



The Effect of Surgical Technique and Portal Hypertension on Operative Blood Loss in Recipients Receiving Liver Transplantation

Lars Cornelis Pietersen^{1*}, Elise Sarton², Carla van Rijswijk³, Maarten Tushuizen ME⁴, Hein Putter⁵, Hwai-Ding Lam¹, Andrzej Baranski¹, Ian Alwayn¹, Andries Erik Braat¹ and Bart van Hoek⁴

¹Department of Surgery, Leiden University Medical Center, The Netherlands

²Department of Anesthesiology, Leiden University Medical Center, The Netherlands

³Department of Radiology, Leiden University Medical Center, The Netherlands

⁴Department of Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands

⁵Department of Medical Statistics, Leiden University Medical Center, The Netherlands

Abstract

Background: Liver cirrhosis can cause Portal Hypertension (PH) by increased intrahepatic vascular resistance. Recipients with PH have an increased perioperative bleeding risk in orthotopic Liver Transplantation (LT). Temporary Portocaval Shunts (TPCS) and initial Arterial Reperfusion (IAR) have been introduced as techniques to reduce perioperative blood loss in LT. However, the beneficial effect of both techniques is still controversial and little is known about the use of both techniques in recipients with versus without PH. The aim of this study was to evaluate the effect of a TPCS and IAR in LT on perioperative blood loss in patients with PH (PH group) and without PH (no-PH group).

Methods: Perioperative transfusion requirement of packed Red Blood Cells (RBC) was used as a surrogate marker for perioperative blood loss. Between January 2005 and May 2017 all orthotopic, first LTs (n=214) performed in a single center were retrospectively analyzed.

Results: Multivariate analysis in the no-PH group showed that using a TPCS significantly decreased perioperative blood loss (p=0.01). Instead, in the PH group, using IAR significantly decreased perioperative blood loss (p<0.001).

Conclusion: Using IAR in LT significantly decreases perioperative blood loss in recipients with PH, whereas in recipients without PH a TPCS leads to significantly less perioperative blood loss. Therefore, the use of these techniques, potentially both or depending on presence of PH could be considered in patients receiving LT.

Keywords: Reperfusion; Portosystemic shunt; Liver transplantation; Surgical blood loss; Portal hypertension

Abbreviations

BAR: Balance of Risk; CIP: Cold Ischemic Period; DBD: Donation after Brain Death; DCD: Donation after Circulatory Death; DRM: Donor-Recipient Model; ET-DRI: Eurotransplant Donor Risk Index; FFP: Fresh Frozen Plasma; LabMELD: Laboratory Model for End-Stage Liver Disease; LT: Liver Transplantation; LUMC: Leiden University Medical Center; MELD: Model for End-Stage Liver Disease; PTT: Partial Thromboplastin Time; RBC: Red Blood Cell; SD: Standard Deviation; sRRI: simplified Recipient Risk Index; TPCS: Temporary Portocaval Shunt; WIP: Warm Ischemic Period

Introduction

Liver cirrhosis can cause Portal Hypertension (PH) by increased intrahepatic vascular resistance leading to the development of a congested splanchnic vascular bed. Portal hypertensive related complications, such as bleeding from esophageal varices, spontaneous bacterial peritonitis in relation with ascites and bacterial translocation, kidney failure from hepatorenal syndrome and aspiration

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*Correspondence:

Lars C Pietersen, Department of Surgery, Division of Transplantation, Leiden University Medical Center, Albinusdreef 22333 ZA, Leiden, The Netherlands, Tel: +31-71-5266188;

Fax: +31-71-5266952;

E-mail: L.C.Pietersen@lumc.nl

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related to hepatic encephalopathy, can be fatal if left untreated [1]. The most accurate technique to evaluate PH is by measuring the Hepatic Venous Pressure Gradient (HVPG) [2]. Hepatic venous pressure gradient can be measured via the hepatic vein by subtracting the Free Hepatic Venous Pressure (FHVP) from the Wedged Hepatic Venous Pressure (WHVP). The technique of hepatic vein catheterization with measurement of the HVPG has been proven safe and reproducible and is therefore seen as the gold standard [3]. An HVPG ≥ 10 mmHg is considered as PH. These patients have a significantly higher probability of developing decompensated cirrhosis [4,5] and esophageal varices [6]. In order for variceal bleeding to occur, an HVPG ≥ 12 mmHg is usually required and reduction of HVPG below this threshold value virtually abolishes the risk of bleeding [7].

