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Comparison between thrombelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation

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Abstract

Background: Hyperfibrinolysis is one of the main causes of non-surgical bleeding during liver transplantation (LT). Viscoelastic haemostatic assays, including thromboelastometry (ROTEM®) and thrombelastography (TEG®), can detect hyperfibrinolysis at the bedside. No study has yet demonstrated which device or assay is more suitable for detecting hyperfibrinolysis.

Methods: This prospective observational study compared ROTEM® and TEG® in isolated adult LT. ROTEM® (EXTEM® [tissue factor activation], FIBTEM® [tissue factor activation with platelet inhibition], and APTEM® [tissue factor activation with tranexamic acid/aprotinin]) and TEG® (kaolin-TEG®) were simultaneously performed using arterial blood samples at eight time-points during LT: induction of general anaesthesia, 60 min after skin incision, 10 and 45 min after portal vein clamp, 15 min before graft reperfusion, and five, 30, and 90 min after graft reperfusion. Hyperfibrinolysis was identified per the manufacturers' definitions (maximum lysis >15% in ROTEM® or Lysis30>8% in TEG®) and confirmed with APTEM®; incidence was compared between assays McNemar's test.

Results: Among 296 possible measurement points from 376 consecutive LT recipients, 250 underwent final analysis: 46 measurement points were excluded because of missing assays or flat line. Hyperfibrinolysis was confirmed at 89 (36%) of 250 measurement points: FIBTEM®, EXTEM®, and kaolin-TEG® detected 84 (94%), 41 (46%), and 21 (24%) hyperfibrinolysis, respectively. These hyperfibrinolysis detection rates significantly differed from each other ($P<0.001$).

Conclusions: Tissue factor-triggered ROTEM® tests were more sensitive than contact-activated k-TEG® in identifying hyperfibrinolysis in LT patients. Inhibition of platelet-fibrin interaction in FIBTEM® enhanced sensitivity to hyperfibrinolysis detection compared with EXTEM®.

Key words: clinical laboratory techniques; fibrinolysis; liver transplantation; thrombelastography

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Editor's key points

- Hyperfibrinolysis is a leading cause of non-surgical bleeding during liver transplantation, and is detectable by point-of-care viscoelastic testing.
- In a prospective observational study, three assays were compared in 37 consecutive adult liver transplant patients.
- ROTEM® was more sensitive than TEG® in identifying hyperfibrinolysis, with FIBTEM® being the most sensitive assay.

Liver transplantation (LT) is frequently associated with hyperfibrinolysis, which is one of the main causes of non-surgical bleeding during LT.[1 2] Unfortunately, no standard laboratory test is currently available to rapidly and reliably detect hyperfibrinolysis.

Two widely-available viscoelastic haemostatic assays (VHAs), thrombelastography (TEG®; Haemonetics, Niles, IL, USA) and rotational thromboelastometry (ROTEM®; TEM International, Munich, Germany), are able to detect hyperfibrinolysis at the bedside in a timely manner. In ROTEM®, the combinational use of EXTEM® (tissue factor and phospholipids activations) and APTEM® (tissue factor and phospholipids activations with tranexamic acid/aprotinin) is able to confirm or rule out hyperfibrinolysis. ROTEM® also has a FIBTEM® (tissue factor and phospholipids activations with platelet inhibition) assay that provides a qualitative assessment of fibrinogen status. This assay has potential to better detect hyperfibrinolysis, since FIBTEM® can isolate fibrin polymerization from platelet-fibrin(ogen) interactions in the presence of cytochalasin D as a platelet inhibitor. No study has yet demonstrated which device (TEG® vs. ROTEM®) or assay [kaolin-TEG® (k-TEG®) vs. EXTEM® vs. FIBTEM®] is more suitable for detecting hyperfibrinolysis. The aim of this prospective observational study was to compare hyperfibrinolysis detection between TEG® and ROTEM®.

