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Review Article

A Review Of Viscoelastic Hemostatic Testing As A Diagnostic Tool For Hypercoagulability In Liver Transplantation.

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Abstract

Liver transplantation is a difficult surgical surgery that might cause coagulation problems, such as perioperative hypercoagulability. Liver graft recipients with end-stage liver disease may experience thrombosis or hemorrhage, depending on the situation.
Clinical conditions and associated risk factors. Hypercoagulability can lead to significant problems, including thrombosis in recently transplanted liver arteries.Standard coagulation tests (SCTs) including prothrombin time and activated partial thromboplastin time (aPTT) struggle to detect and monitor hypercoagulability in its early stages. Recent studies.
VETs, including rotational thromboelastometry (ROTEM) and thromboelastography (TEG), show promise in identifying hypercogulability disorders.VETs are more sensitive than SCTs in detecting liver graft recipients at risk of thrombosis by measuring clotting time, clot strength, fibrin and platelet contribution to clot hardness, and fibrinolysis. However,
Evidence-based guidelines for preventing and treating hypercoagulability based on VET results are still needed.

Keywords : *liver; hypercoagulability; thromboelastometry; thromboelastography; liver transplantation.*

INTRODUCTION

Patients with end-stage liver disease (ESLD) usually exhibit rebalanced hemostasis.However, this fluctuating rebalancing can soon lead to bleeding or thrombosis. Hemostasis relies on the balance of procoagulants and anticoagulants, as well as fibrinolytic and antifibrinolytic agents. Hypercoagulability or thrombophilia can result in Thromboembolic events, including portal vein thrombosis and hepatic artery thrombosis, might increase perioperative morbidity and death in liver transplant recipients [1,2].

Standard laboratory coagulation tests (SCTs) cannot distinguish between hypocoagulability and hypercoagulability, thereby leading to unnecessary treatments. This can lead to incorrect blood transfusions and TACO (transfusion-associated circulatory overload). and portal hypertension, which may further worsen bleeding. In contrast to SCT, viscoelastic hemostatic testing (VET) methods such thromboelastometry (ROTEM) and thrombelastography (TEG) often show normal or hypercoagulability [3-5]. Anesthesiologists have the issue of detecting hypercoagulability during surgery due of SCTs' limited ability. SCTs (prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count) have limited usefulness in the perioperative situation because to their slow turnaround time and failure to accurately reflect acute changes in hemostasis. These VET gadgets can detect these alterations. Real-time hemostasis monitoring at the bedside is accessible in some liver transplant centers, but requires instruction and training (6-8. Newer VET devices provide automated measures, making them more user-friendly. In contrast to SCTs, VETs evaluate blood clot flexibility as well as the cellular Plasmatic blood components of the clotting process.

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AIM AND METHOD OF NARRATIVE REVIEW

This review examines the evidence regarding VET-induced hypercoagulability in adult liver transplant recipients, including both intraoperative and postoperative observations. Medline, Scopus, PubMed, and Google Scholar were used to search for English-published literature from January 15, 1995 to May 15, 2024. We included current peer-reviewed and accepted online articles before print. PubMed was searched with the following mesh-created keywords: liver, hypercoagulation, thromboelastometry, thromboelastography, and liver transplantation. Keywords were chosen from the The National Library of Medicine's Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html, accessed on October 7, 2024).

The collected studies comprised randomized controlled trials (RCTs), interventional studies, observational studies, prospective studies, retrospective studies, case series, reports, and reviews on hypercoagulability.After liver transplantation using VET devices, the location of thrombosis and the fate of recipients with thromboembolic events. The VET results were compared to SCT findings.

ROTATIONAL THROMBOELASTOMETRY

ROTEM (Tem Innovations, Munich, Germany) is a point-of-care device that evaluates the viscoelastic properties and kinetics of the coagulation process, including clot formation and lysis, in vitro [9,20].ROTEM analyzes the viscoelastic properties of blood clots and the interplay between coagulation-promoting agents and inhibitors. ROTEM tests include EXTEM, INTEM, FIBTEM, APTEM, and HEPTEM. These tests evaluate the extrinsic coagulation pathway (EXTEM), intrinsic coagulation pathway (INTEM), fibrin contribution to clot firmness (FIBTEM), antifibrinolytic drug effect (APTEM), and heparinase effect on intrinsically activated blood samples (HEPTEM).

