RESEARCH ARTICLE

Clinical Practice of Blood Transfusion in Orthotopic Organ Transplantation: A Single Institution Experience

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Abstract

Background: Orthotopic organ transplantation, a treatment option for irreversible organ dysfunction according to organ failure, severe damaged organ or malignancy in situ, was usually accompanied with massive blood loss thus transfusion was required. We aimed to evaluate the adverse impact of blood transfusion on solid organ transplantation. Materials and Methods: From January, 2009 to December, 2014, patients who received orthotopic organ transplantation at Far Eastern Memorial Hospital medical center were enrolled. Clinical data regarding anemia status and red blood cell (RBC) transfusion before, during and after operation, as well as patient outcomes were collected for further univariate analysis. Results: A total of 105 patients who underwent orthotopic transplantation, including liver, kidney and small intestine were registered. The mean hemoglobin (Hb) level upon admission and before operation were 11.6±1.8 g/dL and 11.7±1.7 g/dL, respectively; and the nadir Hb level post operation and the final Hb level before discharge were 8.3±1.6 g/dL and 10.2±1.6 g/dL, respectively. The median units (interquartile range) of RBC transfusion in pre-operative, peri-operative and post-operative periods were 0 (0-0), 2 (0-12), and 2 (0-6) units, respectively. Furthermore, the median (interquartile range) length of hospital stay (LHS) from admission to discharge and from operation to discharge were 28 (17-44) and 24 (16-37) days, respectively. Both peri-operative and post-operative RBC transfusion were associated with longer LHS from admission to discharge and from operation to discharge. Furthermore, it increased the risk of post-operative septicemia. While peri-operative RBC transfusion elevated the risk of acute graft rejection in patients who received orthotopic transplantation. Conclusions: Worse outcome could be anticipated in those who had received massive RBC transfusion in transplantation operation. Hence, peri-operative RBC transfusion should be avoided as much as possible.

Keywords: Peri-operative transfusion - red blood cells - liver transplantation - kidney transplantation - small intestine

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Introduction

Over these decades, transplantation of specific organ had become a viable therapeutic procedure for irreversible organ dysfunction due to organ failure, severely damaged organ or malignancy in situ. Nevertheless, certain organ transplantation surgery was inherently accompanied with massive blood loss and thus, transfusion of blood components was commonly used. Unfortunately, accumulating evidence indicated that transfusion of red blood cell (RBC) increased the adverse event rate and led to poor prognosis in post-transplantation patients (Xia et al., 2006; Scornik et al., 2009; Massicotte et al., 2012; Rana et al., 2013). Although the significant improvement of surgical techniques and anesthetic practice had markedly decreased the transfusion frequency (Ozier et al., 2008) and even some successful cases of transfusion-free organ transplantation were reported (Massicotte et al., 2012), there was still a considerable variability among medical institutions. The phenomenon could be partially explained by the disparity of surgical practice, anesthetic management, and blood transfusion policy in different centers (Pilar et al., 2015); but the potential pathophysiology remained to be elucidated.

The associations between large amount of blood transfusion requirement and poor outcome in organ transplantation were sometimes multifactorial, complexing systemic analysis for causalities between blood transfusion and organ transplantation. In addition to the co-morbidities of patients, increased risk of immunologic events and bacterial or viral transmission related to blood transfusion complicated the comorbid situations in those who underwent organ transplantation. Although a series of studies had afforded to illustrate the administration of RBC transfusion and its relative effect on the outcome of those receiving transplantation surgery (Carpenter et al.,

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1990; Massicotte et al., 2005), significant surgical blood loss or certain unexpected complication events required indispensable transfusion therapy in these patients. To date, there was still no definite consensus regarding blood component managements in organ transplantations. Therefore, the aim of this study was to evaluate the impact of peri-operative anemia status and RBC transfusion in patients receiving orthotopic organ transplantation, as reflected by the length of hospital stay, complication events and post-transplantation survival. By including the pre-operation, peri-operation, post-operation nadir and final hemoglobin (Hb) levels before discharge, as well as the usage of RBC transfusion before, during and after operation, we attempted to identify certain transfusion-associated variables resulting in poor outcomes for those who had received orthotopic organ transplantation.

