Patient Blood Management in Liver Transplant

Subjects: Transplantation

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Transfusion of blood products in orthotopic liver transplantation (OLT) significantly increases post-transplant morbidity and mortality and is associated with reduced graft survival. Based on these results, an active effort to prevent and minimize blood transfusion is required. Patient blood management is a revolutionary approach defined as a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood while promoting patient safety and empowerment. This approach is based on three pillars of treatment: (1) detecting and correcting anemia and thrombocytopenia, (2) minimizing iatrogenic blood loss, detecting, and correcting coagulopathy, and (3) harnessing and increasing anemia tolerance.

patient blood management | adult and pediatric liver transplant | coagulation

1. Introduction

Orthotopic liver transplantation (OLT) is the standard of care for patients with non-reversible liver disease. It is a challenging procedure encompassing multidisciplinary and coordinated efforts to achieve the best results. Surgical procedures involve significant vessel manipulation in a complex scenario and impaired coagulation due to several factors, including temperature changes, hemodilution, calcium and acid-base imbalance, and other phenomena that may promote bleeding, often leading to the administration of red blood cells to restore oxygen delivery. Nevertheless, the transfusion of blood products in OLT significantly increases post-transplant morbidity and mortality [1][2][3][4] and is associated with reduced graft and patient survival [5][6]. Based on these results, an active effort is required to prevent and minimize blood transfusions and yellow blood products [7][8].

Patient blood management (PBM) is a revolutionary approach, defined as a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood while promoting patient safety and empowerment [8].

This approach is based on three pillars of treatment: (1) detecting and correcting anemia and thrombocytopenia, (2) minimizing iatrogenic blood loss and detecting and correcting coagulopathy, and (3) harnessing and increasing anemia tolerance [9][10][11][12]. The World Health Organization (WHO) recently published a policy brief regarding the urgent need to implement PBM [13].

2. Coagulopathy in Liver Disease

Patients with advanced liver disease have a hemostatic profile that typically includes thrombocytopenia and reduced coagulation factors; however, these alterations are counteracted by fibrinolysis inhibition, decreased protein C, and increased endothelial-derived von Willebrand factor (vWF) and factor VIII (FVIII). Therefore, this system is considered rebalanced in a precarious equilibrium vulnerable to extrahepatic variables such as infection, renal impairment, and volume status [14][15]. Thrombocytopenia is attributed to splenic sequestration and decreased thrombopoietin; however, this situation is offset by an increase in vWF. In fact, platelet procoagulant activity is fully preserved in patients with cirrhosis, and it has been demonstrated that thrombin generation in patients with liver disease and thrombocytopenia remained normal down to platelet counts of 60 × 10^9/dL. In addition, platelet transfusion failed to significantly ameliorate clot firmness in adult patients with platelet counts of 50 × 10^9/dL, assessed using viscoelastic tests [16][17][18]. Although platelet function defects may be present in vitro, the clinical significance of these defects has been debated [19].

Although there are evident defects in the synthesis of vitamin K-dependent coagulation factors and fibrinogen, the synthesis-derived anticoagulant factors, especially protein C, are also reduced. Elevated endothelial-derived FVIII coupled with low protein C contributes to a hypercoagulable state [20][21][22]. In this setting, PT and APTT suggest defective coagulation. However, these tests are not sensitive to deficiencies of anticoagulants or endothelial-derived procoagulant factors and do not represent the balance seen in LT between the pro-and anticoagulant proteins [23].

The fibrinolytic and antifibrinolytic systems may also be imbalanced in patients with cirrhosis. All liver-dependent factors (such as plasminogen) decrease, but tissue plasminogen activator levels are elevated due to decreased liver clearance. Plasminogen is activated by tissue plasminogen activator (tPA) to form plasmin and fibrin degradation products (FDPs). In some populations, this relationship is responsible for a profibrinolytic state. However, evidence suggests that the plasminogen activator inhibitor (PAI) is augmented in some patients with etiologies, such as cholestatic conditions and nonalcoholic steatosis hepatitis, which makes them prone to hypofibrinolysis and a hypercoagulable state [24][25].

Elevated platelet activation markers, thrombin, fibrin generation, and fibrinolysis are expected in patients with liver diseases. Although elevated levels may indicate defective clearance rather than ongoing activation of platelets, coagulation, and fibrinolysis because the liver clears these proteins [26], elevated plasma levels reflect ongoing low-grade disseminated intravascular coagulation with fibrinolysis activation [27].

