Anesthesia care for liver transplantation
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Abstract

Intraoperative transfusion practices for liver transplantation have evolved dramatically since the first transplants of the 1960s. It is important for today's clinicians to be current in their understanding of how transplant patients should be managed with regard to their coagulation profile, volume status, and general hemodynamic state. The anesthesiology team is presented with the unique task of manipulating this tenuous balance in a rapid and precise manner when managing patients undergoing liver transplantation. Although significant progress has been made in reducing blood product administration, it is still common to encounter large volume blood loss in these cases. Increasingly, clinicians are challenged to justify transfusion practices with a stronger evidentiary base. The current state of the literature for transfusion guidelines and blood product management in this particular patient subset will be discussed, as well as a variety of means (both pharmacologic and otherwise) used to reduce the need for transfusion. The aim was to review the latest evidence on these topics, as well as to highlight areas that need further clarification regarding their role in the optimal care of these patients.

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1. Background

Liver transplantation (LTX) has been closely associated with blood transfusion practices since the first transplants in the 1960s. Advances and refinements in transfusion methods have mirrored improved patient outcomes from the earliest experimental efforts when LTX was invariably lengthy, risky, and involving massive transfusion requirements with sometimes fatal hemorrhagic complications [1,2] through today when some patients require no blood transfusion at all. Improvements in patient selection, the shift to venovenous bypass over portacaval shunts [3], and immune suppression resulted in an overall 1-year survival rate of 68% by the mid 1980s [4]. The introduction of cyclosporine, of note, also played a significant role in reducing intraoperative blood loss by reducing the need for splenectomy [5]. Nonetheless, transfusions exceeding 100 red blood cell (RBC) U were common for transplants done at that time, with most centers averaging 20 U per patient [6]. Keeping up with blood losses presented an enormous challenge during this era: massive volume empirical transfusion was the standard practice and blood products accounted for approximately 10% of the total cost of transplantation [7]. By the 1990s, however, further improvements in surgical technique, organ preservation, and the use of intraoperative blood salvage resulted in decreased intraoperative transfusion needs. At the same time, evidence started to emerge associating excessive perioperative transfusions and blood loss with increased morbidity and mortality [8-10]. In addition, new tools such as the thromboelastogram (TEG) improved our understanding of the coagulation profiles of these patients and led to transfusion algorithms associated with a 33% reduction of blood and other intravenous (IV) fluid infusion volume [11]. As a result, practitioners have gradually modified their intraoperative techniques, and transfusion during transplantation is not only much less frequent today but also far more methodical. Some centers achieved average RBC transfusion rates as low as 2 U by the early 2000s [12].

2. Coagulopathy of liver disease

Before attempting to understand the best approach to treating the coagulopathic derangements seen in liver failure, it is essential to understand normal hemostasis. All
coagulation factors are produced in the liver except for von Willebrand factor, which is produced in endothelial cells. In addition, the liver synthesizes important antithrombotic modulating factors (protein S, protein C, and antithrombin III) and key components of the fibrinolytic system (plasminogen and α2-antiplasmin). The liver is also essential for clearance of activated coagulation factors from the circulation, which is functionally impaired in hepatic failure.

