World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v7.i6.86

World J Gastrointest Surg 2015 June 27; 7(6): 86-93
ISSN 1948-9366 (online)

Intraoperative blood loss in orthotopic liver transplantation: The predictive factors

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Author contributions: Pandey CK collected the references, conceived the concept, wrote the manuscript, revised and did the editing works; Singh A, Kajal K, Dhankhar M, Tandon M, Pandey VK and Karna ST wrote the manuscript, revised and did the editing works; all the above authors contributed equally in writing the manuscript, revising and did the editing works.

Conflict-of-interest: We, the authors of the manuscript hereby testify that none of us have received fees for serving as a speaker/consultant/advisory board member for any of organization. None of the authors have received research funding from any organization. None of the authors own stocks and/or shares in their names or concerned organizations. None of the authors own any relevant patents.

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Received: January 12, 2015
Peer-review started: January 15, 2015
First decision: March 20, 2015
Revised: April 13, 2015
Accepted: April 28, 2015
Article in press: April 30, 2015

Published online: June 27, 2015

Abstract

Liver transplantation has been associated with massive blood loss and considerable transfusion requirements. Bleeding in orthotopic liver transplantation is multifactorial. Technical difficulties inherent to this complex surgical procedure and pre operative derangements of the primary and secondary coagulation system are thought to be the principal causes of perioperative hemorrhage. Intraoperative practices such as massive fluid resuscitation and resulting hypothermia and hypocalcemia secondary to citrate toxicity further aggravate the preexisting coagulopathy and worsen the perioperative bleeding. Excessive blood loss and transfusion during orthotopic liver transplant are correlated with diminished graft survival and increased septic episodes and prolonged ICU stay. With improvements in surgical skills, anesthetic technique, graft preservation, use of intraoperative cell savers and overall perioperative management, orthotopic liver transplant is now associated with decreased intra operative blood losses. The purpose of this review is to discuss the risk factors predictive of increased intra operative bleeding in patients undergoing orthotopic liver transplant.

Key words: Liver transplantation; Intraoperative blood loss; Liver disease

Core tip: Liver transplantation has been associated with massive blood loss and considerable transfusion requirements. The bleeding in orthotopic liver transplantation is multifactorial such as etiology and severity of liver disease, preexisting coagulopathy,

previous abdominal surgeries, preoperative hematocrit, surgical techniques and methods of clamping, experience of surgical team, central venous pressure, the use of antifibrinolytics and procoagulants and use of point of care monitoring during the transplantation. The purpose of this review is to discuss the risk factors predictive of increased intra-operative bleeding in patients undergoing orthotopic liver transplant.

Pandey CK, Singh A, Kajal K, Dhankhar M, Tandon M, Pandey VK, Karna ST. Intraoperative blood loss in orthotopic liver transplantation: The predictive factors. *World J Gastrointest Surg* 2015; 7(6): 86-93 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i6/86.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i6.86

INTRODUCTION

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with decompensated end stage liver disease[1]. Historically, liver transplantation has been associated with massive blood loss and considerable transfusion requirements[2]. With improvements in surgical skills, anesthetic technique, graft preservation and overall perioperative management, OLT is now associated with decreased intra operative blood losses[3,4].

Though the origin of bleeding is multifactorial, technical difficulties inherent to this complex surgical procedure and pre operative derangements of the primary and secondary coagulation system are thought to be the principal causes of perioperative hemorrhage[5]. Intraoperative practices such as massive fluid resuscitation and resulting hypothermia and hypocalcemia secondary to citrate toxicity further aggravate the preexisting coagulopathy and worsen the perioperative bleeding. Blood loss during OLT, however remains highly variable. Rate of blood product transfusion may vary between median of two to 13 packed red blood cells (PRBC) units per patient[6].

Blood transfusion (BT) is an independent predictor of post transplant outcome and is associated with a significant increase in morbidity and mortality[7,8]. Intraoperative blood loss is a predictor of poor short and long-term prognosis immediately after LDLT. Excessive blood loss and transfusion during OLT are correlated with reduced graft survival and increased septic episodes and prolonged ICU stay[9].

