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ORIGINAL ARTICLE

Assessment of rotational thromboelastometry for the prediction of red blood cell requirements in orthotopic liver transplantation

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ABSTRACT

BACKGROUND: In liver transplantation most studies were designed to predict massive transfusion rather than whether or not transfusion is required. We hypothesized that (presurgery) data from thromboelastometry may predict perioperative blood requirements.

METHODS: A *post-hoc* analysis of data from a controlled trial was performed with the primary end point of predicting zero red blood cells. Of the 92 patients studied, 6 were excluded because of incomplete EXTEM and/or FIBTEM data. The multivariate models included preoperative variables with a P value <0.10 in the univariate model: age, MELD score, hemoglobin, plasma fibrinogen, platelet count, activated partial thromboplastin time, INR, EXTEM maximum clot amplitude after 10 minutes, EXTEM an FIBTEM maximum clot firmness, plasma creatinine, and donor data.

RESULTS: Blood was transfused to 58% of patients during the surgical procedure and to 34% in the first 24 hours postoperatively. The final model was selected using a backward approach, and fractional polynomials were explored to assess model improvement for the prediction. Hemoglobin was a strong predictor: each 1 g/dL of hemoglobin increase reduced the risk of blood transfusion by 52%. An EXTEM maximum amplitude at 10 min was also a predictor of Red Blood requirement, showing a 64% risk reduction for values between the first quartile (35 mm) and the second quartile (41 mm) but no further improvement for the third and fourth quartiles and resulting in a prediction (ROC AUC of 0.815 [0.771-0.859]).

CONCLUSIONS: Presurgical EXTEM maximum amplitude at 10 min <35 mm is highly predictive of red blood administration during liver transplantation.

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Key words: Thromboelastometry - Blood transfusion - Liver transplantation.

Transfusion of red blood cells (RBC) is performed in 20% to 86% of liver transplantations (LT).[1] Prevention of excessive blood loss is an important objective in the perioperative management of LT because it is associated with postoperative infection, acute lung injury, and reduced graft survival.[2, 3] As a result of improvements in anesthetic, surgical and intraoperative coagulation management.[4, 5] RBC requirements have

been reduced, so the relative importance of preoperative predictors of blood loss should increase. Preoperative hemoglobin (Hb) and Model End-Stage Liver Disease (MELD) Score or its components may correlate with RBC usage.[2, 3, 6-8] However, prediction of blood product requirements in LT based on these preoperative variables is unreliable because Hb and MELD score are not modifiable just before LT, or even in the extended period between anesthesia induction and end of hepatectomy. Also, most prediction studies are of a retrospective nature and were designed to predict massive transfusion (>6 units of RBC) rather than whether or not transfusion is required. Therefore, other preoperative patient data are needed to predict RBC requirement during LT. Rotational thromboelastometry (ROTEM®) assesses the viscoelastic properties of a whole blood sample as a function of time to reflect the function and interaction of plasma, blood cells, and platelets. Although it is recommended to guide hemostatic management during LT,[9] there are no studies evaluating these tests as predictors of blood transfusion. We hypothesized that basal (presurgery) data from ROTEM® may predict perioperative RBC requirements in LT.

Materials and methods

A *post-hoc* analysis of data from a multicenter, Hb-stratified, controlled trial conducted in five teaching hospitals was used. Information of the previous trial has already been published.[10] The Institutional review board approval number was AC 123/10 and any informed consent from human subjects was obtained as required.

Patients

Eligible participants were all adults aged 18-80 years who were scheduled for LT. Exclusion criteria were a history of allergic reaction to fibrinogen concentrate, a known history of thromboembolic events in the last 30 days, known or suspected pregnancy, known presence of congenital bleeding disorder, and warfarin therapy. Also excluded were the following indications for transplantation: familial polyneuropathy and living donors because of variability in surgical technique; acute liver failure, biliary cirrhosis, and sclerosing cholangitis because of high rates of hypercoagulation; and non-heart-beating donors because of higher blood requirements in comparison with heart-beating donors.