The only curative treatment for patients with end-stage liver disease, in most cases decompensated cirrhosis, is Liver Transplantation (LT). Historically, LT has been associated with massive blood loss and considerable transfusion requirements due to PH, but also with associated coagulopathy and Technical Issues [8]. Differences in perioperative blood transfusion requirements in LT are associated with short- and long-term morbidity and patient survival [9-13].

Several surgical techniques, such as a Temporary Portocaval Shunt (TPCS) and Initial Arterial Reperfusion (IAR), have been introduced to limit perioperative blood transfusion requirements in LT. The use of these techniques in LT has been analyzed with conflicting results [14-21]. All these studies do not differentiate between recipients with and without PH.

Therefore, the aim of this study was to evaluate individual determinants for perioperative blood loss, defined as perioperative transfusion of packed Red Blood Cells (RBC), in patients undergoing LT with PH or without PH, as determined by HVPG measurement.

Materials and Methods

All LTs at the Leiden University Medical Center (LUMC), Leiden, the Netherlands, performed between January 2005 and May 2017, when preoperative HVPG measurement was routine, were included. Recipients who received a combined organ, domino, split, auxiliary LT, or retransplantation were excluded from analysis. Recipients underwent standard screening, which included HVPG measurement, abdominal CT, abdominal ultrasound and esophagogastrosocopy. Recipients who did not receive HVPG measurement due to complete portal thrombosis or had received a Transjugular Intrahepatic Portosystemic Shunt (TIPS) were excluded from further analysis. Clinical information was obtained from a prospectively collected database. Covariates included donor demographics, recipient demographics, pretransplant information, intraoperative data, and postoperative outcome. Calculated Model for End-Stage Liver Disease (MELD) scores were included in the recipient analysis.

The Eurotransplant Donor Risk Index (ET-DRI), simplified Recipient Risk Index (sRRI), combined Donor-Recipient Model (DRM) and Balance of Risk (BAR) score were calculated as described previously [22-24].

Definition of portal hypertension

For the purpose of this study, portal hypertension was defined as an HVPG ≥ 12 mmHg, since patients with this HVPG are at highest risk of developing variceal bleeding, and reduction of HVPG below this threshold virtually abolishes the risk of variceal bleeding [7].

Additionally, a sensitivity analysis was performed with PH defined as HVPG ≥ 10 mmHg.

Definition of blood loss

Blood loss was defined as the need for transfusion of RBCs during the first 24 h after start of surgery. Moreover, cell saver volume and Fresh Frozen Plasma (FFP) transfusion were also noted.

Operative techniques recipient surgery

Since May 2010, prior to mobilization and removal of the native liver, a TPCS was performed as standard protocol. After hilar dissection, a TPCS was created by an end-to-side anastomosis of the recipient's portal vein (splanchnic side) to the inferior vena cava at the level of the renal veins. After insertion of the liver graft, a side-to-side caval anastomosis was performed as described previously [25]. Shortly after the introduction of a TPCS, IAR was introduced. In the historic control group, the portal anastomosis and reperfusion were followed by arterial anastomosis and reperfusion, whereas, since the change in protocol, the arterial anastomosis and reperfusion was followed by portal anastomosis and reperfusion. If a TPCS was used, it was divided just before portal reconstruction, using a vascular endo-GIA stapling device (Medtronic, Minneapolis, MN, USA), after which a standard end-to-end portal anastomosis was performed. Finally, biliary reconstruction was performed, preferably with a duct-to-duct anastomosis.

