Original Article

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TANAFFOS

Effect of Fluvoxamine on Interleukin-6 Levels in COVID-19 Patients Hospitalized in ICU: A Randomized Clinical Trial

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Background: Reviewing the laboratory studies, we observe some drugs with other specified applications, which cause serious inhibitory immune responses in the body. Selective Serotonin Reuptake Inhibitors (SSRIs) are among these drugs. Therefore, the current research aimed to evaluate the effectiveness of one of the SSRI drugs called fluvoxamine on the cytokine levels in COVID-19 patients.

Materials and Methods: The current research included 80 patients with COVID-19 hospitalized in ICU in Massih Daneshvari Hospital. They were entered into the research by an accessible method of sampling and then divided into two groups randomly. One of the groups underwent the treatment with fluvoxamine as the experimental group and the other group did not receive fluvoxamine as the control group. Interleukin-6 (IL-6) and CRP levels were measured before the onset of fluvoxamine consumption and when discharging from the hospital in all members of the sample group.

Results: The current study showed that IL-6 levels increased, while CRP levels decreased in the experimental group significantly (P-value≤ 0.01). After consuming fluvoxamine, IL-6 and CRP levels were higher and lower in the females compared to the males, respectively.

Conclusion: Considering the effectiveness of fluvoxamine on IL-6 and CRP in COVID-19 patients, it may ultimately come true to use this drug to improve both psychological and physical conditions simultaneously and leave the COVID-19 pandemic behind with less pathology.

Key words: COVID-19; Cytokine; Fluvoxamine; Interleukin-6; IL-6; CRP

INTRODUCTION

In early 2020, the new virus allocated some titles to itself due to the unprecedented fast transmission. It has been officially called severe acute respiratory syndrome (SARS-CoV-2) that causes Coronavirus disease 2019 (COVID-19) worldwide (1). Nowadays, the massive COVID-19 pandemic, with fast transmission power, has become an emergency problem regarding physical and mental health in just a few months (2). While the outbreak is expanding continuously, some concerns arise regarding society's health (3). However, scientists are trying to develop the COVID-19 vaccine, so making therapeutic strategies to save lives in patients with COVID-19 is really important (4). Corticosteroids and ventilation have been

applied to improve COVID-19 patients, but specified and known treatment has not been recognized for the treatment of COVID-19 so far (5).

Meanwhile, depression and anxiety correlate with COVID-19, which results in weakening of patients' immune response and hence, more severe respiratory symptoms or even death. In this regard, there is a suggestion to use a class of anti-depressant drugs named Selective Serotonin Reuptake Inhibitors (SSRIs). They have antiviral and antioxidant effects and modulate the respiratory symptoms and immune system, besides their main function as an anti-depressant (4). The SSRIs are used for the treatment of different psychiatric disorders and are well-known as the main route of treatment of major depression. It seems that higher doses of SSRIs are more effective in the treatment of major depression (6). They were released to the market after the tricyclic and MAOI drugs and did not have any side effects of earlier anti-depressant drugs, including dry mouth, constipation, sedation, orthostatic hypotension, tachycardia and others (7).

To the best of our knowledge, it is necessary to pay attention to the effective mechanisms of anti-depressant drugs, one of which is decreasing interleukin-6 (IL-6) levels (8). Interleukins are a group of cytokines with complex functions of cell proliferation, growth, and maturation. Cytokines play critical roles in the differentiation of immune cells. The exact function of a particular cytokine is determined by the cell type, responding cell type and immune response phase. Interleukins have pro- and anti-inflammatory effects, which further complicate their characteristics (9). Cytokines also include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors (TNFs), but generally, they are not considered hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a wide range of cells, including immune cells such as macrophages, B lymphocytes, T lymphocytes, mast cells, etc. They are important in health and disease, especially immune responses to infection, inflammation, trauma, sepsis, and cancer (10). According to research findings, it has been demonstrated that IL-6 may play a role in pathogenesis and also biological and somatic consequences of major depression (11), and the level of two cytokines, including IL-6 and TNF-α, are significantly higher in patients with major depression (12). Generally, cytokine dysfunction may correlate with depression (13). Some recent studies on SSRIs and SNRIs represent that anti-depressants can decrease plasma levels in several types of inflammatory cytokines, including IL-6, TNF-α, and CCL-2 chemokine, which are involved in severe COVID-19 (14). These anti-inflammatory effects are more intensive in SSRI drugs (15). SSRIs and SNRIs may be associated with a lower risk of death or intubation in patients with COVID-19 (16). In addition, low cost of SSRIs can be considered an advantage for COVID-19 patients (4). In the meantime, fluvoxamine is a well-known SSRI, which is used for the management of mental disorders and different kinds of chronic pain (17). It is usually applied for the treatment of anxiety and compulsive disorders (7). Now, fluvoxamine is under consideration regarding its advantages in dampening the inflammatory responses in human leukocytes by inhibiting cytokine production (18).

