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Original Article

Comparison of conventional coagulation tests and thromboelastography for preoperatively assessing blood loss and transfusion during orthotopic liver transplantation

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Abstract: Objective: An effective blood loss and transfusion requirements assessment before orthotopic liver transplantation (OLT) may improve intraoperative bleeding management during OLT. Methods: Sixty-five patients were included in this retrospective, observational study. Correlations of conventional coagulation tests (CCTs) and TEG parameters with blood loss and transfusions were determined using Pearson's correlation analysis. The most strongly correlating CCTs and TEG parameters were selected for logistic regression and receive operating characteristic (ROC) curve analyses. Results: Prothrombin activity (PTA) showed a strong correlation with packed red blood cells (PRBCs) and fresh frozen plasma (FFP) transfusions (r=-0.838, P<0.001; r=-0.810, P<0.001, respectively). A logistic regression indicated that PTA was an independent predictor for PRBCs and FFP transfusions. The cutoff values that best predicted the transfusion threshold for PRBCs and FFP was 83.5%. Conclusion: CCTs and TEG cannot accurately assess blood loss, but PTA showed better correlations with and good performance for the prediction of PRBC and FFP transfusions during OLT.

Keywords: Orthotopic liver transplantation, thromboelastography, conventional coagulation tests, blood loss, blood transfusion

Introduction

Orthotopic liver transplantation (OLT) was historically associated with major blood loss, and blood transfusion increased the risks of infection and lung injury, which led to increased morbidity and mortality [1, 2]. Bleeding during OLT is multifactorial due to surgical trauma and hemostatic defects. Coagulopathy of end-stage liver disease is exhibited preoperatively, and further disturbance of hemostatic variables can occur intraoperatively, resulting in massive blood loss [3]. Transfusion practices and coagulation management during OLT vary greatly among different healthcare centers. Aside from conventional coagulation tests (CCTs), point-of-care monitoring based on thromboelastometry or thromboelastography (TEG) can be used during OLT to rapidly diagnose hemostatic variable changes and to guide blood product treatments [4]. CCTs cannot detect fibrinolysis or give an indication of clot stability, nor can they generally detect hypercoagulability [5, 6]. TEG can discriminate between different phases of the coagulation system. As such, TEG can be used for identifying clotting abnormalities and guiding the administration of blood products, thereby decreasing intraoperative blood transfusions during OLT [7]. Although rapid thromboelastography (r-TEG) requires less time than kaolin thromboelastography (k-TEG) to produce complete coagulation results, rapid TEG cannot indicate the need for blood transfusion as quickly as assessing ion imbalance based on arterial blood gas analysis [8]. When massive bleeding occurs during OLT, coagulation should be corrected in a timely manner instead of waiting TEG results. Therefore, effectively assessing blood loss and blood product transfusion requirements prior to OLT is also important.

However, little is known about preoperative factors associated with blood loss that could be used to create truly predictive models of blood transfusion requirements [9].

In our center, CCTs and r-TEG are performed routinely before OLT, and the following parameters are included in the CCTs: prothrombin time (PT), international normalized ratio (INR), fibrinogen (FBG), prothrombin time ratio (PTR), prothrombin activity (PTA), activated partial thromboplastin time (aPTT) and thrombin time (TT). This retrospective study was designed to identify correlations of preoperative CCTs and TEG with blood loss and blood product transfusions occurring during OLT.

Patients and methods

Study population and anesthetic management

After obtaining institutional review board approval, we performed a retrospective analysis of our primary adult OLTs occurring between June 2014 and March 2016, including 65 consecutive adult patients. In this study, no organs from executed prisoners were used, and organs were donated from brain-dead patients. The surgical and anesthetic management methods used were as previously described by Sakai et al [10]. In brief, organ procurement was performed using University of Wisconsin preservation solution. The piggyback technique was used for graft implantation. Packed red blood cells (PRBCs) were administered to maintain a target hematocrit of 30% based on arterial blood gas analysis (RAPIDLab 1265, Siemens AG, Germany). A cell saver device was routinely used, except on recipients with malignant hepatic lesions. In the presence of microvascular bleeding, transfusions of fresh frozen plasma (FFP), platelets, and cryoprecipitate were considered by attending transplant anesthesiologists based on the k-TEG results. No prophylactic antifibrinolytic therapy was used, per our institutional protocol.

