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Fluoxetine for Motor Recovery After Acute Ischemic Stroke: A Randomized Placebo-Controlled Trial

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Abstract: Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials suggest that Fluoxetine enhances motor recovery but its clinical efficacy is unknown in our setting. A randomized placebo-controlled trial was conducted at Neurology and medicine ward of Chittagong Medical College Hospital from 1/1/2013 to 31/12/2013. One hundred and twenty eight patients, aged between 40-60 years with a diagnosis of acute ischaemic stroke who fulfilled the defined inclusion and exclusion criteria were selected for the study. Eligible patients were randomly assigned, using a simple lottery method, in a 1:1 ratio to Fluoxetine (20 mg once per day, orally) or placebo group for 3 months starting within 10 days after the onset of stroke. The primary outcome was the mean change in the Rivermead Mobility Index (RMI) score between inclusion (day 0) and day 90. RMI score was significantly changed from D 0 to D 90 in Fluoxetine group in comparison to placebo group (p<.001) and mean (±SD) improvement of RMI score in 90 days were significantly greater in the Fluoxetine group, than in the placebo group [7.08 (±3.26) vs. 4.40 (±2.53)]. Patients treated with Fluoxetine were nearly 3.2 times more likely to show motor improvement than placebo group and the NNT was 2. In patients with acute ischaemic stroke and with motor deficit, the early administration of Fluoxetine with physiotherapy enhanced motor recovery after 3 months.

Keywords: Fluoxetine, Ischaemic Stroke, Rivermead Mobility Index (RMI), NNT: Number Needed to Treat

1. Introduction

Stroke is caused by either a sudden reduction in the blood supply to the brain or by a hemorrhage. An acute stroke refers to the first 24-hour-period of a stroke event. Most strokes (87%) are ischaemic and the rest (13%) are hemorrhagic. Stroke is the second leading cause of disability in Europe after ischaemic heart disease (IHD) and is the sixth leading cause worldwide. The prevalence of stroke events is expected to increase across the globe as the global population aged over 65 increases [1, 2]. Motor deficits are common after stroke (82% of patients) and are linked with reduced quality of life [3]. At 6 months after stroke, 65% of patients are unable to incorporate a paretic hand effectively into daily activities, which affects subjective well-being. Moreover, even when neurological examination declares the patient wholly recovered, 71% of patients report persistent motor deficits when studied using patient-reported outcomes. Lower extremity motor status is also linked with disability level. Only 37% of persons with stroke can walk after the first week post stroke, after which gait improvement is linked to better quality of life. Hemiplegic patients rank recovery of gait as their top priority [4].

Among the therapeutic strategies under study to improve

long-term outcome after stroke are drugs targeting events that underlie recovery. Drugs that enhance recovery are separate from those that promote neuroprotection or reperfusion in patients with stroke. The value of specific rehabilitation therapies aimed at assisting adaptation to impairment is now well recognized, but therapeutic strategies designed to restore function by minimizing impairment are by comparison poorly developed. Recovery-based drugs have distinct therapeutic targets that are related to plasticity and growth after stroke, and in general, improvements in behavioral outcome are not accompanied by a reduction in infarct volume. Till now, there are no drugs approved in the United States to enhance motor recovery after stroke. For at least 2 classes of drug, serotonergic and dopaminergic, both of which are monoaminergic, existing evidence from human studies supports the possibility for enhancing motor outcome after stroke.
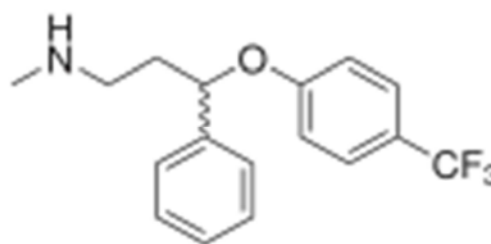
Serotonin normally plays a role in modulating multiple cognitive functions, particularly response inhibition and memory consolidation, and modulates the impact of punishment-related signals on learning and emotion [5-7]. Recent reports suggest potential clinical utility of selective serotonin reuptake inhibitor (SSRI) drugs for promoting improved motor outcome after stroke. Building on several prior smaller studies, [8-10] the Fluoxetine for Motor Recovery after Acute Ischaemic Stroke (FLAME) study was a double-blind, placebo-controlled trial that enrolled non depressed hemiplegic/hemiparetic patients within 10 days of ischaemic stroke onset. Patients were randomized to 3 months of oral fluoxetine (20 mg/d) or placebo. Patients randomized to fluoxetine showed significantly greater gains on the primary end point, change in the arm/leg Fugl–Meyer motor score to day 90 (P=0.003), a remarkable difference of 9.7 points on this 100-point scale [11].

Several different mechanisms might account for these findings. The central mechanism of action for SSRI drugs in the treatment of major depression is via their high affinity for the serotonin transporter; drug binding to the transporter inhibits serotonin removal from the synaptic cleft, with long-term SSRI administration down regulating and desensitizing key serotonin receptors, thereby dampening negative feedback on serotonin release [12]. Other suggested mechanisms of action for SSRI drugs include reducing neural inflammation, enhancing neurotrophin activity, and increasing eurogenesis. Chronic SSRI dosing increases intracortical facilitation and reduces intracortical inhibition, and these changes have been compared with reinstating conditions of developmental critical periods. In addition, serotonin modulates spinal motor control through multiple effects on spinal motor circuits, including regulation of rhythmic activity and control of excitability, by acting on intrasynaptic and extrasynaptic receptors; this may help locomotor function [13-16]. Motor excitability is increased in both hemispheres in stroke patients during motor recovery, In particular, it has been suggested that antidepressant drugs can modulate motor excitability. Acler M et al. investigated motor area excitability in patients with stroke after oral administration of citalopram through transcranial magnetic stimulation. Their findings suggest that treatment with serotonergic drugs can bring about a significant decrease of the motor cortex excitability in stroke patients with effects on both the affected and unaffected hemispheres associated with a better motor recovery [17].

There is very limited number of study regarding evaluation of long term use of Fluoxetine over motor function among stroke patients in the context of Bangladesh. So it is a good opportunity to do a study in this context. The aim of this study was to test whether a 3-month treatment with Fluoxetine would enhance motor recovery when given early after an ischaemic stroke to patients with moderate to severe motor deficits.

Pharmacology of Fluoxetine [18, 19].

Fluoxetine is the prototypic drug of the group of selective serotonin reuptake inhibitors (SSRIs) which are chemically diverse antidepressant that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately to greater postsynaptic neuronal activity. These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.

The primary indication for Fluoxetine is depression. A number of other psychiatric disorders also respond favorably to Fluoxetine, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual disorder, and bulimia nervosa.

Adverse effects: Although the Fluoxetine is considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the Fluoxetine is not without troublesome adverse effects, such as headache, sweating, anxiety and agitation, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug-drug interactions.

Action on stroke patient: Fluoxetines have been used in the treatment of stroke patients, including those with and without symptoms of depression. In a study, Lim CM et al. tested whether Fluoxetine protects neuronal death in a rat cerebral ischemia model of middle cerebral artery occlusion (MCAO). The administration of Fluoxetine intravenously (10 mg/kg) at 30 min, 3 hr, or 6 hr after MCAO reduced infarct volumes to

21.2 ± 6.7%, 14.5 ± 3.0%, and 22.8 ± 2.9%, respectively, of that of the untreated control. Moreover, the neuroprotective effect of Fluoxetine was evident when it was administered as late as 9 hr after MCAO/reperfusion. These neuroprotective effects were accompanied by improvement of motor impairment and neurological deficits. The Fluoxetine-treated brain was found to show marked repressions of microglia activation, neutrophil infiltration, and proinflammatory marker expressions. Moreover, Fluoxetine suppressed NF-κB activity dose-dependently in the post ischaemic brain and also in lipopolysaccharide-treated primary microglia and neutrophil cultures, suggesting that NF-κB activity inhibition explains in part its anti-inflammatory effect. These results demonstrate that curative treatment of Fluoxetine affords strong protection against delayed cerebral ischaemic injury, and that these neuroprotective effects might be associated with its anti-inflammatory effects [20].

2. Material and Methods

A randomized placebo controlled trial was conducted from 1/1/2013 to 31/12/2013. Patients who had an acute ischaemic stroke within 10 days after the incidence that cause hemiparesis or hemiplegia with radiologically verified lesion get admitted to neurology and medicine ward or referred to Neurology OPD of CMCH.

Selection criteria included radiologically (C. T scan of Head) documented ischaemic stroke, have definite motor deficit- hemiplegia, age between 40 to 60 years and ischaemic stroke within 10 days. Exclusion criteria are H/O previous stroke, patient with known depressive illness and on antidepressant, global or sensory Aphasia(Masking detection and assessment of depression),unconscious patients, terminally ill patient, having other severe medical(IHD), or pregnancy which may prevent follow-up. Study populations were selected after fulfilling the selection criteria. All patients were informed about the treatment options and written witnessed consent was taken from the patients or attendance whichever was applicable. Then the patients were allocated randomly to group A and group B. Group A patient was given placebo with physiotherapy and group B patients was given Fluoxetine with physiotherapy. Patient who died or withdrawn from the study within the study period were

considered as dropped out. Then assessment of motor functional deficit at base line using Rivermead Mobility Index scale was done and improvement was assessed on follow up. During assessment of motor recovery patient was assessed in relation with movement in bed, lying to seating capacity, standing ability, walking ability, picking ability, bathing and running capacity. Follow up was done on day 30 and day 90. Mobile phone or telephone number of the patient or first degree relatives was preserved for further communication.

3. Data Processing and Analysis

All the data were checked and edited after collection. The primary outcome was analyzed using the intention to treat (ITT) method. The full analysis set for the ITT method was include all randomized subjects, regardless of their subsequent withdrawal after enrollment. Continuous variables were reported as the means ± SD, and categorical variables were reported as percentages. Baseline characteristics were compared by either Student's t-test for continuous variables or the χ^2 test (Fisher's exact test when the expected value is <5) for categorical data. The primary analysis for efficacy (full-analysis set) was consisted of a comparison of the change in RMI scores at 90 days. To handle the missing data derived from withdrawal and lost to follow-up patients, the series mean value was used for the analysis. A binary logistic regression analysis was performed to control for baseline factors. Statistical significance was defined as P < 0.05 and confidence interval set at 95% level. SPSS (Statistical Package for Social Science) for Windows version 15.0 software was used for the analyses.

4. Result and Observation

4.1. Patterns of Risk Factors Among the Patients in Respect to Study Group

In respect to risk factors of ischaemic stroke both the study groups are similar. There was no significant difference between Fluoxetine and placebo groups in respect of presence or absence of HTN, DM, smoking history, hyperlipidaemia, family history of stroke (Table 1).

Table 1. Pattern of risk factors among the study groups.

Risk Factors		Study Group				Total		Test Statistics
		Group A		Group B				
		N	%	n	%	n	%	
Hypertension	Present	34	51.5	32	48.5	66	51.6	P = 0.724
	Absent	30	48.4	32	51.6	62	48.4	
Diabetes Mellitus	Present	17	41.5	24	58.5	41	32.0	P = 0.185
	Absent	47	54	40	46	87	68.0	
Smoking history	Present	19	50	19	50	38	29.7	P = 1.00
	Absent	45	50	45	50	90	70.3	
Hyperlipidemia	Present	03	60	02	40	05	3.9	P = 0.648
	Absent	61	49.6	62	50.4	123	96.1	
Family History	Present	05	37.8	09	64.3	14	10.9	P = 0.252
	Absent	59	51.8	55	48.2	114	89.1	

4.2. Patterns of Neurological Findings Among the Patients in Respect to Study Group

In respect to neurological findings at presentation both the study groups are similar. There was no significant difference between Fluoxetine and placebo groups in respect to Speech, higher cerebral function and motor function (Table 2).

Table 2. Distribution of neurological findings among the study groups.

Neurological Findings		Study Group				Total		Test statistics
		Group A		Group B				
		N	%	N	%	n	%	
Speech	Normal	49	52.7	44	47.3	93	72.7	
	Aphasia	06	40.0	09	60.0	15	11.7	P = 0.586
	Dysarthria	09	45.0	11	55.0	20	15.6	
Higher Cerebral Function	Oriented	64	50.0	64	50.0	128	100.0	**
	Disoriented	00	00	00	00	00	0.0	
Motor Difficulties	Present	64	50.0	64	50.0	128	100.0	**
	Absent	00	00	00	00	00	0.0	

** No statistics were calculated because Higher Cerebral Function & Motor Difficulties are constant.

4.3. Improvement of Motor Function in Relation to Study Groups

Table 3 shows the difference of motor recovery in Fluoxetine and placebo groups at day 0, 30 and 90 days.

There is statistically significant difference of the mean RMI scores between Fluoxetine and placebo group at 90 days. The Effect Size by standardized Mean Difference (SMD) was 0.55 (Moderate Effect Size as per Cohen's d).

Table 3. Rivermead mobility index at Day 0, 30 & 90 among the study groups.

		MEAN	± SD	RANGE	P value
Rivermead Mobility Index At Day 0	Group A (n=64)	0.89	1.74	0 – 10	
	Group B(n=64)	1.23	1.67	0 – 7	0.256
	TOTAL	1.06	1.71	0 – 10	
		MEAN	± SD	RANGE	
Rivermead Mobility Index At Day 30	Group A(n=54)	2.43	2.64	0 – 15	0.058
	Group B(n=56)	3.34	2.36	1 – 11	
	TOTAL	2.89	2.53	0 – 15	
		MEAN	± SD	RANGE	
Rivermead Mobility Index At Day 90	Group A(n=50)	4.40	2.53	2 – 15	
	Group B(n=49)	7.08	3.26	3 – 14	<0.001
	TOTAL	5.73	3.20	2 – 15	

4.4. Pattern of Muscle Power Improvement Among the Study Group

Muscle power is significantly improve in Fluoxetine group both at day 30 and day 90 in comparison to inclusion day, but not in placebo group (Table 4).

Table 4. Changes of muscle power over time in relation with day 0.

Group	Evaluation day	Muscle power	N	Mean	±SD	P value
B (Fluoxetine)	Day 30 (n=56)	Score ≤2	43	0.49	0.45	.001
		Score >2	13	2.38	0.165	
	Day 90 (n=49)	Score ≤2	36	0.88	0.07	.001
		Score >2	13	2.00	1.335	
A (Placebo)	Day 30 (n=54)	Score ≤2	47	1.70	0.267	.063
		Score >2	7	2.00	0.225	
	Day 90 (n=50)	Score ≤2	40	1.82	0.353	.078
		Score >2	10	2.33	1.155	

4.5. Calculation of Effect Size Measures (Interest in Favorable Cases)

Table 5. Motor improvement between Fluoxetine vs. placebo group.

Patient category	Motor improvement at 90 days		Lost to follow-up	Total
	>4 in RMI	≤4 in RMI		
Fluoxetine	39 (a)	10 (b)	15	64
Placebo	12 (c)	34 (d)	14	64

Case analyzed	ERR*a/(a+b)	CER* c/(c+d)	ABI/ARR* (ERR-CER)	NNT* (1/ARR)	RR* (ERR/CER)	RRR* (1-RR)
A. Base case: Ignoring loss to follow-up cases						
	79.59%	24%	55.59%	1.8(2)	3.32	-2.32
B. Worst case: Lost experimental subjects do poorly and control subjects do well						
	60.94%	40.63%	20.31%	4.9(5)	1.49	-.51
C. Intention to treat analysis: Replacing the missing value by series mean						
	84%	38%	46%	2.2(3)	2.21	1.22

ERR: Experimental Event Rate, CER: Control Event Rate, ARR/ ABI: Absolute Risk Reduction/ Absolute Benefit Increase, NNT: Number Needed to Treat, RR: Relative Risk, RRR: Relative Risk Reduction.

5. Discussion

A positive effect on motor recovery was noted in patients with acute ischaemic stroke who were treated with Fluoxetine for three months in the present study. This effect was assessed as a change in RMI score between day 0 and day 90. Recently, the use of antidepressant drugs as an adjunctive treatment to augment recovery in stroke patients has been studied in small clinical trials [8, 10, 17, 2]. Fluoxetine is a selective serotonin reuptake inhibitor that is widely used in the treatment of major depression including after stroke. It was established in different preclinical studies that Fluoxetine protects neuronal death following ischemia. These neuroprotective effects were accompanied by improvement of motor impairment and neurological deficits. The Fluoxetine-treated brain was found to show marked repressions of microglia activation, neutrophil infiltration, and proinflammatory marker expressions. Moreover, fluoxetine suppressed NF-kappa B activity dose-dependently in the post ischaemic brain and also in lipopolysaccharide-treated primary microglia and neutrophil cultures, suggesting that NF-kappa B activity inhibition explains in part its anti-inflammatory effect. These results demonstrate that curative treatment of Fluoxetine affords strong protection against delayed cerebral ischemic injury, and that these neuroprotective effects might be associated with its anti-inflammatory effects [22].

In 2011, Chollet and colleagues tested adjunctive treatment with Fluoxetine in addition to physical rehabilitation to improve motor recovery from cerebral infarct, with excellent results [11]. In the present study, intervention and control groups were similar in respect of sex, age, locality, nature of work and socioeconomic status. In a study done in Chittagong Bangladesh by Kyastagir et al. found among 59 study patients, male patient was 39(66.6%) and female was 20 (33.3%). [23] In Bangladesh usually males are the privileged gender and get more attention than the female. Also stroke are less common in females during child bearing time. Age group was found similar in the same study done in Chittagong by Kyastagir et al. regarding risk factors of ischaemic stroke hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, family history were found among the study population. However, no significant difference was found between two groups regarding the distribution of risk factors. Stroke is a common atherosclerotic vascular disease and above risk factors is common all over the world [22].

6. Conclusion

The world health organization defines stroke as "the rapidly developing clinical symptoms and/ or signs of focal (at times global) disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" [24].

Among white population in the USA and Canada, the annual incidence rate is between 1 and 2 per 1000 and the prevalence rate is between 4 and 6 per 1000, but the exact figure depends on the age structure of the population under consideration. Japan has the highest death rate. About 25% of death of Japanese men and women of all ages are due to CVA, while for the USA and the corresponding figure is around 10%. [25]

In Bangladesh, there is few data on the incidence of and mortally from stroke in the community. In one study in Dhaka medical college hospital, stroke has been shown as the second commonest cause of emergency admission in the medicine wards and constituted about 10-12% of the total patients in these wards, In another two studies in Chittagong Medical College Hospital and Diabetic Hospital, Dhaka, 2.00 percent and 5.87 percent of the admitted patients, respectively, were suffering from the stroke [23, 26].

In patients with acute ischaemic stroke and with motor deficit, the early administration of Fluoxetine with physiotherapy enhanced motor recovery after 3 months.

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