Transfusion Management and Immuno-hematologic Complications in Liver Transplantation: Experience of a Single Institution

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Keywords

Liver transplantation · Blood transfusion · Hemolysis · Immuno-hematologic event · Transfusion alloimmunization

Summary

Objective: Liver transplantation (LT) has traditionally been associated with major blood loss and consequently high blood transfusion requirements. Our objective was to analyze transfusion management and incidence of immuno-hematologic complications in patients undergoing LT at our institution. **Methods:** A retrospective analysis of immuno-hematologic events and transfusion outcomes was carried out at La Fe University Hospital in Valencia. Data from 654 patients were reviewed: 654 underwent only one LT while 36 underwent second LT. **Results:** Patients received a median of 3 red blood cell (RBC) concentrates, 2 platelets concentrates (PCs) and 2 fresh frozen plasma units (FFPs). Variables significantly influencing RBC transfusions were: the MELD score, hemoglobin levels, and the platelet counts before LT. 27 patients (4.1%) had a positive antibody screening before transplant. Immuno-hematologic events occurred in 8% of the patients, mostly in the first month after LT, and involved hemolysis in 13 cases. Mortality was significantly higher in patients developing immuno-hematologic disorders (42.8 vs. 18.3%; $p < 0.001$). In the multi-variable analysis, only ABO minor incompatibility between donor and recipient significantly increased the appearance of immuno-hematologic incidences (OR 4.92, 95% CI 2.31–10.50; $p < 0.001$). **Conclusion:** Transfusion

management of patients that underwent LT can be complicated by immuno-hematologic problems. Blood banks should implement the DAT test in each transfusion to detect them.

Introduction

Orthotopic liver transplantation (LT) is a common procedure used for replacing the dysfunctional organ damaged by a variety of disorders. Traditionally, it has been associated with major blood loss and consequently high blood transfusion requirements [1]. During the last decade, some improvements in surgical techniques, anesthetic management, and organ conservation as well as better knowledge of hemostatic disorders during the process have significantly contributed to the reduction of the transfusion needs [2]. In spite of this, a great variability in transfusion rates between centers have been published, ranging between 0 and more than 100 red blood cell (RBC) units transfused during the procedure. Some authors have reported that more than 70% of patients undergoing LT were non-transfused [3, 4]. The reasons for these differences are not well known but can be attributed to the surgical technique, the anesthetic management, and the level of strictness followed for transfusion in different centers.

Survival has also improved with time reaching nearly 80% in many series. One of the factors that determine a poor outcome in some studies is the high transfusion requirement of not only RBCs but also fresh frozen plasma (FFP) and platelets concentrates (PCs)

[5]. In addition to the risk of viral transmission, immunologic events related to the transfusion and also to the procedure itself complicate the management of patients who underwent LT [6–8]. Furthermore, some of the immunologic disorders arising during the clinical course of transplantation, such as passenger lymphocyte syndrome (PLS) or recipient alloimmunization against donor RBCs, produce some degree of hemolysis that in exceptional cases can be life-threatening. The antibodies causing the disorder can be of donor or recipient origin [8].

The La Fe Hospital in Valencia has a lot of experience in LT. Our aim was to analyze transfusion requirements and immunohematologic complications related to the procedure in patients that underwent LT during a 7-year period.

Material and Methods

Study Population

The clinical courses of patients undergoing orthotopic LT during the period from January 2006 to December 2012 at La Fe University Hospital were retrospectively reviewed. The clinical and transfusion histories, including immunohematologic complications, were collected from an electronic hospital-based transfusion and clinical database. Inclusion criteria were: age ≥ 18 years, first LT, and availability of electronic medical records. Patients that underwent a second LT were only analyzed for transfusion outcome.

The following variables were recorded for each patient: sex; age; diagnoses; MELD score; hemoglobin; platelets; creatinine; bilirubin; international normalized ratio (INR) and Quick index (QI) before LT; recipient ABO and Rh type as well as antibody screening (indirect antiglobulin test; IAT), donor ABO and Rh type, antibody screening, transfusion rates (packed RBC, FFP and PC) before, during and after the procedure, immunohematologic events at any time after LT, length of admission, and length of patient survival. MELD is a scoring system to assess the severity of chronic liver disease. It is calculated according to a formula including serum bilirubin, serum creatinine, and INR [9].

Outcome variables included number of RBCs, FFPs and PCs intraoperatively transfused.

