An assessment of thromboelastometry to monitor blood coagulation and guide transfusion support in liver transplantation

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BACKGROUND: Rotation thromboelastometry (TEM) has been proposed as a convenient alternative to standard coagulation tests in guiding the treatment of coagulopathy during orthotopic liver transplantation (OLT). This study was aimed at assessing the value of TEM in monitoring blood coagulation and guide transfusion support in OLT.

STUDY DESIGN AND METHODS: Standard coagulation and TEM (EXTEM and FIBTEM) tests were performed at four preestablished intraoperative time points in 236 OLTs and prospectively recorded in a dedicated database together with the main operative and transfusion data. Transfusion thresholds were based on standard coagulation tests. Spearman's rank correlation (ρ), linear regression, and receiver operating characteristic curves were used when appropriate.

RESULTS: EXTEM maximum clot firmness (MCF_{EXTEM}) was the TEM variable that best correlated with the platelet (PLT) and fibrinogen levels ($\rho = 0.62$ and $\rho = 0.69$, respectively). MCF_{FIBTEM} correlated with fibrinogen level ($\rho = 0.70$). EXTEM clot amplitude at 10 minutes ($A10_{EXTEM}$) was a good linear predictor of MCF_{EXTEM} ($R^2 = 0.93$). The cutoff values that best predicted the transfusion threshold for PLTs and fibrinogen were $A10_{EXTEM} = 35$ mm and $A10_{FIBTEM} = 8$ mm. At these values, the negative and positive predictive accuracies of TEM to predict the transfusion thresholds were 95 and 27%, respectively.

CONCLUSION: $A10_{EXTEM}$ is an adequate TEM variable to guide therapeutic decisions during OLT. Patients with $A10_{EXTEM}$ of greater than 35 mm are unlikely to bleed because of coagulation deficiencies, but using $A10_{EXTEM}$ of not more than 35 mm as the sole transfusion criterion can lead to unnecessary utilization of PLTs and fibrinogen-rich products.

Even though intraoperative coagulopathy is nowadays less frequent than it used to be in the early days of orthotopic liver transplantation (OLT), optimal management of blood coagulation remains key to reduce blood loss, minimize the transfusion of allogeneic blood products, and improve overall outcomes.[1,2] The complex coagulopathy of cirrhosis results from a variety of quantitative and qualitative deficiencies of the pro- and anticoagulant plasma proteins, reduced clearance of activated factors, enhanced fibrinolysis, thrombocytopenia, and abnormal platelet (PLT) function.[3,4] Replacement of blood losses with fluids and blood products, the function of the engrafted liver, and the myriad of unexpected intraoperative events further challenge the coagulation system.

Rotation thromboelastometry (TEM) and thromboelastography (TEG) are point-of-care devices that provide a comprehensive, real-time assessment of hemostasis from the start of clot formation to fibrinolysis.[5] The TEM device can be operated at the patient bedside or in the surgical room so that appropriate treatment of any coagulation derangement can be initiated immediately. Since both TEM and TEG are whole blood assays, they can detect functional alterations of PLTs and coagulation proteins, as well as the interaction between cellular elements

ABBREVIATIONS: A10 = clot amplitude at 10 minutes; MCF = maximum clot firmness; OLT(s) = orthotopic liver transplantation(s); PT = prothrombin time; ROC = receiver operating characteristic curves; TEG = thromboelastography; TEM = thromboelastometry.

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TRANSFUSION **;**:**-**.

and plasma factors, that are missed by the standard coagulation tests.[6]

TEM and TEG have been extensively used in cardiac surgery and in the management of the acute trauma patients[7] where they decreased the total amount of blood products transfused[8-13] and improved outcomes. With regard to OLT, the published experience is too scarce to fully evaluate TEM-based transfusion algorithms compared with those based on the standard coagulation tests. In the pioneering work conducted in the early 1980s, Kang and colleagues[14] found a poor correlation between TEG variables and standard coagulation tests. Compared with 47 historical controls monitored by standard coagulation tests, 58 patients monitored by TEG required significantly fewer red blood cell (RBC) transfusions but substantially more fresh-frozen plasma (FFP), PLTs, and cryoprecipitate, so that the total number of allogeneic blood products did not significantly differ between the two groups. In two recent, but substantially smaller, series of patients who were monitored by TEM or TEG during OLT, a better correlation between TEM (or TEG) and the standard coagulation tests was found,[15] and the TEM thresholds that best predicted severe thrombocytopenia and hypofibrinogenemia were defined.[16] Nevertheless, the question whether TEM-based transfusion algorithms produce better outcomes in OLT than those based on the standard coagulation tests remains unanswered.

Solving the above problem would require a large multicenter controlled trial comparing both strategies of coagulation monitoring and transfusion management.[17,18] Meanwhile, scenario analyses aimed at estimating which would have been the transfusion requirements had the transfusion criteria been based either on standard coagulation tests or on the equivalent TEM thresholds may provide limited but useful information.

This study had two main objectives: 1) to identify the TEM variables that best predicted the standard coagulation tests thresholds used as transfusion triggers for plasma, fibrinogen, and PLTs and 2) to estimate the transfusion requirements had the triggers been based on TEM instead of the standard tests. To achieve both goals we simultaneously performed TEM-based and standard coagulation tests at several intraoperative time points in a large series of consecutive patients undergoing OLT and collated the results with the transfusion requirements.

