

Adjunct Triptorelin in the Treatment of Obsessive-Compulsive Disorder in Clients Receiving Selective Serotonin Reuptake Inhibitors (SSRIs)

Faezeh Nikzad¹, Seyed Alireza Sadjadi², Amir Hooshang Mohammadpour^{3,4}, Maliheh Ziaee⁵, Fatemeh Behdani², Seyedeh Maryam Naghibi¹, Seyedeh Narges Nejatifard¹, Mahdieh Ghanbari¹, Ali Akhondpour Manteghi^{2*}

Abstract

Objective: Analog triptorelin is one of the effective agonists for the treatment of reproductive disorders, particularly prostate cancer. Due to results of previous studies, we hypothesized that obsessive-compulsive disorder (OCD) can be effectively treated with the long-term administration of a gonadotropin-releasing hormone (GnRH) analog, namely triptorelin. The aim of this study was to evaluate the effectiveness of triptorelin injection in clients with OCD.

Method: This randomized single-blind clinical trial was performed on 30 clients with OCD who had a Yale-Brown score of > 17 after 8 weeks of treatment. The participants were randomly assigned into two groups of triptorelin and placebo. The clients in the intervention group were treated with Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, in addition to triptorelin three times a month for at least 8 weeks. Clients in the control group received injection of distilled water as placebo three times in addition to the routine treatment. The outcome was evaluated by Yale-Brown OCD scale (Y-BOCS) at the baseline, as well as 4, 8, and, 20 weeks after the end of the treatment.

Results: The mean scores of Y-BOCS in the intervention and control groups was 30.5 ± 67.6 and 30.5 ± 67.6 , respectively, before intervention, indicating no significant difference between the two groups ($P = 0.08$). The comparison of Y-BOCS scores after the intervention showed a significant difference between the two groups in the scores 4 ($P = 0.01$), 8 ($P < 0.005$), and 20 ($P < 0.005$) weeks after the treatment. With regards to the side effects of the medicine, 6.7% ($n = 1$) of the clients in the control group developed headache and 66.7% ($n = 10$) had late period in intervention group. The results revealed a significant difference between the two groups in terms of side effects ($P < 0.005$).

Conclusion: The results of this study showed triptorelin decreased the symptoms of OCD. The effectiveness of triptorelin in the treatment of symptoms in clients with OCD was confirmed in our study. However, due to the limited research addressing this domain, future studies are suggested to clarify this conclusion.

Key words: *Gonadotropin-Releasing Hormone; Obsessive Compulsive Disorder; Triptorelin*

1. Psychiatrist, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
4. Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Department of Community Medicine, School of Medicine, Social Determinants of Health Research Center, Gonabad University of Medical Sciences, Gonabad, Iran.

*Corresponding Author:

Address: Ibn-e-Sina Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Postal Code: 9195983134.

Cell Phone: 98-915 3178675, Tel: 98-51 37112701, Fax: 98-51 37112545, Email: manteghia@mums.ac.ir

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Obsessive-compulsive disorder (OCD) as a neuropsychiatric disorder is characterized by a series of intrusive thoughts and repetitive actions, which is often rooted in a high level of anxiety (1). According to DSM-5, The OCD is recognized as the fourth most common anxiety disorder (2). Recently, OCD has been separated from the class of anxiety disorders in the last version of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) due to new neurological findings. In this regard, OCD is classified as an independent category entitled obsessive-compulsive and related disorders (3). The lifetime prevalence of this condition is estimated at 2%-3% worldwide (1). Commonly, OCD in men starts during childhood and adolescence; however, in females, it emerges after the age 20 (4, 5). The prevalence of OCD in Iran is reported as 11.7%-43.2% (4, 5). Based on epidemiological studies, this disorder is dispersed across various populations at a different extent, representing a variety of DMS indices (6).

According to the pathophysiological studies, the brain corticostriatal systems, amygdala-cortical connections, lateral prefrontal cortex, and anterior cingulate cortex (ACC) are involved in OCD. Based on neuroimaging studies, task-related abnormalities within thalamo-cortico-striatal loops are reported during OCD (7). Moreover, different environmental conditions, including genetic factors, are the other causes of OCD. As a result, the disease is associated with other disorders, including bipolar disorder, anxiety, and depression. Some of the other problems associated with OCD include self-harm, unemployment, drug addiction, commitment of the crime, and various types of skin diseases (8).

