World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.1

World J Hepatol 2013 January 27; 5(1): 1-15
ISSN 1948-5182 (online)

REVIEW

Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation

Feltracco Paolo, Brezzi Marialuisa, Barbieri Stefania, Galligioni Helmut, Milevoj Moira, Carollo Cristiana, Ori Carlo

Feltracco Paolo, Brezzi Marialuisa, Barbieri Stefania, Galligioni Helmut, Milevoj Moira, Carollo Cristiana, Ori Carlo, Department of Medicine UO Anesthesia and Intensive Care, University Hospital of Padova, Via Cesare Battisti, 256, 35128 Padova, Italy

Author contributions: Paolo F and Marialuisa B performed the literature search and drafted the article; all other authors made substantial contributions in completing the manuscript, revising it for important intellectual content, and approving the version to be submitted.

Correspondence to: Feltracco Paolo, MD, Department of Medicine UO Anesthesia and Intensive Care, University Hospital of Padova, Via Cesare Battisti, 256, 35128 Padova, Italy. paolofeltracco@inwind.it
Telephone: +39-49-8218285 Fax: +39-49-8218289
Received: August 9, 2012 Revised: January 7, 2013
Accepted: January 18, 2013
Published online: January 27, 2013

Abstract

Blood loss during liver transplantation (OLTx) is a common consequence of pre-existing abnormalities of the hemostatic system, portal hypertension with multiple collateral vessels, portal vein thrombosis, previous abdominal surgery, splenomegaly, and poor "functional" recovery of the new liver. The intrinsic coagulopathic features of end stage cirrhosis along with surgical technical difficulties make transfusion-free liver transplantation a major challenge, and, despite the improvements in understanding of intraoperative coagulation profiles and strategies to control blood loss, the requirements for blood or blood products remains high. The impact of blood transfusion has been shown to be significant and independent of other well-known predictors of posttransplant-outcome. Negative effects on immunomodulation and an increased risk of postoperative complications and mortality have been repeatedly demonstrated. Isovolemic hemodilution, the extensive utilization of thromboelastogram and the use of autotransfusion devices are among the commonly adopted procedures to limit the amount of blood transfusion. The use of intraoperative blood salvage and autologous blood transfusion should still be considered an important method to reduce the need for allogenic blood and the associated complications. In this article we report on the common preoperative and intraoperative factors contributing to blood loss, intraoperative transfusion practices, anesthesiologic and surgical strategies to prevent blood loss, and on intraoperative blood salvaging techniques and autologous blood transfusion. Even though the advances in surgical technique and anesthetic management, as well as a better understanding of the risk factors, have resulted in a steady decrease in intraoperative bleeding, most patients still bleed extensively. Blood transfusion therapy is still a critical feature during OLTx and various studies have shown a large variability in the use of blood products among different centers and even among individual anesthesiologists within the same center. Unfortunately, despite the large number of OLTx performed each year, there is still paucity of large randomized, 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.

Key words: Transplantation surgery; Liver dysfunction; Liver transplant; Intraoperative bleeding; Intraoperative transfusion; Autotransfusion; Autologous transfusions; Transfusion requirements; Blood salvage; Cell salvage

Paolo F, Marialuisa B, Stefania B, Helmut G, Moira M, Cristiana C, Carlo O. Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. *World J Hepatol* 2013; 5(1): 1-15 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/1.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.1

INTRODUCTION

Bleeding in major surgical procedures involving the liver, such as partial liver resection and liver transplantation (OLTx), occurs almost inevitably and still represents a daunting problem when massive. Although the origin of bleeding during OLTx is multifactorial, technical difficulties and pre-existing abnormalities of the hemostatic system represent the principal causes of significant perioperative hemorrhages. Since there is minimal consensus on transfusion guidelines during OLTx, massive volume empirical transfusion was the standard practice until a few years ago, and blood products accounted for approximately 10% of the total cost of transplantation[1,2].

As anesthesiologic and surgical teams have gained experience blood loss in patients undergoing liver transplantation has decreased substantially and in recent years the procedure is occasionally performed without intraoperative blood transfusion.

A variety of strategies, including acute isovolemic hemodilution, appropriate surgical and anesthesiologic management, and the use of autotransfusion devices have been adopted during the last decade to limit the amount of allogenic blood transfusion. In addition, the extensive utilization of thromboelastogram (TEG) has improved the understanding of intraoperative coagulation profiles of these patients and led to a reduction in blood requirements[3].

However, the intrinsic coagulopathic features of end stage cirrhosis make transfusion-free liver transplantation a major challenge, and despite the improvement in strategies to control blood loss, most patients still bleed extensively. This requires the transfusion of variable amount of blood or blood products and may be associated with increased rates of morbidity and mortality.

Blood bank demands in complicated liver transplant surgery are still high and even though the quality and safety of blood products continue to improve they remain costly and increase the risks encountered by the patient.

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[4,5].

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 OLTx, with studies demonstrating either an increase or a decrease in blood transfusion.

Since the clinical conditions of the candidates who undergo liver transplant surgery are increasingly critical and therefore we cannot predict with accuracy which patients will bleed, in our personal view a cell saver machine should be instituted in all OLTx.

BLOOD LOSS DURING LIVER TRANSPLANTATION

The liver is a highly vascular organ and the transplant procedure usually involves a recipient with severe coagulopathy, portal hypertension, and sometimes previous abdominal surgery. Blood losses and transfusion requirements remain difficult to predict in the intraoperative course of OLTx and many studies have shown discordant results and no uniform conclusions[6]. 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. Blood losses are frequently difficult to measure during OLTx, and quite often they are quantified indirectly by calculating the amount of blood necessary to maintain or reach a predetermined hematocrit (Ht) or hemoglobin (Hb) value. As previously stated, advances in surgical technique and anesthetic management, as well as a better understanding of the risk factors, have resulted in a steady decrease in intraoperative bleeding and transfusion requirements[7]. 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 hemostasis; the potential occurrence of technical difficulties which require massive fluid resuscitation may alter the substantial intraoperative coagulopathy and predispose to further extensive bleeding. Contributing factors to blood loss during OLTx can be categorized as preoperative and intraoperative.

PREOPERATIVE HEMATOLOGIC AND COAGULATION DEFECTS

Hemostatic function is determined by the interaction of the vascular wall, platelets, coagulation factors, and fibrinolytic function. All these components may be abnormal in patients who have a compromised liver function. Anemia is common in these patients as a result of chronic disease, malnutrition, or occult bleeding. Bleeding complications may not be primarily related to impaired coagulation; alterations in haemodynamics and vessel wall function may play a more important role. The hyperdynamic circulation and the presence of portal hypertension are among the most important causes of perioperative bleeding tendency[8]. The aetiology of impaired haemostasis in the advanced liver failure is often multifactorial and may include impaired coagulation factor synthesis, synthesis of dysfunctional coagulation factors, their increased consumption, altered clearance of activated factors, hyperfibrinolysis, disseminated intravascular coagulation (DIC), and platelet disorders.

The reduced hepatic synthesis of clotting factors is also associated with a significant deficit of natural anticoagulants, particularly protein C and antithrombin.

Commonly, the vitamin K-dependent factors decrease first, starting with factor Ⅶ and protein C owing to their short half-life (6 h), followed by reductions_in factor Ⅴ, Ⅱ and Ⅹ levels[9].

Impaired synthesis and altered clearance of the fibrinolytic factors cause complex abnormalities in the fibrinolytic system. One of the most striking mechanisms is an imbalance between tissue plasminogen activator (t-PA) and its specific inhibitor plasminogen activator inhibitor-1 (PAI-1)[10]. Quantitative (thrombocytopenia) and/or qualitative platelet abnormalities (thrombocytopathies) such as impaired platelet adhesion and aggregation are often attributed to splenic sequestration (hypersplenism), but may also occur as a result of platelet destruction mediated by platelet-associated immunoglobulins, impaired hepatic synthesis and/or increased degradation of thrombopoietin by platelets sequestered in the congested spleen[11].

Additional risk factors for extensive bleeding include the injury of collateral vessels developing as a result of portal hypertension, some from the raw surface of the liver, inflammatory adhesions, as well as previous abdominal surgery.

INTRAOPERATIVE FACTORS CONTRIBUTING TO BLOOD LOSS

Complex coagulation disorders may occur during liver transplantation due to the underlying liver disease and haemostatic changes associated with the transplantation. The latter may result from hemodilution, platelet consumption, disordered thrombin regulation, and fibrinolysis. Haemodilution secondary to fluid replacement and the preservation solution from the donor liver can additionally reduce plasma levels of coagulation factors. Variable intraoperative blood loss may ensue in the form of brisk bleeding through a vascular injury and/or appear as diffuse continuous microvascular bleeding mixed with the peritoneal ascites. Technical difficulties predisposing to bleeding include portal vein thrombosis, post-surgical adhesions, and, in children with biliary atresia, previous portoenterostomy. Bleeding is greatly potentiated by the activation of the fibrinolytic system, which occurs both during the anhepatic and reperfusion phases. During the anhepatic phase, circulating levels of PAI-1 are reduced leading to an increase in t-PA. Some patients develop severe coagulopathy early after the reperfusion phase due to an accelerated release of t-PA from the graft endothelium which causes generalized fibrinolysis and significant bleeding[12]. Release of exogenous heparin from the harvested graft after donor heparinization or endogenous heparin-like substances from the damaged ischaemic graft endothelium may also play a role in the coagulopathy at reperfusion[13]. Other intraoperative factors contributing to prolonged hemorrhage include hypothermia, hypocalemia and citrate toxicity. Bleeding during the postanhepatic phase may also be related to disseminated intravascular coagulation and platelet trapping. Platelet trapping has been documented by simultaneous measurement of arterial and venous platelet counts. DIC has been correlated with ischemic damage of the graft liver[14]. Transplantation of an optimal graft restores the patient's clotting function. A dysfunctional graft may not immediately produce clotting factors, thereby leading to prolonged coagulopathy mandating massive transfusions[15].

