Leading article

Viscoelastic haemostatic test based management of coagulopathy in liver transplantation for cirrhosis

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Abstract

Management of coagulopathy is an important consideration in the management of liver transplantation (LT) for end stage liver disease due to cirrhosis. Blood loss and the volume of blood products transfused are key determinants of outcome following liver transplantation. Cirrhosis has traditionally been associated with hypocoagulability and haemorrhage. Greater understanding of the normal haemostatic processes and the derangement associated with cirrhosis has resulted in the concept of rebalanced haemostasis in cirrhosis. This rebalancing and reduction of haemostatic reserves results in an unpredictable and often pro thrombotic haemostatic state in cirrhosis. The predictive value of standard tests of coagulation is diminished in cirrhosis. In contrast, viscoelastic haemostatic tests have demonstrated superior diagnostic and bleeding predicting capabilities in cirrhosis.

Bleeding management protocols including viscoelastic haemostatic test-based algorithms have reduced transfusion requirements without an increase in the incidence of bleeding or thrombotic complications in liver transplantation.

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1.1 Introduction

Management of cirrhotic coagulopathy is an important determinant of outcome in liver transplantation. Deranged coagulation in cirrhosis is compounded in the perioperative period by multiple factors including surgery, anaesthesia, sepsis, hypothermia, and acidosis.
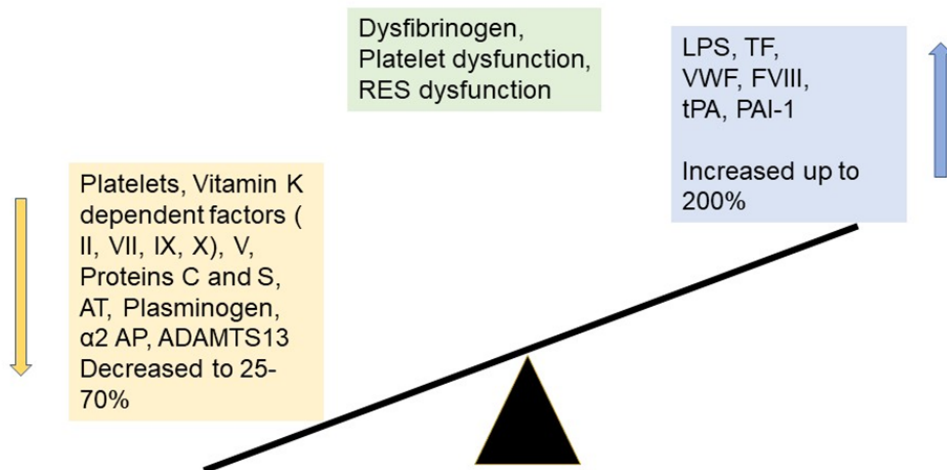
A better understanding of haemostatic abnormalities in cirrhosis, improved diagnostics, use of algorithms for management of bleeding and haemostatic abnormalities characterize modern liver transplantation. Outcomes following liver transplantation have improved dramatically with a 10 year survival of almost 90%[1].

1.2 Pathophysiology of cirrhotic coagulopathy

The complex interplay between the endothelium, plasmatic coagulant and anticoagulant factors, platelets and feedback loops and the changes due to cirrhosis, infection, inflammatory mediators on haemostasis are yet to be completely unravelled[2].

Thrombocytopenia and platelet dysfunction as well as a decrease in coagulation factors II, V, VII, IX, X, anti-thrombin and the vitamin K-dependent coagulation inhibitors protein C and S, occurs in cirrhosis. In contrast, the plasma levels of von Willebrand factor (VWF) and endothelium derived factor VIII increase. Plasma levels of ADAMTS-13; the VWF cleavage protein decreases[3]. These changes predispose to the formation of micro-thrombi, disruption of hepatic sinusoidal perfusion and worsening of hepatic dysfunction. Acquired dysfibrinogenemia in cirrhosis reduces the quality of the fibrin clot[2,4].

