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REVIEW

Massive haemorrhage in liver transplantation: Consequences, prediction and management

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Abstract

From its inception the success of liver transplantation has been associated with massive blood loss. Massive transfusion is classically defined as > 10 units of red blood cells within 24 h, but describing transfusion rates over a shorter period of time may reduce the potential for survival bias. Both massive haemorrhage and transfusion are associated with increased risk of mortality and morbidity (need for dialysis/surgical site infection) following liver transplantation although causality is difficult to prove due to the observational design of most trials. The blood loss associated with liver transplantation is multifactorial. Portal hypertension secondary to cirrhosis results in extensive collateral circulation, which can bleed during hepatectomy particular if portal pressures are increased. Avoiding volume loading and maintenance of a low central venous pressure together with the use of vasopressors have been shown to reduce blood loss and transfusion during liver transplantation, but may increase the risk of renal impairment post-operatively. Coagulation defects may be present pre-transplant, but haemostasis is often re-balanced due to a deficit in both pro- and anti-coagulation factors. Further derangement of haemostasis may develop in the anhepatic and neohepatic phases due to absent hepatic metabolic function, hyperfibrinolysis and platelet sequestration in the donor liver. Point-of-care tests of coagulation such as the viscoelastic tests rotation thromboelastometry/thromboelastometry allow and more accurate and rapid assessment of these derangements in coagulation and guide the use of factor replacement and antifibrinolytics. Transfusion protocols guided by these tests have been shown to reduce transfusion rates compared with conventional coagulation tests, but have not shown

improvements in mortality or morbidity. Pre-operative factors associated with massive transfusion include previous surgery, re-do transplantation, the aetiology and severity of liver disease. Intra-operatively the use of piggy-back technique and avoiding veno-veno bypass has been shown to reduced blood loss.

Key words: Liver transplantation; Massive transfusion; Coagulopathy

Core tip: The management of bleeding during liver transplantation requires an understanding of the unique coagulopathy of liver failure and the ability to recognize the risk factors for massive transfusion. By avoiding massive haemorrhage and transfusion, patients' outcomes after transplantation are likely to benefit.

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INTRODUCTION

The first human solid organ transplantation was performed in 1954 when Dr. Joseph Murray led a team in successfully transplanting a kidney between identical twin brothers[1]. Liver transplantation proved far more difficult as patient decompensation was inevitable and the challenges of operating with massive and uncontrollable haemorrhage were substantial[2]. In 1963, Starzl *et al*[3] published the first case series of 3 patients, two of whom died shortly after the procedure and one bleeding to death on the operating table. Throughout the remainder of the 1960's liver transplantation was an experimental procedure with the first survival beyond a year not coming till 1967[4]. Improvements in surgical outcomes became possible with the dramatic improvement in the graft quality due to the acceptance of the concept of brain death[5], and with the introduction an effective immunosuppressive agent, cyclosporine[4,6]. Survival after liver transplantation has steadily improved[7,8], and orthotopic liver transplantation (OLT) is now an accepted treatment of advanced liver failure.

With the expansion of OLT programs in the early 1980's, there was an increasing demand on blood transfusion services. Butler *et al*[9] reported red blood cell (RBC) transfusion rates in the range of 6-254 units per person in the first few years of their programme. With experience the same group was able to reduce their mean RBC, fresh frozen plasma (FFP) and platelet transfusion rates from 40 to 20 units per patient[10], which was comparable with other groups at the time[11]. The reduction in transfusion rates was attributed to improved surgical technique and faster laboratory processing times to allow more rapid diagnosis and treatment of developing coagulopathies[11]. Despite these advances, liver transplant recipients accounted for up to 25% of all the blood transfused in a hospital[10] and had by far the greatest requirement for blood products of any solid organ transplants[12].

Outcomes following liver transplantation have dramatically improved with 5-year graft survival rates in the United States of at least 70% despite transplants being performed on patients with a worse clinical condition due to the Model for End-Stage Liver Disease (MELD) score based organ allocation system[13]. MELD was adapted by the United Network for Organ Sharing from a survival model used for patients undergoing transjugular intrahepatic portosystemic shunts[14,15], and objectively predicts 3-mo mortality and therefore the need for transplantation[16]. There has been an equally impressive decline in blood product use over the same period[17,18] with case series describing OLT without the use of any blood products[19-23]. Yet despite the notable improvements made in the management of blood loss and transfusion there remains a large variability in transfusion practices[24]. This variability in transfusion practice of a precious resource is an important consideration as there may be implications for transplant morbidity and mortality[25-29]. The impact of blood transfusion on surgical outcomes is an area of active debate, but the impact of massive transfusion is more convincing.

Recent reviews have discussed prediction of blood loss during liver transplantation[30,31], and summarised strategies to reduce blood loss[32,33]. This review will focus on massive haemorrhage in liver transplantation including consequence, prediction, and management as well as considering some of the lessons learned from other surgical specialties such as trauma and obstetrics.

DEFINITION

The classical definition of massive haemorrhage is the loss of one blood volume within a 24-h period[34]. Correspondingly massive transfusion in an adult has commonly been defined as 10 or more units of packed red cells in a 24-h period, which approximates to replacement of one blood volume based on the approximate blood volume of a 70-kg male[35].