Methods

Study population, surgical technique, and anaesthetic management

Under local institutional review board approval (#PRO12120173), a prospective observational study was performed in a single institution on 37 consecutive adult patients who underwent LT from August 1, 2013 – November 30, 2013. Liver grafts from brain dead donors, donation after circulatory death donors, and live donors were included in the study. The surgical and anaesthetic management used have been previously described.[3] Briefly, organ procurement was performed using University of Wisconsin preservation solution. The piggyback technique was used for graft implantation. During the study period, percutaneous veno-venous bypass was only used for live donor LTs. Packed red blood cells (PRBCs) were administered to maintain a 26–30% haematocrit. A cell saver device was routinely used, except on recipients with hepatic malignant lesions. In the presence of microvascular bleeding, transfusions of fresh frozen plasma (FFP), platelets, and cryoprecipitate were considered by attending transplant anaesthetists based on TEG®. Kaolin-TEG® (k-TEG®) was performed using an arterial blood sample at eight standardized measurement points during LT per our institutional protocol.[3] Results of ROTEM® measurements were solely used for observational research and not for clinical management. I.V. ε-aminocaproic acid (125–500 mg) was only administered when both surgical bleeding and hyperfibrinolysis on k-TEG® were observed. No prophylactic antifibrinolytic therapy was used per our institutional protocol.

Coagulation study protocol

Blood samples were drawn simultaneously from an existing arterial catheter. ROTEM® (EXTEM®, FIBTEM®, and APTEM®) and TEG® (k-TEG®) were performed according to the manufacturer's instructions.[3] The minimum run time for 60 min was assured in both TEG® and ROTEM® assays in this study. These tests were performed at the following eight measurement points during LT: at induction of general anaesthesia, 60 min after skin incision, 10 and 45 min after portal vein clamp, 15 min before graft reperfusion, and five, 30, and 90 min after graft reperfusion . All TEG® tests were performed by a designated group of five anesthesiology technicians at a designated space at the hospital. These technicians had more than two years of experience in performing traditional TEG® assays. All ROTEM® tests were performed by one of the investigators (EA).

Diagnosis of hyperfibrinolysis

Hyperfibrinolysis was detected per the manufacturers' definitions (maximum lysis >15% in ROTEM® or Lysis30 >8% in TEG®), where maximum lysis is the reduction of clot firmness in relation to maximum clot firmness within the complete measurement period, and Lysis30 is the percentage reduction of amplitude compared with maximum amplitude (MA), which is measured at 30 min after the time of MA. None of the recently performed alternative hyperfibrinolysis thresholds was used in the current study.[4]

The diagnosis of hyperfibrinolysis was confirmed with normalization of maximum lysis in simultaneously performed APTEM® compared with maximum lysis measured in EXTEM®. APTEM® contains thromboplastin (recombinant tissue factor and phospholipids) as the activators with a fibrinolysis inhibitor (aprotinin or tranexamic acid) and a heparin inhibitor, so it can detect hyperfibrinolysis when compared with EXTEM®. 'An hyperfibrinolysis' pattern in EXTEM® and/or FIBTEM® without correction inAPTEM® was not considered as hyperfibrinolysis, nor was an isolated 'hyperfibrinolysis' pattern in k-TEG®.

Exclusion criteria for analysis

The entire set of VHA data performed simultaneously at each time point was excluded from analysis when any of the VHA measurements (1) were missed (not performed or not recorded as a result of technical reasons), or (2) showed a 'flat line' for more than 30 min. The latter is because of difficulty in differentiating hyperfibrinolysis from other causes (e.g., heparin administration) that lead to flat line.

Statistical analyses

Data are descriptively summarized as the number of measurement points or the number of LT patients with percentage. The sensitivities and specificities of three assays (k-TEG® vs. EXTEM® vs. FIBTEM®) for identification of hyperfibrinolysis were compared using McNemar's test. A P value <0.05 was considered statistically significant. Data were analysed using GraphPad Prism v4.0b (GraphPad Software, Inc. La Jolla, CA, USA).

Results

Patient characteristics

Thirty-seven subjects were enrolled and completed the study protocol. (Table 1). Average age was 57 yr; 76% were male. The median Model for End-Stage Liver Disease (MELD) score was 18. The most common aetiology of end-stage liver failure was post-necrotic cirrhosis (76%). Eight subjects (22%) received live donor grafts. ε-amino caproic acid was administered in 7 subjects who showed both bleeding in the surgical field and a hyperfibrinolysis pattern in k-TEG®, especially based on the result of k-TEG® at 30 min after graft reperfusion. Of 296 possible measurement points, 46 (16%) were excluded because of missing measurements of any one of the assays (27 measurement points) or flat line (19 measurement points) as detected in Table 2.

