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Ondansetron Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder: A Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: Serotonin and dopamine are involved in the development of obsessive-compulsive disorder (OCD). Approximately 40% of OCD patients do not respond to the first-line therapy of treatment using selective serotonin reuptake inhibitors. Reportedly, the response to the treatment is increased by enhancing dopamine blockers.
Objectives: The purpose of this study was to evaluate the efficacy and immunogenicity of ondansetron as a booster in the treatment of OCD patients.
Methods: The present double-blind, randomized clinical trial (RCT) was conducted on 40 patients (16 males and 24 females) aged 18 to 60 years who met the DSM-V-TR-based OCD diagnostic criteria and had a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The patients were randomized to receive standard treatment and ondansetron (8 mg/day) or placebo for 12 weeks. They were examined using Y-BOCS and side-effect checklist at baseline, fourth, eighth, and twelfth weeks.
Results: The patients in both groups were homogeneous and comparable in terms of age, marital sex status, type of obsession, anxiety, depression, age at the onset of disease, and the duration of disease. The Y-BOCS scores in the intervention and placebo groups were 27.15 ± 3.94 vs. 26.15 ± 4.94 at baseline, 25.40 ± 3.75 vs. 25.00 ± 4.79 in the fourth week, 20.85 ± 3.69 vs. 24.05 ± 4.97 ($P = 0.026$) in the eighth week, and 17.95 ± 3.43 vs. 21.65 ± 4.85 ($P = 0.008$) in the twelfth week, respectively. Significant changes occurred between the two groups at weeks 8 and 12; the difference between the two groups was significant ($P = 0.015$), whereas no significant difference was observed between the two groups before week 8.
Conclusions: This 12-week, double-blind, and randomized clinical trial showed that ondansetron was a booster agent with a significant effect on patients with moderate to severe OCD. This study also showed that ondansetron is generally well tolerated by OCD patients. The response to the treatment also increased from the eighth week of treatment onwards. The severity of the disease was decreased at the end of the ondansetron intervention. The adjunct ondansetron treatment was recommended for OCD patients

Keywords: Obsessive-Compulsive Disorder, Ondansetron, Selective Serotonin Reuptake Inhibitor, Yale - Brown

1. Background

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disorder, affecting 2% - 3% of the general population (1). OCD is considered not only as a highly prevalent disease but also as one of the most debilitating diseases of medicine (2, 3). Patients with OCD often experience chronic symptoms that interfere with their economic status and their social, occupational, marital, and family relationships (4). Thus, many aspects of quality of life are negatively affected by OCD, such that there is a relationship between increasing OCD severity and worsening quality of life (5). A recent study examining the prevalence of mental disorders in Kashan, Iran, estimated that the prevalence of OCD was 6.8%, which ranks third after major depressive and anxiety disorders (6). This rate indicates the high prevalence of OCD in Kashan, compared to the 1.8% prevalence in Iran (7). Therefore, finding ways to prevent and treat OCD in Kashan should be one of the top priorities of mental health programs in this city.

OCD demonstrates little response to treatment, and approximately 40 - 60% of patients do not respond satisfactorily to first-line and standard treatment OCD drugs, which are selective serotonin reuptake inhibitors (SSRIs). Thus these OCD patients are known as treatment-resistant (8-10). These individuals are at a high risk of disability and compli-

cations (11), so there is a need to develop better treatments for OCD (12). Accordingly, the topic of "treatment-resistant" in the treatment of OCD has been repeatedly investigated in recent years (13).

To date, various methods and strategies have been proposed to increase the therapeutic response in refractory OCD patients (14). One of the strongest studied strategies is augmentation therapy, which is a strategy that adds antipsychotics to the standard treatment (SSRIs) (12, 15). Due to the side effects of antipsychotic drugs, this treatment is not usually accepted by all patients, so few patients may benefit from it.

There have been different neurotransmitter systems implicated in the aetiology of OCD, including but not limited to the serotonergic system. Also, other neurotransmitter systems such as increased dopaminergic system activity are involved in the pathogenesis of OCD. Thus, the antagonistic effect of atypical antipsychotic drugs may increase the efficacy of SSRIs to treat treatment-resistant OCD patients (15).

Ondansetron is a 5-HT3 receptor antagonist used to treat nausea and vomiting in cancer patients undergoing chemotherapy and radiotherapy (16). It can also be used in patients undergoing surgery and pregnant patients. Serotonin 5-HT3 receptors are located in the ventral part of the brain with GABA receptors in the same site that act indirectly by inhibiting dopamine release from corticomesolimbic system (16).

