21 Minimizing Blood Loss in Recipient Surgery

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21.1 Introduction

Interventions to reduce blood loss during Orthotopic Liver Transplant (OLT) have been surgical, anaesthesia-related and pharmacological. Intraoperative blood loss is a predictor of perioperative outcome following liver resection and transplantation and may have an effect on short-term and long-term survival. The liver plays a central role in the haemostatic system as it synthesizes the majority of coagulation factors and proteins involved in fibrinolysis. Although anticoagulant factors are decreased as well, blood loss during orthotopic liver transplantation can still be excessive in view of interplay between multiple factors. In patients with cirrhosis, the synthesis of coagulation factors can fall short, reflected by a prolonged prothrombin time. Patients undergoing orthotopic liver transplantation are at high risk of bleeding complications. Several authors have shown that thromboelastography (TEG)-based coagulation management and the administration of fibrinogen concentrate reduce the need for blood transfusion. The reduction in blood loss has also led to the successful transplantation of livers in Jehovah's witnesses. Timely prevention and identification of "triangle of death" (hypothermia, acidosis and coagulopathy) play an important role in reducing blood loss. It is well known that blood transfusions are associated with an increased risk of postoperative complications, such as infections, pulmonary complications, protracted recovery and a higher rate of reoperations. Blood loss during orthotopic liver transplantation is currently managed by transfusion of red blood cell concentrates, platelet concentrates, fresh frozen plasma and fibrinogen concentrate. Increasing experience and improvements in surgical technique, anaesthesia care and better graft preservation methods have contributed to a steady decrease in blood transfusion requirements in most liver transplant programmes.

21.2 Why to Minimize Transfusion?

Intraoperative transfusion of at least 6 units of RBCs decreases survival rates during medium- and long-term follow-up after Liver Transplant (LT). RBCs transfusion has been independently correlated with the rate of postoperative infections in the unit-dependent manner [1]. The number of transfused RBCs units during LT is also a predictor of early surgical re-intervention, which in turn increases postoperative mortality threefold. Platelet transfusion is associated with increased postoperative mortality due to a higher prevalence of acute lung injury (ALI). FFP used for volume replacement or pre-emptive nonspecific correction of coagulopathy in the dissec-

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tion phase of LT may exacerbate splanchnic hyperaemia and portal hypertension. A transfusion-free perioperative period was associated with improved early outcomes, fewer infections, reduced dialysis requirement, shorter hospital LOS and a reduction in mortality compared with a transfused group with similar recipient, graft and donor quality variables.

21.3 Coagulation Derangements (Preoperative and Intraoperative)

The new paradigm relies entirely on the concept of a rebalanced coagulation state, where all of the components of the system are significantly altered (both pro- and anticoagulant portions) but maintained in a precarious equilibrium (Fig. 21.1). External disruption of this balance, whether a consequence of disease progression or from intervention, can thrust the balance into bleeding or thrombosis. Liver transplantation represents one of the greatest physiological insults to this balance (Table 21.1).

Disruptions in pro- and anticoagulant factors and portal hypertension increase the risk of haemorrhage. Changes in platelet and endothelial function in liver failure also may delay clot formation. Additionally, patients with liver failure can experience hyperfibrinolysis, dysfibrinogenemia and renal failure, which may further increase the risk of prolonged bleeding.