Based on the unprecedented pandemic of this infectious disease, that all people around the world are involved in, and the lack of a definite treatment for the pandemic, it is a medical emergency to seek effective treatment for COVID-19. Nowadays, several clinical trial researches have been done on the effectiveness of SSRIs in decreasing inflammation, cytokines, and interleukins in COVID-19 patients, and they have achieved remarkable results. Since no research has been done in Iran on the effectiveness of fluvoxamine as a kind of SSRI in improving COVID-19 patients, we aimed to determine the effectiveness of this drug in improvement of COVID-19 patients in the present study. The goals of the current research included evaluating the IL-6 and CRP levels in COVID-19 patients hospitalized in ICU after consuming fluvoxamine, and also comparing the IL-6 and CRP levels in two experimental and control groups.

MATERIALS AND METHODS

This clinical trial study has been registered in Iranian Clinical Trial Registry (IRCT20131115015405N4) and also approved by the ethical committee of Masih Daneshvari Hospital; the code was IR.SBMU.NRITLD.REC.1399.177. It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Then written informed consent was obtained from all participants.

The statistical population of the study included all COVID-19 patients hospitalized in ICU in Masih Daneshvari Hospital from 22 July 2020 to 21 Sep 2020. All participants had positive pulmonary CT-scan and PCR test results and underwent similar antiviral therapies by the ICU physician. For estimating the sample size, it was determined that 942 COVID-19 patients were hospitalized in different hospital wards and 128 COVID-19 patients were hospitalized in ICU at the same time. Thus, by an accessible method of sampling, 80 patients who met the inclusion criteria were entered into the study (Figure 1). It is mentionable that the sample size of 15 cases in each group had been suggested to be sufficient in clinical trial studies (19). At first, a researcher-made demographic information questionnaire was completed by all sample groups and IL-6 and CRP levels were measured. Then, all sample members were dedicated to two matched groups in terms of demographic information randomly. Half of them were allocated to the experimental group, and the other half was allocated to the control group. The experimental group underwent fluvoxamine therapy, but the control group did not. The first dosage of fluvoxamine that was given to patients was 25 mg daily. Then it increased up to 300 mg per day, depending on the patients' endurance to the drug. Meanwhile, Na, K, EKG (QT interval), BUN, Creatinine, and FBS were measured regularly during the research process, all of which were within normal range. The IL-6 and CRP levels were measured again when discharged from ICU. The kit applied for measuring IL-6 was R&D and the kits applied for measuring CRP were Bionik, Delta, and Pars Azmoon.

It is worth mentioning that all groups were monitored daily by a psychiatrist in terms of psychological symptoms, including hypomania symptoms and probable fluvoxamine side effects, both during hospitalization and after discharge from the ICU, for tapering or holding fluvoxamine consumption, in case of any side effects.

Inclusion criteria

Informed consent, consciousness, a definite diagnosis of COVID-19, age over 18 years, not being pregnant, no consumption of substance and having the normal serum level of WBC, NA, K, BUN, Creatinine and FBS, performing EKG (normality of QT interval), and being under non-invasive therapy.

Exclusion criteria

Not having inclusion criteria and also consuming NSAIDs, clomipramine, captopril, diltiazem, zolpidem, ASA, warfarin, MAOIs, lithium and methadone drugs by the patient, and being under invasive therapy.

Instruments for collecting data

1- Researcher-made demographic questionnaire: age, gender, marital status, educational level and job status were determined by this questionnaire.
2- Measuring IL-6 and CRP levels by blood tests.

Data analyzing methods

The obtained data were analyzed with SPSS-22. Descriptive statistical methods, including frequency, percent, mean, and standard deviation (SD) were used to analyze descriptive results. Inferential statistical methods, including MANCOVA, were used for comparing the IL-6 and CRP levels between males and females in the control and experimental groups and the relationship between demographic variables and IL-6 and CRP levels. LSD post hoc test was used for comparing demographic variable and IL-6 and CRP changes. Moreover, independent sample T-test was used for comparing IL-6 and CRP levels between the control and experimental groups after the intervention, and Chi-square test was used for comparing the number of expired patients due to COVID-19 in the control and experimental groups. All hypotheses were tested in a two-tailed manner and with a significance level of 0.05.

