Original Article

Using caffeine on the patients as therapeutic option against treatment-resistant obsessive-compulsive disorder

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Abstract

Introduction: Obsessive-compulsive disorder (OCD) is one of the most common and debilitating diseases. Approximately 40-30% of these patients are resistant to treatment, which auxiliary drugs are used to treat these patients. One of these drugs is caffeine, which is capable of affecting adenosine receptors and interfering with its release and serotonin reuptake. Considering the limitations of previous studies in this area, including lack of control group, this double-blind study compared the effectiveness of caffeine in the management of patients with treatment-resistant OCD in comparison with placebo group. **Materials and Methods:** 62 patients who referred to the psychiatric clinic of Imam Hossein Hospital in Tehran from 2017 to 2018 were enrolled in the study. According to the psychiatrist's interview, patients with OCD were selected randomly in two groups including caffeine and placebo, after having met the criteria for inclusion and obtaining informed consent. Patients were followed for 8 weeks and compared in terms of the severity of OCD before and after intervention using YBOCS questionnaire. **Results:** The two groups of treatment and control were similar in terms of study variables (gender, age, education, age, comorbidity). The mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) in the treatment and control groups before intervention were determined to be 27.16 and 25.4, respectively, which changed to 24 and 27.23 after medication intervention, which exhibited a decrease of about 3 points (12%) in the treatment group, and was statistically significant based on linear regression analysis ($P = 0.009$). Considering other variables, the effect of caffeine was still statistically significant in the two groups. **Conclusion:** Based on the findings of our study, caffeine can reduce the severity of the symptoms of OCD and serve as an auxiliary treatment for OCD.

Keywords: Auxiliary treatment, caffeine, obsessive-compulsive disorder

Introduction

The prevalence of obsessive-compulsive disorder (OCD) in various studies is reported to be 2-3% of the general population.[1] The WHO has ranked it as one of the 10 debilitating medical conditions.[2] The main symptoms of this disease are obsession and compulsion, which involves unwanted and disturbing thoughts, ideas or sensations. The OCD is the result of the usual concerns about the problems of life in which a person considers them to be the result of his own mind. On the other hand, compulsion involves repetitive mental and practical behaviors that the person feels the urge to do in response to the obsessions. Several drugs are used to treat this condition, which selective serotonin reuptake inhibitors (SSRIs) are at the top of the list. About 30-40% of patients do not respond to common treatments and are known to be resistant to treatment.[3]

Regarding the chronic and debilitating course of this disease, various drugs have been used to enhance the drug treatment outcomes (e.g. Augmentation). Due to genetic variation, clinical manifestations and response to treatment, the drugs affecting various neurotransmitters have been previously studied,[4] among

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which the most common are antipsychotics. Despite the fact that some of them have been shown to be effective, there are concerns about long-term complications, most notably tardive dyskinesia and metabolic complications. Therefore, various studies have been done on other effective drugs, including Ondansetrone, Pindolol, anticonvulsants (e.g. Topiramate and Lamotrigine), effective medicines for glutamate receptors (e.g. Riluzole, and Memantine), and an effective medication for opium receptors (morphine), as well as stimulants such as dextroamphetamine and caffeine. Each of these medicines has its own advantages and disadvantages, and few studies have been conducted on their definitive effectiveness; therefore, further studies in this field are necessary.[5] Regarding to the fact that it is preferable to choose a more safe and less complicated drug especially in long-term use, caffeine is chosen in the current study. In addition to the above reasons, other reasons for its selection included: high consumption of caffeine-containing compounds in the community, which increases the probability of drug acceptance by the patient.[6] Its effect has also been studied in reducing the symptoms of OCD by Koran *et al.*, 2009[7] and several other studies,[4-7] which somehow requires further study in this field. Therefore, the current study was aimed to investigate the effect of caffeine on treatment of patients with resistance to OCD in comparison with placebo for treatment of these patients.

Materials and Methods

This double-blind study was performed on patients aged between 18 and 55 who were referred to the psychiatric clinic of Imam Hossein Hospital in Tehran. After a psychiatric interview, patients with known OCD were treated with an effective dose of SSRI according to the DSM IV-TR criteria. Patients were considered to be resistant to treatment after 12 weeks of treatment, with a median effective dose of SSRI, based on the Y-BOCS criteria equal to or greater than 20. Then they were evaluated in terms of inclusion and exclusion criteria. Documenting informed consent was performed after explaining the study for participant. Patients at the beginning of the study were evaluated for the underlying variables, vital signs, type and severity of OCD symptoms according to the Y-BOCS questionnaire, and then were randomly divided into treatment and control groups using a random number table. The use of previous medications was continued and patients treated with either a caffeine tablet or a placebo, which started with a low dose and, within a few weeks, was next given at a maximum dose of 300 mg once a day, depending on the patient's tolerance. Then, the patients were visited weekly and evaluated for drug side effects; if there were any complications or unwillingness to continue the study for any reason, they were excluded from the study. After eight weeks of treatment, the patients were again examined for the severity of the OCD symptoms by Y-BOCS criteria and their results were recorded. At the end of the sampling, the findings at the beginning and the end of the study were compared with SPSS version 23 software, in order to determine the effectiveness of combination therapy with caffeine in comparison with placebo.