Transfusion Management

The hospital transplant coordinator notified the blood bank of an imminent LT once the donor was found and a recipient sample was sent when available. Recipient transfusion history was reviewed. If the previous and current antibody screening test was negative, compatible ABO/Rh RBCs were transfused. Only in cases in which previous or current alloantibodies against RBCs were detected, antigen-negative serologically cross-matched RBC concentrates (between 4 and 8) were transfused. Blood products were ordered by an anesthesiologist.

Immunohematologic Study

During the first 3 months after transplant, in addition to the routine ABO and Rh typing and RBC antibody screening test (IAT), the direct antiglobulin test (DAT) was systematically performed in pre-transfusion compatibility testing in order to detect immunohematologic problems related to hemolysis. ABO and Rh typing and IAT were determined using the automated system ORTHO Autovue Innova (Ortho Clinical Diagnostics, High Wycombe, UK). The DAT was performed on RBCs from ethylene diamine tetraacetic acid samples according to standard methods. When the DAT was positive, further testing using anti-C3d and anti-IgG was performed. If a cold antibody was suspected (positive anti-C3d DAT), the ability of the patient serum to agglutinate saline-suspended RBCs at 20 °C and 4 °C was tested. RBC eluates were prepared and tested by acid elution (Elu-Kitt II, Gamma Biologicals, Houston, TX, USA). Eluates and sera of patients with positive tests were tested for specificity using panels of RBCs with known antigens (Ortho Clinical Diagnostics, Diamed,

Table 1. Characteristics of the study population (2006–2012). Quantitative variables are shown as median (interquartile range)

Total number	654
Sex, number	
Men	478
Women	176
Age, years	54.4 (14.3)
MELD score	17 (10)
Diagnosis, number	
Viral hepatitis (HBV + HCV)	240
Alcoholic cirrhosis	164
Hepatocarcinoma	113
Fulminant hepatic failure	25
Cryptogenetic cirrhosis	20
Primary biliary cirrhosis	14
Autoimmune cirrhosis	18
Liver metastasis	10
Other	50
Biologic parameters	
Hemoglobin, g/dl	11.0 (3.2)
Platelet count $\times 10^9/l$	74.5 (55.7)
INR	1.6 (0.8)
Quick index, %	53.0 (28)
Bilirubin, mg/dl	3.2 (5.6)
Creatinin, mg/dl	0.9 (0.4)
Recipient IAT, number	
Positive	32
Negative	622
Rh compatibility, number	
Identical	501
Compatible	84
Incompatible	70
Days at hospital	17 (12)
Survival	547 (83.6%)
Follow-up months	26.6 (43.8)
IAT = Indirect antiglobulin test.	

Morat, Switzerland, and Mast Group, Bootle, UK). Patients who developed antibodies to RBC antigens, which were considered clinically significant, received blood that was negative for the identified antigen. Organs from death donors were implanted for all patients. The piggyback technique was used for all cases. A cell saver device was routinely used to recover patient blood.

Immunohematologic Complications: Definitions

Minor ABO incompatibility is defined by the presence of ABO antibodies directed against the recipient RBCs in the donor: the donor is group O and the recipient is A, B or AB, or the donor is blood group A or B and the recipient AB. Minor Rh incompatibility is defined by RhD-positive recipients receiving a liver from RhD-negative donors.

PLS was defined as the presence of antibodies (ABO and D antibodies) against the recipient erythrocyte antigens during the first month after LT. Acute idiopathic hemolytic anemia (AIHA) was defined as the presence of positive DAT and non-ABO autoantibodies detected by IAT.

Statistical Analysis

Computer software (SPSS, version 13, SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Descriptive statistics are presented for variables. Results are expressed as mean $\pm$ SD for continuous variables and as numbers with percentages for categorical variables. The Kolmogorov-Smirnov test was employed to investigate the normality distribution of the variables. Categorical variables were compared by means of chi square test or Fisher's exact test. The Mann-Whitney U-test for continuous variables was used to compare the groups when applicable. Univariate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. The statistically significant variables for univariate models were included in a stepwise multiple lineal regression model to assess the risk of blood product transfusion. RBC units, FFPs, and PCs were analyzed as continuous variables and converted from a continuous variable to a categorical variable for some analyses.

Variables influencing patient survival were calculated according to the Kaplan-Meier method and log-rank. Stepwise Cox proportional hazard model was used for multivariate analysis of survival. A p value of less than 0.05 was considered to be significant.