Hyperfibrinolysis

Hyperfibrinolysis was confirmed in 89 (36%) of 250 measurement points (Table 2). Either EXTEM®, FIBTEM®, or both detected each incidence. APTEM® showed normalization of the maximum lysis parameter, confirming hyperfibrinolysis at these time points. Three measurement points were not included; on two occasions (one at 15 min before graft reperfusion and the other at 30 min after graft reperfusion), APTEM® did not correct maximum lysis abnormality in FIBTEM® and on one occasion (at 15 min before graft reperfusion), only k-TEG® showed a hyperfibrinolysis pattern (Lysis30 was 9.1%, while maximum lysis of EXTEM® was 14, that of FIBTEM® was 10, and that of APTEM® was 12). These measurement points were not considered as confirmed hyperfibrinolysis.

Hyperfibrinolysis was observed at all eight measurement points. Hyperfibrinolysis incidence was highest at five min after graft reperfusion (58%), followed by 45 min after portal vein clamp (54%). At baseline, hyperfibrinolysis was detected and confirmed (23%); this was only detected by ROTEM® assays.

Table 1 Subject characteristics and surgical data. Data described as number of patients (%), mean (SD), or median (25th percentile, 75th percentile). * ε-aminocaproic acid (125 500 mg) was administered intravenously. ESLD, end-stage liver disease; MELD, Model for End-stage Liver Disease; PRBC, packed red blood cell; FFP, fresh frozen plasma

	Total study subjects (*n*=37)
Age (yr)	57 (9.3)
Gender - male (%)	28 (76%)
Graft type (%)	
Deceased donor	29 (78%)
Live donor	8 (22%)
Redo liver transplantation	2 (5.4%)
Aetiology of ESLD (%)	
Post-necrotic cirrhosis	28 (76%)
Biliary cirrhosis	6 (16%)
Others	3 (8.1%)
With hepatocellular carcinoma	12 (32%)
MELD Score	18 (14, 33)
Veno-veno bypass used	9 (24%)
Length of surgery (min)	442 (300, 659)
Intraoperative blood transfusion	
PRBC (units)	6 (4, 9)
FFP (units)	4 (2, 6)
Platelet (units)	1 (0, 2)
Cryoprecipitate (units)	1 (0, 1)
Use of antifibrinolytic agent* (%)	7 (19%)
Intraoperative fluid administered	
Crystalloids (ml)	3500 (2400, 5140)
Colloids (ml)	2500 (1500, 3500)
Salvaged blood (ml)	125 (0, 1000)
Estimated total blood loss (ml)	1750 (1000, 3000)

Comparison between k-TEG®, EXTEM®, and FIBTEM®

Among 89 hyperfibrinolysis measurement points, FIBTEM® showed a sensitivity of 94% and a specificity of 99%; EXTEM® showed a 46% sensitivity and a 100% specificity, respectively; k-TEG® showed 23% and 99%, respectively (Table 3). A statistical difference ($P<0.001$) was found in the sensitivities of one assay to the others between FIBTEM®, EXTEM®, and k-TEG®. The specificities between assays did not show statistical difference.

Discussion

This head-to-head comparison of TEG® and ROTEM® in identification of hyperfibrinolysis in 37 adult LT patients demonstrated that ROTEM® assays were more sensitive than k-TEG®. Furthermore, FIBTEM® was more sensitive than EXTEM® in identifying hyperfibrinolysis. Hyperfibrinolysis was confirmed by APTEM® with its normalization of lysis index.

As a point of care device for diagnosis of hyperfibrinolysis, VHAs (ROTEM® and TEG®)[5–7] have replaced traditional laboratory-based diagnostic methods[8 9] including plasma values of D-dimer, thrombin/anti-thrombin complexes, tissue-type plasminogen activator antigen, and fibrin degradation products. In this study, hyperfibrinolysis was observed using VHA throughout the course of LT. Hyperfibrinolysis incidence was highest immediately after reperfusion, which another study also demonstrated.[5] Even at baseline, hyperfibrinolysis was detected and confirmed in 23% of patients, which is consistent with the reported incidence in liver cirrhosis patients.[10–12] To confirm hyperfibrinolysis, we performed APTEM®, in which a fibrinolysis inhibitor (aprotinin or tranexamic acid) is added together with EXTEM® reagents as an activator. The plasmin inhibitor present in APTEM® inactivates plasmin immediately and corrects hyperfibrinolysis *in vitro*. TEG® does not have such a confirmation assay. This so called 'Amicar assay ,' in which ε-aminocaproic acid is added (0.09%) in k-TEG®, has been reported as an institutional protocol,[5] but has not yet been approved by the U.S. Food and Drug Administration.

