

Strategies to avoid empiric blood product administration in liver transplant surgery

ABSTRACT

Massive blood loss has been a dreaded complication of liver transplantation, and the accompanying transfusion is associated with adverse outcomes in the form of decreased patient and graft survival. With advances in both surgical techniques and anesthetic management during transplantation, blood and blood products requirements reduced significantly. However, transfusion practices vary among different centers. The altered coagulation parameters in patients with liver cirrhosis results in a state of “rebalanced hemostasis” and patients are just as likely to clot as they are to bleed. Commonly used coagulation tests do not always reflect this new state and can, therefore, be misleading. Transfusion of blood products solely to correct abnormal parameters may worsen the coagulation status, thus adversely affecting patient outcome. Point-of-care tests such as thromboelastometry more reliably predict the risk of bleeding in these patients and in addition may provide quicker turnaround times compared to routine tests. Perioperative management should also include the possibility of thrombosis in these patients, and the use of low-molecular-weight heparin correlates with better patient survival. This review article aims to highlight the concept of rebalanced hemostasis, limitation of routine coagulation tests, and harmful effect of empiric transfusion of blood products.

Key words: Hepatic anesthesia; liver transplant coagulation; liver transplantation; point-of-care tests; rebalanced hemostasis; transfusion

Introduction

There is convincing evidence that blood product administration decreases patient and graft survival in the setting of liver transplantation. It is also known that practice of transfusion varies widely among different centers. Developments in the understanding of the process of coagulation in end-stage liver disease patients do shed some light as to how these patients may differ in their hemostatic profile from other patients with similar laboratory values but different comorbidities. Understanding this process as well as the implications for

perioperative management of patients undergoing liver transplantation is imperative before any modifications in the practice habits can be expected from anesthesia providers. This review article discuss how abnormal coagulation tests can be misleading if only these numbers are relied upon to make decisions about transfusing these patients and how alterations in their approach toward managing these patients have enabled many centers to decrease their blood product administration.

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Rebalanced Hemostasis

The process of hemostasis is a regulated series of steps that involve platelets, endothelium, and various proteins including clotting factors. They are controlled with intricate feedback mechanisms that maintain the equilibrium between procoagulant and anticoagulant factors as well as the fibrinolytic and antifibrinolytic systems.

Nearly, all the clotting factors and inhibitors are synthesized in the liver. The liver also synthesizes thrombopoietin, a hormone that stimulates platelet production from the liver. Furthermore, the portal hypertension and hypersplenism of chronic liver disease lead to increased sequestration of platelets.^[1,2] Predictably, in liver disease, the synthesis of these pro- and anti-hemostatic factors, as well as the platelets, is adversely affected and that leads to a hemostatic imbalance. While there is decrease in the production of most hemostatic proteins, Factor VIII and von Willebrand's factor (vWF) remain elevated in liver disease. These two factors are synthesized in the vascular endothelium and remain elevated in contrast to the other clotting factors. In cirrhotic patients, ADAMST13, a vWF cleaving enzyme produced by the hepatic cells, is reduced. The imbalance between reduced ADAMST13 activity and increased vWF production by the endothelium correlates with functional liver capacity and may be used to predict long-term survival of cirrhotic patients.^[3] The decrease in the number of platelets is counterbalanced by the increase in vWF factor. This increase in vWF facilitates platelet adhesion and aggregation. In this set of patients, fibrinolytic system is affected as well. While plasminogen and alpha 2-antiplasmin levels are decreased inhibiting lysis, tissue plasminogen activator and plasminogen activator inhibitor-1 are increased, thus favoring fibrinolysis.^[4] In addition, the hemostatic abnormalities vary between acute and chronic liver conditions and between the various etiologies of liver cirrhosis. Patients with chronic liver diseases are said to be in accelerated fibrinolysis as opposed to those in acute liver failure, where fibrinolysis is inhibited.^[5,6]

The changes in hemostatic parameters mentioned above lead to a new state of "rebalanced hemostasis."

Although widely believed that patients with liver dysfunction are "bleeders," there is reason to believe that they are "clotters" as well. This phase of "rebalanced hemostasis" is not static but rather dynamic and can tip toward either bleeding or thrombosis [Figure 1]. This unpredictable nature of hemostasis necessitates a more reliable point-of-care laboratory tests.