Results

Patient Data and Follow-Up

Data from 654 patients were reviewed: 654 underwent only one LT while 36 underwent second LT. Table 1 shows the characteristics of patients receiving a first transplant. Since most variables were not normally distributed, results are shown as median and interquartile range (IQR). Causes of second LT were mainly graft failure, thrombosis of liver artery, and relapse of primary disease. Age and sex distribution of patients undergoing first and second LT were similar. Overall survival was 83.2% with a median follow-up of 927 days.

Transfusion Outcome

Table 2 shows the transfusion outcome of patients in different periods of transplantation. Only 11 patients did not receive any transfusion (1.7%). D-positive RBC concentrates (median 2) were transfused to 5 D-negative patients, while 76 D-negative patients

received any D-positive PC (median 2). Only 1 patient developed a positive antibody screening test, and anti-D alloantibody was identified 8 days after 2 D-positive PC transfusions. This patient was a 49-year-old woman with previous negative IAT. 27 patients (4.1%) had a positive antibody screening test before transplantation: anti-E (8), anti-M (4), anti-D (3), anti-Kpa (2), anti-C (1), anti-c (1), anti-Jka (1), anti-Fyb (1), anti-S (1), anti-Kell (1), panagglutinin (1), anti-P (1), anti-f (1), anti-I (1). There was no significant difference with respect to previous or intraoperative RBC units transfused between positive and negative IAT patients. However, patients with positive IAT overall received more RBCs (10.8 ± 7.4 vs. 7.8 ± 8.0 ; $p = 0.008$) and PCs (5.4 ± 3.6 vs. 3.9 ± 4.4 ; $p = 0.005$) during admission at hospital. Patients that underwent a second LT received more intraoperative RBC transfusions (4.17 ± 2.4 vs. 3.1 ± 2.7 ; $p =$

Table 2. Transfusion outcome of patients under LT

Transfusion	1st Quartile	Median	3rd Quartile
Before transplant			
RBC	0	0	2
PC	0	0	0
FFP	0	0	0
During transplant			
RBC	1	3	4
PC	1	2	2
FFP	2	2	4
After transplant			
RBC	0	2	6
PC	0	1	3
FFP	0	2	4
Total			
RBC	4	8	16
PC	2	3	6
FFP	2	5	10

Table 3. Factors influencing intraoperative transfusion requirement during LT: results of multivariate analysis

	RBC	PC	FFP
MELD score	0.099 (0.017) $p = 0.043$	0.208 (0.007) $p < 0.001$	ns
Hemoglobin, g/dl	-0.477 (0.058) $p < 0.001$	-0.131 (0.022) $p = 0.004$	-0.095 (0.043) $p = 0.053$
Platelets $\times 10^9/l$	-0.095 (0.000) $p = 0.023$	-0.464 (0.000) $p < 0.001$	ns
Bilirubin, mg/dl	ns	0.177 (0.008) $p = 0.007$	ns
Creatinine, mg/dl	ns	0.136 (0.089) $p = 0.006$	0.121 (0.141) $p = 0.006$
Quick index, %	ns	-0.178 (0.004) $p = 0.039$	-0.358 (0.004) $p < 0.001$
ns = Nonsignificant.			
^a Results are shown as regression coefficient (standard error) and p value.			

Table 4. Immunohematologic complications and antibodies identified in patients under LT from 2006 to 2012 (n = 654)

Immunohematologic event	N	Antibody	Antibody detected in	Number of hemolyses detected
Positive direct antiglobulin test	14	negative eluate, unknown origin		0
AHAI due to				
Cold autoantibodies	11	anti-I	serum/plasma	3
Warm autoantibodies	3	panagglutinin against Rh system	eluate	0
Transfusion alloimmunization	2	anti-Kell	serum/plasma	1
	2	anti-D		
	1	anti-Jka		
	1	anti-Lua		
	1	anti-Kpa		
	1	anti-E		
	1	anti-E + anti-Jka		
	1	anti-Le		
Passenger lymphocyte syndrome	6	anti-A	eluate	9
	3	anti-B		
Cold antibody	2	cold antibody active only to 4 °C	serum/plasma	0

Table 5. Univariate and multivariate Cox regression analysis of factors influencing survival after LT

