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Background and Purpose—Iodinated contrast agents used for computed tomography angiography (CTA) may alter fibrin fiber characteristics and decrease fibrinolysis by tissue plasminogen activator (tPA). Thromboelastography (TEG) measures the dynamics of coagulation and correlates with thrombolysis in acute ischemic stroke patients. We hypothesized that receiving CTA before tPA will not impair thrombolysis as measured by TEG.

Methods—Acute ischemic stroke patients receiving 0.9 mg/kg tPA <4.5 hours of symptom onset were prospectively enrolled. For CTA, 350 mg/dL of iohexol or 320 mg/dL of iodixanol at a dose of 2.2 mL/kg was administered. TEG was measured before tPA and 10 minutes after tPA bolus. CTA timing was left to the discretion of the treating physician.

Results—Of 136 acute ischemic stroke patients who received tPA, 47 had CTA before tPA bolus, and 42 had either CTA after tPA and post–tPA TEG draw or no CTA (noncontrast group). Median change in clot lysis (LY30) after tPA was 95.3% in the contrast group versus 95.0% in the noncontrast group (P=0.74). Thus, tPA-induced thrombolysis did not differ between contrast and noncontrast groups. Additionally, there was no effect of contrast on any pre–tPA TEG value.

Conclusions—Our data do not support an effect of iodinated contrast agents on clot formation or tPA activity. **(*Stroke*. 2014;45:462-466.)**

Key Words: thromboelastography ■ thrombosis

The major treatment strategy for acute ischemic stroke (AIS) is pharmacological reperfusion using intravenous tissue plasminogen activator (tPA).[1] In some circumstances, multimodal computed tomography (CT) evaluation consisting of noncontrast CT, perfusion CT, and CT angiography is performed before tPA administration. Although this multimodal approach provides greater information compared with noncontrast CT alone, there is evidence that radiographic contrast agents may interfere with thrombolytic therapy.[2,3] For example, the presence of contrast agents iopamidol and diatrizoate is associated with decreased fibrinolysis by tPA and urokinase.[3,4] Additionally, iohexol and amidotizoate significantly delay the time to optimal reperfusion after tPA administration.[5]

The mass/length ratio of fibrin fibers dictates the number of tPA-binding sites as well as the efficiency of plasmin–fibrin interaction.[4,6] Thick fibers are rapidly degraded, whereas lysis of thin fibers is roughly 2 orders of magnitude slower.[4,6] In pathological states such as hereditary dysfibrinogenemia, the production of extremely thin fibers is associated with a substantial delay in fibrinolysis.[6] Contrast agents may alter the efficacy of thrombolytic therapy through alteration in fibrin fiber structure. Consistent with this idea is the finding that interactions with iohexol and iodixanol as well as other contrast agents result in the production of thinner fibrin fibers and thrombi that are more resistant to lysis by tPA.[6,7]

Thromboelastography (TEG) has been in use since the 1940s, but recent advances in computer technology have made this technique more practical.[8,9] In TEG, dynamic mechanical forces occurring during clot formation and lysis are transduced into electric signals that can be monitored by computer.[9] Thus, TEG provides an integrated, dynamic view of the whole coagulation process.[9] TEG parameters correlate with elevated coagulability associated with ischemic stroke patients, enzymatic versus platelet contributions to thrombosis, and specific effects of tPA on thrombosis and thrombolysis.[8,10] Additionally, a recent study demonstrated that TEG was sensitive enough to detect attenuation in rtPA-induced thrombolysis by experimental manipulations, such as acute exposure to cigarette smoke, producing longer, thinner fibrin fibers.[11]

We performed a prospective study in acute stroke patients to examine the effect of iodinated contrast agents iohexol and iodixanol in clinically relevant doses on rtPA-induced thrombolysis as