Preoperative coagulation test

Several blood samples were drawn simultaneously before surgery from an existing arterial catheter. CCTs were performed according to the manufacturer's instructions, including PT, FBG, aPTT and TT; subsequently, PTA, PTR and INR were calculated by the system (ACL TOP 700). The r-TEG test was performed by a trained biomedical scientist. Testing of the citrated blood samples was conducted within five minutes of collection (Becton Dickinson Vacutainer). The r-TEG parameters include the following: reaction time (R time), clot formation time (K value), alpha angle (α), maximum amplitude (MA), clotting index (CI) and lysis index at 30 min after MA (LY30).

Intraoperative coagulation management

In every case, r-TEG was performed during each phase of OLT, including pre-anhepatic, anhepatic, post-reperfusion, the end of surgery, and as deemed necessary by the anesthesiologist. The sampling for r-TEG was performed by a trained biomedical scientist and analyzed as previously described (Hemostasis Analyzer Model 5000) [8].

Blood loss and transfusion recording

The volumes of blood loss, fluid requirement, transfusion and urine output were recorded to assess intra-operative fluid shifts. Blood loss was estimated as the volume of fluid in the suction bottle minus the volumes of ascites and flushing fluid used on the table; this quantity was then added to the cell saver volume and weight increase of the gauze swabs. These parameters were measured hourly by an anesthetist.

Statistical analysis

The data are descriptively summarized as the mean and standard deviation or median and interquartile range (25^{th} percentile to 75^{th} percentile), as appropriate. The Student *t* test was performed to compare normally distributed data. Pearson's correlation coefficient (*r*) values were calculated for the correlations of preoperative CCTs and r-TEG parameters with intraoperative blood loss and blood product requests. The *r* values were defined as weak ($r<0.3$), moderate ($0.3\leq r<0.7$), or strong ($r\geq 0.7$). After selecting the most highly correlating CCTs or r-TEG parameter, logistic regression and receiver operating characteristics (ROC) curve analyses were performed to determine the optimal cut-off values with the highest specificity for the highest factor. Statistical analyses were performed using SPSS for MAC version 21.0

Table 1. Subject characteristics and surgical data

Variables	
Patient characteristics	
Age (yr)	49.2±9.2
Sex, male/female (n)	50/15
Body mass index (kg/m^2)	22.9±3.1
MELD score	31.5±7.9
Hemoglobin, g/L	112.9±28.8
Hct, %	33.4±7.9
Platelet count, 10^9/L	131.2±100.0
Liver disease	
HBV cirrhosis	40 (61.5%)
With hepatocarcinoma	34 (52.3%)
HCV cirrhosis	5 (7.7%)
With hepatocarcinoma	4 (6.2%)
HBV and HCV cirrhosis	1 (1.5%)
With hepatocarcinoma	1 (1.5%)
Alcohol cirrhosis	7 (10.7%)
With hepatocarcinoma	4 (6.2%)
Hepatic acute/subacute failure	1 (1.5%)
Biliary disease	6 (9.2%)
Primary cirrhosis	7 (10.7%)
With hepatocarcinoma	4 (6.2%)
Type of transplant	
First transplant	64 (98.4%)
Retransplant	1 (1.6%)
Blood loss (mL)	2650 (1600-4500)
Intraoperative blood transfusion	
PRBC (units)	10 (7.5-16)
FFP (mL)	1285 (790-2030)
Platelet (units)	0 (0-1)
Cryoprecipitate (units)	9.5 (0-14)
Intraoperative fluid transfusion	
Crystalloids (mL)	4615 (2400-6100)
Albumin	735 (600-900)
Postoperative blood transfusion	
PRBC (units)	0 (0-4)
FFP (mL)	0 (0-100)
Platelet (units)	0 (0-1)
Cryoprecipitate (units)	0 (0-0)
Mechanical ventilation time (hour)	19 (13-31)
Postoperative hospital stay (day)	23 (19-28)