These definitions are retrospective and often used as the basis for risk prediction models for massive blood loss and the implementation of resuscitative transfusion strategies and protocols. Their use has been questioned particularly in the setting of trauma as it excludes information regarding the patient's condition, institutional transfusion practices and the risk of survival bias as patients who die from exsanguination before receiving 10 units will not be included in the massive transfusion group[36]. Haemorrhage is the main cause

of death following major injury in patients surviving to hospital admission with the highest incidence 1 to 3 h following admission[37]. To address this researchers in trauma suggested more dynamic definitions of massive transfusion including the use of 4 red cell concentrates within one hour with likely on-going need[38], 5-plus units within first four hours of admission[39] or 10 units within 6 h[35]. The PROMPTT trial investigators suggested two different approaches. Rahbar *et al*[35] demonstrated that resuscitation with four or more units (with 1 L crystalloid classed as 1 unit) of fluid within the first 30 min of admission for trauma was significantly associated with 6-h mortality and was a surrogate for sickness in severely bleeding patients. Alternatively Rahbar *et al*[36] using baseline admission characteristics (systolic blood pressure < 90 mmHg, HR > 120 bpm, pH < 7.25 and haemoglobin < 9) were able to develop a latent class model for those at risk of severe haemorrhage and in need a massive transfusion protocol (MTP). The British Committee for Standards in Haematology have suggested a similar dynamic definition as "bleeding which leads to a heart rate of more than 110 beats/min and/or systolic blood pressure less than 90 mmHg"[40] in their most recent guidelines.

In obstetrics massive haemorrhage remains an important cause of morbidity and mortality with 13 death per 100000 maternities in the United Kingdom reported in the most recent confidential enquiry into maternal deaths. Post-partum haemorrhage (PPH) is defined as more than 500 mL from the genital tract within 24 h of birth and subdivided into minor (500-1000 mL), moderate (1000-2000 mL) and severe (> 2000 mL)[41]. These definitions form the basis for activating protocols of resuscitation measures. The Royal College of Obstetrics and Gynaecology state that moderate PPH (1000 mL plus) with on-going bleeding or signs of shock should trigger such measures[41].

Liver transplantation surgery in contrast to trauma and obstetrics is largely an elective or semi-elective procedure where blood loss can be anticipated and a strategized around. Death from exsanguination, common in the early days of transplantation is now a rare event and therefore the traditional definitions of massive haemorrhage/transfusion are less at risk of survivor bias. Defining massive transfusion as 6 unit or more in 24 h has been used in a number risk prediction studies for massive transfusion[42-44].

EPIDEMIOLOGY OF HAEMORRHAGE DURING LIVER TRANSPLANTATION

Liver transplantation requires operating on patients with the pathophysiological changes associated with advanced cirrhotic liver disease. The presence of portal hypertension and the haemostatic changes that occur both as a consequence of hepatocyte death and during the stages of liver transplantation itself are important causes of bleeding that are unique to this procedure.

Portal hypertension

As chronic liver disease progresses hepatocyte death leads to inflammation and the subsequent generation of fibrosis that marks the onset of cirrhosis[45]. Increased intrahepatic vascular resistance (HVR) with maintained portal blood flow requires increased portal pressures. Approximately, 70% of the portal hypertension is attributed to structural factors (fibrosis, vascular re-modelling, vascular occlusion, nodule formation) whilst the remaining 30% is thought to be due to dynamic functional abnormalities in the liver microvasculature[46]. A reduction in intrahepatic vasodilators (of which nitric oxide may be the most important) combined with an increased activity and sensitivity to endogenous vaso-constrictors contribute to the dysfunctional nature of sinusoidal endothelial cells with vasoconstriction of microvasculature and increased HVR[46]. As portal hypertension develops portosystemic collateral vess-els form and blood from the splanchnic circulation is diverted into these collateral vessels[46]. In addition to increased portal blood flow, thinning of arterial walls in these circulatory beds increase the susceptibility for blood loss.

Coagulopathy of liver disease

The liver synthesises most of the circulating proteins of coagulation needed in haemostasis, therefore there is a decreased level of many of these proteins in liver failure[47]. Conventional tests of coagulation are often deranged in advanced liver disease reflecting the deficiency in procoagulant factors. The prothrombin time (PT) and international normalised ratio (INR) are useful markers of hepatic synthetic function. The INR is also used in combination with recipient age, bilirubin and creatinine to calculate the MELD score.

Conventional coagulation tests are, however, poor predicators of peri-procedural bleeding in end-stage liver disease with no increase in bleeding seen in patients undergoing invasive procedures such as cardiac catheterisation[48] or dental extraction[49]. The main source of bleeding seen in liver disease pre-transplant is secondary to variceal haemorrhage, with portal hypertension and splanchnic haemodynamics the proposed mechanism for bleeding rather than coagulopathy.