Anesthesia and surgical management

All patients were placed on a convective air blanket (WarmTouch; Mallincrod Medical, St. Louis, MO, USA). Oxygen was given for 5 min before standard anesthesia management. Arterial and central venous cannulas were placed in all patients. Crystalloid fluid replacement (7 mL/kg per hour) was used to maintain blood volume, and colloids were used to improve hemodynamic status at the discretion of the anesthesiologist. Intravenous calcium was administered to keep the plasma calcium ion concentration within reference range. Normothermia was maintained. Vena cava preservation was attempted in all patients. If preservation was not feasible, venovenous bypass or a complete caval clamp was used and recorded in the patient's electronic case record form. The liver allograft was preserved in University of Wisconsin solution. Prior to reperfusion of the graft, it was flushed with 1000 mL Hartmann's solution at 38 °C to remove air and detritus from the wall of the graft's inferior vena cava. Next, the distal end of the donor's vena cava was closed with a vascular stapler. Vasoconstrictor drugs were administered to compensate for reperfusion syndrome. Blood samples were taken at following times: baseline, anhepatic phase, 30 minutes after graft reperfusion and end of surgery. Laboratory data and transfusion requirements were assessed at each the study phases and analyzed by means of a repeated measurements model taking into account the intra-subject correlation as well as the recurrence of the dependent variable. At the end of surgery, all patients remained mechanically ventilated and were transferred to a surgical Intensive Care Unit.

Intraoperative and postoperative transfusion management

Although thromboelastometry (ROTEM® delta, TEM International GmbH, Muenchen, Germany) was performed in all patients (EXTEM and FIBTEM tests), blood product transfusion was guided by the standard coagulation test criteria.

The protocols for blood transfusion were monitored to ensure consistency and compliance across all the research centers according to the following transfusion criteria: 1) packed RBCs to maintain Hb>8 g/dL; 2) platelet concentrates if blood platelet count fell to 50,000/mm^3; 3) fibrinogen concentrate if fibrinogen levels fell to <1 g/L,; 4) fibrinolysis was treat with intravenous tranexamic acid boluses of 500 mg if >15% lysis at 60 min was detected by thromboelastometry); 5) fresh frozen plasma transfusion (2 U/30 min) only if bleeding persisted despite the aforementioned measures.

Cell saver devices were not used. Hemostatic surgical management followed standard protocol. In each center, a data quality-monitoring procedure was established to ensure that these level checks were done and that the results were recorded and reported in accordance with the study protocol and good clinical practice. Members of the institutional review board and the public health funding agency had access to the patient data throughout the study. Assessments were done regularly at preset follow-up intervals as patients were included in the trial.

Outcomes and statistical methods

The primary end point was the prediction of zero RBC intraoperatively and 24 hours post-surgery. To evaluate the influence of Hb in the prediction, we created two groups: one in which the Hb level was <9.5 g/dL, and one in which it was >9.5 g/dL, according to the random stratification used in the previous trial: The randomization sequence was created using a computer-generated random list, which was then stratified according to whether the baseline hemoglobin concentration was <9.5 g/dL or not and by center (1:1 ratio, in blocks of multiples of two units).[10]

Thromboelastometry was checked at patient arrival at the operating room, before the induction of the anesthesia and prior the infusion of fibrinogen or placebo. Therefore, presurgical thromboelastometry of all patients were included in the analysis.

The multivariate models included preoperative variables with a P value <0.10 in the univariate model testing: age, MELD Score, Hb, plasma fibrinogen level, platelet count, activated partial thromboplastin time, international normalized ratio, EXTEM maximum clot amplitude after 10 minutes (MA10), EXTEM maximum clot firmness (MCF), FIBTEM MA10, FIBTEM MCF, plasma creatinine, and donor data (age, warm and cold ischemia). The final model was selected using a backward approach, and fractional polynomials were explored to assess model improvement for the prediction.