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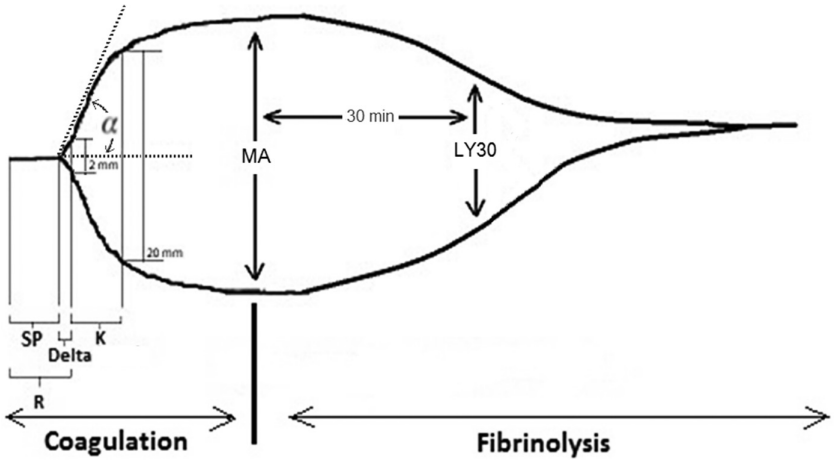

Figure 1. Labeled thromboelastography elastogram.

measured by TEG. Specifically, we hypothesized that thrombolysis by tPA will not be reduced after CT angiography (CTA).

Methods

This study was approved by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston.

Subjects

All stroke patients presenting to Memorial Hermann Hospital Emergency Department (MHHED) and meeting published criteria for receiving intravenous tPA <4.5 hours of symptom onset were screened. Subjects were ≤18 years of age.

Data Collection

All acute stroke patients have blood drawn on arrival at MHHED as standard care. Patients (or their legal guardian or next-of-kin) who agreed to participate were consented for TEG analysis to be performed on residual blood. Within 10 minutes post–intravenous tPA bolus, a second blood draw was obtained. This time was chosen because in previous studies there was a substantial effect of tPA on TEG at 10 minutes. If TEG were eventually shown to predict success of clot lysis or subsequent bleeding, 10 minutes might be soon enough to adjust the tPA dose.[7] TEG values, time of TEG draw and tPA administration, and CTA times were recorded. Additionally, we recorded whether or not a patient received CT perfusion imaging. The timing of CT imaging was at the discretion of the treating physician.

Dosage of tPA and Iodinated Contrast

For patients with estimated glomerular filtration rate >60 mL/min, 350 mg/dL of iohexol (Omnipaque; GE Healthcare) at a dose of 2.2 mL/kg was administered using a Dual Head Power Injector at a rate of 3 mL/s. For patients with estimated glomerular filtration rate between 30 and 60 mL/min, 320 mg/dL of iodixanol (Visipaque; GE Healthcare) at a dose of 2.2 mL/kg was given. For those receiving CT perfusion in addition to CTA, an additional 30 mL of contrast was administered. For tPA, an intravenous bolus dose of 0.09 mg/kg over 1 to 2 minutes was followed by an infusion of 0.81 mg/kg over 1 hour.

Blood Sampling and Processing

TEG Analysis

Seven to 10 mL of whole blood was collected into a citrated tube on patient's arrival before administration of tPA. Blood was held at room temperature and processed <2 hours of collection. Briefly, 1 mL of whole blood was placed into a kaolin vial and inverted 5 times for mixing. Then, 340 μL was pipetted (polyethylene) into the disposable cup in the machine well. Citrate was then reversed with 20 μL of 0.2 mol/L calcium chloride, gently mixed in the cup by pipette, and TEG run on a computerized coagulation analyzer (Model 5000; Haemonetics Corp, MA). Personnel who performed the tests were all trained on the procedure. The following TEG values were documented at the completion of the test: R (minutes), K (minutes); α angle (degrees), maximal amplitude (MA; mm), G (dynes/cm^2), and LY30 (percentage).

TEG Parameters

TEG parameters are represented graphically in a thromboelastogram (Figure 1). SP is the time elapsed from the start of the sample to initial fibrin formation. R is the time from the start of the sample until clot stiffness reaches an amplitude of 2 mm. K is the time elapsed from R until clot stiffness reaches an amplitude of 20 mm. α Angle denotes the angle between the slope of the line starting at R tangential to the TEG tracing with the horizontal axis and measures the rate of clot strengthening. MA is the maximum width of tracing and corresponds with maximum clot strength. LY30 refers to the percentage of clot lysis 30 minutes after MA is calculated. G is a measure of clot strength derived from MA, given by G=(5000×MA)/(100−MA).