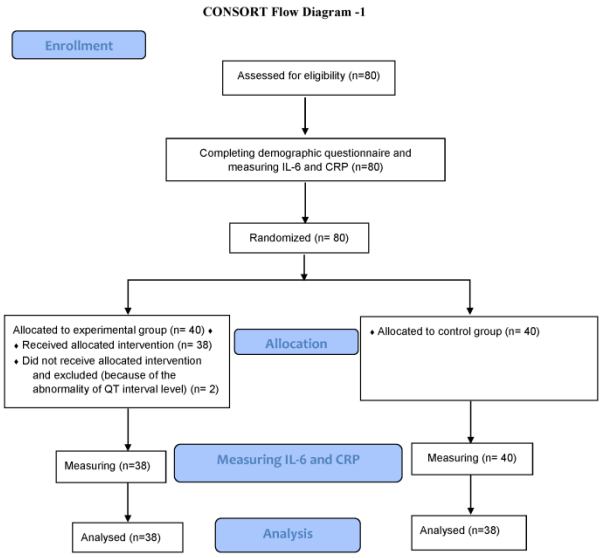


Figure 1.CONSORT Flow Diagram

RESULTS

Two patients out of 80 patients (40 in the control and 38 in the experimental groups) were excluded from the study due to abnormality of QT interval level. Moreover, 56.5% were male and 43.6% were female. The mean age ± SD in females, males and whole sample population were 54.73 ± 10.66, 60.94 ± 15.29, and 57.44 ± 13.07 years, respectively. Other demographic features are presented in table 1. According to table 2, there was a significant difference in the effectiveness of fluvoxamine on IL-6 levels between the experimental and control groups. The IL-6 levels increased significantly (P-value ≤0.01) in the experimental group after consumption of fluvoxamine. The IL-6 levels showed a higher trend in females than males after consumption of fluvoxamine, but not significantly (Figure 2).

According to table 3, there was a significant difference in the effectiveness of fluvoxamine on CRP levels between the experimental and control groups. The CRP level decreased significantly (P-value ≤0.01) in the experimental group after consumption of fluvoxamine (Figure 3). The CRP level was lower in females than males after consumption of fluvoxamine, but not significantly. There was a significant difference between different educational levels with IL-6 levels after receiving fluvoxamine. The IL-6 levels were increased significantly (P-value ≤0.01) in patients with up to high school diploma compared to others. The MANCOVA did not reveal a significant correlation between IL-6 and CRP and other demographic variables. According to table 4, there was no significant difference in mortality rate between the experimental and control groups.

Table 1. The frequency distribution of demographic information divided by gender

		Men N (%)	Women N (%)	Total N (%)
Group	Experimental	24 (54.54)	14 (41.17)	38 (48.71)
	Control	20 (45.45)	20 (58.82)	40 (51.28)
	Total	44 (56.41)	34 (43.58)	78 (100)
Marital status	Single	2 (4.54)	0	2 (2.56)
	Married	42 (95.45)	30 (88.23)	72 (92.3)
	Widowed or divorced	0	4 (11.76)	4 (5.12)
Educational level	Illiterate	4 (9.09)	12 (35.29)	16 (20.51)
	Up to high school diploma	8 (18.18)	0	8 (10.25)
	High school diploma	14 (31.81)	14 (41.17)	28 (35.89)
	Academic education	18 (40.9)	8 (23.52)	26 (33.3)
Job status	Housewife	0	28 (82.35)	28 (35.89)
	Retired	10 (22.72)	0	10 (12.81)
	Employee	6 (13.63)	2 (5.88)	8 (10.25)
	Others	28 (63.63)	4 (11.76)	32 (41.25)

Table 2. The mean level of IL-6 in experimental and control groups

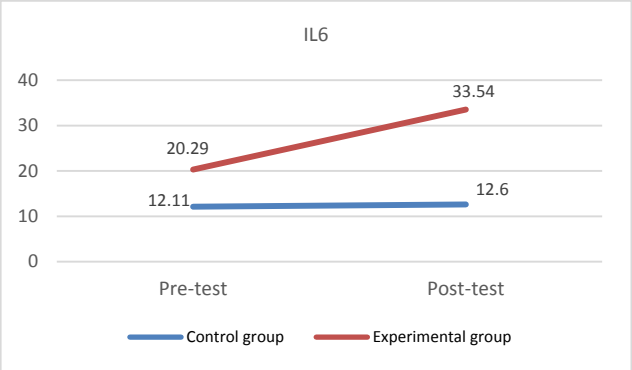
		Experimental group	Control group	T/F	P.V
Men	Post-test	32.11± 26.13	12.29 ±7.09	0.244	0.626
Women	Post-test	35.95 ± 26.23	13.74± 14.88		
Total	Pre-test	20.29 ± 12.23	12.11± 16.29	3.756	0.001
	Post-test	33.85 ± 23.04	12.18 ± 7.32		