Coagulopathy in acute liver failure differs from that in chronic liver failure. In patients with acute liver failure, thrombocytopenia is less common than in patients with cirrhosis; coagulation factors decrease in plasma, and fibrinolysis is particularly inhibited, whereas normal or hyperfibrinolysis is present in cirrhosis [28][29]. This phenomenon explains why thromboembolic events increase with greater liver function decompensation. Thus, patients with compensated cirrhosis have a 1% incidence of portal vein thrombosis, whereas patients with decompensated cirrhosis have an 8–25% incidence [30].

However, hemorrhagic events are common, often explained by reduced platelet count, decreased levels of coagulation factors, and fibrinolysis inhibitors [30]. Bleeding is divided into portal pressure-driven, mucosal, or prolonged puncture wound bleeding caused by premature clot dissolution [14].

In the perioperative context of liver transplantation, this rebalanced hemostasis is quickly vulnerable; therefore, decisions must be made to maintain hemodynamic stability and oxygen delivery to the tissues, avoiding futile overcorrections that promote prothrombotic environments, among other catastrophic complications.

3. Hemostatic Drugs

3.1. Antifibrinolytics

While performing a LT, systemic fibrinolysis is not a significant predictor of mortality and is often transient in the anhepatic and reperfusion phases [31]. In the late anhepatic stage and postreperfusion period, fibrinolysis is caused by tPA being released from vessels but not being cleared by the liver. Clinical evidence for the use of antifibrinolytics during LT supports this practice [31][32].

Aprotinin was the first antifibrinolytic agent used during OLT [33]. There is a strong association between increased transfusion due to intraoperative fibrinolysis and bleeding during OLT [34]. The clinical use of aprotinin was suspended in 2007 after serious safety concerns in high-risk cardiac surgery patients were raised [33][35][36]. Suspension was lifted in Canada and Europe after the health authorities concluded that the respective studies suffered from significant flaws.

However, tranexamic acid (TXA) has become the most used antifibrinolytic agent worldwide. A meta-analysis [37] demonstrated that TXA infusion (10 mg/kg/h) reduces RBC and FFP transfusions compared with placebo. Additionally, the prophylactic use of TXA (bolus: 30 mg/kg plus infusion at 16 mg/kg/h) has been documented. Nowadays, antifibrinolytic therapy is restrictively used due to the potential risk of arteria hepatic thrombosis in most liver transplant centers [38]. EACA-treated patients have received more significant amounts of RBC, plasma, platelets, and cryoprecipitate with repeated bolus injections or prolonged infusion (EACA, from 5–10 to >10 g). The results did not show a difference in thromboembolic events between the EACA and non-EACA groups. Badenoch et al. [39], in patients treated with TXA (n = 367), reported a decrease in RBC and plasma requirements versus matched non-treated cohorts without increased HAT, portal vein, and other venous thromboses. The HALT-IT RCT showed an increased risk of thromboembolic events in patients with gastrointestinal bleeding treated with TXA [40].

Potentially fatal complications in OLT are intracardiac thrombosis (ICT) and pulmonary thromboembolism (PE), occurring in 0.36–4.0% of cases. Intraoperative mortality rates are as high as 30–55%, and overall mortality is as high as 45–68%. Antifibrinolytic therapy and ICT/PE association have not been established; however, TXA or EACA can hinder attempts at clotting dissolution by intravenously administered tPA [41][42]. ICT/PE occurs within 30 min of the reperfusion phase [43][44]. Transesophageal echocardiogram can be used for early diagnosis, and antifibrinolytics should be withheld in high-risk OLT cases during this phase.

3.2. Fibrinogen Concentrates

The use of fibrinogen concentrate (FC) overcomes the limitations of cryoprecipitates. Furthermore, it avoids an increase in factor VIII and von Willebrand factor, a prothrombotic factor in patients with cirrhosis [42][43][44][45]. All products are indicated to actively treat bleeding in patients with congenital fibrinogen deficiency. Stolt [41] reported on in vitro samples with fibrinogen concentrate supplementation the effectiveness of correcting coagulation testing resulting in higher plasma fibrinogen concentrations and improved clot strength. However, the selected dose for restoring clot strength in cardiac surgery patients differed among the three groups, and these results have implications for the choice of concentration and dosing [42].

FC has been shown to increase fibrin polymerization in viscoelastic testing with less variability than cryoprecipitate. This results in an increase in fibrinogen levels in plasma in a more predictable manner [41][45]. The manufacturing of FC mitigates pathogen transmissions [46] and minimizes allergic and other transfusion-related reactions [47].