The TEG machine was validated for quality assurance through daily quality control procedures using normal and abnormal controls.

Study Design

1. To examine the effect of iodinated contrast on thrombosis in the absence of tPA, we compared TEG values between patients receiving CTA before pre–tPA TEG draw and patients who did not receive CTA before pre–tPA TEG draw (Figure 2).
2. To explore our primary hypothesis that iodinated contrast impairs thrombolysis by tPA, we compared post–tPA LY30 values between patients receiving CTA before tPA and post–tPA TEG draw and patients who did not receive CTA before tPA and post–tPA TEG draw (Figure 3).

Statistical Analysis

The null hypothesis was tested in all analyses. Continuous variables with normal distributions were reported as mean±SD, whereas variables without normal distributions were reported as median and quartiles.

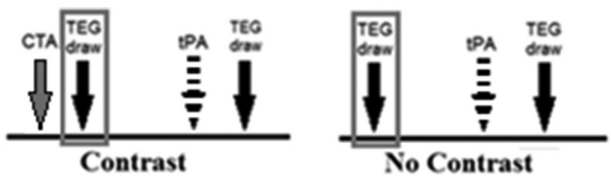

Figure 2. Effect of iodinated contrast on thrombosis in the absence of tissue plasminogen activator.

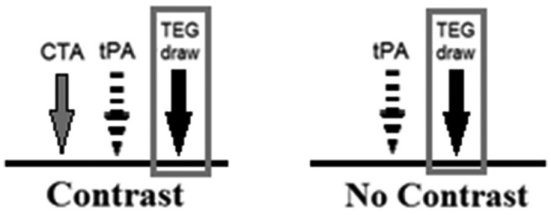

Figure 3. Effect of iodinated contrast on tissue plasminogen activator–induced thrombolysis.

Categorical variables were reported as frequency and percentages. The differences between groups were evaluated using *t* test (or Wilcoxon rank-sum test) and χ^2 test (or Fisher exact test) as appropriate. Quantile regression was performed to compare the median of TEG parameters between different groups. Additionally, multivariable quantile regression models were fitted to compare the median of TEG parameters between groups after controlling for the effect of confounders. The identification of confounders was based on both a priori and empirical considerations. First, variables shown previously to be correlated with TEG parameters (eg, age, smoking status, and antithrombotic medications) were included in the analysis. Second, in a univariable analysis using *P* value <0.20, we identified factors that both differed between contrast and noncontrast groups and were associated with TEG parameters. The covariates were considered to be confounders if the regression coefficient of the independent variable, that is, presence of contrast, varied by >20% when the covariate was added to or deleted from the final model. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC), and a *P* value <0.05 was considered significant.

Results

Our cohort consisted of 136 AIS patients receiving tPA. Patients with errors in TEG processing, missing data, or patients for which TEG blood draw times or CTA times could not be accurately ascertained were excluded (n=22), leaving 114 patients for analysis. The demographics of patients studied are listed in Table 1. There were no differences between groups, but a trend for differences in platelet count (*P*=0.06), small vessel occlusion (*P*=0.06), and diabetes mellitus (*P*=0.09) was observed.

For our analysis of the effect of CTA on baseline pre–tPA TEG, 37 patients had CTA before TEG versus 77 having CTA after tPA or no CTA (Figure 2). In our multivariable Quantile regression models, we compared the median of pre–tPA TEG parameters between CTA and no CTA groups, while controlling for several potential confounders as described in Table 2. No significant differences were found in any of the TEG parameters between the 2 groups (Table 2), indicating that the speed of clot formation was comparable between the 2 groups as was clot strength.

For the examination of the effect of CTA on tPA activity, 47 patients received a CTA before post–tPA TEG draw, whereas 42 patients did not (Figure 3). After controlling for several potential confounders in our final Quantile regression model, as explained in Table 3, no differences in median of post–tPA LY30 were found, indicating that the presence of contrast does not alter tPA-induced thrombolysis as measured by TEG.