Exclusion criteria

Pregnancy, History of drug abuse (based on patient report or file contents), Suicidal history (based on patient report or file contents), The presence of psychotic symptoms based on the patient's report, Unwillingness to continue study or failure to follow protocols, Cardiovascular disease (arrhythmia, high blood pressure, ischemic heart disease, etc.) according to a patient report and other diseases that can have a negative effect on caffeine, Complications during treatment.

Sample size

As described by Koran, *et al.* (5), sample size for both the treatment and control group was determined to be 62. The formula is defined as follows:

μ_1 =20 (mean Y-BOCS for the first week of the caffeine group), μ_2 =8.7 (SD for the first group), S_1 =13 (mean Y-BOCS for the fifth week in caffeine group) and S_2 = 8.4.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 * (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Results

A total of 62 patients (31 in the treatment group and 31 in the control group) were enrolled in the current study. However, 22 patients (12 from the treatment group and 10 from the control group) were excluded from the study. Of the remaining 40 patients, 11 (6 in the treatment group and 5 in the control group) were excluded from the follow-up due to complications. The frequency of male patients in the treatment and control groups was recorded to be 42.1% (8 cases) and 38.1% (8 subjects), respectively. The frequency of female patients in the treatment and control group was 57.9% (11 cases) and 61.9% (13 cases), respectively. Furthermore, there was no significant difference between the two sexes. The mean age of the patients in the two groups was approximately the same, and the two groups were similar in terms of the age of the onset of the disease. In addition, the frequency distribution of education in the two groups is almost the same [Table 1].

As indicated in Table 2, the frequency of OCD symptoms in the two groups was compared, which is almost the same in the two groups.

In Table 3, two groups were compared in terms of drug side effects when receiving caffeine intervention. As known, more patients experienced adverse effects (14 in comparison with 9) in the treatment group, among this adverse effects, sever anxiety symptoms was the most frequently detected types.

In statistical analysis, the difference in side effects observed in the two groups was statistically significant (P = 0.056), which in fact exhibited the effectiveness of the drug when comparing with placebo group. Table 4 shows that the type of simultaneous treatment in the two groups was approximately the same.

The average consumption of tea and coffee was compared in two groups of treatment and control, and average consumption was based on the average number of tea/coffee cups per day which was almost the same in the two groups [Table 5].

Descriptive statistics (mean and standard deviation) of OCD were calculated in terms of YBOCS in both groups before and after drug intervention. The results showed that the severity of OCD in the treatment group was slightly higher than the control group before the intervention, but after the medication intervention, the mean OCD severity in the treatment group was lower when comparing with the control group [Table 6].

To investigate the effect of caffeine on YBOCS questionnaire, linear regression analysis was performed using SPSS version 22 software. The results of linear regression analysis demonstrated that the mean score of YBOCS in the placebo group was 3.37 points (beta coefficient for intervention variable: 3.37) more than the group receiving caffeine ($P = 0.009$). In other words, taking caffeine has a significant effect on the YBOCS score [Table 7].

Regarding the effect of caffeine on YBOCS score after age control, linear regression analysis revealed that the mean score of YBOCS in the control group was 3.36 points higher than the mean of this score in the intervention group, where this difference was statistically significant ($P = 0.010$). Furthermore, the findings depicted that the age of the subjects had no effect on the relationship between caffeine consumption and YBOCS score [Table 8].

Linear regression results indicated that the mean score of YBOCS in the control group after controlling the effect of age of onset was 3.42 points higher as compared to the mean of this score in the treatment group ($P = 0.009$). On the other hand, age does not affect the relationship between caffeine consumption and YBOCS [Table 9].

Given the gender effect, the effect of caffeine consumption on YBOCS score exhibited that the mean score of YBOCS in the control group was 3.58 points higher than the mean of this score in the treatment group ($P = 0.004$). Additionally, the analysis showed that the gender has a significant effect on the YBOCS score after the intervention. As a result, women's score is 2.8 on average more than men [Table 10], where the female score was more than that of men (2.8 points; Table 10).