Materials and Methods

From January, 2009 to December, 2014, patients who received orthotopic organ transplantations (including liver, kidney, and small intestine) at Far Eastern Memorial hospital, a tertiary medical center with core competence of organ transplantation, were enrolled. Clinical data containing patient age, gender, organ transplanted, peri-operative anemia status, usage of allogeneic RBC transfusion, estimated blood loss (EBL) during surgery, the length of hospital stay (LHS) from admission to discharge and from operation to discharge, complication events post operation and the mortality rate at a 1-year interval. For the evaluation of anemia status before and after transplantation surgery, the Hb level at admission and before operation, the nadir Hb level post operation and the final Hb level before discharge were collected. Neither autologous blood transfusion nor blood cell salvage nor point-of-care monitoring in coagulation was utilized during the operation. Patients with acute rejection of graft transplanted, septicemia with clinical symptoms or microbiological evidence, respiratory events (such as lung edema, pleural effusion, and respiratory failure), renal events (such as acute renal failure), bleeding or thromboembolic events (including deep vein thrombosis, pulmonary embolism, acute myocardial infarction, and cerebrovascular events) were regarded as complication events. All the clinical data were obtained via the electronic chart review.

We utilized the unconditional logistic regression model to calculate the odds ratio (OR) in evaluation of the relationship of peri-operative anemia status and transfusion of RBC products to the outcome (including the LHS from admission to discharge and operation to discharge, as well as complication events such as septicemia and acute rejection of graft transplantation) of orthotopic transplantation-received patient, with the estimation of 95% confidence interval (CI). Data were expressed as either mean ± standard deviation (SD), medium (interquatile range, IQR), or OR (lower-higher limits of 95% CI). All statistical analyses were performed by the statistical software SPSS (version 15.0; SPSS Inc., Chicago, USA). Statistical significance was determined if a P value was less than 0.05.

Results

From January, 2009 to December, 2014, a total of 105 patients received orthotopic organ transplantation surgery at Far Eastern Memorial Hospital. The demographic features were listed in Table 1. Among these, 49 patients received liver transplantation, 48 received kidney transplantation, and another 8 received small intestine transplantation. The Hb level at admission and before operation were 11.6±1.8 g/dL and 11.7±1.7 g/dL, respectively; while the nadir Hb level post operation and the final Hb level before discharge were 8.3±1.6 g/dL and 10.2±1.6 g/dL, respectively. The median units of RBC products transfused in pre-operative, peri-operative and post-operative periods were 0, 2, and 2 units, respectively, with IQR of 0 to 0; 0 to 12; and 0 to 6 units. The median EBL was 250 mL with IQR of 50 to 1500 mL. The LHS from admission to discharge and from operation to discharge were 28 and 24 days with IQR of 17 to 44 and 16 to 37 days, respectively. The case number of post-operative complication events with acute rejection, septicemia, respiratory, renal, bleeding, and thromboembolic complications were 12 (11.4%), 33 (31.4%), 7 (6.7%), 5 (4.8%), 6 (5.7%), and 5 (4.8%), respectively. The overall one-year mortality of patients receiving orthotopic organ transplantation was reported to be 12.4%.

Anemia status and blood transfusion practice before and after operation in each kind of orthotopic organ transplantation were shown in Table 2. For patients who received liver transplant, the pre-operative Hb level, the nadir Hb level post operation and the final Hb level

Table 1. Demographic characteristics in orthotopic organ transplatation

Variales	
Age (year)	52 (43-58)
Gender (Male/Female)	77/28
Organ transplant (n)	
Liver	49
Kidney	48
Small intestine	8
Hb level (g/dL)	
Admission	11.6±1.8
Pre-OP	11.7±1.7
Nadir	8.3±1.6
Discharge	10.2±1.6
RBC product used (unit)	
Pre-OP	0 (0-0)
Peri-OP	2 (0-12)
Post-OP	2 (0-6)
EBL (mL)	250 (50-1500)
LHS from admission to discharge (day)	28 (17-44)
LHS from OP to discharge (day)	24 (16-37)
Complication (n)	
Acute rejection	12
Septicemia	33
Respiratory	7
Renal	5
Bleeding	6
Thromboembolic	5
One-year mortality (%)	12.4

*Hb, hemoglobin; OP, operation; LHS, length of hospital stay.

before discharge were 12.0±1.8 g/dL, 8.4±1.4 g/dL and 10.5±1.5 g/dL, respectively. The median units of RBC products transfused peri-operatively and post-operatively were 12 and 4 units with IQR of 4 to 22 and 2 to 10 units, respectively. The median EBL was 2500 mL with IQR of 1000 to 5000 mL. For those who underwent kidney transplant, the pre-operative Hb level, the nadir Hb level post operation and the final Hb level before discharge were 11.4±1.5 g/dL, 8.4±1.8 g/dL and 9.8±1.7 g/dL, respectively. The median EBL was 50 ml with IQR of 30 to 100 mL. Furthermore, for those who received small intestine transplant, the median units of RBC products transfused peri-operatively and post-operatively were 5 and 18 units with IQR of 2 to 6 and 6 to 23 units, respectively. The median EBL was 325 mL with IQR of 150 to 450 mL. In contrast, rare transfusion of RBC product was performed in kidney transplantation whether peri-or post-operatively.