The haemostasis in liver failure is neither shifted towards bleeding nor thrombosis, but has been referred to as a balanced coagulopathy[50]. Thrombocytopenia and reduced platelet function is offset by elevated levels of von Willebrand factor (vWF) and decreased levels of ADAMTS 13 (a metalloprotease which cleaves vWF)[51]. All pro-coagulant proteins are reduced in hepatic insufficiency with the exception of factor Ⅷ, but so too are the levels of anti-coagulants antithrombin and protein C and S[50]. It has been suggested that the relative excess of plasma coagulation factors in health provides a "margin of safety" to account for physiological or pathological stresses to the system[50]. Without this excess of coagulation factors the balanced coagulopathy of liver failure can be thought of as more susceptible

to the perturbations associated with the perioperative period.

This revised understanding of the coagulopathy of liver failure challenges the ubiquitous use of plasma to correct abnormal blood tests and should focus the use of blood products to manage overt microangiopathic bleeding[2]. In fact, the aggressive correction of derangements in INR without supportive evidence of impaired clotting may not only be unnecessary, but harmful in and of itself. In portal hypertensive rats subjected to a period of haemorrhage, replacing the exact volume lost with blood results in an increase in portal pressures by 20%[52], higher rates of haemorrhage and worse outcome[53]. This has subsequently been demonstrated in patients with severe acute upper GI bleeds. Those treated with a restrictive transfusion strategy had lower portal pressures, lower rates of further bleeding and higher rates of survival compared to those treated with a liberal stratergy[54].

Phases of transplantation

During the pre-anhepatic phase of transplantation the surgeon has to perform a hepatectomy whilst contending with the numerous porto-systemic collaterals and the hyperdynamic, dilated, thin walled splanchnic circulation. Adhesions from previous surgery can be another source of blood loss[2]. During the anhepatic phase, hepatic synthesis and clearance is absent, and hyperfibrinolysis can increase rapidly with the accumulation of tissue plasminogen (t-PA)[55]. Plasma t-PA increases the conversion of plasminogen to plasmin. The end result is that during the anhepatic phase fibrinogen production is stopped and the consumption of fibrin is promoted leading to a rapid consumption of the primary building block of clot formation and increased blood loss[56]. In the neohepatic phase, fibrinolysis is further stimulated by the release of t-PA from the ischaemically injured endothelium of the donor liver[57]. Platelet counts commonly decrease due to sequestration into the sinusoids, extravasation of platelets into disse spaces and phagocytosis by Kupffer cells[55].

CONSEQUENCES OF MASSIVE BLOOD LOSS AND MASSIVE TRANSFUSION

Transfusion of RBCs and blood products has been linked to adverse outcomes in OLT patients[28,58]. Even modest transfusion requirements have been linked to prolonged lengths of hospital stay, with the use of of more than 6 units of red cells having the greater impact in decreased survival rates[44]. de Boer *et al*[59] demonstrated a dose related effect in one year survival rates, with a HR of 1.37 per unit of platelets and 1.07 per unit of packed red blood cells, in their multivariate analysis of a cohort of 433 adult OLT patients.

Both short and long-term survival appears to be affected by intraoperative massive blood transfusion (MBT). Rana *et al*[28] found that an intraoperative blood transfusion of > 28 units was as significant risk factor for decreased 3 mo survival in a study of 233 consecutive liver transplant recipients performed by the same experienced surgeon. Intraoperative blood transfusion greater than 5 units was independently associated with reduced 3 and 5 years survival in a study of 102 living donor liver transplant patients[60].

Observational studies have demonstrated a link between blood loss and transfusion requirements and increased morbidity in OLT patients. Transfusion requirements of > 17.5 packed red cell units and > 3.5 platelet units in a study including 291 consecutive OLT patients were found to accurately predict the requirement for post-transplant renal replacement therapy[29]. Transfusion of > 2 units of packed red cells was identified as a risk factor for development of surgical site infections in liver transplant recipients[61]. Intraoperative blood loss was also found to be the main determinant of early surgical re-intervention after OLT[62].

It is important to highlight that studies investigating outcomes following liver transplantation are limited by their observational nature in that they demonstrate association and not causality between blood loss, transfusion requirements and morbidity and mortality outcomes.

PREDICTION OF MASSIVE TRANSFUSION IN LIVER TRANSPLANTATION

A number of studies have identified factors associated with massive blood loss and transfusion requirements in liver transplant patient populations (Table 1)[42-44,60,63-79]. Risk factors can be classified based on the perioperative period and surgical factors.

Preoperative risk factors

Patient, donor organ or other factors that increase the duration or technical difficulty of the surgical procedure such as previous abdominal surgery[25,60,73,80] or redo transplantation[42] are independently associated with higher blood loss and transfusion requirements. Observational studies suggest that haemostasis, coagulopathy and risk of bleeding differ according to the cause of liver failure. For instance, patients with primary biliary cirrhosis exhibit a preserved capacity for thrombin generation and less fibrinolytic activation during the anhepatic phase compared with other cirrhotic states[81]. Case series of patient with portal vein thrombosis undergoing liver transplantation report greater operation times and consumption of blood products[80,82]. Increasing age of the recipient has been reported as predictor of MBT in a number of studies[42,72,79]. McCluskey *et al*[42] found age to be a weak predictor and the authors remarked that age is likely to be a surrogate for other unidentified risk factors.