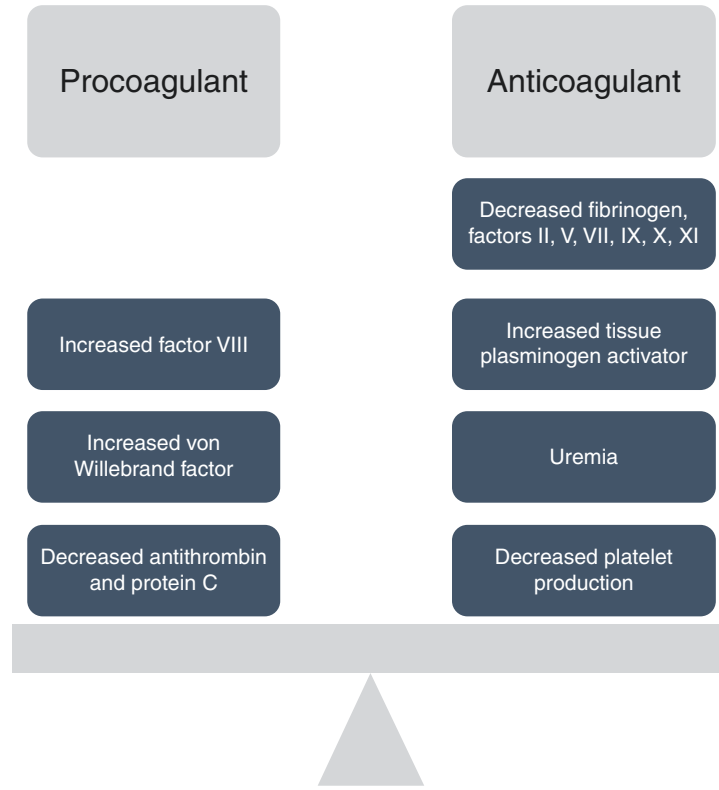

Fig. 21.1 Rebalanced coagulation in liver disease

Table 21.1 Changes in haemostatic system of patients with chronic liver disease

Anticoagulant	Procoagulant
Thrombocytopenia	Elevated levels of von Willebrand factors (vWf)
Platelet dysfunction	Decreased levels of ADAMTS-13
Enhanced production of nitric oxide and prostacyclin	Increased factor VIII level
Factors II, V, VII, IX, X & XI deficiency	Decreased levels of protein C, protein S, antithrombin, α2-macroglobulin and heparin cofactor II
Lack of vitamin K	Low levels of plasminogen
Low fibrinogen	
Low levels of α2-antiplasmin, factor XIII and TAFI	
Elevated t-PA levels	

21.4 Risk Factors (Recipient, Surgery and Graft-Related Risk Factors)

Patient-related factors are pre-operative high MELD score, severe coagulopathy (platelet count <50,000 and low fibrinogen) and low haematocrit and renal dysfunction. The recipients present differing degrees of preoperative haemostasis disorders and may also present intraoperative coagulopathy. Changes in the production and clearance of coagulation proteins in the course of LT may lead to severely disturbed haemostasis, further aggravated by ischaemia of the hepatic graft and the splanchnic network [2]. Hyperfibrinolysis has been described as a major cause of non-surgical bleeding during LT. The results for many potential predictive variables (age, starting haemoglobin value, international normalized ratio [INR], platelets count, creatinine, albumin and second OLT) for intraoperative bleeding are conflicting. It has been shown that central venous pressure (CVP) and the splanchnic venous pressure are key factors in the haemostatic balance during liver surgery [3, 4], a fact that is supported by the finding that maintaining a low CVP intraoperatively significantly reduces blood loss and the need for transfusion during liver transplantation and liver resection [3–5]. The donor's older age is associated with a higher risk of massive transfusion.

Other technical factors, such as the decreased size of the donor liver, portal vein hypoplasia and an inadequate graft-recipient body weight ratio, were associated with transfusion requirements in several studies. Prolonged cold ischaemia time and poor graft function due to decreased production of coagulation factors also significantly increase the risk of massive transfusion [6].

21.5 Prevention of Excessive Bleeding

Identifying and planning the management of patients at high risk of bleeding is the key to minimize blood loss and can be implemented as early as the preoperative assessment visit. Interestingly, several patient and operative characteristics were associated with an increased risk of receiving a transfusion of blood products. Specifically, older patients and individuals with more comorbidities were at markedly higher risk of receiving a transfusion. Patients are categorized into good risk and bad risk in terms of need for blood and blood product reserves [7]. Patients with severe liver failure have significant derangement of their clotting function due to impaired production of procoagulant and anticoagulant factors. Traditional coagulation studies are limited by the short time needed for the result and provide little information about the dynamics and strength of clot formation. According to a recent study, a parameter derived from ROTEM, the time required for the maximum clotting velocity, can identify cirrhotic patients at high risk of bleeding. VETs can be an aid in LT by limiting the transfusion of labile blood products, probably at the cost of an increase in the transfusion of fibrinogen. VETs lack sensitivity for the diagnosis of hyperfibrinolysis. It is wise not waiting for the appearance of typical hyperfibrinolysis plots to use antifibrinolytics if other clinical features are present such as diffuse or massive bleeding. Inhibition of clot lysis in

VET is another approach to promoting haemostasis. Amongst specific actions to minimize perioperative blood loss and transfusion requirements during LT, we can distinguish nonpharmacological and pharmacological interventions.