In the pathologic state of end-stage liver disease (ESLD), numerous disturbances in this delicate balance arise. The coagulation system is adversely affected by low levels of prothrombotic factors and antithrombotic modulators at the same time. Deficiency in coagulation factors prolongs the prothrombin time (PT) and activated partial thromboplastin time; on the other hand, low level of antithrombotic compounds may result in a hypercoagulable tendency. At the same time, the fibrinogen level is generally normal or increased, but excessive sialic acid content in fibrinogen molecules results in the synthesis of functionally abnormal fibrinogen [13]. Dysfibrinogenemia and low levels of factor XIII compromise fibrin polymerization. Furthermore, the fibrinolytic system is also affected by liver disease because the levels of plasminogen and α2-antiplasmin can be low, whereas an enlarged endothelial area may increase the level of tissue plasminogen activator. In addition, despite normal or even increased platelet production, the number of platelets in circulation is substantially reduced in the presence of portal hypertension with splenic sequestration, and major platelet dysfunction is commonly seen in these patients. Hepatorenal syndrome, accelerated platelet consumption, decreased platelet survival time, sequestration of platelets in the regenerating liver, bone marrow suppression by alcohol and hepatitis virus, nutritional deficiencies, decreased thrombopoietin production [14], and toxic effects of methanol on megakaryocytes present additional stressors on the platelet system. Further dysfunction arises from decreased arachidonic acid and adenine nucleotides in the platelets. The result is the production of undersized and hypofunctional platelets, which are impaired in their ability to aggregate. Results of platelet function studies vary considerably and do not predict bleeding tendency with much reliability. On the vascular level, significant endothelial dysfunction exists largely because of impaired nitric oxide metabolism and vasodilatation; the reduced elasticity exacerbates the platelet and vessel wall interaction.

In summary, hepatic dysfunction brings forth exceedingly complex changes in the natural balance of the normal state of hemostasis: the imbalance between coagulation and its inhibition, as well as fibrin polymerization and fibrinolysis results in all forms of coagulopathy. Treating this global hemostatic imbalance is the sine qua non of managing patients for LTx. Other complicating conditions, such as renal insufficiency and surgical bleeding, make a transfusion-free LTx a major challenge.

3. Hemostasis and transfusion during LTx

Blood bank demands for these cases remain high despite the trend of sharply declining transfusion volume during the last 2 decades. The quality and safety of blood products continue to improve; yet, they remain costly and increase the risk encountered by the patient while providing often questionable benefit.

The primary purpose for transfusion of packed red blood cells (PRBCs) should be to increase oxygen-carrying capacity [15]. The decision of when a patient should be transfused with PRBCs, however, remains an area of great variability in practice today, in part because there is scant evidence supporting one practice over another. In particular, there is little published data in support of PRBC when the hemoglobin (Hgb) level is more than 7 g/dL, even if the patient has cardiac comorbidities [16,17]. It is not easy to determine whether oxygen-carrying capacity is adequate or not: although transfusion of other blood components can be guided by specific laboratory tests, the clinician often looks at the combination of hemodynamic parameters, electrocardiogram, and lactate levels to formulate the treatment plan. The use of a lower Hgb threshold for PRBC transfusion in appropriately selected patients is becoming increasingly more common. This is in no small part as a result of numerous studies showing a negative association between transfusion rate of PRBCs and survival [10,18-21].

As the intraoperative events during LTx proceed, the already substantial coagulopathy of these patients is further radically altered. Each stage of the procedure imparts complex changes, which influence the choice of fresh frozen plasma (FFP), cryoprecipitate, and platelet transfusions. During the preanhepatic phase, the primary issue is usually surgical bleeding. Concurrent fluid resuscitation results in a gradual decline in coagulation factors and platelet count [22]. Simultaneously, a gradual temperature decline may exacerbate these problems. The anhepatic phase is notable for a significant array of alterations in hemostasis: platelets and coagulation factors continue to decline, and in the absence of hepatic clearance, the accumulation of tissue thromboplastin compounds the dysfunction. Finally, the neohepatic phase is most notable for the reperfusion of the graft liver and the resultant reperfusion syndrome. A severe coagulopathy coincides with this event and is multifactorial in its etiology: reperfusion hypothermia, ionized hypocalcemia, dilutional coagulopathy, quantitative and qualitative defects in platelets, heparin effect [23], fibrinolysis, and the release of a variety of humoral substances from the grafted liver. In rare instances, excessive activation of coagulation may also occur at this time [24].

