Thromboelastography Parameter Predicts Outcome After Subarachnoid Hemorrhage: An Exploratory Analysis

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OBJECTIVE: **Hypercoagulability after subarachnoid hemorrhage (SAH) is well described and may be platelet mediated. Thromboelastography (TEG) provides a global assessment of coagulation. We sought to determine whether the maximum amplitude (MA) parameter of TEG, a measure of platelet strength and function, is associated with outcome after SAH.**

METHODS: **One hundred ten TEG analyses were performed for patients with moderate-to-severe SAH and compared with 6 healthy age- and sex-matched controls. TEG indices included MA, G value (G), alpha angle, and thrombus generation and were correlated to functional outcomes and laboratory tests including complete blood count, erythrocyte sedimentation rate, high sensitivity C-reactive protein, fibrinogen, and D-dimer, obtained on post-bleed days (PBDs) 1, 3, 5, 7, and 10.**

RESULTS: **MA was significantly elevated compared with controls on PBD 3 (70.0 mm ± 4.5 mm vs. 64.1 mm ± 6.5 mm; $P = 0.02$), PBD 5 (72.6 mm ± 5.3 mm vs. 64.1 mm ± 6.5 mm; $P = 0.003$), PBD 7 (73.0 mm ± 5.4 mm vs. 64.1 mm ± 6.5 mm; $P = 0.003$), and PBD 10 (73.4 mm ± 6.0 mm vs. 64.1 mm ± 6.5 mm; $P = 0.005$). G was significantly elevated compared with controls on PBD 3 ($P = 0.03$), PBD 5 ($P = 0.01$), PBD 7 ($P = 0.01$), and PBD 10 ($P = 0.02$). The only biomarker associated with poor outcome was CRP. Multivariate logistic regression demonstrated an association between elevated MA and outcome (odds ratio 39.1, $P = 0.006$) independent of CRP, age, Hunt Hess grade, and transfusion.**

CONCLUSIONS: **TEG indices are associated with poor outcome after SAH and may identify a platelet-mediated hypercoagulable state. The association between MA and outcome was stronger than that between traditional biomarkers and was independent of age and Hunt Hess grade.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a devastating neurological condition that affects nearly 30,000 people annually in the United States, accounting for up to 25% of stroke-related deaths.[1]

SAH has been associated with abnormalities of coagulation and fibrinolysis, and studies demonstrate elevations of D-dimer, thrombin, and other coagulation-related products in both blood

Key Words
- Coagulopathy
- Functional outcome
- Hypercoagulable state
- Platelet
- Subarachnoid hemorrhage
- Thromboeleastography

Abbreviations and Acronyms
AA: Alpha angle
CRP: C-reactive protein
CT: Computed tomography
DCI: Delayed cerebral ischemia
ESR: Erythrocyte sedimentation rate
ICU: Intensive care unit
INR: International normalized ratio
MA: Maximum amplitude
MP: Microparticle
MRS: Modified Rankin score
OR: Odds ratio
PAF: Platelet-activating factor
PBD: Post-bleed day
PT: Prothrombin time
PTT: Partial thromboplastin time
SAH: Subarachnoid hemorrhage
TEG: Thromboeleastography
TG: Thrombus generation
V curve: Velocity curve

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and cerebrospinal fluid in patients after SAH.[2-4] These elevated levels of coagulation biomarkers have also been shown to correlate with worse clinical outcomes.[5-8] The pathophysiology of hypercoagulability after SAH is thought to be primarily platelet mediated, initiated by subarachnoid blood-induced endothelial injury, and subsequent platelet activation.[9,10] Platelet-mediated neurotoxicity and microthrombosis after SAH has also been demonstrated in animal models.[11]

Thromboelastography (TEG) is a point of care test that measures clot formation, clot strength, and clot dissolution. The technology uses whole blood instead of plasma, which better accounts for the effect of cellular elements of coagulation.[12] The cell-based model of hemostasis is currently favored over the traditional "cascade" model of coagulation, because the cell-based model incorporates the role of tissue-factor bearing cells and platelets, the cellular requisites for coagulation. Although the cascade model is helpful in understanding hemostasis in vitro, it does not fully explain it in vivo.[13,14] Studies using TEG have demonstrated a platelet-mediated hypercoagulable state after SAH by showing elevations in the maximum amplitude (MA) parameter, a marker of platelet function, in the post-bleed period.[15] In addition, investigators have also demonstrated a trend for an association of MA with long-term outcomes in patients after SAH, although these were not statistically significant.[16]

In this study, we hypothesized that 1) TEG may identify a platelet-mediated hypercoagulable state after SAH, 2) elevated MA may be associated with poor short-term functional outcome, as defined by the 7-point modified Rankin scores (mRS), and 3) MA may be more closely associated with outcomes after SAH than other coagulation and inflammatory biomarkers.

