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Association of Phlebotomy on Blood Product Transfusion Requirements During Liver Transplantation: An Observational Cohort Study on 1000 Cases

Luc Massicotte, MD,[1] Zoltan Hevesi, MD,[2] Cédrick Zaouter, MD,[1] Lynda Thibeault, MD,[3] Pierre Karakiewicz, MD,[4] Louise Roy, MD,[5] and André Roy, MD[6]

Background. During the past 2 decades, transfusion requirements have decreased drastically during orthotopic liver transplantation (OLT), and transfusion-free transplantation is nowadays increasingly common. Understanding that liberal intravenous volume loading in cirrhotic patients may have detrimental consequences is key. In contrast, phlebotomy is a method to lower central venous pressure and portal venous pressure. The objective of this study was to determine the effectiveness and safety of phlebotomy in the early phase of blood transfusion, blood loss, renal function, and mortality. **Methods.** The present study evaluated the impact of phlebotomy on bleeding, transfusion rate, renal dysfunction, and mortality in 1000 consecutive OLTs. Two groups were defined and compared using phlebotomy. Multivariate logistic and linear regression models were used to determine predictors of bleeding, red blood cell (RBC) transfusion, renal dysfunction, and mortality. **Results.** A mean of 0.7 ± 1.5 RBC units was transfused per patient for 1000 OLTs, 75% did not receive any RBCs, and the median and interquartile range (25–75) were 0 for all blood products transfused. The phlebotomy was associated with decreased transfusion (RBCs, plasma, platelets, cryoprecipitate, albumin), with less bleeding, and with an increased survival rate, both 1 mo and 1 y. Phlebotomy was not associated with renal dysfunction. **Conclusions.** The practice of phlebotomy to lower portal venous pressure was associated with reduced blood product transfusions and blood loss during liver dissection without deleterious effect on renal function.

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INTRODUCTION

A significant decrease in blood loss and blood product requirements has been observed during orthotopic liver transplantation (OLT) during the past 2 decades.[1–4] This achievement could be explained through the increasing experience, improvements in surgical and anesthetic techniques, and a better understanding of the various hemostatic abnormalities encountered during OLT.

Transfusion of blood products is associated with mortality and morbidity.[5–10] To reduce bleeding and transfusion of blood products, one must understand the physiology and coagulation abnormalities associated with cirrhosis. Patients with cirrhosis and portal hypertension have an altered blood volume distribution.[11,12] The cirrhotic liver causes a blood flow impediment in the portal vein and an increased secretion of compensatory vasoactive substances that increases splanchnic pooling.[12,13] The

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[1] Anesthesiology Department, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[2] Anaesthesiology Department, University of Wisconsin, Madison, WI.

[3] Epidemiology Department, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[4] Urology Division, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[5] Internal Medicine Department, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[6] Hepatobiliary Division, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

Correspondence: Luc Massicotte, MD, Anesthesiology Department, Centre Hospitalier de l'Université de Montréal, 1000, St-Denis, Montreal, QC H2X 0C1, Canada. (luc.massicotte@umontreal.ca).

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conventional strategy for optimizing cardiac output was limited to generous intravenous fluid administration (crystalloid, colloid, plasma)—to maintain arterial pressure and end-organ perfusion—during periods of caval compression and clamping. This approach has been increasingly questioned and replaced on the basis of our improved understanding of the physiology of end-stage liver disease.[14] This hypothesis may partly explain the decreased need for blood transfusion when a low central venous pressure (CVP) is maintained.[2] In our previous study, a low CVP was achieved by phlebotomy and adhering to restrictive fluid management before the anhepatic phase. The phlebotomy consisted of withdrawing blood from the introducer of the pulmonary artery catheter without any crystalloid or colloid volume replacement at the beginning of the case while CVP was monitored. Avoiding hemodilution led to a preservation of the coagulation factors level. Typically, because portal venous pressure cannot be measured reliably intraoperatively, CVP is often used as a surrogate measure.[15] Fluid restriction to reduce portal congestion requires liberal use of vasopressors, and the concern of systemic—and especially renal—hypoperfusion is often raised; but, unfortunately, there are a limited amount of data available on this issue, and the published evidence is contradictory.[6,16]

The primary outcome of this study was to confirm the short-term effect of the phlebotomy on blood product requirements in adult liver transplant recipients (on a larger scale than our previous 100 patients). The secondary objectives were to study the influence of phlebotomy on bleeding, renal dysfunction, and survival. Our hypothesis was that phlebotomy would decrease transfusion rate and blood loss and would be associated with an increased survival, potentially at the expense of renal function.

MATERIALS AND METHODS

Design

An observational cohort study was conducted on 1000 consecutive patients undergoing liver transplantation at the Centre hospitalier de l'Université de Montréal from October 2002 to May 2019 without any exclusion. This observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.[17] An informed and written consent was not necessary according to our review ethics board (REB#15.113).