Table 2. Peri-operative Anemia Status and Blood Transfusion Practice in Classification of Orthotopic Organ Transplantation

Variales	Liver	Kidney	Small intestine
Hb level (g/dL)			
Pre-OP	12.0±1.8	11.4±1.5	12.3±1.2
Nadir	8.4±1.4	8.4±1.8	6.9±1.7
Discharge	10.5±1.5	9.8±1.7	10.0±1.1
RBC product used (unit)			
Pre-OP	0 (0-0)	0 (0-0)	0 (0-0)
Intra-OP	12 (4-22)	0 (0-0)	5 (2-6)
Post-OP	4 (2-10)	0 (0-1)	18 (6-23)
EBL (mL)	2500 (1000-5000)	50 (30-100)	325 (150-450)

Hb, hemoglobin; OP, operation; EBL, estimated blood loss.

Univariate analysis for peri-operative anemia status and transfusion of RBC product in prediction of transplanted patients' outcomes were revealed in Table 3. It seemed that neither pre-operative anemia status nor pre-operative RBC transfusion prolonged the LHS from admission to discharge and from operation to discharge. Instead, peri-operative transfusion of RBC product was significantly associated with both prolonged LHS from admission to discharge (OR: 4.50, 95% CI: 1.83-11.22, P<0.001) and from operation to discharge (OR: 3.42, 95% CI: 1.39-8.53, P=0.006). Post-operative RBC transfusion was also markedly associated with both prolonged LHS from admission to discharge (OR: 13.77, 95% CI: 4.75-42.67, P<0.001) and from operation to discharge (OR: 8.72, 95% CI: 3.10-26.55, P<0.001). In addition, peri-operative transfusion of RBC product was significantly associated with acute rejection response of the transplanted graft (OR: 5.33, 95% CI: 1.11-25.68, P=0.048). Furthermore, both peri- and post-operative transfusion of RBC product were significantly associated with post-operative septicemia (OR: 7.07, 95% CI: 2.41-23.22, P<0.001, in the group of peri-operative transfusion; OR: 5.32, 95% CI: 1.83-17.44, P<0.001, in the group of post-operative transfusion, respectively).

Discussion

The present study evaluated the influence of anemia status and blood component transfusion in orthotopic organ transplantation before, during and after operation. Our main finding indicated that both peri-operative and post-operative blood transfusion were associated with not only prolonged LHS, either from admission to discharge or

Table 3. Univariate Analysis for Peri-operative Anemia Status and Transfusion of RBC Product in Prediction of Transplanted Patients' outcomes

	LHS from admission to discharge (day)				Acute rejection			
	≥30	<30	Crude OR (95% CI)	P value	With	Without	Crude OR (95% CI)	P value
Pre-OP Hb level (g/dL)								
<10	5	6	0.29 (0.03-1.51)	0.815	1	10	0.76 (0.02-6.35)	0.808
≥10	44	50			11	83		
Pre-OP transfusion								
Transfused	5	0	N/A	N/A	0	4	N/A	N/A
Not transfused	44	56			12	89		
Intra-OP transfusion								
Transfused	35	20	4.50 (1.83-11.22)	<0.001	10	45	5.33 (1.11-25.68)	0.048
Not transfused	14	36			2	48		
Post-OP transfusion								
Transfused	42	17	13.77 (4.75-42.67)	<0.001	8	51	1.65 (0.41-7.97)	0.640
Not transfused	7	39			4	42		
Pre-OP Hb level (g/dL)								
<10	2	9	0.29 (0.03-1.51)	0.194				
≥10	41	53						
Pre-OP transfusion								
Transfused	3	2	1.50 (0.19-11.73)	0.955				
Not transfused	40	60						
Intra-OP transfusion								
Transfused	30	25	3.42 (1.39-8.53)	0.006				
Not transfused	13	37						
Post-OP transfusion								
Transfused	36	23	8.72 (3.10-26.55)	<0.001				
Not transfused	7	39						

Hb, hemoglobin; OP, operation; LHS, length of hospital stay; OR, odds ratio; CI, confidence interval; N/A, not applicable.

from operation to discharge; but as well as post-operative septicemia in transplanted patients. But the most important finding was that peri-operative blood transfusion increased the risk of acute rejection of the transplanted graft.

