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Research Paper

Fluoxetine Versus Citalopram in Improving Post-stroke Motor Function: A Comparative Single-blind Clinical Trial

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ABSTRACT

Background: One of the significant concerns of ischemic stroke patients is movement disabilities after stroke. Various drugs have been introduced to reduce these complications. However, the use of antidepressants is still under more studies.

Objectives: This study explored the impact of fluoxetine and citalopram on improving motor function following ischemic stroke.

Materials & Methods: This study was a single-blind clinical trial conducted on patients hospitalized with ischemic stroke (from January 2021 to July 2022). According to the inclusion and exclusion criteria, patients were in one of three groups (fluoxetine, citalopram, placebo). Then, their movement disorder and performance level were evaluated using The National Institutes of Health Stroke Scale (NIHSS) in the first, 30, 60 and 90 days after stroke.

Results: Based on our results, all three investigated groups showed significant decreases in the NIHSS scale during 90 days (P=0.018). However, fluoxetine caused the greatest reduction of the three groups. In addition, citalopram significantly lowers lower limb NIHSS in one month and two months compared to fluoxetine and placebo (P=0.003 and P=0.013, respectively). However, when the average NIHSS of the upper limb was examined during 90 days, the investigated drugs did not cause a significant decrease (P=0.253).

Conclusion: Considering motor dysfunction after ischemic stroke, fluoxetine and citalopram treatments can be a suitable treatment suggestion to improve the motor status of patients and thus improve their health.

Keywords: Fluoxetine, Citalopram, Stroke, Ischemic stroke, Motor function

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Highlights

• Lower limb the National Institutes of Health Stroke Scale (NIHSS) scores were reduced by fluoxetine and citalopram during 90 days.

• In lower limbs, fluoxetine reduced NIHSS scores more than citalopram.

• Upper limb NIHSS scores were not reduced significantly by fluoxetine and citalopram during 90 days.

Introduction

After cardiovascular disease and cancer, stroke is the third greatest cause of death across the globe. Annually, roughly 33% of stroke victims are disabled [1]. There are two types of strokes, ischemic strokes (blockage of blood flow to the brain) and hemorrhagic strokes (sudden bleeding in the brain) [2, 3]. Ischemic stroke accounts for almost 80% of all strokes [4]. Risk factors for stroke include age, gender, blood pressure, smoking, high lipid profile and diabetes [5, 6]. Age, especially age above 55 and high blood pressure are among the highest risk factors for the situations above [7, 8]. CT scans and MRIs are used to diagnose strokes [9]. The treatment of these patients is thrombolytic medications, such as antiplatelets, plasminogen activators, and thrombolytic agents [10, 11].

Serotonin is a neurotransmitter that modulates motor and other brain functions [12]. Research in the laboratory has examined the effects of therapeutic medications on neurotransmitters and consequently, their impact on brain functional recovery [13]. These medications include selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and citalopram, paroxetine and sertraline, as well as serotonin/norepinephrine reuptake inhibitors (SNRIs) like venlafaxine [14-16]. When this neurotransmitter (Serotonin) is produced from platelets, it promotes platelet aggregation. Therefore, the concept that medications that block this neurotransmitter, termed SSRIs or SNRIs, might be connected with the restoration of cerebral blood flow in the continuation of cerebral ischemic stroke is supported [17].

In animal research, fluoxetine has demonstrated positive long-term benefits on brain function recovery and infarct volume reduction [18]. In human investigations, it causes decreased stroke recurrence and improved patient sensorimotor performance [19, 20]. In animal experiments, citalopram has shown neurogenesis effects. This medication also enhances somatosensory function following a stroke [21]. Using the NIH stroke scale/score, clinical investigations have demonstrated that citalopram reduces the risk of vascular events and improves motor function [22].

In light of the variations between fluoxetine and citalopram and the difficulties we confront in patients with ischemic stroke, this study aimed to explore the impact of fluoxetine and citalopram on improving motor function following ischemic stroke.

Materials and Methods

Study design

This research was a placebo-controlled, single-blind clinical trial conducted in northern Iran. This study was done on individuals diagnosed with ischemic stroke who were hospitalized between January 2021 and July 2022.

Inclusion and exclusion criteria

The patients had a computerized tomography (CT) scan at the time of referral and, if necessary, a magnetic resonance imaging (MRI), the findings of which were validated by a neurologist to diagnose an ischemic stroke. The inclusion criteria were as follows: Aged above 18 years, developed hemiparesis or hemiplegia following the first ischemic stroke that occurred during the previous 24 hours and a score equal and higher than 2 for the motor components of NIHSS (sum of the score of motor impairment in the upper and lower limbs). The exclusion criteria were as follows: Patients admitted to the ICU with an ischemic stroke and loss of consciousness from the onset; history of psychiatric disorders in patients, mood disorders (which were evaluated using screening for mood disorders before patient discharge using diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) criteria; having disorders such as aphasia, cognitive pathology, or any form of movement issue before stroke; pregnancy and breastfeeding; patients receiving psychiat-

ric medications; existence of any kind therapeutic contraindications, including renal failure (glomerular filtration rate below 30), abnormal liver function tests, hyponatremia, and a prolonged QT interval; the emergence of any significant adverse effects of the medicine during therapy, such as agitation, hypertension, or serotonin syndrome symptoms; patients who received thrombolytic drugs; and Patients who did not complete the 3-month treatment period. [11] Patients under treatment with one drug as a standard treatment for ischemic stroke (daily Clopidogrel 75 mg or Aspirin 80 mg)

Sample size

Based on a 95% confidence interval (CI) with 80% power and standard deviation difference equal to 5 with a range of 5 units, 30 percipients were calculated for each group. Due to data collection restrictions (time limit, single-center and non-referral of certain patients included in the research), the sample size for each group was decreased from 30 to 20 participants.

Interventional therapy and blinding

To examine the effects of two kinds of selective serotonin inhibitors, long-acting and short-acting, which have differing pharmacodynamics, 20 patients were separated into three groups: A) Fluoxetine, B) Citalopram and C) Placebo. In this trial, citalopram (20 mg pill from Abidi Co.), fluoxetine (20 mg capsule from Arya Co.), and the placebo were disguised as starch. These medications were put into capsules of the same color and size (capsule size: 3) in the hospital's clean room. The average weight of capsules filled with fluoxetine (group A) was 10±2 mg (the initial therapeutic dose) and 20±2 mg. The average weight of the capsules filled with citalopram (group B) was 10±2 mg and 20±2 mg (the initial therapeutic dose) and the average of placebo capsules (group C) was 20±2 mg; these capsules were packaged in white cans. They were packaged in identical containers, so the patient was not informed of the medication they received.

Considering that most patients were old, group A began with a starting dosage of 10 mg fluoxetine orally daily, subsequently raised to a maximum dose of 20 mg daily. In contrast, group B started with a starting dose of 20 mg daily. A daily dose of 5 mg citalopram was administered orally and according to the findings of the drug's impact the dose was gradually raised until it reached the maximum amount of 20 mg daily. It should be noted that in addition to treatment with fluoxetine and citalopram, they also received standard treatment for ischemic stroke, including daily clopidogrel 75 mg and Aspirin 80 mg. For group C, a placebo consisting of a starch mixture was placed into the capsule. The treatment period for the patients was three months, and the medications were administered within the first week following the stroke with the patients' informed agreement (and, if required, the assent of their first-degree relatives). All patients got the conventional stroke treatment protocol and one hour of physiotherapy. In line with the patient's motor impairment, they were followed up in the hospital twice a week, and the technique used to accomplish this (Figure 1). Additionally, underlying diseases were matched among the treatment groups. Also, there was no investigation of the infarct volume in the patients.

Study instruments

NIHSS was utilized in this investigation to measure motor impairment in patients [23]. This scale has 11 components (for each item, scores range from 0 to 4). A score of 0 on each item indicates normal performance in that ability, whereas a score of 1 or more shows impairment. This scale was used to evaluate the motor score of the upper and lower limbs on the first, 30th, 60th and 90th days. In this study, the researcher assessed the NIHSS criterion without blinding himself or herself to the treatment allocation.

Statistical analysis

In addition to analyzing the data using the statistical program SPSS software, version 22.0, the data's normality was also examined. Quantitative data are presented in this study as Mean±SD, whereas qualitative data are presented as frequency and percentage. To explore the link between qualitative and quantitative variables, the chi-square test and independent t-test were employed, respectively. The statistical test of repeated measurements was used to examine the effect of medications at various time intervals. In contrast, the general linear model test investigated the link between medicines and their impact at a particular period. In addition to the above-described instances, the paired t-test has also been used to explore the effects of medications across two distinct periods. In this study, the significance level was <0.05.

Results

In this interventional trial, 60 patients were evaluated to determine the efficacy of fluoxetine and citalopram compared to the control group on improving motor function following an ischemic stroke, based on the inclusion and exclusion criteria.

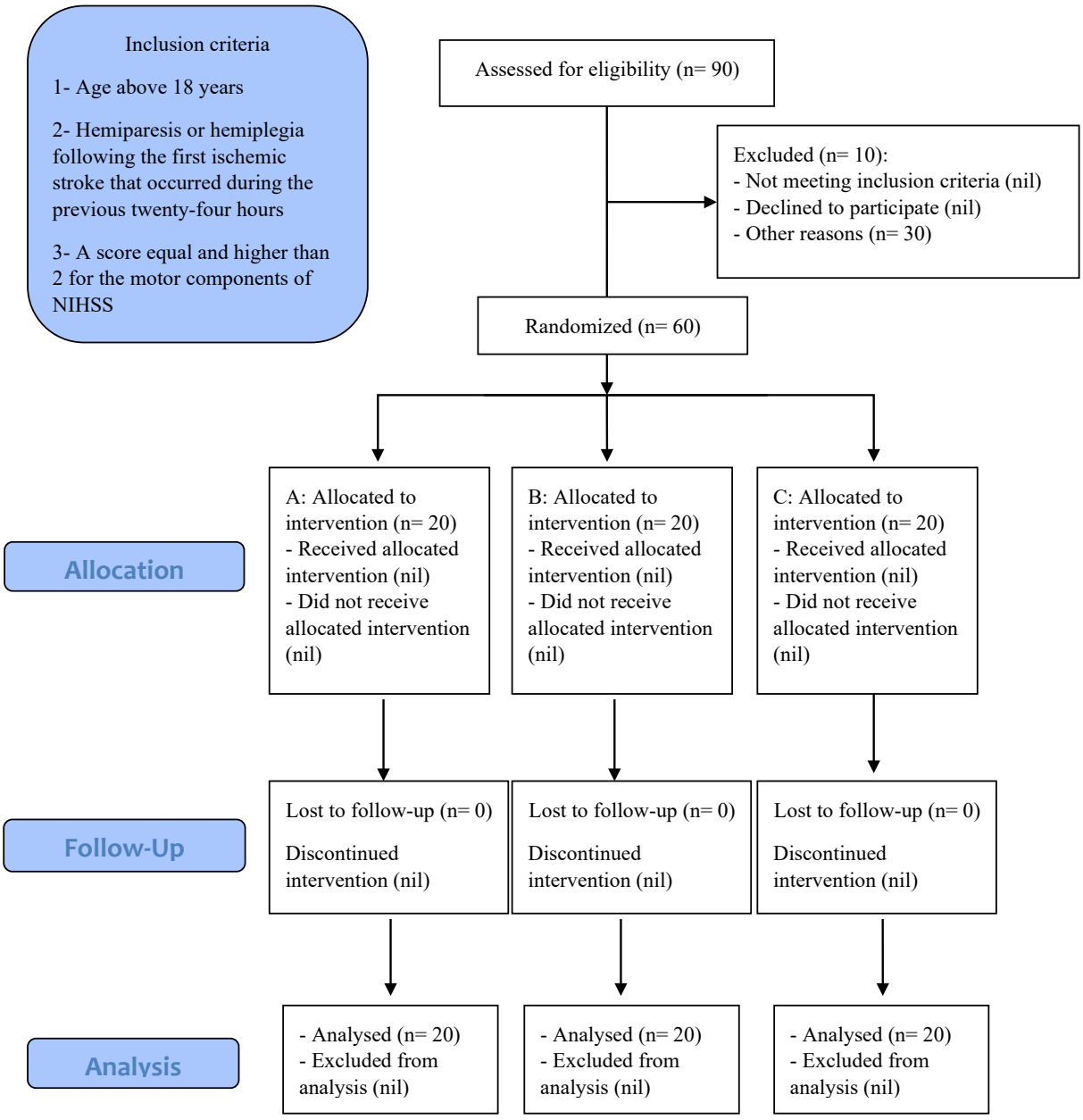

Figure 1. Consort flow chart

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This research's oldest and youngest patients were 91 and 33, respectively. Although there was a roughly 4-year age difference between the individuals getting the serotonin inhibitor medicine and those receiving the placebo, the age distribution across the three treatment groups was identical (P=0.274) (fluoxetine: 69.37±10.77, citalopram: 68.50±11.20, placebo: 73.90±11.69). The placebo (9, 45.0%) and fluoxetine (8, 40.0%) group had the most females, whereas the citalopram group contained the most males (14,70%). However, there was no significant correlation between gender and treatment groups (P=0.747).

Using the NIHSS instrument, we assessed the influence of medications on patients' mobility status. There was a significant association between the three groups over the various periods of the research in the lower limb but not in the upper limb (P=0.018) (Table 1).

In addition, citalopram, like fluoxetine, was effective on patients' mobility status at the beginning of the research compared to all other times (P<0.001). Also, considering we used the minimum therapeutic doses of citalopram and fluoxetine, the studied patients had no side effects.

Table 1. Comparing changes in three treatment groups for upper and lower limbs

Variables		Mean±SD				P*
		Day 0	Day 30	Day 60	Day 90	
Upper limb	Fluoxetine	2.35±1.309	1.55±1.432	1.35±1.309	1.25±1.333	0.253
	Citalopram	2.00±0.973	1.10±1.210	0.90±1.119	0.80±1.056	
	Placebo	2.35±1.182	1.95±1.395	1.50±1.318	1.50±1.395	
	P*	0.550	0.146	0.296	0.219	-
Lower limb	Fluoxetine	2.20±0.894	1.20±0.768	1.10±0.852	1.00±0.795	0.018*
	Citalopram	1.70±1.081	0.85±0.745	0.55±0.826	0.65±0.988	
	Placebo	2.40±1.188	1.95±1.356	1.50±1.235	1.40±1.142	
	P*	0.109	0.003*	0.013*	0.063	-

*P<0.05 is significant.

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Discussion

In this single-blind clinical trial, we compared the efficacy of fluoxetine and citalopram in improving motor function following an ischemic stroke.

In the current study and in the time intervals from the beginning of the intervention to the following 90 days, the investigated drugs had a positive effect on the reduction of the average NIHSS score in the lower limb; this reduction was greater for fluoxetine than for citalopram and greater than for placebo. Statistically, this difference was significant. In the same investigation on the state of upper limb motor function, although there was a difference as previously, such that the difference from the beginning of the trial to the 90th day was more significant for citalopram than for fluoxetine and placebo, no significant difference was detected. In the research of medications administered over time, there was no significant difference between them for improving upper limb motor function. In the lower limbs, a separate scenario exists. One and two months following the beginning of the trial, there was a significant difference between these three medications in terms of the improvement of the NIHSS motor score in each of the given periods. Citalopram is more effective than fluoxetine during both periods.

In a meta-analysis by Elsnhory et al. done on 7165 patients, fluoxetine was found beneficial in enhancing motor function based on the NIHSS comparison. However, this effect takes time and its impact is transient [24]. Also, in the study of Liu et al. which was included in the previous meta-analysis, it was stated that the effect of fluoxetine in studies with smaller sample sizes was able to improve motor function as measured by the NIHSS scale. Still, in studies with larger sample sizes, this significance decreases. In addition, they note that the increased risk of seizures, hyponatremia, and bone fractures in stroke patients associated with the use of fluoxetine should be considered [25]. In the research of the mechanism of this treatment, investigations have revealed the anti-inflammatory and antioxidant effects of this drug on the protection of neurons in these patients, as well as the increased expression of brain-derived neurotrophic factor (BDNF), anti-apoptotic and increased expression of hemeoxygenase-1 (HO-1) [26-30]. In terms of the efficacy of this treatment on stroke patients, the studies mentioned above are comparable to ours. Nevertheless, further research is required to determine the drug's long-term or short-term effects and inclusion criteria. It is essential to evaluate the advantages and risks of this medication. Fluoxetine should not be administered to stroke patients who do not have mood issues. Although this medicine improved the Fugl-Meyer motor scale or Barthel index, it failed to meet the modified Rankin scale and NIHSS requirements [25].

Regarding citalopram, a meta-analysis suggests that SSRIs help enhance the motor function of stroke patients. However, this result was only observed in the sub-analysis, including citalopram (not fluoxetine). In addition, they noted that it is preferable to focus more on the effect of this medicine in randomized control trials [31]. In intervention research by Savadi Oskouie et al. administering 20 mg of this medicine vs placebo for three months produced satisfactory results in terms of

safety and tolerability for the recovery of motor function in stroke patients [32]. Also, in a trial by Acler et al. the treatment of 10 mg of this medicine for at least four months improved the NIHSS score of stroke patients [33]. The theorized mechanism of action of citalopram is the drug's influence on apoptotic indicators and its ability to inhibit the production of inflammatory mediators [34-36]. The research mentioned above on citalopram is comparable to our concept.

In a similar study conducted by Asadollahi et al. a 90-day study of functional improvement with the Fugl-Meyer motor scale and with citalopram, fluoxetine, and placebo drugs in patients following ischemic stroke concluded that no significant difference between citalopram and fluoxetine, but both medicines can improve motor function in comparison to placebo [37]. Using the NIHSS scale, there was no significant difference in the averages of these three medications in the time preceding the study, as was the case in our study; thus, this study is comparable to ours.

The administration of two medications, citalopram, and fluoxetine, to individuals suffering from mobility difficulties after a stroke still requires investigation. The indicated mechanisms are based on animal studies, and further clinical research is necessary to study them further. Patients' conditions must be evaluated before prescribing fluoxetine and citalopram, and it is best to begin treatment in those with mood disorders and lower limb movement problems. The length and onset of pharmacological effects require further research.

This study also has limitations. The spread of the coronavirus, limited access to hospitalized patients suffering from cerebral ischemia stroke, and no investigation of the infarct volume in the patients are the limitations of this study.

Conclusion

Citalopram and fluoxetine are more successful in treating lower limb movement problems in stroke patients than upper limb movement disorders. Compared to the commencement of the trial and the 90th day, administering these two medications one and two months after the study's inception provided greater results.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Babol University of Medical Sciences, Babol, Iran (Code: IR.MUBABOL.REC.1399.279) and approved the Ethics Clinical Trial of Iranian Registry of Clinical Trials (IRCT) (Code: IRCT20210307050617N).

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Authors contributions

Conceptualization: Payam Saadat, Romina Hamzehpour and Pouyan Ebrahimi; Methodology: Mahmoud Haji Ahmadi; Investigation: Payam Saadat, Fatemeh Karimi and Pouyan Ebrahimi; Writing the original draft: Pouyan Ebrahimi; Writing, review, and editing: Pouyan Ebrahimi, Payam Saadat, Fatemeh Karimi, and Romina Hamzehpour; Funding acquisition: Payam Saadat; Resources: Payam Saadat and Romina Hamzehpour; Supervision: Payam Saadat and Pouyan Ebrahimi.

Conflict of interest

The authors declared no conflict of interest.

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