We compared the diagnostic characteristics of k-TEG®, EXTEM®, and FIBTEM® in detecting hyperfibrinolysis. The entire assays showed excellent specificity. However, the sensitivity of each test was markedly different; the highest value was demonstrated by FIBTEM® (94%), followed by EXTEM® (46%). K-TEG® had a sensitivity of only 23%.

Several points regarding this study are noteworthy. First, the mechanisms behind the superior sensitivity of FIBTEM® over EXTEM® in detecting hyperfibrinolysis are of interest. The superior sensitivity of FIBTEM® as compared with EXTEM® has also been reported by Dirkmann and colleagues[13] in an *in vitro* study using whole blood from healthy volunteers. FIBTEM® is a modified EXTEM® test in which the whole blood sample is activated with thromboplastin (recombinant tissue factor and phospholipids) with a heparin inhibitor and a platelet antagonist (cytochalasin D); the latter inhibits platelet cytoskeletal reorganization by disrupting actin microfilaments, and thus blocks fibrinogen/

Table 2 Incidence of hyperfibrinolysis during liver transplantation. *†Two reasons for exclusion from the analysis. ‡One measurement was not included because of lack of confirmation of detected hyperfibrinolysis pattern. §One of each category was not included because of lack of APTEM confirmation of detected hyperfibrinolysis. Baseline, at induction of general anaesthesia

	Missing measurements*	Flat line†	Measurement points included	Hyperfibrinolysis confirmed with APTEM® (% measurements)	k-TEG®	EXTEM®	FIBTEM®
TOTAL	27	19	250	89 (36)	21	41	84
Baseline	0	3	34	8 (23)	0	2	6
60 min. after skin incision	1	1	35	16 (46)	0	6	15
10 min. after portal vein clamp	1	0	36	10 (28)	2	3	10
45 min. after portal vein clamp	1	1	35	19 (54)	4	9	18
15 min. before graft reperfusion	18	2	17	7 (41)	3 [1]‡	6	7 [1]§
Five min. after graft reperfusion	3	3	31	18 (58)	10	14	17
30 min. after graft reperfusion	3	5	29	6 (21)	1	1	6 [1]§
90 min. after graft reperfusion	0	4	33	5 (15)	1	0	5

Table 3 Diagnostic characteristics of each assay. *Hyperfibrinolysis is confirmed with normalization of maximum lysis in APTEM® as compared with that in EXTEM®. Positive, positive for hyperfibrinolysis per definition of the assay; Negative, negative for hyperfibrinolysis per definition of the assay; PPV, positive predictive value; NPV, negative predictive value

	Non-hyperfibrinolysis	Hyperfibrinolysis*	ASSAY	Sensitivity	Specificity	PPV	NPV
k-TEG® Positive	1	21	k-TEG®	23.4	99.4	95.5	70.2
k-TEG® Negative	160	68					
EXTEM® Positive	0	41	EXTEM®	46.1	100	100	77
EXTEM® Negative	161	48					
FIBTEM® Positive	2	84	FIBTEM®	94.4	98.8	97.7	97
FIBTEM® Negative	159	5					

fibrin binding to platelet glycoprotein IIb/IIIa. Platelet-induced clot retraction is often misinterpreted as hyperfibrinolysis on VHA, but platelet activation and clot retraction are well known to inhibit fibrinolysis. Kunitada and colleagues[14] demonstrated that inactivation of platelets by pre-treatment with cytochalasin D abolished platelet-induced inhibition of lysis and increased tPA binding to fibrin clot. Katori and colleagues[15] also demonstrated in a TEG® experiment that abciximab, a glycoprotein IIb/IIIa receptor antagonist, abolished the platelet-induced masking effect of hyperfibrinolysis. They suggested that the contractility force transmitted via platelet glycoprotein IIb/IIIa receptors, which bind the polymerized fibrin network to the platelets' actin cytoskeleton, is the major contributor to clot strength. Therefore, a glycoprotein IIb/IIIa receptor antagonist (e.g., abciximab) prevents platelets from exerting contractile force on the fibrin network, which allows tPA, along with plasminogen, to bind to the fibrin surface and convert plasminogen to plasmin, leading to fibrinolysis. Since platelets are the source of continuous production of large amounts of active plasminogen activator inhibitor 1 (PAI-1), which stabilizes the blood clot,[16] inhibition of platelets might reduce the release of PAI-1.