Rebalanced haemostasis in cirrhosis at a low level leading to high risk of bleeding and thrombosis. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS 13), antithrombin (AT); α2 antiplasmin (α2 AP); lipopolysaccharide (LPS); tissue factor (TF); tissue plasminogen activator (tPA); plasminogen activator inhibitor (PAI-1); reticuloendothelial system (RES).

Figure 1: Rebalanced haemostasis in cirrhosis. Courtesy of Klaus Görlinger, Munich, Germany.
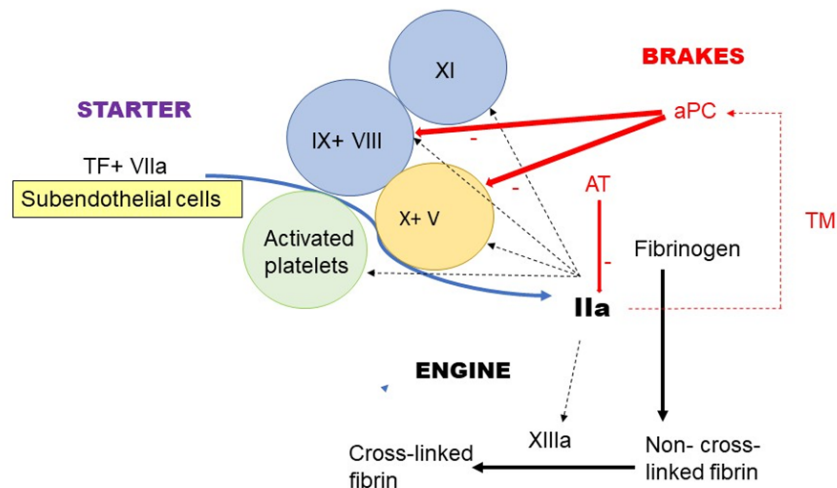
Car-based model of haemostasis; activated protein C(aPC), antithrombin (AT), tissue factor (TF), thrombomodulin (TM), coagulation factors V, VIII, IX, X, and XI, activated coagulation factor VII (VIIa), activated coagulation factor XIII (XIII a). (2)

Figure 2: The "car-based model of haemostasis" provides a mechanistic overview of the deranged haemostasis in cirrhosis. Courtesy of Klaus Görlinger, Munich, Germany.

The deranged extrinsic pathway with deficiencies of factors VII, X, V, and II is compared to the defective 'starter' of an old car. The resulting delay in starting (prolonged cranking!) is reflected by a prolonged prothrombin time and increased international normalized ratio.

Amplified coagulation induced by high levels of thrombin generated by factor VIII overactivity is comparable to the engine of the old car 'revving away'. The effect of thrombocytopenia is countered by the large VWF multimers and reduced levels of ADAMTS-13.

Anticoagulant and fibrinolytic mechanisms, act as 'brakes' controlling the pro-coagulant mechanisms thereby limiting the clot.

Low levels of antithrombin and activated protein C in cirrhosis – the malfunctioning 'brakes' – allows coagulation to continue, unchecked. This reflects the increased thrombotic risk in cirrhosis.

An increase of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) with a simultaneous decline in plasminogen and alpha^2 antiplasmin levels induce an imbalance in the fibrinolytic system[2].

'Rebalanced haemostasis' with reduced reserves is the net result of these changes. A pro-thrombotic or anti-thrombotic state could be precipitated by a variety of triggers including bleeding, infection, malignancy, and liver transplantation surgery[4,5].

1.3 The phases of liver transplantation

- **Pre-anhepatic phase**

  During this phase intraperitoneal varices are ligated, and the native liver is prepared for explant. Severe coagulopathy, acidosis, hypoglycaemia, and bacteraemia are potential complications during this phase.

- **Anhepatic phase**

  Vascular disconnection and explant of the liver marks the onset of the anhepatic phase. Progressive lactic acidosis, coagulopathy and hypoglycaemia characterize this phase. Though the plasma fibrinogen declines, significant bleeding is uncommon during this phase.

