Coagulopathy during liver transplantation

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Abstract

In this review article, we aimed to mainly review the principles for the management of hemostasis, changes that occur in the hemostatic system, and the techniques to reduce hemorrhage during liver transplantation. Hemostasis is a defense mechanism that may ensue from vascular damage and hemorrhage and consists of multiple phases which involve cellular and humoral elements of coagulation. In the presence of a cause, such as trauma-induced liver injury or hepatic failure that may trigger coagulopathy, the process becomes more problematic, and moreover, severe coagulation disorders may arise in daily practice unless the situation is intervened correctly and on time. During liver transplantation, the implementation of transfusion and coagulation management algorithms based on the point of care tests may reduce blood loss and transfusion requirement. Moreover, antifibrinolytic therapy and a low central venous pressure with restrictive fluid administration reduce bleeding.

Keywords: Bleeding, coagulopathy, liver transplantation

Introduction

The target health strategy today focuses on minimizing morbidity and mortality while minimizing the cost of healthcare services at the same time. Studies have demonstrated that the transfusion of blood products is associated with significantly reduced survival in the first postoperative year after liver transplantation and that the transfusion >2 units is an independent risk factor.\(^{1,3}\) Transfusions may do harm and/or their administration selects sicker or more unstable liver transplant recipients. In addition, Reichert et al.\(^{4}\) revealed that the lifetime without the need for dialysis after liver transplantation decreased in patients that received >12 units of erythrocyte suspension (ES), >11 units of fresh frozen plasma (FFP), and >2 units of platelet suspension (PS). On the other side, no increase was observed in the frequency of postoperative pulmonary embolism in patients receiving FFP and ES transfusions during liver transplantation surgery.\(^{5}\)

The total per unit cost of ES transfusion, including the costs of donor, per unit production, preparation, possible side effects, transfusion-transmitted diseases and hemovigilance, was estimated at approximately 1400 Euros.\(^{6}\) Masciotte et al.\(^{7}\) stated that they administered none or only 2–3 units of blood products to 80% of the patients in the study conducted in 2012. It is now known that mortality and morbidity are associated with bleeding and transfusion; however, the 5-year survival rate has increased from 72% in 1998 to 90% in 2010 owing to the advances in surgical techniques, anesthesiology, and immunology. Nevertheless, it is out of doubt that the strategies adopted to ensure the rational use of blood and blood products are of the major factors underlying this improvement.

In this opinion article, we aimed to mainly review the principles for the management of hemostasis, changes that occur in the hemostatic system, and the techniques to reduce hemorrhage during liver transplantation.
**Rebalanced Hemostasis**

Prohemostatic factors and antihemostatic factors are synthesized in the failing liver, and are therefore, decreased in parallel. Moreover, there are additional prohemostatic factors derived from the endothelium or subendothelium which are increased, e.g., vWF and factor VIII. They also help to compensate for deficiencies in platelet number and function. It would not be wrong if we consider liver as a conductor because almost all circulating coagulation factors and inhibitors as well as the components of the fibrinolytic system are synthesized in the liver. In the coagulation cascade, tissue damage induces the release of the vWF from endothelium leading to the adhesion and aggregation of platelets and the generation of thrombin. It is followed by the formation of fibrin from fibrinogen. The resultant fibrin is stabilized with FXIII while plasmin, which is converted from plasminogen by plasminogen activator, cleaves fibrin into fibrin degradation products. In the absence of coagulopathy, this process proceeds in a balanced manner. Thrombin generation is normal or even increased in these patients due to the concurrent (unbalanced) reduction in pro and anticoagulants.

**What changes occur in the hemostatic system within the scope of liver cirrhosis?**

Both the production and the clearance of coagulation factors becomes impaired due to decrease of hepatocytes and blood flow in the liver. The modulation of the prothrombotic and antithrombotic systems collapses; however, contrary to the popular belief, such patients are not considered as “auto-anticoagulated patients.” Despite the prolonged PT, PTT, and INR, there is no continuous bleeding owing to the presence of varying levels of rebalancing in both pans of coagulation balance. Nevertheless, this balance is so delicate and not as stable as in healthy patients that it can be disrupted by any intervening infection, surgery, or injury. Moreover, the risk of thrombosis can be considered as dangerous as bleeding in these patients; therefore, the maintenance of the newly formed balance is of significant importance.

