Predictors of Hemorrhage Volume after Intravenous Thrombolysis

Sang Hyun Shon, MD,* Sung Hyuk Heo, MD, PhD,* Bum Joon Kim, MD, PhD,* Hye-Yeon Choi, MD, PhD,* Youngnam Kwon, MD,* Sang Hun Yi, MD,* Ji Sung Lee, PhD,† Young Seo Kim, MD, PhD,‡ Hyun Young Kim, MD, PhD,‡ Seong-Ho Koh, MD, PhD,‡ and Dae-Il Chang, MD, PhD*

Background: Symptomatic intracerebral hemorrhage (sICH) is one of the most feared complications after administration of intravenous recombinant tissue plasminogen activator (IV rtPA). The aim of this study was to determine correlations between hemorrhage volume (HV) after IV rtPA treatment and risk factors for sICH. *Methods:* We analyzed 318 patients from the stroke registries of 4 hospitals in Korea. We confirmed hemorrhage by computed tomography (CT) or magnetic resonance imaging within 36 hours. Patient groups were classified by HV (0, 0-10, 10-25, and greater than 25 mL). Based on the HV, we evaluated the following: (1) predictors for hemorrhage; (2) rates of sICH according to various sICH definitions; and (3) 3-month functional outcomes after IV rtPA treatment. *Results:* Among the 318 patients, hemorrhage occurred in 72 patients. HV was significantly correlated with atrial fibrillation (OR = 3.38, 95% CI = 1.87-6.09), early CT changes (OR = 3.17, 95% CI = 1.69-5.93), and dense artery sign (OR = 1.90, 95% CI = 1.07-3.39). Compared with the groups with HV less than 25 mL, patients with an HV of greater than 25 mL were more likely to have higher mortality rates (33.3% versus 11.8%) and worse outcomes at 3 months (good: 8.3% versus 50.3%; excellent: 0% versus 33.7%). *Conclusions:* HV after IV rtPA is an important predictor of clinical outcomes. Atrial fibrillation, early CT changes, and dense artery sign were significantly associated with large HVs; therefore, these patient factors might be considered before and after thrombolytic treatment. **Key Words:** Intracranial hemorrhage—thrombolytic therapy—patient outcome assessment—cerebral infarction.

Introduction

Intravenous recombinant tissue plasminogen activator (IV rtPA) is the only proven thrombolytic agent for the treatment of acute ischemic stroke. Recently, although the time window for IV rtPA administration increased to 4.5 hours after stroke onset, studies are ongoing to find a more effective and safer thrombolytic agent, as there are several limitations of IV rtPA treatment. One of the most feared complications is symptomatic intracerebral hemorrhage (sICH). In a pooled analysis of 6 previous IV rtPA stroke trials, 5.9% developed sICH compared to 1.1% among patients who received placebo.[1] This complication is especially more important in Asian stroke

From the *Department of Neurology, Kyung Hee University College of Medicine, Seoul, South Korea; †Clinical Research Center, Asan Medical Center, Seoul, South Korea; and ‡Department of Neurology, Hanyang University College of Medicine, Seoul, South Korea.

Received May 7, 2016; revision received June 17, 2016; accepted June 26, 2016.

This work was supported by a grant from Kyung Hee University in 2014 (KHU-20140716).

Address correspondence to Sung Hyuk Heo, MD, PhD, Department of Neurology, Kyung Hee University Hospital, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea. E-mail: shheo73@khu.ac.kr.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.06.035

patients with a high risk of hemorrhage and it limits the use of rtPA.[2]

Studies such as the National Institute of Neurological Disorders and Stroke (NINDS) trial, the European Cooperative Acute Stroke Study (ECASS) II, and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) have suggested different definitions of sICH.[3-5] Various definitions of sICH have complicated the analysis of thrombolytic therapy trials, and there has been an increasing trend for studies to suggest various sICH rates due to the application of different definitions. Hematoma volume is known to be the most important predictor of outcome in ICH.[6,7] In addition, hemorrhage volume (HV) after intra-arterial thrombolysis also had an impact on the prognosis of ischemic stroke.[8] However, the prognosis of ischemic stroke patients according to HV after IV rtPA has not been reported.