The risk of allogenic blood transfusion extends beyond viral transmission and includes allergic reactions, alloimmunization, bacterial sepsis, transfusion related acute lung injury (TRALI), volume overload, graft *versus* host disease (GVHD), renal failure and immunosuppressive effects[10]. Persistence of soluble and cell associated antigens in the circulation of the recipient after allogenic blood transfusion is considered to result in immune down regulation[11]. Significant association between allogenic BT and immune suppression including graft survival, recurrence of malignancies, impaired cell mediated T-cell and natural killer (NK) cell activity and deterioration in liver regeneration has been shown by studies[12].

Preoperative identification of factors predictive of increased intra operative bleeding in patients undergoing OLT is useful not only for availability of blood products and initiation of blood salvage with the most appropriate strategy but also to consider the timing and advisability of transplantation.

From a comprehensive review of literature, we were able to identify the following factors associated with increased risk of intraoperative bleeding during OLT and liver resection.

PREOPERATIVE RISK FACTORS

Etiology of liver disease

The extent of resection and the size of tumor are predictive of perioperative blood transfusion[13]. Cockbain *et al*[14] concluded that hilar cholangiocarcinoma resections are a risk factor for excessive bleeding due to the technical difficulty as these resections may include lymph node dissection, caudate resection, resection and reconstruction of hepatic inflow. On the other hand, OLT for hepatocellular carcinoma (HCC) was found to be negative predictor for massive blood transfusion in a retrospective study by Cywinski *et al*[15].

Severity of liver disease

Assessment of severity of liver disease is most commonly done by Child Pugh Turcotte (CTP) and Model for end stage disease (MELD). Association of severity of liver disease with perioperative blood loss is controversial. Findlay *et al*[16], Massicotte *et al*[17], and Roullet *et al*[18] in their recent study concluded that it is not an independent predictor of bleeding and blood product requirement.

Contradictory to these findings, McCluskey *et al*[19] derived a risk index for the prediction of massive blood transfusion in OLT. In their derived risk index, two of the variables included in calculating the MELD score-preoperative creatinine and International Normalized Ratio (INR) were found to be independent predictors of bleeding, although the MELD score itself was less predictive. In consistence, Mangus *et al*[20] found high MELD scores to a one of the risk factors found to be significantly associated with increased bleeding and transfusion requirements. Frasco *et al*[3] also showed a positive association between MELD score and transfusion requirement during OLT. In 2006, a high MELD scores (> 30) was found to be significantly associated with increased bleeding and transfusion requirements compared to patients with low MELD scores (< 30)[21]. Higher MELD score was found to be

highly statistically significant predictor of massive blood transfusion in a recent retrospective study by Cywinski *et al*[15]. Thus, if a MELD score is greater than 30 or patient is Child grade B or C, it is prudent to assume the probability of increased blood loss perioperatively even though studies show conflicting results.

Preexisting coagulopathy

Impaired hemostasis in patients with advanced liver disease is multifactorial. Predominant factors includes impaired coagulation factor synthesis, synthesis of dysfunctional coagulation factors, accelerated consumption of coagulation factors and platelets, splenomegaly causing platelet sequestration and consumption, altered clearance of activated coagulation factors including factors of the fibrinolytic pathway contributing to hyperfibrinolysis, Accelerated intravascular coagulation and fibrinolysis (AICF) and qualitative disorders of platelet function are all contributory[22,23].

Recent advances in the understanding of the coagulopathy in patients with liver disease have led to the concept of the rebalanced theory of hemostasis in these patients as alterations in both anti and procoagulant pathways balance each other in patients with liver disease[24].

It has been shown that correction of coagulation defects before the anhepatic phase is not necessary[25]. There is a relatively poor correlation between bleeding and laboratory indices of coagulation (PT/INR) in patients with chronic liver disease[22,23]. Pre transplant higher INR and lower platelet counts were found to be highly statistically significant predictors of higher intraoperative blood product usage in retrospective study by Cywinski *et al*[15].