PREDICTORS OF TRANSFUSION REQUIREMENTS

The most important variables affecting transfusion requirements include the severity of disease [Child-Turcotte-Pugh Score, United Network for Organ Sharing priority for transplantation or in recent years model for end-stage liver disease (MELD) classification], preoperative prothrombin time (PT), history of abdominal operations, and Factor Ⅴ levels. The Child classification is a measure of disease severity that includes assessments of ascites, encephalopathy and measurements of serum bilirubin and albumin. MELD gives a score based on how urgently the patient needs a liver transplant within the next three months. Its impact on transfusion requirements at the time of transplantation may be difficult to predict. The length of cold ischemia time has also been associated with short-term graft dysfunction and negative effects on perioperative red blood cell (RBC) transfusion requirements. Other variables include cholestasis, splenomegaly, the preoperative haematocrit value, use of the piggyback transplantation method, and operative time[16]. Patients with chronic active hepatitis have more advanced disease and require more blood products than patients with primary biliary cirrhosis[17]. Previous upper abdominal surgery tends to have vascularised adhesions which may render liver dissection hemorrhagic. Portal vein hypoplasia and decreased donor liver size, presenting a technical challenge for the surgeons, were predictive of blood loss[16]. Use of a partial liver graft, as in living-donor liver transplantation, creates a graft with a raw surface that can bleed after reperfusion[14]. The risk of primary nonfunction after transplantation of poor quality cadaveric graft increases proportionately with the degree of steatosis. Graft dysfunction further necessitates massive transfusions[18]. Inadequate graft-recipient body weight ratio, poor graft preservation and prolonged cold ischemia time have also been associated with increased intraoperative bleeding tendency[14]. Massicotte *et al*[6] in a retrospective study of 206 successive liver transplants found that the three most important variables related to the number of RBC units transfused were: the starting international normalized ratio (INR) value, the starting platelet count, and the duration of surgery.Plasma transfusion did not decrease the amount of RBC transfusions.

Deakin *et al*[19] showed that in their population of 300 adult liver transplantations, blood urea nitrogen level and platelet count had an independent correlation with transfusion necessity. Ramos *et al*[20] looking for useful variables for the preoperative identification of patients likely to require transfusion of RBCs could not show a statistically significant relationship between preoperative coagulation parameters and need for intraoperative blood products. However, age, Child class, diagnosis, INR, Hb level and the effect of intraoperative portacaval shunt placement were close to significance on the amount of blood transfusion. They concluded that preoperative normalization of Hb level and placement of intraoperative portacaval shunt could diminish the need for RBC transfusion during OLTx. In a multivariate linear regression analysis of 526 liver transplants Mangus *et al*[21] demonstrated that predictors of estimated blood loss were age, MELD score, preoperative hemoglobin, initial fibrinogen, initial central venous pressure, and total anesthesia time. Specific predictors of RBCs usage were age, MELD score, preoperative hemoglobin, initial fibrinogen, and anesthesia time. On the contrary, Massicotte *et al*[22] found that only two variables were linked to RBC transfusion: starting hemoglobin value and phlebotomy. In their study the MELD score did not predict blood losses and blood product requirement during OLTx.

Steib *et al*[23] looking at the preoperative factors associated with high blood loss in 510 consecutive patients undergoing OLTx, were unable to correctly identify patients at risk for intraoperative hemorrhage. In the recent study by Roullet *et al*[24], MELD score did not appear as a risk factor for bleeding or transfusion requirements during OLTx, nor did previous upper abdominal surgery, preoperative coagulation defects, or Hb level. They concluded that the preoperative risk factors for bleeding and transfusion during OLTx were of little clinical usefulness and therefore blood products should always be available during the procedure. Given the poor predictive value of the single preoperative variable even in a homogeneous population some authors recommend that centres evaluate their practice individually in order to identify the centre-specific risk factors and high risk patients for perioperative transfusion[25].

TRANSFUSION PRACTICE DURING OLTx

Blood transfusion therapy has remained a critical feature in OLTx and various studies have shown a large variability in the use of blood products among different centers and even among individual anesthesiologists within the same center[2]. The decision of when a patient should be transfused with RBCs still remains a greatly discussed issue, in part because there is scant evidence supporting one practice over another. For example, conflicting results derive from the adoption of different triggers for blood transfusion or different inter-centre protocols or protocols not driven by coagulation monitoring or with or without the use of antifibrinolytics. Evidence that liberal RBCs transfusion thresholds are associated with better outcomes than a more restrictive approach is still lacking, and a remarkable variability in this practice continues to be observed. In particular, there is little published data in support of RBCs transfusion when the Hb level is above 7 g/dL, even if the patient has cardiac comorbidities[15,26]. Some authors recommend to keep the hematocrit between 30% and 35%; others think it advisable and acceptable to maintain it between 26% and 28%[27,28]. In the study by Steib *et al*[23] RBCs were administered to maintain Ht levels at 30%. Even though OLTx surgery is widely seen as a highly specialized procedure, strict guidelines for optimal use of packed red blood cells have not been developed. The influence of the amount of transfusion of various blood components on clinical outcome after liver transplantation has not been studied in detail. Blood transfusion is generally considered a surrogate marker for sicker patients and complex surgery, and its role on outcome has not been precisely defined in large trials[7].

Fresh frozen plasma transfusion

The standard indication for fresh frozen plasma (FFP) infusion is clotting improvement; in some centres FFP is still administered for volume replacement in case of hemodynamic derangement. Many consider transfusing FFP while waiting for laboratory results reasonable and preferable to not giving coagulation factors in time[29]. Freeman *et al*[30] support the view that FFP administration is not essential during OLTx and that platelets and fibrinogen concentrates may be given when platelet count and fibrinogen level fall to below 50.000 mm^3 and 1 g/L, and human serum albumin can be used as a volume expander. Liver removal during surgery leaves the patient anhepatic for a period of time, which further complicates the coagulation. This phase is associated with a decrease in Factors Ⅷ and Ⅴ, a decrease in fibrinogen, and an increase in fibrinolysis. FFP is expected to improve complex coagulation disorders in case of severe bleeding as it contains all coagulation factors and inhibitors. FFP should be treated with solvent-detergent to inactivate viral particles and decrease the risk of viral infection. Treated plasma has lower factor Ⅷ and alpha-2 antiplasmin activity, but patients who receive treated FFP demonstrate a similar correction of the INR and activated partial thromboplastin time (aPTT), and they have transfusion requirements similar to those of patients who receive untreated FFP[30]. Whether FFP should always be used for treating a patient with major blood loss during OLTx is still not completely defined. In addition there is currently no consensus on the volume of FFP or rate of infusion required to prevent or treat intraoperative persistent bleeding; in the common practice 10-15 mL/kg are usually administered. Because of the lack of universally shared guidelines, beside some centre-specific indications[28], both the amount and timing of FFP administration during OLTx still seem guided by experienced clinical judgment, local practices

and the assistance of timely coagulation tests (including near-patient tests).

Platelets transfusion during OLTx

Although there is no consensus regarding the appropriate threshold, platelet concentrates are frequently administered during OLTx for the prevention or treatment of bleeding. However, intraoperative platelet transfusions have been identified as a strong independent risk factor for patient survival after OLTx, in addition to RBCs[31]. The negative impact of platelet transfusions is independent from other well known risk factors, in accordance with the adverse effects of platelets discovered in experimental studies. In animal models of liver transplantation, studies have demonstrated that platelets are involved in the pathogenesis of reperfusion injury of the liver graft by inducing endothelial cell apoptosis. This effect is independent of ischemia-related endothelial cell injury and cannot simply be explained by activation of the coagulation system and aggregation of platelets at the site of endothelial cell injury[32]. In addition, platelets contain many cytokines and vasoactive and inflammatory mediators which are rapidly released on activation by various stimuli after reperfusion. The specific causes that lead to a worse outcome following platelet transfusion have not been examined, however, several factors have been considered such as the risk of viral transmission, the potential for bacterial contamination especially for platelets stored at room temperature[33], the risk of alloimmunization, graft *vs* host disease, nonspecific immunosuppressive effects, and acute lung injury (ALI) or adult distress respiratory syndrome (ARDS). Recent studies show that it is not RBC, but, in fact, plasma-rich blood products, such as FFP and platelet transfusions, that are linked to the development of ALI/ARDS[34]. Pereboom *et al*[35] demonstrated that platelet transfusion during OLTx is associated with increased postoperative mortality due to heavy lungs because of severe lung edema in accordance with the clinical diagnosis of transfusion-related acute lung injury (TRALI)/ARDS. The increased rate of graft loss after platelet transfusion did not result from the specific adverse effects of transfused platelets such as an increased occurrence of graft-related thrombotic complications, but it was caused by higher rate of patients' death with a well functioning graft. Due to the difficulty in discerning whether a bleeding complication during OLTx is a result of the lack of platelets or defects in other hemostatic systems it seems reasonable not to transfuse patients based on a low platelet count alone. Given the reported detrimental effects of platelet transfusion, it is advisable to transfuse them only if significant bleeding complications do occur which are mostly attributable to low platelet count or dysfunctional platelets as demonstrated by on-site coagulation monitoring. Considering that the appropriateness of different blood components administration schemes has not been evaluated in randomised studies, a specific approach targeted to the individual needs may be reasonable. In addition to surgical and anesthetic measures to minimize intraoperative blood loss, a conservative and more targeted use of blood products, weighing the short-term benefits *vs* increased postoperative risk for adverse events in each individual patient, should be considered.

