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# Optimized Detection of hyperfibrinolysis in Liver Transplantation through Viscoelastic Test with Direct Prothrombin Activation

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## Abstract

Hyperfibrinolytic activity may arise in any phase of liver transplantation (LT). Viscoelastic assays (VET) for the evaluation of haemostasis play a crucial role in the early diagnosis of hyperfibrinolysis. ClotPro´s ecarin test (ECA), which was initially designed for the monitoring of the action of thrombin inhibitor drugs, appeared to detect fibrinolysis in a higher number of patients, more frequently, and earlier than other VET. We hypothesized that a cut-off point of 15% for the maximal lysis (ML) in ECA would be used to suggest treatment with antifibrinolytics and direct verbal reporting of this critical result by the laboratory to reduce replacement of blood products.

**Keywords** *Transplant, fibrinolysis, ecarin, viscoelastometry, thrombin*

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## 1. Methods

This is a prospective study being conducted at the Hepatobiliary and Liver Transplant Unit in collaboration with the Department of Clinical Biochemistry between May 18, 2023, and May 22, 2024, including graft characteristics, post-transplantation complications, metabolic outcomes, and patient/graft survival.

### 1.1. Patient Selection

Thirty-seven adults were included who underwent cadaveric LT. The study complied with the provisions of the Declaration of Helsinki. Exclusion criteria were age under 18 years, acute liver failure, multiorgan transplantation, liver re-transplantation procedure, and the situation if the patient did not consent to the study. Blood samples were drawn from a cannula introduced into the central venous catheter, which was solely dedicated to the purpose of blood sampling throughout the surgery. For each test, samples were collected in 2.7 ml citrate Vacuette and 3.0 mL EDTA plasma tubes (BD Vacutainer®, Becton Dickinson) and performed at three critical phases of the surgical procedure: baseline, anhepatic, and post-reperfusion.

### 1.2. Viscoelastometry Testing (VET)

The whole blood samples were processed immediately using the ClotPro analyzer (Enicor GmbH, Munich), a modified thromboelastometry system with 6 independent test channels, similar to TEG and ROTEM methods. In ClotPro, clot formation is measured with a stationary pin and rotating cuvette, continuously detecting changes in viscoelastic properties. This system includes tests like the extrinsically activated test (EX), fibrin-based clot test (FIB), ECA test, aprotinin (AP), and tissue plasminogen activator (TPA) tests for fibrinolysis. Reagents come in ready-to-use dried form in pipette tips, eliminating the need for handling. Results provide viscoelastic wave traces and quantitative parameters similar to ROTEM.

### 1.3. Fibrinolysis Detection with ECA Test

Hyperfibrinolysis was defined using the manufacturer's prespecified threshold value. ML was determined as 15% if maximal clot firmness (MCF) decreased by at least 15% during testing. This finding may be due to two causes. Firstly, ecarin directly converts prothrombin to meizothrombin, which can cleave fibrinogen. In the ECA test, citrated blood is not recalcified, so clotting and fibrinolysis occur under low calcium conditions. The absence of calcium accelerates fibrinolysis, likely because fibrinolysis inhibitors are calcium-dependent, making the clot more susceptible to profibrinolytic effects [1].

Thus the clot that was formed in the blood sample is more susceptible to profibrinolytic effects, which susceptibility facilitates dynamic detection of fibrinolytic tendencies. Overactivation of the fibrinolytic system causes loss of trace signal over time due to digestion of the clot. No patient was administered tranexamic acid during surgical procedure.

### 1.4. Statistics

Data presented as median [p25-p75] for continuous variables, except venous and arterial ischemia and fibrinogen concentrate expressed as mean ± SD; for categorical variables presented as percentages. Data analysis was conducted using the software IBM SPSS 26.0 (SPSS Inc, Chicago, Illinois, USA). Differences between groups were tested using the Mann-Whitney

U-test, the Pearson chi-square test or Fisher's exact test, as appropriate.

## 2. Results

### 2.1. Characteristics of LT

Of the 37 LT performed, 15 involved hepatocellular carcinoma and 9 involved alcoholic liver disease. In the no-fibrinolysis group, other cases included polycystic liver disease, primary hyperoxaluria, autoimmune hepatitis, and 2 cases of sclerosing cholangitis. The hyperfibrinolysis group included a case of metabolic liver disease and 2 cases of primary biliary cirrhosis. Clinical characteristics are summarized in (Table 1).