- **Reperfusion and neo hepatic phase**

  This phase begins with reperfusion of the graft via the inferior vena cava and portal vein. Impaired cardiac contractility, hypervolemia, arrhythmia, coagulopathy and bleeding, acidosis and hyperkalaemia contribute to haemodynamic instability. Reperfusion injury mediated by inflammatory mediators and reactive oxygen species contribute to multiple organ dysfunction[1,6].

1.4 Utility of conventional tests of coagulation and viscoelastic tests in assessing cirrhotic coagulopathy

All tests of coagulation are limited by the inability to accurately reflect in vivo haemostasis. Patients with cirrhosis are not "auto anticoagulated"[3]. Thrombosis rather than bleeding is more likely even when standard tests of coagulation suggest hypocoagulability[4,7,8].

Prothrombin time (PT) and international normalized ratio (INR)

Prothrombin time reflects the extrinsic coagulation factors[3-5]. It is a variable included in risk assessment and decision-making tools such as Child-Turcotte-Pugh, MELD scores and Kings College criteria.

Standard tests of coagulations such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) reflect the activity of procoagulant factors. They do not reflect endothelial cell-coagulation factor interaction nor the activity of protein C and protein S[3-5]. In cirrhotics, bleeding associated with invasive procedures and LT correlate poorly with results of INR and other standard tests of coagulation[2,4,9,10]. Preoperative correction of coagulopathy with plasma and other blood products guided by standard tests of coagulation, the resulting volume expansion and

increased portal and systemic venous pressures exacerbates bleeding during surgery and is associated with increased mortality[11].

Use of INR to guide haemostatic therapy with coagulation factors and factor concentrates in cirrhotics risks overtreatment and thrombosis[4,9].

In the rapidly evolving setting of bleeding during LT the long turnaround time could lead to empirical transfusion of blood products before test results become available. This usually results in overtreatment with blood products.

Viscoelastic haemostatic testing (VHT)

Viscoelastic tests of coagulation such as Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM) are dynamic, global tests of coagulation with a short turnaround time. These tests can define the haemostatic abnormality with a high degree of accuracy enabling the minimum effective haemostatic intervention to be implemented.

In contrast to conventional tests, VHT performed on whole blood, reflects in-vivo the interaction between platelets, leukocytes, erythrocytes, plasmatic pro- and anticoagulants. They are limited by the inability to quantify the role of the endothelium in coagulation. ROTEM and equivalent parameters in TEG provide information regarding clot formation (CT, CFT, alpha angle), clot firmness (A5, A10, MCF, and MA) and clot stability (ML, CLI30, CLI60) within a short turnaround time enabling virtually 'real time' targeted haemostatic therapy in the setting of LT. Viscoelastic tests also detect hypercoagulability; often under estimated in the cirrhotic patients[2]. Compared to conventional coagulation tests, VHTs have superior diagnostic and predictive value of haemostasis and bleeding during LT[12, 13].

The ability to detect normal haemostasis and hypercoagulability reduces the use of blood products, a distinct advantage in the setting of LT[14].

VHT diagnostics should ideally be implemented in combination with a bleeding management algorithm[15].

VHT guided haemostatic therapy is associated with a significant reduction in bleeding, transfusion requirements, massive transfusion rate without an increase in thrombotic complications[2,12]. Additional advantages of VHT therapy include a significant reduction in re-operation for bleeding, acute kidney injury, length of hospital stay and in-hospital mortality[7].

Platelet function changes rapidly and unpredictably as a result of liver graft ischaemic reperfusion injury[16]. Impedance aggregometry, a point of care platelet function test, can predict bleeding and thrombosis in liver transplantation. Its ability to assess the effects of antiplatelet drugs is an added advantage[2,17].

In liver transplantation VHT guided platelet transfusion reduces platelet transfusion by up to 75% of without excess bleeding compared to prophylactic platelet transfusion triggered by a platelet count below $50 \times 10^3/mm^3$ [18].

1.5 Blood products in liver transplantation: Less is more

Prophylactic transfusion of blood products, prior to invasive procedures, surgery and in managing bleeding during liver transplantation has declined significantly. Avoidance of fluid overload contributes to reducing perioperative transfusion. Correction of abnormal of coagulation guided by standard tests inevitably results in administration of blood products. In a cirrhotic patient with portal hypertension, often with underlying impaired cardiac function, administration of fluids results in a further increase in portal venous and central venous pressure and excessive bleeding. The bleeding risk is reduced by aiming for a low portal vein pressure guided by a policy of goal directed use of intravenous fluids and blood products[8].