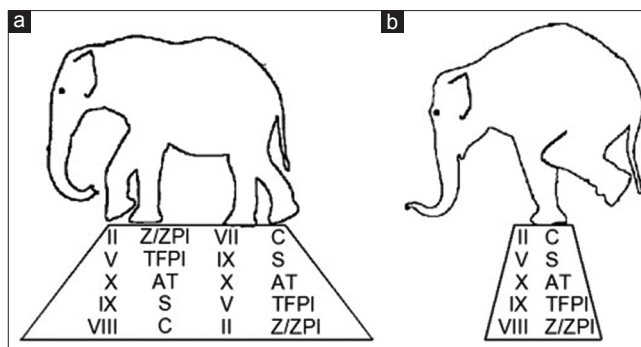


Figure 1: Hemostatic balance (reproduced with permission). (a) Under normal conditions, there are higher levels of pro- and anti-coagulant proteins than are needed for minimal hemostatic function. This functional "excess" allows for a high degree of stability – the hemostatic balance tends to be maintained even under stress. (b) When the levels of pro- and anti-coagulant factors are reduced by hepatic insufficiency, there may not be a tendency to hemorrhage or thrombosis/disseminated intravascular coagulation. However, the hemostatic balance is much harder to maintain in the face of stressors such as infection. AT: Antithrombin, ZPI: Protein Z-related protease inhibitor, TFPI: Tissue factor pathway inhibitor, C: Protein C, S: Protein S

Why Coagulation Tests Performed in Patients with Chronic Liver Disease Misguide Us?

While tests such as platelet count, activated partial thromboplastin time (aPTT), and prothrombin time (PT) predict coagulopathy in healthy individuals, they are less informative in patients of liver dysfunction. In reality, they misinterpret the hemostatic changes that take place in liver dysfunction. The measured platelet count does not take into account the elevated vWF levels, and the PT and aPTT are only a reflection of the pro-hemostatic factors. The limitations imposed by the routine hemostatic tests have led to the misguided practice of prophylactic transfusion of these patients.

Conventionally, PT and aPTT have been used to predict the coagulopathy in liver disease. However, this does not reflect the true picture in these groups of patients as these tests measure only the procoagulants in plasma (Factor II, VII, and X and fibrinogen). They do not take into account the simultaneous alterations in anticoagulants, protein C and S, antithrombin, and tissue factor pathway inhibitor. As a result, they cannot be used to reliably predict the risk of bleeding in these patients with altered hemostasis.^[7,8] In addition, these routine tests may also have longer turnaround times, hence the need for point-of-care tests such as viscoelastic tests (VETs) and thrombin generation assay.

Other Methods that Assess Hemostasis

Point-of-care tests

In the light of the above inadequacies, point-of-care tests such as VETs gained popularity. The commonly used

devices are thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These tests better reflect the interaction between platelets and coagulation factors. The different thromboelastometry parameters measure fibrin formation, clot strength, clot firmness, and fibrinolysis and thus permit a more goal-directed transfusion therapy. Measurement of TEG functional fibrinogen (TEG FF) or fibrinogen rotational thromboelastometry-ROTEM quantifies the contribution of fibrinogen to clot strength and thus avoids inappropriate platelet transfusion.^[9] TEG and ROTEM-guided transfusion is associated with reduction in the use of fresh frozen plasma (FFP), platelets, and red blood cell (RBC) and increased use of factor concentrates.^[10]

Thrombin generation assay

A less commonly used test is the thrombin generation assay. These special tests measure the endogenous production of thrombin by adding phospholipids and thromboplastin to platelet-poor plasma. The ability to form thrombin is assessed by the thrombomodulin–thrombin complex, which in turn activates the Vitamin K-dependent protein C system. In the presence of thrombomodulin, the generation of thrombin was found to be the same, even increased, in those with liver disease compared with healthy volunteers.^[6,11] The major drawback is the complexity of the procedure and the lack of availability in many centers.