Previous abdominal surgery

Cywinski *et al*[15] in their retrospective study reported that higher intraoperative blood product usage was more frequent in patients undergoing OLT with history of previous upper abdominal surgery. This result has been concordant with the results of previous studies by Steib *et al*[4], Palomo Sanchez *et al*[9] in which previous abdominal surgery was independently associated with massive transfusion intra operatively[9]. However, this association was not derived in studies by other investigators[18,26].

Findlay *et al*[16] did not find any significant association between retransplantation and blood usage. These results were similar to previously published results of Motschman *et al*[27].

Preoperative hematocrit

Transfusion requirements depend not only on the intraoperative blood loss but also on the threshold for when transfusions of different products are initiated. Therefore, comparison of intraoperative transfusion requirements from different studies may be inherently biased by inability to account for differences in transfusion triggers and clinical practices. Low starting hemoglobin (Hb) value represents the most important indicator for the need for transfusion as shown by Massicotte *et al*[6]. Despite pre operative hemoglobin being an important predictor of intra operative RBC transfusion in various studies; the cut off threshold for the same has not been clearly reported in them[20]. In a study by Steib *et al*[4], one of the three preoperative risk factor predictive of high blood loss was preoperative low Hb. The investigators concluded that patients with an initial low Hb below 10 gm/dL would require transfusion in order to reach the selected trigger point in their study.

SURGICAL RISK FACTORS

Surgical technique of OLT

The conventional method for liver transplantation requires clamping of both portal flow from the viscera and caval flow from the lower body.

Piggyback hepatectomy (PGB) is a surgical technique increasingly utilized in both DDLT and LDLT. The pseudonym Caval preservation technique is justified because it avoids clamping of the vena cava while maintaining flow from the lower body back to the heart throughout the transplant. Preservation of cardiac preload maintains hemodynamic stability and avoids large infusions of fluid volume, vasopressors, and need for venovenous bypass (VVB). The total duration of warm ischemia time is significantly reduced, as one less anastomosis is required prior to reperfusion.

The conventional method would seem to be associated with lesser blood loss and transfusion requirements because PGB is technically more demanding and time consuming than the conventional approach. However, studies suggest otherwise.

Maguns *et al*[20] concluded that blood loss and blood product usage with PGB technique are similar to or better than those for the conventional technique. It is the preferred method in high-risk patients such as the elderly or those with poor physiologic reserve and may be associated with less perioperative morbidity and mortality.

Previously published studies also concluded that PGB is a potentially superior technique given its benefits of avoiding VVB, maintaining hemodynamic and physiologic stability, decreasing warm ischemia time and association with significantly lower blood loss and transfusion requirements[28]. As summarized by an analysis by the Cochrane database[29], no trial has till date shown superiority of one technique over the other.

Clamping methods

Blood losses during liver resection are usually greatest at the stage of parenchymal transaction. Selective clamping of the vasculature prevents excessive blood

loss during this phase. Commonly used methods for clamping are: (1) Complete inflow occlusion (Pringle maneuver) - Method most commonly used. Blood loss associated with this method is lesser than the intermittent method. Greater degree of ischemic injury to the liver parenchyma is however reported with this method; and (2) Intermittent clamping or (ischemic preconditioning technique)-This technique has shown to reduce ischemic injury during liver resection, more so in cirrhotic livers. On a comparative analysis however, intermittent clamping has been shown to be associated with more bleeding than the continuous clamping method[30].

Technical improvement in surgery

Amongst the newer devices available for liver parenchymal transaction, the Cavitron Ultrasonic Surgical Aspirator (CUSA) is universally used[31]. Lesurtel *et al*[32] compared four different techniques of liver transaction in a prospective randomized clinical trial. Techniques compared were - conventional clamp crushing technique, CUSA, Hydro-jet, and a dissecting sealer in 100 non-cirrhotic patients undergoing major liver resections. Significantly reduced resection time, costs along with a significant reduction in intra operative blood loss was seen with the clamp-crashing technique.

