

## Thromboelastometric Profile in Patients with Prothrombotic Risk Factors Undergoing Liver Transplantation

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### Abstract

**Background:** Orthotopic liver transplantation (OLT) is a highly complex procedure and can offer difficult intraoperative control in patients with coagulopathy. The present study aimed to evaluate the profile of coagulation by Rotation thromboelastometry (ROTEM®) in the intraoperative of patients with prothrombotic risk factors submitted to liver transplantation.

**Methods:** A prospective, observational pilot study, in which 24 patients submitted to OLT, of both sexes and age from 18 years, were included in the period from October 2014 to June 2017. Three samples were taken intraoperatively to analyze the profile of coagulation through the thromboelastometry assays (EXTEM, FIBTEM, INTEM and HEPTTEM).

**Results:** In the analysis of the tests in the EXTEM (clotting time [CT] and maximum clot firmness [MCF]) and INTEM (MCF), there was hypocoagulation along the OLT, with no statistical difference between the values obtained. In the FIBTEM tests (amplitude in 10 minutes [A10] and MCF), there was reduction in the neohepatic phase (stage III) in relation to the beginning of surgery (stage I), with statistical significance (P=0.0424 and 0.0227, respectively). In the analysis of CT in the INTEM, there was an increase in the stage III in relation to stage I and anhepatic phase (stage II), with statistical significance (P=0.0004 and 0.0012, respectively). The fibrinolytic activity by maximum lysis (ML) was higher in the stage I and stage II in relation to stage III, when analyzed by the EXTEM, presenting statistical significance (P=0.0016 and 0.0035, respectively).

**Conclusion:** In patients with prothrombotic risk factors, data from the ROTEM® analysis showed some statistically significant changes, but we cannot say that it showed tendency to hypocoagulation, when there was not significance in most other tests. Therefore, in the FIBTEM tests the consumption of fibrinogen was more accentuated in stage III in relation to stage I and in relation to stage III, when analyzed by INTEM CT and EXTEM ML, the presence of heparin was higher and fibrinolysis was less pronounced, respectively.

**Keywords:** Liver transplantation; Coagulation disorders; Thromboelastometry; Prothrombotic.

### Abbreviations:

OLT: Orthotopic Liver Transplantation; ROTEM: Rotation Thromboelastometry; CT: Clotting Time; ML: Maximum Lysis; Hb: Hemoglobin; MCF: Maximum Clot Firmness; A10: Amplitude in 10 minutes; ANOVA: Analysis of Variance; MELD: Model for End-Stage Liver Disease; PAI-1: Plasminogen Activator Inhibitor type-1; t-PA: Tissue Plasminogen Activator; u-PA: Urokinase-type Plasminogen Activator.

### Introduction

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with late stage decompensated liver disease [1]. Intraoperatively, control of coagulation disturbances may be

challenging, especially in patients presenting with coagulopathy and portal hypertension [2].

Historically, OLT has been associated with transfusion of large amounts of blood derivatives [3-7]. Currently, there is a progressive reduction of perioperative blood loss due to advances in surgical skills, anesthetic management and coagulation monitoring in general [8-12].

Although the cause of hemorrhage is multifactorial, complex and profound coagulation changes are common during liver transplantation. A such, baseline coagulation status and additional intraoperative disorders (e.g. hemodilution, consumption of factors and hyperfibrinolysis) contribute to intraoperative blood loss [13-18].

It is important to note that cirrhotic patients have a decrease in procoagulant factors (leading to bleeding) and anticoagulant factors (leading to thrombosis). They may also present with thrombocytopenia, hyperfibrinolysis and von Willebrand factor abnormalities [19,20].

Nevertheless, some poorly studied patients may present with prothrombotic risk factors and high hemostatic capacity due to modified local flow dynamics and several acquired and genetic factors. This population presumably include patients with Budd-Chiari syndrome, protein C deficiency, malignant disease, multiple organ transplants and chronic renal failure, as well as retransplantation for portal vein or hepatic artery thrombosis, pre-existing thrombotic diseases and non-alcoholic steatohepatitis (NASH) [13,20-27].

Other risks for hypercoagulability also include primary biliary cirrhosis and primary sclerosing cholangitis, as well as high levels of coagulation factors (thrombin-antithrombin complex) and plasminogen activator inhibitor type 1 (PAI-1) are higher [21-26]. Although several studies have shown coagulation changes during the intraoperative period of patients undergoing liver transplantation, there are few studies specifically evaluated patients with prothrombotic risk factors. In this study, we evaluated the thromboelastometric profile of this group of patients.