MATERIALS AND METHODS

Patients

We evaluated 265 consecutive OLTs performed in 253 patients at the Hospital Clinic of Barcelona between January 2007 and December 2009. Twenty-nine cases were excluded from the final analysis because the TEM tests could not be performed due to technical or logistical problems. Patient characteristics, details of surgery, intraoperioperative bleeding, transfusion requirements, and the results of the standard and TEM-based coagulation tests were prospectively recorded in a computerized database. The MELD (model for end-stage liver disease) score was weighted for hepatocarcinoma according to Sharma and colleagues[19] (range, 6-40). Blood products were transfused according to a preestablished protocol with RBCs suspended in saline-adenine-glucose-mannitol, methylene blue–photoinactivated plasma, pooled PLT concentrates, and cryoprecipitate or manufactured fibrinogen concentrate (Haemocomplettan, CSL Behring GMBH, Marburg, Germany). RBCs were transfused to maintain the hemoglobin (Hb) level higher than 80 g/L. Transfusion of non-RBC blood products was based on clinical grounds and guided by the results of the standard coagulation tests according to a preestablished guideline. The thresholds for selecting plasma, fibrinogen (or cryoprecipitate), and PLTs were prothrombin time (PT) ratio of greater than 1.7, plasma fibrinogen level of less than 1.3 g/L, and PLT count of less than 50×10^9/L, respectively. The selected blood product was transfused whenever there was active bleeding and prophylactically at the time of graft reperfusion. In the presence of hypofibrinogenemia, plasma was given only when the PT ratio was kept at greater than 1.7 after having corrected the plasma fibrinogen level. The transfusion management of unusual complications was decided by consensus between the anesthesiologist and the hematologist. The study was approved by the ethics and research committee of the Hospital Clinic of Barcelona.

Blood sampling

Blood samples for standard and TEM-based coagulation tests were taken at preestablished time points during OLT: after induction of general anesthesia (T1 or baseline), at the end of the hepatectomy (T2), 20 minutes after graft revascularization (T3), and 90 minutes after graft revascularization (T4). The blood samples were collected in tubes containing 0.11 mol/L sodium citrate (BD Vacutainer, Becton Dickinson, Plymouth, UK) from a nonheparinized arterial catheter after discarding the first 10 mL.

Tromboelastometry

Rotation TEM was carried out on recalcified whole blood by means of the four-channel ROTEM gamma device operated according to manufacturer instructions and with the type and concentration of reagents as provided by Pentapharm (Munich, Germany). The TEM device was placed in the operating room, where it was operated by trained nurses under the supervision of an anesthesiologist and a hematologist. Blood samples were tested just after collection. The TEM tests routinely performed were EXTEM and FIBTEM. EXTEM is considered to reflect the

extrinsic activation of hemostasis whereas FIBTEM, which added cytochalasin D to inhibit PLT activity, is considered to reflect the contribution of fibrinogen to clot formation. The TEM variables investigated were 1) the clotting time, defined as the time (seconds) from start of measurement to initiation of clotting; 2) clot formation time, defined as the time (seconds) from initiation of clotting until a clot firmness of 20 mm is recorded; 3) maximum clot firmness (MCF), defined as the maximal amplitude (mm) of the graphical trace of clot firmness; and 4) alpha angle (α), defined as the tangent to the graphical trace at an amplitude of 2 mm.

Standard coagulation assays

Blood samples were centrifuged at $16{,}000 \times g$ for 5 minutes just after collection (Centrifuge 5415 C, Eppendorf Ibérica, Madrid, Spain) and the supernatant plasma was transferred to polypropylene tubes. The PT was measured on a coagulation analyzer (BCS XP, Siemens Healthcare Diagnostics, Deerfield, IL) according to the manufacturer's directions and reported as PT ratio. On this platform, the international sensitivity index of the thromboplastin reagent was 1.08, so that the PT international normalized ratio was very close to the crude PT ratio. Fibrinogen concentration was measured in g/L by the PT-derived method, with values below 2 g/L being checked by the Clauss method on a coagulometer (KC-1A, Amelung, Lemgo, Germany) using fibrinogen reagent (Diagnostica Stago, Asnières, France) according to the manufacturer's instructions. Previous experience with that platform had shown that fibrinogen concentration, as measured by the Clauss method, rarely decreases below 1.3 g/dL while the PT-derived result lies higher than 2 g/dL. All the standard coagulation tests were performed by dedicated personnel and results were available at the patient bedside by 20 minutes after blood collection.

Statistical analyses

Continuous variables were expressed as median and interquartile range. The chi-square test or the Fisher's exact test were used for qualitative or dichotomized variables, and the Mann-Whitney test for continuous variables. A two-tailed p value of less than 0.05 was taken as representing significance. Correlation between the standard coagulation tests and those performed on TEM was analyzed by Spearman's rank correlation coefficient (ρ) and linear regression. Receiver operating characteristic curves (ROC), expressed as area under the curve, were used to determine the threshold of the TEM variables that best predicted the transfusion triggers for plasma, fibrinogen, or PLTs. Sensitivity, specificity, and the positive and negative predictive values were calculated for each of the previously selected cutoff values. All analyses were performed with computer software (SPSS, Version 17, SPSS, Inc., Chicago, IL).

RESULTS

The main features of the 236 OLTs at the time of surgery and the characteristics of the liver transplantation are summarized in Table 1. The results from the TEM-based and the standard coagulation tests at the baseline time (T1) are shown in Table 2. Figure 1 displays the evolution of the standard coagulation values, the Hb, and the TEM variables (MCF_{EXTEM} and MCF_{FIBTEM}) during the liver transplantation. MCF_{EXTEM} was the TEM variable that best correlated with the PLT count and the fibrinogen level ($\rho = 0.62$ and $\rho = 0.69$, respectively; Fig. 2). MCF_{FIBTEM} was correlated with fibrinogen level ($\rho = 0.70$). No TEM vari-

TABLE 1. Patient characteristics, type of transplant, type of donor, and blood component transfusion