Deakin *et al*[26] also concluded that that technical improvement in surgery has led to a threefold reduction in the blood transfusion rate. The changes enumerated were-increased use of diathermy dissection with meticulous suture ligation of vessels difficult to control by diathermy, increase use of VVB and the use of sophisticated coagulation devices like Argon Beam Coagulator. This study was done in the pre PGB technique era and these surgical techniques have more or less become the norm in OLT.

Experience of the surgical team

The experience of the surgical team was found to be an independent predictor of transfusion[33]. Steib *et al*[4] concluded that there is a significant decrease in the number of patients undergoing high blood loss with the progressive experience of the surgical team, but it was not found to be an independent predictor of blood loss and transfusion requirements.

INTRAOPERATIVE MANAGEMENT INFLUENCING TRANSFUSION REQUIREMENTS

Role of central venous pressure

Performance of liver resection under low central venous pressure (CVP) has been extensively studied[34]. Low CVP (defined as a pressure < 5 mmHg) can be attained by volume contraction, vasodilators, forced diuresis, adequate neuromuscular blockade, reduction of respiratory tidal volume and applied PEEP.

Conservative transfusion policy and volume contraction reduces perioperative transfusion requirement by avoidance of fluid overload. Prophylactic correction of deranged routine tests of coagulation results in administration of large volumes of plasma and/or platelet concentrates. Pathophysiological changes in patients with ESLD including portal hypertension and numerous collaterals, increased plasma volume with redistribution of plasma volume to splanchnic bed, and disturbed cardiac function with peripheral vasodilatation, causes rapidly administered fluids and blood products to further increase the portal and central venous pressure. This results in bleeding with surgical trauma probably due to venous congestion[35].

Jones *et al*[36] were the first to show that intra operative blood loss during liver resection correlated almost linearly with the CVP. The safety and benefits of restricted intra operative fluids and low CVP in patients undergoing liver transplant was studied by Schroeder and colleagues. They compared outcome variables of patients with two different fluid policies in two different centers. The target in the intervention group of a low CVP (< 5 mmHg) was achieved by fluid restriction, whereas a normal CVP of (7-10 mmHg) was maintained in the other group in the second center. Decreased transfusion requirements of RBC, FFP and platelets was observed in the low CVP group as compared with the normal CVP group[37].

The maintenance of a low CVP intra operatively in cirrhotic patients undergoing liver resection was not associated with any significant increase in mortality and morbidity. Significantly reduced intraoperative transfusion of blood and blood products along with decreased hospital stay was observed in the low CVP group. There was no derangement in postoperative hepatic and renal function in the study group[38].

Hashimoto *et al*[39] studied the effect of prophylactic phlebotomy and withdrawal of calculated amount of blood (0.7% of the patient's body weight) *vs* no withdrawal of blood in a randomized prospective study of healthy donors scheduled for partial liver resection for LDLT. At the beginning of parenchymal transection CVP was significantly lower in the phlebotomy group [median 5 (range 2-9) cm H_2O *vs* 6 (range 2-13) cm H_2O) as compared with controls. Post operative outcomes were comparable between the groups[39].

In another study in liver transplant recipients, Massicotte *et al*[35] achieved a low CVP by volume contraction and intraoperative phlebotomy. Expansion of blood volume post phlebotomy (at the beginning of the case) was not done. They concluded that avoidance of plasma transfusion; starting Hb value and maintenance of a low CVP prior to the anhepatic phase were associated with a significant decrease in blood and blood products during this study[35].

On the other hand maintenance of a low CVP during liver resections is associated with a increased risk of complications including air embolism, systemic

tissue hypoperfusion and renal failure[7,35,37]. In their study Schroeder and colleagues observed an increase in 30 d mortality and dialysis requirements with higher post operative peak creatinine levels in patients with low intra operative CVP[37].