## Methods

This prospective observational pilot study was approved by the Institutional Review Board of the General Hospital of Fortaleza, Brazil (#794061). Written informed consent was obtained from the enrolled patients or their next of kin.

We studied adult patients ( $\geq 18$  years old) who received an orthotopic liver transplantation from October 2014 to June 2017 and had a presumed prothrombotic coagulations status according to some authors [13,20-27], such as: Budd-Chiari syndrome, protein C deficiency, malignant disease, multiple organ transplants, chronic renal failure, retransplantation for portal vein and hepatic artery thrombosis, portal vein and hepatic artery thrombosis, primary biliary cirrhosis.

All patients were submitted to liver transplantation by the piggyback surgical technique [4,12]. During the surgery preconditions of hemostasis were maintained within adequate ranges: pH  $\geq 7.3$ , Temperature  $\geq 36^\circ\text{C}$ , ionic calcium  $\geq 1.1$  mmol/L<sup>-1</sup> and hemoglobin (Hb)  $\geq 8$  g/dL<sup>-1</sup>.

Blood samples were collected hourly for blood gas analysis and at three times for rotational thromboelastometry (ROTEM®, Pentapharm, Germany): at the beginning of surgery (stage I) per before the portal vein anastomosis on anhepatic phase (stage II) and before the anastomosis of the bile ducts in the neohepatic phase (stage III).

Thromboelastometric variables from the assays EXTEM, INTEM, FIBTEM, APTEM and HEPTEM were recorded. Signs of hypocoagulation and presence of microvascular bleeding were inspected for and, upon its detection per a protocol for hemostatic support was initiated (table 1). Obtained thromboelastometric variables were compared to normal values [28,29].

ROTEM®	Coagulopathy	Treatment Options
EXTEM CT>80-100 s	↓ plasma factors	PCC: 25-40 IU/kg <sup>-1</sup> and/or FFP: 15-20 ml/kg <sup>-1</sup>
EXTEM A10<30 mm ou MCF<35 mm, FIBTEM MCF>9 mm	↓ platelets	Platelets: 1U for each 7 to 10 kg or 1 apheresis or 1 buffy coat
EXTEM A10<30 mm ou MCF<35 mm, FIBTEM MCF<9 mm	↓ fibrinogen	Fibrinogen (g)=MCF in ΔFIBTEM (mm) x weight (kg)/140
INTEM CT>240S e CT <sub>HEPTEM</sub> /CT <sub>INTEM</sub> < 0.8	↑ heparin	Protamine: 50-100 mg
INTEM CT>240S e CT <sub>HEPTEM</sub> /CT <sub>INTEM</sub> ≥ 0.8	↓ plasma factors	FFP: 15-20 ml/kg <sup>-1</sup>
EXTEM ML>15% e APTEM ML<15%	↑ fibrinolysis	EACA: 50 mg/kg <sup>-1</sup>
PCC: Prothrombin Complex Concentrate; FFP: Fresh Frozen Plasma; EACA: Epsilon Aminocaproic Acid		

**Table 1:** Algorithm for treatment of coagulation disorders and fibrinolysis according to ROTEM®.

For normality, the D'Agostino & Pearson and Shapiro-Wilk tests were performed. In the parametric tests, analysis of variance (ANOVA) was used and the significance was studied by the Tukey's test for multiple comparisons with a 95% confidence interval. In non-parametric tests, Friedman and Kruskal-Wallis tests were used in association with the Dunn's test for multiple comparisons.

## Results

In the study period, 24 patients were identified with a presumed prothrombotic coagulations status, and their demographic and surgical data are summarized in table 2.

Coagulation parameters from EXTEM (Clotting time [CT] and maximum clot firmness [MCF]) and INTEM (MCF), Showed a tendency of progressive hypocoagulation along the OLT, Although not statistically significant (p > 0.05), as described in table 3. In the

FIBTEM tests (amplitude in 10 minutes [A10] and MCF), showed a reduction in stage III in relation to stage I, with statistical significance (P < 0.05), as described in table 3.