During any hemostatic intervention, the risk of thromboembolic complications must be considered. HAT is the most feared event in the OLT population, with an incidence of 3–9% [48], a re-transplantation rate prevalence of 53%, and a mortality rate between 27% and 58% [49][50]. A review of 634 consecutive patients found that cytomegalovirus (CMV) infection and accessory hepatic artery reconstruction were significant predictors of HAT [47]. Evidence also showed that the patient's age, indication for OLT, cold ischemic time, surgical time, and blood transfusion volume were not risk factors for HAT [48]. The incidence of HAT was 4.5% in OLT patients receiving FC and PCC compared with 3.6% in those who did not receive these concentrates [51]. Fibrinogen administration to correct hypofibrinogenemia has a positive effect on surgical bleeding. Fibrinogen concentrates effects on increasing plasma fibrinogen by 0.5 g/L has not been determined in OLT patients, and the administration should be adjusted to replace plasma fibrinogen levels in the range of expected values; it is highly recommended that it be guided by thromboelastometry [52].

3.3. Prothrombin Complex Concentrate

PCC has a higher concentration of factors than FFP (a difference of 0.8 to 1.2 IU/mL), allowing a rapid recovery of vitamin K-dependent factors in warfarin-treated patients without circulatory overload [51][53]. ESLD has reduced production of FII, FV, FVII, FIX, and FX [54][55][56]; four-factor PCC may help restore deficient factors, except for FV [56].

In contrast to modern four-factor PCCs containing significant amounts of proteins C and S, rFVIIa does not contain anticoagulants and is associated with increased thromboembolic events, particularly arterial thrombosis in liver transplantation, and should therefore be avoided [57]. In patients with severe liver damage due to active bleeding or invasive procedures, similar recoveries (1.3–1.4 IU/kg) have been observed among FII, FIX, and FX. The median dose of PCC in this case series was 25.7 IU/kg (1500 [1000–4000] IU). No adverse events, including thrombosis, were observed [54]. A dose of 25 IU/kg of PCC was used if EXTEM-CT above 80 seconds for active hemorrhage in

266 LT cases after restoring fibrinogen levels. PCC was used in 34.9% (*n* = 93) of the patients compared with 14.7% (*n* = 39) [55].

3.4. Thrombopoietin Receptors Agonist (TPO)

TPO has been approved in chronic liver disease (CLD) patients programmed for invasive procedures. The published studies demonstrated a reduction in the need for platelet transfusions by enhancing the TPO receptor activation, increasing megakaryocyte progenitor proliferation, and ultimately increasing platelet production [58][59]. The effects of TPO agonist have not been studied in patients programmed for a liver transplant, and the main controversy is the risk of thromboembolic events. The safety profile for OLT has yet to be established. There is no recommendation for their use in this setting.

4. Pediatric Considerations

Sufficient differences between pediatric and adult patients needing OLT require independent yet complementary documents. Children have distinct diseases, clinical susceptibilities, and physiological responses that distinguish them from those of adults. Significant differences among newborns, infants, children, and adolescents have been found [60]. A multidisciplinary pediatric OLT evaluation team should be skilled in pediatric conditions and adequately communicate LT's processes, risks, and benefits to the family and the child. Indications for LT in the pediatric population include biliary atresia, metabolic/genetic conditions, acute liver failure, cirrhosis, liver tumor, immune-mediated liver, biliary injury, and other conditions. Acute liver failure (ALF) or acute decompensation may rapidly progress to death or irreversible neurological damage [61].

Despite coagulopathy for liver disease, pediatric patients also acquire coagulopathy due to the dilution of clotting factors. This complication depends on the type of fluid therapy and volume of transfused RBC. Anesthetic challenges during this stage include the maintenance of hemodynamic stability by adequate fluid and blood product administration and correcting coagulation abnormalities. Acquired fibrinogen deficiency should be treated with the substitution of cryoprecipitates or the intraoperative administration of FC (50 mg/kg) to treat hypofibrinogenemia (ROTEM FIBTEM maximum clot firmness < 7 mm) during major pediatric surgery. Substitution with other coagulation factors (FXIII levels > 60%) should be indicated with laboratory or viscoelastic testing results. FFP might help treat severe hemorrhage as an adjunct to primary treatment with coagulation factors. However, it has been shown that FFP does not adequately increase plasma fibrinogen concentration. A 20–30 mL/kg volume dose should be administered to increase fibrinogen concentration. Moreover, it should only be considered after excluding other factors influencing hemostasis (fibrinogen deficiency, hyperfibrinolysis, acidosis, hypothermia, and low platelet count or impaired platelet function).

Cardiac surgery results showed that fibrinogen concentrate is as efficient and safe as cryoprecipitate. Unfortunately, no study has assessed the response to fibrinogen concentration after FFP administration in children with liver transplants [61].