Furthermore, the hemostatic balance in the presence of acute or chronic liver failure varies depending on the etiology of the disease – cholestatic or noncholestatic. For instance, there are fewer hemostatic changes in primary sclerosing cholangitis and primary biliary cirrhosis compared to parenchymal diseases. While thrombocytopenia is less common in acute failure and fibrinolysis is partially affected, the deficiency of procoagulant and anticoagulant factors significantly decreases. The predisposition to thrombosis also increases as obesity is often accompanied by nonalcoholic fatty liver disease. The incidence of portal vein thrombosis is nearly 1% among healthy people, whereas this rate goes up to 26% in patients with cirrhosis which shows predisposition to thrombosis. The fall in the production of the antithrombotic compound has been claimed to be the cause of that situation. The use of new-generation anticoagulant and antiplatelet drugs other than low molecular weight heparin (LMWH) may be beneficial for prevention of hypercoagulable conditions in these patients. However, as there is not sufficient data supporting the use of these drugs, LMWH is still the most secure alternative today. On the other hand, the anti-Xa assay does not correctly indicate the accurate level of these drugs in blood. The vitamin K antagonists are typically monitored with INR, but hemostatic management is complicated because the target level cannot be known in these patients because of the increased INR.

**Primary Hemostasis**

Although the platelet production either remains normal or shows increase in the case of liver failure accompanied by portal hypertension, the production of thrombopoietin may decrease later in the process as a result of alcohol use, hepatitis viruses, and inadequate intake of nutritional supplements. Ultimately, the platelet production lessens over the time, but concomitant splenic sequestration and hepatorenal syndrome lead to increased platelet consumption, which shortens the lifetime. Furthermore, the reduction of the arachidonic acid and adenine nucleotide levels in platelet results in the emergence of dysfunctional platelets with inadequate aggregation. In addition, impaired endothelial nitric oxide metabolism and vasodilation disrupt the elasticity of platelet as well as its adhesion to the vascular wall. The fall of metalloprotease ADAMTS 13, which limits the impact of the von Willebrand factor on platelet and increases the adhesion of platelets. The composition of all the factors mentioned above results in the elevation of FVIII ensuring the adhesion of the VWF platelets – the carrier for F VIII factors in plasma – to the subendothelium. The reduced hepatic clearance compensates approximately 200% increase in the endothelial release.

However, even if the platelet count decreases, the generation of thrombin is protected in cirrhosis patients owing to all these adaptive mechanisms. Only 5% of thrombin is available when blood clotting starts. In addition, the reduction of the alpha 2 antiplasmin and plasminogen, which are among the key components of the fibrinolytic system, that develops in parallel with the decrease of the anticoagulant proteins C, S and anti-thrombin 3 enhances the susceptibility to thrombosis.

**Secondary Hemostasis**

The level of the vitamin K-dependent factors II, V, VII, IX, X falls by 25–70%. Even though the fibrinogen level is normal
or elevated in these patients, there is abnormal fibrinogen production (dysfibrinogenemia) due to the presence of high sialic acid content. Also, the scarcity of Factor XIII degrades fibrin polymerization resulting in increased susceptibility to bleeding. [14]

The reduced levels of natural anticoagulant proteins present together with reduced levels of procoagulant proteins. The resistance to thrombomodulin occurs in patients with liver disease. These changes cause to rebalanced hemostasis.

**Predictors**

McCluskey index is a scoring system which is used to predict the bleeding risk based on the parameters including age, hemoglobin, platelets, INR, creatinine, and albumin. [15] It is rated from 0 to 8, and scores > 5 indicate the need for > 6 units of ES. Another study suggested the MELD score > 25, ascid, varicose veins, platelets, hemoglobin, the level of fibrinogen and fibrin degradation products, and the presence of hemorrhage to be the predictors as well. [12] According to Esmat Gamil et al., [16] presence of ascids and INR exceeding 1.6 are independent predictors of increased intraoperative blood loss.