EXTEM, like PT/INR, evaluates tissue factor activation and provides insights into the extrinsic coagulation system. INTEM, like aPTT, monitors contact activation and provides insights into the intrinsic coagulation process. FIBTEM use cytochalasin D, an actin polymerization inhibitor, to prevent platelet involvement in clot formation.

Only the influence of fibrin production and polymerization will be measured.ROTEM examines several parameters, including coagulation time (CT), clot formation time (CFT), A5 (clot firmness amplitude 5 min after CT), A10 (clot firmness amplitude 10 min after CT), and maximal clot firmness.CT refers to the time it takes to initiate a clot until it achieves a firmness of 2 mm. CFT evaluates clot dynamics by measuring the time required to raise clot firmness from 2 to 20 mm. MCF represents the maximum.

THROMBOELASTOMETRY TEG

The usual kaolin-activated TEG was used to measure clot strength and detect hypercoagulability in citrated blood samples. TEG parameters (Haemonetics Corp, Boston, MA, USA) are as follows: The R-time (3-8 min) characterizes clot initiation, whereas the K-time (1-3 min) defines clot formation kinetics. The MA (51-69 mm) reflects the maximum clot firmness amplitude due to fibrin-platelet interactions. Hypercoagulability was classified as any MA result > 69 mm, as shown in Figure 2 [23, 24].

The measurement approach involves slowly oscillating a cup in TEG and measuring changes in viscoelasticity using a suspended pin connected to a torsion wire. In contrast, the cup remains stable in ROTEM while the pin oscillates, resulting in changes in viscoelasticity.A system of LEDs and mirrors detects light. The pin is stabilized using a ball-bearing, allowing for mobile use at the patient's bedside. ROTEM combines the EXTEM and FIBTEM assays to accurately distinguish between fibrin and platelet contributions to clot firmness [25].

Standard coagulation tests (SCTs): SCTs include the activated partial thromboplastintime (aPTT, 30–40 s), prothrombin time (PT, 11 to 13.5 s), international normalized ratio(INR, 0.8–1.1), and the plasma fibrinogen concentration (Clauss method, 2 to 4 g/L). SCTsare usually measured semi-automatically in citrated platelet-poor plasma.Thus, the platelet's contribution to the coagulation process is missing. Platelet count is often measured in ethylenediamine tetraacetic acid (EDTA) using a Coulter Counter [26-30]. EDTA is a chelating agent that helps to alleviate heavy metal poisoning. EDTA doesn't distort red.Pseudothrombocytopenia can occur when automated hematological analyzers detect platelet counts instead of blood cells.

DISCUSSION

Normal hemostasis requires a careful balance of pro- and anticoagulants, as well as an equilibrium between fibrinolysis and fibrinolysis inhibitors [3, 4, 35, 36]. If the balance is not maintained, hypocoagulability or hypercoagulability will occur. The hepatocytes of ESLD Insufficient production of vitamin K-dependent coagulation factors (II, VII, IX, and X), as well as inhibitors like protein C and S, might disrupt the balance.The non-hepatic vascular endothelium produces and releases higher levels of vWF and coagulation factor VIII. Reduced activity of the vWF-cleaving enzyme ADAMTS13 in the liver can cause microthrombi development [37-40]. In ESLD, plasminogen and alpha2-antiplasmin levels fall, but tPA and PAI-1 levels rise [41]. Infection and sepsis can cause disseminated intravascular coagulation. (DIC). Recent research suggests that acute liver failure may be caused by a shutdown of fibrinolysis rather than hyperfibrinolysis.

Despite evidence of hypocoagulability in SCTs, recipients with liver cirrhosis are more likely to experience thrombosis rather than hemorrhage. [41-44]

Can VET detect hypercoagulability during and after liver transplantation?

Several studies have examined hypercoagulability in liver transplant recipients using VETs. Kamel et al. published one of the few prospective observational studies that found a substantial postoperative stepwise rise.The FIBTEM (MCF) increases the risk of thrombosis, especially on postoperative days 5 and 7. FIBTEM is an ROTEM assay that measures fibrin's contribution to clot hardness, as seen in Figure 4. Figure 4 depicts an assay that measures the contribution of fibrin to clot stiffness. Increased fibrin contribution to clot stiffness was not linked to higher fibrinogen plasma levels [7]. Yassen et al.