Table 3. The mean level of CRP in experimental and control groups

		Experimental group	Control group	T/F	P.V
Men	Post-test	28.07 ± 19.22	45.25 ± 14.93	0.003	0.958
Women	Post-test	21.33 ± 6.35	37.8 ± 7.88		
Total	Pre-test	40.89 ± 12.12	38.31 ± 24.23	- 2. 68	0.014
	Post-test	26.23 ± 16.63	42.38 ± 12.84		

Table 4. The mortality rate, in experimental and control groups

	Mortality rate (%)	X^2	P.V
Experimental group	42	0.2	0.45
Control group	35		



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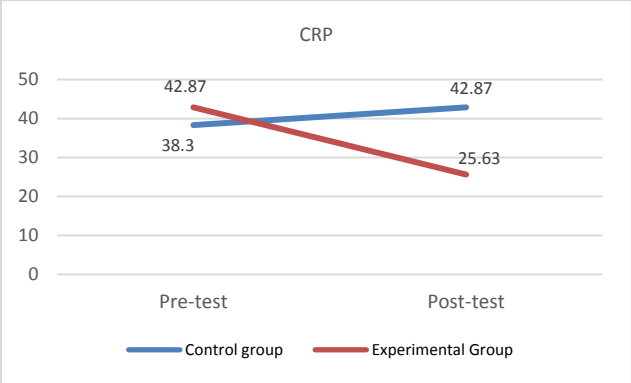

Figure 3. The mean level of CRP in experimental and control groups

DISCUSSION

The findings of the current study showed that most of the participants were married, had high school diploma, and not-determined jobs. It was shown that IL-6 and CRP were significantly increased and decreased in the experimental group, respectively. So, the study's hypothesis regarding the effectiveness of fluvoxamine on IL-6 and CRP levels and their difference between the patients who had consumed fluvoxamine and patients who had not, was approved significantly.

In addition, there was not a significant difference in the mortality rate due to COVID-19 between the experimental and control groups. Considering the findings, it can be concluded that fluvoxamine may effectively improve many COVID-19 symptoms resulting from cytokine storm, which is the most dangerous outcome of this disease after pneumonia (20). Furthermore, it was demonstrated that IL-6 levels were higher, while CRP levels were lower in females than males after consuming fluvoxamine. However, this finding is congruent with other researches, which have shown males are at higher risk of deteriorated conditions of COVID-19 and its mortality compared to females, regardless of age (21).

Studies containing results similar to the current study are limited, but in the following, we aim to present the findings of some researches in this regard. Some studies have shown that outpatients with COVID-19 who had been treated with fluvoxamine were less likely to suffer exacerbated symptoms over 15 days compared to those who had received a placebo (22). A study on 460 patients with COVID-19 who had received anti-depressant drugs (SNRIs and SSRIs) during hospitalization indicated that they were at a lower risk of mortality and intubation. Also, just a few numbers of them (28 persons) were hospitalized in ICU and there was a reverse and significant correlation between anti-depressant drugs and intubation or mortality risk COVID-19 patients (16). It has been also demonstrated that melatonin is beneficial in the treatment of COVID-19, which reduces cytokine storm, subsequent progression to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), or even death (23). Some other psychotropics, including haloperidol and valproic acid, are recently approved by FDA, as anti-SARS-COV-2 drugs (24). In addition, since there is opposed functioning between norepinephrine and serotonin, drugs that facilitate serotonin transmission may dampen the cytokine storm related to COVID-19. These drugs consist of SSRIs, tricyclic anti-depressants (TCA), Monoamine oxidase inhibitors (MAOIs) and 5HT2C agonist lorcaserin (25). Besides, catecholamines, including norepinephrine, play a fundamental role in exacerbation of potentially fatal cytokines associated with COVID-19 (26), and fluvoxamine, which has a low nanomolar affinity for

Sigma-1 receptors, along with anti-inflammatory effects, may represent a therapeutic approach for the treatment of the cytokine storm and saving the lives of COVID-19 patients (20).

As shown, some studies have confirmed the effectiveness of anti-depressant drugs in improving COVID-19 patients, which are partly congruent with the findings of the current research. Nevertheless, few studies exist in this regard due to newly diagnosed COVID-19 that prevented us from making more detailed comparisons and discussions.

CONCLUSION

The findings of the current study represent that fluvoxamine may improve the treatment of COVID-19 patients hospitalized in ICU, especially females. These findings about the treatment of COVID-19 may be promising. We suggest anti-depressant drugs, especially fluvoxamine, as a new therapeutic strategy for the treatment of COVID-19, considering their simple accessibility and low cost.

Limitations

The sample population was small in the current study because all of them were selected just from hospitalized patients in ICU of Massih Daneshvari Hospital due to the fast transmission of the coronavirus and impossibility of accessing patients in other hospitals or places. But it was tried to consider the generalizability of the achieved data as much as possible.

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