Data are expressed as frequencies and percentages for categorical variables and as median (interquartile range) for continuous variables, or are specified otherwise. A Fisher's Exact Test was used for categorical variables and a Mann-Whitney Test for continuous variables. A logistic generalized linear mixed model for RBC transfusion by repeated measures was fitted using penalized quasi-likelihood based on restricted maximum likelihood with intercept declared as random and the rest of factors as fixed effects.[11] Convergence criteria and positiveness of the estimated G matrix were checked for all models. Since standard goodness of fitting measures are not suitable with these models, we checked them in a standard logistic regression by fitting the obtained explanatory linear predictors.

The area under the receiver operating characteristic curve (ROC AUC) for repeated data was calculated with the predicted models using the GlimRoc SAS macro.[12] Fibrinogen, EXTEM and FIBTEM missing data (which were always <9% of the cases) were imputed using the expectation-maximization algorithm, which relies on the flexible and reasonable missing at random assumption.[13] A sensi-

tivity analysis was conducted using only the observed data (*i.e.*: without any imputation) and the results lead to the same conclusions.

In order to find cut off values, the results were divided in four quartiles groups according to the distribution values of each particular variable.

The analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Significance was set at a two-sided P value of 0.05.

Results

Of the 92 patients studied, six were excluded because the ROTEM® data were incomplete. Of the remaining 86 patients, before surgery 18 had an Hb lower than 9.5 g/dL and 68 had an Hb higher than 9.5 g/dL. Characteristics of patients, donors, and surgical data are shown in Tables I, II. Patients with Hb<9.5 g/dL were sicker and their overall hemostatic and coagulation data were impaired in comparison with patients with Hb >9.5 g/dL. Except for the cold ischemia time, which was longer in the lower Hb group, there were no differences in donor data and surgical technique between groups. Blood was transfused to 58% of patients during the surgical procedure and to 34% in the first 24 hours postoperatively. Patients with Hb<9.5 g/dL showed more hemorrhagic complications, had a higher incidence of reperfusion syndrome, and overall had a greater blood product and fluid requirement during surgery and during the first 24 hours postoperatively (Table III). However, no differences were found in retransplantation and in-hospital mortality.

Odds ratio and ROC analysis are expressed in Table IV. Hb moderately predicted RBC requirement in patients with an Hb level <9.5 g/dL but was a strong predictor of RBC requirement in patients with an Hb level >9.5 g/dL. For each 1 g/dL of Hb increase, there was a

TABLE I.—*Patient and donor characteristics.*

	Hb<9.5g/dL N.=18	Hb>9.5g/dL N.=68	Total N.=86	P value
Patient characteristics				
Sex (male)	15 (83.3%)	53 (77.9%)	68 (79.1%)	0.597
Weight (kg)	75 (70-82)	77 (63-92)	76 (64-91)	0.924
Age (years)	54 (49-64)	55 (50-63)	55 (50-63)	0.468
Height (cm)	166 (162-175)	168 (162-174)	167 (162-174)	0.808
BMI (kg/m^2)	26 (24-28)	26 (24-30)	26 (24-30)	0.861
MELD	22 (20-26)	15 (10-19)	16 (12-21)	<0.001*
Hb (g/dL)	8.7 (8.3-8.9)	12.1 (10.9-14.0)	11.5 (9.9-13.6)	<0.001*
Platelet count (10^3/mm^3)	55 (42-91)	78 (54-99)	72 (50-99)	0.052
PTT	1.46 (1.30-1.72)	1.19 (1.08-1.32)	1.22 (1.09-1.36)	<0.001*
INR ratio	0.89 (0.39-1.30)	1.45 (1.10-2.00)	1.02 (0.50-1.40-)	0.003**
Fibrinogen (g/L)	1.45 (0.90-1.80)	2.02 (1.60-2.51)	1.88 (1.50-2.40)	<0.001*
Fibrinogen <1 g/L	6 (33.3%)	2 (3%)	8 (9.3%)	<0.001*
EXTEM				
MA10 (mm)	30 (28-34)	39 (34-44)	36 (31-42)	<0.001*
MCF (mm)	38 (34-42)	49 (42-54)	45 (40-51)	<0.001*
Lysis (%)	5 (2-10)	5 (2-9)	5 (2-9)	0.722
FIBTEM				
MA10 (mm)	6 (4-10)	9 (7-10)	9 (6-10)	0.028**
MCF (mm)	7 (5-10)	9 (7-11)	9 (7-11)	0.012**
Donor characteristics				
Age (years)	62 (44-74)	59 (50-70)	60 (50-70)	0.618
Height (cm)	168 (160-175)	168 (160-176)	168 (160-176)	0.662
Sodium (mmol/L)	135 (131-137)	136 (131-139)	136 (131-139)	0.293

