Original Article

Balanced Blood Product Transfusion during Adult Liver Transplantation

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Abstract

Background: Orthotopic liver transplant (LT) is often associated with massive blood loss and significant transfusion requirements. Recent recommendations for resuscitation strategy in massive bleeding include the transfusion of balanced blood products, fresh frozen plasma (FFP), platelets, packed red blood cells (PRBC), and restricted use of crystalloids.
Objectives: To evaluate whether the intraoperative transfusion ratio of fresh frozen plasma to packed red blood cell units (FFP: PRBC ≤1:1 versus >1:1) plays a positive role in reducing PRBC transfusion in LT.
Methods: This is a retrospective study of 84 liver transplant recipients who received at least one PRBC unit during the surgery. The patients were grouped into those who received intraoperative FFP: PRBC ratio ≤1:1 (low ratio) versus the ratio>1:1 (high ratio). Selected perioperative variables were compared between the two groups.
Results: Patients in the low-ratio versus high-ratio group had lower intraoperative requirements for PRBC (P<0.001). Importantly, in the high-ratio group, the mean postoperative PRBC transfused units were 1.76 times that of the low-ratio group (incidence rate ratio [IRR], 1.76; 95% CI=1.07-2.90). There was a significant difference between the two groups in preoperative body mass index (P=0.047), hemoglobin (P=0.005), and surgical time (P=0.071); moreover, all the variables were higher in the high-ratio group. After adjusting the variables, postoperative PRBC consumption in the low-ratio group was 43% less than that in the high-ratio group (P=0.007).
Conclusion: The intraoperative low-ratio transfusion was associated with a reduced need for total PRBC transfusion in LT.

Keywords: Blood component transfusion, Coagulation disorders, Homeostasis

1. Background

Liver transplantation (LT) is still associated with massive blood loss and transfusion (1). Transfusion of blood components is associated with adverse consequences in the surgeries, such as a higher rate of hepatic artery thrombosis (2), increased risk of graft loss (3, 4), and postoperative infections (5). Hence, reducing the need for blood component transfusion is one of the main goals in the perioperative period of LT. Coagulation test results for intraoperative transfusion in LT are accepted but may have a significant limitation since the time interval from blood sampling to obtaining results may make a rapid diagnosis of progressive coagulation disorders impossible. This 'coagulopathy gap' has been described in previous studies (6). Therefore, balanced transfusion is a strategy that can reduce the total need for blood components during liver transplantation.

Studies are emerging to support a balanced transfusion ratio in the LT. In a retrospective and single-center study of LT recipients, those who received fresh frozen plasma (FFP), platelets, and packed red blood cell (PRBC) > 1: 1: 2 versus <1: 1: 2 had lower requirements for PRBC, as well as intraoperative blood products, and showed improved one-year survival (7). In another study, liver transplant patients who received a plasma/PRBC transfusion ratio of ≥ 0.85:1 (high) were compared with those who received a ratio of <0.85:1 (low), and the results showed that during LT, the high-ratio group required fewer PRBC transfusions (8).

Patients undergoing LT are prone to severe bleeding. However, the risk of thromboembolic complications is high due to complex changes in the coagulation system of end-stage liver disease. Indeed, the predisposition to hypercoagulability is the common often-underestimated feature of the disease (9). Hence, determining the optimal transfusion ratio in LT is essential. There is no consensus on the topic, and further research is necessary to assess the utility of this strategy in LT and the potential outcomes.

2. Objectives

This study aimed to evaluate whether the intraoperative ratio of transfused plasma to red blood cells (≤1:1 versus >1:1) can positively reduce PRBC transfusion in LT.

3. Methods

3.1. Study design and participants

This retrospective study included 84 adult patients who had undergone LT at the Organ Transplant Center of Mashhad University of Medical Sciences, Mashhad, Iran, between April 2018 and

December 2021. The sample size was determined using the intraoperative RBC transfused variable in the study by Pagano MB et al. ([8]) with a test power of 90%, α=0.01, and β=0.09. Data were collected using the center's electronic medical records system and patient charts. Inclusion criteria were transplant recipients ≥18 years who underwent primary LT and received at least one PRBC unit during the surgery. On the other hand, patients with dual organ transplants, recipients who underwent coronary artery bypass graft or stent implantation, portal vein thrombosis (PVT) cases detected before or during LT, and those who had emergency re-operation for early postoperative bleeding due to the lack of surgical homeostasis were excluded from the study. The surgical technique was piggyback for all cases. The liver grafts were cold-preserved with the University of Wisconsin solution.

