An approach to TEG based transfusion in cirrhosis: An alternative perspective of coagulation disorders

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INTRODUCTION

The liver is essential to maintaining haemostasis1. 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 state3. 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 diminished in cirrhosis patients by acute clinical conditions like systemic infection, altered volume status and renal function.

Given our current understanding of coagulation status in cirrhosis patients, there is considerable inquisitiveness in tests of coagulation that could provide a truly global picture 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 capture the entirety of the in-vivo coagulation dysfunction, such as the effect of blood flow, endothelial tissue factor, platelet function, and use of plasma rather than whole blood4,5. Despite such concerns, these CCTs are commonly used to guide 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 evaluate hypercoagulable, hypocoagulable, and re-balanced coagulation status to guide blood transfusion, indicate the requirement of anticoagulation if any, and for the selection of anticoagulation therapy6.

However, the precise strategy for TEG to guide blood product transfusion needs to be clarified. 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 established7-9. 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

According to the Cell-Based Model of Haemostasis, coagulation occurs not as a "cascade" but in three overlapping stages; 1) The initiation phase occurs on tissue factor (TF) bearing 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 action moves from the TF-bearing cell to the platelet surface. The procoagulant stimulus is amplified in which platelets adhere, are activated, and accumulate activated cofactors on their surfaces; 3) The propagation phase in which the "tenase" and "prothrombinase" complexes assembled on the platelet surface generate large amounts of thrombin, necessary to form a haemostatic fibrin clot10.

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 111. 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 coagulation defects once the acute condition resolves. This cell-based model also explains why local haemostatic changes at the injury site do not override the systemic haemostatic balance. Consequently, CCTs may remain the same in a patient with liver disease with clinically apparent bleeding.

Figure 1: Concept of re-balanced haemostasis in cirrhosis.
ACLF: Acute on chronic liver failure; AKI: Acute Kidney injury; DIC: Disseminated intravascular coagulation; NO: Nitric oxide; VTE: Venous thromboembolism; t-PA: Tissue plasminogen activator; TAFI: Thrombin-activated fibrinolysis inhibitor.

Figure 2: Dynamic Coagulation Profile in Cirrhosis
ACLF: Acute on chronic liver failure; DAMP: Damage-associated molecular patterns; PAMP: Pathogen-associated molecular patterns; TF: Tissue factor

As per Hoffman's concept of the cell-based model, bleeding can occur if there is abnormal platelet plug formation or reduced thrombin generation and subsequent fibrin clot formation at the site of vascular injury (disorders of primary and secondary haemostasis, respectively). The liver plays a vital role in blood coagulation in primary and secondary haemostasis11. 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 calcium2.

Patients with cirrhosis may experience bleeding complications due to haemostatic failure or non-haemostatic causes. The term 'spontaneous haemostasis-related bleeding' in cirrhosis has recently been introduced to distinguish bleeding due to haemostatic abnormalities from bleeding related to portal hypertension, traumatic or iatrogenic vascular lesions, or peptic ulcers. It is defined as an unprovoked haemorrhagic event of an unexplained cause. However, it should be emphasized that patients with liver disease experience fewer spontaneous bleeding events and that bleeding is related chiefly to portal hypertension in most patients with cirrhosis. Portal hypertensive bleeding is primarily driven by increased portal pressure and is less relevant to abnormal haemostasis. This was conclusively shown by the lack of protection conferred by recombinant factor VII against variceal rebleeding13,14. Notably, a bleed not primarily caused by haemostatic failure can become a haemostatic bleed due to severe blood loss and consumption of haemostatic factors. Bleeding (tertiary haemostasis disorder) can also be due to premature platelet or fibrin clot dissolution or excessive fibrinolysis, which in liver disease has been anointed 'accelerated intravascular coagulation and fibrinolysis' (AICF).

The mechanism behind AICF is uncertain, evident as mucosal or puncture wound bleeding. Hyperfibrinolysis parallels liver dysfunction; mild systemic fibrinolysis is found in 30-45% of cirrhotic patients, and clinically evident fibrinolysis is seen in 5-10% of the patients. AICF can be distinguished from disseminated intravascular coagulation (DIC) by increased factor VIII levels (Figure 1) 16,17. The 3 phases of coagulation in liver disease resulting in a "re-balancing" of haemostasis are given in Table 118,19.