Data are given as: median (P25, P75) or N. (%); MELD: Mayo End-Stage Liver Disease.
BMI: Body Mass Index; Hb: hemoglobin; MA10: maximum amplitude at 10 min; MCF: maximum clot firmness.
*P<0.001; **P<0.05.

TABLE II.—*Surgical characteristics.*

	Hb<9.5g/L N.=18	Hb>9.5g/L N.=68	Total N.=86	P value
Surgical characteristics				
Piggyback	18 (100)	67 (98)	85 (99)	1.000
Portocaval shunt	4 (22)	12 (18)	16 (19)	0.735
Vena cava clamp	0 (0)	2 (3)	2 (2)	1.000
Lowest mean blood pressure (mmHg)	72 (65-90)	85 (75-102)	84 (70-102)	0.057
Temperature before reperfusion (ºC)	35.1 (34.6-35.5)	35.4 (34.9-36)	35.4 (34.8-36)	0.123
Temperature after reperfusion (ºC)	34.9 (34.3-35.4)	35.1 (34.3-35.6)	35 (34.3-35.5)	0.399
Cold ischemia (min)	415 (338-490)	323 (250-413)	344 (266-430)	0.018*
Warm ischemia (min)	35.9 (34.3-35.4)	35.1 (34.3-35.6)	35 (34.3-35.5)	0.547
Reperfusion syndrome (%)	9 (50%)	15 (22%)	24 (28%)	0.036*
Vasoconstrictor requirements (%)	14 (78%)	45 (66%)	59 (68%)	0.406
Hemorrhagic complications (%)	5 (28%)	2 (3%)	7 (8%)	0.004*
Thrombotic complications (%)	0 (0%)	2 (3%)	2 (2%)	1.000

Data are given as median (P25, P75) or N. (%).
*P<0.05.

TABLE III.—*Blood product transfusion intraoperatively and intraoperative plus 24 h postoperatively.*

	Hb<9.5g/dL N.=18	Hb>9.5g/dL N.=68	Total N.=86	P value [1]
Intraoperative				
RBC (units)	4 (2-5)	0.5 (0-2)	1 (0-3)	<0.001*
No RBC	2 (11%)	34 (50%)	50 (58%)	0.003**
≥6	3 (17%)	3 (4%)	6 (7%)	0.103
≥10	1 (6%)	0 (0%)	1 (1%)	0.209
FFP (units)	0 (0-2)	0 (0-0)	0 (0-0)	0.037**
Platelets (mL)	250 (0-300)	0 (0-250)	0 (0-260)	0.096
Preemptive fibrinogen (g)	2.5 (0-6)	1 (0-3)	1 (0-4)	0.073
Preemptive fibrinogen N. (%)	10 (55.5%)	35 (51.5%)	45 (50.2%)	0.758
Additional fibrinogen (g)	3.5 (0-6)	0 (0-0)	0 (0-2)	0.003**
Additional fibrinogen N. (%)	13 (72%)	16 (23.5%)	29 (33.7%)	<0.001*
Tranexamic (%)	3 (17%)	13 (19%)	16 (19%)	1.000
Crystalloids (mL)	1700 (1400-2500)	2434 (1786-3725)	2178 (1600-3365)	0.054
Colloids (mL)	0 (0-1000)	0 (0-500)	0 (0-500)	0.225
Bicarbonate (mL)	50 (0-200)	50 (0-250)	50 (0-250)	0.858
Intraoperative plus 24 h postoperatively				
RBC (units)	5 (3-7)	2(0-3.5)	2 (0-4)	<0.001*
No RBC	0 (0%)	29 (43%)	29 (34%)	0.004**
≥6	8 (44%)	7 (10%)	15 (17%)	0.002**
≥10	3 (17%)	0 (0%)	3 (3%)	0.008**
FFP (units)	1 (0-3)	0 (0-0)	0 (0-1)	0.002**
Platelets (mL)	250 (0-300)	0 (0-260)	0 (0-292)	0.125
Fibrinogen (g) surgery and 24 h	3.5 (0-6)	0 (0-0)	0 (0-2)	0.003**
Fibrinogen (g) overall	6.5 (5-8)	1.8 (0-4)	3 (1-5)	<0.001*