	OR	95% CI	p
<i>Univariable analysis</i>			
RBC transfused before LT	1.041	1.014–1.068	0.002
PC transfused before LT	1.143	1.079–1.211	0.000
FFP transfused before LT	1.064	1.015–1.115	0.009
RBC transfused intraoperatively	1.140	1.075–1.209	0.000
PC transfused intraoperatively	1.224	1.041–1.439	0.014
RBC transfused during admission	1.062	1.044–1.079	0.000
PC transfused during admission	1.086	1.061–1.112	0.000
FFF transfused during admission	1.046	1.017–1.075	0.002
HCV virus	1.764	1.157–2.688	0.008
Immunohematologic events	1.833	1.062–3.164	0.030
<i>Multivariable analysis</i>			
HCV virus	1.620	1.075–2.441	0.021
RBC transfused during admission	1.042	1.023–1.062	0.000

0.001) and more RBCs during admission (9.1 ± 5.2 vs. 7.8 ± 7.9 , $p = 0.004$) than patients that underwent a first LT. PC and FFP transfusions were not statistically different.

Table 3 shows the variables that significantly influence the risk of transfusion for different blood products.

Immunohematologic Complications

A total of 49 immunohematologic events were detected during the analyzed period: 14 positive DATs of unknown origin, 11 cold autoantibodies, 9 PLS, 10 post-transfusion alloimmunizations, 2 warm autoantibodies, 2 cold antibodies, 1 DAT due to immunoglobulin treatment. Table 4 describes the most important data. Median of appearance of these events was 19 days after LT. One RhD-positive patient received RBCs from an anti-D-sensitized donor without consequences.

The percentage of patients with minor ABO incompatibility was significantly higher for patients affected by immunohematologic events than for the rest of patients (19.6% vs. 4.2%; $p < 0.001$), and all except one PLS occurred in patients with minor ABO incompatibility. Only 3 cases had Rh incompatibility between donor and recipient. None of the patients receiving Rh-incompatible livers developed an anti-D alloantibody.

Patients that suffered any immunohematologic incident received significantly more RBCs during admission (11.1 ± 9.5 vs. 7.5 ± 7.7 ; $p = 0.001$) and also overall RBC (19.7 ± 14.8 vs. 11.7 ± 14.3), PC (9.2 ± 17 vs. 5.2 ± 7.2), and FFP transfusions (8.6 ± 6.3 vs. 7.2 ± 7.0); $p < 0.001$ for all cases.

Mild hemolysis was detected in 13 cases (9 PLS, 1 transfusion alloimmunization and 3 cold autoantibodies). The remaining cases did not develop symptoms. Mean hemoglobin and bilirubin was

Fig. 1. Kaplan-Meier curves representing cumulative patient survival according to the development or not of an immunohematologic event. $p = 0.034$.

Fig. 2. Kaplan-Meier curves representing cumulative patient survival according to number of intra-operative RBC units transfused. $p = 0.003$.

6.8 ± 1.6 g/dl and 8.9 ± 8.6 mg/dl, respectively, for 13 patients with proved hemolysis. Patients affected by PLS received corticosteroids and RBC transfusions as treatment. Changes in the transfusion regimen had to be made (from A or B to O) in order to avoid hemolysis. According to a univariate analysis, the development of an immunohematologic event significantly determined a worse outcome. Figure 1 shows the survival plots of patients with or without

immunohematologic events. With a similar follow-up, mortality was significantly higher in patients with immunohematologic disorders (42.8% vs. 18.3%; $p < 0.001$). In the multivariate analysis, only ABO minor incompatibility between donor and recipient significantly increased the appearance of immunohematologic incidences (OR 4.92, 95% CI 2.31–10.50; $p < 0.001$).

Factors Affecting Survival after LT

None of the following variables had any influence on survival: MELD score, age, sex, previous positive IAT, minor ABO incompatibility, Rh incompatibility. Results of univariable and multivariable survival analysis are shown in table 5. Figure 2 represents cumulative patient survival according to number of intraoperative RBCs transfused (until 5 and more than 5).

Discussion

Transfusion is an essential tool in the management of patients undergoing LT. The coagulopathy developed as well as the low platelet counts and hemoglobin levels detected in advanced disease increases the transfusion requirements as compared to other solid organ transplantations [10]. This is, to our knowledge, the first study that has exhaustively reviewed the transfusion outcome and the immunohematologic complications occurring after LT in a high number of patients from a single institution.