METHODS

Study Population

Twenty-two patients were enrolled in a prospective observational study of moderate-to-severe SAH, defined as Fisher group III, admitted to an academic Level I trauma center at the University of Pennsylvania Neuroscience Intensive Care Unit between August 2011 and July 2015. The Institutional Review Board at the Hospital of the University of Pennsylvania granted approval of the study protocol. Informed consent was obtained from the patient's legal representative. Inclusion criteria were defined as aneurysmal SAH admitted within 24 hours of ictus and aged >18 years. Patients with SAH from antecedent head trauma, ischemic or hemorrhagic stroke, vascular malformations, or other secondary causes were excluded. The control group consisted of 6 healthy age- and sex-matched volunteers. Control subjects were healthy individuals without any known comorbidities, not taking antithrombotic or anticoagulant medications. All control subjects were consented for this study.

SAH was established radiographically by admission computed tomography (CT) scan. Patients were characterized by admission Hunt and Hess grade and modified Fisher grade. Hunt and Hess classifications were determined by the admitting intensive care unit (ICU) fellow and based on the clinical examination obtained from the Emergency Room. Fisher grade was determined on the basis of the initial head CT. Demographic data, including age and sex, as well as clinical and laboratory data were recorded. Comorbidity data, including hypertension, coronary artery disease, prior stroke, diabetes, and tobacco and alcohol use were also documented. Aneurysm size and location were documented from 4-vessel catheter cerebral angiography. Recorded standard laboratory parameters included complete blood count, erythrocyte sedimentation rate (ESR), fibrinogen, D-dimer, high sensitivity C-reactive protein (CRP), prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and chemistry panel. TEG values were also obtained, as discussed in more detail later. The primary outcome measure was degree of disability on hospital discharge, as measured by mRS. Poor outcome was defined as mRS of 3 or higher at hospital discharge.[17] Secondary outcomes included delayed cerebral ischemia (DCI), presence of angiographic vasospasm, sonographic vasospasm as defined by transcranial Doppler values >200 cm/sec, cerebral infarction, and 90-day mortality.

Management

All patients received standard of care for aneurysmal SAH according to a previously published local protocol,[18,19] which included aggressive prehospital and preoperative resuscitation, early aneurysm occlusion, observation and supportive care in the ICU with invasive hemodynamic monitoring, and aggressive prevention and treatment of intracranial hypertension and DCI, consistent with published guidelines.[20]

Blood Sampling: Laboratory Studies

TEG (TEG 5000; Haemoscope Corporation, Niles, Illinois, USA) analysis of peripheral blood samples on trial patients was performed on post-bleed days (PBDs) 1, 3, 5, 7, and 10, in accordance with instructions from the manufacturer. Whole blood samples were uniformly obtained by arterial line to minimize platelet shearing. Blood samples were collected in pediatric, citrated blue-top tubes to prevent clotting and immediately placed on ice. Samples of both control and trial patients were recalcified before TEG analysis with calcium chloride, and the time between blood draw and TEG was standardized (20–25 minutes). Before analysis, samples were mixed with heparinase (an agent to neutralize heparin) and kaolin (an activator of the indirect pathway of the clotting cascade used to reduce variability and running time).

Thrombelastography

The TEG apparatus consists of an oscillating cup and a suspended stationary pin suspended. A 0.36-mL sample of whole blood is placed in the cup. As the cup moves, clot is generated and binds the cup and the pin. The movement of the pin is defined by the kinetics and strength of clot formation, and this movement generates a standard TEG tracing that reflects the patient's hemostasis profile.

Standard TEG curves were thusly obtained from standard tracings for all patients and controls. Thrombus velocity curves (V curve), which represent the first derivative of changes in clot resistance expressed as a change in amplitude per unit time (mm × 100/sec), were also recorded for all patients. Parameters from the V curve include time to maximum rate of thrombus generation (in minutes), maximum rate of thrombus generation (in minutes), and thrombus generation (TG, area under the curve). The following commonly used parameters from TEG and V curves were prespecified for analysis of hypercoagulability: MA, a