A better understanding of the deleterious effects of transfused blood products, the pathophysiology of haemostasis in cirrhosis, the advancements in diagnosis disorders of haemostasis and use of transfusion protocols have enabled transfusion free liver transplantation with excellent outcomes[8].

Strategies to reduce of allogenic blood transfusion include use of cell salvage, restrictive fluid therapy, VHT guided correction of disordered haemostasis, protocolized management of bleeding and specialized surgical and anaesthetic teams[1,2].

Increased need for blood products and massive transfusion are predictors of adverse outcome following liver transplantation[12,19]. The poor outcome may in part reflect the severity of underlying cirrhosis and related organ dysfunction[3,4,9].

Use of packed red blood cells, fresh frozen plasma and platelets are predictive of poor graft survival following LT[20,21].

Despite use of high volumes (10-20 mL/kg body weight), fresh frozen plasma is ineffective in correcting coagulopathy and stopping bleeding caused by impaired thrombin generation in cirrhosis while increasing the risk of transfusion associated circulatory overload, transfusion associated acute lung injury, immune modulation, portal hypertension, nosocomial infection, sepsis, and mortality[2,11].

Adverse effects of transfused platelets are not entirely related to haemostasis but may be related to platelet derived cytokines, vasoactive substances and the role of platelets in reperfusion injury[22].

In the setting of liver transplantation, platelet transfusion and rapid changes in platelet function are associated with graft liver damage and worse outcome. Platelet transfusion can exacerbate portal and pulmonary hypertension[23].

Platelet transfusion is considered a high-risk haemostatic intervention particularly during reperfusion and is a risk factor for acute lung injury, graft loss and poor 1 year survival following liver transplantation[19-21].

Though not clearly proven in the setting of liver transplantation, a supranormal fibrinogen level could compensate for thrombocytopenia[2].

Recombinant activated factor VII (rFVIIa) when used in a setting of impaired thrombin generation increased the risk of arterial thromboembolic complications without a significant reduction in transfusion requirement or mortality[2,24].

1.6 Use of viscoelastic haemostatic test-based algorithms for management of perioperative bleeding

The protocolized, viscoelastic haemostatic test-based management of bleeding is a strategy proven to reduce transfusion and adverse outcomes in liver transplantation.

The Essen University ROTEM A5 algorithm provides guidance for thromboelastometry-guided haemostatic interventions in bleeding associated with liver transplantation and in cirrhotic patients undergoing major visceral surgery or invasive procedures[2,25]. Use of the algorithm resulted in a reduction in transfusion requirements without an increase in bleeding or thrombotic events[2,12,19].

The ROTEM A5 based algorithm is recommended to be performed at induction to assess baseline haemostasis. Testing is repeated in the presence of coagulopathic bleeding in the pre anhepatic phase, at 5-10 minutes in the anhepatic phase, repeated at 30-45 minutes, 5-10 minutes into the post reperfusion phase, repeated at 30-45 minutes and at skin closure. The frequency of testing is increased in the presence of haemorrhage and after haemostatic interventions[2].

Prior to testing, hypothermia (core body temperature <35°C), acidosis (pH <7.2), hypocalcaemia (ionized calcium less than 1mmol/l) and haemoglobin less than 7g/dL should be corrected as these impair thrombin generation. Fibrinolysis is enhanced in an acidotic environment.

Management of hyperfibrinolysis

The use of antifibrinolytics during liver transplantation resulted in a significant reduction in transfusion requirements. VHT guide treatment of hyperfibrinolysis is as effective as prophylactic administration of antifibrinolytics while minimizing the risk of thrombotic complications[2].