OLTx WITHOUT BLOOD/BLOOD PRODUCTS

For many uncomplicated recipients OLTx has been safely performed without transfusion of any blood products, especially when maximum blood loss was limited to 2500-3500 mL[36]. Even though, as aforementioned, the reports from various centres attest to the high variability of transfusion requirements, a confirmed trend toward a significant reduction in the use of blood products is being observed nowadays[2]. Massicotte *et al*[6] reported that up to 79% of their patient population did not need any red cell transfusion during surgery. Transfusion-free OLTx in Jehovah's witnesses, in combination with preoperative stimulation of red cell production using recombinant human erythropoietin and iron, cell salvage, volemic replacement and tolerance of moderate anemia, have been associated with favourable results[37]. Limiting transfusions to situations where clinical bleeding and/or severe anemia are present has been shown to reduce many perioperative complications. Bloodless strategies also include meticulous surgical technique and the intraoperative hemodilution procedure, where the patient's blood is removed and replaced with non-blood products (5% albumin and crystalloid solution) whenever feasible. The patient's blood is later reinfused during the operation as needed or routinely after liver implantation. Acute normovolemic hemodilution preserves the integrity of the red blood cells and clotting factors, ensuring the availability of safe, fresh autologous blood. Contraindications to the hemodilution procedure include coronary heart disease, significant anemia, and severe pulmonary hypertension. Both prophylactic (prior to incision) and intraoperative administration of recombinant activated Factor Ⅶa has been considered by some authors to prevent intraoperative blood transfusion in Jehovah's witnesses or markedly reduce it in non-Jehovah's witnesses[36,37].

INTRAOPERATIVE BLOOD TRANSFUSION, COMPLICATIONS AND OUTCOME

The impact of blood transfusion has been shown to be important and independent of other well-known predictors of posttransplant outcome, such as recovery of graft function, infectious disease, renal failure, and other comorbidities. Older studies have observed that an increased blood requirement was associated with many adverse events in the postoperative period, including higher rates of graft failure and patient mortality[18]. Cacciarelli

et al[38] reviewed 225 adult OLTx recipients and showed a significant improvement in both patient and graft survival when less than 5 U of RBCs were transfused intraoperatively. Ramos *et al*[20] showed that even a moderate number of blood transfusions was associated with a longer hospital stay and that transfusion of more than 6 U of PRBCs was associated with diminished survival. In pediatric patients, increased blood product administration appeared as a significant independent negative predictor of long-term patient survival[39]. As Hendriks *et al*[39] stated intraoperative transfusion of RBCs was the sole predictor of surgical reintervention after OLTx. Patients with reinterventions had a three-fold higher mortality during the observation period and had significantly longer hospital stay compared with patients without reinterventions. Whether the difference in outcome is related to the transfusion as an independent risk factor or whether the transfusion is a marker for a technically more difficult surgery remains unclear[14]. However, multiple observations underline that every attempt to control blood loss and reduce transfusion requirements should be practiced in order to lessen the probability of surgical reintervention and improve in-hospital morbility and overall outcome. The immunosuppressive effect and the induction of several complications may account for the negative correlation between the intraoperative blood transfusion and postoperative outcome. Common complications of massive transfusions are immunologic adverse effects, metabolic derangement, infectious exposure with increased septic episodes, and acute lung injury. Transfusion-related immunological adverse effects include anaphylactic reactions, hemolysis, graft *vs* host disease, and nonspecific immunosuppressive effects. Large volumes of allogenic blood result in the infusion of large amounts of foreign antigens in both soluble and cell-associated forms. The persistence of these antigens in the circulation of the recipient is considered to result in impaired cell-mediated and natural killer cell activity, and deterioration in liver regeneration[40,41]. Severe metabolic derangement from massive transfusion may occur as a consequence of dilutional coagulopathy, dilutional thrombocytopenia, DIC, citrate toxicity, metabolic alkalosis, hypocalcemia, hypomagnesemia, hyperkalemia, acid/base disturbances and hypothermia[42]. Blood products transfusions have been identified as a risk factor for TRALI, ALI and ARDS[43].

ARDS is a serious multifactorial complication after OLTx most likely caused by fluid overload from crystalloid liquid infusion or massive transfusion and reperfusion syndrome[44]. The risk of developing ALI/ARDS seems to be higher after transfusion of FFP or platelets than after RBC[34]. Other postoperative complications associated with blood transfusion include perioperative myocardial infarction, postoperative low-output cardiac failure, and increased tumor recurrence[45-47]. In addition, exposure to multiple units of allogenic blood increases the risk of developing abnormal antibodies which makes future crossmatching more difficult and time-consuming[48].

INTRAOPERATIVE STRATEGIES TO REDUCE BLOOD LOSS

Anesthesiologic management

Properly balanced intraoperative fluids, use of predefined or "individualized" transfusion triggers, and prophylactically administered pharmacologic agents capable of reducing blood loss may have a positive impact on amount of bleeding and transfusion requirements. Avoiding excessive fluid administration and maintaining relative hypovolemia have been firmly advocated. As demonstrated during hepatic resections, maintaining a low central venous pressure (CVP) *via* volume restriction, phlebotomy, or both, has been shown to decrease surgical blood loss and promote graft decongestion. A low CVP has been recommended to minimize blood loss during explantation of the liver. With the "classical" cava-cava technique severe hemodynamic instability may ensue when inferior vena cava is clamped in the presence of hypovolemia; on the other hand with the wider application of the "piggy-back" technique measures to maintain CVP below 5 cm H_2O have become possible. Massicotte *et al*[49,50] reported that maintaining a low CVP before the anhepatic phase was of utmost importance to decrease blood loss and transfusion rate. However, the debate on an optimal CVP value to prevent major bleeding during OLTx is still not solved; in fact, although a low CVP is associated with reduced blood loss, it also carries a higher risk of complications such as air embolism, systemic tissue hypoperfusion, and renal failure. Schroeder *et al*[51] demonstrated that intentionally lowering the CVP to decrease blood loss during OLTx was associated with significant morbidity and mortality; the postoperative peak serum creatinine level, the need for dialysis, and 30-d mortality were higher in patients who had low CVP. Many transplant surgeons prefer that the CVP be kept "low" after reperfusion of the graft to avoid venous congestion of the new graft, but any quantification of this "low" number is futile. During liver transplantation there is no evidence to support decreasing CVP and effective circulating blood volume to levels currently practiced during hepatic resections surgery; this practice might compromise vital organ perfusion[52]. Diuretics also often play a role in achieving euvolemia and can help in reducing transfusion requirements. The osmotic activity of mannitol can aid in removing free water within abdominal organs, particularly in the setting of hepatorenal syndrome, thus preventing hepatic distension once the graft is reperfused. Due to the lack of adequately powered, randomized, prospective controlled trials further investigations are needed to determine which patients would benefit from restrictive volume management in the intraoperative period of OLTx. Intraoperative coagulation abnormalities have long been thought of as major culprits for blood loss and transfusion requirements. They may be aggravated by unrecognized hypothermia and acidosis. Hypothermia likely occurs when large volumes of unheated fluids are admin-

istered; acidosis affects hemostasis as well, probably by inhibition of platelet function[53]. Among the strategies to attenuate surgical bleeding by reducing both graft and portal vein pressure the use of lower tidal volumes (6-8 mL/kg) and very low positive end-expiratory pressure, have also been advocated[3].

Thromboelastography

Besides standard coagulation tests (i.e., PT, aPTT, fibrinogen levels), TEG allows a rapid on-site assessment of the functional clotting status. Its use permits the assessment of both cellular and humoral components of whole blood coagulation and fibrinolysis, instead of a single procoagulation or anticoagulation parameter. Results can be obtained fairly quickly, the onset of clot formation within a few min and platelet function within 45 min. The prognostic value of intraoperative standard tests on bleeding or blood component requirements is poorly documented and controversial.

TEG, on the other hand, can assist anesthesiologists in treating intraoperative bleeding by identifying the cause and facilitate selective use of blood components and specific drug treatments[54]. In various studies the amount of blood usage was significantly reduced when TEG monitoring was compared to the conventional "clinician-directed" transfusion management. Wang *et al*[55] demonstrated that the same was true for FFP administration during OLTx as well. Fewer units of FFP were required to keep the TEG reaction time within an accepted transfusion threshold compared with the PT/INR. TEG may also diagnose a heparin-like effect after reperfusion and determine the lowest efficient dose of protamine to correct the prolongation of the reaction time representing the rate of initial fibrin formation[28].

In addition, TEG may help document the prothrombotic state that sometimes occurs in post liver transplant patients because of deficiencies in antithrombin Ⅲ and protein C causing potentially disastrous hepatic artery thrombosis[56].

Even though the usefulness of TEG in complex coagulation defects has been questioned[57], recent literature does reaffirm that the use of TEG and rotation thromboelastometry in more rational transfusion algorithms can reduce the number of blood products transfused[58].

Surgical techniques to reduce blood loss

The importance of surgical experience and skill during hepatic dissection and meticulous hemostasis has long been recognized as important in determining the amount of intraoperative blood loss. One of the first techniques introduced to reduce intraoperative bleeding was the application of the venovenous bypass (VVB) during the anhepatic phase of "classic" OLTx. By decompressing the splanchnic and retroperitoneal circulations, venovenous bypass contributes to reduce blood loss and avoids important hemodynamic changes caused by a variable reduction in venous return to the heart. Another extensively adopted method is the piggy-back technique, which consists of performing the anastomosis of the retrohepatic inferior vena cava of the donor liver directly to the recipient inferior vena cava, thus avoiding extensive dissection of the retroperitoneum in this area. In recipients with portal hypertension and multiple venous collaterals this technique may reduce the anhepatic time and the amount of bleeding. Another advantage of the piggy back technique is the shorter warm ischemia time during implantation of the graft as only one cavo-caval anastomosis has to be performed, compared to the two end-to-end anastomoses of the inferior vena cava in the "classic" technique. While the proponents of the extensive use of venovenous bypass claim that it improves hemodynamic stability, reduces blood loss, and reduces the incidence of postoperative acute renal failure[59], many authors have shown an association between VVB and an increased transfusion of blood products. This increase in the amount of intraoperative bleeding during VVB has been attributed to fibrinolysis, hemolysis, and platelet activation by bypass tubing[60-62]. Miyamoto *et al*[63] demonstrated significantly lower blood transfusion requirements in patients in whom the "piggyback" technique was used, compared with patients transplanted using the "classic" technique. According to the recent statements from the Cochrane database[64] no superiority of one over another technique seems to emerge from the examined trials. Based on the available studies there is currently no evidence to recommend or refute the use of piggy-back method during OLTx as far as the amount of bleeding and blood product consumption is concerned.

