Original Article

Escitalopram Improves Cognition Function in the Ischemic Stroke Patients

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Abstract

Background & Aims: Cognition impairment is a common manifestation of ischemic stroke patients. The cognition function is modulated by serotonin levels in the brain. The serotonin levels of brain are changed during ischemic stroke. Therefore, we hypothesis that intervention in serotonin reuptake may improve the cognition function in the patients. We evaluated and compared the effect of escitalopram and fluoxetine on ischemic stroke patients.

***Materials & Methods*:** A hundred patients whose ischemic stroke was confirmed by neurologist were enrolled in this interventional study at Imam Khomeini Hospital, Urmia, Iran. All treatments and interventions performed based on a standard approach. The first group received escitalopram(10 mgd/day) as an adjuvant treatment and second group received fluoxetine (10 mgd/day). The cognition function of the patients was measured by Dementia Rating Scale (DRS) in the 5th and 95th days after final diagnosis. Statistical analysis was carried out using IBM SPSS Statistics software version 23.

***Results*:** In this study about 54.1% of patients were female and the rest 45.9% were male. Gender and smoking had no influence on cognition function. There was no difference in the cognition function of the patients with posterior and anterior circulation impairment. Our finding showed escitalopram but not fluoxetine improved the cognition function significantly (p=0.032). Age and creatinine levels had a significant correlation with cognition function before(DRS1) and after (DRS2) treatment and with their difference(DRS2-DRS1). While serum urea levels were correlated with the difference of DRS before and after treatment (Pearson correlation, -.318, -.397 and P= 0.026, 0.005 respectively)

***Conclusion*:** The results of this study recommends that escitalopram can be used as an adjuvant medicine to improve the cognition function in the ischemic stroke patients. The creatinine and urea levels may be a good biomarker to prescribe escitalopram in the ischemic stroke patients.

Keywords: Cognition; Escitalopram; Fluoxetine; Ischemic Stroke

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Introduction

Ischemic stroke is a one of most come central nerves system disorder that leads to death and disabilities (1). Cognition impairment is a common manifestation of ischemic stroke in the patients (2). The cognition impairment exacerbates the patients' post stroke quality of life (3). After an ischemic stroke, micro and macro lesions in the hippocampus and the white matter are

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considered as the mechanism causing cognitive impairments (4). At the molecular level, the growth factors, oxidative stress, inflammation, and neurotransmitters contribute in the post-stroke cognitive impairment (5, 6). Neurotransmitters have a well-documented role in cognition function in health and disease (7).

Serotonin, a neurotransmitter, controls the motor activities, cognition, and memory in the human and other organisms (8). Some studies have found that serotonin manipulation may be a helpful option to improve the cognition function (9). The serotonin levels of brain are changed during ischemic stroke, and restoration of synaptic serotonin with pharmacological agents improve both cognition and depression in the patients (10). The effectiveness of selective serotonin reuptake inhibitors (SSRIs) to recover stroke patient's disability was not confirmed, but the improve of the cognition function were observed in the limited clinical trials and experiments (11-13). Several generations of SSRIs were designed and developed during the last decades (14).

Escitalopram and fluoxetine are two main medicines belonging to SSRIs (15, 16). Escitalopram is the S enantiomer of citalopram and shows some superior therapeutic efficacy than citalopram and fluoxetine (17). The half-life times for escitalopram and fluoxetine are 27-33 and 24-96 hours, respectively (18, 19). Escitalopram interacts with the allosteric binding sites at the serotonin transporter, while fluoxetine inhibits transportation with a none allosteric mechanism (20). In other word, escitalopram is more specific inhibitor and has less effect on neurotransmitters other than serotonin. However, fluoxetine affects cholinergic neurotransmitters in addition to inhibition of serotonin levels.