Drug therapy is considered the principal method for the treatment of OCD. In this regard, selective serotonin reuptake inhibitor (SSRIs) is the treatment of choice for this disorder due to its high efficacy and few complications (11). Fluvoxamine is one of the most effective agents for the treatment of OCD, depression, and anxiety disorder (9). In addition, paroxetine (10), clomipramine (11), citalopram, and sertraline (12) are the other effective pharmacological agents for OCD. However, these treatments are effective only in half of the clients with OCD. The use of these medicines may lead to some complications such as serotonin syndrome or serotonin toxicity, nausea, indigestion, constipation, or diarrhea. Due to the challenge of the use of common medicine (unresponsiveness and the serious complications), search for new approaches to treat this disorder is highly important (13, 14).

The results of a study conducted on hypersexual clients revealed a decrease in obsessive-compulsive symptoms after using antiandrogenic drugs (15). Therefore, it was inferred that gonadotropin-releasing hormones (GnRH) are involved in obsessive-compulsive pathophysiology. The effectiveness of some antiandrogenic factors, such as cyproterone acetate, flutamide, and triptorelin, have been observed in a few clients with OCD (16). The use

of a composition comprising at least one substance within the group GnRH-analogs for the production of a drug for the treatment of OCD was recorded in a study conducted by Eriksson et al (17). In another study performed by Eriksson it was found that the antiandrogenic agents were effective in the treatment of OCD (18).

Analog triptorelin is one of the effective agonists for the management of reproductive disorders, particularly prostate cancer. In this analog, the replacement of D-tryptophan with glycine leads to further stability in β -II-Turn structure and its increased power for binding to the GnRH receptor. In addition, it reduces the metabolic elimination of triptorelin against endopeptidases (19).

The previous studies on the effectiveness of triptorelin in OCD are very limited and often have major methodological problems. In this study, it was hypothesized that OCD can be effectively treated with the long-term administration of a GnRH analog, namely triptorelin. The present study was the first attempt to examine the potential effects of triptorelin in the treatment of OCD in Iran. The aim of this study was to evaluate the effectiveness of triptorelin injection in the treatment of OCD.

Materials and Methods

This randomized single-blind clinical trial was performed on a control group and 30 clients referring to the outpatient psychiatric clinics of several hospitals, including Ibn Sina, Qa'im, and Imam Reza, as well as the private clinics of Mashhad during 2018.

Inclusion and Exclusion Criteria

The inclusion criteria included:

- 1) Age range of 18-64 years
- 2) Enough uptake of selective serotonin reuptake inhibitors, benzodiazepine, or antipsychotic with no effect on the level of Gonadal steroid hormones
- 3) Yale-Brown OCD scale (Y-BOCS) score of > 17 eight weeks after the treatment. On the other hand, the exclusion criteria included:

- 1) Presence of other simultaneous psychiatric disorders
- 2) Affliction with medical illnesses
- 3) Substance abuse other than cigarettes
- 4) Use of other medicines, except for one SSRI
- 5) Sensitivity reactions or other intolerable side effects induced by triptorelin use
- 6) Pregnancy and lactation
- 7) Presence of bone diseases or any other diseases with contraindication for triptorelin

Study Design

All clients were diagnosed with OCD based on psychiatrist interview and based on DSM-5:

- A. Presence of obsessions, compulsions, or both
- B. The obsessions or compulsions are time-consuming (eg, take more than 1 hour per day) or cause clinically significant distress or impairment in

social, occupational, or other important areas of functioning.

- C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication) or another medical condition.
- D. The disturbance is not better explained by the symptoms of another mental disorder (20).

Subsequently, the participants were randomly assigned to two groups of intervention and control. Three injections of triptorelin monthly in addition to SSRI was administered for the intervention group .

The clients in the intervention group were treated with one SSRI.

Drug administration and its dosage and titration were conducted by psychiatrists. The clients who did not tolerate triptorelin or had any drug complications were considered to be irresponsive to treatment .