Baseline $A5_{EXTEM}$ > 25 mm or a flat-line in FIBTEM (CT_{FIBTEM} > 600 s) are markers of an increased risk for hyperfibrinolysis[26]. Hyperfibrinolysis during the dissection phase indicated by a ML > 15% (LI60 >85%), is unlikely to resolve spontaneously, is associated with worse outcome and is treated with tranexamic acid[2].

Increased tissue plasminogen activator (tPA) accompanied by a reduction in plasminogen activator inhibitor -1(PAI-1) during the anhepatic phase reaches a peak after reperfusion of the liver graft. Hyperfibrinolysis developing at the end of the anhepatic phase or after reperfusion is mostly self-limiting. In the absence of severe bleeding, hyperfibrinolysis on VHT during the anhepatic or reperfusion phase should not be treated with tranexamic acid if it is self-limiting and not associated with sever bleeding.

A flat-line FIBTEM (CT_{Fib} > 600s) is associated with a high incidence of hyperfibrinolysis during liver transplantation.

Diffuse bleeding with LIEXTEM >85% in the dissection phase or LIEXTEM > 50% in the anhepatic or reperfusion phase is treated with tranexamic acid[3].

Hyperfibrinolysis during liver transplantation is aggravated by the deficiency of fibrinogen and factor XIII, and colloids (hydroxyethyl starch).

Prophylactic tranexamic acid is avoided if patients have prior portal vein thrombosis or other thrombotic complications[2].

Management of impaired clot firmness during liver transplantation

The role of fibrinogen and platelets in forming a stable clot is analogous to the complementary role of bricks and cement. A deficiency of fibrinogen is compensated by the platelets and vice versa. A higher fibrinogen concentration could reduce the requirement for platelet transfusion and associated adverse effects[2].

In the setting of liver transplantation, EXTEM, FIBTEM and PLTEM (which reflects the platelet contribution to clot firmness characterized by the difference between EXTEM and FIBTEM clot firmness) prove useful in identifying the effect of disorders of fibrin polymerization and platelet dysfunction[2].

$A5_{EXTEM}$ and $A5_{FIBTEM}$ correlate with A10 and MCF and are indicators of clot firmness. These are used as predictors of thrombocytopenia, and hypo-fibrinogenemia and are considered superior to platelet count and fibrinogen levels as predictors of bleeding and need for blood transfusion[2, 12].

In a patient with bleeding and $A5_{EXTEM}$ <25mm, could be due to impaired clot strength due to a fibrinogen deficiency/fibrin polymerization issue or a low platelet count/platelet dysfunction issue[2]. $A5_{EXTEM}$ <25mm with $A5_{FIBTEM}$ <8mm is sug-gestive of a fibrinogen deficiency/fibrin poly-merization issue while $A5_{EXTEM}$ <25mm and $A5_{FIBTEM}$ >8mm suggests thrombocytopenia. An $A5_{EXTEM}$ less than 19mm reliably predicts a platelet count of less than $50 \times 10^3/mm^3$ [3].

A major limitation of standard viscoelastic haemostatic assays is that they can only detect platelet dysfunction related to the thrombin receptor pathway. Tests of whole blood impedance aggregometry are required to identify platelet function defects related to other pathways[2].

Management of impaired thrombin generation

In cirrhotics, deficiency of factor II, VII, IX, X and V contributes to impaired thrombin generation. During liver transplantation, bleeding with a

prolonged CT_{EXTEM} >75s but a normal $A5_{FIBTEM}$ indicates a thrombin generation defect[2,12].

Reduced thrombin generation in LT can be more effectively treated by using 4 factor prothrombin complex concentrate (4F-PCC) rather than FFP[27]. The use of low dose 4F-PCC containing vitamin K-dependent coagulation factors as well as anti-coagulating factors are associated with minimal risk of thromboembolic complications[28]. In a patient with bleeding with a normal EXTEM CT, a prolonged CT_{INTEM}, not corrected in HEPTEM, FFP could be used as a source of factors V, VIII, and XI which are not contained in fibrinogen concentrate and 4F-PCC[2].