Patient characteristics	Median (interquartile range$_{25\text{-}75}$)
Age (years)	55 (47-61)
Sex, male/female (n)	164/72
Body mass index (kg/m)	26 (23-29)
MELD score	18 (12-22)
MELD weighted for HCC	22 (17-24)
Child-Pugh score (points)	9 (6-11)
(group)	A = 60, B = 64, C = 112
Liver disease	n = 236
HCV cirrhosis*	67
Hepatocarcinoma	63
Alcoholic cirrhosis*	38
Familial amyloid polyneuropathy	17
Hepatic acute/subacute failure	8
Biliary disease*	9
HBV cirrhosis*	6
Primary non-function	4
Budd-Chiari	2
Others	22
Type of transplant	n = 236
First transplant	208
Liver plus kidney transplant	11
Retransplant > 1 month	11
Retransplant < 1 month	6
Type of donor	n = 236
DBD	195
DCD	13
Donor of familiar amyloidotic polyneuropathy	17
Living donor	11
Blood component transfusion	Median (interquartile range$_{25\text{-}75}$)
RBCs (units)	3 (0-5)
FFP (mL)	996 (0-1503)
PLTs (yes/no)	49/187
Fibrinogen-rich products† (yes/no)	62/174

* Without hepatocarcinoma.
† Cryoprecipitate or human fibrinogen concentrate.
DBD = donor after brain death; DCD = donor after cardiac death; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus.

able was well correlated with the PT ratio, including the latency time until the clot initiation and the alpha angle (data not shown). MCF_{EXTEM} at T1 was the TEM variable that best correlated with the Child/MELD score ($\rho = -0.60$ and $\rho = -0.46$, respectively). Agreement between MCF values and standard coagulation tests did not significantly change across MELD scores (data not shown).

To find an early TEM variable that could be useful in guiding transfusion therapy, we investigated the correlation between MCF_{EXTEM} and the clot amplitude at different time points during the clot formation (Fig. 3). Clot amplitude at 10 minutes (A10) emerged as an accurate and convenient predictor of MCF_{EXTEM}.

By using ROC analysis, we identified the TEM cutoff values that more accurately predicted the thresholds of the standard coagulation tests used as transfusion triggers for PLTs and fibrinogen-rich products. MCF_{EXTEM} of 40 mm and MCF_{FIBTEM} of 8 mm were the best predictors of the fibrinogen transfusion trigger (1.3 g/L), the former also being the best predictor of the PLT transfusion trigger (50×10^9/L). When a similar analysis was done using the A10 instead of the MCF_{EXTEM}, the cutoff values that best predicted the transfusion trigger for fibrinogen were $A10_{EXTEM}$ of 35 mm and $A10_{FIBTEM}$ of 8 mm, the former being also highly predictive of the PLT transfusion trigger. No TEM variable was able to accurately predict the PT ratio used as threshold for plasma transfusion (PT ratio $\geq$ 1.7). Figure 2 illustrates the transfusion thresholds for both the TEM and the standard coagulation tests.

Table 3 summarizes the accuracy of the selected $A10_{EXTEM}$ values to predict the transfusion triggers based on the standard coagulation tests. As can be seen, the negative predictive accuracy of the TEM-based thresholds was high, assuring that values of MCF_{EXTEM} of greater than 40 mm or $A10_{EXTEM}$ of greater than 35 mm negate the need for PLT or fibrinogen transfusion. Nevertheless, the positive predictive accuracy was low, which indicates that many patients with MCF_{EXTEM} of less than 40 mm or $A10_{EXTEM}$ of less than 35 mm did not meet the criteria for transfusion of PLTs or fibrinogen based on the standard coagulation tests. These "false positive" results from MCF_{EXTEM} and $A10_{EXTEM}$ might represent a case of either undertransfusion on the current criteria or, alternatively, overtransfusion had the criteria for PLT and fibrinogen transfusion been based on TEM tests.

TABLE 2. Results of the standard and TEM coagulation tests at the beginning of liver transplant

Coagulation test	Median (interquartile range$_{25-75}$)
CT_{EXTEM} (sec)	77 (62-98)
CFT_{EXTEM} (sec)	176 (124-261)
MCF_{EXTEM} (mm)	44 (36-52)
MCF_{FIBTEM} (mm)	10 (7-14)
PLTs ($\times 10^9$/L)	73,000 (49,000-111,000)
Fibrinogen (g/L)	2.1 (1.6-2.8)
PT ratio	1.57 (1.32-1.90)

CFT = clot formation time; CT = clot time.