All patients underwent general anesthesia with standard induction of fentanyl (1-2 g/kg), propofol (0.5-2 mg/kg), and muscle relaxants, either succinylcholine or cisatracurium. Maintenance of anesthesia was with isoflurane (0.5-1.0 minimum alveolar concentration). Continuous intraoperative monitoring and blood sampling were enabled using a radial arterial line and a central venous catheter. Intravenous fluids contained 1%-2% albumin in saline solution. To reduce bleeding during LT, restrictive fluid management techniques were used before the anhepatic phase of surgery. Sodium bicarbonate was applied to correct excessive metabolic acidosis (base excess< -6.0).

3.2. Management of perioperative transfusion of blood components

The need for intraoperative blood transfusion was determined using hemoglobin levels based on serial arterial blood gas testing and evaluation of bleeding at different stages of the surgery. In this study, hemoglobin levels below 8 g/dL or ongoing bleeding were the thresholds for PRBC transfusions. During LT, the clinical findings of coagulopathy play an essential role in the anesthetist's decision to transfuse plasma and platelets. Moreover, intraoperative clinical coagulopathy correction was under the aid of rotational thromboelastometry (ROTEM@ TEM International GmbH, Munich, Germany). Postoperative clinical coagulopathy with platelet counts less than 20×10^9 / L was the threshold for the platelet transfusion.

3.3. Data collection

The clinical data were collected by retrospectively reviewing the electronic medical database of our transplant center. The patients were grouped into those who received intraoperative FFP: PRBC ratio≤1:1 (low ratio) versus the ratio of>1:1 (high ratio). Preoperative variables considered for analysis included the donor risk index (DRI), which

emphasizes the significance of donor factors for the success of liver transplants ([10]). The DRI has been developed to quantitatively predict the risk of graft failure after LT. The parameters for calculating DRI included age, height, cause of death, race, donation after cardiac death, partial/split liver graft, organ location, and cold ischemic time in hours. Furthermore, DRI can be used to assess the risk of hepatic artery thrombosis after LT ([11]). Other preoperative variables considered for analyses included the recipient's age, gender, body mass index (BMI), indication for LT, Model for End-Stage Liver Disease (MELD) score calculated using serum bilirubin, serum creatinine, and International Normalized Ratio (INR), pretransplant hemoglobin, INR, and platelet count. These variables were the last preoperative data.

Intraoperative data collected for analyses included duration of surgery, cold and warm ischemia time, intraoperative transfusions units (PRBC, FFP, cryoprecipitate, and platelets), use of tranexamic acid, fibrinogen concentrate, and last arterial pH level.

The postoperative data for analysis were hemoglobin level, platelet count, INR; the amount of transfusion of FFP, cryoprecipitate, PRBC, and platelets during the intensive care unit (ICU) stay; early postoperative complications, such as the hepatic artery or portal vein thrombosis, and duration of stay in the ICU.

3.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 16). The results of the categorical and continuous variables were expressed as numbers (%) and mean (SD), as well as median (range), respectively. The Kolmogorov-Smirnov test was used to assess the normality of the variables. The Mann-Whitney test or Student's t-test and the chi-square test or Fisher's exact test were also employed for continuous and qualitative variables, respectively. The Poisson regression model was used to assess the relationship between postoperative PRBC use and variables that may be confounding factors, such as BMI, preoperative hemoglobin, and duration of surgery. A P-value less than 0.05 was considered statistically significant.

4. Results

A total of 42 patients were studied in each study group. The mean age of recipients was 46.3±13.9 years, and most were male (61%). The most common causes of LT were hepatitis B virus-cirrhosis (32%), followed by cryptogenic cirrhosis (23%). The overall MELD score was 19.2±4.5. Table 1 tabulates the pre-transplant characteristics and variables of both patient groups.

Table 2 compares the intraoperative variables

Table 1. Relationship between pre-transplant variables and groups with high and low plasma ratios

Variables	Low-ratio group (n=42) FFP:PRBC ≤ 1:1	High-ratio group (n=42) FFP:PRBC>1:1	P-value
Male gender, No. (%)	30 (71.4%)	31 (73.8%)	0.807*
Age (years)	45.3 (13.5)	47.4 (14.5)	0.540**
Body mass index, kg/m²	23.7 (4.4)	25.7 (4.5)	0.047**
MELD score	19.2 (4.2)	19.2 (4.9)	0.826**
Cause of liver transplant			
HBV cirrhosis	15 (17.9 %)	12 (14.2 %)	
HCV cirrhosis	2(2.4%)	2(2.4%)	
Autoimmune	6(7.1%)	10 (11.9%)	0.361*
Cryptogenic	8(9.5%)	11(13.1%)	
HCC	2(2.4%)	4(4.8%)	
Others	9(10.7%)	3 (3.6%)	
Accompanying systemic disease, No. (%)			
Hepatorenal syndrome	1(1.2%)	0(0%)	0.314*
HE (grade III, IV)	3(3.6%)	2(2.4%)	0.645*
Pre-op Hemoglobin (g/dL)	10.41 (1.4)	11.43 (1.8)	0.005**
Pre-op Platelets(10⁹/L)	86.50 (52.45)	83.0 (58.9)	0.651**
Pre-op INR	1.70 (0.5)	1.6 (0.48)	0.182**
Donor risk index	1.20 (0.18)	1.25 (0.23)	0.653**