Severity indexes of liver disease have been investigated as predictors of blood loss during liver transplant surgery. The Child-Turcotte-Pugh (CTP) score uses

Table 1 Studies evaluating red blood cell transfusion requirements and prediction variables in adult liver transplantation

Ref.	No. of patients	Population	Data methodology	Outcomes	Final model prediction variables	Performance of model
Motschman *et al*[63]	83	OLT	Retrospective univariate and multivariate	RBC transfusion requirement	History of previous GI bleed, Previous RUQ surgery	
Deakin *et al*[64]	300	OLT	Retrospective univariate and stepwise multivariate	⩾ 7 units RBC	Urea levels and platelet count	Specificity 62% Sensitivity 68%
Findlay *et al*[65]	583	OLT	Retrospective univariate and multiple linear regression analysis	RBC transfusion requirement	Age, creatinine and bilirubin	R = 0.22
Steib *et al*[66]	410	OLT	Retrospective univarite and stepwise multivariate analysis	High blood loss ⩾ 12 units RBC	Preoperative Hb, previous abdominal surgery, preoperative FDP	Sensitivity 18% Specificity 98%
Pirat *et al*[67]	40	OLT	Bivariate and multiple linear regression	RBC transfusion requirement	Preoperative albumin	R = 0.48
Ramos *et al*[44]	122	OLT	Univariate and multivariate regression	> 6 units RBC	UNOS class and placement of caval shunt	
Massicotte *et al*[68]	206	OLT	Retrospective univariate and multivariate logistic regression	> 4 units RBC	Starting INR, platelet count and duration of surgery	
Yuasa *et al*[69]	635	LDLT (adult and pediatric)	Univariate	Arbitrary high blood loss quartile (344 ± 272 mL/kg)	Univariate = age < 1 yr, Hct < 30%, T-Bil > 20 mg/dL, BUN > 30 mg/dL. Dx Pre-op atresia, Re transplantation	
McCluskey *et al*[42]	460	OLT	Multivariate regression. Risk index internally validated	> 6 units RBC in 24 h	Age > 40, Hb < 10 g/dL, NR 1.21-1.99 and > 2, platelet < 70, creatinine > 110 mmol/L female and > 120 mmol/L males, albumin < 28 h/L and redo transplant	C statistic model = 0.79
Mangus *et al*[70]	526	OLT "piggy back"	Univariate and multivariate regression	RBC transfusion requirements	Pre-op Hb MELD score, Initial CVP	
Massicotte *et al*[71]	505	OLT	Nomogram risk model based on multivariate regression analysis		FFP transfusion. High starting Hb and phlebotomy protective for blood loss	Bootstrapped AUC prediction model = 89.8%
Araújo *et al*[72]	758	OLT	Retrospective univariate and multivariate regression	RBC requirements	PT, Hb, age, liver malignancy	R = 0.30
Bang *et al*[73]	555	LDLT	Multivariate regression	Intraoperative blood loss > 1000 mL	MELD, albumin, ascites and previous abdominal surgery	
Roullet *et al*[74]	148	OLT	Univariate and multivariate regression	> 8 units RBC and loss of > 1 blood volume	Preoperative Hb and Child-Pugh A protective for blood loss > 1 blood volume	
Esmat Gamil *et al*[43]	286	OLT	Univariate and multivariate logistic regression	> 6 units RBC	INR > 1.6, Ascites	
Li *et al*[60]	181	LDLT	Univariate and multivariate regression	> 6 units RBC	Platelet count < 70 × 10^9/L, Hb < 100 g/L, fibrinogen < 1.5 g/L and previous abdominal surgery	
Wu *et al*[75]	522	LDLT	Univariate and multivariate regression	Re-exploration for hemostasis	> 10 mL/kg FFP transfusion	
Varotti *et al*[76]	219	OLT	Univariate and multivariate regression	RBC transfusion requirements	MELD	
[77]	291	OLT (no malignancy or re-transplant)	Multivariate logistic regression	RBC transfusion requirements	Baseline Hb and Fibrinogen	
De Santis *et al*[78]	166	OLT "piggy back"	Univariate and multivariate regression	Blood product requirements	Child-Pugh, preoperative Hb and INR, graft ischemia time	
Cywinski *et al*[79]	804	OLT	Multivariate regression Bootstrapping for prediction model	RBC and cell saver requirement, > 20 and > 30 RBC units usage	MELD and preoperative platelet count	RBC + CS > 20 units c = 0.70 (RBC + CS > 30 units c = 0.67

OLT: Orthotopic liver transplantation; LDLT: Living donor liver transplantation; RBC: Red blood cells; GI: Gastrointestinal; RUQ: Right upper quadrant; UNOS: United Network for Organ Sharing; INR: International normalized ratio for prothrombin activity; FFP: Fresh frozen plasma; Hct: Hematocrit; Hb: Hemoglobin; PT: Prothrombin time; MELD: Model for End-Stage Liver Disease; CVP: Central venous pressure; AUC: Area under the curves.

levels of serum bilirubin, albumin, PT and the presence of ascites and encephalopathy to quantify of disease severity. Multiple studies have included the CTP score in multivariate analyses of factors associated with increased blood loss during liver transplantation with diverging results[44,60,68,78]. De Santis *et al*[78] found in a population of 166 "piggy-back" OLT that the CTP score together with haemoglobin and graft ischaemia time to be associated with blood and blood products transfusion requirements. A CTP class A was found to be a protective risk factor for bleeding more than one blood volume in a study including 148 OLT patients[74].