It is possible that contrast only has an effect at higher doses. Patients having both CT perfusion and CTA receive an additional 30 mL of contrast. In our cohort, 34 patients received both CT perfusion and CTA before tPA (high-dose contrast group), whereas 42 patients did not receive any contrast before tPA. We found no significant difference in post–tPA LY30 between the high-dose and noncontrast groups (*P*=0.57; data not shown).

Table 1. Comparison of Demographics and Medical History

Demographics	Contrast Group (N=37)	Noncontrast Group (N=77)	*P* Value
Age, y	67.2±15.3	63.5±14.7	0.23
Men	18 (48.7)	44 (57.1)	0.40
Hypertension	28 (75.7)	65 (84.4)	0.26
Hyperlipidemia	15 (40.5)	20 (26.0)	0.11
Diabetes mellitus	8 (21.6)	29 (37.7)	0.09
Coronary artery disease	6 (16.2)	10 (13.0)	0.64
Smoking	7 (19.4)*	16 (21.6)†	0.79
Aspirin	13 (35.1)	24 (31.2)	0.67
Clopidogrel	7 (18.9)	12 (15.6)	0.66
Coumadin	1 (2.7)	3 (3.9)	1.0
Small vessel occlusion	1 (3.3)‡	13 (20.0)§	0.06
Platelet count, mEq/L	240.8±65.1	211.5±80.4	0.06
Glucose, mg/L	119.0 (104.0, 135.0)	120.0 (105.0, 151.0)	0.52
INR	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)‖	0.21
Hemoglobin, mEq/L	14.4±5.5	13.9±1.9	0.60
Baseline NIHSS	7.0 (5.0, 13.0)	8.0 (4.0, 13.0)¶	0.67

Demographics are reported as mean±SD, frequency (percentage), and median (1st quartile, 3rd quartile); *P* values are obtained by *t* test (or Wilcoxon rank-sum test) for continuous variables and χ^2 test (or Fisher exact test) for categorical variables. INR indicates international normalized ratio; and NIHSS, National Institutes of Health Stroke Scale.

*N=36.
†N=74.
‡N=30.
§N=65.
‖N=75.
¶N=75.

Table 2. Effect of Iodinated Contrast on Thrombosis in the Absence of Tissue Plasminogen Activator (tPA)

Pre–tPA TEG Values	Contrast (n=37)	Noncontrast (n=77)	*P* Value
R, min	3.9 (2.9, 5.8)	4.3 (3.8, 6.0)	0.12
K, min	1.4 (1.2, 1.9)	1.7 (1.3, 2.2)*	0.10
α Angle, °	68.1 (64.4, 71.5)	66.5 (58.6, 70.2)	0.30
Maximal amplitude, mm	65.7 (63.6, 67.7)	66.4 (62.3, 68.3)	0.63
G, dynes/cm^2	9.5 (8.8, 10.5)	9.7 (8.5, 11.4)	0.61

Thromboelastography (TEG) values are listed as median (1st quartile, 3rd quartile). Quantile regression was performed for all pre–tPA TEGs. *P* values were obtained to compare the median of pre–tPA TEG values between contrast and noncontrast groups by likelihood ratio test after adjusting for potential confounders: age, aspirin use, clopidogrel use, smoking status, baseline platelet count, and diabetes mellitus (only for maximal amplitude).

*N=76.

Discussion

Our study is the first to examine the effect of the interaction between iodinated contrast and tPA in AIS patients on clotting dynamics and thrombolysis in real time as measured by TEG. In our multivariable Quantile regression model for pre–tPA TEG parameters, we controlled for potential confounders, namely, age, aspirin use, clopidogrel use, smoking status, baseline platelet count, and diabetes mellitus, and in our final multivariable Quantile regression model for post–LY30, we controlled for age, smoking status, aspirin use, and clopidogrel use. Our results support our hypothesis that the presence of contrast from CTA does not impair blood clotting or tPA-induced thrombolysis. Specifically, clot lysis occurring during 30 minutes after the clot achieved maximum strength (LY30) was not significantly different between contrast and noncontrast groups. In support of the current finding, a recent systematic review investigating the effects of contrast media on recanalization after AIS found no effect of contrast on rates of recanalization after thrombolytic therapy in AIS patients.[12]

