Cost and outcome of liver transplantation

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Chapter 7

Outcome and Costs of Conventional versus Restricted Blood Product Transfusion Policy in Liver Transplantation

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ABSTRACT

Retrospective studies have indicated that blood product usage during liver transplantation is associated with increased postoperative complication rates and lower graft and patient survival. Therefore, some centers have adopted a restrictive transfusion protocol. However, cost-effectiveness of a restrictive transfusion has not been demonstrated. In a prospective study, we aimed to compare a conventional transfusion protocol with a restricted transfusion protocol.

A total of 433 primary liver transplantations in three Dutch transplant centers were included. Two centers used a conventional transfusion protocol (n=291), and one center used a restricted transfusion protocol (n=142). Data on patient and graft survival as well as recipient-related costs and complications were collected.

The restricted transfusion protocol had more DCD donors, a longer warm ischemia time, more split livers and significantly more recipients with cardiac comorbidity. The restricted transfusion protocol was associated with the use of significantly less blood products and a higher percentage of patients that were transplanted without the use of any blood products. Overall postoperative complication rate, patient survival and graft survival were as good in the restricted transfusion protocol as in the conventional transfusion group. After propensity score analysis Costs for blood product transfusions were significantly less in the restricted transfusion group, but overall hospital costs were not different.

In conclusion, the use of a restricted transfusion protocol in liver transplantation is as safe as a conventional transfusion protocol. In the current study the cost of a conventional and a restricted transfusion protocol were not different.

1 INTRODUCTION

The use of blood products during liver transplantation is known to adversely affect postoperative outcome in terms of patient and graft survival as well as the number of reinterventions[1-6]. Even though advances in surgical and anesthesiologic techniques have enabled a substantial reduction of intraoperative transfusion of blood products, transfusion-free transplantations are only achieved in a minority of patients[6-8]. Several approaches specifically aimed at reducing the need for blood products have been introduced[6,9]. Antifibrinolytic agents have been shown to reduce the need for transfusion of blood products[10,11]. Intraoperative use of a cell saver may limit the number of allogeneic blood products transfused, but studies in liver transplantation give contradictory results[12]. Lowering central venous pressure may also decrease the need for allogeneic blood products[13]. Furthermore, a simple and pragmatic approach to reduce the number of transfused blood products is a restrictive perioperative transfusion policy. The cornerstone of a restrictive transfusion policy is avoidance of blood loss due to fluid overload combined with reduced use of blood products by using higher transfusion thresholds.

The relationship between a higher amount of intraoperatively transfused blood products and lower patient survival is at least partly biased by the underlying disease severity of the patient. Apart from this, the amount of transfused blood products also appears to have an independent effect on survival[1]. Besides this effect on survival, restricted use of blood products also impacts cost-effectiveness of liver transplantation[12,14]. The obvious direct relation is that less transfusions result in a reduction of blood product-associated costs, but using less blood products may also result in fewer costs due to reduced transfusion-related morbidity[15].

Since there is no international consensus regarding transfusion policy in patients undergoing liver transplantation, transfusion protocols differ considerably on national and institutional levels[16-19]. Existing differences in institutional transfusion protocols in patients undergoing liver transplantation enable the comparison of safety, efficacy and cost-effectiveness of a restrictive transfusion protocol versus a conventional transfusion protocol. In the Netherlands liver transplantations are being performed in three centers which share a single national waiting list and a patient-centered allocation system, prioritizing patients based on their MELD scores (Model for End-Stage Liver Disease). In two liver transplant centers a conventional transfusion protocol is used, whereas a restrictive transfusion protocol is used in the third center. In this study we aimed to identify the factors responsible for transfusion-free transplantation and we analyzed these factors on outcome parameters and costs in patients undergoing liver transplantation.