Another prospective observational study examined perioperative platelet activity using ROTEM platelet (whole blood impedance a).In liver transplant recipients, ROTEM platelet activity was assessed by whole blood impedance aggregometry (Tem Innovations, Munich, Germany). This study reported a significant The study also examined how splenectomy during liver transplantation affected platelet count and function. The study indicated that splenectomy improves platelet function as early as postoperative day 3, with some cases exceeding the normal range.

The Incidence of Thromboembolic Events

Table 1 summarizes published studies on hypercoagulability in liver transplant recipients, including the incidence of thromboembolic events. Despite extended standard coagulation tests, liver transplant recipients have demonstrated normal or In 2010, Lisman et al. documented hypercoagulability during and after surgery [44]. Arshad et al. (2013) found that a hypercoagulable state can result in significant thromboembolic events [51].Arshad et al. (2013) found that this can cause significant thromboembolic events [51]. According to Salami et al.'s retrospective research, the rate of venous thromboembolism in liver transplant patients can reach 4.5%. recipients [5]. Hypercoagulability is a hereditary predisposition that can lead to thromboembolic events [52, 53]. According to Zamper et al. (2017) [54], VET devices can help assess and treat hypercoagulability. Earlier in 2005, Lerner et al.The clinic reported four liver transplant recipients who experienced intra-operative cardiopulmonary thromboembolism during surgery. Despite being hypocoagulable on SCTs, the four patients were not monitored.

VET due to a lack of VET devices at this facility. Two recipients died, and two survived.Lerner et al. conducted a systematic evaluation of similar case reports. They were able to trace 13 documented intraoperative occurrences. VETs can diagnose hypercoagulability when SCTs fail, which is the most significant finding [2].In 2008, Warnaar N et al. conducted a comprehensive evaluation of 74 cases with intra-operative pulmonary embolism and/or intracardiac thrombosis, with a 68% death rate (50/74). There were just twenty honorees

A VET device was used for monitoring. TEG detected hypercoagulability in eight participants, whereas four had their blood samples clotted prior to testing. In 2013, Krzynicki et al.A retrospective database assessment of 124 patients found that over 15% of orthotopic liver transplant recipients were hypercoagulable according to viscoelastic tests. 15.53% of the samples had high G-values.The authors found that patients with cholestatic biliary disorders had higher rates of hypercoagulability (42.9% with primary biliary cirrhosis and 85.7% with primary sclerosing).

cholangitis). The study found that SCTs cannot diagnose hypercoagulability, which can lead to damage for recipients [8].of native TEG, and short Rtimes were seen in 6.80% of native-heparinase TEG.

Clevenger and Mallett (2014) reported that hepatic patients may have a rebalancing of hemostasis. Failure to recognize this balancing can increase patients' risk of hypercoagulability and thrombosis. ROTEM/TEG guided patient blood management PBM policies aim to enhance patient outcomes by reducing inappropriate blood transfusions and coagulopathic bleeding during and after liver transplantation [55].

In 2018, Kamel et al. found that liver transplants saw a significant postoperative stepwise increase in FIBTEM (MCF), peaking on day 7.Increased FIBTEM MCF was linked to a higher risk of thromboembolic events, rather than greater fibrinogen levels in blood.

When to Expect Hypercoagulability in Liver Transplantation?

Hypercoagulability and thrombus development can occur during or after transplant surgery. According to Wu et al., portal vein thrombosis is most common in hospitalized liver cirrhotic patients, with a frequency of 0.5% to16% [56].

According to Gologorsky E et al., the risk of intra-cardiac thrombus or pulmonary embolism during liver transplantation is between 1% and 6%. Seven patients receiving liver transplantation experienced intra-cardiac thrombosis shortly after graft reperfusion [13].16% [56].Lerner et al. reported four comparable occurrences during liver transplantation, even when no antifibrinolytic medication was used [2]. Intraoperative usage of antifibrinolytics such ε-aminocaproic acid (ε-ACA) and tranexamic acid has been suggested as a potential cause. Thus, the usage of any antifibrinolytics or Coagulation-promoting drugs should only be utilized for bleeding and pathologic TEG/ROTEM results, not as a

preventative measure [3,57,58].In 2016, Protin et al. reported a case of abrupt intra-cardiac thrombosis during the anhepatic phase in a hemodynamically stable recipient [59].