PHARMACOLOGICAL STRATEGIES TO REDUCE BLOOD LOSS

Antifibrinolytic drugs

Hyper-fibrinolysis plays a significant role in non-surgical blood loss requiring massive transfusion. Antifibrinolytics will decrease bleeding only in cases where it is caused by enhanced fibrinolysis but they are potentially harmful in patients with prothrombotic states like Budd-Chiari syndrome, retransplantation, fulminant liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, transplant for malignant disease, portal vein thrombosis[65]. Of the two groups of antifibrinolytics available, lysine analogues [epsilon aminocaproic acid (EACA) and tranexamic acid] and serine protease inhibitors (aprotinin), tranexamic acid (TA) is more commonly used. EACA is a synthetic lysine analogue that competitively inhibits the binding of plasminogen to lysine residue on the surface of fibrin and prevents conversion of plasminogen to plasmin. It may also prevent plasmin degradation of platelet glycoprotein Ib receptors, thus preserving platelet function[66]. EACA has demonstrated less antifibrinolytic potency than tranexamic acid. In a prospective, double-blinded, placebo-controlled, randomized study by Dalmau *et al*[67], prophylactic EACA did not reduce intraoperative total red blood cell transfusion during OLT. In addition its use may be associated

with renal complications such as acute tubular necrosis, renal infarction, myopathy, pigment-induced renal complications, glomerular capillary thrombosis and elevated excretion of beta-2 microglobulin. Tranexamic acid prevents plasmin-mediated conversion of fibrinogen to fibrinogen split products by competitively binding to the lysine binding sites on the plasminogen molecule. As compared to EACA, its antifibrinolytic activity is 6-10 times more potent, and higher in peripheral compartments like kidney, intestines, and prostatic tissues. Strong evidence that TA reduces blood transfusion in various types of surgery has been provided in a recent review, even though its effects on thromboembolic events and mortality remains uncertain[68]. In liver transplant surgery the effectiveness of TA in reducing blood transfusion is still under critical evaluation. Years ago, Boylan *et al*[69] demonstrated that administration of tranexamic acid (20 mg/kg) was associated with significantly less intraoperative blood loss and reduced transfusion requirements. No patient had hepatic artery or portal vein thrombosis. More recently, Dalmau *et al*[70] did not find any significant difference in blood loss and transfusion requirements with TA (10 mg/kg per hour) or aprotinin. Thromboembolic events, reoperations and mortality were similar in both groups. Massicotte *et al*[71] compared the efficacy of TA *vs* aprotinin during OLTx. They found no intergroup difference in intraoperative RBC transfusion per patient, final Hb concentration, and the percentage of OLTx cases requiring no blood product administration. In their experience, administration of aprotinin was not superior to TA with regards to blood loss and blood product transfusion requirement.

A study published in 2011 by the Cochrane Hepato-Biliary Group[72], which included all randomised clinical trials that compared various methods of decreasing blood loss and blood transfusion during OLTx, 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.

Aprotinin

Even though a reduction in intraoperative bleeding and transfusion requirement with aprotinin has very frequently been reported, aprotinin use has recently been reduced and criticized as it was related to an increased mortality in cardiac surgery[73].

Antifibrinolytic effect of aprotinin is complex and includes inhibition of plasmin, contact activation system (*via* kallikrein inhibition) and inhibition of tissue-plasminogen activator production. In addition to antifibrinolysis, aprotinin also has antithrombotic effects, which may be due to selective blockade of proteolytically activated thrombin receptors on platelets[74]. The European Multicentre Study of Aprotinin in Liver transplant showed that both high dose and regular dose of aprotinin attenuated fibrinolytic activity, and decreased blood loss and red blood cell transfusion requirements during OLTx[75]. The blood-saving effect of aprotinin was particularly evident when surgery was complicated with significant blood loss. Subsequently, several other reports supported these findings[76,77]. However, parallel to its widespread utilization, concerns arose about the safety of aprotinin and an increased risk of thrombotic complications has been reported[78]. Thromboembolic phenomena are among the most undesirable complications during liver transplantation manifesting as hepatic artery thrombosis, venous thromboembolism, and pulmonary thromboembolism. Lentschener *et al*[78] reported that prophylactic use of large dose aprotinin decreased blood loss and transfusion requirement only when OLTx was associated with significant blood loss, but it did not alter the postoperative outcome. Because of its potential side effects, they recommend that aprotinin should not be systematically administered to patients undergoing OLTx.

It should be noted that most of the data contributing to the increased thromboembolic risk with aprotinin came from a single study - the BART trial[74], whereas in the recent years its negative side effects have been consistently reconsidered.

Molenaar *et al*[79] demonstrated that both aprotinin and TA significantly reduce RBC transfusion requirements; intraoperative use of FFP was significantly reduced with aprotinin but not with TA. No increased risk of hepatic artery thrombosis, venous thromboembolic events or mortality was detected in patients who received antifibrinolytics. No significant difference in the proportion of thromboembolic episodes or other serious adverse events between the aprotinin-treated groups and controls was also reported in the recent review by Gurusamy *et al*[72] and Liu *et al*[80] performed a meta analysis to study the effect of aprotinin on the intraoperative requirement for blood products and the postoperative outcomes. They observed that aprotinin can reduce the intraoperative requirement of blood product, and has no significant effect on the incidence of laparotomy for bleeding, thrombotic events and mortality. A Cochrane Intervention Review (2011)[81] on anti-fibrinolytic use for minimising perioperative allogenic blood transfusion concluded that anti-fibrinolytic drugs provide worthwhile reductions in blood loss and the receipt of allogenic red cell transfusion. Aprotinin appears to be slightly more effective than the lysine analogues in reducing blood loss. The lysine analogues are effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects.

However, given the high risk of type I and type Ⅱ statistical errors because of few trials and the small sample size in some trials, the authors stated that further large clinical randomized multicentre controlled trials are likely needed to confirm the specific advantages of aprotinin in liver transplantation surgery.

Recombinant factor Ⅶa

Recombinant activated Factor Ⅶa (rFⅦa) complexes directly with tissue factor (TF) released from the subendothelium at sites of vascular disruption. The TF-rFⅦ

a complex then activates the remainder of the common coagulation cascade *via* activated factor X. Additionally, rFVIIa may bind to activated platelets, which also concentrates factor X activation to sites of tissue injury. The factor Xa generated by these two mechanisms ultimately drives the thrombin burst, which cleaves fibrinogen to fibrin, thus initiating the formation of the fibrin meshwork critical to secondary coagulation and clot stabilization[82].

Nieman *et al*[83] demonstrated that in a selected group of patients with prolonged PT and high MELD score, the prophylactic application of rFVIIa at the start of the OLTx may reduce perioperative transfusion requirements. However, the prophylactic administration of rF VIIa during orthotopic liver transplantation has lead to inconclusive results; there was a trend across studies toward reduced red blood cell transfusion requirements with prophylaxis, but neither operating room time nor length of stay in the intensive care unit was reduced[84-86]. Nowadays the strength of evidence is low or moderate for intraoperative blood saving capability when given as prophylaxis; furthermore use of rFVIIa has been associated with an increased rate of thromboembolic events in intracerebral hemorrhage and cardiac surgery[87]. Therefore the prophylactic administration may not be the most efficient use of this drug; it should instead be seen more as a "rescue therapy" to control bleeding in situations of major perioperative bleeding where other therapies have failed[88]. Case reports and studies with small number of patients found this drug beneficial in correcting clotting alterations, reducing frank surgical bleeding, controlling clotting failure due to graft reperfusion, or stabilizing clotting functions before the closure of the abdomen[89,90].

Recombinant activated factor VIIa 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 OLTx has been demonstrated in many reports; no effects on thromboembolism or mortality have been found in various trials[87]. However, the experience with this drug is still too limited and the benefit/risk ratio not completely evaluated. The role of recombinant factor VIIa during OLTx still remains to be completely defined. 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[91].

BLOOD SALVAGE DURING OLTx

The use of intraoperative blood salvage and autologous blood transfusion has been for a long time an important method to reduce the need for allogeneic blood and the associated complications[92].

By reducing the demand for heterologous transfusion this strategy can prevent or diminish the exposure to transmissible infectious diseases. The use of cell salvage has become an important part of intraoperative management of Jehovah's Witnesses who refuse allogeneic blood or blood products transfusion on religious grounds[93].

The principle of cell salvage consists of collecting RBCs from the operative fields, storing the blood in a reservoir, separating the components, and transfusing. Blood collection is carried out with a dedicated double-lumen device, one for suction and the other for adding a predetermined volume of anticoagulant to the aspirated blood. After storage the blood is centrifuged and the RBCs are washed and filtered across a semi-permeable membrane which removes free haemoglobin, plasma, white blood cells, platelets and heparin. The process of concentration by centrifugation enables the plasma, platelets, and irrigating solutions to be removed, as well as 70%-90% of the soluble contaminants and the so called "biochemical debris" present in the salvaged blood. The salvaged blood may then be transfused after being re-suspended in normal saline. The resultant hematocrit ranges between 50%-80%[15]. Although the safety of cell-salvaging procedure has been widely demonstrated[94] intraoperative red blood cell salvage and autologous transfusion is not routinely used in major liver surgery as cost-effectiveness is still an unsolved concern[95].

