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Assessment of Hyperfibrinolysis in Cirrhotic Patients Undergoing Orthotopic Liver Transplantation. A Retrospective Observational Study

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ABSTRACT

Introduction: Prophylactic antifibrinolytics are recommended for patients at risk to develop significant hyperfibrinolysis during liver transplantation, identified by the preoperative thromboelastometry. Even with this approach, postreperfusion hyperfibrinolysis is frequent, often leading to increased bleeding and transfusion requirements.The aim of this study was to assess hyperfibrinolysis and to predict postreperfusion hyperfibrinolysis based on preoperative standard coagulation tests (SCTs) and thromboelastometry in liver transplant patients without an indication for antifibrinolytic prophylaxis and/or therapy until graft reperfusion.

Methods: The study group included cirrhotic patients undergoing orthotopic liver transplantation. Preoperative and at 10 minutes after graft reperfusion, the following data were recorded for each patient: SCTs, complete blood counts and rotation thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany). From ROTEM measurements we used standard parameters and indices calculated from the first derivative of the clot firmness curve.Hyperfibrinolysis was defined as maximum lysis >15% in EXTEM or by an increase in MCF in APTEM compared to EXTEM (DMCF) more than 7% of EXTEM MCF.

Results: Using ML>15% preoperative and postreperfusion hyperfibrinolysis were identified in 20% and 22 % of the patients and were not correlated with SCTs, fibrinogen levels, platelet number, with clot amplitude or thrombus formation on ROTEM.Using DMCF criteria, preoperative hyperfibrinolysis was present in 34% of the patients and was associated with decreased thrombus formation (AUC, p=0.021) and decreased clot elasticity in EXTEM (p=0.01). When DMCF criteria was used postreperfusion, hyperfibrinolysis was present in 42% of the patients, could not be correlated with preoperative ROTEM standard or derived parameters and was associated with decreased MCF in EXTEM and FIBTEM (p= 0.04 and 0.006) and delayed and decreased thrombus formation.

Conclusions: The reported incidence of hyperfibrinolysis in cirrhotic patients before and during liver transplantation depends on the ROTEM-based definition used. The difference between APTEM and EXTEM identifies more patients with hyperfibrinolysis than ML>15% criteria and was associated with a decrease in thrombus formation and elasticity both preoperative and post graft reperfusion.

Key words: liver transplant, hyperfibrinolysis, bleeding

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INTRODUCTION

Hyperfibrinolysis has been described in liver cirrhosis patients, but the timing, the severity and the role in bleeding complications are still a matter of debate (1-3). Hyperfibrinolysis often occurs during liver transplant procedures during the anhepatic and neohepatic phases. In the anhepatic phase, the tendency towards increased fibrinolysis is due to the reduced clearance of tissue plasminogen activator (t-PA) with relatively stable concentrations of PAI-1, while in the neohepatic phase it is due to the increased release of t-PA from endothelial surfaces (4,5).

During liver transplant procedures hyperfibrinolysis is often associated with coagulopathic bleeding and increased transfusion requirements (6,7). It is well established that antifibrinolytic drugs (aprotinin and tranexamic acid) can reduce perioperative bleeding and blood product transfusions in patients undergoing liver transplantation (8,9). However, the use of antifibrinolytics in the liver transplant setting is not standardised. Following the withdrawal of aprotinin in 2012, most transplant centers now use tranexamic acid. The prophylactic use of antifibrinolytics has been restricted in many transplant centers to the patients that will probably develop significant bleeding due to hyperfibrinolysis during the surgery and will benefit most from the administration of an antifibrinolytic drug (8).

Recent data shows that preoperative thromboelastometry can identify the patients at a high risk to develop hyperfibrinolysis during liver transplantation and prophylactic antifibrinolytics may be used in these cases (10). Even with this approach, postreperfusion hyperfibrinolysis develops frequently, being considered as one of the criteria of the postreperfusion syndrome (6).

The aim of this study was to assess the incidence of hyperfibrinolysis and to predict postreperfusion hyperfibrinolysis based on preoperative standard coagulation tests (SCTs) and rotational thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) in liver transplant patients without prophylactic or therapeutic antifibrinolytic therapy until graft reperfusion.