Regarding the level of education, linear regression results indicated that the mean score of YBOCS in the control group was 3.51 points higher than the mean of this score in the treatment group ($P = 0.007$). On the other hand, the results showed that education did not affect the relationship between caffeine consumption and YBOCS score [Table 11].

Table 1: Frequency of education in two groups

Education	Treatment group		Control group		Total
	Frequency	Percent	Frequency	Percent	
Illiterate	0	0%	1	4.8%	2.5%
Under the diploma	8	42.1%	6	28.6%	35%
Diploma	3	15.8%	4	19%	17.5%
Higher than diploma	8	42.1%	10	47.6%	45%
Total	19	100%	21	100%	100%

Table 2: Comparison of OCD symptoms in two groups of treatment and control

The type of obsessive symptoms	Treatment group		Control group		Total
	Frequency	Percent	Frequency	Percent	
Washing	1	5.6%	3	14.3%	10.3%
Obsessional thought	1	5.6%	0	0	2.6%
Mixed	16	88.9%	18	85.7%	87.2%
Total	18	100%	21	100%	100%

Table 3: Comparison of drug side effects in treatment and control groups

Side effect type	Treatment group		Control group	
	Frequency	Percent	Frequency	Percent
Exacerbation of anxiety	7	36.8%	1	4%
itching	0	0	1	4%
Sleep disorder	2	10.6%	2	9.6%
Irritability	0	0	2	9.6%
Sexual dysfunction	0	0	1	4%
Gastrointestinal symptoms	3	15.8%	0	0
Edema	0	0	1	4%
Sadness and suicidal idea	0	0	1	4%
Headache	2	10.6%	0	0
Total	14		9	

Table 4: Comparison of treatment and control groups in terms of type of treatment, concurrent with caffeine

Type of treatment	Treatment group		Control group		Total
	Frequency	Percent	Frequency	Percent	
SSRI	0	0	2	9.5%	5%
SSRI+Antipsychotic	7	36.8%	5	23.8%	30%
SSRI+TCA	0	0	1	4.8%	2.5%
Antipsychotic+SSRI+TCA	6	31.6%	8	38.1%	35%
SSRI+Mood stabilizer	1	5.3%	0	0	2.5%
+Mood stabilizer Antipsychotic+SSRI	3	15.8%	5	23.8%	20%
Other Ingredients	2	10.5%	0	0	5%

Table 5: Average consumption of tea and coffee in two groups

	Average consumption of a cup of tea per day	The standard deviation	Average consumption of a cup of coffee a day	The standard deviation
Treatment group	4.7	3.6	1	0.00
Control group	3.2	2.2	1.5	0.7
Total	3.9	3	1.25	0.5

Table 6: Descriptive statistics of OCD in terms of Y BOCS in both groups before and after drug intervention

Variable		Before medication intervention average			After medication intervention average		
		Number	Before medication intervention average	The standard deviation	Number	After medication intervention average	The standard deviation
Severity of obsession according to YBOCS	Treatment group	19	27.16	6.89	14	24	7.25
	Control group	21	25.40	7.74	13	27.23	6.59

Table 7: Linear regression analysis for evaluation of the effect of caffeine consumption on YBOCS score

	Unstandardized Coefficients		Standardized Coefficients	t	*P*
	B	SE	Beta		
Base factor	8.413	3.007		2.798	0.008
YBOCS score before intervention	0.470	0.086	0.614	5.442	<0.001
Intervention	3.371	1.226	0.31	2.749	0.009

The mean score of YBOCS in the control group was determined to be 2.71 points higher than the mean of this score in the treatment group, where this difference was statistically significant ($P = 0.02$). Based on the data presented in herein, the type of treatment did not affect the relationship between caffeine consumption and YBOCS [Table 12].

After examining the effects of symptoms and YBOCS scores before the intervention, linear regression results indicated that the mean score of YBOCS in the control group was 2.63 points higher than the mean of this score in the treatment group ($P = 0.038$). In addition, the type of symptoms do not affect the relationship between caffeine consumption and YBOCS score [Table 13].

Discussion

Caffeine is one of the most commonly used substances worldwide[8] and its effects on CNS have been studied more than any other substance. Despite concerns about the risk of caffeine abuse; to the best of our knowledge, there has not been any evidence about the risks of taking its usual doses as an acceptable daily intake (ADL),[9] The American Psychiatric Association also does not consider caffeine use disorde in the DSM 5 diagnostic criteria, and it only addresses the caffeine toxicity and its withdrawal. Therefore, concerns about its abuse are less than before, especially with regard to the different effects on the nervous system that are similar to those of some psychiatric drugs.

