Review Article

Blood transfusion practices in liver transplantation

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ABSTRACT

Blood loss and blood transfusion have been inherently associated with liver transplantation. Bleeding has been attributed to the various factors which are associated with chronic liver dysfunction. Various surgical and anaesthetic strategies have been developed over the years to reduce bleeding and also to optimise the usage of various blood and blood products perioperatively. The present day success of liver transplantation can be attributed to these issues where transfusion practices have changed. Although several centres are successfully performing liver transplantations in large numbers, there is still a large variability in the usage of blood and blood products perioperatively among the institutions and even among different anaesthesiologists from the same institution. The present article deals with the various factors confounding this concept of blood transfusion practices and the various strategies adopted to reduce the transfusion requirements in the perioperative period.

Key words: Autologous transfusion, bleeding, blood and blood products, blood salvage, blood transfusion, liver failure, liver transplantation

INTRODUCTION

Liver transplantation (LT) is presently a viable option for patients with end-stage liver disease (ESLD). LT has improved and progressed over the last few decades with the advancement in surgical techniques, perioperative care and immunosuppressive medications. Despite these advances, controversy exists related to the intraoperative management, especially related to the intraoperative fluid and blood and product transfusion. Institutions use protocols based on individual preferences or institutional practices with little or no evidence. There are no existing accepted standards of care in managing this complicated and highly controversial issue. A good understanding of the pathophysiology of ESLD and associated comorbidities has a profound impact on the intraoperative management and decision making.

The surgical procedure of LT can be broadly divided into three phases.

- Preanahepatic phase/dissection phase-native hepatectomy is completed
- Anhepatic phase – from native hepatectomy (clamping of native portal vein till anastomosis of graft portal vein and reperfusion of grafted liver)
- Neohepatic phase – reperfusion of grafted liver till completion of biliary anastomosis and shifting to the intensive care unit.

TRANSFUSION PREDICTORS

Blood loss and transfusion requirements remain difficult to predict in the intraoperative course of LT and many studies have shown discordant results and no uniform conclusions.[1] Blood loss during LT is a common consequence of pre-existing abnormalities of the haemostatic system, portal hypertension with multiple collateral vessels, portal vein thrombosis, previous abdominal surgery, splenomegaly, and poor 'functional' recovery of the new liver [Table 1]. The intrinsic coagulopathic features of end-stage cirrhosis along with surgical technical difficulties make transfusion-free LT a major challenge.

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Table 1: Hemostatic abnormalities in liver disease[3]

Hypocoagulability
Deficiency of coagulation factors by impaired synthesis
Synthesis of abnormal clotting proteins (dysfibrinogenemia)
Impaired clearance of activated coagulation factors and degraded fibrin
Vitamin K deficiency
Hypercoagulability
Decreased levels of antithrombin, protein C or protein S by impaired synthesis
Enhanced fibrinolytic activity
Increased levels of circulating t-PA by impaired hepatic clearance
Reduced synthesis of fibrinolytic inhibitors
Quantitative and qualitative platelet defects
Splenomegaly caused by portal hypertension leads to platelet sequestration and destruction
Thrombopoietin deficiency due to cirrhosis leads to low platelet production
Disturbed platelet-vessel wall interaction
Inhibition of GP IIb/IIIa by increased levels of fibrin degradation products
Degraded platelet receptors by increase in plasmin levels
Disseminated intravascular coagulation
Consumption of coagulation factors and platelets
Hyper fibrinolysis
Impaired platelet function due to fibrin degradation products, secondary to hyper fibrinolysis

GP – Glycoprotein; PA – Plasminogen activator

In general the predictions are based on the severity of liver disease, preoperative coagulation function, recipient's clinical status, quality of the donor liver, and experience of the transplantation team. However, the risk of bleeding still seems to vary from centre to centre depending on various factors such as the severity of recipient's clinical conditions, surgeon's preferred technique, the duration of surgery, the duration of the anhepatic phase, and the time to graft function. Many preoperative conditions and unforeseen intraoperative events impart complex changes to the recipient's spontaneous haemostasis; the potential occurrence of technical difficulties, which require massive fluid resuscitation may alter the substantial intraoperative coagulopathy and predispose to further extensive bleeding.[2]

Coagulation monitoring-traditional coagulation monitoring/thromboelastography (TEG):[4-6]

Hepatic dysfunction leads to complex changes in the balance between normal haemostasis and imbalance between coagulation and its inhibition as well as fibrin polymerisation and fibrinolysis leading to all forms of coagulopathy. Successful management of this global haemostatic imbalance is essential for the successful management of patients for LT.