Data are expressed as number of patients (%), mean (SD), or median (25th percentile, 75th percentile). MELD, model for end-stage liver disease; Hct, haematocrit; HBV, hepatitis B virus; HCV, hepatitis C virus; PRBCs, packed red blood cells; FFP, fresh frozen plasma.

(IBM Inc., Chicago, IL, USA). For all analyses, two-sided *p* values <0.05 were considered statistically significant.

Results

Patient demographics

The main features of the 65 patients at the time of surgery and the surgical characteristics of the OLTs are presented in **Table 1**. The mean (±SD) age and model of end-stage liver disease (MELD) score were 49.2±9.8 years and 31.5±7.9, respectively. The median volume of intraoperative blood loss was 2650 (1600-4500) mL, the median crystalloid infusion was 4615 (2400-6100) mL of acetated Ringer's solution, and the median volume of albumin, 10% was 435 (300-700) ml. During OLT, patients received 10 (7.5-16) units of PRBCs, 1285 (790-2030) mL of FFP, 0 (0-1) units of platelets, and 9.5 (0-14) units of cryoprecipitate. The preoperative CCT and TEG parameters are shown in **Table 2**.

Preoperative CCT and TEG correlations with intraoperative blood loss and blood product transfusions

The preoperative CCT and TEG correlations with intraoperative blood loss are summarized in **Table 3**, and those with blood product transfusions are presented in **Table 4**. The PT, INR, FBG, PTR, PTA and TT of the CCTs were moderately correlated with intraoperative blood loss (r=0.332, P<0.01; r=0.404, P<0.01; r=-0.373; r=0.403, P<0.01; r=-0.477, P<0.001; r=0.417, P<0.01, respectively), whereas APTT was weakly correlated with intraoperative blood loss (r=-0.283, P<0.05); PTA was more strongly correlated with intraoperative blood loss than were the other CCTs parameters. The TEG parameters of R time, K value, α angle, MA and CI were moderately correlated with intraoperative blood loss (r=0.381, P<0.01; r=0.402, P<0.01; r=-0.363, P<0.01; r=-0.337, P<0.01; r=-0.423, P<0.01, respectively), but CI was more strongly correlated than the other TEG parameters. Regarding the intraoperative blood product requests, PTA showed strong correlations with PRBC and FFP transfusions (r=-0.838, P< 0.001; r=-0.810, P<0.001, respectively), and these correlations were stronger than the correlations of other CCT parameters. Moreover, the CI of TEG showed moderate correlations with PRBC, FFP, platelet and cryoprecipitate transfusions (r=-0.424, P<0.01; r=-0.524, P<0.01; r=-0.695, P<0.01; r=-0.464, P<0.01, respectively), and the other TEG parameters exhibited weaker correlations than those of the

Table 2. Preoperative CCTs and TEG parameters

Variables	
PT, S	15.4±8.2
INR	1.4±0.8
FBG, g/L	2.3±1
PTR	1.4±0.8
PTA, %	69.8±25.2
APTT, S	37.9±12.6
TT	16.1±5.8
R time, min	5.5±1.9
K time, min	3.5±2.9
α, deg	58.4±13.8
MA, mm	49.0±14.0
CI	-2.2±4.6
LY30	0.8±1.1

Data are described as the mean ± SD. PT, prothrombin time; INR, international normalized ratio; FBG, fibrinogen; PTR, prothrombin time ratio; PTA, prothrombin activity; aPTT, activated partial thromboplastin time; TT, thrombin time; R time, reaction time; K time, clot formation time; α, alpha angle; MA, maximum amplitude; CI, clotting index (CI); LY30, lysis index at 30 min after MA.