Our findings, although consistent with studies examining clinical variables such as functional outcome, do not necessarily contradict the findings of other in vivo and in vitro studies that demonstrate an effect of contrast on tPA-induced thrombolysis.[3–6,13] Previous research has demonstrated that increasing concentrations of tPA reduce the impairment of thrombolysis by contrast. Thus, failure to find an effect of contrast in studies such as ours in which tPA was administered clinically could be a function of drug concentration if effective clinical dosages are higher than those resulting from in vitro or ex vivo administration of tPA.[12,14] Additionally, clinical administration of tPA results in significant variability in plasma tPA.[15] In comparison to studies in which fixed, known concentrations of tPA were added to blood samples, the levels of tPA in our study would presumably be more variable, limiting our ability to detect a small interaction between contrast and tPA. Studies that demonstrated an interaction between contrast and thrombolysis have found that this effect is proportional to the dose of contrast.[3] Thus, it is possible that the levels of contrast in the current study were too low to significantly impact tPA-induced thrombolysis. A recent study found that in patients receiving CT angiography before cardiac catheterization, iohexol prolonged mean lysis onset time with tPA as the thrombolytic agent.[3] Our study examined lysis occurring over a 30-minute interval from blood drawn 10 minutes after tPA bolus. Therefore, we might have failed to capture an initial delay in thrombolysis resulting from contrast–tPA interaction starting immediately after the bolus or occurring earlier in the process of clot lysis. Despite these considerations, based on our data, it is unlikely that systemic thrombolysis by doses of tPA given to stroke patients is significantly affected by the amount of contrast administered as a result of obtaining a CTA.

Table 3. Effect of Contrast on Tissue Plasminogen Activator (tPA)-Induced Thrombolysis

Post–tPA TEG Values	Contrast (n=47)	Noncontrast (n=42)	*P* Value
Clot lysis (LY30), %	95.3 (93.4, 95.6)	95.0 (90.1, 95.9)	0.74

LY30 values are listed as median (1st quartile, 3rd quartile). Quantile regression was performed for post-LY30. *P* values were obtained to compare the median of post-LY30 between contrast and noncontrast groups by likelihood ratio test after adjusting for potential confounders: age, smoking status, aspirin use, and clopidogrel use. TEG indicates thromboelastography.

A limitation of this study is that clots formed ex vivo in TEG may not be representative of clots found in cerebral arteries causing AIS. Previous research at our institution found that the percentage of patients with complete recanalization of proximal middle cerebral artery occlusions 2 hours after tPA was 18%.[16] In contrast to in vivo clots, clots formed in TEG are almost entirely lysed by 30 minutes (LY30=95% and 95.3% in noncontrast and contrast groups, respectively). Thus, it is possible that the greater efficacy of tPA in lysing ex vivo clots formed in TEG could mask a small interaction between tPA and contrast that might occur in vivo at the location of the intracerebral clot.

Another limitation of the present study is that coagulation measures from more established fibrinolytic tests, such as D-dimers and fibrinogen assays, were not collected. Although these assays differ from TEG in that they provide static, indirect measurements of in vivo thrombolysis, they would have been useful in confirming the lack of an effect of contrast on tPA-induced thrombolysis we observed using TEG. However, previous studies have confirmed the sensitivity of detection of fibrinolysis by TEG in numerous clinical settings where a significant advantage is earlier results from a point-of-care test.[17–19]

An additional limitation in this study is the sample size. Our small sample size may not be adequate to detect a small but genuine effect of contrast on tPA-induced thrombolysis. However, even if a small difference were to exist, it will be

unlikely that this effect would be clinically meaningful given the absence of an effect in the current study.

In summary, the current data do not support an impairment of tPA-induced clot lysis by iodinated contrast or an effect of contrast on thrombosis independent of an interaction with tPA. Furthermore, TEG may be a useful method for assessing the effect of tPA as evidenced by lytic activity seen in all samples post-tPA. Whether TEG is sufficiently sensitive to detect variables decreasing tPA-induced lysis remains a question and needs further study.