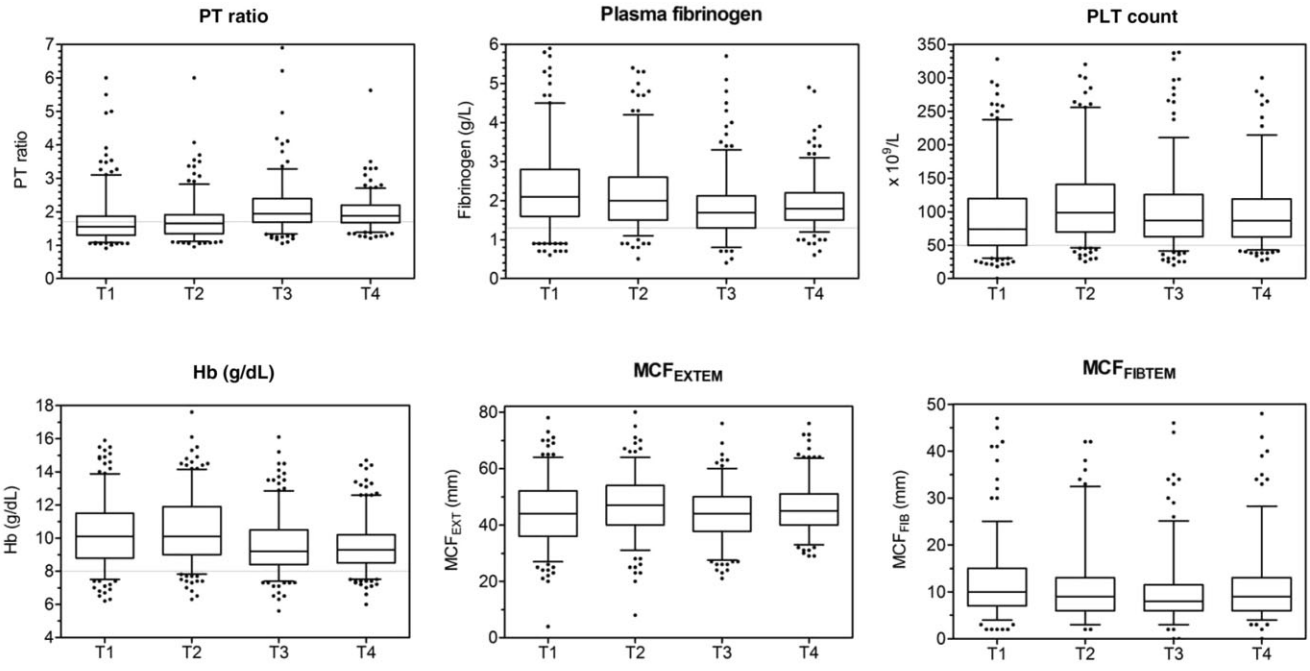

Fig. 1. Box-and-whiskers plot of standard and TEM coagulation tests and Hb at different time points during liver transplant (T1 = baseline; T2 = end of hepatectomy; T3 and T4 = 20 and 90 minutes, respectively, after graft reperfusion). The boxes stand for the median and the lower and upper quartiles; the whispers represent the 95% confidence interval.

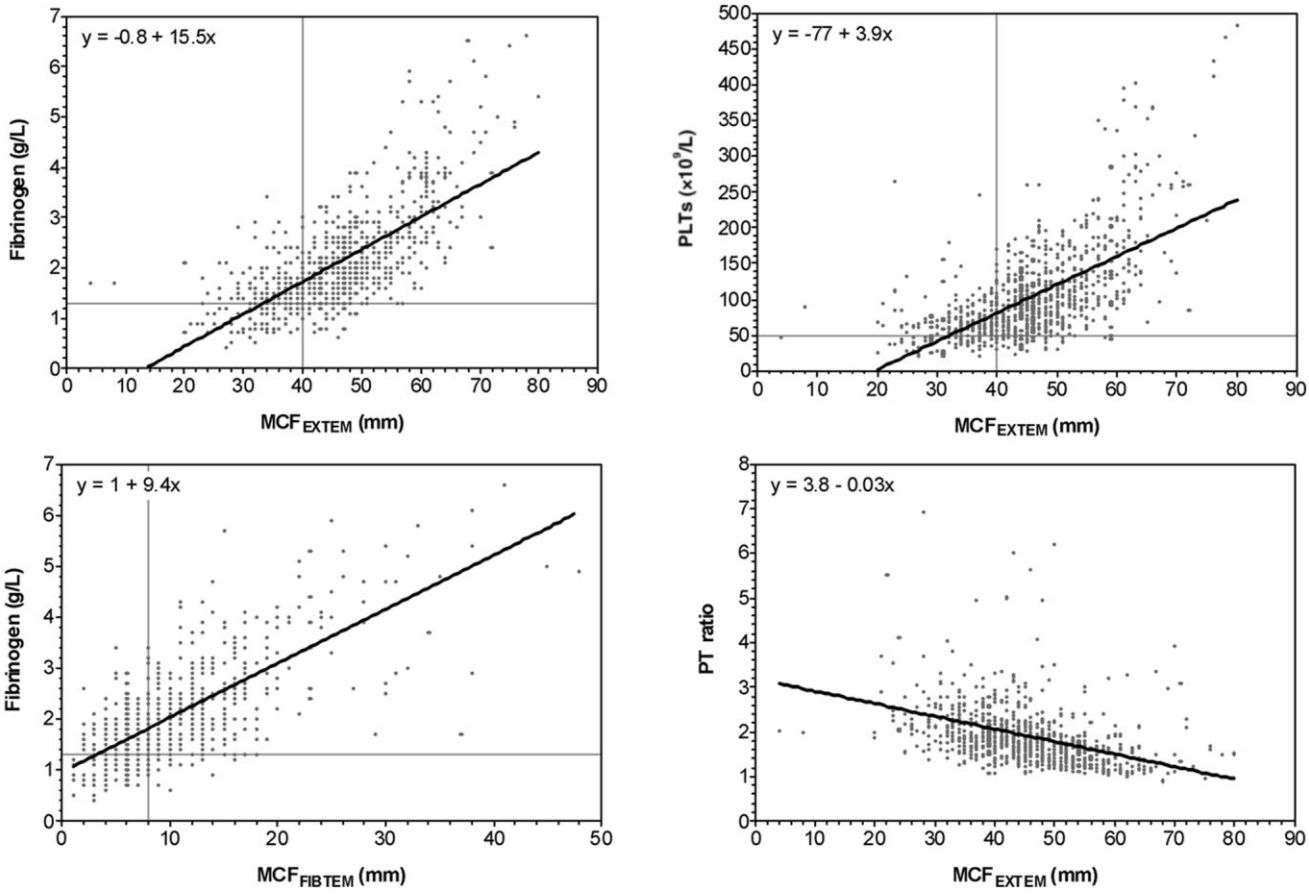

Fig. 2. Best linear regression between MCF_{EXTEM} and the results of standard coagulation tests. Horizontal lines represent the transfusion triggers based on the standard tests. Vertical lines represent the equivalent TEM-derived thresholds for transfusion of PLTs and fibrinogen-rich products. Points in the upper left quadrant correspond to cases that would have been transfused according to TEM but were not based on the standard tests: PT and MCF.