Why We Need To Minimize Transfusion during Liver Transplantation

Blood transfusion

Transfusion of blood and blood products is associated with the complications such as infection, sepsis, reduced graft function, renal injury, and immunosuppressive effects, leading to increased mortality and morbidity after liver transplantation.^[12-15] It is now well known that transfusion of blood and blood products is associated with a negative patient outcome and with increased mortality.^[16,17] In addition to infection, risk factors such as alloimmunization, transfusion-related acute lung injury (TRALI), excessive intravascular volume, and immunosuppressive effects are of particular interests in a patient of liver transplant. Improvements in transfusion practices have led to a drastic reduction in the incidence of infection following transfusion of blood and blood products.^[18,19]

Platelets transfusion

In patients of liver cirrhosis, the thrombocytopenia is balanced by the increase in vWF multimers and the practice of prophylactic transfusion of platelets seems to be more harmful than helpful. Platelet transfusion is associated with severe pulmonary complications, primarily TRALI and acute

respiratory distress syndrome.^[16] Both conditions damage the alveolar lining and increase pulmonary permeability leading to pulmonary edema and hypoxia. Some of the theories to explain this are transfer of antileukocyte antibodies from platelets, leading to cytotoxic activation,^[20] accumulation of inflammatory mediators in stored platelets,^[21] pulmonary platelet sequestration,^[22] cell debris from ischemic donor leading to pulmonary aggregates,^[23] and release of endotoxins from donor liver after reperfusion.^[24] The method of platelet preparation is yet another factor that predicts transfusion reaction. Plateletpheresis, where only one donor is used, is associated with fewer transfusion reactions compared to either platelet-rich plasma or buffy coat-based preparation.^[25] Nevertheless, trying to avoid platelet transfusion is prudent. TEG may be more helpful in this regard as it gives a better idea of platelet functions opposed to measuring platelet count by itself.^[26]

Fresh frozen plasma transfusion

Transfusion of FFP is also associated with TRALI. Damage to endothelial cells by inflammatory mediators have been implicated as a causative factor.^[27] The development of TRALI after plasma products (platelets and FFP) has a 10-fold increase in mortality after liver transplantation.^[9] The prophylactic use of FFP has been associated with a concomitant increase in splanchnic and portal hypertension, leading to a vicious cycle of more bleeding and hence more transfusion.^[28] In fact, a study by Massicotte *et al.*^[29] showed that transfusion of plasma was directly linked with an increase in RBC transfusion and that it negatively affected patient outcome. Patients who received plasma had 20% decrease in 1-year survival compared to those who did not.

Red blood cells transfusion

The use of RBCs was also involved in a host of complications such as hemolytic reactions, graft versus host disease, and transfusion-related sepsis besides infection.^[30] One-year survival rates were 4.2 times higher in those who were not transfused compared to those transfused four or more RBC units.^[29] Transfusion of the blood is said to alter the immunity level, leading to what is called as transfusion-related immunomodulation. This could further increase the incidence of transfusion-related infection.^[31,32] Boyd *et al.*^[33] showed that patients with previous transfusion had anti-RBC antibodies, which predicted poorer survival postliver transplant. Another reason presumably responsible for poorer outcomes following blood transfusion is the presence of residual amounts of donor leukocytes present during RBC transfusion.^[34] To counter this, leukoreduction technologies are being used currently.^[35,36] In addition, the transfusion of allogenic blood products leads to a decrease in immunity and more postoperative infections and multiple organ failure.^[31,32]

Poor Correlation between Coagulation Tests and Bleeding

With the exposure of the endothelium and the interaction of tissue factor and Factor VII, a series of enzymatic reactions take place, leading to the formation of thrombin. This ensures the conversion of fibrinogen to fibrin clot as shown in Figure 2. This procoagulant drive is counterbalanced by the interaction of thrombin with thrombomodulin present on the endothelium, activating protein C. Protein C interacts with protein S to downregulate thrombin.^[37] Coagulation tests such as PT and APTT measure the conversion rate of fibrinogen to fibrin.^[38] However, these tests are done without the inclusion of thrombomodulin and thus not taking into account the thrombin–thrombomodulin interaction and the role of protein C in balancing the procoagulant state.^[39]