Patients that underwent LT at La Fe University Hospital had acceptable transfusion requirements as compared to previous studies, and blood supply is not currently a problem [11–14]. A special characteristic of patients undergoing LT is the reported high incidence of alloantibodies against RBC antigens as compared to other patient populations. Boyd et al. [6] showed a high percentage of alloimmunized patients (9%), and this variable significantly determined poor patient survival. The presence of alloantibodies in the recipient can make it difficult to find compatible blood and leads to transfusions of incompatible RBCs in some cases. In our study, the percentage of alloimmunized patients is low as compared to another series (4%) [6], and this variable did not influence survival. However, these patients received more RBC and FFP transfusions during admission to hospital.

There is a great variability in transfusion predictors in different studies probably related to the population and variables included in the analysis [11–17]. The variable that has most frequently been related to transfusion is preoperative hemoglobin [2, 15–16, 18]. In our study, prior lower levels of hemoglobin significantly increased the transfusion requirements of all blood products (RBCs, PCs, FFPs). When analyzing factors that influence PC and FFP requirements, the preoperative values of platelet counts and QI increased the PC and FFP transfusion needs, respectively. In general, these results seem quite logical because they show high blood product requirements for patients showing worse hematologic and analytic parameters and therefore worse clinical status before transplantation. We did not analyze variables related to surgery or anesthesiology, so this could explain some of the differences with other studies. The surgical technique used in our center (Piggyback hepatectomy) has shown to reduce intraoperative blood transfusions [14].

Our analysis supports the negative impact of RBC transfusions on survival. In fact, blood transfusion has been shown to be an important and independent factor that has a negative impact on survival after LT [3, 12, 19–21]. The immunologic effect on the recipient, an increased susceptibility to infections, and transfusion-re-

lated immunologic adverse effects such as anaphylactic reactions, hemolysis and acute lung injury could explain the negative effect of RBCs transfused on outcome. Our group had shown previously that the morbidity and mortality in patients undergoing liver re-transplantation is increased [22]. The current analysis confirms higher RBC requirements for patients undergoing liver re-transplantation, which could explain among other factors the lower survival rate.

Post-transplant immune hemolysis is a well-recognized complication after solid organ transplantation [23–26]. Hemolysis in the context of LT can occur due to autoimmunity, PLS, or antibody-passive transfusion [27–29]. Transfusion-related immunologic effects can also cause hemolysis, mainly due to the production of alloantibodies in the recipient against antigens on the surface of transfused RBCs. Our study reveals that immunohematologic events are quite common after LT (around 8%) and clearly more frequent in minor ABO incompatibility transplants. PLS is mostly detected in solid organ transplantation, and antibodies against the Rh and ABO antigens are mostly involved [24, 30]. A 20–40% incidence of biochemical PLS in LT has been reported in patients with minor ABO mismatch, occurring within 3 weeks after the procedure [7]. We detected a higher incidence of PLS than reported by previous studies, with more than 30% in minor ABO incompatible transplants. Most cases showed mild hemolysis and were treated only by compatible RBC transfusion. Transplant-associated AIHA is known to appear rarely in solid organ transplantation, being much common after marrow/peripheral blood transplantation. However, in pediatric patients that underwent combined liver and small bowel transplantation Li et al. [25] found 6 patients (6%) presenting with warm AIHA and severe hemolysis. Our results showed serologic evidence of cold AIHA in about 1.7% of patients, but clinical hemolysis was rarely present. Decrease of hemoglobin without hemorrhagic events in the first months after LT should lead to suspicion of PLS or another hemolytic event that must be studied and correctly treated if necessary. In fact, we detected 13 cases of hemolysis that in most cases was mild and had no clinical significance. However, they create a problem for blood banks that must suspect the different situations to apply the best transfusion management. The Valencia Blood Bank policy of systematically doing a DAT in each transfusion allows the early detection of immunologic problems. It has to be noted that the presence of immunohematologic events has negative influence on survival in the univariable analysis, but not in the multivariable analysis. This subgroup of patients received more RBC transfusions during admission to hospital than patients without immunologic problems, which could explain the lower survival rate.

In conclusion, transfusion management of patients that underwent LT is often complicated by immunologic events arising from transfusions or graft or autoimmunity misbalance. The blood bank should implement measures such as the DAT test in each transfusion to serologically detect the above problems. RBC transfusion seems to have a negative impact on survival, and a continuous effort to reduce the blood product requirements must be made.

Author Contribution

Pilar Solves analyzed data and wrote the paper, Nelly Carpio designed the study and collected data, Federico Moscardo analyzed data, Aima A. Lancharro and Isabel Cano collected data, Angel A. Moya, Rafael Lopez-Andujar, and Miguel Angel Sanz analyzed data.

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Disclosure Statement

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