Intraoperative Management

Coagulation disorders diagnosed from conventional tests were not treated preemptively with blood products in the absence of overt bleeding either before or at the time of transplantation. Such disorders were only treated if diffuse intraoperative nonsurgical bleeding was observed: plasma was transfused if the international normalized ratio (INR) value was >1.5 (at a dose of 10–15 mL/kg), platelets if platelet count was $<30 \times 10^9$/L (at a dose of 1 apheresis of a pool of 5 units), and cryoprecipitate if fibrinogen was <2 g/L (at a dose of a pool of 5 units). Red blood cell (RBC) units were transfused when hemoglobin (Hb) concentration was between 60 and 70 g/L. The first 300 patients received aprotinin[18] as an antifibrinolytic, and the last 700 received tranexamic acid (30 mg/kg as a bolus and 16 mg/kg/h as an infusion until graft reperfusion).[19] All livers were procured from brain death donors.

Anesthesiologists have attempted to lower CVP by about 33% using phlebotomy (7–10 mL/kg) and by restricting volume infusion or a combination of both techniques, as previously described.[2,20] CVP was monitored from the pulmonary artery catheter. Criteria for phlebotomy were an Hb concentration >85 g/L and a normal renal function (baseline creatinine value ≤104 μmole/L). This technique was well described in previous reports.[2] No venovenous bypass was used, and >96% of the transplantations were performed using a total vena cava replacement technique. Transesophageal sonography was not used except for very few cases, neither rotational thromboelastometry.

Data Collection, Exposures, and Outcomes

Baseline population characteristics, including baseline laboratory values, and intraoperative and postoperative data were prospectively collected with a standardized report form during and after each OLT. Collected intraoperative data included duration of surgery, baseline and preanhepatic CVP, volume of fluid resuscitation, type of fluid used, volume of phlebotomy performed, blood products transfused, volume of cell saver reinfused, and intraoperative bleeding. Mortality at 1 mo and 1 y was collected. Renal dysfunction was evaluated with acute kidney injury (AKI) score (0 = increase creatinine <1.5 times from baseline, 1 = increase between 1.5 and 1.9 times from baseline, 2 = increase between 2.0 and 2.9 times from baseline, 3 = increase ≥3 times from baseline) at day 2 and 7 postoperatively. The incidence of continuous venovenous hemodialysis (CVVH) and hemodialysis was evaluated at day 7 (data were collected only for the last 486 OLTs, data retrieval for the first 514 OLTs was not possible because data were not numerized).

The outcomes of interest were the quantity of blood products transfused intraoperatively (RBC, plasma, platelets, cryoprecipitate, and albumin) total blood lost (measured from the cell saver minus irrigating fluid plus sponges), mortality at 1 mo and 1 y, renal dysfunction (AKI at day 2 and 7), and incidence of CVVH and hemodialysis at day 7 from patients who benefited from phlebotomy and the ones who did not.

Statistical Analysis

Continuous variables are reported as means with standard deviations or medians with interquartile range for skewed distributions and discrete variables as proportions. Univariate mixed logistic regression models were used to assess the association of a total of 22 variables with (1) transfusion of ≥1 RBC units; (2) blood loss (binary using the median, 900 mL); (3) blood loss (continuous variable); (4) AKI at day 2 (binary, no = AKI score 0, yes = AKI score (1 + 2 + 3)); (5) AKI at day 7 (binary, no = AKI score 0, yes = AKI score (1 + 2 + 3)); (6) incidence of CVVH at day 7 (binary yes or no); (7) hemodialysis at day 7 (binary yes or no); and (8) mortality at 1 y (binary). For the analysis of renal dysfunction, patients who were already on CVVH or dialysis and the ones who had renal transplantation were excluded. Phlebotomy was considered as a binary variable: yes or no. A mixed logistic and linear multivariate model was used by incorporating the significant factors identified in the univariate analysis. Statistical analyses were performed using SPSS version 26.

RESULTS

A total of 1000 OLTs were performed on 908 patients during the study period (826 patients had 1 OLT, 72 had 2 OLTs, 10 had 3 OLTs). Five hundred thirty-six patients underwent phlebotomy, and 464 patients did not. In the phlebotomized group,

493 ± 200 mL was withdrawn with a minimum of 100 mL and a maximum of 1200 mL. Table 1 compares demographic and health characteristics for both groups. There were no demographic differences between the groups except for gender, and there were more men in the phlebotomy group (70% versus 62%, $P = 0.007$). The phlebotomy group was healthier in terms of baseline Hb, INR, platelet count, fibrinogen, creatinine, bilirubin score, model of end-stage liver disease–Na score, and percentage of hepatocellular carcinoma. The baseline CVP was the same for the groups but was lower in the phlebotomy group just before vena cava clamping (7.6 ± 3.4 versus 8.7 ± 4.4, $P < 0.001$). The mean intraoperative transfusion of RBC units for all 1000 cases was 0.7 ± 1.5. The median and the interquartile range (25–75) were 0 for all blood products transfused. A total of 74.6% of patients did not receive any RBC units. Patients who were transfused with RBC units received a mean of 2.6 ± 2.0 RBC units (median, 2 [1–3]). Table 2 depicts transfusion rate, bleeding, and survival for both groups. The phlebotomy group had less transfusion of crystalloid and all blood products (RBCs, plasma, platelet, cryoprecipitate, and albumin) and less bleeding (1109 ± 1076 versus 1700 ± 1709 mL, $P < 0.001$; median, 800 mL [500–1300] versus 1100 mL [700–2200]). Interestingly, the final Hb value was higher in the phlebotomy group (100 ± 21 versus 87 ± 17, $P < 0.001$). Figure 1 shows the percentage of OLTs plotted against the number of RBC units transfused for both groups. Most patients (91%) in the phlebotomy group avoided exposure to RBC transfusion, whereas nearly half (53%) in the control arm were transfused at least 1 unit of RBC ($P < 0.001$).