Multivariate analysis found an association between pre-operative MELD scores and blood products usage or massive blood loss in different liver transplant patient populations such as hepatitis B related cirrhosis[83], living donor[73], piggyback[70] and mixed OLT populations[76,79]. MELD was significantly associated with patients requiring the use of blood products, but failed to predict those requiring massive blood transfusions[79]. MELD was also a poor predictor of blood loss or blood transfusion requirements in a series of 350 patients with mean MELD scores of 20 ± 10[71]. It is important to note to mention that the reported mean transfusion requirement was only 0.5 ± 1.3 unit which is lower than the reported by other studies in similar populations[76].

Preoperative haemoglobin is an important predictor of blood transfusion in a number of multivariate models[42,60,66,70,72,77,83]. Preoperative haemoglobin of more than 12.6 g/dL was found to be a protective factor for blood loss of one blood volume or more in a series of 148 patients receiving OLT[74]. Thrombocytopenia pre-transplant is also associated with massive blood transfusion requirements[60,80].

Coagulation variables such as the INR and fibrinogen are predictors of blood loss and transfusion requirements. A cut-off INR of $\geqslant$ 1.6 was found to be predictor of > 6 units blood transfusion requirement in an study of 286 patients receiving OLT[43]. Preoperative INR values were also found to be independent predictors of risk for MBT in a study of 460 liver transplant recipients[42]. Fibrinogen levels below 1.5 g/dL were associated with increased risk for transfusion of > 6 units of RBC in living donor related transplant patients[60].

The presence of ascites was found to be predictive of a transfusion requirement of > 6 units RBC[43] and of high intraoperative blood loss (> 1000 mL)[73]. The development of ascites may serve as a marker of portal hypertension with an associated increase in collateral circulation and dilated blood vessels that may be transected during surgical dissection.

Models to improve prediction of blood loss and MBT requirements have been developed from preoperative risk predictor variables that are readily accessible to the clinician during the preoperative assessment. The McCluskey risk index for MBT includes seven preoperative variables: Age > 40 years, haemoglobin concentration ($\leqslant$ 10.0 g/dL), INR 1.2-1.99 and > 2), platelet count $\leqslant$ 70 × 10^9/L), creatinine (> 110 μmol/L for female subjects and > 120 μmol/L for male subjects,) and repeat transplantation. The model was internally validated achieving a high c statistic (0.79)[42]. External validation of the McCluskey index attained reasonable sensitivity (80%) and specificity (84.21%)[84]. However, more recently, Cywinski *et al*[79] also attempted to create a prediction model for intraoperative blood product requirements based on preoperative variables. The authors used several advanced statistical techniques to analyse data from 804 primary OLTs performed during a 9-year period. Although, they found a strong relationship between transfusion and postoperative mortality, the model proved to be an unreliable predictor of transfusion requirements[79].

Surgical factors

Advances in surgical techniques and experience have been crucial for the reduction in blood loss. The piggyback technique involves a single anastomosis of the donor vena cava to the recipient inferior vena cava and a shortened warm ischemic time[85]. Additionally, the preservation of the recipient's vena cava reduces the requirement for extensive resection of the retroperitoneum. Large case series of patients undergoing OLT using the piggyback technique report a reduction in transfusion requirements[86-88] compared with the classic technique or use of veno-venous bypass. Veno-venous bypass has been found to be an independent predictor for increased blood loss and transfusion requirements[44,89]. It is thought that the contact with the bypass circuits triggers fibrinolysis, haemolysis and platelet activation, thus impairing or worsening haemostasis. Despite the encouraging data from case series, a Cochrane review that included two trials with high risk of bias comparing the piggyback with the conventional method of liver transplantation did not find enough evidence to recommend or refute the use of the piggyback method[85].

MANAGEMENT OF MASSIVE BLOOD LOSS

Lessons from the Battlefield

Many of the developments in the management of the exsanguinating patient have come from the trauma literature and the experience gained by treating military casualties in the Iraq and Afghanistan wars. Haemorrhage is the leading cause of death in the first hour following traumatic injury and causes 40% of all trauma deaths[90]. Treatment of massive haemorrhage was historically concerned with restoration of the circulating volume using crystalloids until a transfusion trigger was met (commonly 6 g/L) after which packed red cells were to be given. Both British and American guidelines advised only giving FFP after the loss of approximately one blood volume and aiming for an INR < 1.5[34,91]. Coagulation abnormalities with trauma patients were thought to be as a result of closed head injury or iatro-

genic due to massive blood transfusion or excessive fluid resuscitation. Two papers from 2003 challenged this concept and demonstrated that patients presenting with major trauma commonly had a significant coagulopathy that was present before resuscitation had commenced and was an independent predictor of mortality[92,93]. This coagulopathy was termed acute coagulopathy of trauma.

