing therapy and averting inappropriate transfusion during surgery and in the ICU. Monitoring coagulation with functional fibrinogen TEG for goal-directed fibrinogen substitution seems more appropriate and avoids unnecessary platelet transfusions. This is particularly significant in LT as platelet administration is associated with a substantial decline in one-year survival[62].

Fibrinolysis and orthotopic liver transplant

It is well known that increased fibrinolytic activity can occur at any juncture during LT. However, it is significantly enhanced during the an-hepatic period due to a lack of tissue plasminogen activator (tPA) clearance[63]. Also, it may become most enunciated in the post-reperfusion stage by an erratic upsurge in tPA, leading to diffuse uncontrolled bleeding due to primary hyperfibrinolysis[64]. If the graft function is good, hyperfibrinolysis after reperfusion is usually self-limiting and does not require treatment. However, in the presence of an inadequately functioning graft, it may persist[65]. During LT, prophylactic antifibrinolytic agents were often used in earlier years because of the high mortality associated with tremendous blood loss, and the potential peril associated with antifibrinolytics was small if any. As massive bleeding is less frequent nowadays, there is a preference towards the selective use, only in high-risk patients, of antifibrinolytics. Systemic fibrinolysis can be efficiently detected using VETs (demonstrated by increased or worsening LY30 and LY60), which may not be possible with CCTs. Thus, the transfusion requirement may be decreased with VET use in liver transplantation, where hyperfibrinolysis commonly occurs.

TEG and hypercoagulability

The risk of developing VTE is similar in cirrhotic and non-cirrhotic[15,23]. Hypercoagulability on TEG can either be due to shortened R or K, enhanced clot strength (MA), or a combination of both. Huang *et al*[66] observed a significantly shorter R in cirrhosis with non-malignancy PVT. Zanetto *et al*[67] found that elevated MA was associated with PVT in cirrhotic patients with hepatocellular carcinoma. Given that malignancy itself could also cause hypercoagulation, the clinical use of TEG in this setting may be questionable. In another study, hypercoagulability was defined as the presence of at least two of the following criteria: reduced R, reduced K, raised α, or increased MA as compared to the reference range, hypercoagulability was not associated with PVT in cirrhosis[68].

In cirrhotic patients with raised CCTs, we tend to avoid prophylactic anticoagulation in hospitalized patients. Presently European Association for the Study of the Liver

Clinical Practice Guidelines in cirrhosis do not recommend using viscoelastic tests to identify the risk of VTE[23]; further prospective studies may explore the utility of TEG in predicting the risk of VTE during hospitalization.

Acute intracardiac and PE is rare, although a well-recognized, potentially fatal complication of LT, associated with high mortality. Krzanicki *et al*[69] demonstrated hypercoagulation state is quite common during liver transplantation. A review of 27 case reports of TE in orthotopic LT showed that the TEG was hypercoagulable in greater than 70% of cases[70]. Also, hypercoagulable TEG patterns correlated well with the formation of intracardiac thrombi. Indeed, a quick inspection of the rapid TEG after 5 or 10 min of clotting time might predict thrombosis, demonstrated by the increase in the maximum amplitude. The clinical importance of hypercoagulability on TEG during LT is yet to be recognized. However, it would appear unreasonable to transfuse blood products or avoid anticoagulants based on raised CCTs, when a hypercoagulable state is seen on TEG.

Patients with cirrhosis and VTE should be treated with anticoagulation, similar to other non-cirrhotic patients. In patients at increased risk of bleeding, unfractionated heparin (UFH) is the preferred anticoagulant owing to its shorter half-life (45 min) and availability of an effective antidote-protamine sulfate. aPTT is the most commonly used test to monitor UFH therapy. Although the anti-Xa activity assay is used explicitly for monitoring low molecular weight heparins, as they primarily inhibit factor Xa, it may also be superior to aPTT for titrating UFH[71].

Given that heparin activity mainly depends on the liver-derived activity of the heparin cofactor antithrombin III, monitoring heparin therapy with CCT in patients with cirrhosis is challenging. TEG may provide a better representation of *in vivo* heparin effect than aPTT[72,73]. A higher concentration of heparin tends to be associated with larger R-values, with a dose-dependent effect. Levels of anti-factor Xa activity correlate with the R-value of the TEG. In addition, TEG can help diagnose and treat heparin-induced coagulopathy. Thus, platelet and enzymatic hypercoagulability display on TEG mandates aggressive treatment with a direct thrombin inhibitor.

LIMITATIONS OF TEG

Like any other investigation, TEG is also associated with certain limitations. It measures blood coagulation *in vitro* instead of flow within a vasculature and does not reflect the endothelium's function in coagulation. Inherently, the test is less sensitive to platelet adhesion, von Willebrand's factor interactions and protein C and S system. TEG results do not correlate with the effects of hypothermia, as TEG is performed at 37 °C. Kaolin cannot effectively detect alterations in the extrinsic coagulation pathway, as it only activates the intrinsic coagulation pathway. Thus, INR is still the gold standard for monitoring warfarin therapy, and TEG may overlook a clinically significant coagulopathy. TEG detects fibrinolysis only when the tPA levels are five times normal. Studies have shown that using plasmin-α2-antiplasmin as a biomarker for fibrinolysis can detect fibrinolytic activation in over 80% of severely injured patients, whereas TEG detected hyperfibrinolysis in only 5%-18% of the cases. Each TEG run generally takes 30 min to an hour, and only a few cases can run simultaneously, unlike CCT. Therefore, optimizing TEG use is essential in providing appropriate patient laboratory testing. Additionally, it should be performed by trained personnel and is susceptible to technical variations.

CONCLUSION

VETs of haemostasis are increasingly used as "point-of-care" tests, providing a real-time, dynamic decisiveness of complex coagulation aberrations (hypocoagulability, hypercoagulability and hyperfibrinolysis) in cirrhotic patients. In cirrhosis, all patients undergoing a high-risk invasive procedure or actively bleeding should undergo TEG on evaluation, if available. Any reasonable TEG-based strategy will likely represent an improvement over strategies using traditional coagulation tests. The best approach will be to use the TEG supplemented by platelet count and fibrinogen. TEG is a promising diagnostic modality, but given the limited clinical trials, there are no consensus guidelines for using TEG. Further prospective studies are required to validate citified TEG algorithms in the context of patients with cirrhosis.

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