Use of antifibrinolytics

Hyperfibrinolysis plays a significant role in nonsurgical blood loss in patients undergoing OLT requiring massive transfusion of blood products. Hyperfibrinolysis always occurs late in the anhepatic phase and immediately after the reperfusion of the graft. An increased level of t-PA because of an increased release from the damaged ischaemic endothelium of the graft and lack of its hepatic clearance in the anhepatic phase is the principal causative factor. Also there is associated consumption of alpha-2 antiplasmin and plasminogen activator inhibitor type-1 (PAI-1)[5,40]. The beneficial effects of antifibrinolytics to reduce the bleeding and transfusion requirements in patients undergoing cardiac surgery initiated the assessment of antifibrinolytics in liver transplant.

Dalamu *et al*[41] documented a significant reduction in PRBC transfusion in a prospective double blind randomized study conducted to compare the efficacy of prophylactic infusion of tranexamic acid (TA) or epsilon aminocaproic acid (EACA) with placebo in reducing blood loss and transfusion requirement during LT. In this study, TA and EACA were given prophylactically at a rate of 10 and 16 mg/kg per hour respectively. Thirty-one percent of patients in the TA group did not receive any PRBC transfusion. Also the TEG profiles of the patients given TA in the reperfusion phase were better in TA group. There was no difference in transfusion requirements after OLT, or thromboembolic events, reoperations or mortality between the groups. Boylan *et al*[42] found that a larger dose, *i.e.*, 40 mg/kg per hour of TA reduced not just the intraoperative blood loss but also the transfusion of plasma, platelet and cryoprecipitate. However a Cochrane Hepato-Biliary Group metaanalysis, did not show a significant reduction in blood and blood product requirements in patients receiving tranexamic acid *vs* controls[43].

Nehaus *et al*[44] first reported Aprotinin use in a study in 1989. They reported decreased blood loss, transfusion requirements and duration of surgery with the use of aprotinin in the dose of 2 million KIU (Kallikrien inhibitory units). Studies by Porte *et al*[45], Findlay *et al*[46] have also shown that there is a decrease in transfusion requirement with use of aprotinin. In a review of the use of aprotinin in OLT, Lentschener and colleagues concluded that prophylactic use of large dose aprotinin decreases blood loss and transfusion requirements only when OLT is associated with significant blood loss and does not alter postoperative outcomes[47]. The efficacy of TA *vs* Aprotinin in reducing blood loss and transfusion requirements during OLTx was studied by Massicotte *et al*[48]. Administration of TA and Aprotinin was found to be comparable in terms of intraoperative blood loss and transfusion requirements. Molenaar *et al*[49] in their study concluded that although both Aprotinin and TA significantly reduced RBC transfusion requirements; significant reduction in intraoperative FFP transfusions was achieved with Aprotinin only. Post operative thromboembolic events and mortality was not increased in patients receiving antifibrinolytics.

However, other studies failed to show a significant difference in the transfusion of red blood cells, fresh frozen plasma (FFP), cryoprecipitate, and platelets between the aprotinin-treated group and the placebo group[50].

Use of newer procoagulants

Recombinant factor VIIa (rFVIIa) till date is approved by the United States Food and Drug Administration (FDA) for hemophilia only, but a large number of case reports and studies have reported the use of rFVIIa in uncontrolled hemorrhage due to trauma or surgery including OLT.

Hendriks *et al*[51] first reported that prophylactic administration of 80 μg/kg of rFVIIa in adult cirrhotic patients undergoing OLT led to significant reductions in median total PRBC requirements, although one of the treated patients developed hepatic artery thrombosis. Lodge *et al*[52] were not able to demonstrate any reduction in RBC requirement in rFVIIa-treated patients compared to placebo. The efficacy of rFVIIa in reducing intraoperative blood loss is only modest at the cost of an increased incidence of thromboembolic episodes specially in patients with intracerebral hemorrhage and those undergoing cardiac surgery[53]. Thus, rFVIIa cannot be recommended as a universal prophylaxis to reduce transfusion requirements during OLT particularly considering the high cost of rFVIIa.

Use of point of care monitors of coagulation

New point of care tests are now available which allow monitoring of the haemostasis in the operation theatre which is essential in patients with pre-existing haemostatic abnormalities or in profusely bleeding patients with complex and rapidly changing coagulation profile. Devices assessing viscoelastic properties of whole blood are available include thromboelastography (TEG), rotation thromboelastometry and Sonoclot analysis.