**TABLE 1:** Clinical characteristics of liver recipients and surgery data.

| | No fibrinolysis group | Hyperfibrinolysis group (ML>15% in ECA) | p-Value |
|---|---|---|---|
| Number | 24 | 13 | |
| Age, year | 61 (52-67) | 62 (54-67) | 0.814 |
| Male | 67 | 77 | 0.425 |
| MELD score | 12(9-16) | 16(12-21) | 0.212 |
| Alcoholic disease | 6 | 3 | ns |
| Chronic Hepatitis C Virus (CHVC) | 1 | - | - |
| Chronic Hepatitis B Virus (CHBV) | 2 | 1 | ns |
| Hepatocarcinoma | 10 | 5 | ns |
| Acute hepatic failure | 1 | 1 | ns |
| Others | 4 | 3 | ns |
| **Preoperative data** | | | |
| Haemoglobin, g/dL | 11.1 (10.1-12.8) | 11.2 (10.0-12.5) | 0.863 |
| Platelet count, $10^9$/L | 119 (79-158) | 103 (54-129) | 0.189 |
| INR (international normalised ratio) | 1.2 (1.1-1.4) | 1.4 (1.3-2.2) | ***0.049*** |
| Fibrinogen, g/L | 261 (205-360) | 222 (149-315) | 0.189 |
| Creatinine, µmol/L | 70(53-97) | 70(53-133) | 0.460 |
| **Intraoperative variables** | | | |
| Venous ischemia, min | 290 (213-354) | 268 (212-285) | 0.363 |
| Arterial ischemia, min | 333 (274-383) | 298 (268-317) | 0.423 |
| Transfusion avoidance | 10 | 1 | **0.057** |
| RBC, units/patient | 0.5 (0-1.3) | 2 (1-2) | 0.062 |
| Plasma, units/patient | - | - | - |
| Platelets, units/patient | 0 (0-0) | 0 (0-1) | 0.089 |
| Fibrinogen concentrate, g/patient | 0 (0-2) | 3 (1.5-5.8) | ***0.008*** |

### 2.2. Maximal Lysis Values in ECA- Tests in each Phase of Surgical Procedure

A total of 222 tests were performed, with 24 excluded from evaluation due to technical error. Based on the cut-off value, increased fibrinolytic activity was observed in 14 samples of 13 patients (1 at baseline, 10 anhepatic and 3 post-reperfusion) with just one patient with the EX ML increased. Table 2 lists the patients with ML greater than 30% and a negative EX test.

**TABLE 2:** Patients in anhepatic phase with ML > 30% and negative EX-test.

| Preoperative | | | Anhepatic phase | | Neohepatic phase | |
|---|---|---|---|---|---|---|
| | EX-test | ECA-test | EX-test | ECA-test | EX-test | ECA-test |
| P1 | 0 | 2 | 0 | 99 | 0 | 0 |
| P12 | 0 | 0 | 0 | 79 | 0 | 0 |
| P13 | 0 | 0 | 0 | 59 | 0 | 0 |
| P14 | 0 | 0 | 0 | 48 | 0 | 0 |
| P15 | 1 | 0 | 9 | 38 | 0 | 0 |
| P16 | 0 | 0 | 0 | 33 | 0 | 0 |
| P17 | 0 | 0 | 0 | 30 | 0 | 40 |

## 3. Discussion

Our study confirms that the ECA test detects hyperfibrinolysis in more liver transplant (LT) patients, particularly during the anhepatic phase, compared to the EX plus FIB protocol, using a specific ML threshold. The hyperfibrinolysis group required more blood product transfusions. Incorporating ECA into VET-based transfusion algorithms could reduce the need for fibrinogen concentrate and red blood cells [2]. VET is the first-line method for assessing hyperfibrinolysis in many institutions. However, no study has shown which device or assay is most suitable [3]. ECA offers greater sensitivity than EX, identifying a subgroup of LT patients with poorer coagulative profiles, reflecting the heterogeneity of end-stage liver disease. It also provides insights into the inhibition of platelet-fibrin interaction in FIB, with enhanced sensitivity compared to EX [4], allowing for quicker pharmacologic intervention with antifibrinolytic agents in cases of significant bleeding [5].

Fibrinolysis, triggered by t-PA release in microcirculation, may be missed by classical viscoelastometry tests like EX and FIB, which reflect the balance of t-PA and PAI-1 in venous blood. ECA, performed in non-recalcified citrated blood, is more sensitive to t-PA, offering a more detailed view of fibrinolysis activation. However, fibrinolysis detected by ECA during the anhepatic phase is often self-limiting and may not always require antifibrinolytic treatment.

In conclusion, ECA is more effective in detecting hyperfibrinolysis during LT, though manufacturers' reference values are based on healthy individuals. Understanding antifibrinolytic use helps anesthesiologists make better decisions. A limitation is the lack of hyperfibrinolysis confirmation through AP and/or TPA tests, which highlight clot resolution failure. Further research using a 30% ML threshold is proposed as it is more clinically relevant, facilitating

early intervention while considering tranexamic acid's contraindications in specific transplant cases.

**Funding**

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**Conflicts of Interest**

None.

**Abbreviations**

**LT:** Liver Transplantation
**VET:** Viscoelastometry Testing
**ECA:** Ecarin Test Performed on Clotpro Analytic Platform
**ML:** Maximal Lysis
**EX:** Extrinsically Activated Test Performed on Clotpro Analytic Platform
**FIB:** Fibrin-Based Clot Test Performed on Clotpro Analytic Platform
**AP:** Aprotinin Test Performed on Clotpro Analytic Platform
**TPA:** Tissue Plasminogen Activator Test Performed on Clotpro Analytic Platform
**MCF:** Maximal Clot Firmness
**VETALT:** VET-based Transfusion LT Algorithms

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