Caffeine can be considered as a drug in the treatment of some disorders, including OCD, because the mechanism of its main effect is the adenosine A1, A2 receptor antagonist. The A1 receptor has a regulatory and inhibitory role in the release of various neurotransmitters, including tryptophan, serotonin, and noradrenergic neurotransmitter systems; its inhibition results in the release of these important neurotransmitters and the effect on their reabsorption, which is recognized in the pathophysiology of OCD.

Moreover, the inhibition of A2 receptor increases the dopamine transfer across the postsynaptic *dopamine* D2 receptors, which increased dopamine release occurs only at high doses of caffeine. Therefore, it is different from stimulants such as amphetamine and cocaine.

Therefore, there is less concern about the recurrence of psychosis and mania induction in controlled consumption.[10] Another caffeine's mechanisms of action is the increase in dopamine D1 receptors in the prefrontal cortex, which is associated with its effects in regulating attention and working memory function and can have a therapeutic effect for ADHD. On the other hand, it increases the ability to shift attention, and can also play a key role in reducing the obsessive thoughts and the compulsive behaviors; additionally, its impact on mood, energy, fatigue and working ability can make the patient more easily confronted with OCD symptoms.[11] Of course, it can be expected that the presence of ADHD and depression or their lower diagnostic thresholds are capable of affecting the effectiveness of caffeine. In the present study, the presence of depression with ADHD was considered as exclusion criteria but has not been screened for sub-threshold symptoms. Therefore, it is likely that part of the improvement in obsessive-compulsive symptoms is due to the improvement of associated disorders.

The results of this study indicate that the use of caffeine has a significant effect on the reduction of OCD (based on the YBOCS), which is in line with other studies including Koran *et al.*[7] in which caffeine consumption has reduced the severity of OCD based on the YBOCS. However, the rate of reduction

Table 8: Linear regression analysis for investigating the effect of caffeine consumption on YBOCS in terms of age

	Unstandardized Coefficients		Standardized Coefficients	t	*P*	95% CI for B	
	B	SE	Beta			Low limit	Upper limit
Base factor	8.265	3.482		2.374	0.022	1.243	15.287
YBOCS before intervention	0.468	0.091	0.611	5.126	<0.001	0.284	0.652
Intervention	3.368	1.241	0.310	2.714	0.010	0.865	5.870
Age	0.006	0.065	0.010	0.087	0.931	-0.125	0.137

Table 9: Linear regression analysis for determining the effect of caffeine consumption on YBOCS in terms of age

	Unstandardized Coefficients		Standardized Coefficients			95% CI for B	
	B	SE	Beta	t	*P*	Low limit	Upper limit
Base factor	9.165	3.399		2.696	0.010	2.309	16.021
YBOCS score before intervention	0.469	0.087	0.612	5.379	<0.001	0.293	0.645
Intervention	3.421	1.241	0.315	2.756	0.009	0.918	5.924
Age of start	-0.036	0.074	-0.056	-0.490	0.627	-0.186	0.114

Table 10: Linear regression analysis for assessing the effect of the caffeine consumption on YBOCS in terms of sex

	B	SE	Beta	t	*P*	95% CI for B	
						Low limit	Upper limit
Base factor	2.533	3.892		0.651	0.519	-5.316	10.382
YBOCS score before intervention	0.496	0.083	0.647	5.939	<0.001	0.327	0.664
Intervention	3.584	1.177	0.330	3.044	0.004	1.210	5.958
Sex	2.888	1.287	0.244	2.244	0.030	0.292	5.483

Table 11: Linear regression analysis for examining the effect of caffeine consumption on YBOCS based on the educational level

	Unstandardized Coefficients		t	*P*	95% CI for B	
	B	SE			Low limit	Upper limit
(Constant)	8.05	3.02	2.66	0.011	1.95	14.15
YBOCS before intervention	0.42	0.09	4.60	<0.001	0.23	0.59
Intervention	3.51	1.23	2.86	0.007	1.03	5.99
Educational level						
Higher than diploma						
Illiterate and under the diploma	2.71	1.49	1.82	0.076	-0.29	5.73
Diploma	2.19	1.58	1.39	0.173	-1.00	5.39

Table 12: Effect of caffeine consumption on YBOCS score based on the type of treatment using linear regression

