Sulfonylurea Pretreatment and In-Hospital Use Does Not Impact Acute Ischemic Strokes (AIS) Outcomes Following Intravenous Thrombolysis

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Background and Purpose: Preliminary studies have indicated that sulfonylurea drugs (SUD) may confer protection against cerebral swelling and hemorrhagic transformation in severe acute ischemic stroke (AIS). We sought to determine whether pretreatment and in-hospital use of SUD may be associated with better outcomes in diabetic AIS patients treated with intravenous thrombolysis (IVT). *Subjects and Methods:* We analyzed consecutive diabetic AIS patients treated with IVT during a 3-year period. Pretreatment with SUD, admission NIHSS (National Institutes of Health Stroke Scale) score, NIHSS at 48 hours, and modified Rankin Scale (mRS) at discharge were documented. Patients who discontinued SUD during hospitalization were excluded. Symptomatic intracranial hemorrhage (sICH) was defined as imaging evidence of ICH with NIHSS score increase of greater than or equal to 4 points within 72 hours. Early neurological improvement was defined as an NIHSS score decrease of greater than or equal to 4 points or NIHSS score of 0 at 48 hours. Cerebral edema was documented by neuroradiology reports. Favorable functional outcome (FFO) was defined as discharge mRS of 0-1. *Results:* A total of 148 diabetic AIS patients were evaluated (mean age 64 ± 11 years, 49% men, median admission NIHSS score: 8 points). We identified 42 (28%) cases pretreated with SUD. The prevalence of complications and favorable outcomes did not differ ($P > .1$) between patients pretreated and nonpretreated with SUD: sICH (2% versus 5%), cerebral edema (5% versus 4%), early neurological improvement

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(42% versus 43%), in-hospital mortality (12% versus 5%), and FFO (22% versus 32%). *Conclusions:* Pretreatment and in-hospital use of SUD appears not to be associated with early favorable outcomes and lower likelihood of potential complications in diabetic AIS patients treated with IVT. **Key Words:** Intravenous thrombolysis—sulfonylurea—safety—cerebral edema—favorable outcome—strokes.

Introduction

Diabetic patients with acute ischemic stroke (AIS) have increased mortality risks and higher rates of stroke recurrence and are commonly treated with antidiabetic medications including sulfonylurea drugs (SUD).[1-3] The emerging literature correlates SUD with early efficacy and safety outcomes both in diabetic and nondiabetic patients with severe AIS patients. More specifically, the preclinical use of SUD has been shown to reduce infarct volume, decrease mortality rate, and improve functional outcome in the setting of acute cerebral ischemia.[4-9] In addition, animal models have indicated that SUD may be associated with decreased rates of hemorrhagic transformation and decompressive surgery for cerebral edema in AIS.[10,11] The reported benefits of SUD have been related to its inhibition of Sur1-Trpm4 channel which is selectively expressed in ischemic neuronal tissue after stroke and regulates oncotic swelling.[12,13] In contrast, several retrospective studies have shown no added benefit of SUD in diabetic AIS patients.[14-16] To date, only 1 study has investigated the association of SUD pretreatment with outcomes in diabetic AIS patients who are treated with intravenous thrombolysis (IVT).[17] In view of the above considerations, we sought to evaluate the potential association of SUD use during preadmission and hospitalization period with efficacy and safety outcomes in diabetic AIS patients treated with IVT.

Methods

This was a retrospective analysis of prospectively evaluated AIS patients treated with IVT. Details regarding the prospective IVT registry of our tertiary care stroke center have been previously described.[18-20] We analyzed data specifically from consecutive diabetic AIS patients who were treated with IVT in our tertiary care stroke center from January 2012 to December 2014. Diabetes was diagnosed via reported past medical history or newly diagnosed according to National Institute of Diabetes and Digestive and Kidney Diseases guidelines.[21] Baseline characteristics include demographics, vascular risk factors, admission NIHSS (National Institutes of Health Stroke Scale) scores, and preadmission use of SUD. Admission serum glucose and admission systolic and diastolic blood pressure (SBP and DBP) levels were recorded as previously described.[18-20] AIS patients with history of diabetes who were taking SUD preadmission but did not continue during hospitalization were excluded from the study. AIS patients without diabetes were also excluded from the present analysis. We also excluded diabetic AIS patients receiving endovascular reperfusion therapies in addition to systemic thrombolysis.

Data were evaluated for safety (symptomatic intracranial hemorrhage [sICH], in-hospital mortality, hemicraniectomy, and cerebral edema) and efficacy (early neurological improvement and favorable functional outcome [FFO]) outcomes. We defined sICH as any evidence of ICH on brain computed tomography accompanied by an increase in NIHSS score of greater than or equal to 4 points and deemed causative of worsening.[18,22] A blinded neuroradiologist evaluated neurodiagnostic images for cerebral edema. Early neurological improvement was defined as an NIHSS score decrease of greater than or equal to 4 points or an NIHSS score of 0 at 48 hours.[23] Death during hospitalization and hemicraniectomy were also documented. FFO at discharge was defined as a modified Rankin Scale score of 0-1. Institutional review board approval for this study was granted based on the prospectively maintained acute ischemic stroke database at our institution (10-01003-XP).

Statistical Analyses

Continuous variables are presented as mean ± standard deviation (normal distribution) and as median with interquartile range (skewed distribution). Categorical variables are presented as percentages with their corresponding 95% confidence intervals (95% CI). Statistical comparisons between 2 groups were performed using χ^2 test, or in case of small expected frequencies, Fisher's exact test. Continuous variables were compared by the use of the unpaired *t*-test or Mann–Whitney *U*-test, as indicated. Furthermore, the associations of SUD (sulfonylurea drug) uses with different binary outcomes (e.g., FFO, sICH) were assessed using univariable and multivariable logistic regression models adjusting for potential confounders. Variables with a P value of <.2 on univariable analyses were included as candidate variables in multivariable logistic regression models. In multivariable analyses, we tested the statistical significance hypothesis under the likelihood ratio test with an alpha value of .05. We reported all associations as odds ratios (ORs) with their corresponding 95% CI. Statistical significance was achieved in multivariable logistic regression models with a two-tailed value of $P < .05$. The Statistical Package for Social Sciences (version 22.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analyses.