These drugs are major treatment options to cure many diseases and disorders ranged from depression to mental disorders (21). We hypotheses that using SSRIs, the restoration of serotonin synaptic levels may improve the cognition function in the patients. We evaluated and compared the effect of escitalopram and fluoxetine on the cognition function ischemic stroke and meanwhile, the laboratory findings were recorded and analyzed. Routine laboratory tests is good tools to evaluate the prognosis of ischemic stroke patients (22). It is possible that this finding help us to find the indication that a drug would be effective treatment.

Materials & Methods

A hundred ischemic stroke patients who accepted and signed the enrollment consent form participated in the study. Biomedical Research Ethics Committee of Urmia University of Medical Sciences approved the research proposal and issued an ethical code that was IR.UMSU.REC.1400.306. According to the WHO protocol and based on CT scan results, laboratory finding and physical examination, the ischemic stroke was confirmed. The cases divided into two 50 patient groups. In a single blind study, the first group received escitalopram (10 mg/day) and the second received fluoxetine (10 mg/day). The patients underwent SSRIs therapy for three months the 5th day after stroke until 95th day. The standard treatment was performed for each patient, and the SSRIs therapy was used as a complementary adjuvant. The inclusion criteria were: being aware, lack of previous cerebral parenchyma lesions, dementia, major depression, suicide history, usage of drugs which are absolute contraindication for citalopram and fluoxetine, and thyroid disorders history, re-stroke, severe trauma, and severe side effects for SSRIs. The cognition function was evaluated with Dementia Rating Scale just before and after SSRIs therapy (23). The demographic and laboratory finding were recorded that included age, gender, smoking status, impaired circulation location (posterior-anterior), fast blood sugar, C-reactive protein, white blood cell count, neutrophil count, lymphocyte count, platelet count,

erythrocyte sedimentation rate, red blood cell count, and hemoglobin, cholesterol, triglyceride, urea, and creatinine levels.

Results

A descriptive analysis of variables in a total population is represented in table 1. The variables showed no significant change between gender except for the serum cholesterol and hemoglobin levels that were significantly higher in male than female (see table 2). About 54.1 percent of the patients were female and the rest 45.9 were male. The cognition function evaluation showed that the DRS1 and DRS2 had no significant difference between genders. There was no difference in the cognition function between smoker and nonsmokers. However, the FBS, hemoglobin, and cholesterol levels were significantly different between them. The patients with anterior and posterior circulation impairment had no significant difference in cognition function. However, the mean neutrophil levels were higher in the patients with anterior circulation involvement than patients with posterior circulation involvement (Figure 1).

Table 1. General characteristic of 100 enrolled patients.

	Minimum	Maximum	Mean	Std. Deviation
C-reactive protein	.00	3.00	1.9388	6.89810
Neutrophil	10.70	91.80	62.2677	14.28043
Lymphocyte	4.90	140.00	27.3958	17.04673
Platelet	44.90	605.00	272.7928	116.49327
Creatinine	.60	3.72	1.1994	.43691
Fast blood sugar	45.00	343.00	117.4227	66.35115
Erythrocyte sedimentation rate	4.20	95.00	45.5240	16.97527
Hemoglobin	9.30	19.20	14.4022	2.41583
Red blood cell count	3.250	6.400	4.80765	.644424
White blood cell count	1.09	152.00	10.6674	15.04188
Cholesterol	4.40	788.00	204.3651	105.31296
Triglyceride	72.00	769.00	213.0230	133.11099
Urea	.90	280.00	41.0480	31.64976
DRS1	60	111	91.89	11.991
DRS2	55	120	96.01	14.787
AGE	32.00	92.00	65.8646	13.58220
DRS2-DRS1	-35.00	39.00	4.6970	12.00294

Table 2. Gender difference in the laboratory variables

	Gender	Mean	Std. Deviation	Std. Error Mean
Hemoglobin	female	12.6063	1.85345	.46336
	male	15.3600	2.13325	.38948
Cholesterol	female	174.8089	83.89966	12.50702
	male	236.8049	117.31799	18.32199