The lower sensitivity of k-TEG® to EXTEM® is noteworthy. Thrombin activatable fibrinolysis inhibitor (TAFI) is activated by thrombin; activated TAFI (TAFIa) protects the fibrin clot by inhibition of tPA-mediated fibrinolysis. Conversion to TAFIa is greatly enhanced by high concentrations of thrombin. Nielsen and colleagues[17] demonstrated that TAFI primarily contributed to contact pathway protein-mediated attenuation of fibrinolysis, although they used plasma rather than whole blood. Unlike EXTEM®, which uses tissue factor and phospholipids as activators, k-TEG® uses kaolin, which is a contact pathway (or intrinsic pathway) activator. Use of the intrinsic pathway activator in k-TEG® explains, at least in part, the lesser sensitivity of k-TEG® in identifying hyperfibrinolysis. Of note, other than the activators or the additives in each assay, the mechanical feature of each VHA could also contribute to the difference found in the study, which could be checked performing the k-TEG® assay in the ROTEM® system and EXTEM® assay in the TEG® system.

In clinical practice, k-TEG® and EXTEM® have been used as the standard hyperfibrinolysis detection assays of each VHA. In comparing these assays, EXTEM® was superior to k-TEG®, with a two-fold higher sensitivity. This result indicates that the choice of VHA (TEG® vs. ROTEM®) matters in reporting the incidence of hyperfibrinolysis and/or interpreting reported incidences of hyperfibrinolysis. We also applied a manufacturer's definition of hyperfibrinolysis to FIBTEM®, which provided sensitivity more than two-fold superior to EXTEM®. In clinical LT management, using ROTEM® (especially FIBTEM®) would allow detection of hyperfibrinolysis more often than k-TEG® (or EXTEM® only), which could lead to an increased opportunity for pharmacologic intervention with anti-fibrinolytic agents when facing clinically significant bleeding.[5] However, all clinicians should be aware that the manufacturers' reference values used in definition of hyperfibrinolysis are based on results derived from healthy volunteers. As such, the diagnostic characteristics of each assay observed might not necessarily be translated into a clinical impact in management of LT, in which most hyperfibrinolysis is self-limited without warranting therapeutic interventions.[18]

This study has several limitations. First, no clinical management was altered based on the results of ROTEM®, as this device

was used only for observational research purposes during the study period. Therefore, no clinical correlation between hyperfibrinolysis and clinical bleeding was examined. Second, because of limited funding, we were not able to perform extrinsically activated TEG® assays at all eight measurement points: functional fibrinogen TEG® as the counterpart of FIBTEM®, and rapid-TEG® as the counterpart of EXTEM®. Based on the study results, it would be expected that functional fibrinogen TEG® followed by rapid-TEG® could yield a higher sensitivity than k-TEG® in detecting hyperfibrinolysis. Third, we excluded all 'flat line' VHA results[19 20] from analysis, as this phenomenon is multifactorial, combining hyperfibrinolysis, a heparin-like substance, and/or decreased clotting factors (platelet, fibrinogen, and other coagulation factors).[21] Exclusion of the flat line data could underestimate the incidence of hyperfibrinolysis. Fourth, although EXTEM® was not as sensitive as plasmin/anti-plasmin complex concentrations in detecting hyperfibrinolysis,[22] we did not measure plasmin/anti-plasmin complex or D-dimer concentrations along with VHAs.

In conclusion, tissue factor-triggered ROTEM® tests were more sensitive than contact-activated k-TEG® in identifying hyperfibrinolysis in adult LT patients. Furthermore, inhibition of platelet-fibrin(ogen) interaction in FIBTEM® enhances sensitivity to hyperfibrinolysis compared with EXTEM®.

Authors' contributions

Study design/planning: T.S., K.A.T.
Study conduct: E.A.
Data analysis: T.S., S.Y.L.
Writing paper: E.A., T.S., K.A.T., S.Y.L.
Revising paper: all authors

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Declaration of interest

K.A.T. is currently participating in a clinical study sponsored by Tem International. The other authors declare no conflicts of interest.

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