Thrombelastography Detects the Anticoagulant Effect of Rivaroxaban in Patients With Stroke

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Background and Purpose—Factor Xa inhibitors are prescribed for stroke prevention in atrial fibrillation. Managing such patients is challenging especially if they are eligible for thrombolysis because there is no rapidly available test to detect the effect of such medications. Thrombelastography analyzes the dynamics of coagulation and can be rapidly performed. We sought to determine whether thrombelastography can detect the anticoagulation effect of factor Xa inhibitors in patients with stroke.

Methods—Blood from 10 patients with stroke was analyzed by thrombelastography at baseline and 2 to 18 hours after rivaroxaban administration.

Results—Increased R, K, and δ were seen at 2, 4, and 6 hours, while G, maximum amplitude, α-angle, and LY30 were decreased. Baseline R was 5.8±0.5 when compared with 11.4±1.0 at 2 hours. R remained prolonged at 18 hours. Other thrombelastography parameters were normal by 18 hours.

Conclusions—Thrombelastography can detect the anticoagulant effect of factor Xa inhibitors in patients with stroke and might be useful in the emergency management of those eligible for thrombolysis. (Stroke. 2014;45:880-883.)

Key Words: factor Xa ■ rivaroxaban ■ stroke ■ thrombolytic therapy

Factor Xa inhibitors (fXaI) are being used for preventing strokes in patients with atrial fibrillation. The management of patients with acute stroke taking fXaI is challenging, especially if they are eligible for thrombolysis because there is no rapid and widely available test to detect the anticoagulant effect of fXaI. Although studies have reported prolongation of prothrombin time and activated partial thromboplastin time for fXaI, these results were inconsistent depending on the assay reagent used, making these tests unreliable. Other tests, such as Russell viper venom time, 1-step prothrombinase-induced clotting time, Hep-test, and factor Xa chromogenic assays, lack specificity and are not commercially available.

One method that could be useful is thrombelastography, which can rapidly analyze the dynamics of coagulation and provide quantitative measures of clot formation. Although prolongation of thrombelastography parameters within 2.5 hours after a single dose of rivaroxaban 10 mg has been demonstrated in 11 healthy male volunteers, such trends have not been investigated in patients receiving a higher dose of the medication for stroke prevention, and who may also be hypercoagulable when compared with healthy controls.

Our goal was to investigate whether thrombelastography can detect the antithrombotic activity of fXaI in patients with ischemic stroke. We studied rivaroxaban but results should apply to other fXaI.

Methods

This study was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. Patients >17 years with ischemic strokes requiring anticoagulation with rivaroxaban were screened. Exclusions included contraindication to anticoagulation. Consent was obtained from all subjects. Venous blood was drawn at baseline and at 2, 4, 6, and 18 hours after drug administration. All patients received rivaroxaban based on creatinine clearance.

Statistical Analysis

Continuous variables with normal distributions were summarized by mean (±SD), and variables with skewed distributions were summarized by median and interquartile range. Categorical variables were described with frequency and percentages. Comparison of thrombelastography parameters between baseline and 2, 4, 6, and 18 hours was assessed considering time as a categorical variable in a generalized estimating equations model with an autoregressive correlation matrix to account for the correlation within patients. All statistical
Our aim was to determine whether thrombelastography can quickly and accurately detect the anticoagulation effect of FXa inhibitors in patients with stroke. Our results indicate that FXa inhibitors increase the time to clot formation, while decreasing the strength of the clot itself, as evidenced by increased R, K, and G and decreased angle (measures of time to clot formation), with an associated decrease in G and MA (measures of clot strength). These effects are seen within 2 to 4 hours after dosing, consistent with the known pharmacokinetic properties of the drug and extend ≤6 hours. At 18 hours, a trend toward normalization to baseline was observed for all thrombelastography parameters. The only parameter still abnormal at 18 hours was R, which depends on coagulation factors affected by the direct inhibition of factor Xa. These results suggest that R could be extremely useful to signify the extent of a patient’s anticoagulation, especially when the time of the last dose is unknown.