Stage III clotting time of INTEM showed a statistically significant elongation in comparison with stages I and II (P < 0.05), as illustrated in figure 1. Further, CT<sub>HEPTEM</sub> / CT<sub>INTEM</sub> ratio of stage III was reduced when compared with previous samples, without statistical significance, as described in table 3. Clotting time elongation at INTEM was detected in 17 patients (70.8%); between these patients, protamine was administered to 5 (29.4%) in stage III, 2 (11.8%) in stage II and 2 (11.8%) in both stages I and III.

Variable	Patients (n=24)
Age	51.8 (± 9.4) years*
Weight	67.4 (± 13.9) kg*

<b>Gender</b>	
Male	13 (54.0%)
Female	11 (46.0%)
Score MELD	24.0 (± 6.9)*
<b>Causes</b>	
Hepatocellular carcinoma	11 (46.0%)
PSC and PBC	05 (21.0%)
Retransplantation for hepatic artery thrombosis	04 (17.0%)
Portal thrombosis	02 (8.0%)
CRF and C virus	02 (8.0%)
<b>ABO Group</b>	
O	12 (50.0%)

A	09 (37.5%)
B	02 (8.3%)
AB	01 (4.2%)
Duration of surgery	341.7 (± 81.9) min*

\*Mean ± SD (Standard Deviation), MELD: Model for End-Stage Liver Disease; PSC and PBC: Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cirrhosis (PBC); CRF: Chronic Renal Failure

**Table 2:** Demographic and surgical characteristics of the patients studied.

Fibrinolytic activity, as evaluated with maximum lysis of EXTEM, was significantly higher ( $P < 0.05$ ) in stages I and II in comparison with stage III, as depicted in figure 2. Treatment with epsilon aminocaproic acid (EACA) was administered in 3 patients (12.5%), being one in stage I and two in stage II (table 3).

Tests	Normal range	Stage I	Stage II	Stage III	P Value
EXTEM	CT (38-79 s)	76.25 ± 25.13	78.88 ± 24.52	103.3 ± 85.9	NS
	MCF (50-72 mm)	53.21 ± 12.7	49.75 ± 12.95	50.46 ± 12.59	NS
FIBTEM	A10 (7-23 mm)	14.8 ± 9.682	10.71 ± 7.715	9.625 ± 4.862	0.0424*
	MCF (9-25 mm)	16.53 ± 10.69	12.37 ± 9.209	11.21 ± 5.213	0.0227*
INTEM	MCF (50-72 mm)	51.96 ± 12.97	49.04 ± 15.09	48.63 ± 9.65	NS
CT <sub>HEPTEM</sub> / CT <sub>INTEM</sub>	> 0.8	0.85 ± 0.08	0.76 ± 0.20	0.75 ± 0.19	NS

Data are shown as Mean ± Standard Deviation. ANOVA test, Friedman test and Kruskal-Wallis test were used to compare groups. Stage I = beginning of surgery; stage II = anhepatic phase; stage III = neohepatic phase; CT = clotting time; MCF = maximum clot firmness; A10 = amplitude 10 min after CT; NS: not significant; (\*stage I vs. stage III); \* $P < 0.05$ .

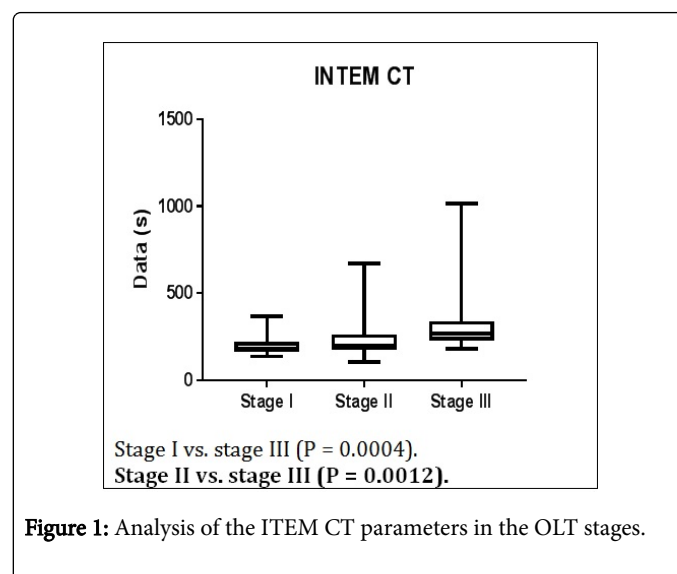
**Table 3:** Analysis of the tests of the EXTEM, FIBTEM, INTEM and HEPTEM in the stages of the OLT.