2 METHODS

2.1 Patients

All patients undergoing a liver transplantation in one of the three Dutch liver transplant centers between September 2004 and September 2009 were included in this study. During the study period, 627 liver transplantations were performed at the three participating centers. One hundred forty-nine liver transplantations were excluded because of combined organ transplantation (n=24), pediatric liver transplantation (n=68), living donor liver transplantation (n=7), retransplantation of primary liver transplantation before September 2004 (n=41), and retransplantation occurring more than one year after primary liver transplantation (n=9). The remaining 478 liver transplantations were included in this study, 433 primary liver transplantations and 45 retransplantations within the first year of primary transplantation. Data were derived from the prospective COLT (Cost and Outcome of Liver Transplantation) study database, which includes detailed information on recipient, donor and surgical characteristics as well as outcome variables up to one-year after transplantation. The multicenter COLT study started in September 2004 and includes all liver transplantations performed in the Netherlands with the aim of comparing detailed patient-level cost and outcome information in a national population. Because of an ongoing study on the influence of Fresh Frozen Plasma (FFP) and Red Blood Cell (RBC) transfusion on survival after liver transplantation[1], a cost and outcome comparison on the use of blood products was originally set up alongside the COLT study by including details about blood loss as well as information about the utilization of blood products and autologous blood transfusion using a cellsaver.

2.2 Blood product transfusion protocols

In both centers with a Conventional Transfusion Protocol (CTP), intraoperative transfusion triggers were based on laboratory findings. RBC concentrates were administered when hemoglobin (Hb) levels dropped below 5.0 mmol/L (8.05 g/dL). Administration of FFP was directed by the results of a coagulation test. FFP was administered when the activated partial thromboplastin time or prothrombin time was prolonged by more than two times the normal value or when fibrinogen plasma levels were < 1 g/L. Platelet concentrates were administered when platelet count was < 50 x 10^9/L.

In the center with a Restricted Transfusion Protocol (RTP), blood product transfusion was never based solely on laboratory findings. The decision to transfuse was always based on a combination of clinical observations and laboratory thresholds that were similar to the centers with a CTP. Abnormal coagulation tests were only used to guide transfusion of FFP or platelet concentrates in the presence of clinically overt bleeding. Hence, in the absence of excessive bleeding, abnormal coagulation tests were not corrected by infusion of blood products. Prophylactic correction was therefore not applied in the RTP group. Moreover, a very restrictive infusion policy toward the use of crystalloids was used with the aim to avoid fluid overload.

2.3 Clinical outcome

The primary outcome parameter was 30-day postoperative mortality. Secondary outcome parameters included one-year and five-year patient and graft survival rates and costs.

2.4 Cost analysis

Costs were determined in accordance with the Dutch guidelines for economic evaluations in health care for the entire hospitalization period of the recipient, from the start of transplantation until discharge from the hospital[20]. Costs of organ procurement and outpatient follow-up were excluded from the cost calculations since the use of blood products during the recipient operation was not expected to have an impact on these costs. Retransplantation during hospital admission was taken into account and was considered a reintervention of the primary transplantation. Staff costs were calculated by multiplying the minutes of work with the cost per minute. Additional costs for social security, off-hour work and allowances were included. Costs of blood products, materials, and medication were determined by multiplying the amount of used materials with the unit cost. Equipment costs were calculated based on equivalent annual costs, including depreciation as well as the opportunity cost aspect of capital[21]. Housing and overhead were calculated by adding 10% and 35% to staff, material, and equipment costs. Standard prices were used for each day of intensive care unit (ICU) and hospital stay on a surgical or hepatology ward[20]. All reinterventions were priced individually. Since all costs were incurred within one year, no discounting was applied. Analysis was carried out using 2015 costs in euros (€).

2.5 Statistical analyses

Continuous variables were tested with the parametric independent samples T-test or the nonparametric Mann-Whitney U test depending on the underlying distribution. Normality was tested by the Kolmogorov-Smirnov-test. Categorical variables were tested with the chi square test and survival analysis was performed using the Kaplan-Meier method with the log-rank test.