MATERIAL AND METHODS

Patient selection

This is a single-center, retrospective, observational study of coagulation profiles in cirrhotic patients undergoing orthotopic liver transplantation. After the approval of the institutional ethics committee, adult patients with liver cirrhosis undergoing orthotopic liver transplantation with grafts from brain dead donors in a 2 year period were included in the study group. Informed consent was waived by the IRB due to the observational retrospective nature of the study. Exclusion criteria were: chronic kidney failure, hematologic diseases, pregnancy, chronic anticoagulant and antiplatelet therapy, recent therapy with blood derivates or procoagulant treatments within the last 7 days prior to enrollment. Patients with preoperative criteria for the administration of prophylactic antifibrinolytic therapy (A10 in EXTEM<25 mm, flat line in FIBTEM or CT+CFT in EXTEM longer than 280 sec) (10) or receiving intraoperative antifibrinolytic therapy before graft reperfusion were excluded from the study. Patients with incomplete data were also excluded from the study.

Laboratory analysis

Preoperative and at 10 minutes after graft reperfusion, the following data were recorded for each patient: SCTs, complete blood count and rotation thromboelastometry (ROTEM®, Pentapharm, Germany).

Standard coagulation tests

Blood samples for laboratory analysis and rotational thromboelastometry were drawn simultaneously, assuring minimal venous stasis preoperatively. After graft reperfusion, blood samples were drawn from an indwelling arterial catheter after removing 3 dead space volumes of blood from the pressure tubing. In each patient 3 blood samples were drawn: one EDTA tube for complete blood count and 2 citrate tubes (for the ROTEM assay and for conventional coagulation tests). Conventional coagulation tests included prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT) and fibrinogen level (Clauss method).

Rotational Thromboelastometry

Whole blood coagulation was assessed using ROTEM (TEM International GmbH, Munich, Germany). Standard citrated blood samples (1:9 ratio of citrate to blood by volume) were kept at room temperature until analysis within 60 minutes after collection. The tests were performed using standard reagents, cups, and pins from the manufacturer (TEM International GmbH, Munich, Germany).

Thromboelastometric assays use citrated whole blood (300 µL per assay), which is recalcified and activated using different activators: tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway) or ecarin (11). In EXTEM assay, the extrinsic pathway of coagulation is revealed by recalcification and addition of tissue thromboplastin. The

FIBTEM assay is obtained by the addition of a potent platelet inhibitor (cytochalasin D) to the EXTEM assay, blocking platelet activation; in this way platelet contribution to clot formation and clot strength is eliminated in FIBTEM(11, 12). APTEM is a modified EXTEM assay where the activation is realised also with tissue factor, but hyperfibrinolysis is blocked by adding tranexamic acid (11). INTEM assays are activated by recalcification and addition of ellagic acid and phospholipids, revealing the intrinsec pathway of coagulation (11).

Each ROTEM assay reports the following information regarding clot formation: CT (clotting time, in seconds), CFT (clot formation time, in seconds), MCF (maximum clot firmness, in millimeters). From ROTEM measurements we used standard parameters and indices calculated from the first derivative of the clot firmness curve: Maximum Velocity (MaxVel), Time to Maximum Velocity of clot formation (t- MaxVel) and area under the curve (AUC) as surrogate markers of thrombin generation (13). First derivative parameters of whole blood clot formation using thromboelastometry indirectly reflect the course of thrombin generation, can provide extensive information on hemostasis and are useful especially in patients with severe hemostasis problems (14).

Hyperfibrinolysis was defined as maximum lysis >15% in EXTEM within 60 minutes after clotting time (the manufacturer's definition) or by an increase in MCF in APTEM compared to EXTEM (DMCF criteria) more than 7% of EXTEM MCF(15).

Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilks test and if normally-distributed, data were expressed as mean and standard deviation (SD). If significantly skewed, median and interquartile range were used as appropriate. Continuous variables were compared between the groups using a Student's t-test or Mann-Whitney U test. Statistical tests were assumed to have reached significance at the conventional level of 0.05. Statistical analyses were performed using SPSS Statistics v 23.0 (IBM).

RESULTS

Between 2014 and 2016 were included in the study group 50 patients with liver cirrhosis with a mean age (±SD) of 47.73 (±14.34) years. The patient's characteristics are shown in *table 1*.

Using as hyperfibrinolysis criteria the maximum lysis higher than 15%(ML>15% criteria), preoperative hyperfibrinolysis was identified in 20% of the patients (n=10) and was not correlated with preoperative SCTs (p=0.91 for PT and p=0.16 for aPTT), fibrinogen levels (p=0.71) or platelet number (p=0.51). The presence of preoperative ML>15% was not correlated with preoperative clot amplitude in EXTEM or FIBTEM (p= 0.608 and respectively 0.513).