Table 3 demonstrates the evolution of the renal function between patients who had phlebotomy and the ones who did not. Creatinine values (baseline, day 2, and day 7) were higher in the no phlebotomy group. Also, we can see the proportion of patients in each category of AKI (0 to 3) at day 2 and 7 postoperatively. Patients who underwent phlebotomy needed less CVVH and conventional hemodialysis on day 2 and day 7.

Table 4 resumes baseline characteristics and perioperative variables for patients who were candidates for phlebotomy (baseline Hb ≥85 g/L and creatinine value ≤104 μmole/L). Of these 548 patients, 410 had phlebotomy (70.2%), and 174 did not have phlebotomy (29.8%). Demographic values were the same for both groups. The group of phlebotomy was healthier in terms of baseline Hb, INR, and CTP score. The baseline CVP was the same but was lower at the time of clamping vena cava in the group phlebotomy. Blood losses were lower (1063 ± 956 versus 1358 ± 1226 mL, $P = 0.002$) in the group that underwent phlebotomy, and there was less transfusion of RBCs, plasma, and cryoprecipitate as well.

Of the patients who were candidates for phlebotomy (Table 4), Table 5 shows the sickest patients in terms of INR value and CTP score (according to the median). Again, transfusions of blood products and blood loss were less in the phlebotomy group.

Table 6 separates the phlebotomy group according to the volume of blood withdrawn using the median: 450 mL. Patients with a large volume of blood removed had decreased blood product transfusions and blood loss.

TABLE 1.

Baseline characteristics and perioperative variables

Variables	Total (N = 1000)	Phlebotomy (n = 536)	No phlebotomy (n = 464)	*P*
Baseline characteristics				
Gender (male) (%)	66	70	62	0.007
Age (y)	51.9 ± 11.4	51.9 ± 11.0	52.1 ± 11.4	0.196
Weight (kg)	78 ± 18	78 ± 18	77 ± 18	0.521
Height (cm)	169 ± 9	170 ± 10	169 ± 9	0.122
Preoperative hemoglobin (g/L)	105 ± 24	114 ± 23	90 ± 18	<0.001
Preoperative INR value	1.9 ± 1.0	1.6 ± 1.3	1.9 ± 0.9	<0.001
Preoperative platelet count ($\times 10^9$ pl/L)	94 ± 61	98 ± 59	89 ± 64	0.019
Preoperative fibrinogen (g/L)	2.16 ± 1.26	2.33 ± 1.19	2.01 ± 1.30	0.009
Preoperative creatinine (μmol/L)	102 ± 73	91 ± 72	115 ± 73	<0.001
Preoperative bilirubin (μmol/L)	126 ± 150	96 ± 116	169 ± 176	<0.001
CTP score	9.9 ± 2.6	9.0 ± 2.5	10.6 ± 2.4	<0.001
MELD-Na score	22.4 ± 8.5	20.4 ± 7.5	24.1 ± 8.0	<0.001
Retransplantation (REDO) (%)	11	7	16	<0.001
HCC (%)	12	16	8	<0.001
Intraoperative variables				
CVP at the start of surgery (mm Hg)	13.2 ± 4.9	12.9 ± 4.7	13.4 ± 5.1	0.112
CVP before vena cava clamping (mm Hg)	8.1 ± 3.9	7.6 ± 3.4	8.7 ± 4.4	<0.001
Threshold for RBC transfusion	61 ± 11	61 ± 9	61 ± 11	0.985
Length of surgery (min)	248 ± 66	246 ± 64	251 ± 67	0.219
Blood reinfused from cell saver (%)	77	78	76	0.784
Intraoperative fluid management				
Intraoperative crystalloid (mL)	4001 ± 1618	3851 ± 1509	4178 ± 1723	0.002
Albumin 5% (mL)	219 ± 728	154 ± 594	295 ± 853	0.002
Synthetic colloid (mL)	381 ± 403	387 ± 392	373 ± 415	0.598
Intraoperative urine output (mL)	414 ± 309	435 ± 293	401 ± 347	0.060

Continuous variables expressed as mean ± SD.

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell; REDO, 2 liver transplantations or more.

TABLE 2.