	Unstandardized Coefficients		t	*P*	95% CI for B	
	B	SE			Low limit	Upper limit
(Constant)	9.25	3.76	2.46	0.019	1.64	16.87
YBOCS before intervention	0.51	0.107	4.72	0.000	0.28	0.72
Intervention	2.71	1.33	2.05	0.048	0.02	5.40
Type of treatment						
SSRI+TCA+AP						
SSRI	0.90	2.29	0.39	0.695	-3.74	5.55
SSRI+Antipsychotic	-2.72	1.68	-1.62	0.114	-6.12	0.68
SSRI+TCA	-1.77	4.65	-0.38	0.705	-11.21	7.65
SSRI+mood stabilizer	-2.17	4.40	-0.49	0.625	-11.09	6.75
SSRI+MS+AP	-2.54	2.01	-1.26	0.214	-6.62	1.53
Other	1.69	2.71	0.62	0.538	-3.81	7.19

Table 13: The effect of caffeine consumption on YBOCS score by type of symptoms using linear regression analysis

	Unstandardized Coefficients		t	*P*	95% CI for B	
	B	SE			Low limit	Upper limit
(Constant)	8.72	2.89	3.01	0.004	2.87	14.57
YBOCS score before intervention	0.48	0.08	5.82	<0.001	0.317	0.65
Intervention	2.63	1.23	2.14	0.038	0.148	5.11
Type of symptoms						
Mixed						
Washing	5.29	2.51	2.11	0.041	0.22	10.36

in our study, based on the mean of YBOCS, decreased in the treatment group by about 12% before the use of caffeine from 27.16 to 24, which was statistically significant. While Koran *et al.* showed a decrease from 27.9 to 13 after consuming caffeine; in the other word, it decreased by about 54%, which was significantly higher compared with our study. This difference can be interpreted that our study has a control group and its statistical analysis is based on the YBOCS before the intervention and the control group, while the study of Koran, *et al.* has no control group; therefore, the presence of the control group in our study is capable of increasing the validity of this findings. Another point that seems to be is that the duration of follow-up in our study was 8 weeks but in the study of Koran *et al.* was lasted for 5 weeks, which could point out that how long is caffeine effective?

Moreover, the average dose of caffeine consumed in this study was 300 mg per day, which was administered from the beginning with the same dose and 24 patients continued until the end of the study. While the average dose for each patient was about 150 mg per day in our study, since it started with low dose caffeine and reached a maximum of 300 in terms of patient tolerance within 1-2 weeks, due to side effects, some patients received a lower dose to the end of study. The observed difference in patient tolerance to this drug and the incidence of adverse events can be due to genetic differences between different races, in metabolic processes and the elimination of drugs or differences in sensitivity of the receptors. A study by Fredholm *et al.*[12] has also shown that the median dose of caffeine-containing products around the world is about 76-70 mg per day, but in some parts of the world, including the United States and Canada, is greater than this amount (238- 210 mg per day), whereas it reaches 400 mg per day in Sweden and Finland.

Lara *et al.*[13] noted that high doses of caffeine (about 400 mg/day) can exacerbate anxiety symptoms, but the effect of caffeine anxiety depends on the genetic vulnerability of an individual, including the adenosine receptor gene polymorphism. Therefore, its anxiety dose is not the same in all people. Accordingly, it can be concluded that if caffeine is to be used as a medicine, the dose should be determined according to the tolerance of each patient. After considering the effects of variables such as age, gender, education level, age of onset, type of obsessive-compulsive symptoms and type of treatment, the effect of caffeine on the reduction of OCD was significant. Where none of the above variables has had a disturbing role in the effectiveness of caffeine.

Interestingly, patients' gender had a significant effect on OCD after intervention, so that the mean number of YBOCS in women was 2.8 above men. Of course, it should be taken in to consideration that our sample size is composed of about 60% women and 40% male, and this difference may be influenced by the number of samples on the average number of YBOCS.

Pathophysiologically, caffeine can be effective in reducing the symptoms of OCD, and clinically, the clinical findings of the present study can confirm its effectiveness for treatment-resistant OCD. Due to the size of the samples, we had to use the sensitivity analysis to analyze the findings. Regarding to the limitations of this study, further studies are needed to confirm its efficacy in order to be more confident about the effectiveness of this drug. Based on the findings presented herein, the patient's attitude toward taking caffeine is important in its choosing. Furthermore, the dose should be determined according to the tolerance of each patient to minimize its complications. Considering these points can increase the likelihood of patient collaboration and the effectiveness of treatment in future studies.

Conclusion

Based on the findings presented, caffeine can reduce the severity of the symptoms of obsessive-compulsive disorder and serve as an adjunct therapy in the obsessive-compulsive disorder. However, further studies are needed to confirm its effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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