21.5.1 Nonpharmacological Interventions

Fluid management is considered a key player in haemostatic management. Avoiding excessive fluid transfusions and maintaining low CVP during dissection phase is a well-established measure to minimize intraoperative blood loss. Fluid restriction not only helps one to maintain low CVP but also prevents dilutional coagulopathy associated with excessive transfusion of crystalloids and colloids. Relative hypovolaemia due to low CVP might also increase the risk of significant tissue hypoperfusion, air embolism, as well as acute renal failure. Standard coagulation tests do not reflect the functional haemostatic status. Therefore, the use of modern viscoelastic tests such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) allows us to assess humoral and cellular components of the haemostatic system (both coagulation and fibrinolysis), helping to identify the cause of intraoperative bleeding, targeting specific problems and evaluating management. Recent guidelines of the European Society of Anaesthesiology recommend to use perioperative global coagulation tests (TEG/ROTEM) for targeted management of coagulopathy in patients undergoing LT [8].

Another important surgical measure to reduce perioperative blood product transfusions is use of intraoperative cell salvage (CS). Nowadays, a "stand by" set-up rather than routine application of CS is recommended. It must be emphasized that as salvaged washed erythrocytes do not contain clotting factors or platelets, haemostatic replacement therapy must be managed accordingly. To minimize the risk of bacterial contamination it is recommended to start collecting blood after the removal of ascitic fluid and cease it once biliary anastomosis begins.

21.5.2 Pharmacological Interventions

21.5.2.1 Antifibrinolytics

Derivatives of the amino acid lysine, 6-aminohexanoic acid (aminocaproic acid) and 4-(aminomethyl) cyclohexanecarboxylic acid (tranexamic acid), are grouped in the class of medications named antifibrinolytics. Fibrinolysis is an important process developing during anhepatic phase and progressing massively after reperfusion due to the alterations in haemostatic system (t-PA) [8] (Fig. 21.2). Hyperfibrinolysis or dysfibrinogenemia should be suspected in the presence of mucosal (gum) bleeding or late bleeding (such as hours post line placement), suggesting that clot has formed and prematurely dissolved. According to the current guidelines, consider administration of antifibrinolytic drugs when fibrinolysis is either confirmed in viscoelastic tests (TEG/ROTEM) or is clinically evident from microvascular oozing, but not as a routine practice [9].

21.5.2.2 Prothrombin Complex Concentrate (PCC)

Prothrombin complex concentrate (PCC) comprises either 3 or 4 vitamin K-dependent procoagulant factors (II, ± VII, IX, X) and the anticoagulants protein C and S, extracted from pooled plasma. PCCs can improve haemostasis where loss or dilution of prothrombotic factors is contributing to bleeding. In LT a dose of 25 iu/kg is advocated if there is severe bleeding associated with prolonged clotting time on VETs (TEG R time or EXTEM Clotting time > 80 s) after excluding a HLE. PCC may be the ideal therapy to restore thrombin generation in dilutional coagulopathy.

21.5.2.3 Fibrinogen Concentrate

Fibrinogen concentrate substitution was also found to restore MCF after in vitro haemodilution in blood from LT recipients, its potential role in the treatment of dilutional coagulopathy. Cryoprecipitate is still used as the most abundant source of fibrinogen. It is recommended that as fibrinogen concentrates contain standard doses of fibrinogen, carry lower risk of pathogen and