Blood loss, transfusion, and mortality data per transplantation

Variables	Total (N = 1000)	Phlebotomy (N = 536)	No phlebotomy (n = 464)	*P*
% without RBC transfusion	75	91	53	<0.001
RBC transfusion (unit/pt)	0.7 ± 1.5	0.2 ± 1.0	1.3 ± 1.9	<0.001
Final hemoglobin (g/L)	94 ± 20	100 ± 21	87 ± 17	<0.001
Plasma transfusion (unit/pt)	0.4 ± 1.6	0.1 ± 1.0	0.7 ± 2.0	<0.001
Platelet transfusion (unit/pt)	0.3 ± 1.7	0.1 ± 1.1	0.6 ± 2.1	<0.001
Cryoprecipitate transfusion (unit/pt)	0.8 ± 2.9	0.4 ± 1.9	1.2 ± 3.7	<0.001
Blood loss (mL)	1382 ± 1434	1109 ± 1076	1700 ± 1709	<0.001
Survival rate at 1 mo (%)	95.3	95.9	94.8	0.483
Survival rate at 1 y (%)	87.6	91.3	84.4	0.008

Continuous variables expressed as mean ± SD.
RBC, red blood cell.

Table 7 (A–F) shows logistic regression and multivariable analysis to find variables linked to the following: A, transfusion of ≥1 RBC units; B, bleeding of more than the median (900 mL); C, bleeding (as a continuous variable); D, AKI (1 + 2 + 3) at day 2; E, AKI (1 + 2 + 3) at day 7; and F, mortality at 1 y.

In Table 7, for A, 3 variables were linked to transfusion of ≥1 RBC units: baseline Hb, phlebotomy, and plasma transfusion. For each increase of 1 g/L of baseline Hb from the mean, the risk of transfusing at least 1 RBC decreased by 3.8%. When phlebotomy was performed, the risk decreased by 73%. The risk increased by 110% when plasma was transfused.