Transesophageal echocardiography (TEE) monitoring during surgery can detect intra-cardiac thrombus and forecast cardiac function decline [9].Salami et al. reported a 4.58% incidence of postoperative thrombotic events, including vascular thromboembolism in the portal vein or hepatic artery [5]. Arshad et al. identified a link between thrombosis before and after surgery. This phenomenon is associated with pre-operative hypercoagulability that does not resolve. Immediately following transplantation [51].

Platelet Role in Hypercoagulability

ESLD can cause platelet sequestration in the spleen and hypersplenism, leading to thrombocytopenia (20, 21). Thrombocytopenia balances platelet aggregation caused by increased vWF and decreased ADAMTS13 activity [4]. Restrictive platelet transfusion in this state and during liver transplantation is critical.To avoid aggravating portal hypertension and increasing mortality. Yassen et al. and Hegazy et al. conducted two investigations in liver transplant recipients to examine platelet function during surgery and 21 days afterward using the ROTEM platelet device. They showed decreased platelet function and count during and during the transplantation operation. Platelet function took two weeks to restore after donation. Survivors recovered much, but non-survivors recovered less.TRAPTEM, an ROTEM platelet function assay activated by thrombin receptor activating peptide 6, successfully differentiated 3 month survivors from non-survivors and individuals at risk of hypercoagulability. In both investigations, some recipients had ROTEM platelet function above the upper normal range on postoperative days 14 and 21. A considerable increase in platelet function was linked to thrombocytosis (18, 19).

Splenectomy Enhances Hypercoagulability

Performing an intra-operative splenectomy after living donor liver transplantation prevents platelet destruction and lowers antibody generation, leading to longer platelet survival and thrombocytosis. Yassen K et al. and Hegazy E et al. published ESLD reduced platelet function and required two weeks for recovery after transplantation. Figure 4 shows that splenectomy improved platelet recovery as early as postoperative day 3 and exceeded normal levels in some patients by postoperative days 14-21.

Some recipients reached the normal range by postoperative day 14-21, as illustrated in Figure 4. Platelet function should be examined beyond 3 weeks after liver donation, especially during the follow-up period when recipients receive the least monitoring.Acetylsalicylic acid inhibited platelet function exclusively in ARATEM-activated tests, with minimal effect on ADPTEM and TRAPTEM [19].

Thromboprophylaxis Required Despite Pathologic SCT Results

This review emphasizes the importance of venous thromboprophylaxis for ESLD patients undergoing liver transplantation during hospitalization and throughout the process. Notably, the evidence suggests that only A limited percentage of liver patients receive VTE prevention. Prophylaxis involves compressing muscles sequentially during surgery and administering anticoagulants afterward. This can include unfractionated heparin infusion, subcutaneous low-molecular-weight heparin injection, and oral aspirin. Pharmacological prophylaxis differs amongst transplant centers due to the lack of standardized protocols. An evidence-based unified VTE prophylactic regimen for liver transplant recipients [60–62].

The lack of clear norms may stem from a fear of bleeding. Due to insufficient data and limited randomized controlled trials, thromboprophylaxis for liver patients is classified as low evidence-based. European Guidelines advise caution when using low-dose unfractionated heparin (LMWH) (Grade 2C Recommendation).

Low levels of antithrombin from decreased hepatic production and higher consumption provide a problem for heparin therapy [57,58,63,64]. Thromboprophylaxis for liver transplant patients with chronic Patients with liver illness should be aware of individual variances and disparities between disorders. Patients with cirrhosis who are hospitalized or immobilized and have no contraindications should get VTE prophylaxis using either LMWH or UFH.

Portal vein thrombosis (PVT) prevention: There are no agreed-upon criteria for this topic, making it a source of debate [68]. Villa et al. found that enoxaparin is both effective and safe for preventing PVT. Furthermore, the low molecular weight Heparin has been shown to improve survival by decreasing bacterial translocation and hepatic decompensation [69]. Von Köckritz et al. [70] suggest that individuals with cirrhosis who are awaiting liver transplantation or resection may benefit from PVT prevention.

Hepatic Artery Thrombosis (HAT) Prophylaxis

Individuals at high risk of HAT may benefit from prophylactic dosing of unfractionated and low-molecular-weight heparin during the immediate perioperative period.The evidence for or against aspirin to prevent HAT is minimal. (Level of evidence III, grade C) [71, 72].