Table 3. Correlation with blood loss during OLT

Variables	*r* value	Sig.
CCTs		
PT	0.332**	0.007
INR	0.404**	0.001
FBG	-0.373*	0.002
PTR	0.403**	0.001
PTA	-0.477**	0.000
APTT	0.283*	0.022
TT	0.417**	0.001
TEG		
R time	0.381**	0.002
K time	0.402**	0.001
α	-0.363**	0.003
MA	-0.327**	0.008
CI	-0.423**	0.000
LY30	-0.172	0.170

r is Pearson's correlation coefficient; *, $P<0.05$; **, $P<0.01$.

CI. In summary, the TEG parameters were more weakly correlated than the CCT parameters with intraoperative blood loss and blood product transfusions during liver transplantation, and only PTA showed strong correlations with PRBC and FFP transfusions.

Logistic regression and ROC curves analysis

The CCT parameter PTA was selected for logistic regression and ROC curve analyses because only this parameter showed strong correlations with PRBC and FFP transfusions. A logistic regression model of PTA associated with PRBCs and FFP indicated that PTA is an independent predictor for PRBC and FFP transfusions. The data and regression equation for PRBC and FFP transfusions are presented in **Table 5**. The cut-off values for independent PTA with the sensitivity and specificity that best predicted the transfusion threshold for PRBCs and FFP are shown in **Table 6**. ROC curves for the prediction of the transfusion of PRBCs and FFP are presented in **Figure 1**.

Discussion

In this study, the correlations of CCT and TEG parameters with blood loss and blood product requirements during OLT were retrospectively assessed using data from 65 consecutive cases of adult OLT. The CI was the TEG parameter that was most moderately correlated with blood loss and blood transfusion, and these correlations were stronger than those of the other parameters. In addition, the PTA of CCTs showed similar results. However, PTA showed strong correlation with PRBC and FFP transfusions and shows good performance for the prediction of PRBC and FFP transfusions. Thus, although both CCTs and TEG cannot accurately assess blood loss, the PTA showed better correlations with and prediction value for PRBC and FFP transfusions.

Patients with end-stage liver disease most often exhibit profound changes in hemostatic variables. Reduced coagulation factor activities can commonly be observed in end-stage liver disease because the liver synthesizes nearly all the coagulation factors, including FII, FV, FVII, FVIII, FIX, FX, FXI, FXII and FXIII [11]. As massive blood loss, hemodynamic instability and multiple organ failure may be caused by coagulopathy, a high-quality preoperative assessment of coagulation conducted by an anesthesiologist is required for the welfare of the liver transplant recipient. A model for massive blood transfusion was created by McKlusky, and its risk index consists of seven variables: age >40 years, Hb concentration <100 g/L, platelet count $<70\times10^9$, creatinine >100 μmol/L for

Table 4. Correlation with blood product transfusions during OLT

Variables	PRBCs		FFP		Platelets		Cryoprecipitate	
	r	Sig.	r	Sig.	r	Sig.	r	Sig.
CCT								
PT	0.447**	0.000	0.454**	0.000	0.252*	0.043	-0.001	0.995
INR	0.549**	0.000	0.654**	0.000	0.506**	0.000	0.295*	0.017
FBG	-0.548**	0.000	-0.508**	0.005	-0.496**	0.000	-0.373**	0.002
PTR	0.540**	0.000	0.647**	0.000	0.500**	0.000	0.288*	0.020
PTA	-0.838**	0.000	-0.810**	0.000	-0.520**	0.000	-0.496**	0.000
APTT	0.368**	0.003	0.370**	0.002	0.386**	0.001	0.182	0.147
TT	0.480**	0.000	0.375	0.002	0.449**	0.000	0.237	0.057
TEG								
R time	0.216	0.084	0.349**	0.004	0.383**	0.002	0.344**	0.005
K time	0.444*	0.000	0.518**	0.000	0.662**	0.000	0.456**	0.000
α	-0.362**	0.003	-0.433**	0.000	-0.639**	0.000	-0.392**	0.001
MA	-0.424**	0.020	-0.495**	0.000	-0.681**	0.000	-0.393**	0.001
CI	-0.456**	0.000	-0.524**	0.000	-0.695**	0.000	-0.464**	0.000