Because a conventional or restricted transfusion protocol was not randomly assigned to patients, potential confounding covariates had to be addressed. Propensity score stratification was used to identify variables that were unbalanced between patients which were transplanted with a restricted transfusion protocol and those who were not[22]. Sixteen covariates which might affect clinical outcome were: donor cause of death, donor type (DCD/DBD), donor age, donor risk index (DRI)[23], cold ischemia time, warm ischemia time, type of graft, recipient age, recipient gender, transplantation indication, pre-transplant MELD score, recipient Body Mass Index (BMI), pre-transplant cardiac comorbidity, pre-transplant pulmonary comorbidity, pre-transplant insulin dependent diabetes mellitus (IDDM), and pre-transplant dialysis. These covariates were entered in a stepwise (backward) multiple logistic regression model when p-value ≤ 0.10 to determine potential confounding. The area under de receiver operating characteristic curve (C-index) for this model was determined.

Multivariate predictors (*p*-value ≤ 0.05) from the logistic regression model were used to calculate a propensity score for each patient. Patients were then sorted by propensity score and clustered into quintiles. After this stratification the effect of conventional or restricted transfusion on clinical outcome was analyzed. The Mantel-Haenszel odds ratio, a composite of the odds ratios derived from each quintile, was calculated.

A *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 23.0.0.3 (IBM Corporation, Somers, NY) and R version 3.3.0 (R Foundation, Vienna, Austria).

3 RESULTS

3.1 Donor, graft, and recipient characteristics

Four hundred thirty three adult patients undergoing a first liver transplant procedure using a full size graft were included in this study. Of these 433 patients, 291 patients underwent transplantation using a conventional transfusion protocol (CTP), for 142 patients a restricted transfusion protocol (RTP) was used. In Table 1 baseline characteristics of both groups are given. For determination of the DRI score, race was considered white and location was considered local for all donors. Variables with p ≤ 0.10 were entered into multivariate analysis and are indicated with an asterisk (*).

Table 1. Preoperative donor, graft, and recipient characteristics of CTP versus RTP.

Donor characteristics	**CTP (n=291)**	**RTP (n=142)**	***p*-value**
Donor type			0.008*
donation after brain death	238 (82%)	99 (70%)	
donation after circulatory death	52 (18%)	40 (28%)	
domino transplantation	1 (0.3%)	3 (2%)	
Donor cause of death			0.422
trauma	55 (19%)	29 (21%)	
stroke	190 (66%)	88 (63%)	
anoxia	10 (3%)	9 (6%)	
other cause of death	35 (12%)	13 (9%)	
Donor age (years)	48 (6 - 78)	47 (16 - 86)	0.414
DRI	1.48 (0.86 - 2.44)	1.53 (0.82 - 2.84)	0.097*
Graft characteristics			
Cold ischemia time	473 (185 - 1090)	456 (153 - 849)	0.221
Warm ischemia time	31 (14 - 71)	44 (27 - 93)	< 0.001*
Graft type			0.033*
whole	282 (97%)	130 (92%)	
reduced	3 (1%)	2 (1%)	
split	6 (2%)	10 (7%)	

Table 1. Preoperative donor, graft, and recipient characteristics of CTP versus RTP (continued).

Recipient characteristics	CTP (n=291)	RTP (n=142)	*p*-value
Recipient age (years)	52 (16 - 70)	53 (16 - 68)	0.596
Recipient gender (male)	187 (64%)	82 (58%)	0.190
Indication			0.179
cholestatic liver disease	59 (20%)	39 (27%)	
parenchymal liver disease	144 (49%)	62 (44%)	
metabolic liver disease	12 (4%)	11 (8%)	
vascular liver disease	3 (1%)	0 (0%)	
fulminant liver failure	21 (7%)	7 (5%)	
liver tumor	52 (18%)	23 (16%)	
MELD score	15 (2 - 40)	16 (2 - 40)	0.427
Body mass index	25.7 (15.6 - 38.1)	24.9 (13.3 - 52.5)	0.301
Cardiac history	13 (4%)	18 (13%)	0.002*
Pulmonary history	12 (4%)	12 (8%)	0.065*
Diabetes mellitus (insulin dependent)	48 (16%)	25 (18%)	0.829
Pre-transplant dialysis	7 (2%)	8 (6%)	0.126