It is becoming apparent that arbitrary and generous administration of blood products is neither beneficial nor supported by evidence. Aggressive efforts to normalize the patients' coagulopathy with large volumes of blood products can lead to a hypervolemic state and a paradoxical increase
in transfusion requirements. Citrate-associated ionized hypocalcemia usually leads to reduced vascular tone and compromised myocardial contractility, necessitating frequent supplementation. Limiting transfused products to situations where clinical bleeding and/or severe anemia is present, therein maintaining a low central venous pressure (CVP), has been shown to improve outcome in both liver resection [25-27] and LTx [28], although this remains somewhat controversial [29].

In the postoperative period, as the grafted liver begins to function, the coagulopathy gradually improves. Typically, fibrinolysis and heparin effects gradually dissipate within about 2 hours. Often, by the end of surgery, the coagulation factors and platelet count begin to increase toward baseline levels. Oozing in the presence of an acceptable coagulation profile and TEG may indicate surgical bleeding. Persistent coagulopathy and nonsurgical bleeding may be caused by a poorly functioning graft with ischemic or immunologic injury. Further normalization of coagulation postoperatively depends on graft function. Generally, with adequate graft function, coagulation factor levels steadily approach normal values, and the PT and activated partial thromboplastin time return to normal values within a few days.

4. Reducing the need for blood transfusion

It is important to remember that every treatment carries some amount of inherent risk, and transfusion is no exception to this rule. Transplant recipients may be at greater risk for such adverse events because of more frequent exposure to blood products than the average patient. Vigilant monitoring for acute or subacute reactions is vital.

Acute, life-threatening transfusion reactions are fortunately quite rare; nonetheless, new signs or symptoms arising during a transfusion must be taken seriously. Examples include acute hemolytic transfusion reactions (ABO incompatibility), infusion of a bacterially contaminated unit, transfusion-associated lung injury, and severe allergic reactions or anaphylaxis. Subacute transfusion complications are generally more insidious and easier to miss. These can include fluid overload, hypothermia, hypocalcemia, hyperkalemia, and acid-base disturbances. Increasing attention is being brought to the role of the immune response to transfusions as a potential cause for decreased graft survival and heightened mortality rates [19,30,31]. Although it is not entirely clear what accounts for this transfusion-associated increase in morbidity and mortality, there is increasing support of an effect known as transfusion-related immunomodulation [32]. In addition, it has been shown that patients who received large amounts of blood intraoperatively carry a higher risk of infection, gastrointestinal and intra-abdominal complications, and prolonged hospital stay, all of which have a negative impact on survival [33]. Emerging studies are demonstrating similar increases in mortality with FFP administration [18] and platelets [10].

Decreases in the administration of FFP, platelets, and cryoprecipitate have begun to follow the same rate of decline seen with PRBCs, and evidence-based transfusion thresholds for these other products are lacking. A recent study by Massicotte et al [34] demonstrated no clear connection between coagulation defects and blood products required during LTx; this group does not routinely administer platelets or FFP, yet they still maintain a very low PRBC transfusion rate. When platelets are given, there are data favoring the use of apheresed single-donor concentrates [35].

Thromboelastography has been put into practice by many centers for LTx. The benefits of TEG-based transfusion algorithms have been espoused for more than 2 decades [11]. Its use permits the assessment of both cellular and humoral components of whole blood coagulation and fibrinolysis, instead of singular parameters of procoagulation or anticoagulation. Standard tests of coagulation are not sufficient in determining whether a decrease in coagulation factors is the result of hemodilution or coagulopathy [36]. The TEG not only provides information about coagulopathy (factor deficiency and fibrinolysis) but also is used in vitro to assess the effect of treatments such as antifibrinolytic therapy, cryoprecipitate, FFP, platelets, and protamine. It can also be useful in identifying the occasional hypercoagulable patient with ESLD, who may benefit from low-dose heparin treatment [37]. After administering these corrective factors based on the in vitro TEG, a follow-up TEG is run to reassess the efficacy of the treatment, therein aiding the planning of further interventions. Using the TEG intraoperatively has become more standardized, automated, and user-friendly over the years. Although its use is not universal and its benefit during LTx has been questioned [38], it remains a valuable intraoperative adjunct to many.