Thrombocytopenia, secondary to hypersplenism, has a high prevalence and impairs coagulation. Platelet administration must always be weighed against the risk of hepatic artery thrombosis in the new graft in the pediatric population [62].

Perioperative treatment with an antifibrinolytic agent reduces bleeding and transfusion requirements in pediatric LT and hepatectomy, with high bleeding risk [63]. Bleeding prevention should be considered a patient-based multimodal approach. Antifibrinolytic agents may play a central role in perioperative bleeding prophylaxis in the pediatric population [64].

Tranexamic acid should be administrated at a loading dose of 10 mg/kg over 15 min, followed by a 5 mg/kg maintenance infusion, to maintain adequate plasma concentrations. Tranexamic acid is necessary for all children undergoing surgery with a significant bleeding risk to treat fibrinolysis but not for routine prophylaxis. Post-reperfusion fibrinolysis is common in marginal grafts (e.g., donation after cardiac death) and should be considered in patients with cirrhosis undergoing liver resection [61][65].

The reference ranges for the ROTEM parameters in children are age dependent. Children aged 0–3 months exhibited accelerated coagulation and firm clot firmness despite showing prolonged standard plasma coagulation test results. In addition, platelet count and FXIII contribute to clot firmness in children's fibrinogen concentration, as measured with the ROTEM assay. In addition, children aged 4–24 months showed 2.5% percentiles for clot strength, indicating a low reserve when exposed to hemodilution and blood [64][65][66]. Viscoelastic tests during pediatric LT are well-established. The main objective of perioperative coagulation management is to prevent severe coagulopathy and avoid thromboembolic complications and graft thrombosis in pediatric OLT.

In 2008, the NHS Quality Improvement Scotland released a report based on health technology assessment that integrated evidence such as clinical effectiveness, cost and benefits, organizational aspects, and more about patients. Viscoelastic testing is recommended instead of standard coagulation tests during cardiac surgery, and (National Institute for Health and Care Excellence, UK) guidelines recommend viscoelastic tests to monitor coagulation during and after surgery. It is associated with lower mortality risks, reduced complications, and lower transfusion rates and hospitalization time [66][67].

5. Blood Conservation Technics in Liver Transplantation

Several blood conservation strategies should be used for live-donor liver transplantation (LDLT). Postoperative blood conservation involves limited blood sampling and pediatric drainage tubes. Intraoperative techniques include Acute Normovolemic Hemodilution (ANH), cell salvage, and specialized surgical techniques. Combining preoperative blood augmentation with ANH can be especially effective in OLT, allowing the removal of greater quantities of whole blood without causing significant perioperative anemia. Surgical techniques to control portal hypertension and blood loss during OLT in recipients are also essential for blood conservation. Hepatic congestion is unique to OLT and is associated with impaired function of the transplanted lobe. With refining surgical techniques, blood transfusions in OLT have been significantly reduced. Strategies that aim to minimize blood loss

and transfusion should be developed. Intraoperative blood salvage autotransfusion (IBSA) reduces the need for allogeneic blood transfusions [68]. A study of 150 consecutive OLT patients showed that IBSA reduced the need for blood transfusion [69]. The risk of bacterial infection in the operative field seems plausible; however, this has not been demonstrated [70].

Cell salvage is globally used in liver transplants as a blood conservation technique. A recent systematic review reported that no data were found indicating whether cell salvage usage resulted in a reduction of transfusion requirements. The use of cell salvage did not increase HCC recurrence and did not affect mortality. Moreover, they found no data for other measures, including perioperative complications. All studies included in this systematic review were observational and had a small sample size; despite the insufficient evidence to state a recommendation, the authors' conclusion favors its use to reduce blood transfusion in this setting [71].

6. Patient Blood Management Consideration for Acute Liver Failure

In patients with acute liver failure (ALF), the principles of pillar one from the PBM program should be focused on avoiding iatrogenic blood loss; anemia treatment to normalize laboratory parameters is often tricky secondary to the acute illness and timing of presentation, and based on the current evidence, the hemostasis in ALF indicates a "rebalanced" state [72]. Prophylactic transfusion of blood products is undesirable and unwarranted [72]. Without a clear benefit, it may expose patients to complications such as volume overload and transfusion reaction, immunomodulation, and graft rejection [72]. Viscoelastic tests have also gained more recognition as potential tools in evaluating coagulopathy in patients with liver disease [72].

The recommendations for treating coagulation abnormalities and blood loss in patients with CLD have been ported to patients with ALF. The treatment should be coagulation support in the evidence of bleeding with the same objectives as patients with CLD. However, specific research for subgroups of patients with ALF and ACLF must be conducted to provide more personalized and precise treatments.

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