

The Risk of Hemorrhagic Transformation After Thrombolysis for Acute Ischemic Stroke in Chinese Versus North Americans: A Comparative Study

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Background: There is a widespread belief that Asians are more susceptible to hemorrhagic transformation (HT) after receiving recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke (AIS). However, this has not been examined in clinical practice. This study aims to compare the incidence of symptomatic hemorrhagic transformation (SHT) among thrombolysis-treated AIS patients in China and in the United States. *Methods:* We compared 212 consecutive patients receiving thrombolysis within 4.5 hours of onset ± endovascular therapy from an American (n = 86) and a Chinese Stroke Center (n = 126). SHT was defined using various definitions based on the National Institute for Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) trials, European-Australian Cooperative Acute Stroke Study 2 (ECASS2), and a modified version of Safe Implementation of Thrombolysis in Stroke-Monitoring Study (mSITS-MOST) study criteria. We used Firth logistic regression to adjust for confounding variables and to identify potential predictors. *Results:* American patients were older, and had higher prevalence of diabetes, hypertension, cardiac disease, and prestroke use of antithrombotics. They also had higher baseline serum glucose, shorter onset-to-treatment time, and fewer endovascular treatments. The rates of SHT were higher in the American cohort compared to the Chinese cohort: 18.6% versus 14.3% based on NINDS definition of SHT; 15.1% versus 12.7% based on ECASS2; and 11.6% versus 7.2% based on mSITS-MOST. However, none of these differences were significant (unadjusted and adjusted *P* values > .05). Fatal HT was comparable in Americans versus Chinese (8.1% versus 8.7%). Serum glucose emerged as an independent predictor of SHT (*P* = .024). *Conclusions:* In our cohorts, the rate of SHT after thrombolysis is equivalent between Chinese and North American stroke patients. **Key Words:** Stroke—thrombolysis—rt-PA—hemorrhagic transformation—Chinese—Americans.

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Introduction

Stroke is imposing an increasing burden on China. Currently, there are 2.5 million of new stroke cases in China every year.¹ According to a meta-analysis of community-based studies,² age-standardized incidence of first-ever stroke in Chinese is 1.2-1.7 times higher than Caucasian populations, and the prevalence of stroke in China is 2.37%.³ Furthermore, age-standardized mortality of stroke in China rose by 28.8% in the past 2 decades.⁴

Ischemic stroke is the major type of stroke in China.² Based on a recent nationwide population-based survey, acute ischemic stroke (AIS) constitutes 77.8% of all strokes, and intracranial hemorrhage (ICH) constitutes 15.8% in China,⁵ compared to the United States where 87% of strokes are ischemic and 10% represent ICH.⁶ Thrombolysis with recombinant tissue plasminogen activator (rt-PA) remains the mainstay treatment for AIS since pivotal trials confirmed its efficacy.⁷⁻¹⁰ However, these trials consisted predominantly of North American and European patients and the evidence for rt-PA use in China is sparse.¹¹ Based on the only nationwide stroke registry in China, 12.6% of AIS patients are eligible for thrombolysis, but barely 1.6% receive the treatment,^{11,12} which is lower than corresponding rates in the European Union (3.3%),¹³ United States (3.0%-8.5%),¹⁴ and Canada (8.9%).¹⁵

Asians tend to have higher susceptibility to bleeding,^{16,17} and the limited use of rt-PA in China is largely attributed to the fear of symptomatic hemorrhagic transformation (SHT).¹¹ Indeed, analyses of the Get With The Guidelines database (GWTG) showed that Asians have higher risk of SHT after rt-PA.¹⁸ On the contrary, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), which included over 60% Asian subjects, showed similar SHT rate in the standard-dose rt-PA arm compared to previous trials, which predominantly included Caucasian patients.¹⁹ However, randomized controlled trials usually adopt ideally controlled conditions to optimize their internal validity,²⁰ limiting real-life generalizability of the results.^{20,21} In the pivotal rt-PA trials, for example, individuals with multiple comorbidities,^{7,19} outside certain age range,^{8,10} and presenting with severe clinical symptoms (National Institutes of Health Stroke Scale [NIHSS] >25)⁸ or extensive infarct on imaging^{8,10} were excluded. However, observational studies can reveal the effectiveness in real-world practice in an unselected population.²² No study has directly examined the incidence of SHT in Asian and Western settings in clinical practice outside the controlled clinical trial setting.

Methods

Patients

We reviewed prospectively collected clinical and radiological data for 212 consecutive AIS patients treated

with intravenous rt-PA within 4.5 hours of symptom onset with or without subsequent endovascular therapy (EVT) at Jinling Hospital in Nanjing, China and Beth Israel Deaconess Medical Center in Boston, Massachusetts between February 2013 and December 2016. The start date was chosen because the latest American Heart Association guidelines for thrombolysis were updated in January 2013. The diagnosis of ischemic stroke was based on persistent neurological deficits and confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients had a follow-up CT (n = 148) or MRI (n = 64) after treatment with rt-PA thrombolysis within 1-3 days to assess for hemorrhagic transformation (HT). Antithrombotics were started 24 hours after thrombolysis in the patients whose post-treatment scans were negative for ICH.

Definitions of HT

The following definitions of HT were applied as outcomes in the current study: any HT (any newly developed ICH on the CT or MRI after rt-PA, which was not observed on the initial scan before thrombolysis); Heidelberg definition (newly developed parenchymal hematoma on post thrombolysis scans)²³; National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trials definition (newly developed ICH along with any neurological worsening or death)⁷; European-Australian Cooperative Acute Stroke Study 2 (ECASS2) definition (new ICH with >4 points increase in NIHSS)¹⁰; Modified Safe Implementation of Thrombolysis in Stroke Monitoring Study criteria (mSITS-MOST) definition (new parenchymal hematoma with >4 points increase in NIHSS)^{24,25}; we defined fatal SHT as any newly observed ICH followed by in-hospital mortality. Detailed clinical and imaging features of these definitions are summarized in [Supplemental Table 1](#).

Follow-Up

Trained investigators recorded the functional outcomes of patients using modified Rankin's Scale (mRS) 90-day after symptom onset via telephone or face-to-face interview in the native language of each center.

Statistical Analysis

Continuous data were presented as mean \pm standard deviation and analyzed with the Student's *t* test if normally distributed, otherwise they were presented as median value with interquartile ranges and Mann-Whitney *U* test was used. Categorical data were expressed as frequencies and percentage and compared using chi-square tests or Fisher's exact tests when appropriate.

We used the Firth logistic regression to adjust for confounding variables and to evaluate independent predictors of SHT (per NINDS definition). Firth logistic regression,

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