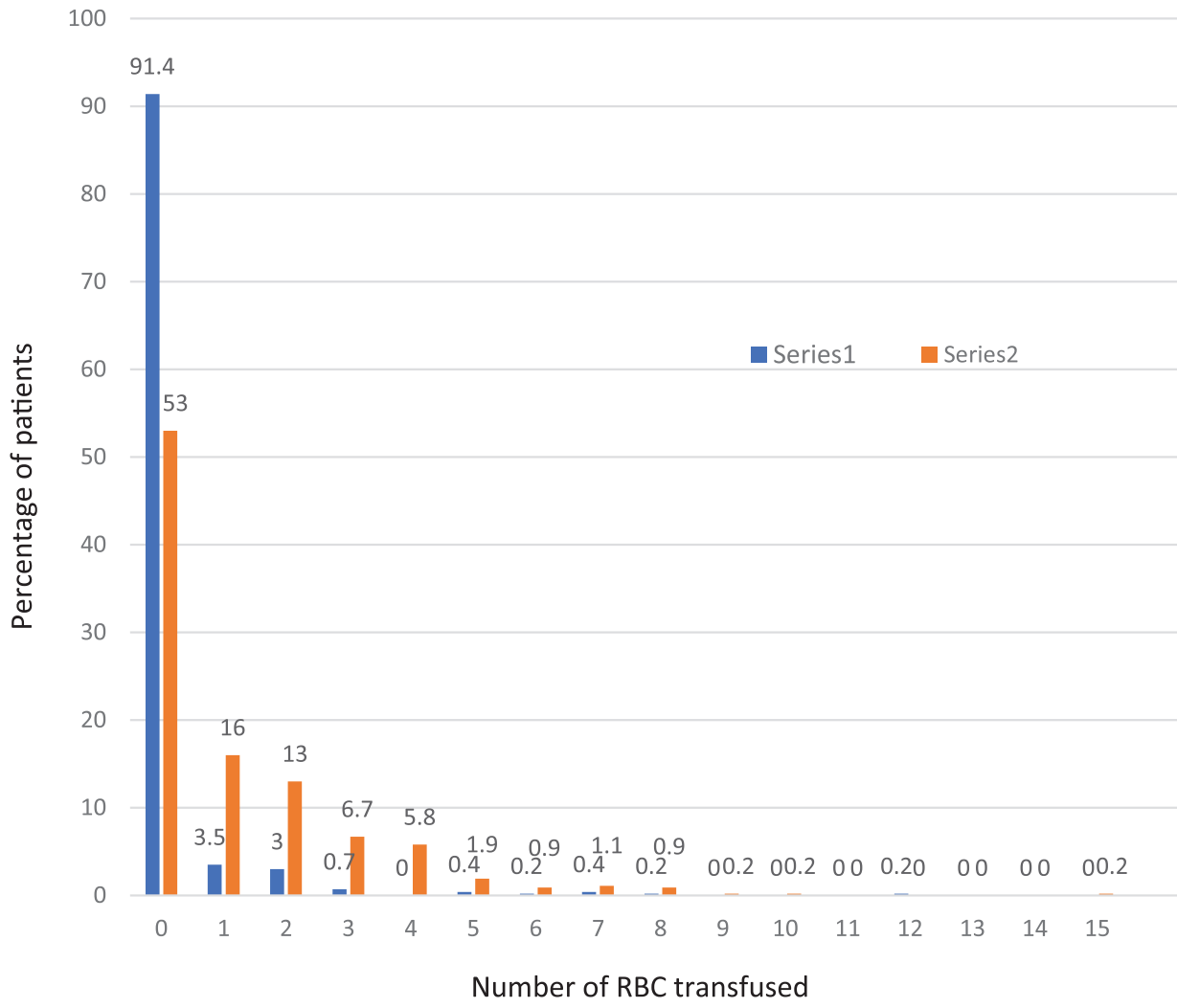

FIGURE 1. Percentage of patients by the number of RBCs transfused for groups with or without phlebotomy. Series 1: phlebotomy. Series 2: no phlebotomy. RBC, red blood cell.

TABLE 3.

Evolution of the creatinine in postoperative and AKI

Variables	Total (N = 1000)	Phlebotomy (N = 536)	No phlebotomy (n = 464)	*P*
Baseline creatinine (μmol/L)	102 ± 73	91 ± 72	115 ± 73	<0.001
Creatinine value at day 2 (μmol/L)	133 ± 73	121 ± 69	143 ± 74	<0.001
AKI at day 2 (% of patients in each category)	0 = 68.5%	0 = 69.4%	0 = 67.3%	
	1 = 13.1%	1 = 12.4%	1 = 14.0%	
	2 = 12.9%	2 = 12.6%	2 = 13.3%	
	3 = 5.5%	3 = 5.6%	3 = 5.3%	
Creatinine value at day 7 (μmol/L)	106 ± 73	98 ± 70	115 ± 76	<0.001
AKI at day 7 (% of patient in each category)	0 = 84.1	0 = 86.6	0 = 81.3	
	1 = 6.5	1 = 5.1	1 = 8.1	
	2 = 5.8	2 = 4.9	2 = 6.8	
	3 = 3.6	3 = 3.3	3 = 3.8	
AKI (1 + 2 + 3) at day 2	32%	31%	33%	0.689
AKI (1 + 2 + 3) at day 7	16%	13%	19%	<0.001
CVVH within 7 d	6%	3%	9%	<0.001
Hemodialysis within 7 d	3%	1%	6%	<0.001

0 = increase creatinine <1.5 times from baseline
1 = increase creatinine between 1.5 and 1.9 times from baseline.
2 = increase creatinine between 2.0 and 2.9 times from baselines.
3 = increase creatinine ≥3.0 times from baseline.
AKI, acute kidney injury; CVVH, continuous venovenous hemodialysis.

TABLE 4.

Baseline characteristics and perioperative variables for patients who had criteria to have a phlebotomy (Hb value ≥85 g/L and starting creatinine ≤104 μmole/L)

Variables	Total (N = 584)	Phlebotomy (n = 410)	No phlebotomy (n = 174)	*P*
Baseline characteristics				
Gender (male) (%)	67	69	61	0.077
Age (y)	51 ± 11	51 ± 11	52 ± 11	0.255
Weight (kg)	78 ± 18	78 ± 18	76 ± 18	0.116
Height (cm)	170 ± 9	170 ± 9	169 ± 9	0.304
Preoperative Hb (g/L)	117 ± 20	120 ± 20	107 ± 19	<0.001
Preoperative INR value	1.9 ± 1.0	1.6 ± 1.3	1.9 ± 0.9	<0.001
Preoperative platelet count ($\times 10^9$ pl/L)	96 ± 61	99 ± 61	90 ± 61	0.114
Preoperative fibrinogen (g/L)	2.29 ± 1.30	2.38 ± 1.22	2.11 ± 1.30	0.124
Preoperative creatinine (μmol/L)	71 ± 16	70 ± 16	72 ± 16	0.410
Preoperative bilirubin (μmol/L)	108 ± 129	106 ± 111	119 ± 160	0.061
CTP score	9.3 ± 2.5	7.5 ± 2.5	10.5 ± 2.6	0.049
MELD-Na score	20.5 ± 8.2	20.3 ± 7.9	20.9 ± 8.9	0.461
Intraoperative variables				
CVP at the start of surgery (mm Hg)	12.8 ± 4.6	12.8 ± 4.7	12.7 ± 4.5	0.712
CVP before vena cava clamping (mm Hg)	7.8 ± 3.6	7.6 ± 3.4	8.3 ± 4.0	0.037
Length of surgery (min)	245 ± 61	247 ± 63	241 ± 54	0.243
Blood loss (mL)	1151 ± 1051	1063 ± 956	1358 ± 1226	0.002
Blood reinfused from cell saver (%)	75	78	69	0.153
Intraoperative fluid management				
% without RBC transfusion	88	93	75	<0.001
RBC transfusion (unit/pt)	0.3 ± 0.9	0.1 ± 0.7	0.6 ± 1.2	<0.001
Final Hb value (g/L)	100 ± 20	102 ± 20	95 ± 19	<0.001
Plasma transfusion (unit/pt)	0.2 ± 0.8	0.1 ± 0.6	0.3 ± 1.1	0.001
Platelet transfusion (unit/pt)	0.2 ± 1.2	0.1 ± 1.1	0.3 ± 1.5	0.195
Cryoprecipitate transfusion (unit/pt)	0.4 ± 1.9	0.3 ± 1.6	0.7 ± 2.6	0.030
Intraoperative crystalloid (mL)	3917 ± 1419	3889 ± 1445	3984 ± 1356	0.456
Albumin 5% (mL)	196 ± 620	178 ± 663	241 ± 501	0.259
Synthetic colloid (mL)	373 ± 392	365 ± 390	391 ± 398	0.482
Intraoperative urine output (mL)	460 ± 304	459 ± 283	463 ± 351	0.901
Survival rate at 1 mo (%)	99	99	97	0.645
Survival rate at 1 y (%)	93	95	86	0.037

