Cerebral Microbleeds are an Independent Predictor of Hemorrhagic Transformation Following Intravenous Alteplase Administration in Acute Ischemic Stroke

Nandakumar Nagaraja, MD, MS,*† Nudrat Tasneem, MD,† Amir Shaban, MD,† Sudeepta Dandapat, MD,† Uzair Ahmed,† Bruno Policeni, MD,‡ Heena Olalde, RN,† Hyungsub Shim, MD,† Edgar A. Samaniego, MD, MS,† Connie Pieper, MD,† Santiago Ortega-Gutierrez, MD, MS,† Enrique C. Leira, MD, MS,† and Harold P. Adams Jr, MD†

Background and Purpose: Intravenous alteplase (rt-PA) increases the risk of hemorrhagic transformation of acute ischemic stroke. The objective of our study was to evaluate clinical, laboratory, and imaging predictors on forecasting the risk of hemorrhagic transformation following treatment with rt-PA. We also evaluated the factors associated with cerebral microbleeds that increase the risk of hemorrhagic transformation. *Methods:* Consecutive patients with acute ischemic stroke admitted between January 1, 2009 and December 31, 2013 were included in the study if they received IV rt-PA, had magnetic resonance imaging (MRI) of the brain on admission, and computed tomography or MRI of the brain at 24 (18-36) hours later to evaluate for the presence of hemorrhagic transformation. The clinical data, lipid levels, platelet count, MRI, and computed tomography images were retrospectively reviewed. *Results:* The study included 366 patients, with mean age 67 ± 15 years; 46% were women and 88% were white. The median National Institutes of Health Stroke Scale (NIHSS) score was 6 (interquartile range 3-15). Hemorrhagic transformation was observed in 87 (23.8%) patients and cerebral microbleeds were noted in 95 (25.9%). Patients with hemorrhagic transformation tended to be older, nonwhite, have atrial fibrillation, higher baseline NIHSS score, lower cholesterol and triglyceride levels, and cerebral microbleeds and nonlacunar infarcts. Patients with cerebral microbleeds were more likely to be older, have hypertension, hyperlipidemia, previous history of stroke, and prior use of antithrombotics. On multivariate analysis race, NIHSS score, nonlacunar infarct,

From the *Department of Neurology, University of Florida College of Medicine, Gainesville, Florida; †Department of Neurology; and ‡Department of Radiology, Carver College of Medicine, University of Iowa, Iowa.

Received July 3, 2017; revision received November 10, 2017; accepted December 22, 2017.

Conflict of interest: Nandakumar Nagaraja: Consultant as stroke adjudicator for Women's Health Initiative Extension Study. Nudrat Tasneem: No disclosures. Amir Shaban: No disclosures. Sudeepta Dandapat: No disclosures. Uzar Ahmed: No disclosures. Bruno Policeni: No disclosures. Heena Olalde: No disclosures. Hyungsub Shim: No disclosures. Edgar Samaniego: Consultant for Microvention. Connie Pieper: No disclosures. Santiago Ortega-Gutierrez: Consultant for Stryker. Enrique C Leira: Receives salary support from the NINDS. Harold P Adams: Receives funding from NIH for his role as Co-PI of the University of Iowa RCC.

Department/institution where work was performed: Department of Neurology, University of Iowa.

Address correspondence to Nandakumar Nagaraja, MD, MS, Department of Neurology, University of Florida College of Medicine, HSC PO BOX 100236, Gainesville, FL 32610-0236. E-mail: Nandakumar.nagaraja@neurology.ufl.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.12.044

and presence of cerebral microbleeds were independently associated with hemorrhagic transformation following treatment with rt-PA. *Conclusions:* Presence of cerebral microbleeds is an independent predictor of hemorrhagic transformation of acute ischemic stroke following treatment with rt-PA.