Blood salvaging techniques are controversial during OLTx as well, since some studies demonstrated their effectiveness in reducing allogeneic RBCs requirements and safety, while others reported higher blood loss, mainly through fibrinolysis, and increased costs[7,96,97]. Hendriks *et al*[98] reported a remarkable increase in transfusion requirements in liver transplant recipients where cell saver blood was returned. They hypothesised that excessive blood loss was a consequence rather than a cause of transfusion of cell saver blood. The need for an increased amount of RBCs, FFP, cryoprecipitate, and platelets in autotransfused patients was also demonstrated by other studies[99,100]. The increased blood loss in recipients receiving cell saver blood has been attributed to the release of fibrinolytic compounds from blood cells in the collected blood and/or from the transplanted liver, that are not washed out by the cell saver[99]. As opposed to the above-mentioned reports many other studies underline that cell salvage is efficacious in reducing the need for allogeneic blood transfusion in adult elective surgery, as evidenced by a recent Cochrane Collaboration meta-analysis of various studies[101]. Waters *et al*[102] in a review of the cell salvage data from 2328 surgical patients suggested that cell salvage can be significantly less expensive than allogenic blood. Older experiences in patients undergoing liver transplantation with large volumes of blood loss, demonstrated that besides its medical benefits intraoperative autologous transfusion was also cost-effective. Use of intraoperative autologous transfusion resulted in conservation of erythrocytes and reduction in exposure to homologous blood and blood components[103]. Similar observations were also reported in a prospective study on 660 adult liver transplant pa-

tients published more recently[104].

Sankarankutty *et al*[105] demonstrated that when cell saver was used during OLTx more than half of the blood lost was recovered and was almost entirely available for reinfusion after processing. Substantial reduction in FFP and a lesser reduction in platelet requirement was also seen.

Nowadays the use of cell salvage to collect and reinfuse shed, autologous blood during OLTx is a common practice when high blood loss is anticipated. It is, in fact, a complementary method that can replace blood in proportion to the volume lost. However, when compared with the cost of providing allogenic blood, it becomes cost effective when at least two or more units of blood can be salvaged and reinfused. Massicotte *et al*[95] demonstrated that when cell salvage autotransfusion was used systematically for every patient (75 OLTx) there was enough blood salvage to retransfuse 65% of the cases; in their centre with a low transfusion rate, it saved a mean of 21 g/L of Hb per patient or two RBC unit transfusions.

Even though the collection of a recipient own blood from surgical sites may result an effective, safe and cost-effective procedure, there are some relative contraindications due to the presence of certain materials incorporated into the salvaged blood that could potentially harm the patient upon readministration[106]. These include contaminants such as stool, urine, or blood aspirated from contaminated or septic wounds, intestinal leaks, intra-abdominal infections, and malignant cells.

Bacterial contamination

Bacterial contamination of intraoperatively cell salvaged and processed blood is a known phenomenon even if the technique is applied to so-called "sterile" operations[107,108].

Contamination may occur during blood sampling and washing. It may originate from intestinal flora or it may be blood-borne in the recipient. Retrograde contamination of the shed blood from the bile duct has been demonstrated as well[101]. The most common source of contamination is thought to be the skin and the environment. The use of cell salvage has been contraindicated in cases where there is potential contamination with enteric contents, however, the relationship between the transfusion of contaminated cell-salvaged blood and an increased risk of systemic infection is not clear. Feltracco *et al*[109] in a prospective observational study of 38 patients undergoing OLTx found samples of processed salvaged blood positive for microorganisms in 68.4% cases. A variety of microorganisms were cultured, i.e., *Staphylococcus* (73%), *Escherichia coli* (4%), *Propionibacter* (4%) and *Candida* (8%). All the patients in this study had blood cultures obtained on postoperative days 1 and 3, and none was positive for the organisms previously cultured from the salvaged blood. Studies on transfusion of microbiologically contaminated salvaged blood have demonstrated no adverse outcomes nor an increase in postoperative infectious complications[109,110]. Therefore, potential contamination should no longer be considered an absolute contraindication to the use of intraoperative cell salvage during OLTx.

Blood salvaged from patients with liver tumor

The presence of hepatocellular carcinoma has been considered a contraindication for the use of blood salvaging techniques due to the theoretical risk of reintroducing neoplastic cells into the circulation and disseminating the tumor. In 1986 the American Medical Councils stated that cell salvage was contraindicated in cases of malignancy[111].

However, in clinical practice the use of autologous transfusion from salvaged blood of patient with malignant disease has been diffusely reported in different surgical settings, such as urological cancer and gynaeoncology surgery[112,113]. In various studies on surgical patients with malignant disease autologous transfusion with cell salvaged blood did not increase recurrence rates and was effective at reducing allogenic blood requirements. The use of leucocyte depletion filters (LDFs) has been proposed to improve cell salvage safety, to reduce the number of malignant cells in the blood recovered during cancer surgery, and to attenuate the side-effects[114]. In a prospective observational study on 32 patients undergoing OLTx for hepatocellular carcinoma, Liang *et al*[115] investigated the presence of tumour cells in shed blood and the efficiency of cell salvage in combination with a LDF at removing them. Tumour cells were present in the cell saver reservoir in 62.5% of patients and after processing tumour cells were still detected in 75% of those. After passing through an LDF, tumour cells were only detected in 10% of samples where the tumour had ruptured intraoperatively. Because of the incomplete elimination of tumour cells in the autologous blood, in circumstances where the potential rupture of the tumor may occur intraoperatively the authors raise concerns on the opportunity of reinfusing the salvaged blood. In the report by Catling *et al*[116], the cell saver used in combination with LDFs significantly reduced the number of tumour cells from salvaged blood. After collecting the blood from the field and processing it, viable cells were demonstrated in 62% of samples, but once the processed salvaged blood was passed through an LDF no tumor cells were found, only tumour cell fragments, which were unable to cause metastases. Muscari *et al*[117] reported no difference in the incidence of neoplastic recurrence with the use of cell saver during liver transplantation for hepatocarcinoma. Various authors also confirm that the use of cell salvage is useful to reduce the exposure to allogenic blood during liver transplantation for hepatocellular carcinoma and is cost-effective as well[95,115]. Filtration through leucodepletion filters in association with irradiation (25 Gy) prior to transfusion of recovered blood has also been proposed to increase the safety of blood salvaging procedure in cancer surgery[118]. Other potential complications associated with cell salvage include non-immune haemolysis, air embolus, febrile non-haemolytic transfusion reactions, coagulopathy, contamination with cleansing solutions and incomplete

washing leading to contamination with activated leucocytes, cytokines, and other microaggregates[92]. Abnormal suctioning of RBCs may cause sheer stress injury, which can result in haemolysis and therefore reduction in return of RBCs[119]. Saline washing of red cells increases sodium levels and decreases potassium and calcium levels; potassium and calcium continuous monitoring and supplementation may be necessary during autologous transfusion of salvaged blood. An inadeguate washing of administered blood could result in renal insufficiency and failure. As the washing process discards all platelets and clotting factors leaving only the red cells re-suspended in normal saline, the reinfusion of large amount of blood from the cell saver machine may determine coagulation disturbances. Large volume transfusion of salvaged blood can, in fact, cause postoperative hypofibrinogenemia, thrombocytopenia, prolonged prothrombin and partial thromboplastin time and elevated fibrin split products[120]. FFP, platelet and cryoprecipitate administered in association with reinfusion of salvaged blood may prevent the cell saver induced coagulopathy.

CONCLUSION

Improvements in organ preservation, surgical technique, anesthesiologic care, as well as in postoperative intensive care management have contributed to a steady reduction of transfusion requirements in the perioperative period and have increased the number of patients undergoing OLTx without any need for blood products[92,121].

Because of the progressive increased severity of end stage liver disease of candidates undergoing OLTx with the "MELD rules" for graft allocation, and the poor quality of many donor livers, the bleeding risk correlated with the surgical manoeuvres may be relevant with inevitable consequences on the amount of transfusions. 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 "individualizing" the transfusion triggers. The understanding that perioperative blood loss and blood transfusions have a negative impact on postoperative outcome has led to emphasize 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.

REFERENCES

1 **Liu LL**, Niemann CU. Intraoperative management of liver transplant patients. *Transplant Rev* (Orlando) 2011; **25**: 124-129 [PMID: 21514137 DOI: 10.1016/j.trre.2010.10.006]

2 **Ozier Y**, Pessione F, Samain E, Courtois F. Institutional variability in transfusion practice for liver transplantation. *Anesth Analg* 2003; **97**: 671-679 [PMID: 12933381 DOI: 10.1213/01.ANE.0000073354.38695]

3 **Hannaman MJ**, Hevesi ZG. Anesthesia care for liver transplantation. *Transplant Rev* (Orlando) 2011; **25**: 36-43 [PMID: 21126662 DOI: 10.1016/j.trre.2010.10.004]

4 **Maxwell MJ**, Wilson MJA. Complications of blood transfusion. Continuing Education in Anaesthesia. *Crit Care Pain* 2006; **6**: 225-229 [DOI: 10.1093/bjaceaccp/mkl053]

5 **Romero FA**, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; **3**: 83-92 [PMID: 21603030 DOI: 10.4254/wjh.v3.i4.83]

6 **Massicotte L**, Sassine MP, Lenis S, Roy A. Transfusion predictors in liver transplant. *Anesth Analg* 2004; **98**: 1245-1251, table of contents [PMID: 15105195 DOI: 10.1213/01.ANE.0000111184.21278.07]

7 **de Boer MT**, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. *Dig Surg* 2005; **22**: 265-275 [PMID: 16174983 DOI: 10.1159/000088056]

8 **Martell M**, Coll M, Ezkurdia N, Raurell I, Genescà J. Physiopathology of splanchnic vasodilation in portal hypertension. *World J Hepatol* 2010; **2**: 208-220 [PMID: 21160999 DOI: 10.4254/wjh.v2.i6.208]

