Effect of Adding Risperidone to Fluoxetine in Treatment of Obsession Compulsion Disorder Patients

Faezeh Tatari[1], Habibollah Khazaei[1], Fahimeh Jahandar[1], Mansour Rezaei[2*]

1. Department of Psychiatry, Faculty of Medicine, Kermanshah University of Medical Sciences
2. Department of Biostatistics and Epidemiology, School of Public Health, Social development and health promotion research center, Kermanshah University of Medical Sciences, Kermanshah, Iran.
* Corresponding author: PhD, Department of Biostatistics and Epidemiology, School of public Health, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran, Tel: +98-831-4274618 (-21), Fax: +98-831-4276477, Email: rezaei39@yahoo.com

Abstract: Obsessive-compulsive disorder (OCD) has the lowest response to treatment among anxiety disorders. Although specific serotonin reuptake inhibitors are effective in the treatment of this disorder, about 50% of these patients experience no improvement by these medications. According to the lower response of OCD to treatment compared with other anxiety disorders, the goal of many studies is to use additional treatments. This study aimed to evaluate the effect of adding risperidone to fluoxetine in these patients. In a double-blind randomized clinical trial, one group received the treatment with fluoxetine-placebo while another group was under treatment with fluoxetine-risperidone. The "Yale–Brown Obsessive Compulsive Scale" was used to assess obsession severity before treatment, 6 weeks and 12 weeks after treatment. 88 patients with OCD (cleaning obsessions) were involved in the study. The cure rate was compared in the two groups by using Friedman, Chi-square, U Mann-Whitney and t tests.
In this study, 6 weeks after the treatment, cure rate with risperidone in 12 patients (66.7%) was higher than the placebo in6 patients (33.3%). However, after that the mean of Yale–Brown Scale in the two groups was similar (15.2 (6.0) vs. 15.2 (5.1); (P=0.982). According to the present study, adding risperidone to fluoxetine did not have a long-term effect on increasing the response to treatment in patients with OCD.
[Faezeh Tatari, Habibollah Khazaei, Fahimeh Jahandar, Mansour Rezaei. **Effect of Adding Risperidone to Fluoxetine in Treatment of Obsession Compulsion Disorder Patients.** *Life Sci J* 2013; 10(11s):153-157]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 27

Key words: obsessive-compulsive disorder, fluoxetine, risperidone

Introduction

Obsessive-compulsive disorder is repetitive obsessive thoughts or actions that cause a person to be distressed, interfering with his life (Soltanifar, 2007). The prevalence of this disorder is reported to be different in various societies. But generally, the life-time prevalence has been reported to be 3.2% to 4% (Farnam, 2008). Symptoms usually begin during adolescence, in over 50% of patients symptoms start in the early teenage years. About 85% of patients have experience long periods of sickness making this a chronic disorder (Fenske, 2009 and Farnam, 2008). Although specific serotonin reuptake inhibitors (SSRIs) have been successful in treating these patients, reports suggest that about 50% of patients do not improve with these medications (Michihiko, 2005).

Fenske and Sechunk (2004) believe that if SSRIs do not result in a satisfactory therapeutic response, the best option is to begin combination therapies. One of the combination therapies is to add an atypical antipsychotic drug. It has been reported in studies that risperidone had the most powerful clinical evidence to be used as additional treatment in OCD (Fenske, 2009).

Lorrin et al (2000) believe that adding a known neuroleptic like risperidone to SSRI in the treatment regimen of patients with OCD will be beneficial (Lorrin, 2000).

In a double-blind clinical trial, Mc Dagel et al reported the efficacy of risperidone in the treatment of patients with OCD, during which the patients' symptoms had significantly decreased (Christopher, 2000).

Sareen et al (2004) conducted a study to assess the efficacy of antipsychotic drugs in treating OCD in which the symptoms of some of the patients with OCD had been exacerbated by using these drugs (Sareen, 2004).

Since the studies about the efficacy of atypical antipsychotic drugs are very few and inconsistent, in a double-blind randomized clinical trial we compared the effect of a fluoxetine-risperidone therapeutic regimen with fluoxetine-placebo in treating patients with OCD.

Materials and Methods

After receiving the ethics committee approval, this double-blind randomized clinical trial with placebo as the control was conducted in Farabi

hospital affiliated to Kermanshah University of Medical Sciences in 2011-2012.

The sample size was determined to be at least 60 patients with a confidence interval of 95% and a power of 90%. In this study, 44 patients received fluoxetine-placebo while 44 patients were in fluoxetine-risperidone group.