## Discussion

This study aimed to evaluate the thromboelastometric profile of patients traditionally presumed to have a large hemostatic reserve, less fibrinolysis, low risk of blood loss and a greater predisposition to hypercoagulation or high risk of thromboembolic complications [24,27,30].

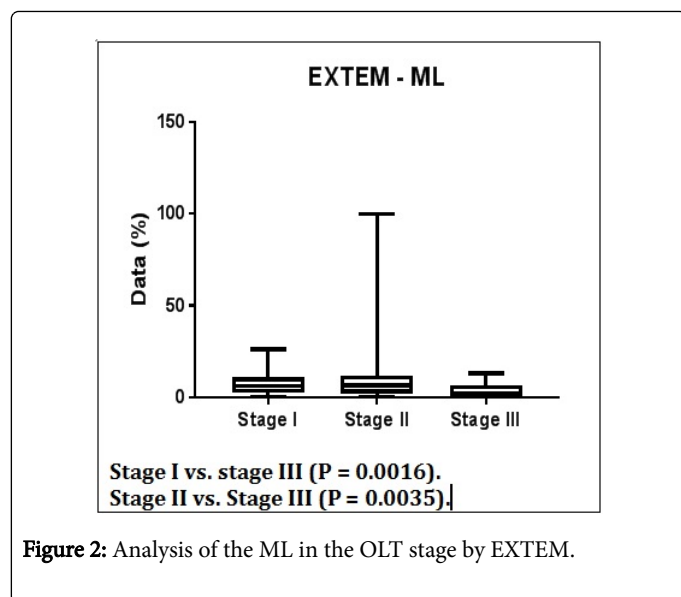
Krzanicki et al. [31] observed in a retrospective study with 124 patients undergoing OLT and monitoring with TEG<sup>®</sup>, a high rate of hypercoagulability in patients with primary biliary cirrhosis (85.7%) and in those with primary sclerosing cholangitis and fulminant hepatic insufficiency (50%).

Ritter et al. [26] evidenced in a retrospective study that hemostatic parameters such as platelet counts, coagulation factors (II, V, VII, IX and X) and antithrombin III presented less changes in patients with primary biliary cirrhosis and primary sclerosing cholangitis, when compared with chronic hepatitis.



**Figure 1:** Analysis of the ITEM CT parameters in the OLT stages.

Friedman test; stage I=beginning of surgery; stage II=anhepatic phase; stage III=neohepatic phase; CT=clotting time;  $P < 0.05$ .



Friedman test; stage I=beginning of surgery; stage II=anhepatic phase; stage III=neohepatic phase; ML=maximum lysis;  $P < 0.05$ .

The OLT has been historically connected with hemostatic reserve depletion, large bleeds and demand for hemostasis support measures. However, in patients whose hemostatic reserve has not been depleted, the use of certain blood products (factor concentrates) or synthetic compounds (such as desmopressin, antifibrinolytics and recombinant factor VIIa) may be associated with thrombotic complications [20,22,25,30].

The historical difficulty in identifying patients with prothrombotic states has been to find an accurate method of assessing the hemostatic reserve. Currently, global coagulation methods are progressively more widely available and are believed to reflect the state of coagulation more broadly and accurately. However, the definition of which test would be the gold standard for assessing coagulation status (or hemostatic reserve) follows elusive [20,30].

Another difficulty is that many liver transplant centers do not have these exams. In these cases, due to the inability to evaluate hemostasis in real time, the anesthesiologist is forced to orient their conduits based on predefined labels on hemostasis in certain etiologies of cirrhosis. In this sense, in a patient predicted to be "prothrombotic", it is possible that a given pro-hemostatic therapy is summarily contraindicated or postponed due to fears of thromboembolic events. The use of antifibrinolytics, for example, is usually contraindicated or used with restrictions in patients with a prothrombotic tendency [20,30].

In this series, cryoprecipitate, fresh frozen plasma, platelets, prothrombin complex concentrate, antifibrinolytic, fibrinogen concentrate and protamine were administered, when considered necessary as suggested by the intraoperative findings in ROTEM<sup>®</sup>, according to the algorithm of Table 1.

However, in spite of corrections with blood products, there was hypocoagulation in the thromboelastogram throughout the liver transplantation, corroborating with the blood loss, hemodilution and the consumption of coagulation factors that occur along the OLT [6,7,20].