Ondansetron modulates the return of dopamine in the nucleus pathways to the mesolimbic system. The 5-HT3 receptors are co-located with GABA receptors; therefore, it may have an indirect inhibitory effect on corticosteromesolimbic dopamine release, which ultimately results in reduced dopamine-induced repetitive behaviors (17).

There were some studies on the efficacy of ondansetron augmentation for OCD patients. Pallanti et al. investigated the effect of ondansetron augmentation in 14 patients with inadequate response to SSRI therapy. Patients were treated with a low dose of ondansetron for 12 weeks at a dosage of 0.25 mg twice daily for 6 weeks and then titrated to 0.5 mg twice daily for 6 weeks. At last, 9 patients experienced a treatment response with a 25% reduction in the Yale - Brown Obsessive Compulsive Scale (Y-BOCS) score (18).

Also, in a 12-week, single-blind study published in 2014 by Pallanti et al., the efficacy and tolerability of ondansetron as an augmentation therapy were investigated in 21 OCD patients who did not respond to SSRI treatment. They found that ondansetron augmentation was associated with a 27% decrease in Y-BOCS score in this study; 57% of patients responded to treatment (19). There are few studies in this field in Iran. In a study published in 2010 by Soltani et al., 42 patients were treated with ondansetron and fluvoxamine or fluoxetine for 8 weeks, which showed a positive effect of ondansetron (20). Heidari et al. in 2014 investigated the effect of ondansetron augmentation on 46 OCD patients treated with fluvoxamine. Accordingly, ondansetron showed superior over the placebo in patients treated with fluvoxamine (21).

2. Objectives

There are limited studies conducted to test the efficacy of ondansetron augmentation in the treatment of refractory OCD. The present study aimed to investigate the efficacy of ondansetron augmentation in the treatment of refractory OCD, using a randomized placebo-controlled clinical trial.

3. Methods

3.1. Design and Setting

The current double-blinded clinical trial was conducted on a group of OCD outpatients undergoing treatment, referred to private and public psychiatric clinics in Kashan, Iran.

In this study, the sample size was considered 20 people in each group according to the results of previous studies with 95% confidence interval and 20% type II error. The study population was selected through nonprobability and purposive sampling.

3.2. IRCT and Ethics

This study is registered in Iranian Registry of Clinical Trials (IRCT2017012332145N1) and approved in the ethics committee of Kashan University of Medical Sciences (IR.KAUMS.REC.1396.66).

3.3. Sample and Sampling

Inclusion criteria were patients who were resistant to treatment and were recruited from patients referred to psychiatric clinics in the city of Kashan who had undergone OCD treatment for at least three months after a psychiatrist's diagnosis. Exclusion criteria were acute and severe physical illness during the study, no follow-up for four weeks, severe complications during treatment, and childbearing age in women, and lack of reliable contraceptive methods.

3.4. Patient Allocation and Randomization

The treatment process was randomly allocated. The permuted block randomization method was used because of the gradual referral of patients to maintain balance in the groups so that the difference in the number of samples in both groups was 2 to 3 at each time point (blocks of 4 and 6). After the evaluation of inclusion and exclusion criteria, the patients were asked to sign the consent form. Random concealment was conducted, and the number was assigned to every patient. Each patient received treatment by a nurse who was blinded to the intervention and placebo according to the permuted block randomization list number. Nobody could change the assignment after registration in iterance. Placebo was the same as the treatment in shape and form. The patient and therapist were both blind to the treatment.

3.5. Arms

Participants entered in two arms. Arm 1 received standard treatment and ondansetron (8 mg/day); arm 2 received standard treatment with a placebo for 12 weeks. Both drugs were made in equal coverage so that the researcher and the patients were blind to the drug allocation. Ondansetron (Sobhan Company) was started at a dose of 8 mg daily and continued for 12 weeks for patients. The placebo was completely similar to the original drug.

3.6. Follow Up

The patients were similarly followed and measured regardless of the arm. All patients were visited 8 times by a manager psychiatrist: the first visit for randomization and drug prescription, the second visit at the end of the first week, the third visit at the end of the second week and then every two weeks until the end of the study (twelfth week). The psychiatrist measured Y-BOCS scores for patients admitted to the fourth, eighth, and twelfth-week visits. Response to treatment was defined as the change in Y-BOCS score from baseline until the end of the study and a comparison between the two drugs.