The prevention, evaluation and treatment of coagulopathy remain the central theme in the perioperative care of LT. Early correction of coagulopathy and thrombocytopenia, monitoring of prothrombin time and fibrinolytic indices, and close observation of the surgical field are essential components of management.

A 'gold standard' test to monitor coagulation has remained elusive. Little agreement exists on what laboratory values should trigger an intervention. Accordingly all currently available tests –TEG, sonoclot analysis, and standard tests including prothrombin time, partial thromboplastin time, INR, fibrinogen levels and platelet counts, have all been recommended depending on individual/institutional choices and preferences. TEG and rotational thromboelastometry usage have been shown to rationalise usage of blood products and also facilitate the diagnosis of hyper coagulable states.

ANAESTHESIA TECHNIQUES TO REDUCE BLOOD TRANSFUSION

Among the various strategies to substantially reduce the amount of blood product transfusions and the associated side-effects, intraoperative blood salvage has been considered and still is an important method of blood conservation. However, controversy still surrounds its usefulness during LT, with studies demonstrating either an increase or a decrease in blood transfusion. Intraoperative blood salvage has gained wide acceptance and were a routine practice in all centres and reduces the use of donor red blood cells and thus avoids hypervolemia. Use of cell saver also helps in washing bank blood before transfusion. Cell saver has been shown to be cost-effective, conserves blood bank resources and reducing overall costs.

Changes in the anaesthetic management have also contributed significantly to the reduction in blood loss and use of blood and blood products. Circulatory stability achieved by the use of vasopressors intraoperatively is also associated with improvement in systemic vascular resistance and improved blood pressure and organ perfusion. Use of vasopressin, intra-operatively also contributed to improved organ perfusion, reduced splanchnic blood flow, thus reducing intra-abdominal blood loss.[7] Reduction of the anahepatic phase time, cold ischemic time and total surgical time have significantly contributed to the reduction in blood loss and transfusion needs. Another significant factor which has contributed to

this is the use of low CVP intraoperatively either by fluid restriction or diuresis. This has also improved portal blood flow and oxygen delivery to the graft and improved graft function.

CONTROL OF BLOOD LOSS AND TRANSFUSION MANAGEMENT

Blood loss has always been a central issue in LT and remains a major cause of morbidity and mortality. Blood transfusion is an independent factor associated with poor outcome in LT. The risks associated with transfusion have always motivated refinements in surgical techniques. The risks associated with transfusion may be varied. These include acute haemolytic transfusion reactions (ABO incompatibility), infusion of contaminated blood, transfusion-associated lung injury, severe allergic reactions, subacute complications which may be missed include fluid over load, hypothermia, hypocalcaemia, hyperkalaemia, acid – base disturbances, a paradoxical increase in transfusion requirements. Hypocalcaemia itself can lead to coagulopathy in addition to reduced vascular tone and compromised myocardial contractility, needing frequent supplementation. Transfusion related immune modulation has been another factor that may contribute to the poor outcome. Large volume transfusion is associated with higher risk of infections, gastrointestinal and intra-abdominal complications.[2,7,9]

The relationship between intraoperative blood use, the effects on immunomodulation and an increased risk of postoperative complications, such as infections, gastrointestinal, intra-abdominal, and/or pulmonary complications, prolonged recovery, and a higher rate of reoperation has been repeatedly demonstrated.[10,11]

The average blood loss and its usage in LT has undergone a quantum change over the decades, which has reduced from average 20 units of packed red cells to average of 2–3 units currently. This also indicates refinements in surgical and anaesthetic techniques. The amount of blood and blood products used is determined by the amount of surgical blood loss and transfusion triggers adopted.[8] Acceptance of lower transfusion triggers like Hgb of 7 g/dl, platelet count > 40,000, INR 1.5–2, fibrinogen > 100 mg/dl, and use of haemodynamic parameters, electrocardiography and lactate levels have all contributed to a reduction in blood and product usage.

