Gender Differences in Exclusion Criteria for Recombinant Tissue-Type Plasminogen Activator

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Background: Gender differences in the use of recombinant tissue-type plasminogen activator (r-tPA) in stroke are complicated. In this study, we investigated gender differences using r-tPA exclusion criterion in a stroke population. *Methods:* We analyzed the data from ischemic stroke patients aged 18 years or older from the Greenville Health System stroke registry on r-tPA administration between January 2010 and December 2013. We identified exclusion criterion and used specific clinical factors to determine gender differences in stroke patients receiving r-tPA. *Results:* Of the 633 patients who were eligible to receive r-tPA, less than half received r-tPA (n = 241) whereas 422 were not able to receive r-tPA. Of the 241 patients who received r-tPA, 49.4% were female and 50.6% were male. Of the 422 patients who did not receive r-tPA, more women (235) were excluded from r-tPA than men (187) ($P < .05$). There were no gender differences in warning signs and contraindications in female versus male stroke patients ($P > .005$). There were however gender differences in age group as more women (38%; n = 235) were more likely to be excluded if they are more than 80 years old than men (19%, n = 187). *Conclusions:* Within a large stroke population, exclusion criteria for r-tPA in women and men were similar with regard to race, initial National Institutes of Health Stroke Scale score, warning signs, and contraindications, but were different in the age group population exclusion criterion for intravenous r-tPA. We observed that intracerebral hemorrhage and match on computed tomography perfusion/magnetic resonance imaging or visible infarct greater than one third of the middle cerebral artery distribution were absolute criteria for exclusion. **Key Words:** Gender—ischemic stroke—recombinant tissue-type plasminogen activator (r-tPA)—contraindication.

Introduction

The incidence rates for stroke are known to be different for women and men across all age groups,[1] and this reflects the observed different outcomes following acute ischemic stroke in women when compared with men.[2-8] Several studies have focused on gender differences or similarities as a tool to facilitate an increase in the use of recombinant tissue-type plasminogen activator (r-tPA) in an acute stroke population.[9-13] Findings from these studies suggest an interaction between gender and thrombolytic therapy, which affects the outcome in acute ischemic stroke. This interaction was directly linked to a gender difference in outcome when compared with the control group,[14] and was consistent with previous findings of a poorer functional outcome in women when compared with men.[11,15] The observed gender differences in the functional outcome of r-tPA were attributed to the following confounding factors[16]: hospital care for acute stroke,[17] prevalence of disease, or biological differences.[18] These findings are also related to gender differences in clinical or demographic factors such as age, comorbidity, prestroke

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functional status, and stroke severity.[19] In support of this idea, Martínez-Sánchez et al[20] reported that women have worse outcomes in adult ischemic stroke patients up to 50 years old, and that this effect is not shown in younger patients between ages 15 and 30 years. One explanation is that maybe women are not aggressively evaluated as men, and that this may affect their treatment and use of tPA, or maybe strokes are more disabling and occur more frequently in women,[21] indicating that gender differences in stroke and r-tPA use are a complex issue. These studies[14,22] found no gender difference in outcomes. Other studies[23-25] identified a gender difference that benefited women: one on neurological functional improvement and the other on the rate of arterial recanalization. Several recent studies[7,26-29] reported that any observed gender difference in stroke treatment and outcome is actually small, and that this difference actually diminished when only data for stroke patients eligible for r-tPA are analyzed.[28] Despite this result, women are less likely to receive intravenous (IV) r-tPA when compared with men.[30] This finding indicates that true gender difference in response to r-tPA is yet to be fully understood. It is important to point out that most of the existing studies on stroke patients eligible for r-tPA[27,31-34] have not led to a clear understanding of the problem or to feasible strategies to identify and eliminate any gender disparity in the use of r-tPA. This challenge suggests a different approach to determine gender differences in the use of r-tPA. Using data for the exclusion criteria for thrombolytic treatment, we determined gender differences in stroke patients in a center with an active patient protocol for r-tPA use in thrombolytic treatment. We analyzed clinical and demographic factors to determine gender in a stroke population.

Study Design

This was a retrospective, population-based study of adults (aged ≥18 years) with acute ischemic stroke among residents of an 8-county region of Upstate South Carolina who presented to Greenville Health System (GHS)—a primary stroke center—between 2010 and 2013. This represents a metropolitan population that is representative with regard to median age and median income, as well as percentage of those who are black, women, below the poverty line, and high school graduates. The study was performed using data that pertained to r-tPA administration in a prospective registry of stroke patients in GHS. The GHS stroke registry is a major contributor to the Get with the Guidelines program launched by the American Heart Association (AHA) and American Stroke Association to support continuous quality improvement of hospital systems for patients with stroke and transient ischemic attack.[35] We analyzed the data collected between January 2010 and December 2013 to investigate gender differences in the exclusion criteria in patients with acute ischemic stroke. We identified the demographics and clinical characteristics of male and female patients who were excluded from the use of r-tPA. Precisely, we examined the demographic factors including age group structure, race, and gender characteristics for exclusion. In addition, we identified clinical factors such as warning signs and contraindications, stroke severity as measured by the retrospective National Institutes of Health Stroke Scale (NIHSS), and brain imaging; and major comorbid conditions. The main outcome measure is the assessment of gender differences in the exclusion criteria for r-tPA excluded patients after implementing the less restrictive criteria of 4.5 hours prior to onset of stroke. The GHS Ethics Committee approved this study.

Statistical Analysis

Using the database between 2010 and 2013 for exclusion criteria, we analyzed gender differences in the use of thrombolysis on acute ischemic stroke patients. The major reasons for the exclusion are tabulated. All data are presented as raw frequencies and weighted percentages or means with standard errors. Descriptive statistics include means or median (interquartile range), and relative frequencies for continuous and categorical data. In the first set of analysis, we determined gender differences in the demographics of patients who received and did not receive r-tPA to identify specific clinical characteristics and differences. We then identified patients who were excluded from r-tPA, and specific reasons for the exclusion. We compared using differences in proportions with 95% confidence intervals. These comparisons included demographic factors, medical history, NIHSS on admission, risk of mortality, medications prior to admission, and initial exam findings that indicate warning signs and contraindications for exclusions. Finally, using a multivariable logistic regression model, we examined the clinical characteristics in gender differences in patients who did not receive r-tPA. All statistical analyses were performed using SAS Statistical Software (SAS Statistical Software, Cary, NC).

Results

A total of 2138 acute ischemic stroke patients were admitted between January 1, 2010, and June 30, 2013. Of the 2138 patients, 633 were eligible to receive r-tPA, excluding 62 patients who received r-tPA at an outside facility. Less than half of the eligible patients received r-tPA (n = 241) whereas 422 were not able to receive r-tPA. Of the 241 eligible patients, 119 (49.4%) women and 122 (50.6%) men received r-tPA (Table 1). As shown in Table 2, of the 422 patients who did not receive r-tPA, 235 women were excluded from r-tPA compared to 187 men ($P < .05$). More women were excluded especially those aged more than 80 years, where 90 women (38%) did not receive r-tPA compared to 35 men (19%). About 79% Caucasian and 20% African–American women were excluded whereas