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Disclosures

None.

References

1. Molina CA, Saver JL. Extending reperfusion therapy for acute ischemic stroke: emerging pharmacological, mechanical, and imaging strategies. *Stroke*. 2005;36:2311–2320.
2. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655–1711.
3. Dehmer GJ, Gresalfi N, Daly D, Oberhardt B, Tate DA. Impairment of fibrinolysis by streptokinase, urokinase and recombinant tissue-type plasminogen activator in the presence of radiographic contrast agents. *J Am Coll Cardiol*. 1995;25:1069–1075.
4. Gabriel DA, Jones MR, Reece NS, Boothroyd E, Bashore T. Platelet and fibrin modification by radiographic contrast media. *Circ Res*. 1991;68:881–887.
5. Pislaru S, Pislaru C, Szilard M, Arnout J, Van de Werf F. In vivo effects of contrast media on coronary thrombolysis. *J Am Coll Cardiol*. 1998;32:1102–1108.
6. Gabriel DA, Muga K, Boothroyd EM. The effect of fibrin structure on fibrinolysis. *J Biol Chem*. 1992;267:24259–24263.
7. Jones CI, Goodall AH. Differential effects of the iodinated contrast agents Ioxaglate, Iohexol and Iodixanol on thrombus formation and fibrinolysis. *Thromb Res*. 2003;112:65–71.
8. Elliott A, Wetzel J, Roper T, Pivalizza E, McCarthy J, Wallace C, et al. Thromboelastography in patients with acute ischemic stroke. *Int J Stroke*. September 27, 2012. http://onlinelibrary.wiley.com/doi/10.1111/j.1747-4949.2012.00919.x/abstract. Accessed August 13, 2013.
9. Srinivasa V, Gilbertson LI, Bhavani-Shankar K. Thromboelastography: where is it and where is it heading? *Int Anesthesiol Clin*. 2001;39:35–49.
10. Gonzalez E, Kashuk JL, Moore EE, Silliman CC. Differentiation of enzymatic from platelet hypercoagulability using the novel thrombelastography parameter delta (delta). *J Surg Res*. 2010;163:96–101.
11. Barua RS, Sy F, Srikanth S, Huang G, Javed U, Buhari C, et al. Acute cigarette smoke exposure reduces clot lysis–association between altered fibrin architecture and the response to t-PA. *Thromb Res*. 2010;126:426–430.
12. Dani KA, Muir KW. Do iodinated contrast agents impair fibrinolysis in acute stroke? A systematic review. *AJNR Am J Neuroradiol*. 2010;31:170–174.
13. Morcos SK, Thomsen HS, Exley CM; Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). Contrast media: interactions with other drugs and clinical tests. *Eur Radiol*. 2005;15:1463–1468.
14. Dzialowski I, Puetz V, Buchan AM, Demchuk AM, Hill MD; Calgary Stroke Program. Does the application of X-ray contrast agents impair the clinical effect of intravenous recombinant tissue-type plasminogen activator in acute ischemic stroke patients? *Stroke*. 2012;43:1567–1571.
15. Collen D, Topol EJ, Tiefenbrunn AJ, Gold HK, Weisfeldt ML, Sobel BE, et al. Coronary thrombolysis with recombinant human tissue-type plasminogen activator: a prospective, randomized, placebo-controlled trial. *Circulation*. 1984;70:1012–1017.
16. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, et al; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med*. 2004;351:2170–2178.
17. Palmer JD, Francis DA, Roath OS, Francis JL, Iannotti F. Hyperfibrinolysis during intracranial surgery: effect of high dose aprotinin. *J Neurol Neurosurg Psychiatry*. 1995;58:104–106.
18. Steib A, Gengenwin N, Freys G, Boudjema K, Levy S, Otteni JC. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. *Br J Anaesth*. 1994;73:645–648.
19. Genét GF, Ostrowski SR, Sørensen AM, Johansson PI. Detection of tPA-induced hyperfibrinolysis in whole blood by RapidTEG, KaolinTEG, and functional fibrinogenTEG in healthy individuals. *Clin Appl Thromb Hemost*. 2012;18:638–644.