Acute coagulopathy of trauma is characterised by ooze-type bleeding from mucosal regions, serosal surfaces and vascular access sites distinct from simple massive bleeding[94]. It consists of endogenous primary pathologies - disseminated intravascular coagulation (DIC) and acute coagulopathy trauma shock (ACOTS), and exogenous secondary pathologies that mimic DIC and ACOTS - hypothermia, acidosis, anaemia and dilutional coagulopathies[95]. Similarities between the pathophysiological changes that occur in liver transplantation have been discussed in a recent review on haemostasis in liver transplantation[96]. Derangements in thrombin-thrombomodulin-protein C system lead to anticoagulation in both trauma and liver transplantation patients[96]. Catecholamine release during traumatic injury is thought to directly damage the endothelium resulting in progressive de-endothelialisation. High levels of syndecan-1, a marker of endothelial degradation is association with inflammation, coagulopathy and increased mortality in trauma patients[97], and patients with end-stage liver disease have recently been demonstrated to have significantly higher levels than controls[98]. These levels are further elevated following graft reperfusion during liver transplantation.

MTPs with fixed ratios of red cells to plasma more closely approximating whole blood transfusions came to the fore following a retrospective analysis of United States army combat patients requiring massive transfusion. Those that were treated with a high plasma to RBC ratio had a significantly improved survival to hospital discharge compared with those treated with low ratio transfusion, primarily through decreasing death from haemorrhage[99]. These results led to a proliferation of studies reporting beneficial outcomes from high plasma:RBC ratio MTPs in trauma[100,101] as well as obstetrics[102,103]. Part of the benefit must be attributed to the decreased delay in obtaining blood products and improved communication between the laboratory and the team treating the patient. One criticism of the studies investigating MTPs is that they are largely retrospective before and after studies that are subject to survivor bias. Given the lack of high quality trials the Canadian National Advisory Committee on Blood and Blood products took the decision in 2011 that fixed ratio formula based care could not be recommended as a standard of care[104]. In an attempt to address these concerns two large concurrent prospective multicentre trials have been conducted in severely injured adult civilian trauma patients.

The observational trial PROMMTT, demonstrated reduced 30-d mortality in patients treated with a higher FFP/Platelet to red cell ratio early in resuscitation and went on to inform the design of the randomised control trial PROPPRR[105,106]. Here, while 30-d mortality was not improved in patients treated with a 1:1:1 ratio *vs* 1:1:2 (plasma:platelets:red cells), fewer patients died from exsanguination in the first 24 h[107]. Criticism of the use of fixed ration protocols cite the potential waste of blood products and the one-size fits all approach to massive haemorrhage. MTPs promote the early use of plasma and platelets, which might otherwise be delayed if waiting for conventional laboratory coagulation test results to guide treatment. The increasing availability of point of care (POC) haemostatic tests such as the viscoelastic assays, rotational thromboelastometry (ROTEM™) and thromboelastometry (TEG™), provide an alternative. Tapia *et al*[108] demonstrated that TEG™ guided resuscitation was superior to standardized MTP resuscitation of penetrating trauma patient and Karkouti *et al*[109] were able to demonstrate a significant reduction in transfusion rates for all blood products for patients undergoing cardiac surgery through a ROTEM™ based algorithm. Recent state of the art papers on the management of traumatic haemorrhage have viscoelastic tests integrated into MTPs[38,110-112]. In the presence of uncontrolled haemorrhage, fixed ratio transfusion packages are instigated converting to viscoelastic test-guided goal-driven resuscitation once bleeding slows[110]. While trials comparing fixed ratio-guided resuscitation with viscoelastic test-guided in liver transplantation are lacking it is usually a well-controlled procedure and most centres have access to POC coagulation monitors to guide transfusion, the fixed ration MTP's are possibly only required in the most uncontrolled of settings.

Fluid management

Another strategy to reduce blood loss is fluid restriction similar to liver resection surgery. However, excessive fluid restriction may have deleterious consequences including hemodynamic instability and postoperative renal impairment. Schroeder *et al*[113] conducted a retrospective record review comparing two liver transplant centres using "low" central venous pressure (CVP) (< 5 mmHg) and "normal" CVP (7-10 mmHg) targets during liver transplant. Even though transfusion rates were reduced, increased rates of postoperative renal failure and 30 d mortality were observed in the "low" CVP group.

Reduction of blood loss through maintenance of a low CVP must be balanced against adequate tissue perfusion. Static pressure measurements such as CVP are unreliable indicators of volume status and adequacy of organ perfusion[114]. Dynamic (pulse and stroke volume variation) and thermodynamic (Intrathoracic Blood Volume Index) have demonstrated superior performance compared to static pressure measurements in terms of volume status assessment and preload dependence prediction in critical care and perioperative settings[115]. Studies looking at the performance of dynamic parameters during liver transplant surgery have

produced mixed results[116,117] and their impact on liver transplantation outcomes requires further research.