The inclusion criteria of the study were: patients aged 18-65, having cleaning OCD, and those not already receiving any treatments.

The exclusion criteria were: lack of the patient's consent, simultaneously having a psychotic disorder and any other disorders of axis I, substance abuse, or suicidal thoughts, Yale Brown scale less than 16, intolerance of the drugs used in the study, age less than 18 years or over 65 years, and other OCDs except cleaning type.

Before performing the study, the study's method and voluntary participation were explained; then, if the patients desired to participate, they completed a written consent.

The participants were the outpatients of the psychiatry clinic who had the diagnostic criteria of OCD based on the 4th Edition of the Diagnostic Statistical Manual of Mental Disorders (revised text) DSM-IV-TR with a Yale-Brown Scale of at least 16. Yale-Brown Scale of thought-action obsession is a reliable-valuable scale for assessing different aspects of OCD, considering the symptoms severity, and response to treatment. The scale contains 10 components among which 5 measure obsessive thoughts while 5 components evaluate compulsive actions. In each of the two cases, the time spent for the thoughts or acts, the resistance against the symptoms, the interference with functioning, the distress caused by the disorder and the degree of control over the symptoms are evaluated with a score between zero and 4 (none to severe). The maximum score of this scale is 40 (Soltanifar, 2007 and Storch, 2006). The reliability of this scale has been proven in the previous studies so that the reliability between the investigators was 98% in 40 patients with an internal consistency (alpha coefficient) of 89% (Goodman et al in 1998, quoted by Fati in 1991) (Fati, 1991).

Among the 88 patients who were involved in the study, 28 individuals were excluded from the placebo group due to not referring and 14 from the risperidone group (10 due to not referring and 4 due to side effects). Among the 4 patients in the risperidone group, 3 developed severe drowsiness and 1 mentioned severe gastrointestinal complications; after exclusion, these patients were treated and followed up by the physician. Finally, the 60 patients were divided into two groups of 30 cases. Fluoxetine dose in both groups was 20 milligrams (mg) in the first week, 40 mg in the second week and 60 mg in the third week (Sadock, 2009).

Risperidone dose in the first week was 0.5 mg which increased to 1 mg at night, in the second week (Horcajadas, 2006). The placebo dose was the same as risperidone. In all of the cases, the dose of all medications was fixed until the end of the study.

The study duration was 12 weeks and assessment by Yale-Brown Scale was performed before starting the treatment, 6 weeks and 12 weeks after treatment.

The statistical analysis was done based on Friedman analysis of variance for comparison of three time assessment Yale-Brown Scales in each group. One sample Kolmogorov-Smirnov (KS) test used for test of normality for quantitative variables. According to the result of the KS test we used the independent sample t test for comparison of age and Yale-Brown Scales means between two groups and we used Mann-Whitney U test for duration. Chi-square tests used for comparing sex, education level, family history, job category and improvement after 12 weeks between two groups and also between improved and none improved patients. But we used Fisher's exact test for comparing complications and improvement after six weeks in two groups. We used SPSS 16.0 software for data entry and data analysis.

Results

The mean (SD) age of the patients was 30.7 (9.9). The mean disease duration in the placebo and the risperidone groups was respectively 24.9 (39.0) and 25.7 (18.8) months. There was no significant difference between the two groups regarding age, sex, disease duration, family history, the primary Yale-Brown Scale mean score, education and occupation (table 1).

Fifty three patients (88.3%) improved, among whom 28 were in the risperidone group (93.3%) and 25 in the placebo group (83.3%). The time to achieve remission in 18 patients (30%) was 6 weeks after beginning treatment; 12 patients (66.7%) were in the risperidone group and 6 individuals (33.3%) were in the placebo group (P=0.148) and the other patients improved after 12 week.

Yale-Brown Scale in both group were statistically different (P<0.001) in three times measurements (before treatment, 6th and 12th weeks after treatment), (table 2).

Table 1. Comparison of demographical variables between the two groups [frequency (%) or mean (SD)]

Variables		Placebo	Risperidone	P value
Age (Year)		30.3 (9.2)	29.6 (10.4)	0.774*
Duration of disorder (month)		18.9 (25.7)	24.9 (39.0)	0.926**
Yale-Brown primary scale		29.2 (4.8)	28.5 (5.7)	0.644*
Education	Primary	9 (30%)	10 (33.3%)	0.061#
	Low literacy	3 (10%)	10 (33.3%)	
	High school	5 (16.7%)	5 (16.7%)	
	Diploma and high	13 (43.3%)	5 (16.7%)	
Sex	Male	3 (10%)	9 (30%)	0.053#
	Female	27 (90%)	21 (70%)	
Family history	no	7 (23%)	6 (20%)	0.754#
	yes	23 (77%)	24 (80%)	
Job	unemployed	7 (23.3%)	6 (20%)	0.323 #
	employed	4 (13.3%)	1 (3.3%)	
	housewife	19 (63.3%)	23 (76.7%)	

