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BLOOD MANAGEMENT (KA TANAKA, SECTION EDITOR)

Update on Coagulation Monitoring in Liver Transplantation

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Abstract

Purpose of Review This article provides an update on coagulation monitoring for patients undergoing liver transplantation and focuses on emerging data from the newest generation of viscoelastic testing devices.

Recent Findings New generation, cartridge-based viscoelastic testing (VET) devices (TEG 6s, ROTEM sigma, Quantra with QStat cartridge) offer less inter-operator variability with greater ease of use and application at the point of care. Data on use of these cartridge-based VET devices in liver transplantation is limited.

Summary The coagulopathy of liver disease affects both procoagulant and anticoagulant factors, resulting in a 'rebalanced hemostasis'. The phases of liver transplantation present unique and dynamic challenges to blood management in these patients. VET is the preferred method of coagulation monitoring in liver transplantation with demonstrated benefits in decreased blood transfusion requirements, blood loss, and cost. Newer cartridge-based VET technologies have purported improvements over older technologies. More thorough investigation is needed in the use of these newer VET devices in liver transplantation.

Keywords Coagulopathy of liver disease · Liver transplantation · Rebalanced hemostasis · Viscoelastic testing · Fibrinolysis

Introduction

Liver transplantation surgery has historically been associated with large-volume blood loss resulting in the requirement for transfusion of large amounts of blood products. Additionally, the coagulopathy of liver disease is complex, with cirrhotic patients being both at increased risk for bleeding as well as clotting. Decreased blood loss during liver transplantation due to advancements in both surgical techniques and anesthetic management [1–3] has allowed focus to shift to a more targeted approach to the transfusion of blood component therapy for these patients. The use of point-of-care viscoelastic testing (VET) has emerged as the primary monitoring modality to provide real-time data on coagulation status during liver transplantation. Newer generation VET devices have proposed benefits over the older generation of VET devices. This review provides a summary of the most recent literature available on coagulation monitoring in liver transplantation.

Coagulopathy of Liver Disease

The coagulopathy of patients with end-stage liver disease is multifaceted. Attention has historically focused on cirrhotic patients' increased risk of bleeding, with particular focus on transfusion of fresh frozen plasma (FFP) to correct decreased levels of coagulation factors in this patient population. The international normalized ratio (INR) remains a major factor in the model of end-stage liver disease (MELD) scoring system that contributes to patient status on the organ allocation waitlist. However, patients with end-stage liver disease have profound disturbances in components of coagulation that contribute to bleeding as well as components that contribute to clotting [4, 5]. This interplay is often referred to as the 'rebalanced' state of coagulation in the patient with end-stage liver disease.

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Platelet Derangements

End-stage liver disease is associated with thrombocytopenia, due largely to portal hypertension resulting in congestive splenomegaly and platelet sequestration as well as reduced levels of thrombopoietin (TPO) [6]. Additionally, defects in platelet function resulting from endothelial release of nitric oxide and prostacyclin may increase the propensity for bleeding. Alternatively, increased von Willebrand Factor (vWF) and decreased levels of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13, which cleaves bound platelet-vWF) levels shift the platelet activation and aggregation back towards normal, even in the setting of severe thrombocytopenia [7]. Thus, the decision to transfuse platelets should not depend on platelet count alone.

Coagulation Derangements

Decreased synthetic function of the cirrhotic liver leads to a marked decrease in both pro-coagulant factors (factors II, V, VII, X, and XI and fibrinogen) and anti-coagulant factors (protein C, protein S, and antithrombin). Dysfibrinogenemia in cirrhosis may also increase the risk of bleeding, while Factor VIII levels may be increased due to increased vWF (which binds factor VIII and protects it from cleavage by plasma proteases) and increase the risk of clot formation.

Fibrinolysis Derangements

Perturbations in synthetic function of the cirrhotic liver also leads to reduction in levels of thrombin-activatable fibrinolysis inhibitor (TAFI) and alpha-2-antiplasmin which, along with increased levels of tissue plasminogen activator (t-PA) due to decreased hepato-endothelial clearance, increases fibrinolysis in this patient population. Low levels of plasminogen and increased plasminogen activator inhibitor (PAI) counteract this effect.