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.

TABLE 5.

Baseline characteristics and perioperative variables for patients who had an Hb value ≥85 g/L, starting creatinine ≤104 μmole/L, INR >1.5, and CTP score >10

Variables	Total (N = 156)	Phlebotomy (n = 92)	No phlebotomy (n = 64)	*P*
Baseline characteristics				
Gender (male) (%)	65	71	58	0.004
Age (y)	50 ± 11	49 ± 12	52 ± 11	0.455
Weight (kg)	79 ± 19	85 ± 23	77 ± 16	0.187
Height (cm)	170 ± 9	170 ± 9	169 ± 9	0.328
Preoperative Hb (g/L)	107 ± 17	108 ± 15	98 ± 13	0.670
Preoperative INR value	2.4 ± 1.1	2.3 ± 1.1	2.4 ± 0.9	0.962
Preoperative platelet count ($\times 10^9$ pl/L)	81 ± 53	79 ± 63	82 ± 57	0.969
Preoperative fibrinogen (g/L)	1.5 ± 0.9	1.4 ± 0.8	1.5 ± 1.1	0.206
Preoperative creatinine (μmol/L)	70 ± 16	66 ± 17	73 ± 16	0.464
Preoperative bilirubin (μmol/L)	196 ± 170	184 ± 128	198 ± 211	0.078
CTP score	12.0 ± 1.1	11.7 ± 1.2	12.1 ± 1.2	0.381
MELD-Na score	25 ± 7	24 ± 6	26 ± 7	0.414
Intraoperative variables				
CVP at the start of surgery (mm Hg)	14.8 ± 5.2	15.2 ± 6.5	14.4 ± 5.1	0.712
CVP before vena cava clamping (mm Hg)	9.1 ± 3.7	8.9 ± 2.8	10.1 ± 4.0	0.078
Length of surgery (min)	251 ± 61	253 ± 61	250 ± 63	0.716
Blood loss (mL)	1495 ± 1268	1143 ± 824	2363 ± 1908	<0.001
Blood reinfused from cell saver (%)	81	89	74	<0.001
Intraoperative fluid management				
% without RBC transfusion	76	94	50	<0.001
RBC transfusion (unit/pt)	0.5 ± 1.1	0.1 ± 0.2	1.3 ± 1.6	<0.001
Final Hb value (g/L)	92 ± 16	92 ± 15	91 ± 17	0.419
Plasma transfusion (unit/pt)	0.4 ± 1.2	0.1 ± 0.5	1.0 ± 2.0	<0.001
Platelet transfusion (unit/pt)	0.2 ± 1.2	0.1 ± 1.1	0.3 ± 1.5	0.195
Cryoprecipitate transfusion (unit/pt)	0.4 ± 1.9	0.3 ± 1.6	0.7 ± 2.6	0.030
Intraoperative crystalloid (mL)	3960 ± 1492	3933 ± 1574	3982 ± 1379	0.614
Albumin 5% (mL)	202 ± 491	98 ± 317	363 ± 648	<0.001
Synthetic colloid (mL)	440 ± 438	448 ± 430	427 ± 451	0.779
Intraoperative urine output (mL)	390 ± 293	382 ± 234	401 ± 365	0.153
Survival rate at 1 mo (%)	97	98	95	0.081
Survival rate at 1 y (%)	89	94	81	<0.001

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.

TABLE 6.

Baseline characteristics and perioperative variables for patients who had a volume of phlebotomy higher or lower than the median (450 mL)

Variables	Volume of phlebotomy <450 mL (256 patients)	Volume of phlebotomy ≥450 mL (279 patients)	*P*
Starting Hb (g/L)	114 ± 21	119 ± 21	0.607
Starting INR value	1.7 ± 0.9	1.6 ± 0.8	0.431
Starting platelet count ($\times 10^9$/mL)	101 ± 64	96 ± 55	0.415
Starting fibrinogen (g/L)	2.30 ± 1.15	2.41 ± 1.27	0.563
Starting bilirubin (μmole/L)	99 ± 111	100 ± 109	0.967
CTP score	9.4 ± 2.5	8.9 ± 2.4	0.020
MELD-Na	21.0 ± 7.5	21.3 ± 8.6	0.677
Starting CVP, (mm Hg)	13.6 ± 4.6	12.5 ± 4.7	0.800
CVP at clamping (mm Hg)	8.0 ± 3.3	7.3 ± 3.5	0.638
Blood loss (mL)	1200 ± 1227	1025 ± 911	0.034
RBC transfused (unit/pt)	0.28 ± 1.04	0.15 ± 0.87	0.003
Plasma transfused (unit/pt)	0.22 ± 1.16	0.07 ± 0.77	0.001
Platelet transfused (unit/pt)	0.21 ± 1.35	0.05 ± 0.67	<0.001
Cryoprecipitate transfused (unit/pt)	0.60 ± 2.49	0.11 ± 0.94	<0.001
Final Hb value (g/L)	98 ± 20	101 ± 21	0.396