Hemostasis stage Hypocoagulable state Hypercoagulable state

Primary hemostasis:

Platelet activation and interaction with injured endothelium §

Thrombocytopenia

1) Decreased amount

ü Splenic sequestration

ü Decreased thrombopoietin levels

ü Bone marrow suppression

ü Autoantibody destruction

2) Poor function

ü Uraemia

ü Changes to the vessel wall phospholipid composition

ü Anaemia (HB <7gm/dl):

ü decreased margination § Low levels of ADAMTS

13

§ Increased levels of von

Willebrand factor

§ Increased number of

activated platelets

Secondary hemostasis:

Fibrin clot formation § Low levels of factors II, V, VII, IX, X, and XI

§ Low levels of fibrinogen

§ Vitamin K deficiency (malabsorption in cholestatic disorders) § Elevated levels of factor VIII

§ Decreased levels of proteins C and S

§ Decreased levels of antithrombin, and heparin cofactor II

Fibrinolysis: § Accelerated intravascular coagulation and fibrinolysis:

1) Low levels of factor XIII and thrombin-activated fibrinolysis inhibitor

2) Elevated levels of tissue plasminogen activator

3) Decreased level of α2-antiplasmin

4) Dysfibrinogenemia § Low plasminogen levels

§ Dysfibrinogenemia

§ High plasminogen activator inhibitor

Table 1: The 3 phases of coagulation in liver disease

Bleeding issues have been the prevailing clinical problem for many years, but inappropriate clotting is nowadays recognized and is attributed to changes in the haemostatic equilibrium. In a large case-control study, the relative risk of venous thromboembolism (VTE) in patients with cirrhosis was found to be 1.74 (95% confidence interval [CI] 1.54–1.95) compared with patients without non-cirrhotic liver disease20. These conclusions were mirrored by Wu and Nguyen et al., which showed an increased risk of VTE in cirrhosis (odds ratio, OR 1.23 in compensated cirrhotic patients; OR 1.39 in decompensated cirrhotic patients21. Dysfibrinogenemia (i.e., an altered fibrinogen molecule) may cause

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 cholangitis22.

Portal vein thrombosis (PVT) is the most common macro-thrombotic manifestation in patients with liver disease, occurring in 8% to 18% of patients with cirrhosis18. The risk of PVT increases with worsening liver dysfunction and decreased portal flow. Deep venous thrombosis (DVT) and pulmonary embolism (PE) are other forms of macro-thrombotic complications reported in 5% of hospitalized patients with chronic liver disease (CLD) 18,23. Micro-thrombotic complications include intrahepatic microthrombi ("parenchymal extinction"), resulting in nodules, porto-pulmonary hypertension, and cirrhosis as an ischemic/reinjury process. These often warrant exigent considerations of anticoagulant therapy use.

TESTS OF COAGULATION IN CIRRHOSIS

All currently available laboratory measures of haemostasis have significant limitations in liver disease patients. 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 measures14. 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 correct a prolonged INR in cirrhosis does not change thrombin production (factor II) but exacerbates portal hypertension15,24,25.

Thrombocytopenia is the most commonly encountered haematological abnormality in patients with liver disease. Platelet count thresholds are often stipulated for invasive procedures in patients with severe cirrhosis-related thrombocytopenia. In vitro data suggests that a threshold of 50-55 × 109/L is necessary for adequate platelet procoagulant function, and levels below this range fail to promote thrombin generation26. However, the platelet function related to primary haemostasis (i.e., adhesiveness and aggregation) has not been evaluated. Current guidelines and expert opinion recommend consideration of platelet-raising treatments before high-risk procedures or when active bleeding is experienced in patients with platelet counts below 50,000 x 106/L. However, there is no firm evidence that prophylactic platelet transfusion improves haemostatic potential15,16.