The deterioration of the fibrinogen concentration throughout the surgery was the most significant result among the blood components of this study, similar to the study by Hiippala et al. [32] where they showed that in acute bleeding, fibrinogen was the first coagulation factor to reach critical levels.

Also, severe coagulopathies may occur during OLT, mainly after reperfusion of the hepatic graft, having the release of heparin as a contributing factor [33].

Kettner et al. [34] demonstrated in one study that heparin-modified thromboelastography can identify the significant effects of heparin in the absence of exogenous heparin administration in patients undergoing OLT.

In this study, CT enlargement in the INTEM after reperfusion was represented in more than 53% of the patients due to the effect of heparin, in agreement with the study of Agarwal et al. [35] where they demonstrated in a retrospective and observational study of 211 patients undergoing liver transplantation that the prevalence of heparin was demonstrated in more than 80% of cases after reperfusion of the graft.

It is also important to mention that the fibrinolytic activity by ML in the EXTEM was less pronounced in stage III, measured after one hour of reperfusion, according to most studies, where the correction of hyperfibrinolysis usually occurs within one hour after reperfusion by the presence of hepatic clearance. As it is already well documented that the frequency of disorders associated with diseased organs such as platelet defects, decreased PAI-1, reduced synthesis and release of coagulation factors can lead to compromised hemostasis and hyperfibrinolysis, mainly during the anhepatic phase and immediately after organ reperfusion. The explanation for these findings may be due to the presence of increased levels of tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) in the pre-anesthetic and anhepatic phases, as well as a pronounced release of t-PA of the endothelium of the graft soon after reperfusion and in the presence of the still non performing hepatic graft [36-38].

Himmelreich et al. [38] identified a slight increase in u-PA and t-PA levels during the preoperative period and a slight decrease in the pre-anesthetic and anhepatic phases. On the other hand, Dzik et al. [39] showed that there was a mild to moderate increase in u-PA antigen levels in some patients at the beginning of surgery, but the acute pathophysiological actions of systemic fibrinolytic activity are more influenced by t-PA in the anhepatic phase.

In this series the prominent fibrinolytic activity in the stage I and stage II and low in stage III by EXTEM, contradicted the study by Poon et al. [37] where fibrinolytic activity was low in beginning of surgery and anhepatic phase, rising soon after reperfusion in less than 30 minutes. As the samples were collected around 60 minutes after reperfusion, it is possible that the acute alterations of t-PA have already been dissipated [40-41], being able to explain the difference between the studies.

In this study, 12.5% of patients with hyperfibrinolysis, EACA treatment were effective in agreement as described by some authors in patients with cirrhosis or during liver transplantation [42-43].

ROTEM<sup>®</sup> was able to guide the transfusion when there was a real need. Rouillet et al. [44] concluded that ROTEM<sup>®</sup> is useful for the global evaluation of coagulation and the EXTEM was the most informative to evaluate the entire coagulation process. Therefore, the empirical use of



blood products uncontrolled by ROTEM<sup>®</sup> should not be considered in the current real evidence in the literature [45].

The thromboelastic profile demonstrated in our results suggests that patients historically presumed to be prothrombotic may actually have coagulation within the range of values considered normal [24,27,30]. This finding reinforces the need for increased use of global coagulation tests so that potentially life-saving therapies are not contraindicated or postponed based solely on ill-defined and imprecise labels.

The present study has as limitations the observational nature of the research, small sample and no measurement of intraoperative bleeding. It is important to carry out prospective and randomized studies to be conducted in the future with a larger sample and prothrombotic risk factors derived from an actual hypercoagulability system, such as laboratory tests (anti-phospholipid antibodies, factor V Leiden SNP or protein C and S abnormalities), analyzing whether the administration of small doses of antifibrinolytics would reduce fibrinolysis and consequently bleeding in the perioperative period.

## Conclusion

In conclusion, although the patients in this series may be prothrombotic, our results showed some statistically significant changes, but we cannot say that it showed a tendency to hypocoagulation, when there was no significance in most other ROTEM<sup>®</sup> tests. The diagnosis of the presence of heparin and/or heparinoids was superior in the neohepatic phase, being corrected effectively with the use of protamine, guided by thromboelastometry and moreover, in this research fibrinolysis was more pronounced at the beginning of the transplantation and in the anhepatic phase.

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