Categorical variables are presented as number (percentage,) continuous variables as median (range) because all were non-parametric according to the Kolmogorov-Smirnov test. ***Abbreviations:*** *CTP = conventional transfusion protocol, RTP = restricted transfusion protocol, DRI = donor risk index, MELD = model for end-stage liver disease. * Variables entered in multivariate analysis for propensity score analysis.*

3.2 Transfusion and postoperative outcome

There were significant differences in a number of transfusion variables between both groups (Table 2).

Table 2. Comparison of surgical variables and intraoperative blood transfusion requirements.

Transfusion variables	CTP (n=291)	RTP (n=142)	*p*-value
Blood loss (L)	4.0 (2.5 - 7.0)	3.0 (2.0 - 6.1)	0.015
Allogenic RBC (units)[a]	4 (2 - 8)	3 (0 - 8)	0.226
Autologous RBC (units)[a]	1 (0 - 4)	0 (0 - 0)	< 0.001
FFP (units)[b]	5 (2 - 10)	1 (0 - 6)	< 0.001
Platelets (units)[c]	5 (0 - 10)	0 (0 - 5)	< 0.001
No RBC used	42 (14%)	38 (27%)	0.002
No FFP used	41 (14%)	69 (49%)	< 0.001
No platelets used	99 (34%)	101 (71%)	< 0.001
No blood products used at all	17 (6%)	32 (23%)	< 0.001

Categorical variables are presented as number (percentage), continuous variables as median (IQR). [a] *One unit contained 300 mL.* [b] *One unit contained 250 mL.* [c] *One unit contained approximately 150 mL and was obtained from 5 donors.* ***Abbreviations:*** *CTP = conventional transfusion protocol, RTP = restricted transfusion protocol, FFP = fresh frozen plasma, RBC = red blood cells.*

As expected, patients in the RTP group lost significantly less blood then patients in the CTP group. The transfusion of FFP and platelets was also significantly reduced in the RTP group. The difference between the number of transfused allogenic RBC units was not significantly different. In the RTP group a higher number of liver transplantations were performed without the use of RBC, FFP, platelets or any blood product at all (Table 2).

After transplantation, the hemoglobin level immediately postoperative as well as 24 hours after transplantation was significantly higher in the CTP group (Table 3). The lower Hb had no influence on clinical outcome and ICU length of stay was not different between both groups. Ward stay was significantly longer in the RTP group.

Table 3. Comparison of postoperative outcome.

Postoperative outcome	CTP (n=291)	RTP (n=142)	*p*-value
Immediate postoperative Hb (mmol/L)[a,b]	6.2 (1.21)	5.2 (0.94)	< 0.001
Hb 24h post-transplantation (mmol/L)[a,b]	6.0 (1.11)	5.2 (0.81)	< 0.001
Intensive care stay (days)[c]	3 (2 - 6)	3 (1 - 8)	0.601
Ward stay (days)	15 (11 - 23)	24 (16 - 34)	< 0.001
30-day mortality	15 (5%)	4 (3%)	0.269
One-year patient survival	86%	89%	0.343
One-year graft survival	77%	84%	0.102

[a] To convert the values from Hb to g/dL, multiply by 1.611. [b] Parametric variables are presented as mean (standard deviation). [c] Non-parametric variables are presented as median (interquartile range). ***Abbreviations:*** *CTP = conventional transfusion protocol, RTP = restricted transfusion protocol, Hb = hemoglobin.*

3.3 Cost outcome

The cost data per phase of the transplantation are presented in Table 4.

Table 4. Cost data of transplantation and clinical follow-up in first year after transplantation.

