Rapidly Improving Stroke Symptoms: A Pilot, Prospective Study

Clotilde Balucani, MD, PhD,* Riccardo Bianchi, PhD,† Charles Ramkishun, BS,*† Jeremy Weedon, PhD,‡ Susan Law, DO,* Michael Szarek, PhD, MS,‡ Diana Rojas-Soto, MD,* Sara Tariq, BS,* and Steven R. Levine, MD*§‖

Background: Rapidly improving stroke symptoms (RISSs) are a controversial exclusion for intravenous recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke (AIS). We estimated the frequency of 4 prespecified RISS definitions and explored their relationship to clinical outcome. *Methods:* Pilot, prospective study of AIS patients admitted within 4.5 hours of symptom onset. Serial assessments using National Institute of Health Stroke Scale (NIHSS) were performed every 20 ± 5 minutes until a rt-PA treatment decision was made, independent of the study. Improvement was calculated as the difference between baseline NIHSS and treatment decision NIHSS. RISS was defined as a 4-point or greater improvement, 25% or greater, 50% or greater, and according to the previously reported TREAT (The Re-examining Acute Eligibility for Thrombolysis) criteria. Unfavorable outcome was defined as modified Rankin Scale score more than 1 at 90 days after stroke. Logistic regression determined if RISS definition(s) related to the outcome. *Results:* Fifty patients with AIS were enrolled: mean age 65 years; median baseline NIHSS score 5 (interquartile range, 2-11). RISS frequencies were 10%-22% based on definition. Median treatment decision NIHSS score is 5 (interquartile range, 2-9). Twenty-three (46%) patients received rt-PA. None of the 3 non-TREAT RISS definitions was independently associated with the outcome. Five of fifty (10%) were RISS according to the TREAT criteria, all 5 had good outcome without rt-PA. *Conclusions:* A Serial NIHSS assessment before treatment decision is feasible and may help determine the frequency and magnitude of RISS. This is the first prospective estimate of RISS frequency and outcome according to various prespecified definitions. The TREAT RISS frequency as a more restrictive definition may better predict good outcome of RISS in future, larger studies. **Key Words:** Acute stroke—thrombolysis—tissue plasminogen activator—rapidly improving stroke symptoms—minor stroke—National Institutes of Health Stroke Scale.

From the *Department of Neurology and Stroke Center; †Department of Physiology and Pharmacology; ‡Scientific Computing Center; §Department of Emergency Medicine, SUNY Downstate Medical Center; and ‖Department of Neurology, Kings County Hospital Center, Brooklyn, New York.

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Address correspondence to Steven R. Levine, MD, Department of Neurology and Stroke Center, The State University of New York, Downstate Medical Center, 450 Clarkson Avenue, MSC 1213, Brooklyn, NY 11203-2012. E-mail: steven.levine@downstate.edu.

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Between 4.4% and 44% of "timely eligible" acute ischemic stroke (AIS) patients who present to the emergency departments (EDs) are not treated with intravenous recombinant tissue plasminogen activator (rt-PA) solely because of rapidly improving stroke symptoms (RISS).[1-4] Studies suggest that the outcome of these patients is not invariably benign, bringing into question the decision not to treat them with rt-PA.[5-8]

Subsequent to the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trials,[9] no consensus has been achieved to define RISS.[10,11] The rt-PA package insert (http://www.activase.com), American Heart/Stroke Association Guidelines,[12] European Stroke Organisation,[13] and the National Institutes for Health and Clinical Excellence of the United Kingdom[14] do not specifically or quantitatively define RISS. A further attempt toward consensus for defining RISS has been recently developed.[8]

We obtained pilot, prospective data on frequency and magnitude of RISS, according to 4 prespecified definitions and explored their relationship to clinical outcome.

Methods

Study Population

This pilot, prospective, observational study evaluated adult (older than age 18 years) AIS patients admitted to SUNY Downstate Medical Center in Brooklyn, New York. Eligibility included sudden onset of focal neurologic deficits suggestive of stroke presenting within 4.5 hours of symptoms; a noncontrast computed tomography scan negative for brain hemorrhage or any other brain lesion rather than ischemic stroke. All subjects/designee provided informed consent. The protocol was approved by the SUNY Downstate Institutional Review Board. This study did not interfere with and/or delay the standard screening process aimed at identifying patients eligible for rt-PA. Any treatment decision was made independent of this study by the stroke treating physician.

Protocol

Subjects were administered serial assessments of stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS)[15] performed every 20 ± 5 minutes until a treatment decision (rt-PA vs no rt-PA) was made by the treating physician. RISS study team members were notified via a hospital-wide ED "code stroke" paging system. Baseline NIHSS (b-NIHSS) was defined as the first NIHSS score performed at patient arrival at the ED by 1 member of the RISS study team. All examiners were certified in the NIHSS.

RISS was defined as a measurable improvement of neurologic deficits between 2 clinical evaluations performed at different times, and specifically, as the difference between baseline NIHSS (b-NIHSS) and treatment decision NIHSS (td-NIHSS).

RISS and Outcome Definitions

Prespecified definitions of RISS were (1) change in NIHSS score with 4-point or greater improvement (IMP) or (2) percent change in NIHSS score: 25% or greater or 50% or greater IMP and change in NIHSS score to nondisabling symptoms according to the previously published, The Re-examining Acute Eligibility for Thrombolysis ("TREAT") Task Force Criteria definition.[8]

The TREAT Task Force comprised members of the original NINDS rt-PA Stroke Trial Steering Committee combined with other leaders in the field of stroke and emergency medicine. This Task Force was formed in an attempt to address the rationale and relevance of individual exclusion criteria to rt-PA and to determine if these criteria require clarifications and more precise definitions that could be implemented in the current clinical practice.[8]

Specifically, The TREAT Task Force sought to develop a clinically meaningful definition of RISS that may be used to guide stroke treating physicians' decision to treat or not to treat with rt-PA. Consensus defined RISS as an exclusion criterion for rt-PA as improvement to a mild stroke such that any remaining deficits seem nondisabling.[8] To be nondisabling, none of the following deficits should be present: (1) complete hemianopsia (≥2 on the NIHSS question 3); (2) severe aphasia (≥2 on NIHSS question #9); (3) visual or sensory extinction (≥1 on NIHSS question #11); (4) any weakness limiting sustained effort against gravity (≥2 on NIHSS question #6 or #7); (5) any deficits that lead to a total NIHSS >5; and (6) any remaining deficit considered potentially disabling in the view of the patient or the treating practitioner.[8]

Clinical outcome was defined using the modified Rankin Scale (mRS). Unfavorable outcome was defined as mRS greater than 1 at 90 days after stroke and at 7 days after stroke or discharge.

Statistical Analysis

Descriptive statistics were used to evaluate age, sex, race, and other cardiovascular risk factors between those with RISS and no RISS and between those treated and not treated with rt-PA. The Fisher exact test for categorical variables and the Wilcoxon test for numeric data were used for comparison between groups. Exact logistic regression was used to model 90-day mRS score more than 1 from predictors age, b-NIHSS, time to NIHSS, rt-PA use, and (in separate models) 4 different definitions of RISS. *P* values and 95% confidence limits are based on Mid-P methods.[16]

A secondary analysis was performed to test the diagnostic utility of specific NIHSS score cut points from 1 to 10 to predict mRS more than 1 at 90 days. We generated