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.

TABLE 7.

Summary of the logistic and linear regression model and odds ratios

	Variables	Odds ratio	Lower	Upper	*P*
A: Transfusion ≥1 RBC units	Hb	0.962	0.942	0.980	<0.001
	Phlebotomy	0.267	0.122	0.560	<0.001
	Plasma	2.096	1.581	3.022	0.05
B: Blood loss (binary)	Fibrinogen	0.692	0.542	0.872	0.002
	Creatinine	1.007	1.001	1.013	0.027
	Plasma	3.374	1.680	15.092	0.016
C: Blood loss (continuous)	Fibrinogen	–193.145	–310.949	–75 624	0.001
	Bilirubin	1.492	0.527	2.456	0.003
	Baseline CVP	27.849	1.274	54.424	0.041
	INR	353.145	151.472	554.817	<0.001
D: AKI (1 + 2 + 3) at day 2	Creatinine	0.985	0.976	0.9922	<0.001
E: AKI (1 + 2 + 3) at day 7	Creatinine	0.978	0.970	0.986	<0.001
F: Mortality at 1 y	Phlebotomy	–2.498	–1.554	–4.014	<0.001

AKI, acute kidney Injury; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; RBC, red blood cell.

DISCUSSION

Intravenous fluid loading may result in an increased blood loss because of an increased portal venous pressure and an increased splanchnic venous congestion while providing minimal or no support for cardiac output.[21] In contrast, intravenous vasoconstrictors alter the splanchnic circulation and may decrease portal hyperemia and splanchnic venous congestion[12,13] besides supporting arterial blood pressure. In addition, a restrictive intravenous fluid volume management during the dissection phase was proven to minimize venous congestion and reduce blood loss.[2,21] A reduction of CVP— and therefore portal pressure—can be helpful in minimizing surgical venous bleeding[22,23] because of reduced engorgement of collateral vessels. Methods to lower CVP include phlebotomy.

Overall, patients who underwent phlebotomy as part of their intraoperative OLT care required fewer transfusions (RBCs, plasma, platelets, and cryoprecipitate) and had less blood loss than the patients who did not have phlebotomy. Additionally, the percentage of surgeries without RBC transfusion was higher, and the final Hb concentration was higher as well. Predictably, the CVP at the time of vena cava clamping was lower in the phlebotomy group. Most importantly, the survival rate after 1 y was also better.

Phlebotomy and intravenous fluid restriction are often accompanied by continuous infusion of vasopressors to maintain acceptable blood pressure during OLT surgery. Nonetheless, there is a concern about hypovolemia, hypotension, and vasopressors causing an ischemic renal insult. Schroeder and Kuo[24] compared outcomes at 2 different transplant centers with contrasting OLT clinical protocols, involving low versus normal CVP. In this comparison, the low CVP center had lower transfusion rates; however, unfortunately, postoperative renal impairment, need for dialysis, and mortality within 30 d after surgery were all increased. In another study, Carrier et al[16,25] looked at AKI after OLT on postoperative days 2 and 7. They did not find any association between the use of vasopressors and the incidence of postoperative AKI, and they concluded that the use of vasopressors might be beneficial in liver transplant patients to offset the negative hemodynamic effects of an imbalance in intravenous fluid administration strategy.

Postoperative acute renal failure is a serious concern in OLT. The actual magnitude of this clinical problem is hard to know because of the different definitions and criteria being used in various studies (Risk Injury, Failure, Loss of Function, End-Stage Disease; Kidney Disease Improving Global Outcomes; Acute Kidney Injury Network). Serum creatinine is considered an "imperfect gold standard" for the diagnosis of AKI. Physiopathological classification of AKI includes prerenal and acute postrenal (obstruction) nephropathy and intrinsic acute kidney disease. In OLT, the incidence of AKI ranges from 8% to 94% in various data sets,[12,26] and 8% to 17% of the patients receive renal replacement therapy.[27,28] In our series, since 2013, patients received vasopressin—a drug that is known to redistribute blood volume from the splanchnic to blood volume redistribution—on a regular basis. Unfortunately, we do not have the exact quantity of the different vasopressors used in this series. Regression logistics in Table 7 (D and 6E) show the results of the variables linked to the incidence of AKI on postoperative days 2 and 7. The baseline creatinine value is the only variable we found linked to AKI (1 + 2 + 3). For the analysis of variables to the outcomes, CVVH and dialysis, both outcomes were combined. Sixteen patients were excluded from the analysis because they already were on CVVH or dialysis or had a kidney transplant at the same time of their OLT. With these exclusions and the first 514 OLTs, it was impossible to make a logistic regression; there were too few events (CVVH and dialysis). It is difficult to interpret the intergroup differences in terms of creatinine, incidence of AKI, use of CVVH, and need for dialysis. The phlebotomy group had a better (lower) baseline creatinine concentration, and this persisted through the perioperative period. Intraoperative hypotension—another AKI risk factor—was not studied specifically in this cohort. We concluded with certainty, however, that—based on our data set—phlebotomy does not seem to be linked to AKI, CVVH, or dialysis.