Other Coagulation Concerns Related to Liver Transplantation

Additional factors contribute to coagulopathy during liver transplantation surgery. The etiology of the recipient's liver disease and comorbid conditions also impact the patient's propensity for bleeding or clotting. The presence of antiphospholipid antibodies in patients with hepatitis C and primary biliary cirrhosis place these patients at increased risk of thrombosis [8, 9]. Increased incidence of hypercoagulability on intraoperative thromboelastography (TEG) has been demonstrated in recipients with cholestatic disease (primary sclerosing cholangitis and primary biliary cirrhosis) and acute hepatic failure [10]. Thrombotic risk is also increased in the setting of nonalcoholic steatohepatitis (NASH), independent of other predisposing factors such as diabetes and obesity, due in part to an increase in factor VIII and decrease in protein C in this population [11, 12]. In alcoholic liver disease, the coagulation profile can be further complicated in the setting of acute alcohol intoxication as well as chronic alcohol consumption. In the acutely intoxicated state, patients will often present with prolonged initiation of clot formation contributing to bleeding, while simultaneously presenting with elevated levels of factors VII and VIII and PAI-1(which inhibits fibrinolysis) contributing to increased risk of thrombosis. Factor VII decreases in the setting of chronic alcoholic use [13, 14]. Patients with acute liver failure may develop significant coagulation derangements with profound decreases in coagulation factors and fibrinogen levels with hepatocellular injury along with thrombocytopenia [15, 16]; however, compensatory mechanisms can develop even in acute liver failure to counteract the propensity for bleeding, such as an increase in vWF and decrease in ADAMTS13 [17].

Sequelae of liver disease can also present unique coagulation complications. As portal hypertension progresses, thrombocytopenia may worsen secondary to platelet sequestration in the spleen. Patients with hepatocellular carcinoma demonstrate increased levels of thrombomodulin and reduced activation of fibrinolysis, placing them as a higher thromboembolic risk [18]. In end-stage liver disease patients with spontaneous bacterial peritonitis (SPB), the release of cytokines such as TNF-α, IL-1 and IL-6 worsen platelet dysfunction and coagulation derangement. Bleeding risk is further increased by hyperfibrinolysis, clotting factor consumption, and the production of heparin-like substances during an active infection. Furthermore, the presence of SBP may worsen portal hypertension, increasing variceal formation and bleeding [19].

Due to the increased risk of thromboembolism in patients with liver disease, up to 16% of liver transplant recipients may present for surgery with portal vein thrombosis (PVT) [20]. A subset of these patients, or those presenting with deep venous thrombosis (DVT), may be on anticoagulation therapy for which reversal should be considered (e.g. with prothrombin complex concentrate (PCC) for warfarin reversal) [21]. The patients may be managed with a direct oral anticoagulation (DOAC) medication that may require reversal in the setting of urgent presentation to the operating room in the setting of an accepted organ. There are currently two specific medications that are approved as DOAC-reversal agents. Idarucizumab (Praxbind®) may be administered for the reversal of the direct thrombin inhibitor dabigatran (Pradaxa®) and andexenet alfa (Andexxa®) for the reversal

of direct factor Xa inhibitors apixaban (Eliquis®) and rivaroxaban (Xarelto®). Both reversal agents should be used with caution as they confer some risk of thrombosis within 30 days of administration (4.8% with idarucizumab and 10% with andexenet alpha) [22].

Each phase of liver transplantation surgery presents unique and dynamic challenges to coagulation. During the dissection phase, there is often a degree of blood loss with the potential for massive hemorrhage, depending on the severity of the patient's coagulopathy, as well as pre-existing portal hypertension [23]. During the anhepatic phase, there is an absence of synthetic ability to produce clotting factors. Reperfusion of the new allograft may be associated with coagulopathic bleeding due to acidosis and accumulation of toxins in addition to a heparin-like coagulopathy due to residual heparin that accumulated in the donor allograft. Accumulation of t-PA during the anhepatic phase combined with injured endothelium of the reperfused allograft may lead to hyperfibrinolysis in the early post-reperfusion period. As the transplanted liver begins to function, it will synthesize coagulation factors, metabolize toxins, and restore acid–base balance, resulting in restoration of coagulation [24]. In cases of delayed graft function, coagulopathy and hemorrhage can be profound and persistent in the post-operative period.