r is Pearson's correlation coefficient; *, P<0.05; **, P<0.01.

Table 5. Logistic regression model of PTA associated with PRBCs and FFP

Variables	B	SE	P	OR	95% CI
PRBCs	-0.120	0.032	0.000	0.887	0.833-0.944
FFP	-0.115	0.031	0.000	0.892	0.840-0.947

The regression equation for PRBC transfusion is 9.982-0.12× PTA, and the correlation coefficient R2 for the regression equation equals 0.61. The regression equation for PRBC transfusion is 9.642-0.115× PTA, and the correlation coefficient R2 for the regression equation equals 0.586.

females and >120 μmol/L for males, albumin <24 g/L and repeat transplantation [12]. As a point-of-care monitoring system, TEG was first introduced for OLT coagulation management in 1985, and it can provide numerical information concerning the rate, strength and stability of overall clot formation [13]. Some previous studies have explored the use of CCTs, such as PT, INR and aPTT, and viscoelastic tests, such as TEG and TEM, for the prediction of blood transfusion requirements. In this retrospective study, PTA, which was calculated by the system based on the PT, was moderately correlated with blood loss and strongly correlated with PRBC and FFP transfusions. In addition, the results of the logistic regression and ROC curve analyses showed that PTA exhibits good performance for the prediction of PRBC and FFP transfusions.

One study that used multivariate regression to form a predictive model removed platelet count but included PT as a predictive variable [9]. However, in our study, PT did not show any correlation with blood loss or blood product transfusions. This result corresponds with the research of Tripodi et al, which demonstrated a relatively poor correlation between bleeding and PT in patients with chronic liver disease [14]. Platelet count is often decreased in cases of advanced liver disease, and some mechanisms explaining this phenomenon have been described. However, platelet activity is often increased in liver disease, similar to the von Willebrand factor, which is derived from endothelium [15]. Thus, the function of platelets increases, compensating for the decreasing platelet count in end-stage liver disease; the MA of TEG is reflective of clot strength, which results from interactions between platelets and fibrinogen [16]. The MA of TEG primarily assesses the condition of platelets in liver disease, including platelet count and function. In our retrospective study, the MA was moderately correlated with blood loss and FFP, platelet and cryoprecipitate transfusion, but these correlations were weaker than those of CI.

The INR is commonly elevated in cirrhosis and is used in conjunction with bilirubin and creatinine concentrations to determine the MELD score, which describes the severity of liver disease, and is widely used during OLT [17]. However, our results show that INR is not better than PTA for predicting blood loss and transfu-

Table 6. Cut-off values of PTA with sensitivity and specificity for predicting the transfusion threshold for PRBCs and FFP

Variables	Cut-off	Sensitiviey, %	Specificity, %	AUC	*P* value	SE	CI
PRBCs	83.5	82.6	92.7	0.915	<0.001	0.036	0.893-0.986
FFP	83.5	81.8	90.7	0.902	<0.001	0.038	0.828-0.976