3.7. Measures

A fellow psychiatrist (rater) measured Y-BOCS scores of patients to identify the subjects with the Y-BOCS score of more than 16 despite receiving at least three months of adequate and tolerable SSRI doses. Considering the inclusion and exclusion criteria, the psychiatrist, as a research project manager, selected the eligible patients and obtained written consent from all patients while explaining the study methodology. Then demographic data and information were collected about other confounding variables, including age at OCD onset, duration of OCD, anxiety, and depression.

3.8. Data Analysis

The data were first managed in terms of missing data and out of range values. Then, the study variables were described with measures of central tendency and dispersion indices. Chi-square test and *t*-test or Mann-Whitney test were used for intergroup comparisons of baseline status and post-tests (quantitative or qualitative-percentage of patients responding to treatment or test score). Throughout the study, arms Paired *t*-test and Wilcoxon tests were used to compare the change of the study outcomes during the intervention period and follow up across groups. In these comparisons, the outcome was measured over time. Repeated measures analysis of variance (ANOVA) was used to evaluate the outcome. The effect of confounding variables on outcome was assessed via the analysis of variance and subgroup analysis. The significance level was considered at 5%. The software used for data analysis was SPSS V. 17 (IBM, New York, NY, USA).

4. Results

The mean age of participants was 34.80 $\pm$ 12.05 years in the ondansetron group and 35.70 $\pm$ 11.05 years in the placebo group. This difference was not statistically significant.

The information of study arms in terms of sex, marital status, and age is presented in Table 1. There were no significant differences between the two groups. The mean duration of illness was 11.25 $\pm$ 9.33 in the ondansetron group and 10.90 $\pm$ 8.03 in the placebo group, but this difference was not statistically significant.

In this study, the distribution of intervention groups was evaluated by types of obsession, compulsion, anxiety, and depression. The data from the analysis of these variables are presented in Table 2. Results showed no significant differences in the types of obsession, compulsion, anxiety, or depression present between the two groups.

In this study, the mean Y-BOCS score was evaluated in the two groups at different times after intervention and the mean Y-BOCS scores of each time were compared between the two groups using Independent *t*-test (Table 3).

Figure 1 shows response to treatment according to intervention groups at different times.

5. Discussion

In the present RCT, the groups were comparable in terms of age, gender, marital status, type of obsession, type of compulsion, anxiety disorder, and illness duration. Thus, differences in changes can be attributed to the intervention drug. The ondansetron group had a higher

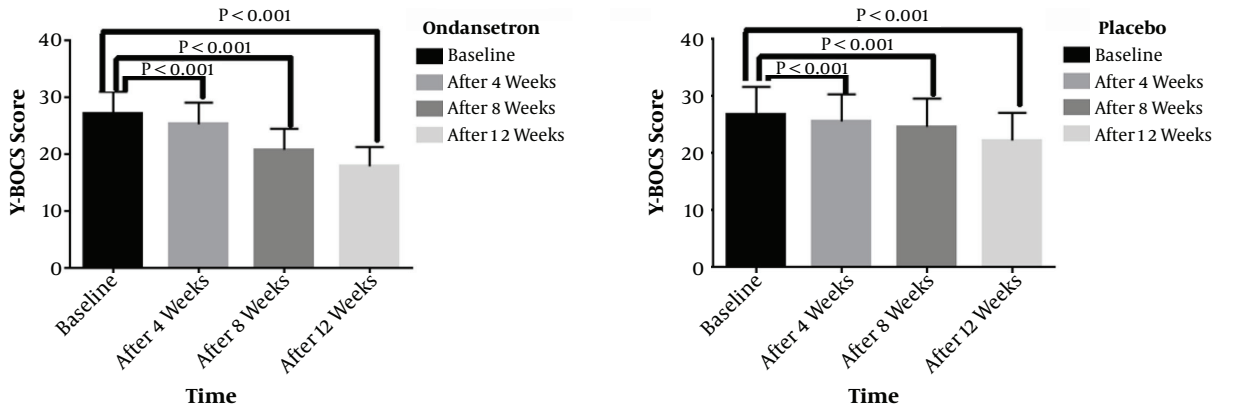

Figure 1. Evaluation of response to treatment according to intervention groups over time

Table 1. Distribution of Participants' Demographic Factors Across Arms[a]

	Groups	
	Endanstrone	**Placebo**
Gender[a]		
Male	8 (40)	8 (40)
Female	12 (60)	12 (60)
Marital status[a]		
Single	2 (10)	0 (0)
Married	16 (80)	19 (95)
Divorced	2 (10)	1 (5)
Age (y)[b]	34.80 ± 12.00	35.70 ± 11.05
Illness duration (y)[b]	11.25 ± 9.33	10.90 ± 8.03

[a]Values are expressed as mean ± SD or No. (%).
[b]P > 0.05, chi Square.
[c]P > 0.05, Independent-sample *t*-test.