Counteracting fibrinolysis with antifibrinolytic agents is another area which has been studied extensively. The most widely used antifibrinolytics include e-aminocaproic acid (EACA), tranexamic acid, and aprotinin. During the anhepatic phase, a rapid rise in tissue-type plasminogen activator occurs in the absence of α2-antiplasmin and plasminogen activator inhibitor, with the net result being an increase in plasmin activity and a hyperfibrinolytic state [39]. The routine use of antifibrinolytics has been controversial because of concerns about hepatic artery thrombosis and other thromboembolic events. Recent critical analyses, however, do not suggest a higher incidence of these feared complications during LTx [40,41]. Nonetheless, these agents are most safely used not in a prophylactic manner but only if fibrinolysis is demonstrated by thromboelastography, preferably after reperfusion with blood flow reestablished. Thromboelastogram-based algorithms for such use have been successfully applied during LTx [42].

Aprotinin is an inhibitor of plasmin, and as well has anti-inflammatory properties, and has been shown to help limit transfusion during LTx [43-45]. Its use, however, is no longer recommended because of recent evidence suggesting a dose-dependent increase in death, renal failure, and cardiovascular
events [46]. The EACA and tranexamic acid are the remaining antifibrinolytic agents in wide use clinically, with the former being the more common. Neither has been studied as extensively as aprotinin, and there are fewer randomized controlled trials confirming their efficacy. Their effect is exerted by inhibiting the conversion of plasminogen to plasmin [39]. The EACA has been safely used when given at a dose ranging from 0.25 to 5 g. Variable rates of success have been demonstrated in its ability to control significant bleeding, and optimal dosing has yet to be firmly established [39]. Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. Although it has been shown to be efficacious in reducing transfusion requirements [47,48], its use during LTx is much less frequent than the other agents.

The role of recombinant factor VIIa during LTx at this point remains to be defined. Its administration provides a novel way to increase the thrombin burst and acutely improve coagulation in the presence of rapid factor consumption. It has been studied in cirrhotic patients for LTx as well as in gastrointestinal bleeding. Although cirrhotic patients are likely to be factor VII deficient, and the data suggest the ability of recombinant factor VIIa to correct PT values when given preoperatively, it has yet to be shown to reduce blood product transfusion in these cases [49-51]. At this point, its use may be limited to the setting of preoperative administration in patients with acute fulminant hepatic failure needing placement of an intracranial pressure monitoring device [52]. Further studies are needed, looking at dose ranging and efficacy related to serum levels achieved.

Use of intraoperative blood salvage has gained acceptance for LTx as another means of reducing transfused donor RBCs and avoiding hypervolemia. Absolute contraindications are somewhat controversial but generally include cases where malignancy or an infectious source (eg, biliary abscess) is present. Recent studies have demonstrated its cost effectiveness, both conserving blood bank resources and reducing overall costs of LTx [53].

5. Circulatory support during LTx

Given this wide array of issues associated with blood and blood product administration, substantial effort has been put into finding adjunctive intraoperative treatments to minimize transfusions. As alluded to earlier, avoiding excessive fluid administration and hypervolemia is one of the intraoperative goals during LTx. Mounting evidence supports maintaining a low CVP via TV volume restriction, phlebotomy, or both [28]. Although not universally used in all centers during LTx, this approach has been widely supported during hepatic resection and has been shown to both decrease surgical blood loss and promote graft decongestion during LTx [28]. Nitroglycerin may be helpful in achieving a lower CVP as well in patients whose blood pressure (BP) can tolerate it. In addition, using lower tidal volumes (6–8 mL/kg) and avoiding positive end-expiratory pressure may help in minimizing preload and therefore decrease the risk for bleeding.