Tripodi *et al.*, in their study, found that thrombin generation in both the controls and patients of cirrhosis were comparable after the addition of thrombomodulin to the tests. They suggested that the bleeding in these patients was more likely due to hemodynamic alterations^[38] than any coagulopathy. Various studies have been conducted to further throw light on the apparent lack of correlation between coagulation parameters and bleeding in cirrhosis. Segal and Dzik reviewed a clinical trial and 24 observational studies to determine whether elevated preprocedural PT and international normalized ratio (INR) were indicative of increased bleeding tendency during the procedure. Procedures such as liver biopsy, bronchoscopy, central venous cannulation, and femoral arteriography were conducted in patients with elevated INR in their review. These studies showed that the risk of bleeding with abnormal parameters was comparable to those with normal parameters. Their review concluded that

an elevated INR did not predict periprocedural bleeding.^[40] In another study, cirrhotic patients who underwent cardiac catheterization were retrospectively reviewed for bleeding complications. One hundred and fifty-seven patients undergoing right heart catheterization (RHC) and 83 patients having left heart catheterization (LHC) were categorized in groups of normal (≤ 1.5 INR) and elevated (≥ 1.5 INR). In both the RHC and LHC groups, there was no significant change in pre- and post-procedure hemoglobin in both the normal and elevated INR group.^[41-44]

Variability in Transfusion Practice Worldwide

Transfusion practices vary in different centers depending on patient selection and surgical conditions.^[45] Findlay *et al.* studied the variation in transfusion practices in liver-transplant recipient over a period of 15 years.^[46-48] The early group (1991–1992) received five times the blood products as compared to the recent group (2005–2006). However, they attributed this to changes in surgical technique.^[49] de Boer *et al.*, in their study, followed up 749 consecutive orthotopic liver transplantation patients between 1989 and 2004. Patients who received any form of transfusion were categorized in two eras, 1989–1996 and 1997–2004. Patients in the latter group received about 30% fewer transfusion of blood products compared to the earlier group.^[17]

How to Avoid Transfusion

Portal venous pressure reduction

Role of surgery

Besides coagulopathy, several other factors are responsible for the intraoperative bleeding seen in liver transplant surgery. Surgical skills seem to be one of them, and an improvement of surgical techniques is associated with a decrease in blood transfusion.^[49] While previously hepatectomy involved inferior vena cava (IVC) cross-clamp, recent surgical techniques use an IVC-sparing technique or the piggyback technique.^[50] This technique has led to shorter operative times with less hemodynamic compromise, reduced use of blood and blood products, and improved survival outcomes.^[51] Preoperative portal decompression with splenic artery trunk embolization described by Li *et al.* reported a shorter surgery duration with a lesser bleeding compared to the venovenous bypass and the piggyback techniques.^[52]

Bleeding attributable to coagulopathy would have simultaneous oozing from multiple sites. Instead, the bleeding that occurs in these patients seems to be predominantly hemodynamic in nature. The esophageal varices that are seen commonly in cirrhotic patients are due to portal hypertension, with abnormal hemostasis playing

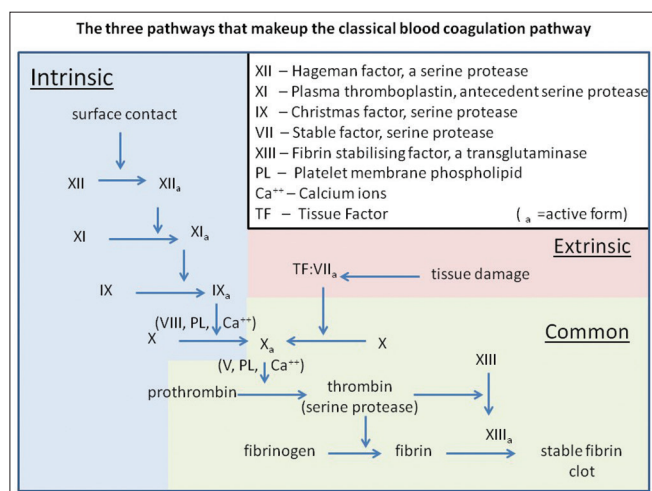


Figure 2: Coagulation cascade. https://commons.wikimedia.org/wiki/File:Classical_blood_coagulation_pathway.png, Creative Commons Attribution-Share Alike 3.0 Unported