Data are given as median (P25, P75) or N. (%).
RBC: red blood cells; FFP: fresh frozen plasma.
[1]P value from the Fisher's Exact Test for categorical variables and from the Mann-Whitney Test for the rest; *P<0.001, **P<0.05.

52% risk reduction for blood transfusion. EXTEM MA10 was also a predictor of RBC administration, showing a risk reduction of 64% for values of EXTEM MA10 between the first quartile (35 mm) and the second quartile (41 mm) and no further improvement for the third and the fourth quartiles, and resulting in a prediction of RBC requirement (ROC AUC of 0.815 [0.771-0.859]) similar to those obtained for Hb or Hb plus EXTEM MA10 (Table IV).

TABLE IV.—*Multivariate analysis of prediction of RBC requirement according to baseline hemoglobin of the patient population.*

Population	Model	Variable	OR [95%CI]	P value	ROC AUC [95%CI]
Patients with baseline Hb<9.5 (N.=18)	A	Hb (per 1 g/dL increase)	0.70 [0.49-1.00]	0.051	0.599 [0.488 -0.710]
Patients with Baseline Hb≥9.5 (N.=68)	B	Hb (per 1 g/dL increase)	0.48 [0.39-0.58]	<0.001	0.830 [0.783 -0.878]
	C	EXTEM MA10 (ref=1st quartile)	1	0.008	0.815 [0.771 -0.859]
		2nd quartile	0.35 [0.16-0.74]		
		3nd quartile	0.42 [0.20-0.89]		
		4th quartile	0.33 [0.15-0.72]		
		1st quartile (ref) vs rest	0.36 [0.20-0.65]	0.001	
	D	Hb (per 1 g/dL increase)	0.49 [0.40-0.60]	<0.001	0.843 [0.796-0.889]
		EXTEM MA10 (ref=1st quartile)	1	0.201	
		2nd quartile	0.49 [0.22-1.12]		
		3nd quartile	0.56 [0.26-1.24]		
		4th quartile	0.47 [0.21-1.08]		
		1st quartile (ref) vs rest	0.51 [0.27-0.95]	0.034	

Hb: hemoglobin; ROC: receiver operating characteristic; MA10: maximum amplitude at 10 min; ref: reference category. Quartiles cut-off points for EXTEM MA10 are 35, 41 and 46 mm.