TEG can assist in treatment of intraoperative bleeding by identifying the cause. In combination with clinical assessment of bleeding, it also facilitates selective replenishment of deficient blood components and use of specific drug treatments (antifibrinolytics). Various studies have demonstrated a significant reduction in intraoperative blood and component therapy with coagulation monitoring through TEG when compared with traditional "clinician-directed" transfusion management. Wang *et al*[54] reported that

the FFP requirement during OLT in patients being monitored with TEG was lower than patients corrected for deranged PT/INR values using accepted transfusion thresholds.

Transfusion trigger

Still no consensus exists on transfusion practices in liver surgeries especially OLT. There is high variability in the use of blood products in liver resection surgeries with most of the use not being evidence based. Most centers follow the ASA practice guidelines for the transfusion of blood products during OLT. The threshold for RBC, plasma and platelet transfusion is a Hb of 60 to 100 g/L; INR value > 1.5 and platelet < 50000/mL, respectively. Despite following these guidelines a wide range of transfusion rates exist between centers and even among anesthesiologists in the same center.

Massicotte *et al*[8] in their prospective study on 206 patients used aprotinin, a low CVP and a transfusion trigger of 60 gm for administering PRBC transfusion. They did not use PGB, VVB or prophylactic correction of coagulopathy. The investigators concluded that coagulation defects were not linked to PRBC transfusion and there is no benefit of prophylactic correction of coagulation disorders in the absence of uncontrollable bleeding. The use of FFP was the strongest predictor for PRBC transfusion and associated with decrease in one-year survival rate[8].

Intraoperative blood salvage techniques

Autologous blood transfusion and intra operative blood salvage has shown to reduce allogeneic blood transfusion in patients undergoing surgery with high risk of intraoperative blood loss and transfusion. These techniques play an important role in management of special patient populations (Jehovah's Witnesses and patients with rare blood groups) undergoing major surgeries including transplantation.

In adult patients undergoing elective surgery cell salvage was concluded to be an efficacious technique in reducing the need for allogeneic blood transfusion by a Cochrane Collaboration meta-analysis[55]. The cost effectiveness of this technique as compared to allogenic blood transfusion was also corroborated by Waters *et al*[56] in their review. It has also been reported to improve conservation of erythrocytes and reduce exposure of patients to blood and blood components[57,58].

Despite above-mentioned evidence the role of cell salvage techniques in OLT remains controversial with studies reporting higher blood loss with its use due to fibrinolysis and increased costs. A increase in transfusion requirements in liver transplant recipients was reported by Hendriks *et al*[33] with the use of cell salvaged blood with salvaged blood hypothesized as a cause of excessive blood loss. Increased requirements of RBCs, FFP, cryoprecipitate, and platelets in patients given cell salvaged blood have been shown by other studies[59,60]. Degradation products of Fibrinolysis in the salvaged blood either from blood cells or from the transplanted liver, that are not cleared by washing of RBC's in the cell saver are postulated to be the cause of increased blood loss in these patients[59].

However with the decrease in intra operative blood loss in patients undergoing OLT; the cost effectiveness of the technique (requiring intraoperative salvage and use of two or more blood units) in comparison to allogenic blood transfusion is questionable. Thus, the use of cell salvage is helpful in OLT case with anticipated high blood loss.

CONCLUSION

Improvements of the surgical techniques, anesthetic management and graft preservation have resulted in development of OLT as the preferred treatment choices in patients with decompensated liver disease. Predictive risk factors for intraoperative blood transfusion have been reviewed. All the predictive models and associations do not have good specificity in predicting patients requiring excessive blood transfusion requirements. Preoperative factors like disease severity, previous surgery, low hematocrit, surgical factors and intraoperative management including use of antifibrinolytics, CVP, FFP transfusion all influence the blood loss and transfusion requirements during OLT.

Changing trends in blood product use intraoperatively and better anaesthetic and surgical management of these patients are perhaps the most important factors that have lead to decreased blood loss and transfusion in patients undergoing OLT.

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