With these issues in mind, we conducted this study with the following objectives: (1) to investigate the role of HV within 36 hours after IV rtPA as a predictive factor for functional outcomes and (2) to identify the predictors of large HV after IV rtPA in our cohort.

Materials and Methods

Subjects

We consecutively recruited ischemic stroke patients treated with IV rtPA until 2011 from the 4 prospective stroke registries of Kyung Hee University Hospital (from January 2003), Kyung Hee University Hospital at Gangdong (from July 2006), Hanyang University Seoul Hospital (from October 2009), and Hanyang University Guri Hospital (from June 2010). As the initiation of stroke registries differs among the participating centers, the study duration also differs. Because the Korea Food and Drug Administration granted approval of IV rtPA treatment within 3-4.5 hours after acute ischemic stroke in November 2011, we did not include the patients who received IV rtPA after 3 hours of symptom onset in this cohort. We exclude patients treated with IV rtPA in a different hospital, transferred to another hospital directly after thrombolysis, and expired within 24 hours after IV rtPA. This study was approved by an independent Ethics Committee at Kyung Hee University Medical Center (KMC IRB 0916-04).

Risk Factors

We analyzed demographic, clinical, radiographic, and admission laboratory data. Multiple studies have identified several risk factors for sICH after IV rtPA and have developed scores to predict outcomes or the probability of sICH after rtPA administration. Simple scores that accurately predict which patients are more likely to benefit from rtPA would be helpful to assist clinicians in the selection of patients for rtPA treatment.

Currently available scores that predict outcomes include the following: (1) Stroke Prognostication using Age and NIH Stroke Scale (SPAN) index[9]; (2) the Glucose, Race, Age, Sex, systolic blood Pressure, and Severity of stroke at presentation (GRASP) score[10]; (3) the hemorrhage after thrombolysis (HAT) score[11]; (4) the Multicenter Stroke Survey (MSS) score[12]; (5) the Sugar, Early infarct sign, hyperDense middle cerebral artery, Age, Neurologic deficit (SEDAN) score[13]; (6) hyperDense middle cerebral artery sign or early CT infarct, prestroke mRS, Age, Glucose, Onset to treatment, admission NIHSS (DRAGON) score[14]; (7) the Stroke-thrombolytic predictive instrument (Stroke-TPI) score[15]; (8) Acute Stroke Registry and analysis is of Lausanne (ASTRAL) score[16]; and (9) Safe Implementation of Thrombolysis in Stroke sICH (SITS-ICH) score.[17] We collected nearly all components of these scales from our stroke registries. The Ischemic Stroke Predictive Risk score (iScore), which contains details of the medical condition after admission, was excluded.[18] Hypodensity on the baseline computed tomography (CT) scan was defined as focal or diffuse areas that on visual inspection were less dense than white matter but had greater density than cerebrospinal fluid.[19] Early CT change included hypodensity of the infarcted tissue, effacement of sulci, and loss of insular ribbon.

sICH and Outcome Measurement

The baseline National Institutes of Health Stroke Scale (NIHSS) score was used for the assessment of initial stroke severity. Rates of sICH defined by 3 large clinical trials were used to compare patients in each HV category. Definitions were as follows: NINDS, some neurological worsening with any CT-documented hemorrhage that was related to the patient's clinical deterioration; ECASS II, any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and SITS-MOST, local or remote parenchymal hemorrhage type 2 on the 22-36 hour post-treatment imaging scan combined with neurological deterioration of 4 points or more on the NIHSS from baseline or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

For short-term outcomes, 24-hour NIHSS score after IV rtPA treatment and craniectomy during hospitalization was obtained. For long-term outcomes, we retrieved the modified Rankin Scale (mRS) at 3 months to classify subjects as having excellent (mRS ≤1) or good (mRS ≤2) outcomes, and the mortality at 3 months was also collected.

HV Measurement

CT scans were routinely obtained before the initiation of rtPA treatment and followed up at 12-36 hours after the treatment. If the patients had multiple follow-up brain images, we selected the brain images performed