To discriminate between both alternatives, we further investigated a group of 140 patients who were above the transfusion threshold at T1 (PLTs $\geq 50 \times 10^9$/L and fibrinogen $\geq$1.3 g/dL), so that they did not receive PLTs or fibrinogen-rich products (Fig. 4). There were 33 patients with $A10_{EXTEM}$ of less than 35 mm and 107 patients with $A10_{EXTEM}$ of at least 35 mm. The blood loss during the hepatectomy was similar in both groups but the proportion of patients falling below the transfusion thresholds at T2 and/or requiring PLTs or fibrinogen-rich products between T2 and T3 was greater in the group with $A10_{EXTEM}$ of less than 35 mm at T1 (Table 4). Among the 33 patients with $A10_{EXTEM}$ of less than 35 mm at T1, 16 (48%) needed PLTs or fibrinogen-rich products between T2 and T3, whereas 17 (52%) neither fell below the transfusion thresholds at T2 nor required any support with PLTs of fibrinogen-rich products between T2 and T3 (Fig. 4). In this latter group, TEM as the sole guide for the correction of hemostasis would have led to unnecessary utilization of PLTs and fibrinogen since these products neither would have prevented a bleeding that did not happen nor would have anticipated a subsequent transfusion that did not take place. In the former group, in contrast, TEM would have anticipated a transfusion that later proved to be necessary.

DISCUSSION

In this study, we analyzed the value of TEM in the assessment of hemostasis in 236 consecutive cases of OLT. To the best of our knowledge, this is the largest study on TEM in the setting of OLT. We found that MCF_{EXTEM} was highly correlated with the PLT count and plasma fibrinogen level and that MCF_{FIBTEM} was a good linear predictor of fibrinogen level. The TEM-based coagulation results were very reliable to rule out the need for transfusion of PLTs and fibrinogen-rich products but they had a low positive predictive accuracy for thrombocytopenia and hypofibrinogenemia. As previously reported by Tripodi and coworkers[20] we found that MCF_{EXTEM} was well correlated

with the Child and MELD scores, even though our patients had more advanced liver disease. In this sense, the characteristics of our patients were comparable to those reported in other recent series of OLT.[21,22]

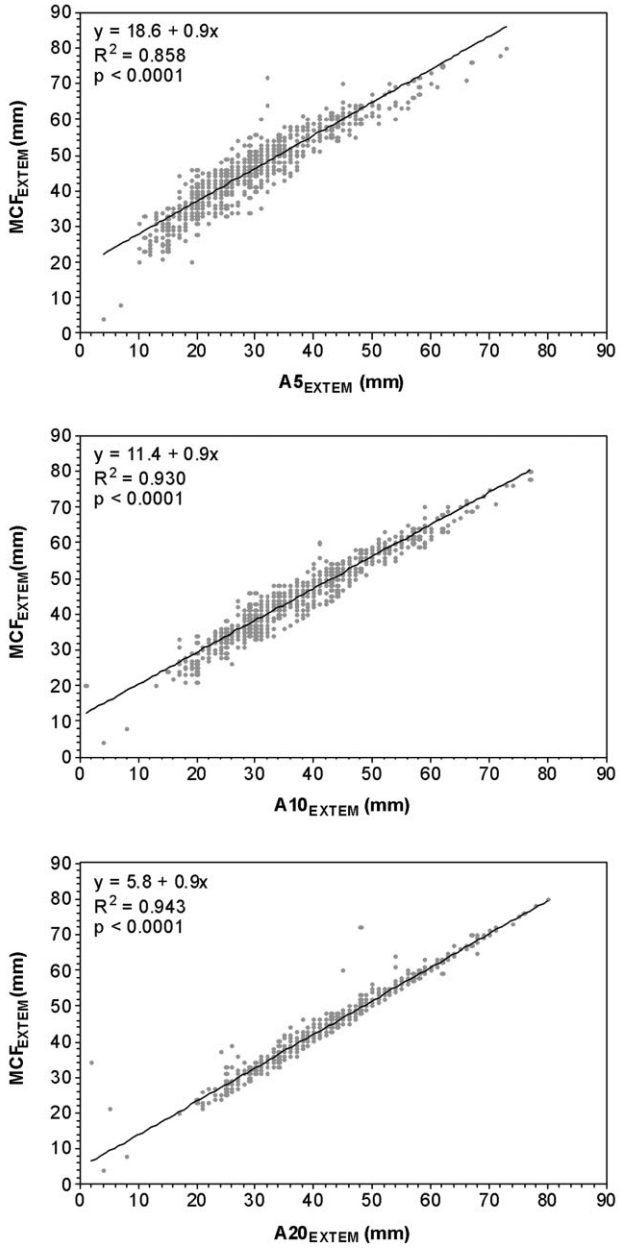

Fig. 3. Correlation between MCF_{EXTEM} and the $A10_{EXTEM}$.

The TEM trace of clot formation has traditionally been evaluated at the point where it reaches the maximal vertical amplitude or MCF,[23] which in the setting of OLT may take up to 30 minutes. To take the greatest advantage of TEM as a point-of-care assay, previous authors have proposed using the trace amplitude at 10 minutes, or $A10_{EXTEM}$, instead of the MCF_{EXTEM}, as an earlier gauge to guide transfusion management.[16] After we systematically tested the clot amplitude at several time points, $A10_{EXTEM}$ emerged as a convenient earlier surrogate of MCF_{EXTEM}. $A10_{EXTEM}$ was on average 9 mm narrower than MCF_{EXTEM} and there was a good linear relationship between both variables, with a slope close to 1 and very little dispersion around the regression line.