Viscoelastic Testing (VET) in Liver Transplantation

Viscoelastic testing (VET) devices comprise several modalities to measure real-time clot dynamics on whole blood samples. Whereas conventional coagulation testing (CCT) such as PT/aPTT, INR, fibrinogen level) measure portions of the coagulation system, VET devices are designed to measure functional coagulation with parameters that calculate time to clot formation, clot strength, and time to clot dissolution. Additionally, there is a significant delay in result reporting for CCTs as they require transport to a central laboratory for sample centrifugation, whereas VET devices provide rapid, real-time results to aid in quicker interpretation and use of the data by clinicians to guide patient blood management decisions. The role of VET use in liver transplantation to measure coagulation parameters and help guide administration of blood component therapy was given a 'strong' recommendation by an international expert working group (ERAS4OLT.org) in 2022 [25]. The ability to understand and interpret VET results to make patient care decisions as it relates to coagulation management during liver transplantation has recently been outlined as one of the core expectations of a liver transplant anesthesiologist [26]. The use of VET to guide transfusion during liver transplantation compared with CCT has been associated with a reduction in blood product transfusions, decreased blood loss, and cost reduction [27, 28]. This cost reduction demonstrated by Smart et al. with a VET-guided compared with CCT-guided bleeding protocol in liver transplantation was due to a reduction in blood products transfused [27], not due to VET use itself as CCT reagents cost approximately $1–5 USD per reagent while VET cartridges cost $50–150 per cartridge [29]. VET has become the preferred method of coagulation monitoring during liver transplantation and has largely replaced CCT where available [30].

First-generation VET Devices

First-generation VET devices assess clot dynamics of citrated whole blood via mechanical probing during clot formation. With these devices, the formation of clot is transduced around a central pin inserted into a cup, with an externally applied force. Changes in the pin movement are used to generate a viscoelastic tracing, either a thromboelastogram (TEG) or thromboelastograph (ROTEM), which is then interpreted by the practitioner. The traditional TEG device (TEG 5000; Haemonetics; Boston, MA) utilizes a stationary pin with a rotating cup, while the traditional ROTEM device (ROTEM delta; Werfen, Bedford, MA) uses a rotating pin with a stationary cup.

The first-generation VET devices require sample and reagent loading into individual cups through manual pipetting with multiple cups per instrument depending on the number of individual tests run. This process takes time, and experienced, technically skilled operators are needed. Thus, there can be significant interlaboratory variability. It is important to note that VET devices do not account for vWF, protein C, or protein S and thereby may not give the full picture of clot dynamics in vivo [31, 32]. Additionally, the original VET devices did not detect platelet inhibition. TEG platelet mapping or impedance aggregometry are specialized tests that can account for platelet contribution to clot formation.

Cartridge-Based VET Devices and Their Use in Liver Transplantation

Several new VET devices have become available in recent years with the emergence of cartridge-based methodologies. These systems employ disposable cartridges that contain lyophilized reagents. This allows for rapid and simultaneous testing of the individual contributions of coagulation factors, platelets, fibrinogen, and fibrinolysis to clot formation and dissolution without the reliance on pipetting across channels. The newer generation of devices for use in liver transplantation include TEG 6s (Haemonetics; Boston, MA), ROTEM sigma (Werfen; Bedford, MA), and Quantra QStat (HemoSonics, LLC; Durham, NC). Parameters for reach device are

Table 1 Comparison of clot dynamic parameters between thromboelastography (TEG), rotational thromboelastometry (ROTEM), and Quantra viscoelastic testing devices