Table 1 - Characteristics of the Study Population (n=50)

	Total study subjects (n=50)
Mean Age	47.73 (±14.34) years
Mean MELD score	15.43 (±6.36)
Gender	
Male	23 (46%)
Female	27 (54%)
Diagnosis	
HVB cirrhosis	2 (4%)
HVC cirrhosis	6 (12%)
HVB+HVD cirrhosis	13 (26%)
Alcoholic cirrhosis	11(22%)
HVB cirrhosis+ hepatocarcinoma	4 (8%)
HVC cirrhosis+ hepatocarcinoma	3(6%)
Wilson's disease	4(8%)
Cryptogenic cirrhosis	7 (14%)

HVB = Hepatitis virus B; HVC = Hepatitis virus C;
HVD= Hepatitis virus D
Data are expressed as mean (and standard deviation, SD) or n (%)
*p statistically significant

Postreperfusion hyperfibrinolysis using ML >15% criteria was found in 22 % (n=11) of the patients and was associated with preoperative hyperfibrinolysis (p=0.03). Postreperfusion hyperfibrinolysis was not correlated with SCTs or ROTEM standard or derived parameters both preoperative or post graft reperfusion (data shown in *table 2*).

Using DMCF criteria (DMCF higher than 7% of MCF in EXTEM), preoperative hyperfibrinolysis was present in 34% (n=17) of the patients and could not be correlated with preoperative fibrinogen levels (p=0.4), platelet number (p=0.314), prothrombin time (p=0.92), MCF in EXTEM or FIBTEM (p= 0.058 and respectively 0.069). However, it was associated with decreased preoperative thrombus formation (AUC, p=0.021) and decreased preoperative clot elasticity in EXTEM (p=0.01).

When DMCF criteria was used, postreperfusion hyperfibrinolysis was present in 42% (n=21) of the patients (*fig. 1*). Postreperfusion hyperfibrinolysis could not be correlated with preoperative SCTs, ROTEM standard or derived parameters, but showed statistically significant correlations with parameters of postreperfusion thrombus formation- decreased clot firmness, increased t-MaxVel, decreased AUC and clot elasticity (*table 3*).

Table 2 - Correlations of postreperfusion hyperfibrinolysis using ML>15% criteria with preoperative and postreperfusion SCTs, standard and derived ROTEM parameters

Parameters (preoperative)	Patients with postreperfusion ML>15% (n=11)	Patients with postreperfusion ML<15% (n=39)	P value (Mann Whitney U test)
PT sec	17.45 (11.9)	20.6 (7.1)	0.99
aPTT sec	46.2 (28.3)	46.3 (14.1)	0.198
Platelets (per µl)	92000 (60250)	70500 (50450)	0.154
Fibrinogen mg/dl	233.7 (117.3)	154 (59)	0.051
EXTEM MCF mm	45 (25)	43 (11)	0.816
FIBTEM MCF mm	13 (13)	9 (9)	0.87
MaxVel mm/sec	11.5 (12)	11 (10)	0.795
t-MaxVel sec	67 (86)	69 (74)	0.88
AUC	4517 (1801)	4235 (1207)	0.563
MCE	83 (85)	73 (36.5)	0.555
Parameters (postreperfusion)			
PT sec	36.7 (22.9)	22.9 (23.5)	0.189
APTT sec	76.9 (73)	72.3 (70.4)	0.149
Fibrinogen mg/dl	100 (34.9)	99 (45.9)	0.09
Platelets (per µl)	65500 (16500)	61000 (44500)	0.664
EXTEM MCF mm	39.5 (4)	40 (13)	0.229
FIBTEM MCF	6 (3)	6 (8)	0.537
MaxVel mm/sec	6.5 (6)	7 (8)	0.337
t-MaxVel sec	130 (88)	107 (154)	0.291
AUC	3933 (370)	3817 (1291)	0.297
MCE	65.5 (13)	61 (38)	0.308

PT = prothrombin time; aPTT = activated partial thromboplastin time; MCF = Maximum Clot Firmness; MCE = Maximum clot elasticity; MaxVel = Maximum velocity of clot formation; t-MaxVel = Time to Maximum velocity of clot formation; AUC = Area under the curve of clot formation
Data are expressed as median (and interquartile range); *p statistically significant

