Journal of Research in Medical and Dental Sciences
2018, Volume 6, Issue 3, Page No: 118-122
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Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Studying Effect of Fluoxetine on Improvement of Motor Performance in Patients with Ischemic Stroke

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DOI: 10.5455/jrmds.20186319

ABSTRACT

Ischemic strokes account for two-thirds of stroke cases, and the complications caused by it impose a lot of psychological and economic burden on both the individual and the society. This study evaluates the effect of one-month treatment on NIHSS and BARTHEL INDEX criteria in these patients. This study is a clinical trial. Patients with stroke symptoms referred to Imam Khomeini Hospital in Urmia. After confirmation of ischemic stroke with CT scan or MRI, and having inclusion criteria, they were divided into case and control groups. Finally, the data were analyzed using SPSS software version 21. After one month the studies conducted showed that fluoxetine was effective on the overall score of NIHSS, facial paralysis score, upper limb movement score, and also on BARTHEL INDEX, but it had no positive effect on lower limb movement and dysarthria. Administration of fluoxetine in patients with ischemic stroke can increase motor performance in these patients.

Key words: Ischemic Stroke, Fluoxetine, Motor Performance, BARTHEL INDEX, NIHSS

HOW TO CITE THIS ARTICLE: Arash Mosarrezaii, Babak Ahmadi Salmasi, Seyed Abdolghafar Taghavi, Studying Effect of Fluoxetine on Improvement of Motor Performance in Patients with Ischemic Stroke, J Res Med Dent Sci, 2018, 6 (3):118-122, DOI: 10.5455/jrmds.20186319

Corresponding author: Arash Mosarrezaii
Received: 25/01/2018
Accepted: 18/03/2018

INTRODUCTION

Cerebrovascular accidents cause death and disability, and the severity of the disease at its onset depends on the affected area of the brain and the size of the damage. Limiting the severity of damage by manipulating molecular mechanisms during illness, especially in animal researches, has caused a promising approach to control the disease [1]. Stroke is one of the main causes of long-term disability in adults and is the second leading cause of death worldwide [2]. In the United States, 700,000 cases of stroke occur every year, of which 600,000 cases are ischemic and 100,000 cases are hemorrhagic. The death resulting from stroke in the United States has been reported at 12% [3]. Diarrhea, sensory disturbances, giddiness, confusion, mental disorders, speech impairment, visual disturbances, and double vision are among the clinical manifestations of stroke. Strokes can, in their extreme form, cause paralysis of the limbs of one side of the patient or even the creation of coma condition in the patient [4, 5]. Several known risk factors including aging, hypertension, diabetes, hyperlipidemia, obesity, smoking, heart disease, coagulation and oral contraceptive position (OCP) are involved in stroke. Investigations have shown that If these risk factors are controlled, it can prevent or reduce the severity of many strokes [6, 7]. About 80% of strokes are due to ischemia, the main causes of which are the critical reduction of blood flow to the brain, diffuse atherosclerosis lesions and small vessel disease. Critical reduction of blood flow to the brain is often caused by the thrombotic or amniotic occlusion of the blood supplying (supportive) artery. Distributed lesions of atherosclerosis disturb compensatory mechanisms in the border region, and small vessel disease leads to the formation of cavity infarctions

in deep brain structures. In all types of ischemic stroke, a sudden loss of regional blood flow is responsible for functional impairment that activates a cascade of pathophysiologic mechanisms and results in tissue damage. When the blood flow goes below the threshold, nerve function is immediately damaged, but it can be improved if the blood flow is restored within a short time [8]. The most effective and only approved treatment to date is the re-establishment of blood flow through thrombolysis in the first hours after the attack. Intravenous use of recombinant plasminogen activator is effective in improving post-stroke outcomes, but the widespread use of this strategy is limited due to the limited golden time of onset of consumption (3 to 4.5 hours), increased risk of symptomatic cerebral hemorrhage, and withdrawal criteria related to it [9]. Therefore, therapeutic interventions that, over a longer period of time, influence the physiological mechanisms affecting the development of ischemic injury and make it possible to heal after ischemic events are an essential requirement. There are evidences for the role of neuroplasticity in restoring the physiological function of ischemic tissue and it has been proven that nerve cell regeneration occurs after a stroke [10]. Many efforts have been made to improve this regeneration in the affected brain. Methods of physiology and pharmacological strategies have been studied and, in some cases, their results have been tested and analyzed using imaging techniques. Studies on monoaminergic drugs have shown that these drugs can improve neuroplasticity of damaged brain tissue and thus reduce the neurological defects and the subsequent disability [11]. Amphetamines have promoted rehabilitation in animal models of acute lesions, while neuroleptic drugs and benzodiazepines have reduced it. There is little evidence about SSRIs' effectiveness in animal studies. However, the overall outcome of studies indicates the neuroprotective performance of these drugs in the brain with ischemia and improvement of nerve regeneration in the hippocampus [12]. Limited clinical trials conducted to investigate the role of SSRIs so far, all suggest their positive effect on improving motor performance of patients with ischemic stroke. The use of MRI in other studies has shown that fluoxetine and paroxetine increase the activity of the motor cortex compared with placebo, both in healthy patients and in patients with ischemic stroke [13]. So, it becomes apparent that increasing attention has been paid to the potential role of SSRI compounds in repairing brain ischemic lesions. Fluoxetine, as SSRI, has a proven role in improving symptoms of post-stroke depression and reducing the effects of depression on social performance. In a study done by Pinto et al (2017), it has been found that SSRIs, especially fluoxetine, can be useful for patients with cerebrovascular accidents and are highly effective in developing new strategies for stroke rehabilitation [14]. In Iran, there was no study done on investigating the role of SSRI drugs on the improvement of motor defects caused by stroke so far, and the need for study in this important area is highly felt. We evaluated the effect of this drug on improving the motor performance of patients admitted to the neurology department of Imam Khomeini Hospital in Ourmia. In this study, in addition to assessing the motor status of the patient using the NIHSS scoring system, the patient's performance in doing daily activities was also measured applying the BARTHEL INDEX criterion; it can, compared to the previous studies, provide better perspective on the drug's effects.

MATERIALS AND METHODS

This study was conducted as a randomized clinical trial on 55 patients referred to Imam Khomeini Hospital in Urmia with diagnosis of ischemic acute stroke. Patients received numbered cards according to the order of hospitalization. The recipients of the cards with odd and even numbers constituted the case and control group, respectively. Criteria for participating in study included focal neurological disorder, age range 18 to 85 years, radiological findings consistent with ischemic stroke, and NIHSS score of 6 to 22. Exclusion criteria included age over 85, major depression or other psychiatric disorders, and patients requiring special care in ICU. Patients were randomly divided into two groups, one receiving the drug and the control group, according to criteria for participating in study and obtaining written consent. The first group, in addition to conventional stroke treatments, was treated daily with fluoxetine 20 mg during one month after the onset of ischemic stroke on the third to fifth day; patients in the second group were received usual treatment after stroke during same period. The patient was excluded from the study if any side effects were appeared due to the drug. The motor performance of patients was evaluated on the first day and the 30th day after treatment by Barthel Index and NIHSS criteria.

Data analysis was performed by SPSS software version 21.

RESULTS

This study was performed on 55 patients with acute ischemic stroke, 28 people of whom were randomly selected in the treatment group (50.9%) and other 27 people (49.1%) were in the control group. The average age was 72.45 years with a minimum of 38 and a maximum of 84 years, but the two groups did not have a significant difference in mean age. The mean age in the treatment group was 71.68 and in the control group was 73.2. A gender study in our patients showed a total of 29 men (52.73%) and 26 (47.27%) women. Comparison of the two groups in terms of NIHSS criterion showed that the mean NIHSS in the group under treatment with fluoxetine was 11.07 and in the control group was 10.30, which was not statistically significant (P = 0.287). BARTHEL INDEX was measured by 29.64 in the treatment group and by 31.67 in the control group, which have not significant difference. Finally, it should be noted that the two groups did not differ significantly in terms of demographic information and initial visit conditions. The first score of NIHSS in the fluoxetine group was 11.07 and in the control group 10.30, which they had not statistically significant difference. The final score of NIHSS after one month was reduced to 4.70 in the case group and to 7.07 in the control group, which was statistically significant (P = 0.001). Facial paralysis score was 0.96 in the fluoxetine group and 1.07 in the control group, which did not show a significant statistical difference (P = 0.066). After one month, the scores were reduced by 0.25 and 0.67, respectively (P <0.05). At first, upper limb movement score was 2.96 in the fluoxetine group and 2.56 in the control group. After a month, the scores fell to 1.07 and 2, respectively (P <0.05). The lower limb movement score was 2.71 in the treatment group and 2.15 in the control group. After one month, the scores reached 1.52 and 1.61, which did not show statistically a significant difference (P = 0.08). The dysarthria score was at first 1.00 in the fluoxetine group and 0.89 in the control group. After one month the scores were 0.39 and 0.63 respectively, which did not show a significant difference (P = 0.138).

Table 1: Comparison of NIHSS score and its subclasses at the beginning of hospitalization and one month later

Row	Indices	Begining of hospitalization		Onemonth after	
		Case	Control	Case	Control
1	Total NIHSS	11.07	10.30	4.50	7.07
2	Facial paralysis	0.96	1.07	0.25	0.67
3	Upper limb movement	2.96	2.56	1.07	2
4	Lower limb movement	2.71	2.15	1.52	1.61
5	Dysarthria	1	0.89	0.39	063

For BARTHEL INDEX, this amount was 29.64 in the fluoxetine group and 31.67 in the control group. After one month the scores decreased to 85.39 and 47.59, respectively, which was statistically significant (P <0.05).

DISCUSSION AND CONCLUSION

Stroke is the second leading cause of mortality in the world. Therefore, paying attention to preventing it by eliminating risk factors such as alcohol, cigarettes, oral contraceptives and other controllable factors such as hypertension and hypercholesterolemia is important. TIA can also produce clinical symptoms similar to full-scale ischemic stroke, but its symptoms will be removed within 24 hours or be significantly reduced; the therapeutic approach is different from that of ischemic stroke.

Currently, intravenous t-PA is used to treat those patients who have initial symptoms during the first 3 hours; several complications including high blood pressure, as well as limiting factors of prescription such as the interval between onset of symptoms and hospitalization and high drug prices cause that it cannot be used by all patients.
In the present study, which evaluated the effect of one-month treatment with fluoxetine on motor performance of patients with ischemic stroke, 55 patients were examined in two groups. The two groups were similar in terms of age and gender demographic factors, which reinforced the results presented; what was specifically noted in the statistical findings was the positive effect of fluoxetine on the total NIHSS scores at the end of one-month period of treatment. The analysis of NIHSS motor components also showed that the drug had a positive effect on facial and upper limb paralysis. However, the studies did not show a significant effect of this drug on the lower limbs and dysarthria and there was no significant difference in this area. The study of Chollet et al, similar to the present study, showed that

fluoxetine can improve motor performance score at the end of the first and third months compared to the first day [15]. In a study conducted by Siepmann et al (2015), it was found that if SSRI is used at the early stages of ischemic stroke, it improves the patient's condition and enhances clinical symptoms. The results of this study showed that the use of SSRI in a patient before the onset of stroke is much more effective than its use after stroke, and it can improve the patient's condition [16]. The study of Acler et al also demonstrated the positive effect of citalopram (another drug of the SSRI family) on the NIHSS score at the end of a one-month treatment period [11]. In our study, the analysis of BARTHEL INDEX score made clear that fluoxetine can have a positive effect on the daily activities of the individual and his/her ability to do personal works. In the study of Dam et al on patients treated with fluoxetine, the BARTHEL INDEX at the end of the treatment period was significantly higher than that of placebo and maprotylline [17]. Also, studies conducted by He YT (2016) showed that if treatment with fluoxetine is continued 90 days after an ischemic stroke, it can improve long-term neurological performance outcomes [18]. Other studies in which for studying fluoxetine and other SSRI drugs the imaging modalities were used such as MRI, all confirmed the positive role of these drugs in improving brain function [19, 20].

Recommendations

1. It is suggested that in future studies, with a larger sample size, the effect of the drug in both case and control groups should be compared with more criteria.
2. In future studies, the patients should be matched in terms of the location of involvement in stroke.
3. In future studies, the patients should be matched in terms of receiving or not receiving physiotherapy to exclude its effect on the results of the study.
4. It is suggested that in future studies, the effect of drug therapy in longer periods be also evaluated, and the effectiveness of different SSRI drugs be compared.

REFERENCES

1. Reis C, Akyol O, Ho WM, Araujo C, Huang L, Applegate R, Zhang JH. Phase I and Phase II Therapies for Acute Ischemic Stroke: An Update on Currently Studied Drugs in Clinical Research. Biomed Res Int. 2017; 2017:4863079. doi: 10.1155/2017/4863079. Epub 2017 Feb 14.
2. Chollet F, Cramer SC, Stinear C, Kappelle L, Baron JC, Weiller C, Azouvi P, Hommel M, Sabatini U, Moulin T, Tardy J, Valenti M, Montgomery S, Adams H Jr. Pharmacological therapies in post stroke recovery: recommendations for future clinical trials. J Neurol. 2014 Aug;261(8):1461-8. doi: 10.1007/s00415-013-7172-z. Epub 2013 Nov 13.
3. Baldwin K, Orr S, Briand M, Piazza C, Veydt A, McCoy S. Acute ischemic stroke update. Pharmacotherapy. Pharmacotherapy. 2010; 30(5):493-514. doi: 10.1592/phco.30.5.493.
4. Ong CT, Wong Y, Sung SF, Wu CS, Hsu YC, Su YH, Hung LC. Sex-related differences in the risk factors for in-hospital mortality and outcomes of ischemic stroke patients in rural areas of Taiwan. PLoS One. 2017 Sep 21; 12(9):e0185361. doi: 10.1371/journal.pone.0185361. eCollection 2017.
5. Ivica B, Gordan D, Iva L, Meri M and Kresimir C. Risk factors and outcome differences Between Ischemic and Hemorrhagic stroke. Acta clinica Croatica, 2009, 48(4):399-403.
6. Mumtaz AM, Muhammad U, Muhammad H . Stroke and its relationship to risk Factors. Gomal J Med Sci. 2009; 7(1): 17-20.
7. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018; 71(2):122-132. doi: 10.1016/j.jacc.2017.10.085.
8. Yoo J, Seo JJ, Eom JH, Hwang DY. Enhanced recovery from chronic ischemic injury by bone marrow cells in a rat model of ischemic stroke. Cell Transplant. 2015;24(2):167-82. doi: 10.3727/096368913X674666.
9. Hajjar K, Keer DM, Lees KR. Thrombolysis for acute ischemic stroke. J Vasc Surg. 2001; 54(3): 69-79.
10. Pariente J, Loubinoux I, Carel C, Albucher JF, Leger A, Manelfe C, Rascol O, Chollet F. Fluoxetine Modulates Motor Performance and Cerebral activation of patients

recovering from stroke. Ann Neurol. 2001; 50(6):718-29.
11. Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009; 256(7):1152-8. doi: 10.1007/s00415-009-5093-7. Epub 2009 Mar 22.
12. Menken M, Munsat TL, Toole JF. The global burden of disease study: implications for Neurology. Arch Neurol. 2000; 57(3):418-20.
13. Francois C , Jean T , Jean- Francois A , Claire T , Emilie B , Catherine L , et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet J neurol. 2011; 10(5): 123- 130.
14. Pinto CB, Saleh Velez FG, Lopes F, de Toledo Piza PV, Dipietro L, Wang QM, Mazwi NL, Camargo EC, Black-Schaffer R, Fregni F. SSRI and Motor Recovery in Stroke: Reestablishment of Inhibitory Neural Network Tonus. Front Neurosci. 2017; 11: 637. doi: 10.3389/fnins.2017.00637. eCollection 2017.
15. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B, Moulin T, Marque P, Pariente J, Arnaud C and Loubinoux I. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011 Feb; 10(2):123-30. doi: 10.1016/S1474-4422(10)70314-8.
16. Siepmann T, Kepplinger J, Zerna C, Schatz U, Penzlin AI, Pallesen LP, Illigens BM, Weidner K, Reichmann H, Puetz V, Bodechtel U, Barlinn K. The Effects of Pretreatment versus De Novo Treatment with Selective Serotonin Reuptake Inhibitors on Short-term Outcome after Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2015 Aug;24(8):1886-92. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.033. Epub 2015 Jun 19.
17. Dam M, Tonin P, De Boni A, Pizzolato G, Casson S, Ermani M, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke. 1996 Jul;27(7):1211-4.
18. He YT, Tang BS, Cai ZL, Zeng SL, Jiang X, Guo Y. Effects of Fluoxetine on Neural Functional Prognosis after Ischemic Stroke: A Randomized Controlled Study in China. J Stroke Cerebrovasc Dis. 2016 Apr;25(4):761-70. doi: 10.1016/j.jstrokecerebrovasdis.2015.11.035. Epub 2016 Jan 25.
19. Pleger B1, Schwenkreis P, Grünberg C, Malin JP, Tegenthoff M. Fluoxetine facilitates use- Dependent excitability of human primary motor cortex. Clin Neurophysiol. 2004; 115(9):2157-63.
20. Gerdelat-Mas A , Loubinoux I , Tombari D , Rascol O , Chollet F , Simonetta M ; Chronic Administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human Motor cortex excitability in healthy subjects. Neuroimage. 2005; 27(2):314-22.