As mentioned previously, platelet count does not account for other factors affecting platelet function in cirrhosis27, which include:

• Uremic platelet dysfunction (e.g., hepatorenal syndrome): Decreased platelet

function with reduced serotonin in alpha granules and dysregulated metabolism of thromboxane A2

• Anaemia: With less than 25% haematocrit, erythrocyte concentration is insufficient

to push platelets towards the vessel, impairing coagulation

• Sepsis and endotoxemia due to bacterial translocation

Recently, fibrinogen levels have emerged as potentially more meaningful than INR to couple with platelet levels as a measure of bleeding risk. The Clauss method for determining fibrinogen is turbidimetric and depends 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 molecule, which may lead to defective fibrinogen-to-fibrin conversion28. In the setting of trauma surgery in patients without underlying liver disease, fibrinogen replacement to achieve fibrinogen levels >200 mg/dl is associated with more effective haemostasis. However, in clinical practice, the most agreed-upon cut-off in the actively bleeding patient with cirrhosis is >120 mg/dl29. Plasma fibrinogen levels less than 100 mg/dl are associated with spontaneous and procedure-related bleeding in patients with cirrhosis. 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. During LT, though there is a good correlation with Clauss at baseline, but after graft reperfusion, fibrinogen levels can fall below 100 mg/dL, and it this correlation does not hold well and could potentially result in overestimation.29,30.

Primary hyperfibrinolysis is an increasingly crucial 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 state31,32.

Thrombin generation assays (TGAs) assess the time of thrombin generation and its decline when small amounts of tissue factor and phospholipids trigger plasma. Thus, TGA can reflect the activity of both pro-and anticoagulant factors 33-34. However, clinical trials are required to test this hypothesis. Because of their method, TGA approximates the in-vivo coagulation balance better than CCTs. Although similar to PT and aPTT, TGA is performed on plasma rather than whole blood.

TEG quantitatively measures the ability of whole blood to form a clot, providing a comprehensive view of coagulation patterns compared to standard laboratory tests, which are limited to developing the first fibrin strands. However, TEG is insensitive to the platelet adhesive protein VWF and the anticoagulant action of the protein C and protein S system; it may lead to an underestimation of haemostatic capacity.18

Principles of Thromboelastography

The principle of this in vitro test is to detect and quantify dynamic changes in the viscoelastic properties of a blood sample during clotting under low shear stress (Figure 3a). TEG results are plotted as 2-dimensional graphs, with time on the x-axis and amplitude (in millimetres) on the y-axis (Figure 3b). A

standard TEG tracing with normal results resembles a cognac glass lying on the side (Figure 4)18. A pronounced prolongation of R is associated with clotting factor levels of 30% or less35. Various activators can be used to assess better different portions 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 tissue factor, causing massive thrombin burst and providing initial results (K time) within 6 min and alpha angle/MA within 15 min36,37. Thus, the results of rapid TEG can be achieved approximately 10 minutes earlier than the kaolin TEG and about 30 minutes earlier than CCTs37. 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 (viscoelastic tests) VETs could be blunted, and subtle changes in coagulation and clot lysis might not be detected18.

(B)

Figure 3: A) Basis of the thromboelastograph; B) Thromboelastograph tracing and the relevant parameters (Kaolin activated)

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Figure 4: Tracing of TEG in various conditions

Nomenclature Definition Function Significance Most closely related CCT

Reaction time or

R-time Time (minutes) to reach an amplitude of 2mm Clot initiation Informs about enzymatic reaction leading to thrombin and fibrin generation.

ü Increased R-time factor deficiency or reduced function, resulting in hypocoagulability

ü Shortened R-time factor hypercoagulability PT and APTT

K-time Time (minutes) from 2- to 20-mm amplitude Clot kinetics Depicts rate of clot development–fibrin polymerization, cross-linking, and platelet interaction.

ü Long K-time hypocoagulability

ü Short K-time hypercoagulability Fibrinogen level and platelet count

Angle or α Slope between R and K Clot kinetics Also depicts the kinetics of clot development.

ü Low-angle hypocoagulability

ü High-angle hypercoagulability

MA Highest level of amplitude achieved by the clot Clot strength Provides assessment of overall clot strength Platelet count and Fibrinogen levels

Coagulation index Composite indicator of coagulation profile A linear combination of the above parameters serving as a global view of the patient's haemostatic profile

ü Increased in hypercoagulable states

ü Decreased in hypocoagulable states

LY30 Degree of lysis (%) 30 min after MA is reached Clot stability Measure of fibrinolysis.

ü Above normal LY30 suggests hyperfibrinolysis No equivalent test

Table 2: TEG components and their clinical implications

TEG Channel Activator Function

Native TEG None Theoretically most sensitive to subtle coagulopathic changes and hyperfibrinolysis.