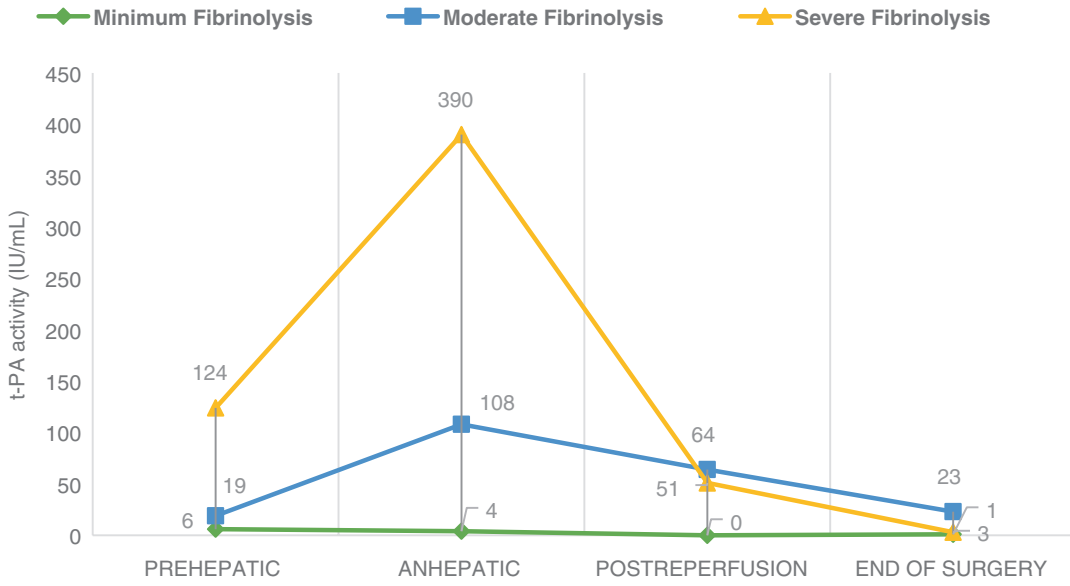

Fig. 21.2 t-PA levels in different phases of transplantation {Adapted from Dzik WH et al. Blood 1988;71(4):1090–1095 [8]}

immune-mediated complications and should be the preferred source of fibrinogen, in comparison to cryoprecipitate, for the treatment of the quantitative functional deficits of fibrinogen in bleeding patients, unless the former is unavailable. The fibrinogen dose can be calculated as follows: Fibrinogen concentrate dose (g) = [target FIBTEM MCF (mm) − actual FIBTEM MCF (mm)] × [body weight (kg)/70] × 0.5 g/mm. Dosing range is 25 mg/kg to 50 mg/kg.

21.6 Others

Piggyback hepatectomy (PGB) is a surgical technique increasingly utilized in both DDLT and LDLT (Caval preservation technique).

21.6.1 Strategies

1. Maintain adequate blood viscosity (Hb).
2. Maintenance of haemostatic conditions for clotting.
3. During the intraoperative period, local haemostasis is the most important factor in the control of bleeding; in this context, surgical technique and meticulous haemostasis are fundamental measures.
4. MAP range between 60 mmHg and 65 mmHg during dissection phase.
5. Maintenance of a low central venous pressure (CVP) and even reduction of CVP by phlebotomy is a beneficial strategy in minimizing blood loss during liver resection or liver transplantation [5].
6. Use of viscoelastic coagulation tests performed bedside (point-of-care [POC]), including rotational thromboelastometry (ROTEM) and thromboelastography (TEG).
7. Use of transfusion algorithms based on VETs can reduce perioperative bleeding and the rate of transfusion of allogeneic blood products [10–12].
8. VETs can be an aid by limiting the transfusion of labile blood products, probably at the cost of an increase in the transfusion of fibrinogen. (VETs may lack sensitivity for the diagnosis of hyperfibrinolysis.)
9. Predictive models to identify higher risk patients for bleeding and transfusions should be developed.

10. Measuring portal pressure intraoperatively and correlation with CVP.
11. Define the nature of the coagulopathy in a given patient who has liver disease at given time.
12. Recombinant factor VIIa (rFVIIa) procoagulant drug can facilitate clot formation through amplifying the thrombin burst and accentuation of platelet function.
13. Prothrombin complex concentrate (frequently) and fibrinogen concentrate use is on the rise.

All the strategies that we may use to reduce or avoid transfusions will have important benefits not only in decreasing transfusion-associated risks [13, 14] but in preserving blood stores and reducing costs as well. Recourse to transfusion may vary depending on the device used, confirming that transfusion thresholds are not well defined. Measures to reduce the filling status of the patient and to lower the CVP through volume contraction and no routine correction of laboratory coagulation test with large-volume blood products are effective and safe.

Key Points

- LT is associated with massive blood loss.
- Bleeding in LT is related to aetiology and severity of liver disease.
- Pre-operative optimisation can reduce transfusion requirement.
- Restrictive transfusion protocols are preferred.
- Viscoelastic test helps reduce transfusion requirement.

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