Prior to the study, the possible side effects of this drug regimen was explained to the clients, and the necessary measures for controlling these side effects were taught to them. All clients were evaluated in terms of triptorelin complications, including hot flashes, headache, backache, legs swelling, weakness, nausea, vomiting, insomnia, diarrhea, decreased libido, sexual disability, and orgasm problems, and they were removed from this study with the emergence of severe complications to be subjected to the necessary treatments (Figure 1).

The participants were tested by a trained psychologist to determine the outcome of OCD. The clients and evaluators were blinded to the type of prescribed drug.

The Y-BOCS was performed at the baseline as well as 4, 8, and 20 weeks after the end of the treatment. The Y-BOCS was used to detect the clients' status during the study. This rating scale was a semi-structured interview assessing the severity and type of symptoms in OCD clients. Unlike other questionnaires, Y-BOCS has a high sensitivity to therapeutic variations and is widely used to evaluate the effectiveness of pharmaceutical and psychological treatments of OCD (21). The scale includes 10 items with a score of 0-40. The clinical response represented a 25% change in the scale score. The score of Y-BOCS in our sample was higher than 17.

Ethical Considerations

This research project was approved by Mashhad University of Medical Sciences (IRCT NO: 20180309039012NT). Informed consent was obtained from all clients. In addition, the participants were assured that personal information will remain confidential. To observe the ethical considerations, the participants were informed of the confidentiality of the data, stages of the study, and research techniques. Moreover, they could withdraw from the project at any stage .

Statistical Analysis

Data were entered in SPSS software (version 21) and analyzed by independent t test and Chi-square test, and

repeated measure ANOVA. P-value less than 0.05 was considered statistically significant.

Results

Based on the obtained results of this study, the mean ages of the clients in intervention and control groups were 34.3 ± 6.7 and 29.8 ± 73.1 years, respectively. The comparison of the two groups in terms of age showed no significant difference ($P = 0.76$). Tables 1 and 2 present the comparison of demographic and clinical information between the two research groups, respectively. Based on the obtained results, there was no significant difference between the two groups in disease signs ($P = 0.85$). In addition, no significant difference was observed between the two groups concerning disease severity ($P = 0.59$). Moreover, the comparison of medicine distribution between the two groups showed no significant difference in this regard ($P = 0.75$).

The mean Y-BOCS scores in intervention and control groups were 30.5 ± 13.7 and 30.5 ± 67.6 , respectively, before the intervention. Therefore, no significant difference was found in the Y-BOCS score between the two groups at the preintervention stage ($P = 0.0.8$). The mean scores of Y-BOCS in the control group 4, 8, and 20 weeks after intervention were obtained as 29.5 ± 33.6 , 29.7 ± 6.02 , and 29.7 ± 4.7 , respectively. However, regarding the intervention group, these scores were estimated at 24.4 ± 13.6 , 24 ± 21.11 , and 20.6 ± 33.2 in the mentioned stages, respectively. The postintervention comparison of Y-BOCS scores between the 2 groups showed a significant difference after 4 ($P = 0.01$), 8 ($P < 0.005$), and 20 ($P < 0.005$) weeks of treatment .

Based on the results of ANOVA, the comparison of the Y-BOCS scores obtained before the intervention with those estimated after the intervention in the intervention group indicated a significant difference four weeks after the treatment ($P = 0.02$). However, no significant difference was observed in this group 8 ($P = 0.37$) and 20 ($P = 0.36$) weeks after the intervention. The comparison of Y-BOCS scores before and after the intervention showed a significant difference in the scores 4 ($P < 0.005$), 8 ($P < 0.005$), and 20 ($P < 0.005$) weeks after the intervention. With regards to the side effects of the investigated medicine, headache and missed period were observed in 1 (6.7%). Moreover, 66.7% ($n = 10$) had late period in intervention group. Accordingly, the results revealed a significant difference between the two groups in terms of side effects ($P < 0.005$).