Volume restriction generally necessitates a heavier reliance on vasopressors. As an alternative to venovenous bypass, using modest doses of vasopressors in euolemic patients has been shown to safely maintain hemodynamic stability during LTx [54] and has not been demonstrated to be as harmful as previously assumed. Because of the typical vasodilated hyperdynamic physiology of this patient group, norepinephrine and vasopressin are often the agents of choice because of their potential to improve circulatory stability and enhance renal perfusion without inducing mesenteric ischemia [55,56]. These agents have also been shown to have positive effects on maintaining glomerular filtration rate and urine output in the setting of hemodynamic shock [57].

Diuretics also often play a role in achieving euolemic during LTx and can assist in reducing transfusion requirements as well [29]. Although these patients are often total body-volume overloaded, they are also generally intravascularly volume depleted. This fact complicates the use of furosemide unless the significant volume overload requires rapid removal. Mannitol, however, has several characteristics that make its use advantageous during LTx. Patients with ESLD may have edema of the abdominal organs because of congestion of blood flow through the fibrosed liver, as well as hypoalbuminemia. The osmotic activity of mannitol can aid in removing free water within these organs, particularly in the setting of hepatorenal syndrome, thus preventing hepatic distension once the transplanted liver is reperfused. It may also provide renal protection during the anhepatic stage. Lastly, mannitol has potential free radical scavenging and antioxidant properties, which may be beneficial [58]. Optimal dosing of mannitol is 0.5–1 g/kg just before cross-clamping or during the anhepatic phase.

6. Future directions for circulatory monitoring

Recent studies of continuous hemodynamic monitoring such as the FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA, USA) during LTx have shown mixed results. On one hand, it has been demonstrated that the FloTrac can measure stroke volume variation values within acceptable proximity of those values obtained using aortic Doppler echocardiography [59]. Conversely, FloTrac assessments of cardiac output had a high degree of variation in this same patient population compared to data obtained using pulmonary artery catheters [60,61].

Increasing attention has been brought in the last 2 decades to the pathophysiology of the hepatic microcirculation. The role of intact microcirculation for postischemic recovery has been demonstrated by correlations between ischemia/reperfusion-induced hepatocellular damage and microcirculatory disturbances [62]. Orthogonal polarization spectral
imaging has been shown to be a valuable tool for intraoperative analysis of ischemia/reperfusion-induced deterioration of the hepatic microcirculation [63]. Orthogonal polarization spectral imaging can be used to accurately quantify the sinusoidal perfusion rate, vessel diameter, and venular RBC velocity [64].

7. Early extubation and fast-tracking

An area of intraoperative practice for LTx that has evolved dramatically in the past 2 decades is early extubation and patient fast-tracking [65]. It is no coincidence that this has coincided with a decline in transfused products. It was prompted by advancements in surgical and anesthetic techniques, along with newer and shorter-acting anesthetic agents, which help to facilitate a rapid and safe emergence. In addition, it was recognized that spontaneous ventilation may improve transplanted organ function by reducing venous congestion of the liver graft. This practice has been advocated by numerous single-center experiences since the late 1990s [66-69], with some centers achieving immediate extubation of up to 80% of patients while maintaining acceptably low reintubation rates after LTx [67,70,71]. The

**Preanhepatic phase:**
- Anesthesia induction
- Invasive monitors (arterial catheter, pulmonary catheter vs. FloTrac/Vigililo)
- Forced air and fluid warmers on
- IV antibiotic, baseline labs (incl. TEG), incision
- Lower CVP to 5 cmH₂O, Restrictive IV fluid, phlebotomy if Hgb > 10 g/dL
- Norepinephrine (or vasopressin) to keep mean BP > 60 mmHg
- Dopamine (or epinephrine) to keep C.O. > 5 L/min
- Maintain Hgb > 7 g/dl, platelets > 40,000, MA (TEG) > 45, fibrinogen > 100 mg/dl
- Mannitol 0.5 g/kg IV over 1 hour, prior to anticipated clamping
- Just before clamping
  - IV heparin 3-5,000 U, if TEG is normal or hypercoagulable
  - Increase CVP to 10 cmH₂O with IVF
  - 25% albumin in severe hypoalbuminemia