Rectification of peri-operative anemia status had become an important issue over the decades, particularly in major surgeries with high risk of massive blood loss such as orthotopic organ transplantation. Yet the consensus of anemia treatment with blood transfusion in patients undergoing transplant surgery had not been established. Although most medical institutions complied with the practice guideline of RBC transfusion with a threshold of Hb level at 6.0 to 10.0 g/dL, there was a wide variability of transfusion trigger among different centers (Pandey et al., 2015). In addition to the different timings and norms in initiating blood transfusion among transplantation surgery and health care teams, the baseline characteristics of transplanted populations contributed to the considerable variability of transfusion trigger and subsequent outcomes (McCluskey et al., 2006).

Recent studies had demonstrated that peri-operative allogeneic blood transfusion had an adverse effect on patients with surgical intervention in various malignancies (Liu et al., 2013; Meng et al., 2013; Ramos et al., 2003; Sugita et al., 2008; Wang et al., 2015). Some of these investigations further indicated that peri-operative transfusion of RBC product, rather than post-operative, was highly associated with prolonged hospital stay as well as increased morbidity and mortality (Ramos et al., 2003; Sugita et al., 2008). Numerous hypotheses had been postulated and the most possible explanation for this phenomenon was blood transfusion-induced immunomodulation. It had been illustrated that peri-operative blood transfusion markedly diminished the number of T cell subgroups, nature killer cells and immunoglobins as well as altered cytokine secretions in patients who underwent oncologic surgeries (Guo et al., 2014; Xing et al., 2014). Reasonably, worse outcome could be predicted for blood transfusion during the peri-operative period in either cancer groups or post-transplantation groups according to their pre-existed immunosusceptibility and medication-associated immunosuppression status. Recently, several studies had proved that incident malignancies, including lymphoma and malignancies in kidney, liver and skin, could develop in the post-transplantation populations (Gu et al., 2012; Li et al., 2012; Yunus et al., 2012).

There were numerous transfusion-associated adverse events reported in the post-transplantation groups. Septicemia had been the major leading cause to mortality in patients who had massive blood transfusion during operation period of transplantation surgeries (Devi et al., 2009; George et al., 1991; Nemes et al., 2005). Graft rejection was also one of the detrimental events in those who underwent orthotopic transplantation. It had been demonstrated that peri-operative blood transfusion was highly associated with reduced graft survival (Devi et al., 2009). These investigations were generally compatible with our results. Furthermore, acute renal failure was reported to be a risk factor increasing the early post-operative mortality in post-transplantation conditions, but was not regarded to be significant in long-term perspectives (Fonseca-Neto et al., 2012).

To avoid excessive blood loss and subsequent blood transfusion in transplantation surgery, some technical improvement and novel equipment were introduced, including medication for minimizing blood loss, point-of-care monitoring in coagulation and intra-operative blood cell salvage (van der Bilt et al., 2007; Wang et al., 2010). It was also shown that both autologous blood transfusion and intra-operative blood cell salvage could reduce the ratio of allogeneic blood transfusion in patients who underwent major operations such as orthotopic transplantation. In the assistance of these specialized devices and techniques, transfusion-free transplantation had been accomplished. To date, successful cases without peri-operative blood transfusion were reported in liver (Garcia et al., 2013), kidney (Hernandez-Navarrete et al., 2013) and heart transplantations (Dallas et al., 2015). Importantly, there were considerable availability and feasibility of these new blood conservation methods performed in certain populations (for example, Jehovah's Witnesses, patients with uncommon blood types or multiple RBC allo-antibodies) that were required for major surgeries accompanied with massive blood loss and transfusion.

The present study had some limitations. First of all, this study was a retrospective study design with a limited case number. Secondly, the baseline characteristics of enrolled subjects who underwent transplantation varied, which suggested bias to a certain degree. Besides, cases with orthotopic heart transplantation were not included in the present study because blood cell salvage was routinely used in the operation, making it difficult to analyze the impact of peri-operative blood transfusion on clinical outcomes and thus some selection biases were inevitable.

In conclusion, the present study revealed that both peri-operative and post-operative blood transfusion were associated longer hospital stay, increased risk of post-operative septicemia, as well as increased risk of acute graft rejection. Worse outcome could be anticipated in those who had massive blood transfusion in transplantation surgeries. Hence, peri-operative blood transfusion should be avoided as much as possible.

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