Statistical analysis

Continuous variables were presented as mean, or median, and Standard Deviation (SD), whereas categorical variables were presented as number and percentage. Univariate analysis between the groups was performed using Student's t-test, chi-square test, or Mann-Whitney U test, where applicable. Possible individual covariates on perioperative transfusion of RBCs were included in a logistic regression analysis with backward selection. A p-value of less than 0.05 was considered significant. Statistical analyses were performed using SPSS software version 25.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

In total, 365 patients received a LT between January 2005 and May 2017. Of these, 151 recipients were excluded (domino, split, or auxiliary LT; n=18), (combined organ transplantation; n=13), (retransplantation; n=43), (high-urgency listing; n=41), (presence of a TIPS; n=27), (complete portal vein occlusion; n=6), (missing values on HVPG; n=3). Of the 214 recipients included in the study, 151 (71%) had PH. Sixty-three recipients (29%) did not have PH.

Donor, transplant and recipient characteristics

Table 1 shows the basic donor, transplant and recipient characteristics of both groups. The mean Balance of Risk (BAR) score (4.5 vs. 5.8; p=0.02), and laboratory Model for End-Stage Liver Disease (labMELD) (12 vs. 15; p=0.02) were significantly lower in the no-PH group. The mean operative time (skin-to-skin) between both groups did not significantly differ (334 min vs. 331 min; p=0.87).

Blood loss

Table 2 shows the hematological, coagulation, and transfusion parameters in both groups. The mean INR before surgery (1.2 vs. 1.4; p=0.04) and mean Partial Thromboplastin Time (PTT) before surgery (16.9 vs. 19.2; p=0.01) were significantly lower in the no-PH group. The mean platelet count before surgery ($151 \times 10^9/L$ vs. $99 \times$

Table 1: Donor, transplant and recipient characteristics. Data are presented as mean \pm SD.

	No-PH group (n=62)	PH group (n=152)	P
Donor age (years)	47 \pm 15	47 \pm 15	0.89
Donor sex (female %)	45%	53%	0.3
Recipient age (years)	54 \pm 11	54 \pm 11	0.12
Recipient BMI (kg/m ²)	27 \pm 5	27 \pm 4	0.64
Recipient sex (female%)	31%	22%	0.22
Medical history (%)			
Metabolic disease	10%	3%	0.09
Cholestatic liver disease	26%	11%	0.01
Alcoholic liver disease	13%	20%	0.3
Malignancy	42%	42%	1
Hepatitis B	2%	4%	0.56
Hepatitis C	2%	7%	0.67
Other cirrhosis	3%	7%	0.04
Other/ unknown	3%	5%	1
ET-DRI	1.79 \pm 0.3	1.85 \pm 0.3	0.45
sRRI	1.81 \pm 0.4	1.91 \pm 0.5	0.06
DRM	1.38 \pm 0.1	1.40 \pm 0.1	0.12
BAR score	4.7 \pm 2.7	5.5 \pm 3.6	0.01
LabMELD	12 \pm 7	15 \pm 7	0.02
Portal vein flow (hepatopetal %)	100%	88%	0.004
Collaterals seen on CT (%)	44%	84%	<0.001
Splenomegaly (%)	56%	73%	0.02
Esophageal varices (%)	53%	81%	<0.001
Liver grafts (DCD %)	37%	45%	0.29
Cold ischemic period (minutes)	550 \pm 116	549 \pm 117	0.65
Warm ischemic period (minutes)	37 \pm 15	36 \pm 9	0.68
Operative time (minutes)	338 \pm 102	328 \pm 72	0.8

SD: Standard Deviation; ET-DRI: Eurotransplant Donor Risk Index; sRRI: simplified Recipient Risk Index; DRM: Donor Risk Model; BAR score: Balance of Risk Score; LabMELD: Laboratory Model for End-Stage Liver Disease Score; No-PH: no-Portal Hypertension; PH: Portal Hypertension

10⁹/L; p=0.002) and mean level of fibrinogen before surgery (3.8 g/L vs. 2.7 g/L; p=0.04) were significantly higher in the no-PH group. The median number of perioperatively transfused packed cells (p=0.13), median number of perioperatively transfused Fresh Frozen Plasma (FFP) (p=0.62) and median volume of Cell Saver transfused (p=0.30) did not significantly differ between both groups.

Multivariate analysis

Multivariate analysis in the no-PH group, including all covariates, showed that the use of a temporary portocaval shunt was independently associated with significantly less transfusion of RBCs (p=0.01). Furthermore, lower recipient BMI also resulted in significantly less transfusion (p=0.03). All other potential confounders did not show a significant difference (Table 3).