**Anhepatic phase:**
- IV fluids to keep CVP around 5 cmH₂O
- Maintain Hgb > 7 g/dl
- Norepinephrine and/or vasopressin to keep mean BP > 60 mmHg and C.O. > 5 L/min
- Bicarbonate infusion to correct base deficit
- IV calcium chloride to sustain normocalcemia

**Neohepatic phase:**
- Reperfusion
- When SVR is declining, IV vasopressin 1-5 U bolus to keep BP > 60 mmHg
- Epinephrine 20-100 mcg boluses if heart rate is less than 60/min
- Euvoolemia: CVP of 5-10 cmH₂O
- Dopamine (or epinephrine) to keep C.O. > 5 L/min
- Norepinephrine and/or vasopressin to keep mean BP > 60 mmHg
- TEE if needed for detailed hemodynamic assessment
- Maintain Hgb > 7 g/dl, platelets > 40,000, fibrinogen > 100 mg/dl
- TEG:
  - Protamine 30 mg IV, if R is more than twofold compared to heparinase-R
  - Maintain MA > 45 mm with platelet transfusion
  - If Ly30 > 8%, IV EACA 5 g over 15 min
- Consider indication for postoperative mechanical ventilation per usual criteria
- Recovery in PACU (if extubated in OR) vs. ICU (if mechanically ventilated)

Fig. 1. Anesthesia guidelines for LTx at the University of Wisconsin.
safety of this practice in liver transplant recipients has been validated by recent multicenter outcome data [72]. Patient benefits and positive outcomes have been noted by several groups, including a decrease in intensive care unit (ICU) length of stay, or an elimination of ICU stays altogether, as well as diminished hospital resource [67,73-75]. Although these results are promising, immediate postoperative extubation after LTx is not yet routine among all centers. Reports emphasize the importance of appropriate patient selection and the use of a protocol-based approach [73]. No universal or routine early extubation pathways currently exist, and their establishment will require additional trials [72].

8. Organizational development for LTx

The complexity of LTx surgery presents a unique challenge for anesthesiology departments in allocating the right level of anesthesiology personnel. Different solutions can be found in various institutions, and the inconsistency of care is noteworthy. A review of the anesthesia literature suggests an enormous variability of clinical care and resource utilization [76,77].

At our institution, the University of Wisconsin, significantly reduced blood transfusion and shorter ICU stays generously rewarded the anesthesiology department’s commitment of organizing a dedicated liver transplant anesthesia team [78]. In addition, the collaborative anesthesia-surgery interactions resulted in a much less tense work environment and considerably increased academic productivity for members of the transplant anesthesia division. Our experience may be a valuable example of gradual transformation, based on the continuous quality improvement principle, for institutions with similar challenges and aspirations. We have made a concerted effort to develop and adhere to an evidence-based protocol for LTx, which is outlined in Fig. 1. We use a “less is more” philosophy with regard to transfusions and only administer blood products when clearly indicated: in our view, the best evidence suggests that liberal transfusion triggers provide a short-term benefit while possibly creating a long-term detriment. Our standardized approach to LTx management is used by our dedicated faculty team and the house staff.

9. Conclusion

An understanding of normal and pathologic hepatic function is critical to the optimal intraoperative management of the patient with ESLD. Anesthetic management during LTx is a rapidly growing field that has evolved dramatically over time. Published evidence-based practice, where available, has a strong potential to reduce the variability of patient care and influence patient outcomes. Identification of evidence-based “best practices” should guide organizational development of the greatly diverse individual transplant centers to improve clinical practice.

The author declares no conflict of interests.

References