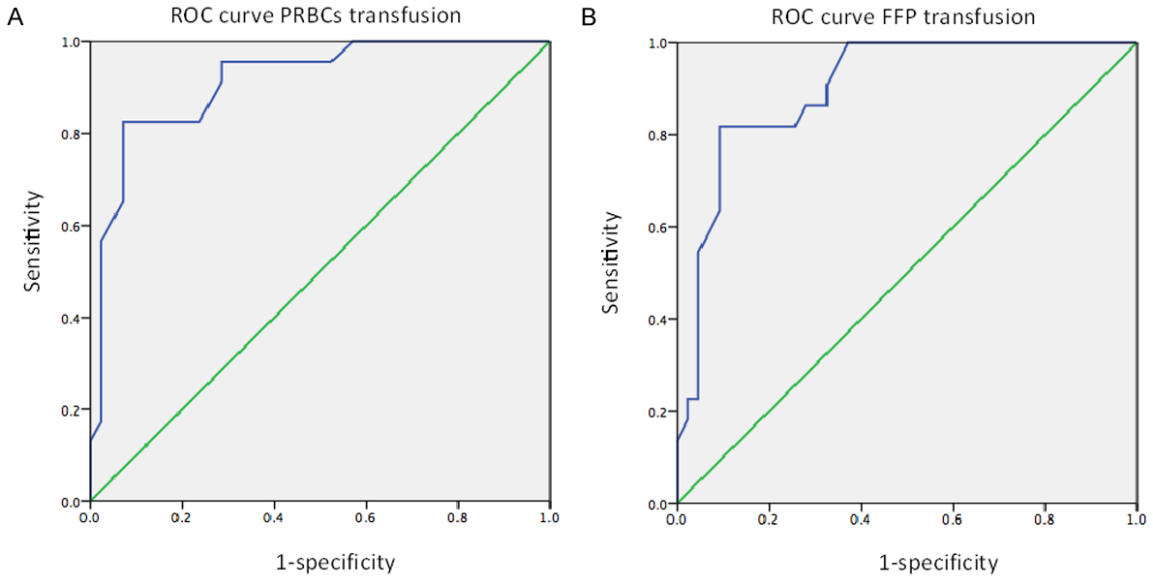

Figure 1. ROC curves for the PTA-based prediction of (A) PRBCs and (B) FFP transfusions. The corresponding data are presented in **Table 6**.

sion requirements. In our future work, we will attempt to develop a new PTA-based model for assessing blood loss and transfusion requirements before OLT. No benefits of transfusion with FFP, platelets, recombinant activated factor VIIa or tranexamic acid have yet been demonstrated as prophylactic interventions in the hemostatic system [18-20]. As such, whether elevated PTA before OLT is a safe and useful prophylactic will be studied in our future work.

Blood loss and transfusion requirements in OLT are multifactorial and can be influenced by liver disease etiology and severity, preexisting coagulopathy, previous abdominal surgeries, preoperative hematocrit, surgical techniques and clamping methods, surgical team experience, and central venous pressure, as well as the use of antifibrinolytics, procoagulants and viscoelastic tests during the transplantation [21]. Anesthetists who are invested in OLTs adequately assess blood loss and transfusion requirements as a first step prior to anesthesia. Although TEG is widely used during OLT, CCTs could not be replaced by TEG for the preoperative coagulation assessment because PTA could be used as a predictor of PRBC and FFP transfusions based on this retrospective study.

Some limitations of this study should be mentioned. Although the von Willebrand factor, vascular disorders, and endothelial cell dysfunction are of concern in cases of microvascular bleeding, they were not assessed prior to OLT [22]. In addition, while this was a retrospective study, standardized management in our center of anesthesia during OLT minimized the confounding variables. Further research should be performed to develop more precise predictive models of blood loss and transfusion.

Conclusion

In conclusion, to the best of our knowledge, this is the first study demonstrating correlations of CCTs and TEG with blood loss and blood product transfusions during OLT. Our findings suggest that PTA is a strong predictor of PRBC and

FFP transfusions. A higher preoperative PTA was found to be indicative of lower PRBC and FFP requirements during OLT.

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Disclosure of conflict of interest

None.

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