Previous authors have reported on values of the clot amplitude at 10 or 15 minutes that best discriminate thrombocytopenia and hypofibrinogenemia and could, therefore, be used as transfusion triggers for PLTs or fibrinogen-rich products. In the trauma patient, Rugeri and colleagues[10] found that $A10_{FIBTEM}$ of 5 mm was the threshold best predicting hypofibrinogenemia (<1 g/L) whereas thrombocytopenia ($<50 \times 10^9$/L) was best predicted by $A15_{INTEM}$ of 46 mm. In liver transplantation, Roullet and colleagues[16] found $A10_{EXTEM}$ as the best predictor for thrombocytopenia at a threshold of 29 mm and hypofibrinogenemia at a threshold of 26 mm. By using ROC analysis, we found that $A10_{EXTEM}$ of 35 mm was the best predictor of the threshold values of the standard coagulation tests on which we currently base the decision to transfuse PLTs and fibrinogen-rich products. From a practical viewpoint, transfusion of PLTs and/or fibrinogen-rich products would be indicated when $A10_{EXTEM}$ is below 35 mm, with $A10_{FIBTEM}$ helping decide which of both products must be transfused first. It should be noted that our transfusion trigger for fibrinogen-rich products, either cryoprecipitate or human fibrinogen concentrate, was 0.3 g/L higher than that used by Roullet and coworkers,[16] a difference that may account for the larger $A10_{EXTEM}$ threshold found in our study.

At the cutoff value of 35 mm for the $A10_{EXTEM}$, the negative predictive accuracy for either thrombocytopenia of less than 50×10^9/L or hypofibrinogenemia of less than 1.3 g/L was 95%, suggesting that a clot amplitude of more than 35 mm at the $A10_{EXTEM}$ virtually excludes the need for PLT or fibrinogen transfusion. In contrast, the positive predictive accuracy was low, so that more patients would

TABLE 3. Accuracy of the A10 in predicting the transfusion triggers for PLTs and fibrinogen

Statistic	$A10_{FIBTEM} \leq 8$ mm and fibrinogen ≤ 1.3	$A10_{EXTEM} \leq 35$ mm and fibrinogen ≤ 1.3	$A10_{EXTEM} \leq 35$ mm and PLTs $< 50 \times 10^9$/L
Sensitivity (%)	86	86	83
Specificity (%)	55	66	62
Positive predictive value (%)	30	37	27
Negative predictive value (%)	95	95	95
Area under the ROC	0.801	0.834	0.798

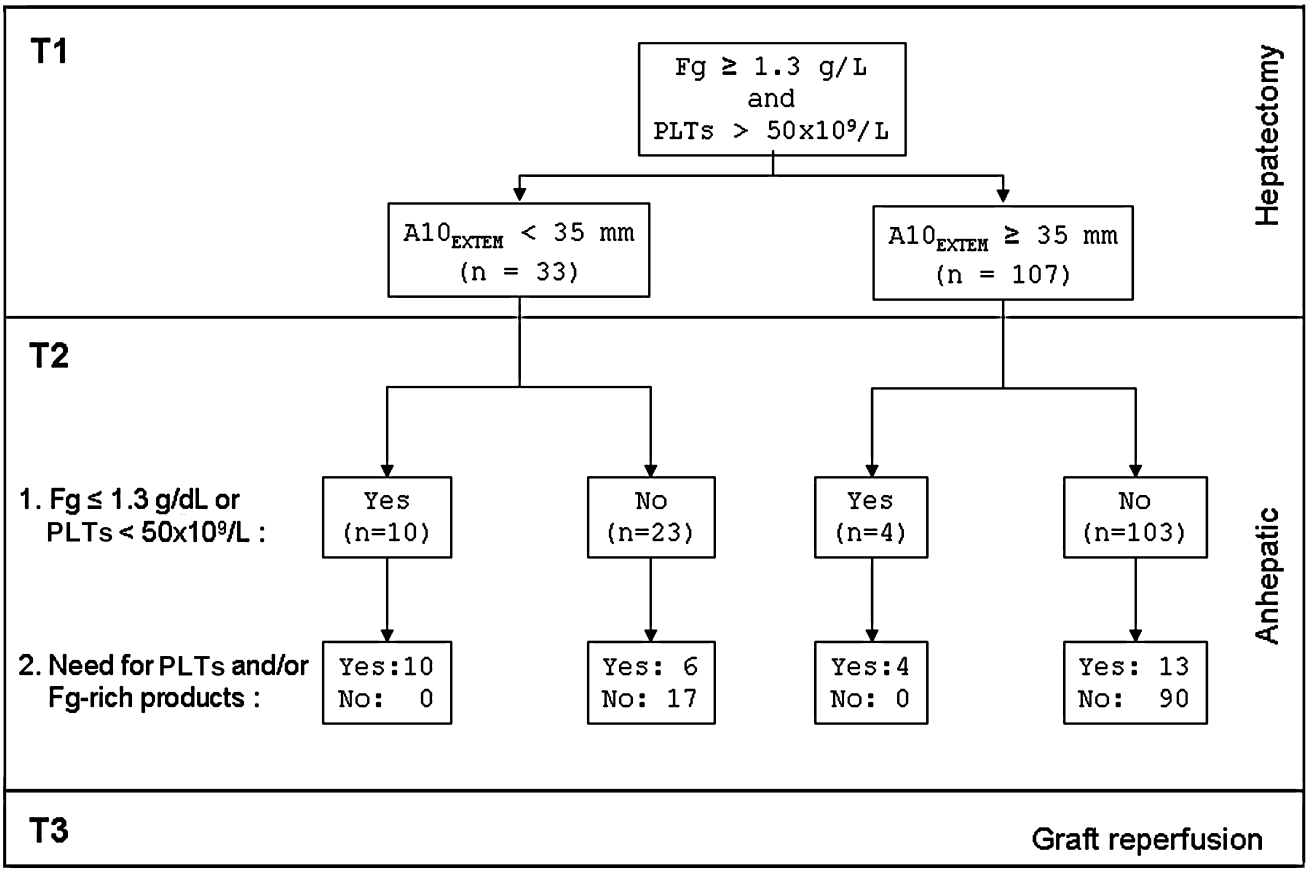

Fig. 4. Intraoperative evolution of 140 patients who did not meet the standard criteria for PLT or fibrinogen (Fg) transfusion at the beginning of the hepatectomy, according to whether they had met the TEM criterion ($A10_{EXTEM}$ < 35 mm) or not ($A10_{EXTEM}$ ≥ 35 mm). T1 and T2 stand for the blood samples taken at start of hepatectomy and the anhepatic phase, respectively.