9 **Kerr R**, Newsome P, Germain L, Thomson E, Dawson P, Stirling D, Ludlam CA. Effects of acute liver injury on blood coagulation. *J Thromb Haemost* 2003; **1**: 754-759 [PMID: 12871412 DOI: 10.1046/j.1538-7836.2003.00194.x]

10 **Castelino DJ**, Salem HH. Natural anticoagulants and the liver. *J Gastroenterol Hepatol* 1997; **12**: 77-83 [PMID: 9076629 DOI: 10.1111/j.1440-1746.1997.tb00351.x]

11 **Sanjo A**, Satoi J, Ohnishi A, Maruno J, Fukata M, Suzuki N. Role of elevated platelet-associated immunoglobulin G and hypersplenism in thrombocytopenia of chronic liver diseases. *J Gastroenterol Hepatol* 2003; **18**: 638-644 [PMID: 12753144 DOI: 10.1046/j.1440-1746.2003.03026.x]

12 **Yost CS**, Niemann CU. Miller's Anesthesia. Anesthesia for Abdominal Organ Transplantation. 7th ed. Philadelphia: Churchill Livingstone Elsevier, 2010: 2155-2184

13 **Bayly PJ**, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73**: 840-842 [PMID: 7880678 DOI: 10.1093/bja/73.6.840]

14 **Murthy TVSP**. Transfusion support in liver transplantation. *Indian J Anaesth* 2007; **51**: 13-19. Available from: URL: http://www.ijaweb.org/text.asp?2007/51/1/13/61108

15 **Massicotte L**, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Reduction of blood product transfusions during liver transplantation. *Can J Anaesth* 2005; **52**: 545-546 [PMID: 15872137]

16 **Devi AS**, Ogawa Y, Shimoji Y, Ponnuraj K. Cloning, expression, purification, crystallization and preliminary X-ray diffraction analysis of the collagen-binding region of RspB from Erysipelothrix rhusiopathiae. *Acta Crystallogr Sect F Struct Biol Cryst Commun* 2010; **66**: 156-159 [PMID: 20124711 DOI: 10.4103/0972-5229.58536]

17 **Spence RK**, Maurer J. Transfusion requirements in liver transplantation. 2006

18 **Palomo Sanchez JC**, Jimenez C, Moreno Gonzalez E, Garcia I, Palma F, Loinaz C, Gonzalez Ghamorro A. Effects of intraoperative blood transfusion on postoperative complications and survival after orthotopic liver transplantation. *Hepatogastroenterology* 1998; **45**: 1026-1033 [PMID: 9756002]

19 **Deakin M**, Gunson BK, Dunn JA, McMaster P, Tisone G, Warwick J, Buckels JA. Factors influencing blood transfusion during adult liver transplantation. *Ann R Coll Surg Engl* 1993; **75**: 339-344 [PMID: 8215151]

20 **Ramos E**, Dalmau A, Sabate A, Lama C, Llado L, Figueras J, Jaurrieta E. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. *Liver Transpl* 2003; **9**: 1320-1327 [PMID: 14625833 DOI: 10.1016/jlts.2003.50204]

21 **Mangus RS**, Kinsella SB, Nobari MM, Fridell JA, Vianna RM, Ward ES, Nobari R, Tector AJ. Predictors of blood product use in orthotopic liver transplantation using the

piggyback hepatectomy technique. *Transplant Proc* 2007; **39**: 3207-3213 [PMID: 18089355]
22 **Massicotte L**, Beaulieu D, Roy JD, Marleau D, Vandenbroucke F, Dagenais M, Lapointe R, Roy A. MELD score and blood product requirements during liver transplantation: no link. *Transplantation* 2009; **87**: 1689-1694 [PMID: 19502961 DOI: 10.1097/TP.0b013e3181a5e5f1]
23 **Steib A**, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. *Can J Anaesth* 2001; **48**: 1075-1079 [PMID: 11744582 DOI: 10.1007/BF03020372]
24 **Roullet S**, Biais M, Millas E, Revel P, Quinart A, Sztark F. Risk factors for bleeding and transfusion during orthotopic liver transplantation. *Ann Fr Anesth Reanim* 2011; **30**: 349-352 [PMID: 21353450 DOI: 10.1016/j.annfar.2011.01.008]
25 **Findlay JY**, Rettke SR. Poor prediction of blood transfusion requirements in adult liver transplantations from preoperative variables. *J Clin Anesth* 2000; **12**: 319-323 [PMID: 10960206]
26 **Hébert PC**, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; **29**: 227-234 [PMID: 11246298]
27 **Klink JR**. Liver Transplantation: Anesthesia. In: Klink JR, Lindop MJ, editors. Anesthesia and Intensive Care for Organ Transplantation. London: Chapman and Hall, 1998: 169-199
28 **Kang Yg**, Gasior TA. Blood coagulation during liver, kidney, pancreas, and lung transplantation. In: Spiess BD, Counts RB, Gould SA, editors. Perioperative Transfusion Medicine. Baltimore, MD: Williams and Wilkins, 1998; 471-492
29 **Dupont J**, Messiant F, Declerck N, Tavernier B, Jude B, Durinck L, Pruvot FR, Scherpereel P. Liver transplantation without the use of fresh frozen plasma. *Anesth Analg* 1996; **83**: 681-686 [PMID: 8831303]
30 **Freeman JW**, Williamson LM, Llewelyn C, Fisher N, Allain JP, Bellamy M, Baglin TP, Klinc J, Ala FA, Smith N, Neuberger J, Wreghitt T. A randomized trial of solvent/detergent and standard fresh frozen plasma in the treatment of the coagulopathy seen during Orthotopic Liver Transplantation. *Vox Sang* 1998; **74** Suppl 1: 225-229 [PMID: 9789533 DOI: 10.1046/j.1423-0410.1998.7440225.x]
31 **de Boer MT**, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *Anesth Analg* 2008; **106**: 32-44, table of contents [PMID: 18165548 DOI: 10.1213/01.ane.0000289638.26666.ed]
32 **Sindram D**, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. *Gastroenterology* 2000; **118**: 183-191 [PMID: 10611167]
33 **Kopko PM**, Holland PV. Mechanisms of severe transfusion reactions. *Transfus Clin Biol* 2001; **8**: 278-281 [PMID: 11499977]
34 **Khan H**, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007; **131**: 1308-1314 [PMID: 17400669 DOI: 10.1378/chest.06-3048]
35 **Pereboom IT**, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. *Anesth Analg* 2009; **108**: 1083-1091 [PMID: 19299765 DOI: 10.1213/ane.0b013e3181948a59]
36 **Hendriks HG**, Meijer K, de Wolf JT, Klompmaker IJ, Porte RJ, de Kam PJ, Hagenaars AJ, Melsen T, Slooff MJ, van der Meer J. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation* 2001; **71**: 402-405 [PMID: 11233901]
37 **Jabbour N**, Gagandeep S, Mateo R, Sher L, Genyk Y, Selby R. Transfusion free surgery: single institution experience of 27 consecutive liver transplants in Jehovah's Witnesses. *J Am Coll Surg* 2005; **201**: 412-417 [PMID: 16125075]
38 **Cacciarelli TV**, Keeffe EB, Moore DH, Burns W, Busque S, Concepcion W, So SK, Esquivel CO. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. *Arch Surg* 1999; **134**: 25-29 [PMID: 9927126 DOI: 10.1001/archsurg.134.1.25]
39 **Hendriks HG**, van der Meer J, de Wolf JT, Peeters PM, Porte RJ, de Jong K, Lip H, Post WJ, Slooff MJ. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. *Transpl Int* 2005; **17**: 673-679 [PMID: 15717214 DOI: 10.1111/j.1432-2277.2004.tb00493.x]
40 **Blumberg N**. Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt. *Transfusion* 2005; **45**: 33S-39S; discussion 39S-40S [PMID: 16086785 DOI: 10.1111/j.1537-2995.2005.00529.x]
41 **Yuasa T**, Niwa N, Kimura S, Tsuji H, Yurugi K, Egawa H, Tanaka K, Asano H, Maekawa T. Intraoperative blood loss during living donor liver transplantation: an analysis of 635 recipients at a single center. *Transfusion* 2005; **45**: 879-884 [PMID: 15934985 DOI: 10.1111/j.1537-2995.2005.04330.x]
42 Transfusions for massive blood loss. Related Resucitation Critical Care. Available from: URL: http: //www.trauma.org/
43 **Brander L**, Reil A, Bux J, Taleghani BM, Regli B, Takala J. Severe transfusion-related acute lung injury. *Anesth Analg* 2005; **101**: 499-501, table of contents [PMID: 16037167 DOI: 10.1213/01.ANE.0000159375.26910.9C]
44 **Li GS**, Ye QF, Xia SS, Chen ZS, Zeng FJ, Lin ZB, Gong NQ, Zhang WJ, Wen ZX, Sha P, Jiang JP. Acute respiratory distress syndrome after liver transplantation: etiology, prevention and management. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 330-334 [PMID: 14607702]
45 **Davis M**, Sofer M, Gomez-Marin O, Bruck D, Soloway MS. The use of cell salvage during radical retropubic prostatectomy: does it influence cancer recurrence? *BJU Int* 2003; **91**: 474-476 [PMID: 12656896 DOI: 10.1046/j.1464-410X.2003.04129.x]
46 **Innerhofer P**, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. *Transfusion* 2005; **45**: 103-110 [PMID: 15647025 DOI: 10.1111/j.1537-2995.2005.04149.x]
47 **Surgenor SD**, DeFoe GR, Fillinger MP, Likosky DS, Groom RC, Clark C, Helm RE, Kramer RS, Leavitt BJ, Klemperer JD, Krumholz CF, Westbrook BM, Galatis DJ, Frumiento C, Ross CS, Olmstead EM, O'Connor GT. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. *Circulation* 2006; **114**: I43-I48 [PMID: 16820613 DOI: 10.1161/CIRCULATIONAHA.105.001271]
48 **Buetens O**, Shirey RS, Goble-Lee M, Houp J, Zachary A, King KE, Ness PM. Prevalence of HLA antibodies in transfused patients with and without red cell antibodies. *Transfusion* 2006; **46**: 754-756 [PMID: 16686842 DOI: 10.1111/j.1537-2995.2006.00793.x]
49 **Massicotte L**, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. *Liver Transpl* 2006; **12**: 117-123 [PMID: 16382461 DOI: 10.1007/BF03016538]
50 **Massicotte L**, Beaulieu D, Thibeault L. Con: low central venous pressure during liver transplantation. *J Cardiothorac Vasc Anesth* 2008; **22**: 315-317 [PMID: 18375342 DOI:

10.1053/j.jvca.2008.01.001]
51 **Schroeder RA**, Collins BH, Tuttle-Newhall E, Robertson K, Plotkin J, Johnson LB, Kuo PC. Intraoperative fluid management during orthotopic liver transplantation. *J Cardiothorac Vasc Anesth* 2004; **18**: 438-441 [PMID: 15365923]
52 **Schroeder RA**, Kuo PC. Pro: low central venous pressure during liver transplantation--not too low. *J Cardiothorac Vasc Anesth* 2008; **22**: 311-314 [PMID: 18375341 DOI: 10.1053/j.jvca.2007.12.009]
53 **Ferrara A**, MacArthur JD, Wright HK, Modlin IM, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg* 1990; **160**: 515-518 [PMID: 2240386]
54 **Afshari A**, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; (3): CD007871 [PMID: 21412912 DOI: 10.1002/14651858.CD007871.pub2]
55 **Wang SC**, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, Chan KH, Mandell S, Tsou MY. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. *Transplant Proc* 2010; **42**: 2590-2593 [PMID: 20832550 DOI: 10.1016/j.transproceed.2010.05.144]
56 **Harper PL**, Edgar PF, Luddington RJ, Seaman MJ, Carrell RW, Salt AT, Barnes N, Rolles K, Calne RY. Protein C deficiency and portal thrombosis in liver transplantation in children. *Lancet* 1988; **2**: 924-927 [PMID: 2902380 DOI: 10.1016/S0140-6736(88)92597-4]
57 **Wegner J**, Popovsky MA. Clinical utility of thromboelastography: one size does not fit all. *Semin Thromb Hemost* 2010; **36**: 699-706 [PMID: 20978990 DOI: 10.1055/s-0030-1265286]
58 **Roullet S**, Pillot J, Freyburger G, Biais M, Quinart A, Rault A, Revel P, Sztark F. Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. *Br J Anaesth* 2010; **104**: 422-428 [PMID: 20185519 DOI: 10.1093/bja/aeq022]
59 **Cheema SP**, Hughes A, Webster NR, Bellamy MC. Cardiac function during orthotopic liver transplantation with venovenous bypass. *Anaesthesia* 1995; **50**: 776-778 [PMID: 7573866]
60 **Fan ST**, Yong BH, Lo CM, Liu CL, Wong J. Right lobe living donor liver transplantation with or without venovenous bypass. *Br J Surg* 2003; **90**: 48-56 [PMID: 12520574 DOI: 10.1002/bjs.4026]
61 **Scholz T**, Solberg R, Okkenhaug C, Videm V, Gallimore MJ, Mathisen O, Pedersen T, Mollnes TE, Bergan A, Søreide O, Klintmalm GB, Aasen AO. Veno-venous bypass in liver transplantation: heparin-coated perfusion circuits reduce the activation of humoral defense systems in an in vitro model. *Perfusion* 2001; **16**: 285-292 [PMID: 11486847]
62 **van der Hulst VP**, Henny CP, Moulijn AC, Engbers G, ten Cate H, Gründeman PF, Klopper PJ. Veno-venous bypass without systemic heparinization using a centrifugal pump: a blind comparison of a heparin bonded circuit versus a non heparin bonded circuit. *J Cardiovasc Surg* (Torino) 1989; **30**: 118-123 [PMID: 2925769]
63 **Miyamoto S**, Polak WG, Geuken E, Peeters PM, de Jong KP, Porte RJ, van den Berg AP, Hendriks HG, Slooff MJ. Liver transplantation with preservation of the inferior vena cava. A comparison of conventional and piggyback techniques in adults. *Clin Transplant* 2004; **18**: 686-693 [PMID: 15516245 DOI: 10.1111/j.1399-0012.2004.00278.x]
64 **Gurusamy KS**, Pamecha V, Davidson BR. Piggy-back graft for liver transplantation. *Cochrane Database Syst Rev* 2011; (1): CD008258 [PMID: 21249703 DOI: 10.1002/14651858.CD008258.pub2]
65 **Makwana J**, Paranjape S, Goswami J. Antifibrinolytics in liver surgery. *Indian J Anaesth* 2010; **54**: 489-495 [PMID: 21224964 DOI: 10.4103/0019-5049.72636]
66 **Sun Z**, Chen YH, Wang P, Zhang J, Gurewich V, Zhang P, Liu JN. The blockage of the high-affinity lysine binding sites of plasminogen by EACA significantly inhibits prourokinase-induced plasminogen activation. *Biochim Biophys Acta* 2002; **1596**: 182-192 [PMID: 12007600]
67 **Dalmau A**, Sabaté A, Acosta F, Garcia-Huete L, Koo M, Sansano T, Rafecas A, Figueras J, Jaurrieta E, Parrilla P. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000; **91**: 29-34 [PMID: 10866882]
68 **Ker K**, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054 [PMID: 22611164 DOI: 10.1136/bmj.e3054]
69 **Boylan JF**, Klinck JR, Sandler AN, Arellano R, Greig PD, Nierenberg H, Roger SL, Glynn MF. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. *Anesthesiology* 1996; **85**: 1043-1048; discussion 30A-31A [PMID: 8916821]
70 **Dalmau A**, Sabaté A, Koo M, Bartolomé C, Rafecas A, Figueras J, Jaurrieta E. The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: a comparative study. *Liver Transpl* 2004; **10**: 279-284 [PMID: 14762867 DOI: 10.1002/lt.20075]
71 **Massicotte L**, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Roy A. Aprotinin versus tranexamic acid during liver transplantation: impact on blood product requirements and survival. *Transplantation* 2011; **91**: 1273-1278 [PMID: 21617589 DOI: 10.1097/TP.0b013e31821ab9f8]
72 **Gurusamy KS**, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database Syst Rev* 2011; (12): CD009052 [PMID: 22161443 DOI: 10.1002/14651858.CD009052.pub2]
73 **Fergusson DA**, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358**: 2319-2331 [PMID: 18480196 DOI: 10.1056/NEJMoa0802395]
74 **Landis RC**, Asimakopoulos G, Poullis M, Haskard DO, Taylor KM. The antithrombotic and antiinflammatory mechanisms of action of aprotinin. *Ann Thorac Surg* 2001; **72**: 2169-2175 [PMID: 11789829]
75 **Porte RJ**, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, Lindgren L, Palareti G, Hermans J, Terpstra OT. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. *Lancet* 2000; **355**: 1303-1309 [PMID: 10776742]
76 **Molenaar IQ**, Begliomini B, Martinelli G, Putter H, Terpstra OT, Porte RJ. Reduced need for vasopressors in patients receiving aprotinin during orthotopic liver transplantation. *Anesthesiology* 2001; **94**: 433-438 [PMID: 11374602]
77 **Findlay JY**, Rettke SR, Ereth MH, Plevak DJ, Krom RA, Kufner RP. Aprotinin reduces red blood cell transfusion in orthotopic liver transplantation: a prospective, randomized, double-blind study. *Liver Transpl* 2001; **7**: 802-807 [PMID: 11552215 DOI: 10.1053/jlts.2001.27086]
78 **Lentschener C**, Roche K, Ozier Y. A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; **100**: 1248-1255 [PMID: 15845662 DOI: 10.1213/01.ANE.0000148125.12008.9A]
79 **Molenaar IQ**, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; **7**: 185-194 [PMID: 17227567 DOI:

10.1111/j.1600-6143.2006.01591.x]
80 **Liu CM**, Chen J, Wang XH. Requirements for transfusion and postoperative outcomes in orthotopic liver transplantation: a meta-analysis on aprotinin. *World J Gastroenterol* 2008; **14**: 1425-1429 [PMID: 18322960 DOI: 10.3748/wjg.14.1425]
81 **Henry DA**, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; (3): CD001886 [PMID: 21412876]
82 **Roberts HR**, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004; **104**: 3858-3864 [PMID: 15328151 DOI: 10.1182/blood-2004-06-2223]
83 **Niemann CU**, Behrends M, Quan D, Eilers H, Gropper MA, Roberts JP, Hirose R. Recombinant factor VIIa reduces transfusion requirements in liver transplant patients with high MELD scores. *Transfus Med* 2006; **16**: 93-100 [PMID: 16623915 DOI: 10.1111/j.1365-3148.2006.00653.x]
84 **Lodge JP**, Jonas S, Jones RM, Olausson M, Mir-Pallardo J, Soefelt S, Garcia-Valdecasas JC, McAlister V, Mirza DF. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005; **11**: 973-979 [PMID: 16035095 DOI: 10.1002/lt.20470]
85 **Planinsic RM**, van der Meer J, Testa G, Grande L, Candela A, Porte RJ, Ghobrial RM, Isoniemi H, Schelde PB, Erhardtsen E, Klintmalm G, Emre S. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 2005; **11**: 895-900 [PMID: 16035081 DOI: 10.1002/lt.20458]
86 **Pugliese F**, Ruberto F, Summonti D, Perrella S, Cappannoli A, Tosi A, D'alio A, Bruno K, Martelli S, Celli P, Morabito V, Rossi M, Berloco PB, Pietropaoli P. Activated recombinant factor VII in orthotopic liver transplantation. *Transplant Proc* 2007; **39**: 1883-1885 [PMID: 17692642 DOI: 10.1016/j.transproceed.2007.05.062]
87 **Yank V**, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Olkin I, McDonald KM, Owens DK, Stafford RS. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; **154**: 529-540 [PMID: 21502651 DOI: 10.1059/0003-4819-154-8-201104190-00004]
88 **Alkozai EM**, Lisman T, Porte RJ. Bleeding in liver surgery: prevention and treatment. *Clin Liver Dis* 2009; **13**: 145-154 [PMID: 19150318 DOI: 10.1016/j.cld.2008.09.012]
89 **Markiewicz M**, Kalicinski P, Kaminski A, Laniewski P, Ismail H, Drewniak T, Szymczak M, Nachulewicz P. Acute coagulopathy after reperfusion of the liver graft in children correction with recombinant activated factor VII. *Transplant Proc* 2003; **35**: 2318-2319 [PMID: 14529927]
90 **Lisman T**, Leebeek FW, Meijer K, Van Der Meer J, Nieuwenhuis HK, De Groot PG. Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology* 2002; **35**: 616-621 [PMID: 11870375 DOI: 10.1053/jhep.2002.31771]
91 **Liumbruno GM**, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion management of patients in the peri-operative period. II. The intra-operative period. *Blood Transfus* 2011; **9**: 189-217 [PMID: 21527082 DOI: 10.2450/2011.0075-10]
92 **Ashworth A**, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth* 2010; **105**: 401-416 [PMID: 20802228 DOI: 10.1093/bja/aeq244]
93 **Jabbour N**, Gagandeep S, Shah H, Mateo R, Stapfer M, Genyk Y, Sher L, Zwierzchoniewska M, Selby R, Zeger G. Impact of a transfusion-free program on non-Jehovah's Witness patients undergoing liver transplantation. *Arch Surg* 2006; **141**: 913-917 [PMID: 17001788 DOI: 10.1001/archsurg.141.9.913]
94 **Cardone D**, Klein AA. Perioperative blood conservation. *Eur J Anaesthesiol* 2009; **26**: 722-729 [PMID: 19448549 DOI: 10.1097/EJA.0b013e32832c5280]
95 **Massicotte L**, Thibeault L, Beaulieu D, Roy JD, Roy A. Evaluation of cell salvage autotransfusion utility during liver transplantation. *HPB* (Oxford) 2007; **9**: 52-57 [PMID: 18333113 DOI: 10.1080/13651820601090596]
96 **Lutz JT**, Valentín-Gamazo C, Görlinger K, Malagó M, Peters J. Blood-transfusion requirements and blood salvage in donors undergoing right hepatectomy for living related liver transplantation. *Anesth Analg* 2003; **96**: 351-355, table of contents [PMID: 12538176 DOI: 10.1213/01.ANE.0000041595.94354.48]
97 **Kemper RR**, Menitove JE, Hanto DW. Cost analysis of intraoperative blood salvage during orthotopic liver transplantation. *Liver Transpl Surg* 1997; **3**: 513-517 [PMID: 9346794]
98 **Hendriks HG**, van der Meer J, Klompmaker IJ, Choudhury N, Hagenaars JA, Porte RJ, de Kam PJ, Slooff MJ, de Wolf JT. Blood loss in orthotopic liver transplantation: a retrospective analysis of transfusion requirements and the effects of autotransfusion of cell saver blood in 164 consecutive patients. *Blood Coagul Fibrinolysis* 2000; **11** Suppl 1: S87-S93 [PMID: 10850571]
99 **Brajtbord D**, Paulsen AW, Ramsay MA, Swygert TH, Valek TR, Ramon VJ, Johnson DD, Parks RI, Pyron JT, Walling PT. Potential problems with autotransfusion during hepatic transplantation. *Transplant Proc* 1989; **21**: 2347-2348 [PMID: 2652762]
100 **Van Voorst SJ**, Peters TG, Williams JW, Vera SR, Britt LG. Autotransfusion in hepatic transplantation. *Am Surg* 1985; **51**: 623-626 [PMID: 3904551]
101 **Carless PA**, Henry DA, Moxey AJ, O'connell DL, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2006; (4): CD001888 [PMID: 17054147 DOI: 10.1002/14651858.CD001888.pub2]
102 **Waters JR**, Meier HH, Waters JH. An economic analysis of costs associated with development of a cell salvage program. *Anesth Analg* 2007; **104**: 869-875 [PMID: 17377098 DOI: 10.1213/01.ane.0000258039.79028.7c]
103 **Williamson KR**, Taswell HF, Rettke SR, Krom RA. Intraoperative autologous transfusion: its role in orthotopic liver transplantation. *Mayo Clin Proc* 1989; **64**: 340-345 [PMID: 2495389]
104 **Phillips SD**, Maguire D, Deshpande R, Muiesan P, Bowles MJ, Rela M, Heaton ND. A prospective study investigating the cost effectiveness of intraoperative blood salvage during liver transplantation. *Transplantation* 2006; **81**: 536-540 [PMID: 16495800 DOI: 10.1097/01.tp.0000199318.17013.c5]
105 **Sankarankutty AK**, Teixeira AC, Souza FF, Mente ED, Oliveira GR, Almeida RC, Andrade CM, Origuella EA, Silva Ode C. Impact of blood salvage during liver transplantation on reduction in transfusion requirements. *Acta Cir Bras* 2006; **21** Suppl 1: 44-47 [PMID: 17013513]
106 **Waters JH**. Indications and contraindications of cell salvage. *Transfusion* 2004; **44**: 40S-44S [PMID: 15585004 DOI: 10.1111/j.0041-1132.2004.04176.x]
107 **Sugai Y**, Sugai K, Fuse A. Current status of bacterial contamination of autologous blood for transfusion. *Transfus Apher Sci* 2001; **24**: 255-259 [PMID: 11791700]
108 **Waters JH**, Tuohy MJ, Hobson DF, Procop G. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. *Anesthesiology* 2003; **99**: 652-655 [PMID: 12960550]
109 **Feltracco P**, Michieletto E, Barbieri S, Serra E, Rizzi S, Salvaterra F, Cillo U, Ori C. Microbiologic contamination of intraoperative blood salvaged during liver transplantation. *Transplant Proc* 2007; **39**: 1889-1891 [PMID: 17692644 DOI: 10.1016/j.transproceed.2007.05.005]
110 **Bowley DM**, Barker P, Boffard KD. Intraoperative blood salvage in penetrating abdominal trauma: a randomised, controlled trial. *World J Surg* 2006; **30**: 1074-1080 [PMID: 16736339 DOI: 10.1007/s00268-005-0466-2]
111 Autologous blood transfusions. Council on Scientific Af-

fairs. *JAMA* 1986; **256**: 2378-2380 [PMID: 3773142]
112 **Nieder AM**, Manoharan M, Yang Y, Soloway MS. Intraoperative cell salvage during radical cystectomy does not affect long-term survival. *Urology* 2007; **69**: 881-884 [PMID: 17482926 DOI: 10.1016/j.urology.2007.01.060]
113 **Connor JP**, Morris PC, Alagoz T, Anderson B, Bottles K, Buller RE. Intraoperative autologous blood collection and autotransfusion in the surgical management of early cancers of the uterine cervix. *Obstet Gynecol* 1995; **86**: 373-378 [PMID: 7651645 DOI: 10.1016/0029-7844(95)00183-R]
114 **Kongsgaard UE**, Wang MY, Kvalheim G. Leucocyte depletion filter removes cancer cells in human blood. *Acta Anaesthesiol Scand* 1996; **40**: 118-120 [PMID: 8904269]
115 **Liang TB**, Li DL, Liang L, Li JJ, Bai XL, Yu W, Wang WL, Shen Y, Zhang M, Zheng SS. Intraoperative blood salvage during liver transplantation in patients with hepatocellular carcinoma: efficiency of leukocyte depletion filters in the removal of tumor cells. *Transplantation* 2008; **85**: 863-869 [PMID: 18360269 DOI: 10.1097/TP.0b013e3181671f2e]
116 **Catling S**, Williams S, Freites O, Rees M, Davies C, Hopkins L. Use of a leucocyte filter to remove tumour cells from intraoperative cell salvage blood. *Anaesthesia* 2008; **63**: 1332-1338 [PMID: 19032302 DOI: 10.1111/j.1365-2044.2008.05637]
117 **Muscari F**, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, Lavayssiere L, Rostaing L, Fourtanier G. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int* 2005; **18**: 1236-1239 [PMID: 16221153 DOI: 10.1111/j.1432-2277.2005.00207.x]
118 **Hansen E**, Bechmann V, Altmeppen J. [Intraoperative blood salvage with irradiation of blood in cancer surgery -- answers to current queries]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2002; **37**: 740-744 [PMID: 12469288 DOI: 10.1055/s-2002-35917]
119 **Waters JH**, Williams B, Yazer MH, Kameneva MV. Modification of suction-induced hemolysis during cell salvage. *Anesth Analg* 2007; **104**: 684-687 [PMID: 17312230 DOI: 10.1213/01.ane.0000255208.96685.2e]
120 **Sherman LA**, Ramsey G. Solid-organ transplantation. In: Rossi EC, Simon YL, Moss GS, Gould SA, editors. Principles of Transfusion Medicine. 2nd ed. Baltimore: Williams and Wilkins, 1996: 635-637
121 **Feltracco P**, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. *World J Hepatol* 2011; **3**: 61-71 [PMID: 21487537 DOI: 10.4254/wjh.v3.i3.61]

P- Reviewers Boucek C, Eghtesad B **S- Editor** Wen LL
L- Editor A **E- Editor** Li JY