Data is presented as frequency (%) or mean (standard deviation).
* Chi-square test ** Mann-Whitney test
APR: PL: plasma, MELD: Model for End-Stage Liver Disease, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HE: hepatic encephalopathy, Pre-op: Pre-operative, INR: International normalized ratio.
NOTE: MELD score calculated by the formula $9.57 \times \log (\text{creatinine}) + 3.78 \times \log (\text{total bilirubin}) + 11.2 \times \log (\text{INR}) + 6.43$, using the online website [19].
Calculation: Donor risk index = exp ([0.154 if age is ≤40 to<50 years]+ [0.274 if age is≤50 to<60 years]+ [0.424 if age is≤60 to<70 years]+ [0.501 if age is≥70 years]+ [0.079 if cause of death (COD)= anoxia]+ [0.145 if COD= cerebrovascular accident]+ [0.184 if COD=other]+ [0.176 if race=African American]+ [0.126 if race=other]+ [0.411 if donation after cardiac death]+ [0.422 if partial/split]+ [0.066 ([170 – height]/10)]+ [0.105 if regional share]+ [0.244 if national share]+ [0.010×cold time]). Used from Feng et al. [20]

between the two groups. During LT surgery, patients in the high-ratio group received significantly more PRBC (P=0.001), FFP (P=0.005), and more FFP plus cryoprecipitate (P=0.008) than patients in the low-ratio group. When evaluating platelets transfused during surgery, 3 cases (7.1%) were in the low-ratio group, and 1 (2.4%) patient was in the high-ratio group. All recipients underwent endotracheal tube extubation in the operating room.

Reoperation because of bleeding and early postoperative complication did not occur. There was only one case of portal vein thrombosis after surgery. Table 3 summarizes the comparison of postoperative variables between the two groups. There were

significant differences between the two groups in terms of postoperative transfused PRBC, and the variable was higher in the high-ratio group (P<0.001).

As shown, BMI, preoperative hemoglobin, and surgical time were significantly different between the two study groups (P=0.047, P=0.005, and P=0.071, respectively), and all the variables were higher in the high-ratio group. The Poisson regression model describes the variables that may be confounding factors for postoperative PRBC use in LT (Table 4). After adjusting the variables, postoperative PRBC consumption in the low-ratio group was 43% less than that in the high-ratio group (P=0.007).

Table 2. Relationship between intraoperative variables and groups with high and low plasma ratios

Variables	Low-ratio group (n=42) FFP:PRBC≤ 1:1	High-ratio group (n=42) FFP:PRBC>1:1	P-value*
Surgical time(min)	342.4 (66.3)	365.1 (50.0)	0.071
Cold ischemia time (min)	178.5 (38.5)	188(50.4)	0.308
Warm ischemia time (min)	51.5(12.8)	50.4 (9.3)	0.687
Intra-op PRBC (units)	3.1 (1.6)	2.2 (1.4)	0.001
Intra-op FFP (units)	2.6 (1.4)	4.5 (1.8)	0.005
Intra-op Cryo (units)	0.6 (1.0)	1.7 (1.8)	0.003
Intra-op FFP+Cryo (units)	3.2 (1.9)	5.8 (3.3)	0.008
Intra-op platelets (units)	0.1 (0.5)	0.04 (0.3)	0.308
Fibrinogen concentrate (g)	0.4 (0.7)	0.6 (0.8)	0.382
Tranexamic acid (mg)	47.6 (148.5)	36.6(172.8)	0.423
Last arterial pH	7.34(0.04)	7.34(0.05)	0.951

Data is presented as mean (standard deviation).
* Mann-Whitney test
APR: PL: plasma, Intra-op: Intra-operative, PRBC: Packed red blood cell, FFP: Fresh frozen plasma, Cryo: Cryoprecipitate.