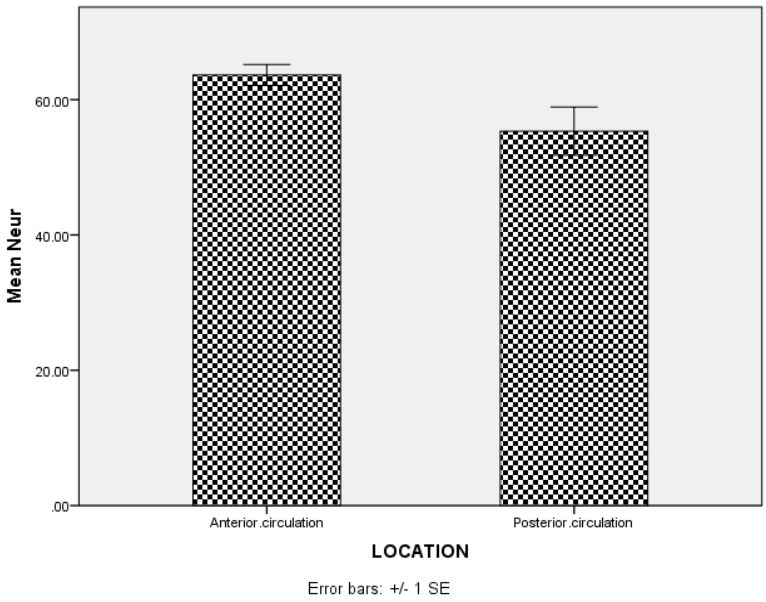

Fig.1. Higher neutrophil levels in the patients with anterior circulation involvement

Escitalopram versus fluoxetine:

The DRS difference before and after treatment showed that fluoxetine had insignificant effect on the patient's cognition function (p=0.564), while the mean was significantly higher in DRS2 than DRS1 (p=0.032). Table 3 shows the statistical finding and figure 2 showed the post treatment cognition between two drugs.

Table 3. The statistical finding of cognition between two groups

	Intervention	Mean	Std. Deviation	Std. Error Mean
DRS1	Escitalopram	92.06	12.679	1.811
	Fluoxetine	91.72	11.404	1.613
DRS2	Escitalopram	99.22	15.571	2.224
	Fluoxetine	92.86	13.392	1.894

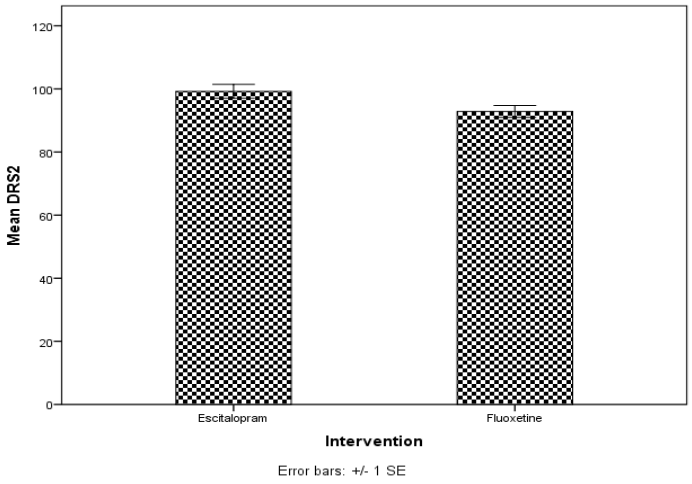

Fig. 2. Cognition levels after treatment with escitalopram versus fluoxetine

Successful and failed treatment with escitalopram:

We consider a significant DRS increases as a successful cognition treatment. The data analysis showed that 54% of patients experienced a successful cognition improvement in the escitalopram group. The mean age of the patients with successful treatment with escitalopram was lower than failed escitalopram treatment. However, the other laboratory and demographic findings had no significant difference between successful and failed treatment with the escitalopram group. Age and creatinine had significant correlation with cognition function before (DRS1) and after (DRS2) treatment and with their difference (DRS2-DRS1). However, serum urea levels are correlated with the difference of DRS before and after treatment. Table 4 shows the correlation study in the escitalopram group.