Conventional TEG Kaolin Activates clotting cascade to expedite results

Rapid TEG Tissue factor + kaolin Activates clotting cascade to expedite results

Functional Fibrinogen TEG GP IIb/IIIa inhibitor Inhibits platelets to isolate the contribution of fibrinogen

Heparinase TEG Heparinase Inhibits heparin; the presence of heparin (endogenous or exogenous) is suggested when this channel shows improved clotting compared to other channels.

Table 3: Various types of TEG assays

Correlation of CCTs and VETs

In acutely ill patients with CLD, strong associations have been observed between TEG measures of clot formation and clot strength and conventional fibrinogen level tests. Nevertheless, weak or inconsistent associations are observed between TEG/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 factors, such as the use of different activators, specimens (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

Procedure-related bleeding is common in cirrhosis patients, but the incidence varies widely41. The risk of bleeding following an invasive procedure is based on factors not reflected by alterations in haemostatic parameters alone but also inherent to a given procedure (table 4) and the clinical situation41. Patients with acute complications of cirrhosis, or patients with ACLF, may represent a subset where the absence of an association between coagulation tests and bleeding risk may not be as straightforward as in stable patients. Moreover, managing complications, such as infection or AKI, rather than haemostatic abnormality may improve patient outcomes. A retrospective study showed that AKI was the only independent risk factor for post-paracentesis hemoperitoneum, with platelet count and INR values not significantly different between patients with or without this complication42.

High-Risk Procedures Intermediate Risk Procedures Lower-Risk Procedures

Intrabdominal/orthopaedic/cardiac surgery Percutaneous endoscopic gastrostomy Paracentesis

Brian or spinal surgery Percutaneous or transjugular liver biopsy Thoracentesis

Intracranial catheter insertion Transjugular intrahepatic portosystemic shunt

Central line placement

Endoscopic mucosal resection or Endoscopic submucosal dissection
Endoscopy (e.g. percutaneous gastrostomy placement, cystogastrostomy, biliary sphincterotomy) Endoscopy (e.g., diagnostic, variceal ligation, uncomplicated polypectomy)
Complicated polypectomy Percutaneous biopsy of extra-hepatic organ or lesions Cardiac catheterization
Natural orifice transluminal endoscopic surgery Trans-arterial or percutaneous HCC therapies Hepatic venous pressure gradient measurement
Lumbar puncture

Table 4: Procedural bleeding risk in patients with cirrhosis

Three recent prospective studies carried out in patients with cirrhosis undergoing invasive procedures, randomized to receive TEG-guided or standard test-based blood product transfusions, clearly demonstrated a decreased requirement for prophylactic blood product transfusions with the use of TEG7-9. Regardless, they could not reveal any association between TEG alterations and bleeding, mainly due to the scarcity of recorded bleeding events. Similarly, TEG did not help to predict failure to control bleeding or prevent rebleeding. No other impact was seen on clinically relevant outcomes. 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, in patients with cirrhosis with abnormal CCT and abnormal TEG R-time and MA undergoing a wide array of invasive procedures without prophylactic administration of blood products, one patient experienced bleeding (0.7%)43. A recent study did demonstrate that a TEG K-time of 3.05 minutes or more was a weak predictor of bleeding in

90 patients with cirrhosis undergoing central venous cannulation (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 appear to alter the post-procedural outcome. Nevertheless, coagulation tests can be used to assess the severity of liver disease or the patient's baseline haemostatic status 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)15,16,45,46. However, in patients with severe derangements in coagulation or thrombocytopenia undergoing a moderate to high-risk procedure, decisions about prophylactic blood transfusions should include discussions about potential benefits and risks7,16, as depicted in figure 5.

Parameters EASL 2022 ISTH 2021 AASLD 2021 AGA 2021
PT/INR Against routine evaluation and correction Against correction Against correction Against routine evaluation and correction a
Platelet count Against correction b Against correction b Against correction Against routine evaluation and correction a
Fibrinogen Against routine correction Against routine evaluation Against correction No specific recommendation
TEG Against routine evaluation c Do not use routinely
Do not use routinely

No specific recommendation

Table 5: Thresholds for coagulation parameters prior to high-risk procedures in patients with cirrhosis.

a: In case of severe coagulopathy, prophylactic blood transfusions should be considered case-to-case by evaluating potential benefits and risks in consultation with a haematologist.

b: If the bleeding cannot be controlled by the local haemostasis method, administration of platelet concentrate or thrombopoietin receptor agonist can be considered if the platelet count is <50,000 x 106/L.

c: It may provide a baseline coagulation status and guide in the case of bleeding events.