Table 1. The Comparison of Other Demographic Information between Intervention and Control Groups

Variables	Intervention group		Control groups		P-value	
	Number	Percent	Number	Percent		
Gender	Male	5	33.3	3	20	0.41
	Female	10	66.7	12	80	
Marital Status	Single	8	53.3	5	3.33	0.27
	Married	7	46.7	10	66.7	
Family History	Yes	6	40	6	40	1
	No	9	60	9	60	
Admission	Yes	3	20	4	26.7	0.67
	No	12	80	11	73.3	
Education level	Primary	0	0	3	20	0.34
	Under High school	4	26.7	3	20	
	High school	5	40	5	40	
	Academic	6	33.3	4	26.7	

Table 2. The Comparison of Diseases Signs between Intervention and Control Groups

Variables	Intervention group		Control groups		P-value	
	Number	Percent	Number	Percent		
Diseases signs	Checking	4	26.7	3	20	0.85
	Washing	2	13.3	5	33.3	
	Obsession	2	13.3	1	6.7	
	Washing and thought	3	20	3	20	
	Washing and checking	3	20	2	13.3	
		1	6.7	1	6.7	
Disease status	Mild	4	26.7	5	33.3	0.69
	Severe	11	73.3	10	66.7	
Medicine distribution	SSRI	6	40	8	53	0.75
	SSRI+ap	8	53	6	40	
	SSRI+TCA	1	6.7	1	6.7	

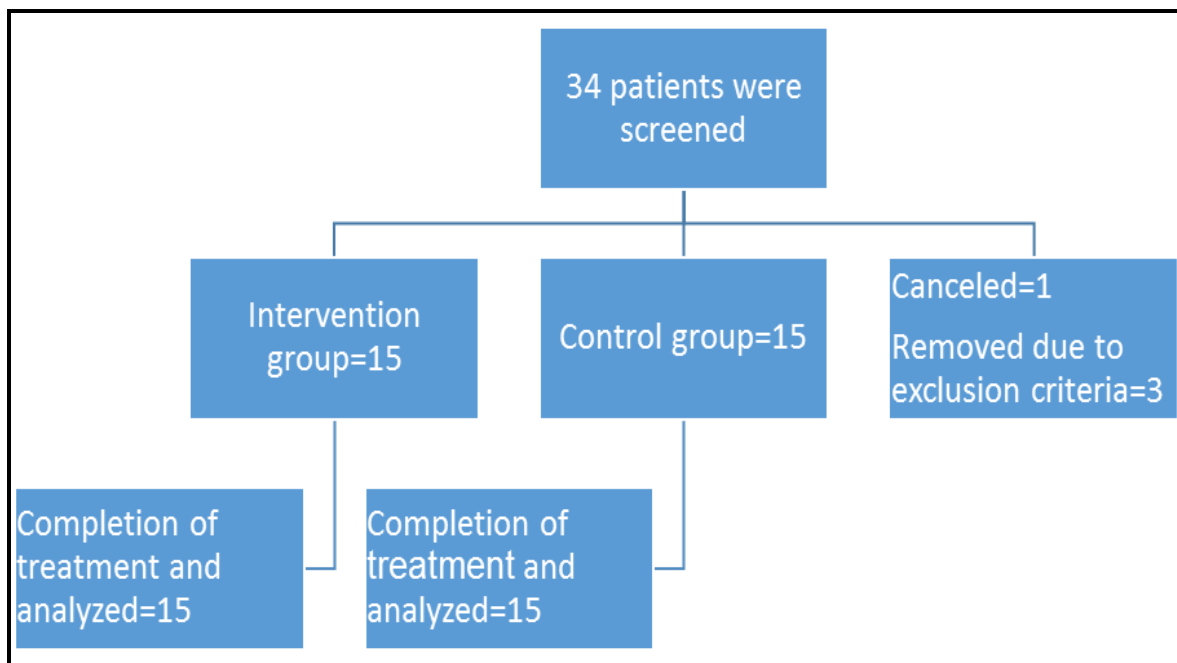


Figure 1. Obsessive Compulsive Patients Inclusion Diagram

Discussion

This randomized single-blind clinical trial study was performed to evaluate the effectiveness of triptorelin injection in clients with OCD. Our results showed triptorelin decreased the symptoms of OCD and its effectiveness in the treatment of OCD symptoms was confirmed.

