Acute Ischemic Stroke with Very Early Clinical Improvement: A National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Trials Exploratory Analysis

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Background: A high proportion of patients excluded from recombinant tissue plasminogen activator (rt-PA) treatment because of rapid improvement occurring before treatment decision had incomplete recovery. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trials dataset allows for systematic analyses of very early postrandomization improvement (VEPRIM) in stroke severity as a National Institutes of Health Stroke Scale (NIHSS) score was available for all subjects enrolled in the study at baseline ($NIHSS_B$) and at 2 hours after randomization ($NIHSS_{2H}$). We explored various definitions of VEPRIM to characterize predictive values for clinical outcomes. *Methods:* Post hoc analyses of the NINDS rt-PA Stroke Trials were conducted. VEPRIM was defined as the difference between the $NIHSS_B$ and the $NIHSS_{2H}$ scores using 3 approaches: raw, percent, and normalized change. We assessed the association between VEPRIM and 3-month favorable outcome (mRS score of 0-1), symptomatic intracerebral hemorrhage (sICH), and death. *Results:* In the 624 subjects, every VEPRIM definition was independently associated with an increased probability of favorable outcome: for each unit of change within the VEPRIM definitions, there were 2%-24% (all $P < .05$) relative increased probability of favorable outcome, 2%-15% (all $P < .05$) decreased likelihood of death, and 2%-13% (all $P < .05$) decreased likelihood of sICH. Adjusting for $NIHSS_B$ and prestroke mRS scores, there was a significant rt-PA treatment effect for improvement seen for all 3 VEPRIM definitions. *Conclusions:* VEPRIM predicted favorable outcomes independent of definition and treatment arm. Patients

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with VEPRIM by any definition, while doing better than patients without VEPRIM, also derived increased clinical benefit when treated with rt-PA compared to placebo. Even with VEPRIM, a substantial percentage of patients had unfavorable outcomes.
Key Words: Acute stroke—thrombolysis—stroke outcomes—tPA—rapidly improving stroke symptoms—minor stroke.

Introduction

Rapidly improving stroke symptoms was one of the exclusion criteria in the National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator (rt-PA) Stroke Trials.[1] The exclusion criterion specified: "patient has major symptoms that are rapidly improving by the time of randomization."[2] The NINDS rt-PA Stroke Trials[1,3] excluded 10% of the 17,324 screened patients because of rapidly improving stroke symptoms.

The original intent of this exclusion criterion was to avoid treating patients with transitory ischemic attacks or patients presenting the "Lazarus effect"—nearly back to normal after a major stroke, who would likely do well without treatment, given the concern for increased bleeding risk from rt-PA.[4]

Rapid improvement has become one of the most common, subjective, and poorly defined reasons for excluding patients from rt-PA treatment, partly because it relies on clinical judgment without specific quantitative aspects.[4]

In 8%-44% of acute ischemic stroke patients arriving within the rt-PA treatment window, a documented reason for exclusion from rt-PA was rapid improvement.[5-8] There is currently no established and accepted consensus ("gold standard") for defining rapid improvement,[9] The NINDS rt-PA Stroke Trials[1] dataset allows for systematic analyses of very early postrandomization improvement (VEPRIM) in stroke severity) as a National Institutes of Health Stroke Scale (NIHSS)[10] score was available for all subjects enrolled in the study at baseline ($NIHSS_B$) and at 2 hours after randomization ($NIHSS_{2H}$).

Therefore, the NINDS rt-PA Stroke Trials dataset can provide unique "natural history" data (the placebo arm) on subjects with VEPRIM and exploratory data on treatment effect (the rt-PA arm) within the 4.5-hour rt-PA treatment window.

We analyzed The NINDS rt-PA Stroke Trials[1] dataset (1) to explore various definitions of VEPRIM and (2) to characterize the frequency, magnitude, correlates, and predictive value of VEPRIM on clinical outcomes, with and without rt-PA.

Methods

The NINDS rt-PA Stroke Trials[1] were approved by the institutional review board at each of the participating sites, and each subject enrolled provided a written informed consent. The institutional review board ruled that post hoc analyses of these data are exempt from being considered human subjects research as it was performed on the publicly available dataset that was totally deidentified.

Subjects

We evaluated the NINDS rt-PA Stroke Trials[1] dataset (n = 624). Details of the methodology and demographics have been previously published.[1,2] Per protocol, subjects underwent $NIHSS_B$ at 2 hours post treatment ($NIHSS_{2H}$), at 24 hours, at 7-10 days, and at 3 months. All NIHSS scores were performed by certified examiners.[11]

Very Early Postrandomization Rapid Improvement

We defined VEPRIM in several ways. We used raw change between $NIHSS_{2H}$ and $NIHSS_B$ scores. We further categorized the raw change in NIHSS in 3 ways: (1) 4 point improvement or higher, (2) 25% improvement or higher, and (3) 50% improvement or higher. These cut-points were believed to be clinically significant through consensus with several NINDS rt-PA Stroke Study trialists and other stroke leaders (unpublished data). The 4 point improvement or higher on the NIHSS was used by the pilot NINDS t-PA Trials Investigators to quantify a meaningful improvement from treatment.[12,13] In addition, several other published studies have used a 4 point improvement or higher definition for rapid improvement in stroke symptoms.[5,14,15]

We also examined the percent change[16] and the normalized change[17] in NIHSS scores. Percent change was defined as the difference between the $NIHSS_{2H}$ score and $NIHSS_B$ score divided by the $NIHSS_B$ score.

For those with improvement or no change, normalized VEPRIM equaled NIHSS (%) change in the $NIHSS_{2H}$ score minus the $NIHSS_B$ score, divided by $NIHSS_B$ score identical to the percent change. For worsening, normalized change was calculated as follows:

$$\text{If } NIHSS_B - NIHSS_{2H} < 0 \text{ (worsened between scores)},$$
$$\text{normalized change} = (NIHSS_B - NIHSS_{2H}) \times 100/(42 - NIHSS_B)$$

Analysis of the change variables was based on the actual value, but for visualization, we divided the entire cohort into approximate octiles, keeping whole numbers at each cut-point. For raw NIHSS change, there was an increase higher than 2, a 1-2 increase, no change, and decreases of 1, 2, 3-4, 5-7, and higher than 7. For percent change, there was an increase higher than 20%, a 0%-20% increase, no change, decreases of 1%-11%, 12%-19%, 20%-34%,