Vasopressors

A variety of pharmacological agents can produce selective vasoconstriction of the splanchnic vascular bed and reduce portal blood flow. Vasopressin, octreotide and phenylephrine are examples of agents that have been studied as potential interventions for blood loss reduction during OLT. Use of low dose vasopressin (0.04 U/min) infusion during the dissection phase was associated with reduce blood loss compared with control group in a retrospective non randomised study of 110 OLT patients[118].

The effect of an octreotide infusion was studied in a randomised controlled trial of 79 patients undergoing OLT. The study found that an octreotide infusion was associated with an increased urine output during the operation compared to control, but it failed to show any significant difference in terms of blood loss or blood transfusion requirements[119].

Phenylephrine administration was found to be associated with decreased blood loss and lower lactate levels compared to patients receiving inotropes (dobutamine or dopamine) for cardiovascular support during liver transplant[120]. Phenylephrine was also found to be useful in restoring systemic arterial pressure following phlebotomy aimed at reduced portal venous pressure and thus blood loss during the dissection phase of OLT[121].

Transfusion thresholds and coagulation monitoring

There is significant variability among liver transplantation centres in methods of coagulation monitoring, transfusion triggers and transfusion protocols[24]. There is no evidence supporting specific haemoglobin or haematocrit triggers for packed RBC transfusion in OLT. However, data from other surgical and critical care populations indicates that transfusion strategies targeting lower perioperative haemoglobin levels are safe and can lead to a reduction in RBC transfusion. A transfusion threshold of 70 g/L for hemodynamically stable critically ill is suggested by data from the Transfusion Requirements in Critical Care trial[122]. The Transfusion Reduction Threshold Reduction Trial (TITRe2) compared the outcomes of a large population of cardiac surgical patients finding no evidence of harm with the use of a restrictive threshold of 75 g/L compared with a "liberal" threshold of 90 g/L[123]. Similarly, results from a randomized surgical trials of hip surgery patients with pre-existing cardiovascular disease indicate that a restrictive RBC transfusion strategy is not associated with harm[124]. Some guidance can also be extrapolated from a randomize study performed in the setting of severe acute gastrointestinal bleeding excluding massive exsanguinating bleeding, concurrent acute coronary syndrome, stroke or peripheral vascular disease. All patients received endoscopic and treatment for bleeding within 6 h if required. Patients were randomized to a "liberal" RBC transfusion threshold of 90 g/L or "restrictive" of 70 g/L. Thirty-one percent of patients in both groups had cirrhosis and bleeding was due to oesophageal varices in 21% of the patients. The authors observed improved mortality rates, reduced risk of further bleeding, and less complications such as pulmonary oedema, in patients randomised to the restrictive strategy.

There is some evidence that erythrocytes stimulate thrombin generation and play a concentration dependant role in accelerating the initial coagulation reaction[125]. Therefore, higher haemoglobin concentrations may be desirable during acute bleeding associated with hemodynamic instability.

Blood loss during liver transplant surgery can occur in a slow and protracted manner or can be rapid and cause severe hemodynamic instability limiting the applicability of haemoglobin thresholds. During exsanguinating blood loss transfusion should be guided by the rate of bleeding and the likelihood of surgical control: Guided by transfusion indicators and POC testing where possible and guided by fixed ratio transfusion of RBC, plasma and platelets when bleeding is acute and time does not permit real time assessment of the coagulation status.

Viscoelastic tests of coagulation (TEG™, ROTEM™) provide a dynamic picture of the interaction of the whole blood coagulation and fibrinolytic systems. Viscoelastic methods have faster turnaround times compared to traditional tests and are POC or bedside tests, performed in close proximity to the patient in the operating room or critical care areas.

The use of POC viscoelastic methods of coagulation monitoring and their inclusion in blood and blood products transfusion algorithms has been found to be associated with reduced blood and blood products requirements in cardiac surgery[126]. A Cochrane review including 9 RCTs concluded that the use of ROTEM™ or TEG™ to guide transfusion strategies in patients with massive bleeding appears to reduce the amount of bleeding and requirement for blood and blood products, but found no evidence of benefit in terms of morbidity and mortality[127].

Another Cochrane review studying interventions to reduce blood loss in liver transplantation analysed two randomised studies using thromboelastography in liver transplant populations[128]. The studies were both single centre and included a population of adults undergoing OLT[129,130]. The authors concluded that thromboelastography-guided transfusion was associated with a reduction in FFP transfusion requirements but had no impact on 3-year survival rates, RBC or platelet transfusion requirements. The trials were however deemed to have a high risk of bias by the Cochrane reviewers.

Viscoelastic tests can detect the presence and degree of fibrinolysis at different stages of the transplant procedure and can be used effectively to guide the need

for and response to anti-fibrinolytic therapy[131].