TABLE 4. Standard coagulation tests, blood loss, and transfusion requirements at the end of hepatectomy (T2) according to $A10_{EXTEM}$ at the start of hepatectomy (T1) in patients who did not meet the standard transfusion criteria for PLTs and fibrinogen-rich products at T1

	$A10_{EXTEM}$ at T1		
Finding	<35 mm (n = 33)	≥35 mm (n = 107)	p value
Below the transfusion trigger at T2			
PT ratio >1.7	59%	27%	0.001
Fibrinogen <1.3 g/L	28%	4%	<0.001
PLTs <50 × 10^9/L	6%	0	0.055
Hb <80 g/L	0	9%	0.117
Blood loss and RBC transfusion between T1 and T2, median (interquartile range)			
Blood loss (mL/kg)	15 (10-20)	12 (8-20)	0.432
RBCs (units)	0 (0-1)	0 (0-1)	0.819
Blood loss and transfusion over the whole liver transplant, median (interquartile range)			
Total blood loss (mL/kg)	44 (32-65)	39 (30-61)	0.256
RBCs (units)	3 (1-4)	2 (0-4)	0.136
FFP (mL)	1.034 (245-2.042)	500 (0-1.246)	0.009
Fibrinogen-rich products*	36%	14%	0.010
PLTs	15%	7%	0.154

* Cryoprecipitate or human fibrinogen concentrate.
T1 = baseline; T2 = end of hepatectomy.

have been transfused with PLTs and/or fibrinogen-rich products had the transfusion criteria been based on TEM instead of the standard coagulation tests.

The poor positive accuracy of TEM to predict hypofibrinogenemia and/or thrombocytopenia has already been reported in several clinical settings, including liver transplantation,[16] cardiac surgery,[12,13] and the trauma patient.[10] In a recent study on pediatric cardiac surgery comparing TEM-guided transfusion therapy with the standard of care, the former led to greater use of PLT and fibrinogen transfusion, although the overall prevalence of allogeneic exposure was reduced because of lower use of plasma and RBCs.[13]

There is no biologic reason for the TEM-derived transfusion thresholds to match exactly with those of the standard coagulation tests. Since TEM is a whole blood assay, it is sensitive to functional defects of fibrinogen and PLTs that can be missed by the standard Clauss assay or the PLT count. In patients with advanced liver disease, circulating fibrinogen is defective due to excessive sialilzation, which impairs fibrin polymerization and leads to a clot of reduced strength.[24] PLT function is often impaired in liver disease because of a variety of molecular mechanisms[25] and it can worsen during liver transplantation.[26] Moreover, TEM is sensitive to interactions between elements in whole blood that are not appraised by the isolated determination of each one of them.[6,27] It can, therefore, be speculated that TEM-derived transfusion thresholds would identify a group of patients who might benefit from the transfusion of PLTs or fibrinogen despite such transfusion not being indicated based on the standard coagulation tests. To gain insight on this issue, we conducted a "what if" analysis comparing the outcome at the end of hepatectomy between patients who would have been transfused with PLTs or fibrinogen based on the TEM-derived thresholds and patients who would have not. We circumscribed this analysis to the hepatectomy, instead of a more advanced and perhaps clinically relevant phase of the OLT, to avoid the interference by events happening before the period under examination (e.g., a blood transfusion given because of hemorrhage at a previous period). Our results indicate that using the TEM-derived thresholds might have led to unnecessary utilization of PLTs and/or fibrinogen-rich products in about half the instances in which $A10_{EXTEM}$ was below 35 mm while, in the other half, it would have anticipated a transfusion of such products that eventually proved necessary at a later time.

It must be noted that in this study, we did not explore the potential advantages of TEM as a point-of-care device because of the short delay in having the results of the standard coagulation test, which were available at the surgical room nearly at the same time as the TEM results. It is quite possible that longer turnaround times in performing the standard coagulation tests, and the subsequent longer delay in the correction of hemostatic derangements, might have yield somewhat different results.

Some reports on TEM or TEG[28-30] suggest that both the latency time until the clot starts to form and the alpha angle can help guide the transfusion of plasma. In this study, however, we failed to find any TEM variable whose correlation with the PT ratio was good enough to be useful in guiding the transfusion of plasma. It should be noted that the PT has proved to be a poor predictor of bleeding risk in many clinical settings and that any threshold used to guide the transfusion of plasma is inherently arbitrary.[31] Furthermore, in patients with cirrhosis the PT underestimates the generation of thrombin,[3] and recent data suggest that infusion of plasma does not improve the generation of thrombin despite normalization of the PT.[32,33] Moreover, there are wide differences among institutions, and even within the same institution, in the use of plasma during OLT suggesting that this blood component may be overtransfused in some cases.[1,28,34] Since overtransfusion of plasma is not innocuous because it may contribute to increased bleeding[1,35] and poorer outcomes,[22,36] our results call for further research on the optimal coagulation test on which to base the indication of this blood component.

In summary, our results show that $A10_{EXTEM}$ is an early and convenient TEM variable to guide the transfusion of PLTs and fibrinogen-rich products during OLT. Patients with $A10_{EXTEM}$ of at least 35 mm are unlikely to bleed because of coagulation deficiencies. On the other hand, clinical judgment must be exercised before using the $A10_{EXTEM}$ of less than 35 mm as the sole transfusion criterion because it might lead to unnecessary utilization of PLTs and fibrinogen-rich products.

