The Effects of Pretreatment versus De Novo Treatment with Selective Serotonin Reuptake Inhibitors on Short-term Outcome after Acute Ischemic Stroke

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Background: Selective serotonin reuptake inhibitors (SSRIs) administered in patients following acute ischemic stroke have shown to improve clinical recovery independently of changes in depression. Animal studies have demonstrated that sustained SSRI treatment is superior to short-term SSRI in evoking neurogenesis but how this benefit translates into humans remains to be answered. We hypothesized that in acute ischemic stroke patients, SSRI treatment started before the event leads to improved short-term outcomes compared to de novo SSRI treatment poststroke. *Methods:* We performed an exploratory analysis in consecutive acute ischemic stroke patients and compared patients already receiving fluoxetine, citalopram, or escitalopram with those who started treatment de novo. *Results:* Of 2653 screened patients, 239 were included (age, 69 ± 14 years; 42% men, baseline median National Institutes of Health Stroke Scale score, 7 [IQR, 10]). Of these patients, 51 started treatment with SSRI before stroke and 188 were prescribed newly SSRIs during hospitalization. In the adjusted multivariate logistic regression models, SSRI pretreatment was associated with favorable functional outcome at discharge defined as a modified Rankin Scale score of 2 or less (odds ratio [OR], 4.00; 95% confidence interval [CI], 1.68-9.57; $P < .005$), improved early clinical recovery (OR, 2.35; 95% CI, 1.15-4.81; $P = .02$), and a trend toward prediction of superior motor recovery (OR, 1.82; 95% CI, .90-3.68; $P < .01$). *Conclusions:* Our data suggest that SSRI pretreatment may improve clinical outcomes in the early stages of acute ischemic stroke supporting the hypothesis that prolonged SSRI treatment started prestroke is superior to poststroke SSRI. **Key Words:** SSRI—ischemic stroke—neuroprotection—neurogenesis—prestroke SSRI—poststroke SSRI.
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Although reperfusion therapy of acute ischemic stroke via intravenous thrombolysis improves both short-term and sustained poststroke recovery, acute ischemic stroke is still among the leading causes of disability with residual impairment present in up to 75% of stroke survivors and total annual costs of up to $74 billion in the United States alone.[1,2] Among supplementary strategies to improve poststroke outcome, administration of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram, and escitalopram following acute ischemic stroke was shown to improve motor recovery and decrease disability, even in patients without depression.[3-6] Particularly, the brain plasticity–modulating effects of fluoxetine are considered to improve motor recovery in stroke patients treated with this SSRI which is further supported by a recent randomized, double-blind, placebo-controlled trial (FLAME—fluoxetine for motor recovery after acute ischemic stroke—trial).[3]

Based on animal studies, possible mechanisms whereby SSRIs might ameliorate motor and functional recovery were suggested to be mediated by stimulation of neurogenesis with possible migration of new cells to damaged brain regions, neuroprotection through anti-inflammatory effects, improved autoregulation of cerebral blood flow, and modulation of the autonomic adrenergic nervous system.[4,7-9] In a rat model, chronic, but not acute, administration of antidepressants such as fluoxetine increased hippocampal cell proliferation, suggesting that in humans prestroke sustained administration of SSRIs might be superior to poststroke SSRI treatment in improving functional recovery.[10]

As recently proposed by Chollet et al,[11] it is important to generate clinical data on the influence of potentially brain plasticity–stimulating agents such as SSRIs, in order to form the basis for new investigational pharmacological strategies translating the insights derived from preclinical research. Although a recent observational study in acute ischemic stroke patients indicated that prestroke SSRI prescription is not associated with increased stroke severity, it remains unclear to date whether pretreatment with SSRI before stroke onset has beneficial effects on motor recovery and disability following acute ischemic stroke in humans.[12]

In this study, we hypothesized that pretreatment with fluoxetine, citalopram, or escitalopram is related to early clinical recovery, improved motor function, and short-term favorable functional outcome and is superior to poststroke SSRI in improving recovery.

Materials and Methods

We performed an exploratory data analysis of male and female consecutive patients with acute ischemic stroke, aged over 18 years, who were admitted from 2008 to 2012 to the Dresden University Stroke Center within 3 days following symptom onset and were entered into our institutional stroke database that contains data extracted from medical records and prospectively collected functional and motor outcome parameters.

We included 2 specific groups of patients: (1) patients who were treated with fluoxetine, escitalopram, or citalopram for depression before stroke onset and (2) patients who were treated de novo with one of these SSRIs (initiation of SSRI therapy during acute stroke unit hospitalization). We selected these specific SSRIs as they both are widely used in Europe and constitute first-line therapy in poststroke depression and supportive therapy in patients with pronounced impaired motor function at our clinic following institutional standards.[13] To avoid disguise of SSRI effects by severe stroke with infaust prognosis, we excluded patients with malignant middle cerebral artery infarction and basilar artery thrombosis requiring treatment in an intensive care unit setting, space occupying brain stem or cerebellar infarction, and death during hospitalization.

Baseline and Clinical Outcome Parameters

Data extracted from our institutional stroke database were evaluated for the presence of cardiovascular risk factors (arterial hypertension, diabetes mellitus, nicotine abuse, hypercholesterolemia, and atrial fibrillation), presence of coronary artery disease, previous stroke, and history of depression. Additionally, we assessed serial National Institutes of Health Stroke Scale (NIHSS) scores, prestroke modified Rankin Scale (mRS) scores, performance of intravenous thrombolysis, and etiology of stroke using the Trial of Org 10172 in Acute Stroke Treatment classification.[14] To measure short-term clinical outcome after stroke, we evaluated mRS at discharge, NIHSS score at discharge (overall score, motor scores of upper and lower extremities), and duration of hospitalization. Both NIHSS and mRS have been shown to be valid short-term outcome measures for exploratory clinical studies.[15,16]

Favorable functional outcome was defined as an mRS score of 2 or less at discharge. Early clinical recovery was defined as 4 or more point improvement in the NIHSS from baseline to discharge or NIHSS score of 1 or less at discharge. Furthermore, we analyzed early motor recovery, defined as 2 or more point improvement in the NIHSS motor items (arms and legs) from baseline to discharge or combined NIHSS motor item score (arms and legs) of 1 or less at discharge, as previous research showed that SSRIs have particular effects on motor recovery after stroke.[3]

Statistical Analysis

Continuous and noncontinuous variables are presented as mean ± standard deviation, median (interquartile range [IQR]), and percentage. Student t test, Wilcoxon rank sum, chi-square test, and Fisher exact

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