A number of studies demonstrated the effectiveness of antiandrogenic pharmacological agents on OCD. Long-acting analogs of the GnRH is the most commonly used among these agents. This investigation was done to shed more light on the possibility of using such powerful antiandrogenic agents in the treatment of OCD. Based on the obtained results of our study, Yell Brown score decreased in both groups after the intervention. However, the effectiveness of triptorelin treatment in OCD clients was higher compared to that in the control group. Late period was reported in most of the clients (66.7%) in the intervention group.

For the first time, Erikson et al used a composition comprising of at least 1 substance within the group GnRH-analogs to produce a drug to treat OCD (17). Moreover, Eriksson, assessed the therapeutic effects of long-acting GnRH analog triptorelin on the treatment of OCD during a 48-week period in another study. In the mentioned study, visual analog scale was used for the assessment of the severity of OCD symptoms every week, with a considerable improvement observed in five out of six clients. The mentioned study showed that the antiandrogenic agents were effective in the treatment of OCD (18). This finding was confirmed by our result, which evaluated the effectiveness of an antiandrogenic drug in the treatment of OCD in a one-way blind clinical trial using Y-BOCS.

Few studies confirmed the effectiveness of antiandrogenic agents, such as flutamide (15) and triptorelin (18) in the treatment of OCD clients. The results of these studies are in line with our findings. However, not enough studies have evaluated the effect of using triptorelin, along with the standard therapeutic approaches of OCD. Although SSRIs are the treatment of choice for OCD therapy, they sometimes fail to control the symptoms (22). Therefore, there is always concern on the effectiveness of these medications.

Another study conducted on the hypersexual clients revealed a significant decrease in obsessive-compulsive symptoms after using antiandrogenic drugs (15), thereby confirming the role of GnRH in obsessive-compulsive pathophysiology. The results of a study performed by Peterson et al on the effectiveness of GnRH in four individuals with OCD revealed a relationship between changes in GnRH and the onset or exacerbation of OCD (23). In another study conducted by Eriksson et al on the clients with OCD, eight clients were treated with flutamide (250-750 mg/dL) for eight weeks. The results were evaluated by Y-BOCS for obsessive-compulsive symptoms. They reported no reduction in obsessive-compulsive symptoms, which is indicative of the effects

of GnRH on the mitigation of obsessive-compulsive symptoms.

The results of another study assessing the antiandrogenic agonist on OCD showed that some clients were effectively improved after the administration of long-term GnRH, such as triptorelin. There was a long time interval between the initiation and completion of the treatment (16). The positive impact of cyproterone and flutamide on the treatment of OCD symptoms indicates the role of antiandrogenic effects of this medicine (24). The modulate serotonergic activity and the antidopaminergic-like activity role of GnRH are reported in some studies (25, 26). This is indicative of the role of this hormone in addictive behaviors like alcoholism due to their effectiveness from serotonergic and antidopaminergic activity of some drugs (26). These findings support the hypothesis of the effect of gonadotropin-releasing hormone agonist (triptorelin) on the treatment of clients with OCD. Moreover, the role of triptorelin is confirmed in paraphilias (disorders of sexual preference) and mentally disordered sex offenders in other studies (27, 28), indicating the role of GnRH in performing involuntary behaviors.

Limitation

This study introduced triptorelin as an auxiliary medicine of OCD. The main strengths of this study was the introduction of a new drug as an auxiliary medicine of OCD (triptorelin). This is the second study in the literature that used triptorelin. Due to small sample size, affecting the outcome by uncontrolled intervention variables and the impossibility of long-term follow-up, we could not generalize our findings. Therefore, future studies should be conducted with large sample size and long-term follow-up to check the results obtained from our study. In this regard, future evidences help us to prevent the irreversible side effects of the drug.

Conclusion

This randomized single-blind clinical trial study confirmed the effectiveness of triptorelin injection in clients with OCD. Accordingly, triptorelin decreased the symptoms of OCD and its benefits in the treatment of OCD symptoms was confirmed. Based on other results, Yell Brown score decreased in both groups after the intervention. However, the effectiveness of triptorelin treatment in OCD clients was higher, compared to that in the control group. However, as only few studies assessed the role of antiandrogenic agents, such as triptorelin in the treatment of OCD clients, future studies are suggested to clarify this conclusion.

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Conflict of Interest

None.

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