**Impact of Hemoglobin**

Erythrocytes are known to play an active role in the formation of thrombin as they support platelet aggregation and raise thromboxane A2 synthesis through ADP release. It was found in a study that the covered surface obtained with the use of 20% Htc is 50% smaller than the covered surface obtained with 40% Htc (the platelet count being equal). [17] Decreased haematocrit impairs platelet margination. [18]

**Techniques to Reduce Hemorrhage during Liver Transplantation**

Coagulation monitoring tests used routinely in the laboratories today indicate the outset of thrombus formation. [19] Routine tests include prothrombin time, partial thromboplastin time, INR value, platelet count, and fibrinogen. These tests are not affected by profibrinolytic susceptibility, anticoagulant protein C, antithrombin and tissue factor pathway inhibitor, and endothelium-derived hemostatic process. These tests fail to predict the hemorrhage risk; however, it is clear that volume loading will increase splanchnic and portal pressure and may increase bleeding.

**Viscoelastic tests**

Point of care tests that provide immediate information are medical diagnostic tests performed outside the clinical laboratory and near the side of patient care. The viscoelastic signal obtained through the point of care testing depends on endogenous thrombin formation, fibrin polymerization, and the interaction between fibrin and glycoprotein IIb/IIIa receptor, and evaluates the thrombin-mediated processes. The point of care testing, which can be carried out by a physician, nurse, or laboratory technician using handheld devices without requiring any permanent or specific location, may provide practical changes in patient care. [20] The point of care testing provides rapid results, but the tests are expensive and require training, and moreover, their result can be affected by experience and calibration. Nevertheless viscoelastic tests have become widely used in the setting of liver transplantation because an algorithm based on point of care testing may improve outcome in and reduce the rate of transfusion. [21, 22] ROTEM and TEG are useful in managing intraoperative bleeding, however, it is difficult to compare the two methods. The evaluation of these two methods were studied in trauma patients. [23, 24] However validation and development of separate treatment algorithms is required. Therefore, each patient should be assessed individually.

Vasopressin improves organ perfusion and reduces intra-abdominal blood loss by decreasing the splanchnic blood flow. Clonidine induces the decline of the portal pressure by reducing the sympathetic activity in the splanchnic circulation. Conjugated estrogen has been shown to increase the platelet count by raising the thromboxane B2 and beta-thromboglobulin when it is administered just before the surgery and reperfusion. Cell-saver tumor dissemination technique cannot be applied in the presence of intestinal leakage and abdominal infections. Muscari et al. [25] evidenced that the use of cell saver does not increase the risk of neoplastic recurrence in patients undergoing liver transplantation for hepatocellular carcinoma. During the 1-year follow-up, recurrence was found to be 6.4% with cell salvage and 6.3% without cell salvage. However, this technique has some side effects, such as bacterial contamination, removal of platelets and clotting factors through irrigation, nonimmune hemolysis, air embolism, contamination of irrigation solution, and contamination of the filtrate with activated leukocytes and cytokines due to insufficient irrigation.

**Antifibrinolytics**

As hypofibrinogenemia induces the formation of small and unstable platelet plug, fibrinogen is crucial for the vWF-platelet interaction in primary hemostasis. On the other hand, it is also crucial for secondary hemostasis as the clot stabilized with fibrin only creates a surface for thrombin generation and fibrinogen may be converted into fibrin monomers depending on platelets. All these processes are enzymatic. The use of fibrinogen may
work out in the early phases of bleeding when it is still intact; however, it may not be effective when applied in the later stages of coagulopathy. Fibrinolysis is the leading cause of bleeding during the second and third phases of liver transplantation. Many antifibrinolytic drugs including aprotinin, epsilonaminocaproic acid (EACA), and tranexamic acid have been used for the treatment/avoidance of fibrinolysis. Dalmau et al.\textsuperscript{[26]} reported that using prophylactic EACA did not reduce ES transfusion during liver transplantation whereas tranexamic acid achieved a significant reduction. Boylan et al.\textsuperscript{[27]} indicated that 20 mg/kg tranexamic acid diminished blood loss without causing thrombosis and claimed tranexamic acid to be 6–10 times more potent than others. The EACA, a lysine analog that inhibits the formation of plasmin from plasminogen, has been indicated to be less potent than tranexamic acid but make a higher increase in the incidence of renal failure.\textsuperscript{[28]} Clevenger et al.\textsuperscript{[33]} suggested that the thrombosis risk of tranexamic acid is lower than that of aprotinin.

