Intracerebral hemorrhage (ICH) has high morbidity, and hematoma enlargement (HE) causes worse outcome. Thrombelastography (TEG) measures the dynamics of clot formation and dissolution, and might be useful for assessing bleeding risk. We used TEG to detect changes in clotting in patients with and without HE after ICH.

Methods—This prospective study included 64 patients with spontaneous ICH admitted from 2009 to 2013. TEG was performed within 6 hours of symptom onset and after 36 hours. Brain imaging was obtained at baseline and at 36±12 hours, and HE was defined as total volume increase >6 cc or >33%. TEG was also obtained from 57 controls.

Results—Compared with controls, patients with ICH demonstrated faster and stronger clot formation; shorter R and delta (P<0.0001) at baseline; and higher MA and G (P<0.0001) at 36 hours; 11 patients had HE. After controlling for potential confounders, baseline K and delta were longer in HE+ compared with HE− patients, indicating that HE+ patients had slower clot formation (P<0.05). TEG was not different between HE+ and HE− patients at 36 hours.

Conclusions—TEG may detect important coagulation changes in patients with ICH. Clotting may be faster and stronger in immediate response to ICH, and a less robust response may be associated with HE. These findings deserve further investigation. (Stroke. 2014;45:683-688.)

Key Words: blood coagulation factors ■ cerebral hemorrhage ■ thrombelastography
with an ischemic stroke versus 12% of age-matched controls. Patients with acute ischemic stroke had shorter R, greater Angle, and shorter K, indicating faster clotting. However, TEG has not been reported in patients with ICH.

The objective of this study was to use TEG to detect any changes in clotting characteristics in patients with ICH compared with controls, and whether TEG differed in patients with and without HE. We hypothesized that patients with HE would have less robust clotting after ICH. Our hypothesis is that TEG abnormalities might help us understand the components of any clotting abnormality leading to HE, provide a clue for future therapeutic interventions to prevent HE, and possibly serve as a clinically useful tool to predict patients who will develop HE.

Methods

This prospective study included consecutive patients ≥18 years of age with spontaneous ICH who could consent and have blood drawn for TEG analysis within 6 hours of symptom onset. Patients were excluded if bleeding was because of known coagulopathy (including use of anticoagulants), trauma, or known vascular malformation, or if they had surgical clot evacuation (other than hemiependymectomy or ventriculostomy) or receipt of any hemostatic agents before the baseline TEG draw. After the first 36 patients were enrolled, a second blood draw was obtained after 36 hours on subsequent patients if possible. This protocol change occurred based on observations that initial blood draw was obtained after 36 hours on subsequent patients if possible. Whole blood was collected into a citrated tube on the patient’s arrival at the emergency department. The blood was held at room temperature and taken for processing within 2 hours of collection. The test was run on a computerized TEG coagulation analyzer (Haemonetics Corp, Model 5000; Braintree, Mass). All personnel who performed the testing were trained on the procedure.

R, K, and delta were available within 10 minutes of test initiation; Angle, MA, and G were available within 20 to 30 minutes; and LY30 was available within 30 minutes. The TEG machine was validated for quality assurance through daily quality control procedures using normal and abnormal controls for calibration verification and operational checks. Variability in run-to-run precision, day-to-day precision, and between site and manufacturer was <3%.

Data collected at baseline included age, race, sex, and past medical history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, smoking, and use of outpatient medications as per patient or family report. We also documented results of computed tomography scan without contrast, National Institutes of Health Stroke Scale (NIHSS), glucose, hemoglobin, hematocrit, platelets, prothrombin time, international normalized ratio, and partial thromboplastin time. Brain imaging was obtained at baseline and at 36±12 hours. The ABC/2 method was used for calculating hematoma volume based on ellipsoid volume formula. HE was defined as total volume increase >6 cc or >33%, as used in previous studies.

TEG values were also obtained from controls who were either healthy volunteers or patients seen in our outpatient clinic with nonvascular diagnoses. 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. The differences between groups with respect to demographics, medical history, outpatient medications, and baseline laboratory values were compared using t test (or Wilcoxon rank-sum test) and χ² test (or Fisher exact test) as appropriate.

To compare baseline and 36-hour TEG values between patients with ICH and the control group, we performed simultaneous comparisons of all components of TEG values based on multivariate analysis (Hotelling–Lawley Trace test). If significant differences were observed, post hoc analysis on each individual TEG value was performed using 2 sample t tests to compare the differences in baseline and 36-hour TEG values between patients with ICH and the control group. Multivariable regression models were performed to compare the differences between HE+ and HE− groups while controlling for confounders. The identification of confounders was based on both a priori and empirical considerations. First, the important factors correlated with TEG parameters (eg, age, smoking status, and antithrombotic medications), judged by knowledge and literature, were included in the analysis. Second, we identified the factors that were associated with both group statuses (HE+ and HE−) and TEG parameters at P value<0.25 in univariate analysis. The covariates were considered to be confounders if the regression coefficient of group status varied by >20% when the covariate was added to (or deleted from) the final model. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc; Cary, NC), and a P value <0.05 was considered significant.