Table 2. Distribution of Types of Obsession, Compulsion, Anxiety and Depression Across Study Arms[a]

Variables	Group		P Value
	Ondansetron (8 mg/day)	Placebo	
Obsession type			0.721
Wash	16 (80)	14 (70)	
Check	2 (10)	3 (15)	
Symmetry	0 (0)	1 (5)	
Counting	2 (10)	2 (10)	
Stash	0 (0)	0 (0)	
Compulsion type			0.752
Pollution	20 (100)	19 (95)	
Doubt	0 (0)	1 (5)	
aggression	0 (0)	0 (0)	
Sexual	0 (0)	0 (0)	
The need for symmetry	0 (0)	0 (0)	
Physical	0 (0)	0 (0)	
Anxiety disorder			0.677
Yes	17 (85)	16 (80)	
No	3 (15)	4 (20)	
Depression disorder			0.670
Yes	16 (80)	17 (85)	
No	4 (20)	3 (15)	

[a]Values are expressed as No. (%).

response since the eighth week of the intervention compared to the placebo group. Immediately after the intervention, however, the mean change in Y-BOCS score was similarly decreased over time across groups.

The findings of the present study are consistent with those of Pallanti et al. (19), who documented a higher response in the augmentation of SSRIs with ondansetron compared to treatment with SSRIs. Pallanti et al. documented a higher response in augmentation compared to treatment with ondansetron alone. Hewlett et al. (22) also reported similar results for the response to combination therapy of ondansetron and antipsychotics (18). The response to treatment is also higher than the mean treatment response to antipsychotic augmentation to the main treatment (8). Unlike the findings of the present study, one study showed that intervention in refractory OCD patients treated with ondansetron at a dose of 0.15 mg/kg showed no effects when compared with the placebo group (23). In an 8-week pilot study, treatment with a single dose of on-

Table 3. Evaluation of Mean Y-BOCS Score in the Two Groups at Different Times[a]

Time	Intervention Group		P Value[b]
	Ondansetron (8 mg/day)	Placebo	
Baseline	27.15 ± 3.94	26.15 ± 4.94	0.484
After 4 weeks	25.40 ± 3.75	25.00 ± 4.79	0.770
After 8 weeks	20.85 ± 3.69	24.05 ± 4.97	0.026
After 12 weeks	17.95 ± 3.43	21.65 ± 4.85	0.008
P-value[c]		0.116	

[a]Values are expressed as mean ± SD.
[b]Independent sample *t*-test.
[c]Repeated measure test: P value (time × group).

dansetron (1 mg) three times daily showed a decrease in the YBOCS score in 29% of patients (22). The limitation of their study was the non-randomized and non-controlled, a design limitation addressed by our study. However, the dosage of our intervention was higher.

In contrast to the present study, Pallanti et al. (18) applied low-dose ondansetron. They administered 0.25 mg of ondansetron twice daily for the first six weeks and 0.5 mg twice daily for the second six weeks. Slight changes in individual moods were achieved in the middle of the study; however, at least 25% improvement was observed in the Y-BOCS score at the end of the study (18). Although the duration of the intervention of this study was equal to the present study, the dose of ondansetron in our study was higher, which may justify a better treatment response in the present study. In line with the present study, two studies investigated moderate to severe doses of ondansetron. Soltani et al. (20) administered 4 mg daily ondansetron for 8 weeks combined with fluoxetine, observing that the mean Y-BOCS score reached 6 at the end of the eighth week from the baseline rate of 35, while this change was from 35 to 16 in the placebo group (20). In the present study, despite the 8 mg daily dose, response to treatment was lower with the mean Y-BOCS score reaching 17 from 27 in the ondansetron group and 21 from 26 in the placebo group. Although the baseline Y-BOCS score of patients was 35, which was very severe, patients should not have used medication to treat a psychiatric problem within six weeks before the intervention. There is also no information about the duration of illness, history of previous treatments, and response or non-response to previous cases. Such variables may help the reader to better understand the effect of ondansetron on the disease. Another study showed the effectiveness of ondansetron in both obsession and compulsion dimensions compared to the placebo. Their results indicate 86% improvement of the ondansetron group compared to the placebo group (32%). They reported at least 35% improvement in the Y-BOCS score (21). Despite the same dose, the duration of intervention was longer in the present study. However, the rate of response to treatment was more dramatic in the study of Heidari et al. Although the duration of illness was cited, the weakness of this study was the failure to provide details of the medications used before and after the response. The current finding on the efficacy of ondansetron was previously reported in the study of Pallanti et al. (18) on the combination of SSRIs and antipsychotics. The ondansetron effect can effectively broaden our knowledge on the mechanism of the overlapping effects of SSRI in OCD. Ondansetron indirectly modulates the dopaminergic system through the 5-HT3 receptor block. The 5-HT3 receptor antagonist inhibits dopamine release in productive nuclei by inhibiting dopamine stimulation by morphine-induced cells (23). Thus, inhibition of 5-HT3 function enhances GABA release and inhibits the mesolimbic dopaminergic system. In addition, the 5-HT3 receptor antagonist may regulate the dopaminergic system by the nicotinic acetylcholine receptor antagonism (24). On the other hand, ondansetron's mechanism of action may be mediated by binding to the μ-opioid receptor (25).