In the PH group, multivariate analysis including all covariates showed that the use of initial arterial reperfusion was independently associated with significantly less transfusion of RBCs (p=0.001). Furthermore, the number of platelets before surgery (p=0.01), as well as the labMELD (p=0.003) were identified as individual determinants in the number of perioperatively transfused packed cells. All other

Table 2: Hematological, coagulation, and transfusion parameters before, during and after surgery. Data are presented as mean, or median \pm SD.

	No-PH group (n=62)	PH group (n=152)	P
INR before surgery	1.2 \pm 0.3	1.4 \pm 0.5	0.02
Platelet count before surgery (10⁹/L)	120 \pm 75	94 \pm 57	0.002
PTT before surgery (seconds)	16.7 \pm 4.2	19.2 \pm 7.0	0.01
Fibrinogen before surgery (g/L)	4.1 \pm 5.7	2.7 \pm 1.1	0.04
Packed Cells (units)	3.0 \pm 5.8	4.0 \pm 5.7	0.18
Fresh Frozen Plasma (units)	9.0 \pm 7.1	8.0 \pm 8.5	0.42
Cell Saver (mL)	1203 \pm 985	1105 \pm 1222	0.42

No-PH: no-Portal Hypertension; PH: Portal Hypertension; PTT: Partial Thromboplastin Time

Table 3: Multivariate analysis on perioperative transfusion of RBCs in the no-PH group, by using logistic regression with backward selection.

	B	Std. Error	P	Eliminated in model
(Constant)	1.38	0.78	0.09	
Initial Arterial Reperfusion	-0.39	0.27	0.16	10
Temporary Portocaval Shunt	-0.64	0.23	0.01	
Recipient age (years)	-0.02	0.01	0.09	11
Recipient BMI (kg/ m²)	0.06	0.03	0.03	
Platelet level before surgery (10 ⁹ /L)	0	0	0.07	11
Initial Arterial Reperfusion * Temporary Portocaval Shunt			0.39	

Donor sex, ET-DRI, recipient age (years), recipient sex, LabMELD, collaterals (yes/no), splenomegaly (yes/no), esophageal varices (yes/no), HVPG (mmHg) and fibrogen level before surgery (mg/dl) were eliminated in previous models

No-PH: No Portal Hypertension; ET-DRI: Eurotransplant Donor Risk Index; labMELD: Laboratory Model for End-Stage Liver Disease; HVPG: Hepatic Vein Pressure Gradient

Initial arterial Reperfusion * Temporary Portocaval Shunt=Interaction between Initial Arterial Reperfusion and a Temporary Portocaval Shunt

Table 4: Multivariate analysis on perioperative transfusion of RBCs in the PH group.

	B	Std. Error	P	Eliminated in model
(Constant)	0.72	0.72	0.32	
Initial Arterial Reperfusion	-0.53	0.14	<0.001	
Temporary Portocaval Shunt	-0.06	0.24	0.81	2
Recipient BMI (kg/ m ²)	-0.02	0.01	0.15	10
Platelet level before surgery (10⁹/L)	0	0	0.02	
LabMELD	0.03	0.01	<0.001	
Collaterals	0.43	0.2	0.03	
Fibrinogen level before surgery (mg/dl)	-0.14	0.07	0.051	
Initial Arterial Reperfusion * Temporary Portocaval Shunt			0.47	

Donor sex, ET-DRI, recipient sex, splenomegaly (yes/no), esophageal varices (yes/no) and HVPG (mmHg) were eliminated in previous models

PH: Portal Hypertension; ET-DRI: Eurotransplant Donor Risk Index; labMELD: Laboratory Model for End-Stage Liver Disease; HVPG: Hepatic Vein Pressure Gradient

Initial arterial Reperfusion * Temporary Portocaval Shunt=Interaction between Initial Arterial Reperfusion and a Temporary Portocaval Shunt

potential confounders did not show a significant difference (Table 4). When repeating the analysis with an HVPG cut-off \geq 10 mmHg, no difference in results was seen (Figure 1).