**Volume Restriction**

Low central venous pressure (CVP) prevents congestion in the liver by decreasing blood loss and transfusion requirements. Increased CVP may increase the splanchnic venous pressure and can be detrimental for patients with splanchnic vein thrombosis. On the other hand, this management strategy has some limitations. This is particularly related with decreased arterial blood volume and a hypovolemic, hyperactive circulation in patients with advanced liver cirrhosis. Besides, CVP is not a good indicator of the actual volume status in cirrhotic patients. In hepatorenal syndrome, the traditional target values for CVP usually fail apparently to exclude hypovolemia.\textsuperscript{[29]} Fayed et al.\textsuperscript{[30]} compared the effects of low central venous pressure and transesophageal Doppler-guided fluid management on blood loss and blood transfusion during liver transplantation. According to their comparison, transesophageal Doppler-guided fluid management tended to have less but nonsignificant, blood loss, packed red blood cells, fresh frozen plasma, and platelets, and received significantly less colloid and higher norepinephrine. Urine output was significantly lower in the preanhepatic phase for low CVP group. Lactate was also significantly higher at the end of the anhepatic phase.

Even if all side-effects are ignored, the prophylactic transfusion of blood and blood products cause volume overload and elevates central venous pressure, which induces increase in bleeding. When applied in the preoperative period, phlebotomy reduces the total circulatory volume, thus reducing the need for transfusion.\textsuperscript{[31]} Nevertheless, hypoperfusion should also be avoided during fluid restriction, especially for protection of kidneys and optimization of blood flow to vital organs. Abnormal blood flow is a component of Virchow’s triad and may trigger thrombosis.

**Management of Hemostasis in Liver Transplantation**

The cause of bleeding is mostly multifactorial in these procedures, and as the patients’ status may deteriorate within a few minutes, rapid diagnosis and early treatment is essential. The anesthesiologist should revive the situation quickly, step into action, and take bleeding under control as fast as possible. Several approaches have been raised on this issue. According to the pathophysiology-oriented approach, transfusion should be done only when necessary to treat the patient rather than improving the results of a laboratory test; in other words, the management must be based on improving the patient’s clinical problems.

The concentrates of several factors are available and the factor VII, antithrombin, prothrombin complex concentrate, and fibrinogen concentrations are the most frequently administered factor concentrates.\textsuperscript{[32]}

While 50 ml fibrinogen concentration contains nearly 1 g fibrinogen, there is 250 mg fibrinogen in 100 ml of 1 FFP unit and 225 mg fibrinogen in 15 ml cryoprecipitate.\textsuperscript{[33]} Analyses demonstrated that fibrinogen concentrations can reduce blood loss by 70% and transfusion by 60%; moreover, they completely restore the plasma fibrinogen level.\textsuperscript{[34]} In this manner, they ensure more efficient treatment through decreased exposure to side effects and volume overload.

Prothrombin complex concentrate (PCC) can increase the K-dependent factors by 50% within 30 minutes; this time extends to at least 3 hours with FFP. The administration of PCCs during liver surgery for perioperative bleeding is essentially related to the supplementation of factors or vitamin K antagonist reversal.\textsuperscript{[35]} Nevertheless PCCs may be related with a higher risk of thromboembolic complications and death.\textsuperscript{[36]}

The factor concentrates are prepared at 60°C, and the concerns about infection have decreased to almost negligible levels today. Pugliese et al.\textsuperscript{[37]} showed that the administration of 40 mcg/kg FVIIa reduces the total blood loss, the need for transfusion as well as the incidence of thromboembolic events. Kalichinsky et al.\textsuperscript{[38]} reported that the administration of factor VII in the patients undergoing pediatric liver transplantation at the Warsaw Children’s Hospital just before transfusion corrected coagulopathy and did not lead to any embolic complications. However, prophylactic activated VIIa has been
shown to be of no benefit in liver transplantation, and is only recommended for rescue therapy.