Therapeutic Options for Vascular Thrombus

Vascular thrombosis is a critical complication that requires rapid clinical intervention to restore liver graft perfusion during or after transplantation.The management differs from one

transplant center to the next and is subject to variances.based on the clinical state of each recipient. Most physicians rely on anticoagulants to treat vascular thrombosis. Anticoagulants promote recanalization of key veins, including the portal vein, by dissolving thrombus.Argatroban, an intravenous direct thrombin inhibitor, should be used with caution in patients with liver failure due to its liver-mediated elimination [73,74].

There is no preferred anticoagulant; low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs) such apixaban, rivaroxaban, and dabigatran are evaluated individually (level III, grade C). Management of portal vein thrombosis (PVT) This differs between recipients.Patients with Child-Turcotte-Pugh (CTP) score Class A or B cirrhosis typically receive anticoagulation as treatment. CTP is a cirrhosis severity score.Haematology consultation is necessary for VKAs, LMWH, and DOACs with advanced liver disease (CPT Class B or C). (Level 3, Grade C). A transjugular portocaval shunt (TIPS) inserted using interventional radiology effectively treats chronic PVT and portal hypertension (Level II, Grade B) [33].

Doppler ultrasonography is used to diagnose hepatic artery thrombosis (HAT), which requires prompt thrombectomy either surgery or interventional radiology [33, 75].

Acute intra-cardiac thrombus (ICT) does not always cause hemodynamic instability or necessitate therapy [59]. Routine TEE monitoring during transplant surgery promotes early detection of ICT formation, preventing hemodynamic instability. Heparin is recommended for patients with ICT/PE and no hemodynamic instability. Recombinant tissue plasminogen activator (rTPA) (0.5–4 mg) is recommended for patients with hemodynamic stability. The dose varies according to the severity of the instability (level IV, grade D) [33].

Can VET Monitoring Reduce Thromboembolic Events?

According to De Pietri et al. [76], liver patients may have hypercoagulability due to increased thrombin production, factor VIII and vWF activity, fibrinogen levels, and platelet hyperactivity.VET-guided perioperative use of blood products, anticoagulants, and antiplatelet drugs has shown promising results in reducing major bleeding incidents and thromboembolic events.

There is a dearth of prospective randomized trials and intervention studies comparing VET-guided blood transfusion and therapy to normal perioperative management for liver transplantation.Further research is needed to confirm the effectiveness of thromboprophylaxis in liver transplant recipients.

Encourage the use of VET devices in liver transplant centers to diagnose and treat coagulopathy, a complicated condition that can fluctuate from hypo to hypercoagulation.From one phase to the next throughout the same transplant surgery and perioperative period.

To successfully regulate coagulation and reduce problems, VET should be conducted multiple times before, during, and after surgery. However,A multimodal strategy is necessary to accurately anticipate thrombotic events, as no single test can do so completely. When treating VET parameters during surgery, it's important to consider the current clinical bleeding condition. In the US, 92% of liver transplant hospitals have access to VET, with use rates ranging from 60-80% [77].

Limitations of VET Devices

VET may not always produce faster results than SCT, as some ROTEM parameters, such as MCF or ML, can take 30-60 minutes to complete, comparable to SCT. ROTEM assays include INTEM, EXTEM, HEPTEM, APTEM, and FIBTEM. Activators such as tissue factor and collagenic acid stimulate the coagulation process. Platelet dysfunction can cause hypocoagulability, which activators can hide.

Despite limitations, VET outperforms SCT, which only assesses isolated portions of the coagulation cascade and does not fully capture the intricacy of clot formation in vivo. Native, or NATEM Although Kang et al. [78] established its therapeutic benefit, this method is rarely used in clinical settings as it does not require citration, recalcification, or activator addition.

Native blood without anticoagulants is good for thromboelastography tests since it closely resembles the patients' coagulation.

CONCLUSIONS

VETs are more sensitive and can assist detect patients at risk of thrombosis. Develop evidence-based VET guidelines for preventing and treating hypercoagulability. A multimodal strategy, including SCTs and VETs, can improve diagnosis and management. Individual differences and the liver disease aetiology should be considered when implementing thromboprophylaxis for hospitalized patients with chronic liver disease. To be taken into consideration. Anesthesiologists treating liver transplant recipients should be aware of these changes as they may impact hemostasis and blood management decisions.

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Conflicts of Interest

Klaus Görlinger is the Medical Director of Tem Innovations GmbH in Munich, Germany. The remaining authors state that the research was conducted without any commercial or financial affiliations that could lead to a conflict of interest.

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