Antifibrinolytics

There are 2 major classifications of antifibrinolytic agents, the lysine analogues [aminocaproic acid, Amicar and cyclokapron, tranexamic acid (TXA)], and the trypsin inhibitor (aprotinin, Trasylol). Hyperfibrinolysis may lead to significant blood loss due to diffuse microvascular bleeding, however, much of the fibrinolysis is self-limiting which might help to explain why our ability to predict massive transfusion is difficult and it calls into question the routine prophylactic use of antifibrinolytic therapy. In most circumstances the risk of thromboembolic complications with an antifibrinolytic is low providing an excellent therapeutic index, but in liver failure our inability to identify thromboembolic risk is also limited[132] and therefore the judicious use of these agents is recommended. Patients with a prothrombotic state, such as primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, portal vein thrombosis and Budd-Chiari syndrome, may be at particularly increased risk of thromboembolic complications.

In 1987 Royston demonstrated a dramatic reduction in blood loss with aprotinin in patients under undergoing repeat open heart surgery and its use in cardiac surgery was approved by the Food and Drug Administration in 1993. Concerns regarding an increased risk of renal dysfunction were raised in several observational trials[133,134]. The publication of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) trial raised additional concerns where patients undergoing high risk cardiac surgery were shown to have a significantly higher 30-d mortality when given aprotinin *vs* tranexamic acid or aminocaproic acid[135] led to its licence being withdrawn in a number of countries. A number of concerns regarding the methodology of the BART trial have subsequently been raised and a review by Health Canada found that the trial was too small to reliably assess mortality and concluded that the benefits of aprotinin outweighed it's risks[136]. Studies investigating the aprotinin ban on blood loss in liver transplantation give mixed results with both an increase in blood transfusion rates following its withdrawal[137] and no change[138] being reported.

Several systematic reviews have investigated the use of antifibrinolytics in liver surgery. A recent Cochrane review focused on methods to decrease blood loss and transfusion requirements in liver resection surgery including 33 trials involving 1913 patients with interventions comparing aprotinin *vs* control, TXA *vs* control and TXA *vs* aprotinin[139]. There was no significant difference in 60-d mortality or thromboembolic episodes and while aprotinin was associated with a significantly lower allogenic blood transfusion requirements, it did not confer any outcome benefit. Importantly, the reviewers deemed all the trials to have high risk of bias thus further weakening the strength of the conclusions[139].

In liver transplantation recipients a systematic review and meta-analysis of 23 studies including 1407 patients analysed the effect of either TXA or aprotinin on blood loss, transfusion requirements and incidence of thromboembolic[132]. Blood loss and transfusion requirements were lower with TXA compared to controls, but the thromboembolic risk was unchanged in groups of patient receiving anti-fibrinolytic therapy[132].

In OLT, thromboembolic events are relatively rare and as such trials studying TXA lack statistical power to detect clinically significant important increases on thromboembolic risk[140]. However, it would be prudent to treat with TXA only in presence of fibrinolysis, observed clinically as microvascular bleeding or evidenced by POC test such as TEG™ or ROTEM™. Routine used is no longer recommended in international guidelines[141] and should be carefully considered in patients at risk of thromboembolic complications.

Cell salvage

Intraoperative cell salvage has been adopted in a variety of surgical settings in an effort to reduce allogeneic blood transfusion rates and thus potential complications and cost associated with the transfusion of allogeneic blood[142]. Controversy exists surrounding the use of cell salvage in liver transplantation. The washed RBCs are devoid of clotting factors and platelets and there is potential for accumulation of fibrinolytic factors released by the processed RBC or the transplanted liver. Older studies appeared to substantiate these concerns suggesting that transfusion of salvaged blood was associated with increase blood loss and requirement for blood products[143]. The cost effectiveness of cell salvage has also being questioned[144]. More recent studies have demonstrated the efficacy of cell salvage in reducing the need for allogeneic blood transfusion for both OLT[145] and living donor liver transplantation[146]. The cost effectiveness of cell salvage was also established in a large prospective study including 660 liver transplant patients where a total cost saving of $188618 United States dollars was achieved over the study period[147].

Malignant disease is a relative contraindication for cell salvage due to the risk of metastasis arising from cancerous cells that are not eliminated by the cell salvage process. Intraoperative cell salvage has however been used in the setting of hepatocellular carcinoma with no apparent increase in recurrence rates[148]. Leucocyte depletion filters incorporated into cell salvage circuits have shown to effectively remove malignant cells when used during liver transplantation of patients with non-ruptured hepatocellular tumours[149].

Bacteria can contaminate salvaged red cells when suctioned blood is mixed with biliary, bowel secretions or is in contact with the skin. A study analysing bacterial contamination of salvaged blood during liver transplant found that even though micro-organisms can be observed in to up to 70% of the processed and reinfused units, none of the postoperative blood cultures revealed growth of the same micro-organisms[150]. It is however, advisable to avoid aspiration of blood after initiation

of the biliary anastomosis stage of the liver transplant procedure.

CONCLUSION

The management of bleeding associated with liver transplantation remains an important area of investigation and no one change in clinical practice will have a dramatic impact. What is required is a concerted effort including the identification of patients at risk for massive blood loss, POC evaluation of medically manageable bleeding, and cost effective blood conservation strategies designed specifically for each patient. The beneficiaries of our efforts will be the transplant recipients in prolonged disease free survival and our health care systems in reduce cost per patient by both reducing blood product utilization and hospital length of stay.

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