Management of heparin-like effects

The glycocalyx of the graft liver which is damaged during the period of ischaemia, releases heparinoids during liver graft reperfusion[29]. This manifests as prolonged aPTT and CT_{INTEM}. Shortening of CT_{HEPTEM} compared to CT_{INTEM} confirms the usually transient heparin-like effect. INTEM/HEPTEM CT-ratio greater than 1.25 indicates a significant heparin-like effect which if associated with significant bleeding can be treated with low dose protamine (25-50 mg). Overtreatment with protamine could aggravate bleeding since it inhibits factor V and results in platelet dysfunction[2].

1.7 Perioperative thromboprophylaxis

The risk of thrombosis due to rebalanced haemostasis in patients with cirrhosis must be weighed against the risk of postoperative bleeding complications. Recent guidelines on perioperative venous thromboembolism prophylaxis suggest that the use of pharmacological prophylaxis in patients with severe liver dysfunction should be carefully balanced against the risk of bleeding. Mechanical DVT prophylaxis can be used in most patients. Low-dose unfractionated heparin or low molecular weight heparin can be used in patients at high risk of VTE (Grade 2C)[30].

ROTEM A5 Liver Algorithm. Courtesy of Klaus Görlinger, Munich, Germany.
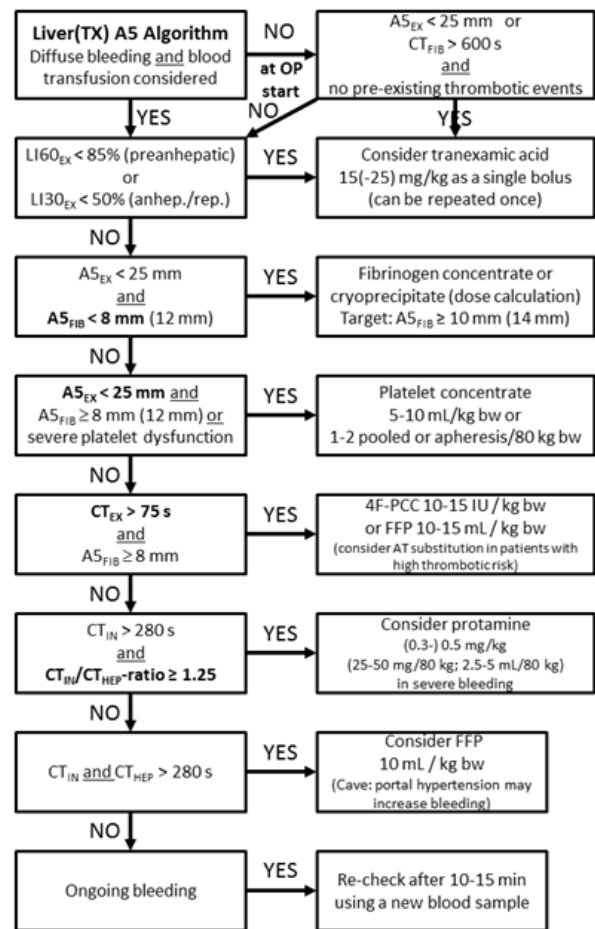
1.8 Summary

Cirrhotic coagulopathy is a key management issue in liver transplantation. Though liver transplantation was characterized by massive bleeding and transfusion of blood products in the past, a steady decline in transfusion requirements has been observed over the past 15 years. This may be due to improvements in perioperative care and a better understanding of the pathophysiology of rebalanced haemostasis and cirrhotic coagulopathy resulting in a radical shift in the management of coagulopathy and transfusion of blood products. Standard tests of coagulation such as prothrombin time, international normalized ratio and platelet count are limited in their ability to predict bleeding, thrombosis and to guide management of bleeding in LT. These tests tend to overestimate the bleeding risk leading to overuse of blood

products. Use of blood products such as fresh frozen plasma and platelets could result in injury of the grafted liver and increased mortality. Use of a restrictive fluid management strategy, viscoelastic testing-based algorithm in combination with a blood management protocol by a dedicated liver transplant team reduce blood product usage without an increased risk of bleeding or thrombosis in the setting of liver transplantation.

Authorship

Conflict-of-interest: Klaus Görlinger works as the Medical Director of Tem Innovations, Munich, Germany.

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