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Effect of fluoxetine on three-year recurrence in acute ischemic stroke: A randomized controlled clinical study

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ABSTRACT

Objective: To evaluate the effect of fluoxetine on three-year recurrence rate of acute ischemic stroke.

Patients and Methods: 404 enrolled patients with acute ischemic stroke were randomly divided into control and treatment groups, and underwent conventional secondary preventive therapy for ischemic stroke. In addition, the treatment group was administered fluoxetine (20 mg daily for 90 days). A three-year follow-up was performed, and indicators related to risk factors of stroke were assessed at day 90 of follow-up. The effect of fluoxetine on the three-year recurrence rate of acute ischemic stroke was evaluated by survival analysis, as well as multifactor Cox regression analysis.

Results: The values of systolic blood pressure, blood total cholesterol, blood low density lipoprotein and glycosylated hemoglobin at day 90 of follow-up were significantly lower in treatment group than control group ($P = 0.002$, $P = 0.002$, $P = 0.018$, $P = 0.011$, respectively). The occurrence rates of epilepsy, gastrointestinal bleeding, syncope, allergic reactions, hemorrhagic infarction, and death were not significantly different between the two groups during the follow-up ($P > 0.05$). The recurrence-free survival rate of ischemic stroke was significantly lower in the treatment group than control group as assessed by the *Kaplan-Meier test* (85.1% Vs 75.7%, $P = 0.016$), as well as the recurrence-free survival rate after day 90 in the three-year follow-up (87.0% Vs 79.3%, $P = 0.043$). Multifactor Cox regression analysis demonstrated treatment with fluoxetine was an independent factor reducing three-year recurrence in acute ischemic stroke (*HR* = 0.594, *95% CI*: 0.376–0.938).

Conclusion: Treatment with fluoxetine for 90 days after acute ischemic stroke significantly reduces the three-year recurrence rate of ischemic stroke.

1. Introduction

Currently, stroke is considered one of the main causes of death worldwide [1]. Ischemic stroke accounts for nearly 80% of all stroke cases and its recurrence rate is about 12% within the first year, and increases to about 30% by five years [2]. Stroke recurrence usually leads to more severe disability and higher mortality rate, imposing a serious socioeconomic burden to the patients and their families [2]. Thus, improving secondary prevention of stroke and reducing its recurrence is prime importance. Recurrence of ischemic stroke might be reduced by enhancing antithrombotic therapy and optimizing the control of traditional stroke risk factors in the early stage after stroke [3–5]. Selective serotonin reuptake inhibitors (SSRIs) have been preliminary confirmed to improve long-term neural functional recovery in ischemic stroke, accompanied or not with post-stroke depression, as well as blood glucose, blood pressure, blood lipid [6]. Additionally, SSRIs also has the effect on inhibiting platelet aggregation [7]. However, effect of SSRIs on ischemic stroke recurrence remain controversial [2,8–14]. Moreover, no any prospective randomized controlled study with multifactor analysis specifically aimed at the post-stroke population, accompanied or not with depression, has been reported yet. We hypothesized that fluoxetine, a representative SSRIs, might reduce ischemic stroke recurrence, and used it in patients with acute ischemic stroke, accompanied or not with post-stroke depression. The patients were then followed up prospectively, and the effect of fluoxetine on the three-year recurrence rate of acute ischemic stroke was evaluated by survival analysis, as well as multifactor regression analysis.

2. Materials and methods

2.1. Patients

The inclusion criteria were: (1) ischemic stroke diagnosis according to World Health Organization criteria [15]; (2) age between 18 and 80 years; (3) initial stroke; (4) within 1 week of onset; (5) signed informed consent by patients or their legal relatives. *The exclusion criteria were*:

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(1) disturbance of consciousness. (2) a previous history of ischemic stroke; (3) pregnancy or lactation in women; (4) self-injury or suicidal tendency, and must receive antidepressant administration; (5) a history of peptic ulcer or gastritis; (6) existing serious heart, liver orkidney dysfunction, serious complications of stroke or malignant tumor; (7) use of benzodiazepines (within 2 weeks) or antidepressants (within 3 months) before stroke; (8) allergies; (9) participation in other clinical studies within 3 months. *The withdrawn criteria were*: (1) severe adverse drug reactions; (2) violation of the principle of blinding rules or randomization during follow-up; (3) existing serious tendency of suicide or self-injury, with the use of antidepressants during follow-up; (4) exit request from patients or their legal relatives.

2.2. Randomization and blinding

The enrolled patients were divided into control and treatment groups, by a random number table, in equal proportions. Randomization was carried out by the same staff, who was forbidden to reveal grouping information or participate in diagnosis and treatment. Single-blinding by evaluator was used in our study. The randomization and patient treatments were blinded for the evaluators who conducted the examinations and observed all of the events during the follow-up, as well as the two data management professionals who recorded all of the information and observation parameters.