Discussion

Our study shows that Hb and the presurgical clot firmness in ROTEM® EXTEM predicts RBC requirement. It also confirms that, in the modern era of LT, other preoperative factors such previous surgery and surgical technique are not primarily determinant. Anemia in cirrhotic patients is multifactorial, hyperferritinemia and macrocytosis are consequences of the nutritional alteration produced by alcoholic cirrhosis, and a low value of ferritin may indicate a bleeding cause of anemia; overall, in cirrhotic patients the prevalence of anemia is around 25%.[14] The baseline Hb concentration of <9.5 g/dL was selected as a cut-off point because it was used to randomize patients in the previous controlled study.[10] However, the number of patients were not restricted to a 50% cutoff, and thus, this 16/86 (18.6%) reflects the observed prevalence in this sample. In patients with an Hb level lower than 9.5 g/dL, efforts to increase Hb level prior to LT may save blood products: even an increase of 1 g/dL may save blood transfusion. The new and important point of our study is that the maximum amplitude at 10 minutes in ROTEM® EXTEM can predict RBC requirements. Presurgical values of MA10 EXTEM <35 mm are highly predictive of RBC administration. We have also determined that values in the second to fourth quartiles of MA10 EXTEM (>40 mm) do not reduce RBC requirement.

Recent predictive studies of blood transfusion focus on massive transfusion,[15, 16] which is now uncommon. Other studies focusing on patients without blood transfusion did not consider graft and thromboelastometry parameters in the prediction of blood transfusion or take into account transfusion of blood products during the first 24 hours postoperatively [17-19] Fayed *et al.*[20] in a living donor liver transplantation, determined that coagulation time and EXTEM MCF were independent predictors of RBC transfusion and that FIBTEM MCF was a dependent predictor. There are major differences between this study and our study: first they used living donors; second, they guided blood transfusion by ROTEM® parameters; and finally, they used a liberal administration of fluid, and the blood product requirements were much higher.

LT is a dynamic surgical procedure involving profound hemodynamic and coagulation changes that are accentuated at reperfusion of the liver graft. A recent review states that thromboelastometry may reduce blood product transfusion in LT.[21] The main contributors to the MCF of the EXTEM are platelets and fibrinogen. In order to avoid blood transfusion, EXTEM MA10 (maximum clot amplitude after 10 minutes) or MCF may be corrected

by administering platelet or fibrinogen concentrate/cryoprecipitate, or both. Therefore, ROTEM® FIBTEM may be useful for guiding the specific correction of fibrinogen. In a previous study [10] we determined that the mean administration of 3.54 g of fibrinogen concentrate will produce an increase of 3.55 mm in EXTEM MA10, an increase of 3.29 mm in FIBTEM MA 10, and a mean increase of 0.3 g/L of plasma fibrinogen. The correction of platelets is more controversial: 50,000/mm^3 has been selected arbitrarily as a cutoff point because it can help thrombin generation,[22] but standard platelet therapy in cirrhotic patients increases platelet count to a very small degree and fails to normalize thromboelastography values.[23] Moreover, in our series basal EXTEM MA10 <35 mm was found in 40% of patients, whereas 23% of patients had a platelet count <50,000/mm^3. Consequently, we suggest correcting initially with fibrinogen if the platelet count is over 50,000/mm^3 and rechecking EXTEM MA10 for further consideration. Only in cases with a platelet count 50,000/mm^3 would a determination of FIBTEM be necessary.

Limitations of the study

This is a *post-hoc* analysis of a previous randomized study, in which both placebo and study groups had similar blood requirements, therefore should not influence the prediction results. Though nearly all cases had complete ROTEM® at different stages of LT, we did not explore other data to predict requirements but focused on presurgical ROTEM® data.

Conclusions

To our knowledge, such a comprehensive analysis of ROTEM® data on blood transfusion requirements has not been performed previously in an LT scenario. In conclusion, basal (presurgical) EXTEM MA10 <35 mm is highly predictive of RBC requirement during LT. Correction of EXTEM MA10 to obtain a range of values between 35 and 40 mm may reduce blood product usage, but this hypothesis remains to be demonstrated in a controlled trial.

Key messages

— Rotational thromboelastometry may predict perioperative RBC requirements in LT.

— Presurgical EXTEM MA10 values > 35 mm showed a 64% of risk reduction of RBC administration

— No further improvement in risk reduction of RBC administration was observed with EXTEM MA10 values > 41 mm.

— Standard platelet therapy in cirrhotic patients fails to normalize thromboelastography values. Consequently, we suggest correcting initially with and rechecking EXTEM MA10 for further consideration.

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