Introduction

Hemorrhagic transformation (HT) of ischemic stroke refers to hemorrhage in the infarct tissue, and it is considered part of the natural evolution of the stroke. It could be due to reperfusion of the infarcted tissue by recanalization or augmented collateral circulation.[1-3] Administration of intravenous alteplase (rt-PA) is the standard medical treatment for patients presenting with acute ischemic stroke (AIS) within the 4.5 hours of symptom onset.[4] However, HT is a complication after ischemic stroke and may result in worse outcome. The risk of HT is increased in patients receiving rt-PA.

Various definitions exist to define symptomatic intracerebral hemorrhage (SICH). The most commonly used classification of HT is that defined in the European Cooperative Acute Stroke Study I (ECASS I). It classified HT as hemorrhagic infarction (HI) type 1 and 2, and parenchymal hematoma (PH) type 1 and 2.[5] HT is classified as symptomatic or asymptomatic on the basis of the evidence and timing of neurological worsening associated with the hemorrhage. Large PH type 2 is associated with poor outcome, but the data on asymptomatic HT are not clear.[6,7]

Several clinical, laboratory, and imaging factors are associated with HT, but only a few are considered independent risk factors.[1,6] Clinical factors associated with the risk of HT include older age, history of diabetes, atrial fibrillation, prior antiplatelet use, higher systolic blood pressure, and increased severity of stroke as measured by the National Institutes of Health Stroke Scale (NIHSS) score. Laboratory factors include hyperglycemia, lower low-density lipoprotein or total cholesterol, and renal impairment. Stroke volume on diffusion-weighted imaging (DWI) and extent of parenchymal attenuation on initial computed tomography (CT) head are associated with HT. Previous studies have evaluated the risk of HT and SICH following administration of rt-PA in patients with cerebral microbleeds (CMs).[8,9] However, the role of CMs as an independent risk factor of HT of ischemic stroke and the factors influencing their development or rupture remain to be determined.

The objectives of our study were (1) to evaluate the independent impact of clinical, laboratory, and imaging factors on the risk of HT following rt-PA and (2) to evaluate the factors associated with CMs as a predictor on HT.

Methods

Study Population

This was a retrospective cohort that included consecutive patients with AIS admitted to University of Iowa Hospitals and Clinics between January 1, 2009 and December 31, 2013. The study was approved by the Institutional Review Board at the University of Iowa. Patients were included in the study if they had (1) received intravenous rt-PA; (2) magnetic resonance imaging (MRI) brain with interpretable DWI, gradient-recalled echo (GRE), and fluid-attenuated inversion recovery (FLAIR) sequences on admission; (3) CT head or MRI brain at 24 (18-36) hours post rt-PA to evaluate for HT; and (4) a discharge diagnosis of AIS. Patients were excluded from the study if they did not have follow-up imaging or had noninterpretable DWI, GRE, and FLAIR images.

The following baseline characteristics were extracted from the University of Iowa stroke registry: (1) demographics, (2) medical history, (3) social history, (4) preadmission antithrombotics, (5) admission NIHSS score, (6) admission blood pressure, (7) laboratory tests (platelets, lipid profile), and (8) discharge disposition.

Imaging Protocol

MRI images were obtained from 1.5T Siemens Espree or 1.5T Avanto clinical scanners (Espree or Avanto; Siemens, Erlangen, Germany). The MRI protocol included DWI, FLAIR, and GRE. The typical parameters for DWI were TR/TE = 2900/79 with b = 0 and b = 1000 sec/mm^2, 5-mm slice thickness, and 2-mm separation; for FLAIR, TR/TE = 9000/99-110, 5-mm thickness, 2-mm separation, flip angle 180 degrees, and acquisition matrix 288 × 384; for GRE, TR/TE = 418-800/18-25, 5-mm thickness, and 2-mm separation. CT images of the head were obtained with 5-mm slices.

Imaging Evaluation

An investigator (N.T.) retrospectively evaluated all DWI images independently while being masked to clinical outcomes. She identified all DWI lesions that were suggestive of AIS and classified them based on (1) laterality (right, left, or both), (2) location (cortex, deep, cortex and deep, brainstem, cerebellum, or multiple locations), (3) vascular territory (anterior cerebral artery, middle cerebral artery,