Figure 5: Algorithm for coagulation factor administration in a cirrhotic patient undergoing an invasive procedure with coagulopathy. FF: Functional Fibrinogen; MA: Maximum amplitude; TPO: Thrombopoietin

a: Limited evidence of TEG for high risk procedures.

Use of TEG in cirrhosis with active bleeding

Bleeding related to portal hypertension, variceal and non-variceal, is managed with local measures and pharmacological therapies to reduce portal pressure rather than pro-haemostatic treatment. The observation that patients on anticoagulants at the time of a variceal bleed do not bleed more or have worse outcomes than patients who are not on anticoagulants confirms that the role of the haemostatic system in variceal bleeding, if present, is minor47. Randomized controlled studies have shown that using VETs to determine transfusion requirements in patients with cirrhosis with variceal and non-variceal bleeding did not result in superior control of bleeding, morbidity or

mortality benefit compared to routine diagnostic tests to guide transfusion48-50. However, blood product transfusion was significantly lower in the VET group. Although the study by Kumar et al. demonstrated significantly lower ICU stay using TEG-guided resuscitation, there was no difference in the hospital stay or other outcomes51. Nevertheless, it is questionable whether VETs help guide transfusion in actively bleeding patients in this setting and whether pro-haemostatic therapy contributes to stopping a variceal bleed when the standard treatment with vasoactive drugs and endoscopic therapy is administered.

In the possibility of failure to control haemorrhage with portal hypertension-lowering drugs, the decision to correct haemostasis should be considered on a case-to-case basis13. Since VETs are quicker and more accurate than routine diagnostic tests and provide information on fibrinolysis, which may prompt antifibrinolytic therapy, they have a theoretical advantage over CCTs in guiding active bleeding.

Unlike pressure-driven bleeding, AICF is basically due to disturbed haemostatic mechanisms16. 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%18.

Using algorithms based on TEG may facilitate targeted transfusions with haemostatic agents, such as FFP, in patients with severe bleeding18. However,

the threshold values of these tests to target transfusion requirements need to be established in appropriate clinical trials.

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 activity52,53. It is thought to be an adaptive response to keep a progressively more procoagulant microvasculature open through endogenous heparinization, thus preventing spontaneous thrombosis.

These endogenous GAGs may exhibit an increased bleeding risk for some patients. Senzolo et al. showed that these GAGs affect haemostasis in patients with cirrhosis and bacterial infection54. Another prospective observational study on patients with cirrhosis and acute variceal bleeding has confirmed the presence of endogenous heparinoids and their association with bleeding-related mortality 55. After appropriate treatment, the coagulation profile resolves, and endogenous heparinoids are cleared, emphasizing the complementary association of the coagulation cascade and the inflammatory pathways.

Although CCTs are insensitive to this Effect, the native TEG is extremely sensitive to the presence of heparin and heparin-like substances. This is detectable by a prolonged R-value on TEG analysis56. Adding heparinase I, which cleaves heparin-like compounds, can reveal the presence of a heparin-like effect (HLE) due to increased GAGs, correlating with an anti-Xa activity57.

Heparinase TEG will normalize the prolongation of the R-value. Thus, TEG helps distinguish between a coagulation factor deficiency and heparin-produced prolongation using heparinase-modified TEG in parallel with the native TEG.

Figure 6: Algorithm for guiding blood product transfusion by TEG. Cryo: Cryoprecipitate; FFP: Fresh Frozen Plasma; Hep R: Heparinase R-Time; CI: Coagulation index; MA: Maximum amplitude

TEG in orthotopic LT

Kang et al. at the University of Pittsburgh introduced TEG-guided transfusion algorithms to treat coagulopathy in OLT in the early 1980s58. 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 there are numerous reports of the success of VET monitoring in reducing transfusion requirements in LT, most of these studies commonly compared the results with historical cohorts having a relatively high baseline transfusion rate59,60. A more recent prospective study of sixty LT patients showed no significant differences with and without VET monitoring though overall transfusion was low, with many patients receiving no transfusion61. As bleeding and transfusion management continues to evolve, it is not easy to extrapolate the results of these earlier studies to the current scenario. Also, the transfusion trigger thresholds described for VET have yet to be validated,

and values may need to be substantially outside the normal ranges before an intervention is indicated.