	CTP (n=291)		RTP (n=142)	
Cost data per surviving patient in first year after transplantation (€)	**Mean cost**	**Mean cost per year survival**	**Mean cost**	**Mean cost per year survival**
Liver transplantation (excl. blood products)	14 332	16 026	17 724	19 003
Peri-operative blood products	4208	4705	3212	3444
Intensive care stay	16 662	18 632	15 920	17 068
Ward stay	10 648	11 907	15 606	16 732
Blood products during clinical follow-up	412	461	505	541
Reinterventions during clinical follow-up	19 623	21 943	20 308	21 773
Immunosuppressives	9243	10 336	9628	10 324
Reinterventions during outpatient follow-up	23 338	26 097	14 637	15 693
Total one-year costs per surviving patient	**98 466**	**110 107**	**97 540**	**104 578**

Abbreviations: *CTP = conventional transfusion protocol, RTP = restricted transfusion protocol.*

Total costs consist of costs incurred both by deceased and surviving patients. Because deceased patients do not incur any more costs a simple division of total costs by the total number of patients would favor the group with the lowest survival. Therefore, total costs of all patients are divided by the survival time of patients generating the mean cost per one-year patient survival.

There were no significant differences in costs for liver transplantation, including costs for blood products, ICU stay, immunosuppressives, and reinterventions, between the two groups. The small difference in total costs could be attributed to a shorter mean ward stay in the CTP group, compared to the RTP group.

3.4 Propensity score analysis

After univariate analysis (Table 1) two donor-related (donor type and DRI), two graft-related (WIT and graft type), and two recipient-related variables (cardiac history and pulmonary history) were used as covariates in the multivariate model. The backward stepwise multiple regression model gave two important covariates regarding conventional or restricted transfusion: type of donor and warm ischemia time (Table 5).

Table 5. Multivariate analysis of transfusion protocol.

Variable	Exp β	95% confidence interval for exp β	p-value
Constant	0.005		< 0.001
Type of donor	0.558	0.313 - 0.993	0.047
WIT	1.146	1.113 – 1.180	< 0.001

These two multivariate significant variables were used to calculate the propensity score for each patient. Patients were sorted by propensity score and clustered into quintiles. The ROC-curve with a c-statistic of 0.850 (95% CI: 0.814 - 0.887) indicated good discrimination of the model between patients with a conventional and a restricted transfusion protocol.

For clinical outcome, propensity score adjusted outcome in patients transplanted with a restricted transfusion protocol was compared to a conventional transfusion protocol (Table 6).

Table 6. Propensity score–adjusted risk of death in patient with RTP compared to CTP.

Outcome	Odds ratio (95% confidence interval)	*p*-value
Graft loss (30 days)	0.238 (0.064 – 0.881)	0.032
Patient death (1 year)	0.476 (0.229 – 0.992)	0.048
Graft loss (1 year)	0.449 (0.241 – 0.836)	0.012

Thirty-day graft and one-year graft and patient survival rate were not significantly different between both groups (Table 3). However, after propensity score analysis, patients in the RTP group had better survival than patients in the CTP.

4 DISCUSSION

This is the first study to assess the difference in outcome and costs between a restricted transfusion protocol and a conventional transfusion protocol. The main finding in this study is that a restricted blood transfusion protocol in patients undergoing liver transplantation is safe. The restricted blood transfusion protocol was associated with a significant reduction in the use of blood products and a subsequent reduction in costs for blood products.

All patients included in the current study were listed on the same national waiting list and underwent a first transplantation. Allocation of an available donor liver was directed by the order of this national waiting list, based on the MELD score. In addition, all transplantations in the three centers were performed by anesthesiologists, hepatologists and surgeons with over five years of experience in liver transplantation. The detailed prospective data collection was done by the same research nurse in all three centers, thereby ensuring uniform information gathering based on individual patients.