Parameter	TEG	ROTEM	Quantra
Time to clot formation	r-time (reaction time)	CT (clot time)	CT (clot time)
Rate of initial clot formation	k-time (kinetic time), α-angle	CFT (clot formation time), α-angle	n/a
Clot strength	MA (maximum amplitude)	MCF (maximum clot firmness)	CS (clot stiffness), PCS (platelet contribution to clot stiffness), FCS (fibrinogen contribution to clot stiffness)
Clot stability (lysis)	LY30 and LY60 (clot lysis 30 and 60 min after maximum clot strength) in % MA	LI30 and LI60 (lysis index 30 and 60 min after start of clot formation) in % MCF	CSL (clot stability to lysis)

summarized in Table 1. The TEG 6s does requires pipetting of the whole blood sample into the cartridge while the ROTEM sigma and Quantra QStat allow for spiking of the citrated whole blood specimen tube directly into the cartridge [33•]. These devices promise benefits over the first-generation VET devices in terms of ease of use (less likely to be affected by experience of the operator) and greater portability, potentially allowing for use at the point-of-care with generation of results more rapidly. Their use and reliability in coagulation monitoring in patients undergoing liver transplantation is beginning to be explored.

TEG 6s

The TEG6s device received FDA approval in April 2016. In this device, once a whole blood sample is pipetted into the cartridge, it is divided across multiple channels, each with different reagents. Clot formation within each channel is assessed simultaneously. The system measures the resonance frequency of whole blood exposed to vibrations caused by the motion of the blood meniscus. The resulting frequency of the sample is measured by illuminating the blood with a light-emitting diode (LED). As the clot forms, the alternation of the resonance is measured by the LED and converted to a graph identical to that of the traditional cup-and-pin method [34]. There are 3 TEG 6s cartridges that are Food and Drug Administration (FDA)-approved and available commercially in the U.S.: the Global Hemostasis cartridge, the Global Hemostasis with Lysis cartridge, and the Platelet Mapping cartridge. The Global Hemostasis cartridge includes four test channels with different reagents for each test: kaolin (CK), kaolin and heparinase (CKH), tissue factor and kaolin (CRT; Rapid TEG), and tissue factor and abciximab (CFF; functional fibrinogen). The Global Hemostasis with Lysis cartridge includes all tests in the Global Hemostasis cartridge, but also has the capacity to monitor fibrinolysis. The Platelet Mapping cartridge allows for assessment of platelet function in the setting of antiplatelet (aspirin and P2Y12 inhibitors) therapy.

Strong correlation between TEG 6s and TEG 5000 values has been reported in multiple clinical settings [35–37], but there is limited data in TEG6s use in liver transplantation. Robson et al. performed a single center, prospective observational study investigating the degree of correlation between TEG 5000 and TEG 6s measurements obtained during liver transplantation [38•]. Whole blood samples were collected from 10 liver transplant recipients at 6 timepoints during the surgery: immediately prior to incision (baseline), 30 min after incision (dissection), 15 min after cessation of blood flow to the liver (anhepatic), 10 and 60 min after reperfusion ('early' and 'late' reperfusion), abdominal muscle layer closure (neo-hepatic). Reaction time (r-time), kinetic time (k-time), alpha angle (α-angle), maximum amplitude (MA), and percent lysis at 30 min (LY30) were collected for each device at each draw. LY30 was not compared as no lysis was detected in any sample. Agreement between measures was poor, with correlation coefficients well below 0.8 for most measures ($r = 0.45$, 0.52, and 0.48 for r-time, α-angle, MA, respectively). There was moderate correlation between the TEG 6s and TEG 5000 measures for k-time ($r = 0.83$). Samples were run on citrated whole blood for the TEG 5000 as well (as the TEG 6s requires citrated whole blood while the TEG 5000 utilizes non-citrated whole blood) with no improved correlation between devices.

A major potential advantage of the TEG 6s device is the ability for coagulation assessment at the site of care, which has been demonstrated in trauma activations as well as in models of ground and air medical transport [39, 40]. The TEG 6s cartridge-based design offers less required pipetting and less susceptibility to external vibration (although this purported feature has been challenged [41]), improving ease-of-use and greater portability. Further validation of TEG 6s through larger studies in patients with end-stage liver disease and development of TEG 6s-based liver transplant transfusion algorithms are needed.