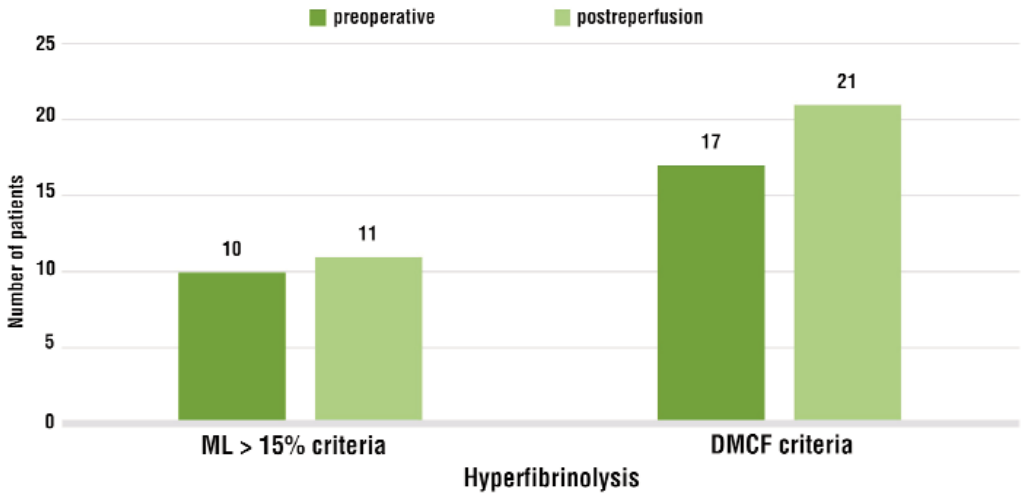

Figure 1: Different incidence of preoperative and postreperfusion hyperfibrinolysis using ML>15% criteria compared to DMCF criteria

ML> 15% criteria= hyperfibrinolysis defined as maximum lysis higher than 15%
DMCF criteria= hyperfibrinolysis defined as difference in clot amplitude between APTEM and EXTEM higher than 7% of EXTEM

Table 3 - Correlations of postreperfusion hyperfibrinolysis using DMCF criteria with preoperative and postreperfusion SCTs, standard and derived ROTEM parameters

Parameters (preoperative)	Patients with postreperfusion DMCF>7% of EX MCF (21)	Patients with postreperfusion DMCF<7% of EX MCF (n=29)	P value (Mann Whitney U test)
PT sec	20.7 (4.1)	16.2 (6.6)	0.07
aPTT sec	47.6 (14.4)	41.7 (20.7)	0.059
Platelets (per µl)	79000 (38000)	92500 (121750)	0.776
Fibrinogen mg/dl	153.5 (71.2)	188.25 (121)	0.363
EXTEM MCF mm	41.5 (11)	45 (15)	0.26
FIBTEM MCF mm	8 (5)	14.5 (19)	0.055
MaxVel mm/sec	10 (8)	12 (12)	0.278
t-MaxVel sec	81 (89)	68 (74)	0.516
AUC	4254 (1166)	4482 (1354)	0.453
MCE	74.5 (29.5)	82 (94)	0.387
Parameters (postreperfusion)			
PT sec	25.6 (28.4)	21.95 (16.5)	0.194
aPTT sec	76.1 (71.5)	50.9 (48.8)	0.023*
Fibrinogen mg/dl	98.35 (59.8)	103 (43.4)	0.354
Platelets (per µl)	54500 (26750)	68500 (49500)	0.116
EXTEM MCF mm	39 (11)	39.5 (11)	0.04*
FIBTEM MCF	5 (4)	7.5 (7)	0.006*
MaxVel mm/sec	6 (6)	7.5 (6)	0.388
t-MaxVel sec	187.5 (157)	66.5 (81)	0.026*
AUC	3621 (1159)	3933 (967)	0.011*
MCE	57 (29)	65.5 (32)	0.01*

PT = prothrombin time; aPTT = activated partial thromboplastin time; MCF = Maximum Clot Firmness; MCE= Maximum clot elasticity; MaxVel = Maximum velocity of clot formation; t-MaxVel = Time to Maximum velocity of clot formation; AUC = Area under the curve of clot formation
Data are expressed as median (and interquartile range); *p statistically significant

DISCUSSION

Similar to previous studies in patients with end-stage liver disease, our results also show preoperative prolongation of standard coagulation tests, low fibrinogen levels and thrombocytopenia (16).