only a minor role.^[53] As portal pressure cannot be measured reliably intraoperatively, central venous pressure (CVP) is often used as a surrogate to read the portal pressure.^[54] Portal hypertension leads to pooling of blood on the venous side of circulation, and so predictably, any fluid transfused leads to increased venous pressure and more bleeding. Lowering the CVP has been shown to reduce the incidence of blood loss and the need for transfusion.^[54-57] This can be achieved by forced diuresis and avoiding prophylactic transfusion in those patients without clinically significant bleeding. A restrictive transfusion practice also avoids the issue of dilution coagulopathy and hence prevents further transfusion of blood products. Maintaining a low CVP is believed to be the most important factor in reducing blood loss and avoiding transfusion of blood products even if it necessitates phlebotomy.^[29] An important parameter to monitor while maintaining low CVP is the renal function. Despite the ongoing debate whether low CVP has a negative effect on renal function, a randomized controlled trial comparing low and normal CVP found a significant reduction in blood loss without affecting kidney function.^[56] In addition to lowering the CVP, other factors such as controlling infections,^[58,59] maintaining normothermia, normocalcemia,^[60] and acid–base balance^[61] also play a part in ensuring adequate hemostasis.

Role of vasopressors

Portal hypertension and low systemic vascular resistance (SVR) due to peripheral vasodilation are essential findings in advanced cirrhosis.^[62,63] Intraoperatively, the effects of low SVR are compounded by the use of anesthetic agents, leading to profound hypotension requiring volume replacement in the form of intravenous (IV) fluids or blood transfusion. The use of vasopressors, such as norepinephrine, has been used to counter this vasodilatory effect. Titrated infusion of vasopressors along with cautious use IV fluids was shown to reduce intraoperative fluid overload.^[64] Another strategy to reduce the pressure in the portal vein is the use of vasopressin, which has been shown to significantly reduce portal venous pressure and flow in the native liver without decreasing the cardiac output in patients undergoing liver transplantation.^[65] Wagener *et al.* demonstrated that patients with liver disease have low endogenous levels of vasopressin and addition of exogenous IV vasopressin resulted in an increase in SVR, thus improving the perfusion pressure.^[66,67] Addition of small bolus dose of vasopressin to treat episodes of hypotension could well be another method to circumvent the need for transfusion.

Thromboprophylaxis

Since there is deficiency of both anticoagulant and procoagulant factors in patients with liver disease, the balance

between the two determines whether the patient is at risk for hemorrhage or thrombosis. Despite the prolonged coagulation parameters in these patients, it is not unlikely for these patients to experience thrombotic events. This is explained by the normal generation of thrombin in liver cirrhosis. The routine coagulation test reflects an anticoagulated state, while global coagulation tests such as thromboelastometry depict a hypercoagulable state.^[68] This increases the likelihood of developing portal vein thrombosis (PVT), deep vein thrombosis (DVT), and pulmonary embolism in these patients. Thrombotic complications are greatly underestimated in cirrhotic patients with only 25% of these patients receiving venous thromboembolism prophylaxis.^[69]

PVT is common among those with established liver cirrhosis, with a prevalence of 11%.^[70] Untreated PVT worsens portal hypertension and increases the risk for death. These patients are also at increased risk for DVT and pulmonary embolism.^[71] The use of low-molecular-weight heparin (LMWH) has been shown to be effective to prevent and treat the thrombotic complications and is associated with better survival.^[72,73] However, the use of LMWH has to be titrated as the potency of LMWH appears to be increased in patients with liver disease as compared to those with normal liver function.^[74] In view of the hemostatic profile in cirrhotic patients, anesthesia providers should be vigilant to the possibility of thrombosis and that liver disease does not protect against thrombosis.

Conclusion

Patients with cirrhosis and liver disease are in a state of rebalanced hemostasis. The practice of prophylactic transfusion should be given up for a more conservative “watch-and-wait” approach. Prolonged coagulation parameters do not reflect the state of rebalanced hemostasis and underestimate the presence of thrombosis. Alternative strategies should be adopted to minimize bleeding during transplant surgery and every effort made to avoid transfusing blood products. Coagulation tests such as thromboelastometer and thrombin generation assay are found to be better predictors of coagulopathy in this group of patients.

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Conflicts of interest

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