ROTEM Sigma

Similar to its predecessor (ROTEM delta), the ROTEM sigma (FDA approved in July 2022) uses a cup and rotating pin to measure clot formation via mechanical transduction. However, like the other new devices, ROTEM sigma offers automation to improve its portability and make it a true point-of-care product. A vacuum-sealed blood sample tube containing citrate and the whole blood specimen is spiked onto the ROTEM sigma cartridge and the blood is subsequently distributed into four parallel chambers. Each chamber contains reagents in a freeze-dried pellet form allowing for simultaneously testing via a rotating pin. FDA approval was granted for clinical setting use in 2022, with two current cartridges available: the Complete and the Complete + Hep. The Complete cartridge contains channels for the INTEM, EXTEM, FIBTEM, and APTEM. The Complete + Hep replaces the APTEM channel with a HEPTEM channel and is intended for use in cardiac surgery [33•].

Strong correlation in thromboelastometry parameters between ROTEM sigma and its predecessor, ROTEM delta, has been demonstrated in healthy volunteers, patients admitted to the intensive care unit (ICU) following surgery for bleeding, and patients admitted to the ICU with elevated fibrinogen levels (assumed hypercoagulability) [42]. Variable results have been reported between functional fibrinogen measurement correlations between ROTEM sigma, ROTEM delta, and Clauss fibrinogen levels in trauma patients and patients experiencing postpartum hemorrhage [43, 44]. The use of ROTEM sigma in patients undergoing liver transplantation has yet to be investigated.

Quantra

The Quantra Hemostasis Analyzer (HemoSonics, LLC, Durham, NC) utilizes sonic estimation of elasticity via resonance (SEER) sonorheometry technology with ultrasound to detect clot dynamics in whole blood. The Quantra with QStat cartridge received FDA approval in November 2022 for use in liver transplantation and trauma. The QStat cartridge provides measures of clot time (CT), clot stiffness (CS), platelet contribution to stiffness (PCS), fibrinogen contribution to stiffness (FCS), and clot stability to lysis (CSL). A multicenter prospective observational study of the Quantra with the QStat cartridge data obtained during liver transplantation compared with measurements obtained from ROTEM delta assays at the same time points demonstrated a strong correlation [45•]. In this study of 125 adult patients undergoing liver transplantation across 5 medical centers, whole blood samples were collected at 3 time points: pre-incision/baseline, during the anhepatic phase, and post-reperfusion. Strong, positive correlations (r ranging from 0.88–0.95) were demonstrated between corresponding output variables on the Quantra QStat and ROTEM delta parameters and there was 90.3% agreement between the two devices for the quantification of fibrinolysis. While more data must be obtained on the use of the Quantra QStat in the perioperative period for patients undergoing liver transplantation, this study suggests the Quantra QStat provides equivalent data as that obtained from the ROTEM delta.

Use of Viscoelastic Testing Devices to Guide Transfusion Therapy in Liver Transplantation

VET results can be obtained during liver transplantation at multiple points during the surgical operation. Baseline values may be helpful in identifying the patient's current hemostatic status upon entering the operating room. VET values obtained during the dissection phase can help guide targeted transfusion therapy in the setting of hemorrhage from the consequences of portal hypertension. VET values obtained peri-reperfusion can help guide targeted transfusion therapy as a de novo coagulopathy develops. Finally, intensivists should be knowledgeable on the use of VET and continue to monitor coagulopathy accordingly in the ICU setting postoperatively. Very importantly, all VET results should be interpreted within the clinical context. As discussed, patients with end-stage liver disease have derangements in pro- and anticoagulant factors and may be at hemostatic equilibrium in a 'rebalanced' state. Targeted blood transfusion and pharmacologic therapy should be reserved only for cases of demonstrated clinical bleeding.

Conclusions

Due to the potential for significant blood loss during liver transplantation due to the coagulopathy associated with end-stage liver disease and the dynamic coagulation challenges during the surgery, coagulation monitoring is critically important to guide blood component and pharmacologic therapy to achieve hemostasis. It has been well established that coagulation management guided by VET results provides many benefits over CCT and has become the preferred method of coagulation monitoring during liver transplantation. New generation VET devices (TEG 6s, ROTEM sigma, and Quantra QStat) offer improvements over first-generation devices. While emerging suggests equivalent testing consistency, high-quality, randomized clinical trial evidence is lacking with these new generation devices. Further investigation validating clinically significant parameters with these cartridge-based VET systems will help improve targeted transfusion algorithms and blood component and pharmacologic therapy practices during liver transplantation.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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