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AB has seen the original study data, reviewed the analysis of the data, and approved the final manuscript and is the author responsible for archiving the study files. JB and AP have seen the original study data, reviewed the analysis of the data, and approved the final manuscript. GMP has seen the original study data and approved the final manuscript. AT reviewed the analysis of the data and approved the final manuscript. JB, EZ, and PT have seen the original study data and approved the final manuscript. JCGV approved the final manuscript.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. Ozier Y, Tsou MY. Changing trends in transfusion practice in liver transplantation. Curr Opin Organ Transplant 2008; 13:304-9.

2. Groenland HN, Porte RJ, Metselaar HJ. Liver transplantation and risk of bleeding. Curr Opin Organ Transplant 2007;12:287-93.
3. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41: 553-8.
4. Warnaar N, Lisman T, Porte RJ. The two tales of coagulation in liver transplantation. Curr Opin Organ Transplant 2008;13:298-303.
5. Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev 2011;(3):CD007871.
6. Bochsen L, Johansson PI, Kristensen AT, Daugaard G, Ostrowski SR. The influence of platelets, plasma and red blood cells on functional haemostatic assays. Blood Coagul Fibrinolysis 2011;22:167-75.
7. Johansson PI, Ostrowski SR, Secher NH. Management of major blood loss: an update. Acta Anaesthesiol Scand 2010; 54:1039-49.
8. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999;88:312-9.
9. Spiess BD, Gillies BS, Chandler W, Verrier E. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. J Cardiothorac Vasc Anesth 1995;9:168-73.
10. Rugeri L, Levrat A, David JS, Delecroix E, Floccard B, Gros A, Allaouchiche B, Negrier C. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Thromb Haemost 2007;5:289-95.
11. Brenni M, Worn M, Bruesch M, Spahn DR, Ganter MT. Successful rotational thromboelastometry-guided treatment of traumatic haemorrhage, hyperfibrinolysis and coagulopathy. Acta Anaesthesiol Scand 2010;54:111-7.
12. Cammerer U, Dietrich W, Rampf T, Braun SL, Richter JA. The predictive value of modified computerized thromboelastography and platelet function analysis for postoperative blood loss in routine cardiac surgery. Anesth Analg 2003;96:51-7, table of contents.
13. Romlin BS, Wahlander H, Berggren H, Synnergren M, Baghaei F, Nilsson K, Jeppsson A. Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery. Anesth Analg 2010; 112:30-6.
14. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr, Starzl TE, Winter PM. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888-96.
15. Coakley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 2006;20:548-53.
16. Roullet S, Pillot J, Freyburger G, Biais M, Quinart A, Rault A, Revel P, Sztark F. Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. Br J Anaesth 2010;104: 422-8.
17. Whitten CW, Greilich PE. Thromboelastography: past, present, and future. Anesthesiology 2000;92:1223-5.
18. Samama CM. Thromboelastography: the next step. Anesth Analg 2001;92:563-4.
19. Sharma P, Harper AM, Hernandez JL, Heffron T, Mulligan DC, Wiesner RH, Balan V. Reduced priority MELD score for hepatocellular carcinoma does not adversely impact candidate survival awaiting liver transplantation. Am J Transplant 2006;6:1957-62.
20. Tripodi A, Primignani M, Chantarangkul V, Viscardi Y, Dell'Era A, Fabris FM, Mannucci PM. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. Thromb Res 2009;124:132-6.
21. Wiederkehr JC, Igreja MR, Nogara MS, Goncalves NL, Wiederkehr BA, Nascimento VB, Coelho IM, Locatelli FP. Analysis of survival after primary liver transplantation: multivariate analysis of 155 cases in a single center. Transplant Proc 2010;42:511-2.
22. Benson AB, Burton JR Jr, Austin GL, Biggins SW, Zimmerman MA, Kam I, Mandell S, Silliman CC, Rosen H, Moss M. Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following liver transplantation. Liver Transpl 2011;17:149-58.
23. Luddington RJ. Thrombelastography/thromboelastometry. Clin Lab Haematol 2005;27:81-90.
24. Martinez J, MacDonald KA, Palascak JE. The role of sialic acid in the dysfibrinogenemia associated with liver disease: distribution of sialic acid on the constituent chains. Blood 1983;61:1196-202.
25. Witters P, Freson K, Verslype C, Peerlinck K, Hoylaerts M, Nevens F, Van Geet C, Cassiman D. Review article: blood platelet number and function in chronic liver disease and cirrhosis. Aliment Pharmacol Ther 2008;27:1017-29.
26. Juttner B, Brock J, Weissig A, Becker T, Studzinski A, Osthaus WA, Bornscheuer A, Scheinichen D. Dependence of platelet function on underlying liver disease in orthotopic liver transplantation. Thromb Res 2009;124:433-8.
27. Lang T, Johanning K, Metzler H, Piepenbrock S, Solomon C, Rahe-Meyer N, Tanaka KA. The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg 2009;108:751-8.
28. Wang SC, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, Chan KH, Mandell S, Tsou MY. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. Transplant Proc 2010;42:2590-3.

29. Kang Y. Thromboelastography in liver transplantation. Semin Thromb Hemost 1995;21 Suppl 4:34-44.
30. Gorlinger K. Coagulation management during liver transplantation. Hamostaseologie 2006;26:S64-76.
31. Segal JB, Dzik WH; Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 2005;45:1413-25.
32. Tripodi A, Chantarangkul V, Primignani M, Clerici M, Dell'era A, Aghemo A, Mannucci PM. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. Intern Emerg Med 2011 Feb 5 [Epub ahead of print].
33. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, Salerno F, Mannucci PM. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology 2006;44:440-5.
34. Ozier Y, Klinck JR. Anesthetic management of hepatic transplantation. Curr Opin Anaesthesiol 2008;21:391-400.
35. Ozier Y, Pessione F, Samain E, Courtois F; French Study Group on Blood Transfusion in Liver Transplantation. Institutional variability in transfusion practice for liver transplantation. Anesth Analg 2003;97:671-9.
36. Triulzi DJ. Transfusion-related acute lung injury: current concepts for the clinician. Anesth Analg 2009;108:770-6.