Table 3. Relationship between postoperative variables and groups with high and low plasma ratios

Variables	Low-ratio group (n=42) FFP:PRBC≤ 1:1	High-ratio group (n=42) FFP:PRBC>1:1	P-value
Hemoglobin (g/dL)	10.41(0.98)	11.43(1.26)	0.270*
INR	2.44(0.78)	2.20 (0.68)	0.191*
Platelets(10⁹/L)	74.3 (38.34)	87.56 (47.02)	0.124*
Post-op PRBCs (units)	1 (1.30)	1.8 (1.87)	<0.001*
Post-op FFP (units)	0.5 (1.27)	1.07 (1.99)	0.084*
Post-op Platelets (units)	1.5 (3.46)	2.04(4.54)	0.733*
HA, PV thrombosis, Yes, No.(%)	1(1.2%)	0 (0%)	0.237 **
ICU length of stay (days)	6.8 (2.6)	6.8(2.1)	0.840*

Data is presented as frequency (%) or mean (standard deviation).
* Mann-Whitney test ** Chi-square test
APR: Post-op=Postoperative, HA, PV thrombosis= Hepatic artery / Portal vein thrombosis, ICU= intensive care unit

Table 4. Poisson regression model describing postoperative PRBC consumption and variables

P-PRBC		IRR [95% CI]	P-value
FFP:PRBC ratio	> 1:1 Ref : ≤ 1:1	- - 0.58 [0.38,0.85]	0.007
Perop Hgb(g/dL)		0.92[0.82,1.03]	0.177
BMI(kg/m²)		1.02[0.98,1.06]	0.283
Surgical Time(min)		1.00[0.99,1.00]	0.065
Constant		0.81 [0.11,5.84]	0.834

APR: IRR: Incidence Rate Ratios, CI: confidence interval, PL: plasma, PRBC: Packed red blood cell, Pre-op: Pre-operative

5. Discussion

Our study indicated that replacing blood loss during LT with low-ratio transfusion significantly reduces the total need for PRBC transfusion in the surgery. Two observational and retrospective studies (7, 8) concluded that balanced blood product transfusion during liver transplantation significantly reduced the need for RBC transfusions. However, the balanced transfusion ratio of blood products varied in the studies. Importantly, platelet transfusions are not necessary in most cases of liver transplant recipients (12). Therefore, platelet transfusion was not included in the balanced transfusion strategy of this study.

Characteristics of the recipient, donor, and procedural factors affect transfusion requirements (13). Furthermore, inconsistent coagulation management with different algorithms of transfusion thresholds and blood component interventions in liver transplantation may result in different balanced transfusion ratios in the surgeries. Moreover, coagulation monitoring methods are very different in LT. The use of ROTEM helps differentiate such specific bleeding disorders as coagulation factor deficiency, thrombocytopenia, hyperfibrinolysis, effects of heparin and protamine, hypofibrino-genemia, and impaired fibrin polymerization. However, some observational studies support the utility of both ROTEM with conventional coagulation test methods in LT.

In patients undergoing LT, the impact of recipient BMI on intraoperative blood loss is controversial. Liver transplantation in obese patients is technically more difficult, resulting in a longer operative time and an increased need for intraoperative blood transfusions (14). Although there are studies that show blood transfusion as BMI increases, there are also studies that report no difference (15, 16). Our study showed a significant difference between the two groups in terms of the recipients' preoperative BMI; however, the operative times were partially significant. The results may be more acceptable as the sample size increases.

Portal vein thrombosis (PVT) is a relative contraindication to LT, depending on the type of PVT, the patient's clinical condition, and the surgeon's experience (17). PVT is associated with longer operative times, ICU and hospitalization, higher blood component transfusions, and reoperation rates (18, 19).

In our study, the diagnosis of PVT before or during LT was one of the exclusion criteria. Further studies are recommended to explain the difference in balanced transfusion outcomes between LT recipients with and without PVT. Finally, the use of a high-balanced transfusion ratio raises concerns about the risk of excessive transfusion, its associated complications, and increased wastage of blood components.

This study has limitations regarding its retrospective, single-center design. Single-center studies provide limited variation of practices and standardized procedures, which may also comprise the generalizability of the results.

6. Conclusion

Reducing the need for blood component transfusions is one of the main strategies in the perioperative period of LT. This study showed that replacing blood loss during LT with low-ratio transfusion significantly reduced the need for PRBC

transfusions in the surgery.

Acknowledgments

Footnotes

Conflicts of Interest: The authors declare that they have no competing interests.

Authors' contributions: SM and HS conceived the original idea and planned the study. SM, HS, RT, and MAA supervised the project. SM, HS, MAA, and NK wrote and revised the manuscript. MAA performed the statistical analysis.

Ethical Approval: The Ethics Committee of Mashhad University of Medical Sciences approved this retrospective study (approval number: IR.MUMS.MEDICAL.REC.1398.441) and waived the need for written informed consent. The research followed the Declaration of Helsinki principles.

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