Due to the nature of the study a center effect could not be ruled out. The better survival rate in the RTP group after propensity score analysis cannot be attributed solely to restricted transfusion. Other transplant center-related factors may have influence on survival as well. However, it is clear from this study that liver transplantation with a RTP is safe and associated with good results, when compared to CTP.

A limitation of our study is its nonrandomized design. A robust statistical method available to control for selection bias is propensity score analysis[24,25]. The C-index for the propensity scores in our study was 0.850, indicating good discrimination between patients transplanted with conventional and restricted transfusion protocols.

When comparing both groups prior to propensity score adjustment, significant differences were found at baseline between covariates for RTP and CTP. Patients in the RTP group were significantly more often transplanted with DCD organs and split livers. Warm ischemia time was longer and more patients in the RTP group had a cardiac history (patients treated for cardiac arrhythmia, congestive heart failure, myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty).

Reanalysis of baseline characteristics after propensity score-based stratification demonstrated that pre-existing differences in covariates were adequately controlled, allowing a meaningful comparison of outcome data. It should be noted that the propensity score analyses cannot control for potentially confounding covariates that are not measured or erroneously measured[26].

Since the use of blood products in itself may be an indicator of the complexity of the transplantation, a simple comparison of liver transplantations requiring no blood products with those who did require blood products potentially introduces bias. There is a considerable risk that ‘technically more difficult’ transplantations would be compared with ‘technically more easy’ transplantations, with a predictable result[27]. Therefore, in the current study we have focused on the differences in outcome and costs in centers with a clearly different transfusion protocol. While a conventional protocol was used in two centers, a protocol intending to prevent transfusion of blood products as much as possible without compromising results, was used in a third center.

As a result of the patient-centered and MELD score-based liver allocation system, using one national waiting list for all three centers, the complexity and case mix of patients was similar in the three centers.

The restricted transfusion protocol reduced the blood loss and associated amount of FFP's and TC's. The number of RBC's was not significantly different. The restricted transfusion protocol increased the proportion of patients that could be transplanted without any blood products. It also reduced costs associated with the use of blood products. More importantly, the postoperative outcome in patients in whom the restricted transfusion protocol was used was good, with an in-hospital mortality of only 3% and a one-year patient survival rate of 89%. After propensity-score adjustment, risk of graft loss and patient death was lower in the RTP than the CTP group.

Since the restricted transfusion protocol is associated with an expected lower postoperative Hb in patients, a potential disadvantage might be a higher incidence of postoperative morbidity associated with inadequate tissue oxygenation. However, in this study we observed no differences in the incidence and severity of postoperative complications (data not shown). These findings confirm the safety of a restricted transfusion protocol in patients undergoing liver transplantation.

In the current study we did not find a reduction in total transplantation-related costs in the restricted transfusion group, compared to the conventional transfusion group. This was mainly due to the fact that the mean ward stay was longer in the center with a restricted transfusion protocol. There were no differences in the mean ICU stay or costs of reinterventions between the groups. Altogether, these data indicate that the observed difference in ward stay was most likely a result of differences in discharge policy, individual doctor's preferences, and logistical issues, rather than a slower postoperative recovery in patients with a restricted transfusion policy.

Even though costs of liver transplantation cannot be easily transferred from one country to another[28], a restricted transfusion protocol seems to be associated with excellent clinical outcome without increasing the number of used resources. These observations call for a wider application of a restricted transfusion protocol in other centers around the world.

A limitation of this study is the fact that the data remain observational. Ideally, a randomized study design would have been chosen. A second limitation of this study is the inability to quantify the performance of a surgical team with respect to blood loss and blood transfusion. Finally, differences between transplant centers, such as discharge policy, may have contributed to outcome and cost differences.

In conclusion, the use of a restricted transfusion protocol in liver transplant recipients is safe and it is associated with good graft and patient survival rates. Although costs for usage of blood products are significantly reduced in patients with a restrictive transfusion protocol, we were unable to demonstrate a significant difference in overall costs.

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