*- independent sample t test, **- Mann-Whitney u test, #- Chi-square test

Table 2. Comparison of the Yale-Brown scale between the two groups [mean (SD)]

Yale-Brown scale	Placebo	Risperidone	P value
before therapy	5.7 (28.5)	4.8 (29.2)	0.644*
in 6th week	7.3 (21.7)	5.9 (21.2)	0.742*
in 12th week	6.0 (15.2)	5.1 (15.2)	0.982*
P value	<0.001##	<0.001##	

*- independent sample t test, ##- Friedman test

Considering cure as 30% decrease in the symptoms based on the Yale-Brown Scale, the cure rate was 90% in the risperidone group and 83.3% in the placebo group (P=0.706).

The patients with a positive family history of OCD showed a lower response to treatment; however, this difference was not significant between the patients who were cured compared to those who had no improvement (P=0.806).

Among all of the participants, 4 patients (6.7%) experienced mild complications all of whom were in the risperidone group (1 with lightheadedness and 3 with mild drowsiness).

Comparing the patients who were cured with those who had no improvement, no significant difference was observed in the terms of mean age, mean disease duration, education, occupation and family history (table 3).

Table 3. Comparing the response rate to treatment based on the demographic variables of the improved and unimproved patients [frequency (%) or mean (SD)]

Variables		Improved patients	Unimproved patients	P value
Age (Year)		31.0 (9.9)	23.4 (6.0)	0.039*
Duration of disorder (month)		26.2 (31.5)	19.5 (23.1)	0.566**
Family history no		11 (84.6%)	2 (15.4%)	1.0#
yes		41 (87.2%)	6 (12.8%)	
Sex Male		42 (87.5%)	6 (12.5%)	0.655#
Female		10 (83.3%)	2 (16.7%)	
Education	Primary	17 (89.5%)	2 (15.4%)	0.931#
	Low literacy	11 (84.6%)	2 (15.4%)	
	High school	9 (90%)	1 (10%)	
	Diploma and high	15 (83.3%)	3 (16.7%)	
Job	unemployed	10 (76.9%)	3 (23.1%)	0.385#
	employed	5 (100%)	0 (0.0%)	
	housewife	37 (88.1%)	5 (11.9%)	
total		52 (86.7%)	8 (13.3%)	

*- independent sample t test, **- Mann-Whitney u test, #- Chi-square test

Discussion

According to the results of the study, until the sixth week after treatment, the response rate in the risperidone group 12 individuals (66.7%) was significantly higher than the placebo group 6 individuals (33.3%) (P=0.148); however, after that until the end of the study, the response rate was similar in both groups. The FDA has already approved SSRIs to treat obsessive compulsive disorder; however, reports suggest that this disease has the lowest response to treatment among anxiety disorders. About 50% of the patients do not improve by using these drugs. Evidence shows that atypical antipsychotic drugs such as risperidone have been effective as the additional treatment in these patients (Lorrin, 2000).

Although the effective mechanism of atypical antipsychotic drugs on OCD symptoms is not exactly known, the effect of these drugs on D2 and 5HT2 receptors has been explained as a part of the effective mechanism (Ramasubbu, 2000).

Kappur et al (1998), based on a PET scan study, showed that a low-dose of atypical antipsychotics was 5HT2 antagonist while in high doses it acts as D2 antagonist (Kapur, 1998).

Some studies have shown that adding low doses of risperidone [1mg/d for 14 weeks (Reigi, 2006), 2mg for 12 weeks (Yun Jung, 2009), 2.2 (0.7) mg for 6 weeks (Christopher, 2000) and 1.5 up to 3.8 mg for 12 weeks (Horcajadas, 2006)] to the SSRIs in treating patients with OCD could increase the response to treatment. But in this study, improvement was evaluated in the two groups and there was no significant difference between the two groups (P=0.706).

Sareen et al (2004) and also Horcajadas et al (2006) in their studies stated that the average dose of antipsychotic in the treatment of OCD is lower than the effective dose in the treatment of psychotic disorders; however, the proper dose of atypical antipsychotics in the treatment of OCD is not available, necessitating further studies to determine the optimal dose (Sareen, 2004 and Horcajadas, 2006).