Each stage of the LT procedure imparts complex changes, which influence the choice of fresh frozen plasma (FFP), cryoprecipitate and platelet transfusions. During the preanahepatic phase, the primary issue is surgical bleeding. Concurrent fluid administration leads to a gradual decline in coagulation factors and platelet count. A gradual intraoperative hypothermia may exacerbate these problems. The anahepatic phase also is associated with significant alterations in haemostasis: Platelet and coagulation factors continue to decline, and in the absence of hepatic clearance, accumulation of tissue thromboplastin further compounds the dysfunction. Finally, in the neohepatic phase, reperfusion of the grafted liver and resultant reperfusion syndrome, lead to severe coagulopathy of multifactorial origin including reperfusion hypothermia, ionised hypocalcaemia, dilutional coagulopathy, quantitative and qualitative defect in platelets, heparin effect, fibrinolysis, release of variety of humoral substances from the grafted liver and excessive activation of coagulation in rare cases.

In the post-operative period, as the grafted liver becomes functional, the coagulopathy improves gradually. Fibrinolysis and heparin effects gradually dissipate within 2 h. By the end of surgery, the coagulation factors and platelet counts increase towards baseline values. Persistent oozing in the presence of acceptable coagulation profile and TEG, indicates surgical oozing. Persistent coagulopathy and nonsurgical bleeding indicates poorly functioning graft with ischemic or immunologic injury. With adequate normalisation of graft function coagulation factor levels normalise in a few days with normal coagulation profile.[9]

Counteracting fibrinolysis and antifibrinolytic agents is another area of concern during LT. Controversy exists in the prophylactic use of drugs to stabilise clot formation and thus reduce blood loss. The risks include hepatic artery thrombosis and thromboembolic events. These agents have been shown to reduce intraoperative blood loss significantly, without evidence of increase in thrombotic complications. Selective use of these agents is recommended not in a prophylactic manner but only when fibrinolysis has been demonstrated by TEG. TEG based algorithms have been proved to be beneficial in this regard. The most widely used antifibrinolytics are E-aminocaproic acid (EACA), tranexamic acid and aprotinin.

Aprotinin is an inhibitor of plasmin and also

has anti-inflammatory properties. It is no longer recommended in LT due to evidence on dose-dependent increase risk of death, renal failure and cardiovascular events. EACA and tranexamic acids have been widely used. They exert their effect by inhibiting conversion plasminogen to plasmin. EACA has been safely used in wide dose range of 0.25–5 g.

Tranexamic acid is a synthetic derivative of amino acid lysine and exerts its antifibrinolytic effect by the reversible blockade of lysine-binding sites on plasminogen. A study published in 2011 by the Cochrane Hepatic-Biliary Group,[13] which included all randomized clinical trials that compared various methods of decreasing blood loss and blood transfusion during LT, reported that there were no significant differences in the allogenic blood transfusion requirements, amount of platelets, FFP, or cryoprecipitate transfused between the tranexamic acid and control groups.

Recombinant factor VII A is not a substitute of clotting factors; in addition, it can also induce other negative pharmacological effects. It seems to be useful in improving coagulation in transplant recipients with refractory hemorrhagic complications serving as a bridge to definitive treatment. Safety of rFVIIa in OLT has been demonstrated in many reports; no effects on thromboembolism or mortality have been found in various trials.[12] However, the experience with this drug is still too limited, and the benefit/risk ratio not completely evaluated. Its administration provides a novel way to increase the thrombin burst and acutely improve coagulation in the presence of rapid factor consumption. It is advisable that TEG monitoring be performed before rFVIIa administration.[13] It is currently been used in the setting of acute fulminant liver failure needing placement of either intracranial pressure monitoring device or invasive lines. Both prophylactic (prior to incision) and intraoperative administration of rFVIIa has been considered by some authors to prevent intraoperative blood transfusion in Jehovah's witnesses or markedly reduce it in non-Jehovah's witnesses.

SUMMARY

Blood transfusion therapy is still a critical feature during LT, and various studies have shown a large variability in the use of blood products among different centres and even among individual anaesthesiologists within the same centre. Unfortunately, despite the large number of LT performed each year, there is still paucity of large randomised, multicentre, and controlled studies which indicate how to prevent bleeding, the transfusion needs and thresholds, and the "evidence-based" perioperative strategies to reduce the amount of transfusion. Evolving strategies to reduce the use of blood and blood products in LT has also reduced the duration of Intensive Care Unit stay and also early extubation.

Even though, the transfusion practices still vary greatly from centre to centre, considerable progress has been made on properly balancing intraoperative fluid, preventing and treating clotting abnormalities as well as on "individualising" the transfusion triggers. The understanding that perioperative blood loss and blood transfusions have a negative impact on postoperative outcome has led to emphasise the need for a critical reappraisal of the traditional heterologous transfusion policies and a re-evaluation of cell salvage as part of a blood conservation strategy in anaesthesia.

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