Table 4. A correlation analysis between variables in the escitalopram group

Variables		Creatinine	Urea	DRS2	DRS1	Age
Creatinine	Pearson Correlation	1	.460**	-.397**	-.318*	.406**
	Sig. (2-tailed)		.001	.005	.026	.003
	N	50	50	49	49	50
Urea	Pearson Correlation	.460**	1	-.249	-.075	.406**
	Sig. (2-tailed)	.001		.085	.608	.003
	N	50	50	49	49	50
DRS2	Pearson Correlation	-.397**	-.249	1	.855**	-.768**
	Sig. (2-tailed)	.005	.085		.000	.000
	N	49	49	49	49	49
DRS1	Pearson Correlation	-.318*	-.075	.855**	1	-.615**
	Sig. (2-tailed)	.026	.608	.000		.000
	N	49	49	49	49	49
Age	Pearson Correlation	.406**	.406**	-.768**	-.615**	1
	Sig. (2-tailed)	.003	.003	.000	.000	
	N	50	50	49	49	50

Discussion

Ischemic stroke is known for its high mortality rate and leading cause of disabilities. Drug-based manipulation of neurotransmitters may be helpful in the treatment and is associated with better treatment outcomes. Serotonin exerts effects on the cells which have its receptors. Platelet, hippocampus and other parts of brain express the receptor of serotonin. Then, serotonin could affect ischemic stroke outcome by modulation the platelet aggregation rate and the brain function in different parts.

Mao et al. evaluated the antidepressant properties of escitalopram and fluoxetine and found the latter drug has a good efficacy (24). The superior performance of escitalopram than fluoxetine was reported by some other studies(13, 25). This difference may be related to the mechanism of actions of drugs where fluoxetine affects the neurotransmitter other than serotonin and escitalopram works more specifically. It is possible that

the unspecific changing of cholinergic and dopaminergic neurons is the main cause of fluoxetine induced poor outcomes in cognition improvement. The escitalopram better performance is maybe due to its specific function in the serotonin but no other neurotransmitters (26).

Several studies have shown that post stroke depression is associated with cognition impairment. Unfortunately, due to some problems, we could not evaluate the depression status before and after treatment to interoperate whether escitalopram improved cognition medicated by reducing the depression rate in the patients or it is the results of direct biochemical brain cognition associated parts.

The cognition shows no significant changes between genders. Therefore, it is not essential variable in habituation and restoration of the cognition. As an outshoot finding, the cholesterol and hemoglobin levels were different between genders that is a well-documented result of gender's hormonal difference.

Elevated creatinine levels do not necessarily mean renal dysfunction. However, the renal function is a predictor of overall stroke patients' survival. Our previous study showed that creatinine and urea levels could predict early mortality in the stroke patients (22).

The finding of this study also showed a negative association between creatinine and pre- and post-stroke cognition. It simply means that higher creatinine levels associated with low cognition function. Tamura et al. showed that renal dysfunction associated with adult cognition impairment (27). The role of brain-kidney axis and renal dysfunction-induced cognitive impairment were reported by others (28-30) . In this study, urea levels had no significant association with cognition before and after treatment, but predicts the improvement of cognition. Therefore, creatinine could predict basic cognition levels and urea could be used for successfulness of treatment. Molecular studies have shown that urea and nitrogen metabolism is important in depression, antidepressant therapy, and cognition by changing nitric oxide metabolism (31). Furthermore, the urea cycle intermediate levels are important in the other mental disorders (32). We observed a negative association between cognitive improvement and age of patients. Our pervious report has shown that age associated with poor outcome (22).

We did not use placebo and then we could not interpret the cognition function without SSRIs therapy. It should be noted that in the study done by Asadollahi et al., escitalopram and fluoxetine showed no difference in the motor recovery and both were better than placebo (33). Due to some problems, we had no serum sampling in this study. It is recommended that the serum levels of drugs be evaluated.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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