Our initial sample size estimate was 67 patients based on differences in TEG observed between patients with ischemic stroke and normal controls in our previous study. This sample size would allow us to detect differences of 0.57 SD for each of the TEG values with a power of 80%. Except for the study statistician, all investigators remained blind to the grouped data throughout the study.

This study was approved by the Committee for the Protection of Human Subjects of The University of Texas Health Science Center at Houston. Informed consent was obtained from each individual before participation in the study.

Results

A total of 77 patients with spontaneous ICH admitted through the Memorial Hermann Hospital-Texas Medical Center Emergency Department from 2009 to 2013 were included, but 3 patients were missing baseline TEG data, leaving a total of 64 for analysis; 36-hour TEG values were obtained...
in the final 27 patients. We also obtained TEG samples from 57 controls.

There was no significant difference between patients with ICH and controls for age (59.0±12.7 versus 54.6±13.1) or sex (male n [%]: 37 [57.8] versus 30 [52.6]).

The $P$ values for simultaneous comparisons of all components of baseline and 36-hour TEG values between patients with ICH and the control group based on multivariate analysis (Hotelling–Lawley Trace test) were both $<0.0001$. Compared with controls, patients with ICH demonstrated faster clot formation within 6 hours of onset; shorter R and delta ($P<0.0001$); and steeper angle ($P<0.05$) at baseline. By 36 hours, patients with ICH had higher MA and G ($P<0.0001$), suggesting the development of stronger clot formation (Table 1).

Eleven of the patients with ICH developed HE. Male sex and previous clopidogrel use were more frequent in the HE+ group ($P<0.05$) compared with HE− group; however, there were no differences in important variables that might be associated with HE (Table 2). Multivariable regression in Table 3 adjusting for potential confounding effects revealed that HE+ patients showed slower (longer K and delta and a trend toward longer R) clot formation compared with HE− patients.

TEG was not different between HE+ and HE− patients at 36 hours, suggesting that any differences in clot formation among the patients with ICH had disappeared by 36 hours (data not shown).

Figure 2 shows a histogram representing the distribution of delta values at baseline between controls, all patients with ICH, and the HE+, and HE− subgroups.

**Discussion**

This is the first study to evaluate coagulation status as reflected by TEG in patients with ICH. Our first major finding was that patients with ICH overall have faster initial clot formation and therefore are hypercoagulable compared with controls, after adjusting for age and sex. We cannot say from our data whether this finding reflects an adaptive hemostatic response to bleeding or is a more generalized acute phase homeostatic response. Our finding that TEG remained abnormal at 36 hours reflecting stronger clot formation, and that patients with HE differed from those without, all suggest a specific response to bleeding.

Our second important finding is that this initial acceleration of clot formation was not seen in patients with HE, possibly indicating that heterogeneity in an adaptive response to ICH might play a role in whether parenchymal bleeding continues or stops. If this observation is confirmed in a larger cohort of patients, it would support procoagulation strategies in the first hours after ICH, particularly those focused on speeding the initial formation of the clot. Many other factors, as already mentioned, likely play a role in HE, and it is unlikely that TEG as a baseline test would be sufficiently precise to identify the subset of patients who are at highest risk for developing HE. However, further understanding of coagulation disturbances as reflected by TEG might help guide the design of therapeutic interventions. One previous study in a mixed neurocritical care cohort (including patients with ICH and traumatic brain injury) suggested that hypocoagulability by TEG (longer R time, smaller angle, and MA) was independently associated with higher mortality.13 However, when the hypocoagulable state was defined according to conventional plasma-based coagulation tests (international normalized ratio >1.3, platelet count <100000, or activated partial thromboplastin time >35 seconds), there was no correlation with worse prognosis. TEG findings are also used to guide transfusion decisions and prohemostatic therapy in the perioperative period.15 Given the application of TEG data to guide specific interventions, such as platelet transfusion, fibrinogen, and recombinant factor VII administration in cardiac, liver transplant, and trauma surgery,15 our preliminary findings support further investigation of a similar potential role for TEG in patients with ICH and HE.

To minimize the overall type I error when comparing various components of the TEG values between patients with ICH and the control group, we performed a multivariate analysis (Hotelling–Lawley Trace test) to simultaneously test the mean differences in TEG values as vector of outcomes. If a significant difference was observed, then we...