Discussion

This cohort study demonstrates that performing a TPCS in LT had a significant benefit on perioperative blood

loss in recipients without PH, while in patients with PH IAR had a significant benefit on perioperative blood loss. Although at first thought the beneficial use of a TPCS in recipients without PH (and not beneficial in recipients with PH) may seem counterintuitive, a possible explanation for this could be the presence of spontaneous portosystemic shunts in recipients without PH. These natural shunts could lead to reduced splanchnic congestion during the clamping of the portal vein, thereby working as a 'natural' TPCS. In recipients without PH, the absence of natural shunts could lead to increased splanchnic congestion during clamping of the portal vein and increased blood loss. Therefore, in these recipients, a TPCS could be of value to reduce perioperative blood loss.

Several studies have analyzed the effect of a TPCS, with contrary results [9-13]. A meta-analysis by Pratskche et al. [26] included six studies with Donation after Brain Death (DBD)-LT. The combined effect of all six studies suggests a lower transfusion requirement for the TPCS group ($p=0.03$). However, the authors remark was that for RBC requirement the I^2 values indicated substantial heterogeneity among the studies ($p<0.05$), which could bring a potential bias to the results. Furthermore, these studies do not describe the HVPG prior to transplantation. The only prospective study that has been performed on this subject [27] did not show a significantly beneficial effect of TPCS on the number of RBCs transfused. However, that study did not stratify for recipients with or without PH.

Another interesting finding in this study was the significant beneficial effect of IAR in recipients with PH. A possible explanation could be that the hepatic artery accounts for less blood volume that perfuses the liver leading to a more controlled reperfusion and quicker and easier hemostasis after reperfusion, resulting in less blood loss.

The beneficial effect of IAR in LT has also been debated in literature. A Cochrane review by Gurusamy et al. [28] included three relatively small randomized studies comparing RBCs transfusion between IAR and IPR [17-19]. This review did not show a statistically significant difference in the number of RBCs transfused, nor in the number of platelets, or FFP transfused. Also, these studies did not stratify for recipients with or without PH. In this study, we chose to use an HVPG ≥ 12 mmHg as cut-off value for PH, since patients with this HVPG are at highest risk of developing variceal bleeding, and reduction of HVPG below this threshold virtually abolishes the risk of variceal bleeding [7]. When repeating the analysis with an HVPG cut-off ≥ 10 mmHg, no difference in results was seen (Figure 1). Although in most LTs with TPCS this was done in combination with IAR, there was no significant interaction between the two techniques.

In the PH-group, the numbers of platelets before surgery, as well as the labMELD were individual determinants in the number of transfused packed cells. Since recipients without PH on average had better liver function, these determinants were not significant in the no-PH group.

In the no-PH group, recipient BMI was also a statistically significant risk factor for blood loss. The relationship between BMI and intraoperative blood loss has been described previously [29]. Obesity could perioperatively lead to a more difficult view of the surgical site, thereby increasing blood loss.

This study has some potential limitations. First, the retrospective character could bring a potential bias. Second, a large number of

recipients were excluded due to various criteria, which caused a lower total number of recipients included in this study. However, the number of 251 included recipients was sufficient to identify statistically significant differences. Due to the retrospective character of the study, it is possible that small changes in protocol have occurred during the study period, even though to our knowledge this is not the case. The major changes in protocol were the use of a TPCS and IAR. Furthermore, all relevant factors were included in the multivariate analysis in order to correct for these.

Strength of this study is that the gold standard HVPG is used for defining portal hypertension. Also, this study included both DBD and Donation after Circulatory Death (DCD) -LT, thereby giving an accurate representation of current clinical practice.

Even though both surgical techniques (TPCS and IAR) only significantly reduced blood loss in one group, using either technique or the combination of both techniques did not lead to a significant difference in mean operative time. The combination could be considered when performing LT. In our experience, the use of a TPCS facilitates access and prevents splanchnic congestion during arterial anastomosis, when performing IAR.

In conclusion, the use of a TPCS in orthotopic LT significantly reduces perioperative blood loss in patients without PH, whereas initial arterial reperfusion significantly reduces perioperative blood loss in patients with PH. Therefore, the use of these techniques, depending on presence of PH, could be considered in patients receiving LT. Alternatively, a combination of both techniques can be used, regardless of the presence of PH, in order to decrease perioperative blood loss.

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