**Point of Care Testing-Oriented Approach**

Another method argued for managing hemostasis during liver transplantation is the management of the patient under the light of POC test result. The algorithms introduced by Roullet et al.\(^{[39]}\) in 2015 are the most recent which recommend the bolus injection of 15 mg/kg tranexamic acid followed by repeated infusion of 10 mg/kg at every 4 hours in case of hyperfibrinolysis; and the administration of 50 mg/kg bolus fibrinogen concentration if the patient does not respond the former. During significant perioperative bleeding, treatment with fibrinogen concentration is recommended when signs of functional fibrinogen deficit exist (Evidence 1C).\(^{[40]}\) These algorithms suggest that if EXTEM A10 is >30 mm, bleeding is not linked with the coagulation defect; if EXTEM A10 is <26 mm, 50 mg/kg fibrinogen concentrate should be injected; if EXTEM A10 is between 26 and 29 mm, the FIBTEM A10 should be reevaluated, and if FIBTEM A10 is <8 mm but fibrinogen >50 mg/kg has already been applied, the patient may benefit from platelet suspension. A10 defines the clot strength reported at 10 min after initiation of clotting. EXTEM contains Tissue Factor as an activator whereas FIBTEM utilizes a platelet inhibitor called cytochalasin. It seems that these algorithms also enable the calculation of the required dose of the factor concentrates. For example, an 80 kg patient should be given 2 g fibrinogen to make a 4 mm increase in FIBTEM MCF (Maximum clot firmness).\(^{[41]}\) Solomon et al.\(^{[42]}\) recommended the administration of 7.6 mg/kg fibrinogen to increase the FIBTEM MCF by 1 mm.

Sonoclot® coagulation is another method using viscoelastometry to measure coagulation in either a plasma sample or whole blood.\(^{[43]}\) The platelet function, activated clotting time, and the clot rate can be evaluated quantitatively. However, the initial fibrin formation is measured by Sonoclot whereas ROTEM and TEG measure the later stage of initial clot formation. platelet count, age, and gender may influence the Sonoclot analyzer results.\(^{[44]}\)

Saner et al.\(^{[45]}\) introduced the pyramid of hemostatic therapy for the patients with the end-stage liver disease and summarized the stages of the hemostatic therapy according to the pyramid (from the basis to the top) as surgical hemostasis, providing basic condition by avoiding acidosis, hypocalcemia, and hypothermia, reversing oral anticoagulant aspirin and heparin therapy, hyperfibrinolysis control, fibrinogen concentrates, achieving adequate platelet presence, and FVII replacements as the ultimate remedy.

### Table 1: Recommendations for the management of perioperative bleeding during liver transplantation

| Recommendation | Level of evidence |
|----------------|-------------------|
| Antifibrinolytic therapy reduces blood loss and transfusion requirements in liver transplantation | B |
| Implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion-associated costs in liver transplantation | B |
| In acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion | 1C |
| rFVIIa should be used only as rescue therapy for uncontrolled bleeding not for prophylaxis | 1A |
| Point of care platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs | C |
| A low central venous pressure and restrictive fluid administration reduce bleeding | B |

Swamy et al.\(^{[46]}\) specified the transfusion thresholds 7 g/dL for Hb; 100 mg/dL for fibrinogen and 40 × 10^4/L for the platelet count. Moreover, Sabate et al.\(^{[47]}\) emphasized that the threshold for platelet count should be kept above 50 × 10^4/L in the presence of hemorrhage.

**Conclusion**

In conclusion, the prophylactic correction of the patients’ preoperative hemostatic disorders through the “watchful waiting” approach, the treatment of existing infections and the optimization of renal status minimize the transfusion-related complications in the patients undergoing liver transplantation.\(^{[48]}\) Besides the expert opinions the recommendations are listed for the management of perioperative bleeding for patients undergoing liver transplantation [Table 1].\(^{[40]}\) It is also important to ensure surgical management of active bleeding; achieve normothermia through low CVP, and keep calcium and pH levels within physiological limits during the intraoperative period. Furthermore, it is possible to avoid hemorrhage in the liver transplant procedures through normalization of the CVP in the postoperative period as well as rapid diagnosis and proper treatment of the complications, such as bleeding and thrombosis.

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**Conflicts of interest**

There are no conflicts of interest.

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