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**Table 1. Comparison of Patients With ICH and Controls With Respect to Baseline TEG and 36-Hour TEG Values**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±SD</th>
<th>$P$ Values for Comparing Baseline TEGs in Patients With ICH and Controls</th>
<th>$P$ Values for Comparing 36-H TEGs in Patients With ICH and Controls</th>
<th>$*P$ Values for Comparing Baseline and 36-H TEGs in Patients With ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4.7±1.7</td>
<td>6.5±4.4</td>
<td>6.1±1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Delta</td>
<td>0.6±0.3</td>
<td>0.9±1.6</td>
<td>0.9±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>K</td>
<td>2.1±1.6†</td>
<td>2.1±2.8</td>
<td>2.1±0.6</td>
<td>0.94</td>
</tr>
<tr>
<td>MA</td>
<td>64.5±14.1</td>
<td>70.7±4.8</td>
<td>64.4±5.8</td>
<td>0.98</td>
</tr>
<tr>
<td>Angle</td>
<td>64.4±10.8</td>
<td>66.4±12.3</td>
<td>61.3±5.8</td>
<td>&lt;0.05‡</td>
</tr>
<tr>
<td>G</td>
<td>10.4±4.1</td>
<td>12.5±2.9</td>
<td>9.3±2.0</td>
<td>&lt;0.05‡</td>
</tr>
</tbody>
</table>

Other $P$ values are obtained by 2 sample $t$ tests; the $P$ values for simultaneous comparisons of all components of baseline and 36-h TEG values between patients with ICH and the control group based on multivariate analysis (Hotelling–Lawley Trace test) were both $<0.0001$. ICH indicates intracerebral hemorrhage; and TEG, thrombelastography.

$*P$ values obtained from paired $t$ test or Wilcoxon signed-rank test where appropriate.

†$P$ value=0.049.

‡$P$ value=0.047.
performed post hoc analysis on each TEG value. Although all multivariate analyses were significant at the 0.05 level, we acknowledge that the $P$ value for a simultaneous comparison of all components of TEG values between 36-hour TEG and baseline values was marginally significant ($P=0.09$). However, we attribute this to the limited sample size in this study and hence caution the interpretation of these particular findings.

In our analysis, male sex and previous clopidogrel use were associated with HE. A higher prevalence of ICH but not HE.
has been reported in men, driven by an excess of deep hemor- rhages. Antiplatelet drug use has been associated with increased risk of hematoma enlargement as well as increased mortality in patients presenting with ICH, although data on this issue are conflicting. The same effect was not seen with aspirin use; however, the low number of patients on aspirin could account for this finding.

Our study has some limitations besides the relatively small sample size of patients with HE and the relatively small number of 36-hour samples. TEG measurements can be operator dependent, and our analysis may be limited by the multiple operators who performed TEG measurements. However, we minimized this with dedicated staff training on the procedure, use of the same equipment, and daily quality control. Our identification of the HE+ group depends on the accuracy of our ICH volume measurement. The inter-rater reliability for the ABC/2 formula in previous studies has ranged from 0.63 to 0.99 and has been used for determining eligibility in ICH trials. In our study, hematoma volume on the baseline and 36-hour scans were calculated independently using the ABC/2 method by 2 authors, and our intraclass correlation was excellent (0.795 for baseline volume and 0.971 for 36-hour hematoma volume). There was 100% agreement on the presence or absence of HE based on the definition used in this study.

Another limitation was the timing of tests. Except in 2 patients, our baseline testing occurred within 6 hours of symp- tom onset during the time that HE most frequently occurs, and there was no difference in time of TEG blood drawn between the HE+ and HE− groups. However, TEG values are dynamic and change within minutes or hours after ICH, and we might have found greater or fewer differences between groups if TEG measurements were made at some other time point after ICH. Many of our patients were critically ill, and 36-hour TEG values may have been affected by the large number of medications and other variables inherent in critical care management. Some patients received blood products and underwent procedures (hemicraniectomy and ventriculostomy) that likely affected the 36-hour TEG measurements although, again, there were no differences between the groups in the occurrence of these events or in blood pressure at baseline or during the next 36 hours.

Conclusions

In conclusion, TEG may detect important coagulation changes in patients with ICH; clotting may become faster and stronger in immediate response to ICH, and a less robust response may be associated with HE. These findings may have relevance to the cause and management of patients with HE and deserve further investigation.

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Disclosures

None.

References


Thrombelastography Detects Possible Coagulation Disturbance in Patients With Intracerebral Hemorrhage With Hematoma Enlargement

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