### Discussion

Blood Sampling and Processing

A total of 7 to 10 mL of blood was collected into a citrated tube and processed in a computerized thrombelastography coagulation analyzer (Model 5000; Haemonetics Corp, Braintree, MA). The machine was validated for quality assurance through daily quality control procedures. Personnel performing the testing were all trained on the procedure. The following thrombelastography values were documented (see online-only Data Supplement for a normal thrombelastography tracing): R (minutes) is the time until clot firmness reaches an amplitude of 2 mm; R-SP or δ (minutes) is the time to reach the maximum speed of initial clot formation, representing the thrombinst burst; K (minutes) is the time to reach the maximum speed of clot strengthening; α angle (°) is formed by the slope of thrombelastography tracing at R from the horizontal and reflects the speed of clot strengthening; maximum amplitude (MA) is the maximum strength of the clot; G (dynes/cm²) measures clot firmness or strength (G=5000MA/(100–MA)) and is higher in clots that are more platelet rich and held together by stronger fibrin matrices; LY30 (% lysis) is the measure of clot lysis over 30 minutes.

### Results

A total of 10 patients, days 1 to 7 after symptoms, were enrolled. Baseline demographics are outlined in Table 1. All 10 patients had blood drawn at baseline and at 2, 4, and 6 hours; 7 out of 10 patients had blood drawn at 18 hours. Thrombelastography results required an average of 24.5 minutes from the time blood was drawn.

Higher R, K, and G and lower angle were seen at 2, 4, and 6 hours, indicating slower clot formation. Significantly lower G and MA suggested less clot strength at 2, 4, and 6 hours (Table 2). R was the only parameter that was different between baseline and 18 hours. Other thrombelastography values were within normal range by 18 hours.

The Figure shows the distribution of thrombelastography parameters at various time intervals. We estimate that an R value cutoff of ≥7 minutes could be evaluated further as a potential cutpoint for identifying patients as being partially anticoagulated.
Limitations of our study include our sample size and the paucity of thrombelastography data between 6 and 24 hours. Compared with a previous study of thrombelastography performed within 2 minutes in healthy volunteers, our thrombelastography analyses took an average of 24.5 minutes (although the pivotal R value was known within 5–10 minutes) and was composed of patients with ischemic strokes who were administered a more clinically relevant dose of the medication. Concurrent medical comorbidities and the simultaneous use of aspirin with rivaroxaban are unlikely

Figure. Box-and-whisker plot of each thrombelastography value at baseline and follow-up. The bottom and top of the box indicate first and third quartiles. Band inside the box is the median. Circles represent outliers with values >1.5 interquartile range away from the first and third quartiles. The ends of the whiskers represent maximum and minimum values without outliers.
to have affected our findings based on previous evidence, showing no interaction between antiplatelet therapy and medical comorbidities with thrombelastography parameters.5 Our results also need to be compared with other assays, confirmed in more patients with other fXaI, and correlated with clinical events to confirm that the use of tissue-type plasminogen activator in patients with stroke with normal thrombelastography is indeed safe.

Our study demonstrates that thrombelastography can rapidly and predictably detect the coagulation status of patients with stroke taking fXaI. Such information may be useful if these patients are being considered for emergent thrombolysis or interventions.

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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL
Supplementary Figure I. A Normal TEG™ tracing. SP (minutes) = time elapsed from when the blood is placed in the TEG™ device until first fibrin formation, R = time until clot firmness reaches an amplitude of 2mm, R-SP or delta (minutes) = time to reach maximal speed of initial clot formation and thrombin “burst,” K = measured from R until clot firmness is 20 mm and measures speed of clot strengthening, α Angle = formed by the slope of TEG™ tracing at R from the horizontal and reflects the speed of clot strengthening, Maximum Amplitude (MA) = maximum strength of the clot, G (dynes/cm2) = measures clot firmness, or strength (G=5,000MA/(100-MA) and is higher in clots that are more platelet rich and are held together by stronger fibrin matrices, LY 30 = measure of clot lysis over 30 minutes, reported as percent lysis.