2.3. Treatments

All treatments were performed by the same neurological treatment team in our hospital, which was forbidden to participate in the randomization, data collection and statistical analysis. Treatments for ischemic stroke and other risk factors for cerebral vascular disease were based on *the Guidelines for the* Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack [16]. On this basis, we uniformly used aspirin for anti-platelet therapy, as warfarin for anticoagulant therapy and atorvastatin for lipid lowering and plaque stabilization therapy. All patients received the same rehabilitation therapy and health education. In addition, the treatment group was administered fluoxetine (20 mg daily for 90 days) manufactured by Eli Lilly company (authorization number: J20120001).

2.4. Observation parameters and endpoint event

Baseline National Institute of Health Stroke Scale (NIHSS) score, creatinine (Cr), glutamic oxaloacetic transaminase (GOT), fasting blood glucose (FBG), glycosylated hemoglobin (GHB), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood homocysteine (HCY), and blood pressure (measured between 8 a.m. and 9 a.m. within 24 h of enrollment) were recorded. Then, the above parameters were re-assessed at day 90 after enrollment. All patients underwent carotid artery color ultrasound, cranial magnetic resonance image and angiography examinations. In case of persistent black stool, gastroscopy was conducted to rule out gastrointestinal bleeding. For patients presenting the symptoms of neurological defects, cranial magnetic resonance was performed to exclude ischemic stroke recurrence. The patients were followed up for 3 years, with ischemic stroke recurrence as the endpoint event.

2.5. Sample size calculation and compliance assessment

Data obtained from 60 patients (30 cases per group) enrolled in a preliminary study were used as reference information in sample size calculation. The recurrence rates of ischemic stroke were 23.3% and 16.7% in control and treatment groups, respectively. With type I error alpha set at 0.05, type II error beta at 0.20, test power at 80%, and expected loss ratio at about 10%, the total sample size was 404 cases, with 202 cases in each group as calculated by the *PASS 11.0* software (NCSS, United State). Patients were instructed to return to the same neurological treatment team for reassessment every 15 days in first 6 months, and every 30 days thereafter. The revisit rates were used to assess compliance.

2.6. Ethical standard

This study was approved by the Shenzhen People's Hospital Ethics Committee. Patients or their legal relatives signed informed consent before enrollment, and had right to withdraw during follow-up.

2.7. Statistical analysis

SPSS 24.0 was used for statistical analysis. The data was imported into *SPSS 24.0* and checked by two data management professionals. For measurement data with skewed distribution, median and quartile were used for description, and *rank sum test* was used for comparisons. Measurement data with normal distribution were presented as mean ± standard deviation, and compared by *t*-test. *Chi-square test* was used to assess count data. *Kaplan-Meier* survival analysis was used to compare recurrence-free survival rate. Cox regression analysis was used to evaluate whether treatment with fluoxetine was an independent factor for three-year recurrence in ischemic stroke. $P < 0.05$ was considered significant.

3. Results

3.1. Baseline data and adverse events, hemorrhagic infarction events, dead events during follow-up

The roadmap of study is shown in Fig. 1. In total, 404 consecutive eligible patients were enrolled between June 2010 and August 2014 in Shenzhen People's Hospital, and divided into control and treatment groups equally and randomly, with 202 patients per group. Baseline characteristics between control and treatment groups were not significantly different (Table 1). Revisit rates were similar in both groups (86.3% Vs 83.0%, $P > 0.05$), suggesting that therapy compliance was not significantly different between two groups. 16 patients were lost to follow up and 1 died in control group, for 14 and 4 patients in treatment group, respectively. The dropout and mortality rates were not significantly different between two groups (7.9% Vs 6.9%, $P = 0.704$; 0.5% Vs 2.0%, $P = 0.368$, respectively). In control group, 1 patient died of a cardiovascular event; in treatment group, 1, 1, and 2 patients succumbed to drowning, severe pulmonary infection, and cardiovascular event, respectively. During follow-up, no significant differences were observed between two groups in epilepsy, gastrointestinal bleeding, syncope, allergic reaction, and hemorrhagic infarction rates (Table 2).

3.2. Comparison of traditional risk factors for stroke at baseline and day 90 of follow-up

Excluding the patients lost to follow up before day 90, there were 198 and 198 patients in control and treatment groups, respectively. At day 90 of follow-up, blood pressure, GHB, TG, TC, LDL-C, HDL-C, HCY, Cr and GOT were reviewed for these patients. Cr and GOT were not significantly different between two groups (Table 3). The reviewed values of systolic blood pressure, diastolic blood pressure, GHB, TG, TC, LDL-C, HDL-C and HCY were all lower than baseline values in both control and treatment groups significantly (all $P < 0.05$; Table 3). Meanwhile, systolic blood pressure, TC, LDL-C and GHB were significantly lower in the treatment group when compared with control values ($P = 0.002$, $P = 0.002$, $P = 0.018$, $P = 0.011$, respectively; Table 3).