Hyperfibrinolysis is identified on rotational thromboelastometry when the maximum clot lysis (ML) exceeds 15% of the maximumclot firmness according to the manufacturer's definition (17). Raza et al demonstrated in a recent study on trauma patients that more than 90% of fibrinolysis activation was not detected by this definition of hyperfibrinolysis (18). In their study, moderate fibrinolysis activation not detected by ROTEM was associated with increased transfusion requirements and worse outcomes (18). Raza et al raised the suspicion that ROTEM is simply insensitive until fibrinolysis activation reaches a certain threshold (18). The lack of sensitivity of ROTEM for detecting moderate hyperfibrinolysis with clinical impact in critically ill patients was also described by Durila (19). In a study using thrombelastography in trauma patients, Chapman demonstrated that lower thresholds than the accepted normal upper bound of lysis index are associated with worse outcomes and suggested that clinically relevant threshold for defining hyperfibrinolysis might be lower than the actual standard definition (20).

As hyperfibrinolysis during liver transplantation was correlated with bleeding (7), valid diagnosis and rapid treatment of hyperfibrinolysis are nesessary for reducing allogenic blood transfusion and decreasing perioperative morbidity and mortality (10). But the issue of hyperfibrinolysis in cirrhotic patients remains under debate, as the results of different studies performed in this population are controversial(1-3). One possible explanation for this discrepancy might be the different methodology used to measure plasma fibrinolytic activity used in different studies. Moreover, the laboratory tests available for hiperfibrinolysis diagnosis (clot lysis time using whole blood or plasma,

euglobulin lysis time) are time- consuming and cannot be used for guiding therapy in emergencies. Whole blood viscoelatic tests are useful for detecting hyperfibrinolysis in different clinical situations, but their sensitivity and thresholds for detecting moderate or low fibrinolysis activations are still unknown. In a recent study in liver transplant patients, Abuelkasem demonstrated increased sensitivity of rotational thromboelastometry compared to thromboelastography in detecting hyperfibrinolysis; FIBTEM assay proved more sensitive for hyperfibrinolysis diagnosis than EXTEM (21). This results could also explain the different incidence of hyperfibrinolysis during liver transplantation reported in different studies(22). In our study, we found different incidence of preoperative and postreperfusion hyperfibrinolysis using two different definitions of hyperfibrinolysis on ROTEM. This result stands in line with the conclusion from the study by Abuelkasem et al that hyperfibrinolysis is poorly defined using viscoelastic tests, lacks standardisation and that a better definition of hyperfibrinolysis is necessary for good clinical practice.

This is the first study to apply the difference between APTEM and EXTEM as a criteria for hyperfibrinolysis and to compare this criteria with the standard definition of hyperfibrinolysis on ROTEM in a population of cirrhotic patients undergoing liver transplantation. The results of our study reveal that hyperfibrinolysis defined using DMCF criteria identifies patients with decreased thrombus formation and elasticity both preoperative and postreperfusion. This definition seems to have a higher impact on clot formation than the standard definition and might be included in the preoperative criteria for identifying patients at high risk of developing hyperfibrinolysis during the surgery, but more research about the clinical impact of hyperfibrinolysis in the transplant setting is needed.

Study Limitations

This was a retrospective, observational study. However, we have a standard management of liver transplant procedures according to institutional protocols, minimizing in this way the confounding variables. Other limitations are the lack of laboratory tests regarding fibrinolysis (other than ROTEM) and the fact that clinical outcomes as bleeding or thrombosis were not evaluated or correlated with the diagnosis of hyperfibrinolysis.

CONCLUSIONS

The reported incidence of hyperfibrinolysis in cirrhotic patients before and during liver transplantation depends on the ROTEM-based definition used. Our results suggest that postreperfusion hyperfibrinolysis could not be predicted from preoperative tests. The difference between APTEM and EXTEM identifies more patients with hyperfibrinolysis than ML>15% criteria and was associated with a decrease in thrombus formation and elasticity both preoperative and post graft reperfusion. In conclusion, this definition could be more reliable for the identification of clinically significant hyperfibrinolysis and of patients that might benefit from antifibrinolytics during liver transplantation, but the clinical implications of this result need more research.

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