In a study by Lykouras et al, the patients treated by risperidone, clozapine and olanzapine experienced symptom exacerbation which resulted from having an underlying psychotic disorder (Lykouras, 2003). However, in the present study we excluded those patients from the beginning.

According to the study by Mark Lander et al (2004), there aren't many systematic studies evaluating OCD exacerbation due to using atypical antipsychotic drugs; however, it seems that these individuals are biologically prone to develop OCD accompanied with schizophrenia (Sareen, 2004).

In a study (Sareen, 2004), the most tolerable side effects of low-dose risperidone (2.2 (0.7) mg) for the patients were increased appetite, restlessness and sedation; while Mc Dagel et al (2003) reported transient mild drowsiness as the most common complication. In our study, among the 4 patients who experienced the mild side effects, 3 suffered from drowsiness.

Based on some studies, age, sex, occupation and disease duration had no effect on response to treatment (Soltanifar, 2007 and Farnam, 2008); consistently, in the present study, no significant correlation was observed between the aforementioned variables and the response to treatment.

According to the results of the present study, up to the 6th week after treatment, the cure rate in the risperidone group was significantly higher than the placebo group; however, after that until the end of the study, the cure rate was similar in both groups.

Regarding the performed studies (Horcajadas, 2006 and Lykouras, 2003), using low-dose risperidone was effective but using high-dose had reverse effects; additionally, since the Asians are slow metabolizers of drugs, the minimum dose of risperidone was used in the present study in order to prevent unexpected side effects. Hence, some studies (Sareen, 2004, Yun Jung, 2009, Christopher, 2000, Horcajadas, 2006 and Lykouras, 2003) had used higher doses of risperidone which might be the probable justification for some of the differences between their results.

Furthermore, Ragel et al (Christopher, 2000) reported that OCD patients with or without tic and schizotypal personality disorders had the same response to risperidone and some of the OCD patients with accompanied obsessive-compulsive personality disorder had a poorer response to treatment. In the present study, the patients were not evaluated in terms of the personality disorder which might be another reason for the difference between our results and the results of the other studies.

Conclusion

According to the results, up to the sixth week after treatment, the cure rate in the risperidone group was significantly higher than the placebo group; however, after that until the end of the study, the cure rate was similar in both groups. Regarding the performed studies, using low-dose risperidone was effective but using high-dose had reverse effects. Additionally, the minimum dose of risperidone was used in the present study in order to prevent unexpected side effects. Hence, some studies had used higher doses of risperidone which might be the probable justification for some of the differences between their results. Furthermore, OCD patients

with or without tic and schizotypal personality disorders had the same response to risperidone and some of the OCD patients with accompanied obsessive-compulsive personality disorder had a poorer response to treatment. In the present study, the patients were not evaluated in terms of the personality disorder which might be another reason for the difference between our results and the results of the other studies.

Limitations

The small sample size and the short study duration were the study limitations; however, it is suggested to conduct further studies with a larger sample size and longer duration. Since the proper effective dose of risperidone for OCD treatment is not known, more studies should be performed with different doses of risperidone to compare and determent proper dosage. Still, long-term studies using antipsychotic as the maintenance therapy in OCD are not available and it is possible that the treatment duration with atypical antipsychotic drugs was not adequate in our study.

References

1. Soltanifar A, Abdollahian E, Nasiraei A. Comparison of fluoxetine and clomipramine effects between children and adolescents with obsession-compulsion disorder. Medical Journal of Mashhad University of Medical Sciences, Fall 2007; 97(50): 315-20.
2. Fenske NJ, Schwenk TL. Obsessive-compulsive disorder: Diagnosis and management. American Family Physician, August 1, 2009; 80: 239-245.
3. Farnam AR, Goreishizadeh MR, Farhang S. Effectiveness of fluxetine on various subtypes of obsessive-compulsive disorder. Arch Iranian Med 2008; 11(5): 522-525.
4. Michihiko M. Perospirone. A novel antipsychotic drug inhibits marble-burying behavior via S-ht receptor in mice in implications for obsessive-compulsive disorder. Journal of Pharmacological sciences, 2005; 99: 154-159.
5. Sareen J, Kirshner A, Lander M, Kjernisted KD, Eleff MK, Reiss JP. Do antipsychotics ameliorate or exacerbate obsessive-compulsive disorder symptoms? : A systematic review. Journal of Feet disorder, 2004; 82: 167-174.
6. Lorrin MK, Alen LR, Micheal AE. Olanzapine augmentation for treatment resistant obsessive compulsive disorder. The Journal of Clinical Psychiatry, Jul 2000; 61(7): 514, 4.
7. Reigi Y, