Fluoxetine for Anterior Ischemic Optic Neuropathy (AION); a Double Blind Randomized Clinical Trial

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Research Article

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Abstract

Background: Fluoxetine enhances the levels of brain-derived neurotrophic factor (BDNF); considering its known improving effects on neurogenesis and plasticity, it seems to improve the Anterior Ischemic Optic Neuropathy (AION). This study aimed to evaluate the effect of Fluoxetine on clinical prognosis of patients with AION.

Methods: In this double-blind placebo-controlled randomized clinical trial, subjects with AION who were referred to Rasool Akram Hospital were divided into two study groups; the fluoxetine group that received 20 mg Fluoxetine daily(n=50) and the control group (n=50) that received placebo for a period of six months. Patients underwent clinical and paraclinical evaluations before and after the trial. This study was a registered trial with IRCT code IRCT20181109041596N1.

Results: One hundred patients were enrolled from August 2019 to December 2020 and assessed in this study. Subjects in Fluoxetine group showed significant improvement in visual acuity in comparison to the placebo group with less score in LogMAR scale (P: 0.008 and 0.002, respectively), improvement in MD parameters of perimetry (P: 0.003 and 0.002, respectively), and decrease in VEP latencies (P (in 1st minute): <0.001 and <0.001, P (in 15st minute): 0.038 and 0.011, respectively). There were no differences in color vision, Rnfl in all dimensions, PSD parameter of perimetry or VEP amplitudes following the trial of Fluoxetine therapy (Ps> 0.05).

Conclusion: Fluoxetine showed promising therapeutic value for patients with AION besides its safety as an additive treatment option to corticosteroids.

Introduction:

Brain-derived neurotrophic factor (BDNF) is believed to play a prominent role in the augmentation of neuronal repair, plasticity, and re-establishment of axonal interactions in nervous tissues including the retina; where it increases in concentration in case of neurodegenerative disorders involving the optic nerve [1],[2][3][4]. Fluoxetine, an antidepressant SSRI have the potential to increase levels of BDNF [5]. Furthermore, Fluoxetine has proper pharmacologic distribution into the retina [6]. Glaucoma and cataracts are among reported side effects of Fluoxetine [7][8]. Fluoxetine should be given at least 6 months to reach its optimal clinical efficacy [9]. Fluoxetine therapy improves functional outcomes, motor performance, Poststroke Anxiety, Depression, and Cognitive Impairment, besides decreasing three-year recurrence in ischemic stroke by the potentiation of neuroplasticity and neurogenesis [10–16]. However, some studies disagree with the clinical efficacy of Fluoxetine in patients with ischemic stroke [17–19]. Fluoxetine has also showed to achieve significant clinical improvement and a more desired prognosis in patients with multiple sclerosis (MS) [20]. Furthermore, Fluoxetin has improved vision in patients with amblyopia likely by improving neuroplasticity in the visual cortex [21] although, another study has opposed its therapeutic

efficacy in amblyopia [22]. Fluoxetine has also been efficient in improving cognitive performance in patients with vascular dementia [23].

Although, Fluoxetine has the potential to increase serum levels of BDNF, it seems to be effective in neurogenesis in the optic nerve and potentiation of plasticity in the visual cortex; hence, the therapeutic effect of Fluoxetine in Anterior Ischemic Optic Neuropathy (AION) by induction of neuronal repair gives us the idea to perform this study in order to assess the effect of Fluoxetine in the clinical prognosis of patients with AION.

Methods And Materials:

This double-blinded randomized clinical trial was aimed to assess the effects of Fluoxetine on the clinical prognosis of patients with non-arteritic Anterior Ischemic Optic Neuropathy (AION).The study population consisted of patients with non-arteritic AION who were referred to Rasool Akram Hospital, Ophthalmology Clinic. Eligible participants were asked to sign the consent form to participate in the study. Inclusion criteria were patients diagnosed with AION with an age of 18 years old and above while the exclusion criteria were over 3 weeks of latency from the beginning of symptoms, visual impairment correlated to other diseases but not due to AION, pregnancy and or being pregnant during the clinical trial, history of using psychiatric drugs with the inclusion of Fluoxetine, and any history of eye trauma or any surgical interventions. Subjects that met the inclusion criteria were randomly selected into 2 groups; the Fluoxetine group were given Fluoxetine capsule 20mg daily for six months and the control group who received placebo. Subjects were evaluated in the initial phase of the clinical study and on the 6th month of the clinical trial, demographic data were obtained through a questionnaire and baseline physical examination was done to assess visual acuity (examed by Snellen chart), IOP (measured by Goldmann tonometer), biomicroscopy with the use of a slit lamp in order to assess for any evidence of cataracts, VEP (Visual evoked potential) assessed by EvokeDx NextGen icVEP to measure both latencies and amplitudes in 1st and 15th minutes, perimetry test which was performed using Carl Zeiss Meditec device, and Rnfl in all dimensions using OCT (optic coherence tomography) which was assessed by Optovu-heidelberg.

Both patients and investigators were unaware of the type of medication received by patients to provide double blinding of the trial. Block randomization using 25 quaternary blocks was used. Concealment was preserved by placing patients in the study groups according to the order of the randomization list.

Analysis

Statistics of quantitative data are presented by means and standard deviations or medium and interquartile ranges and qualitative data are presented by frequencies. For comparison of quantitative variables between study groups, student independent samples T-test or its non-parametric equivalent, Mann-Whitney U test was used while compared T-test or its non-parametric equivalent, Wilcoxon test was used in order to compare the results before and after treatment in each group. For comparison of parameters between study groups, possible confounding biases by baseline characteristics were

addressed by covariance analysis (Bootstrapping for non-parametric data). Sample size was determined 45 cases in each group using G power by consideration of the effect size d : 0.6, alpha error equal to 5 % and power equal to 80%. 10 percent lost to follow up was predicted and 50 patients in each of the two study groups was considered. P-value equal or less than 0.05 was considered statistically significant. IBM statistics SPSS version 22 was used for obtaining statistical analysis.

Results:

One hundred patients with Anterior Ischemic Optic Neuropathy (AION) were enrolled 50 in each of the two study groups from August 2019 to December 2020 (64 males and 36 females) with a mean age of 58.62 ± 12.13 years old. Demographic data are represented in Table 1.

Table 1
Descriptive statistics of baseline parameters and their comparison between study groups

Parameter (#\%)		All cases	Study Group		P-value [a]
			Drug	Placebo	
Age (Mean ± SD/ Q1,Median,Q3)		58.62 ± 12.13	56.68 ± 11.24	60.56 ± 12.79	0.110 [b]
Sex	Male	64 (64%)	36 (72%)	28 (56%)	0.096 [c]
	Female	36 (36%)	14 (28%)	22 (44%)	
Profession	Labor	56 (56%)	30 (60%)	26 (52%)	0.420 [c]
	clerical	44 (44%)	20 (40%)	24 (48%)	
Smoking	Smoker	33 (33%)	21 (42%)	12 (24%)	0.056 [c]
	Non-smoker	67 (67%)	29 (58%)	38 (76%)	
Alcohol	Drinker	13 (13%)	7 (14%)	6 (12%)	0.766 [c]
	Non-drinker	87 (87%)	43 (86%)	44 (88%)	
Opium	Abuser	11 (11%)	7 (14%)	4 (8%)	0.338 [c]
	Non-abuser	89 (89%)	43 (86%)	46 (92%)	
First presentation	Pain	11 (11%)	5 (10%)	6 (12%)	0.749 [c]
	Vision loss	89 (89%)	45 (90%)	44 (88%)	
Family Hx of AION	Positive	20 (20%)	12 (24%)	8 (16%)	0.317 [c]
	Negative	80 (80%)	38 (76%)	42 (84%)	
HTN Hx	Positive	34 (34%)	16 (32%)	18 (36%)	0.673 [c]
	Negative	66 (66%)	34 (68%)	32 (64%)	
DM Hx	Positive	42 (42%)	25 (50%)	17 (34%)	0.105 [c]
	Negative	58 (58%)	25 (50%)	33 (66%)	
IHD Hx	Positive	29 (29%)	17 (34%)	12 (24%)	0.271 [c]
	Negative	71 (71%)	33 (66%)	38 (76%)	
CVA Hx	Positive	2 (2%)	0 (0%)	2 (4%)	0.495 [d]
	Negative	98 (98%)	50 (100%)	48 (96%)	
HLP Hx	Positive	23 (23%)	11 (22%)	12 (24%)	0.812 [c]
	Negative	77 (77%)	39 (78%)	38 (76%)	

Parameter (#\%)	All cases	Study Group		P-value [a]
		Drug	Placebo	

Hx: History, AION: Anterior Ischemic Optic Neuropathy, HTN: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Diseases, TIA: Transient Ischemic Attack, CVA: Cerebrovascular accidents, HLP: Hyperlipidemia

a: comparison between study groups; b: Independent samples T-test; c: Chi-square test d: Fischer exact test

Patients in both groups were equal in baseline characteristics such as age, sex, occupation (laborer or clerical jobs), history of smoking, alcohol abuse, opium abuse, hypertension (HTN), Diabetes Mellitus (DM), Ischemic Heart Diseases (IHD), Cerebrovascular Accidents (CVA) and hyperlipidemia (P-values > 0.05) [Table 1].

Vision loss was the initial presentation of AION in 89% of patients while 11% of patients expressed globe pain as the first presentation. Family history of AION was positive in 20% of cases [Table 1].

Visual acuity score, color vision score, perimetry parameters (MD and PSD), Rnfls in all six dimensions (Nasal, superonasal, superotemporal, temporal, inferotemporal, and inferonasal), VEP amplitudes and latencies on 1st and 15th minutes, and intraocular pressure (IOP) were equal in the baseline measurements between study groups (P-value > 0.05).

Visual acuity score in the LogMAR scale was significantly lower among the Fluoxetine group in the final evaluation in comparison to the baseline result (P-value: 0.008) and in comparison to the final evaluation result of the placebo group (p-value: 0.002). There was no significant difference noted on the visual acuity score of the placebo group before and after the trial (P-value: 0.132) [Table 2]. Also, no significant difference was noted on the color vision on the two groups before and after the trial (P-values > 0.05) [Table 2]. MD parameter in perimetry was statistically significant which is near zero among the Fluoxetine group on the final evaluation in comparison to the preliminary assessment (P-value: 0.003) and in comparison to the final result of the placebo group (P-value: 0.002). No significant improvement was observed on MD parameter on the placebo group (P-value: 0.801. Also, no significant difference was noted on the PSD parameter in perimetry on the Flouxetine group in the final assessment in comparison to the baseline assessment (P-value: 0.217) and in comparison to the final result of the placebo group (P-value: 0.093). The PSD parameter showed no significant improvement in the placebo group too(P-value: 0.076)[Table 2].

Table 2
Descriptive statistics of clinical parameters and comparison between study groups

Parameter (Mean ± SD/ Q1,Median,Q3)			Study Group		P-value [a]	P-value [b]	P-value [c]
			Drug	Placebo			
VA		1st visit	0.78,0.94, 1.30	0.85, 0.94, 1.3	0.312 [d]	0.008 [e]	0.132 [e]
		End of 6th month	0.78 ± 0.33	0.85, 1.00, 1.00	0.002 [d]		
Color vision		1st visit	1.00, 1.00, 4.00	1.00, 1.00, 4.00	0.194 [d]	0.927 [e]	0.502 [e]
		End of 6th month	1.00, 2.00, 3.00	1.00, 2.00, 3.25	0.861 [d]		
Perimetry MD		1st visit	− 23.55 ± 4.86	− 22.07 ± 5.33	0.171 [f]	0.003 [g]	0.801 [g]
		End of 6th month	− 20.07 ± 3.53	− 22.87 ± 4.75	0.002 [f]		
Perimetry PSD		1st visit	8.25 ± 2.81	5.14, 8.62,12.07	0.669 [d]	0.217 [g]	0.076 [g]
		End of 6th month	6.74 ± 3.08	8.04 ± 2.69	0.093 [f]		
Rnfl	Nasal	1st visit	106.76 ± 38.11	63.00, 107.00, 145.00	0.896 [f]	0.732 [g]	0.759 [e]
		End of 6th month	108.63 ± 33.14	104.71 ± 34.82	0.604 [f]		
	Superonasal	1st visit	95.05 ± 35.06	91.80 ± 31.84	0.661 [f]	0.139 [g]	0.112 [e]
		End of 6th month	105.65 ± 29.67	67.25, 92.50, 140.25	0.383 [d]		
	Superotemporal	1st visit	111.79 ± 36.23	114.88 ± 32.89	0.685 [f]	0.678 [g]	0.403 [e]
		End of 6th month	107.80 ± 30.27	68.00, 97.00, 147.75	0.666 [d]		
	Temporal	1st visit	117.12 ± 36.23	78.00, 129.00, 145.50	0.957 [f]	0.662 [e]	0.301 [e]

Parameter (Mean ± SD/ Q1,Median,Q3)			Study Group		P-value [a]	P-value [b]	P-value [c]
			Drug	Placebo			
		End of 6th month	86.25, 101.00, 143.75	73.00, 89.50, 142.00	0.186 [d]		
	Inferotemporal	1st visit	106.40 ± 36.12	117.63 ± 41.31	0.191 [f]	0.940 [g]	0.566 [e]
		End of 6th month	106.08 ± 32.56	73.75, 100.00, 149.00	0.714 [d]		
	Inferonasal	1st visit	116.38 ± 39.93	127.41 ± 46.84	0.251 [f]	0.534 [e]	0.124 [e]
		End of 6th month	82.25, 97.00, 131.25	70.25, 93.00, 161.25	0.864 [d]		
VEP latency 1 minute		1st visit	96.14, 99.85, 124.22	102.34, 106.55, 117.97	0.205 [d]	< 0.001 [e]	0.121 [e]
		End of 6th month	97.72 ± 18.05	112.68 ± 16.88	< 0.001 [f]		
VEP amplitude 1 minute		1st visit	5.35, 7.09, 8.66	5.24, 6.58, 8.91	0.799 [d]	0.409 [e]	0.079 [e]
		End of 6th month	3.44, 7.46, 9.26	6.16 ± 2.89	0.292 [f]		
VEP latency 15 minutes		1st visit	109.65, 119.59, 132.77	102.22, 120.05, 139.03	0.912 [d]	0.038 [e]	0.160 [e]
		End of 6th month	101.95 ± 23.10	89.83, 122.99, 138.69	0.011 [f]		
VEP amplitude 15 minutes		1st visit	2.32, 4.15, 8.85	3.66, 4.93, 7.41	0.138 [d]	0.907 [e]	0.189 [e]
		End of 6th month	6.56 ± 3.07	3.99, 5.73, 8.89	0.749 [f]		
IOP		1st visit	13.00, 15.00, 16.00	13.00, 15.00, 16.00	0.660 [d]	0.967 [e]	0.353 [e]
		End of 6th month	12.75, 14.00, 15.00	12.00, 14.00, 15.00	0.855 [d]		

Parameter (Mean ± SD/ Q1,Median,Q3)	Study Group		P-value a	P-value b	P-value c
	Drug	Placebo			

a: Compare between Drug and Placebo study groups; b: Compare between before and after of parameters between Drug group subjects; c: Compare between before and after of parameters between Placebo group subjects; d: Mann-Whitney U test ; e: Wilcoxon test; f: independent samples T-test; g: Paired samples T-test

Latencies in 1st and 15th minutes in the assessment of VEP were both statistically significantly, lower among Flouxetine group in thefinal assessment compared to their preliminary results (P-values: <0.001 and 0.038, respectively) and in comparison to the placebo group's final result (P-values: < 0.001 and 0.011, respectively). Results indicated that no significant difference was noted in optic nerve latencies on the placebo group before and after the trial (P-values: 0.121 and 0.160, respectively). Also, no significant difference was noted of the Amplitudes in 1st and 15th minutes visual disability assessment by VEP in the Fluoxetin group before and after the clinical trial (P-values: 0.409 and 0.907, respectively) nor to the placebo group's final result (P-values: 0.292 and 0.749, respectively) [Table 2].

Results of Rnfl assessment in all six dimensions using OCT (optic coherence tomography) indicated no significant difference between the preliminary and final evaluation results on both groups (P-values > 0.05)[Table 2].No significant changes were noted in the IOP on both Flouxetine and placebo groups in the baseline and final assessments (P-value > 0.05)[Table 2].

Adverse effects such as glaucoma or cataracts were not reported by any of the Flouxetine group, but some participants reported mild drowsiness or insomnia and there was no lost to follow up.

Discussions:

This study has found Fluoxetine as a safe complement therapeutic option in Anterior Ischemic Optic Neuropathy (AION) with promising improvements in their clinical prognosis.

Since there were no noted serious side effects of Fluoxetine, it seems to be a safe treatment strategy to complement with corticosteroids. However, Fluoxetine has shown improvements in visual acuity, perimetry, and VEP latencies, there were no statistically significant changes in VEP amplitudes, color vision, or Rnfls. Overall, the improvements observed especially in visual acuity are enough evidence to support the desirable effect of Fluoxetine in the prognosis of patients with AION.

The equality of the baseline characteristics such as demographic parameters were ensured and confounding biases were addressed by covariance analysis.

Serum levels of BDNF as a neuroprotective factor increases in case of pathologies involving the optic nerve [1]. Fluoxetine is a BDNF inducer involved in neuronal plasticity and neuroregeneration besides its high penetration into the retina [2][5][7]. Previous studies have showed improvements in visual cortex

plasticity and re-establishment of axonal interactions by Fluoxetine leading to desired clinical efficacy in Amblyopia and improvement in vision [3][4][21].

Since AION is an ischemic disease that involves neural tissue of the retina, therefore, AION is comparable to ischemic stroke in its pathophysiology. Fluoxetine has been reported as an effective treatment option for improving the post-stroke motor function by the acceleration of the neurogenesis and neuroplasticity [11][14–16] [24]. Cognitive performance has improved and three-year recurrence in stroke patients has decreased by Fluoxetine [10][12]. However, some studies have disagreed to the efficacy of Fluoxetine in stroke patients [17–19]. It should be considered that the therapeutic effectiveness of Fluoxetine widely depends on the early initiation of treatment upon the manifestation of symptoms [16]. Fluoxetine has also been effective in improving the clinical prognosis in patients with vascular dementia and multiple sclerosis as examples of other neurodegenerative disorders [20][23]. Futher studies should be considered regarding the effectiveness of Fluoxetine in AION on the early iniation of treatment upon the initial manifestation of symptoms.

Conclusion:

Fluoxetine is a safe complement therapeutic option in Anterior Ischemic Optic Neuropathy (AION) with promising effects on clinical prognosis.

Declarations:

Ethics approval and consent to participate

This study is approved by Ethics Committee of Vice Chancellor for Research & Technology, IUMS (code: IR.IUMS.FMD.REC.1397.093). This study was a registered Trial in 07/01/2019 with IRCT code IRCT20181109041596N1. All patients and control subjects signed the informed consent. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (2013) and its subsequent amendments.

Consent for publication

Informed consent was obtained from all patients whom clinical data were reported in this article to participate in the study and assessments.

Availability of data and materials

The datasets generated during and analyzed during the current study are not available publicly because it is collected on the data repository of the eye research center of Rasool Akram hospital which are intended to be reused in another study too but are available from the corresponding author on reasonable request

Conflicting interest/Competing interests

Authors of this study mentioned no conflicting or competing interests in the subject matters of this article.

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Authors' contributions

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