Blood loss was a secondary outcome in this study, and it was lower in the phlebotomy group. Notably, however, this group was healthier at baseline, including less abnormal laboratory values of coagulation-related parameters. With the logistic and linear regressions, phlebotomy was not linked to blood losses of ≥900 mL (binary) or blood losses analyzed as a continuous variable. This agrees with our previous report.[28] The fact of having considered phlebotomy as a binary variable (yes or no) could explain the absence of a logistic link. Moreover, a technique aimed at reducing blood loss will prove

to be effective with surgeries with large blood loss that is not the case in our center.

Phlebotomy was the only variable linked to postoperative survival at 1 y. These results confirm the previous reports where phlebotomy was associated with a decreased death rate of 30%, 58%, 61%, and 135%.[29–32]

In addition, a retrospective study—involving some members of our research group—found that phlebotomy was associated with less bleeding and fewer RBC units transfusions during liver resection.[33] Our findings confirm their results, including that large volume phlebotomy (≥450 mL) was associated with less blood loss than smaller volume phlebotomy (Table 6).

Phlebotomy is an effective medical intervention to decrease portal venous pressure[21] that is best used as a part of a multiprong evidence-based clinical strategy for liver transplantation. In our cohort, the blood loss difference was 690 mL between the phlebotomy and the no phlebotomy groups. This difference was a significant factor in our transplant center where the typical blood loss is about 1500 mL, but it may be less relevant in other settings where the average blood loss is 5 to 10 L.

There are some limitations to this study. This is an observational study from a single center for a long time period with a low transfusion rate. Despite increased bleeding and transfusions over time, survival improved, probably because of improved patient care. This phenomenon was explained in a previous report.[28] The kind and amount of vasopressors used perioperatively are not reported. Two kinds of antifibrinolytics were used in this series. The first 300 OLTs received aprotinin, and the last 700 received tranexamic acid. Contrary to what Mangano et al[34] reported for cardiac surgery, the incidence of AKI at day 7 (postoperative) was the same, that is, 10%. In a previous article comparing aprotinin and tranexamic acid, we did not find any change in bleeding and transfusion rate.[29] As mentioned earlier, this study is not a randomized controlled study. Use of the matching propensity score could have controlled this weakness, but a major determinant of feasibility of phlebotomy is the clinical impression of the anesthesiologist. This clinical impression is difficult to quantify, and we know that anesthesiologists all work differently.[3,4,28] A total of 584 patients met the criteria in terms of baseline Hb and creatinine to have phlebotomy, but in 174 cases, the anesthesiologist preferred not to do it. Table 4 is a kind of propensity score matching where we find patients who had the criteria to have a phlebotomy (Hb ≥85g/L and creatinine ≤104 μmol/L). A total of 410 patients had phlebotomy, and 174 did not have. These 2 groups are almost comparable except for the starting INR value and CTP score. The phlebotomy group had less bleeding and was less transfused. Of these 584 OLTs, Table 5 shows the sickest patients in terms of INR (INR >1.5 = median) and CTP score (CTP score >10 = median). Of these 156 OLTs, 92 had phlebotomy; the 2 groups are almost comparable again. Those who had phlebotomy had less bleeding and received less transfusion, and their survival rate at 1 y was markedly better. Phlebotomy seems to have a greater effect in sicker patients. These patients probably have greater portal hypertension, and the phlebotomy decreases portal pressure.[21]

The design of this study does allow us to conclude a cause-and-effect relationship. The unique interest of logistic regression with renal dysfunction and mortality was to exclude phlebotomy as a potential cause. There are many other factors that can cause kidney dysfunction or decreased survival. The donor risk index and the cold ischemia were studied in a previous article, and there was no link with transfusion requirement and blood loss.[28]

CONCLUSIONS

In this series of 1000 consecutive OLTs, patients received a mean of 0.7 RBC units, and 75% of them did not receive any RBC transfusions. Patients who benefited from the phlebotomy had a decrease in blood product transfusion (RBC, plasma, platelets, cryoprecipitate) and blood loss and saw an improvement in 1-y survival. Additionally, our data indicate that these benefits did not come at the cost of impaired postoperative renal function. A prospective randomized trial is needed to further evaluate the effectiveness and safety during OLT. This study provides insight that might inform the design of such a trial.

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