The proportion of patients undergoing LT will inevitably have massive blood loss, and there is no doubt that VET can be helpful in these circumstances to facilitate goal-directed therapy and assess the efficacy of any treatment intervention. The short turnaround times of VET (10–20 minutes) are essential for guiding therapy and preventing inappropriate transfusion during surgery and in the intensive care unit (ICU). Monitoring coagulation with Functional Fibrinogen TEG for goal-directed fibrinogen substitution seems more appropriate and avoids unnecessary platelet transfusions. This is especially important in LT as platelet transfusion is associated with considerable reductions in one-year survival62.

Fibrinolysis and Orthotopic LT

It is known that enhanced fibrinolytic activity can occur at any point during LT, particularly during the an-hepatic period, due to a lack of tissue plasminogen activator (tPA) clearance63. This may be further increased during the post-reperfusion stage by a dramatic increase in tPA, leading to diffuse uncontrolled bleeding due to primary hyperfibrinolysis64. In good graft function, hyperfibrinolysis after reperfusion is usually self-limiting and does not require treatment. However, in the presence of a poorly functional or marginal graft, it may persist65. Routine use of prophylactic antifibrinolytic agents was common in the early history of LT, as the mortality associated with massive blood loss was high, and any potential risk associated with the use of antifibrinolytics was small in comparison. Now that massive bleeding is less frequent, there is a

preference towards the selective use, only in high-risk patients, of antifibrinolytics. VETs are particularly useful for detecting the presence of systemic fibrinolysis (demonstrated by increase or worsening LY30 and LY60), which may not be possible with CCT. 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-cirrhotic15,16. Hypercoagulability on TEG can either be due to shortened R or K, increased clot strength (MA), or a combination of both. Huang et al. found a significantly shorter R in cirrhosis with non-malignancy PVT66. Zanetto et al. found that higher MA was associated with PVT in cirrhotic patients with hepatocellular carcinoma67. Given that malignancy itself could also cause hypercoagulation, the clinical use of TEG in this setting may be questionable. In another study, where *hypercoagulability* was defined as the presence of at least two of the following criteria: shortened R, shortened K, increased α, or increased MA as compared to the reference range, hypercoagulability was not associated with PVT in cirrhosis68.

In cirrhotic patients with raised CCTs, we tend to avoid prophylactic anticoagulation in hospitalized patients. Presently EASL Clinical Practice Guidelines in cirrhosis do not recommend using viscoelastic tests to identify the risk of VTE15; further prospective studies may explore the utility of TEG in predicting the risk of VTE during hospitalization.

The sudden development of intracardiac and pulmonary emboli is a rare but well-recognized and potentially fatal complication of LT associated with high mortality. Krzanicki et al. demonstrated hypercoagulation state is quite

common during liver transplantation69. In a review of 27 case reports of TE in orthotopic LT, the TEG was hypercoagulable in more than 70% of cases70. There appears to be some association of intracardiac thrombi with hypercoagulable TEG profiles. Indeed, a quick review 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 seem unreasonable to give blood products or avoid anticoagulant therapy based on raised CCTs, when a hypercoagulable state is seen on TEG.

It is well known that patients with cirrhosis and VTE should be treated with anticoagulation, similar to other non-cirrhotic patients. In patients at high risk of bleeding, unfractionated heparin (UFH) is often used due to its short half-life and reversibility with protamine. APTT is the most commonly used test to monitor UFH therapy. In contrast, the anti-Xa activity assay is of specific value for monitoring low molecular weight heparins (LMWHs), as they predominantly inhibit FXa. It may also be superior to aPTT for monitoring UFH71.

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 aPTT72,73. 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:

• TEG 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 systems.

• 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 tissue plasminogen activator 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 minutes to an hour, and only a few cases can run simultaneously, unlike conventional lab coagulation testing. Therefore, optimizing TEG use is essential in providing appropriate patient laboratory testing.

• 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.

1.	*fibrinogen levels can fall below 100 mg/dL,*	Seminars in Thrombosis and Hemostasis / Full Text - Thieme https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0035-1550434	Originality