The subsequent side effects are unsettling about the administration of this drug in these patients. Interestingly, good tolerability was found in this study, which was in contrast to other previous reports of adverse effects. In the study of Soltani et al., only one patient was excluded from the ondansetron group due to headache (20). In another study (19), only two cases of mild constipation occurred during the trial. The 5-HT3 receptors are located on the myenteric neurons and play a minor role in the transmission of neurotransmitters into the myenteric neurons. The 5-HT3 antagonist will decrease visceral sensitivity and will have inhibitory effects on motor function at the end of the gut (26). Studies on the effect of the 5-HT3 antagonist on the gastrointestinal tract in healthy individuals suggest that constipation is a dose-dependent complication and that the odds ratio of constipation is less at low doses of ondansetron (27).

Unlike the present findings, the cut-off point for drug efficacy was weeks 2 and 8 in the study of Soltani (20) and 6 to 8 weeks in the study of Heidari (21). This was week 8 in the present study. The intervention group had no superiority in response to treatment over the placebo group.

Ondansetron has been more effective in randomized controlled clinical trials (20, 21) than in non-controlled open trials (18, 19), for which there are two methodological explanations. First, in the non-controlled group (18, 19), there was a history of poor treatment response that was effective in non-response. In the control group, however, (20, 21) due to a lack of accurate reporting, patients may have

had a better treatment response than before entering the study. Second, the high-dose ondansetron in controlled studies resulted in better efficacy. Two non-controlled trials (19, 22) reported that the symptoms worsened after ondansetron discontinuation, but none of the controlled clinical trials (20, 21) measured patients' symptoms after the discontinuation of treatment.

Although two clinical trials have reported the beneficial outcome of this therapy, more studies are needed to prove the effectiveness of this drug in the treatment of refractory OCD (20, 21).

It is suggested that future studies should better compare the effect of high and low dose ondansetron on treatment-resistant OCD and the effect of ondansetron on treatment-resistant OCD with longer follow-up duration.

5.1. Limitations

The main limitation of the present study was the lack of follow-up time, which means whether or not the main cause of recurrence or exacerbation of symptoms in OCD after our intervention was due to continued ondansetron in maintenance therapy or due to periodic recurrence of OCD symptoms is difficult to determine. Also, we were unable to eliminate the effect of comorbidities or personality disorders in this intervention. In addition, the small sample size did not allow us to specifically compare the dimensions of the association between OCD subtypes and the therapeutic cause and ondansetron effect pathway. The study, however, contributed to the literature. There are not many long-term studies on the effect of ondansetron on OCD.

5.2. Conclusions

Patients with treatment-resistant OCD can be treated with high-dose ondansetron. Such treatment may have a significantly better response since week 8 compared with the placebo. Overall, the Y-BOCS score showed 88.33% reduction in the ondansetron group at week 12 compared to the baseline, which is a dramatic response.

Footnotes

Authors' Contribution: Zahra Sepehrmanesh supervised the research process. Mehdi Adel developed the hypothesis, designed the project and did the experiments. Afshin Ahmadvand supervised the research. Mojtaba sehat was the statistical advisor of the project. All of the authors were involved in the editing of the final manuscript.

Clinical Trial Registration Code: IRCT2017012332145N1.

Conflict of Interests: The authors declare that they have no conflicts of interest.

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