Fixed Dose IV rt-PA and Clinical Outcome in Ischemic Stroke Patients With Body Weight >100 kg: Pooled Data From 3 Randomized Clinical Trials

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Background and Purpose: The ASA/AHA guidelines recommend a fixed dose of 90 mg of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for acute stroke patients weighing more than 100 kg. We aimed to determine if body weight >100 kg (and receiving <0.9 mg/kg dose) independently influence patient clinical outcomes following IV rt-PA treatment. *Methods:* We pooled data from IV rt-PA treatment arms from 3 randomized controlled clinical trials; NINDS IV rt-PA study, Interventional Management of Stroke 3 and ALIAS (part 1 and 2). Baseline characteristic, hospital course and 90-day mRS were compared between patients >100 kg and those ≤100 kg body weight. Multivariate logistic regression model was used to identify the independent effect of >100 kg body weight on favorable 90-day outcome (defined as mRS 0-2), the rate of symptomatic intracranial hemorrhage, and poor 90-day outcome (mRS 4-6). *Results:* Among 873 patients treated with IV rt-PA, a total of 105 (12%) subjects had body weight >100 kg. Compared with patients having ≤100 kg body weight, the rate of favorable outcome at 90 days was not significantly different among patients with >100 kg body weight (OR: 0.99; 95% CI: 0.91-1.01; p=0.91) , after adjusting for potential confounders. The ordinal analysis did not show any significant shift in the distribution of 90-day mRS score in patients with >100 kg body weight (OR, 0.93; 95% CI, 0.64-1.37; P = 0.74) *Conclusions:* There was no reduction in the rate of favorable outcome in patients with acute ischemic stroke with body weight >100 kg who received <0.9 mg/kg dose of IV rt-PA. Our results support the current recommendations in the ASA/AHA guidelines.

Key Words: Body weight—tissue plasminogen activator—thrombolysis—acuteischemic stroke—clinical outcome

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Introduction

Current guidelines recommend thrombolytic therapy using intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for eligible patients with acute ischemic stroke at a dose of 0.9 mg/kg with a maximum total dose of 90 mg.[1] Therefore, patients with body weight greater than 100 kg receive a lower dose (<0.9 mg/kg) of rt-PA per kilogram body weight. This recommendation was

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Received April 16, 2018; revision received May 27, 2018; accepted June 14, 2018.

Grant Support: none.

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[1]Author completed statistical analysis.

1052-3057/$ - see front matter

Published by Elsevier Inc. on behalf of National Stroke Association.

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.06.016

derived from original dose-escalation studies which revealed increased risk of symptomatic hemorrhage without any evidence of greater neurological improvements in doses >0.85 mg/kg.[2,3] However, whether patients with body weight >100 kg who receive <0.9 mg/kg of IV rt-PA negatively influences the magnitude of benefit from IV rt-PA is unknown.

A posthoc analysis from the National Institute of Neurological Disorders and Stroke IV rt-PA study, by Lou et al,[4] found body weight >100 kg to be an independent predictor of poor outcome among patients who were treated with IV rt-PA and partly attributed this finding to heavier patients receiving a lower dose of IV rt-PA per kilogram body weight. However, this study had a small sample size with only 20 patients with body weight >100 kg.

Using pooled data from 3 randomized control trials we sought to determine the independent effect of receiving a fixed 90 mg dose of IV rt-PA in patients weighing >100 kg for acute ischemic stroke on functional outcome.

Methods

We pooled data from 3 randomized controlled clinical trials including NINDS IV rt-PA study, Interventional Management of Stroke 3 (IMS-III) study and Albumin Treatment of Acute Ischemic Stroke (ALIAS parts 1 and 2). The studies were selected based on uniformity between definitions and time points of variables ascertained. Briefly, the NINDS IV rt-PA trial enrolled patients with acute ischemic stroke within 3 hours from symptom onset and randomized them to either placebo or IV rt-PA (0.9 mg/kg).[5] The estimated body weight was used for IV rt-PA dose calculation in this study. A total of 312 patients were treated with IV rt-PA. IMS-III was a phase III, randomized paralleled arms, open label clinical trial aimed to assess if the combined endovascular therapy and IV rt-PA is more effective than IV rt-PA alone in patients with acute ischemic stroke.[6] A total of 222 patients received only IV rt-PA and estimated body weight was used for dose calculation. And finally, ALIAS parts 1 and 2 evaluated whether albumin 25% administered within 5 hours from symptom onset can further improve the clinical outcome in patients with acute ischemic stroke.[7,8] The trial failed to demonstrate significant outcome benefit and was prematurely terminated. Patients who were eligible for IV rt-PA received IV rt-PA regardless of whether they received albumin or placebo. The estimated body weight was used for dose calculation in this study and 424 patients received only IV rt-PA.

We only included IV rt-PA treatment arms from the aforementioned studies in our pooled data. Patients who received less than 90% of their calculated IV rt-PA dose for various reasons were excluded from our cohort. Baseline characteristics including age, gender, race, and medical comorbidities, along with initial National Institute of Health Stroke Scale (NIHSS) score, admission vital signs and laboratory results, hospital course and complications and 90-day modified Rankin Scale (mRS) score were extracted for all the patients from the original databases.

We compared baseline characteristics, stroke severity, hospital course and complications, and outcome between patients with body weight ≤100 kg and those with body weight >100 kg. The primary endpoint was favorable outcome at 90 days defined as mRS score of ≤2. Ordinal analysis of 90-day mRS was also performed to identify any significant shift among patients with body weight ≤100 kg compared with those having a body weight >100 kg. The rate of symptomatic intracranial hemorrhage (ICH), poor 90-day outcome (defined as mRS ≥4) and 90-day mortality were also measured as secondary endpoints.

In further exploratory analysis, and with the assumption that the dose dependent benefit of IV rt-PA could be possibly more evident in patients with moderate to severe neurological deficits, we excluded patients with mild neurological deficit (defined as NIHSS <8) and therefore compared outcome measures between patients with body weight >100 kg and those with ≤100 kg only among those with admission NIHSS ≥8. In the final set of our analysis, by dichotomizing weight into ≤100 kg, between 101 and 120 kg, between 121-140 kg and > 140 kg, we compared the distribution of the body weight brackets among patients with favorable 90-day outcome (mRS score 0-2) and those without favorable 90-day outcome (mRS 3-6).

Chi-square test and t test were used for categorical data and for continuous data, respectively with a P value <0.05 considered statistically significant. A multivariate logistic regression model was created to identify the possible independent impact of body weight >100 kg on favorable outcome in our cohort. We used the SAS 9.3 software (SAS Institute, Cary, NC) for statistical analysis.

The study was exempted from individual review by the institutional review board as the study and analysis was based on publicly available and deidentified data sets.

Results

A total of 873 patients were included in the final cohort after excluding patients who did not finish at least 90% of the calculated IV rt-PA dose for various reasons. One hundred and five patients had a body weight greater than 100 kg and 768 patients with a body weight ≤100 kg. Patients with a body weight >100 kg were more likely to be younger, men, and black. Additionally, they were more likely to have hypertension, diabetes mellitus, and hyperlipidemia. There was no difference in initial NIHSS score or time from symptom onset to IV rt-PA treatment between the 2 groups (Table 1).

There was no significant difference in 90-day favorable outcome (mRS ≤2) between patients with a body weight

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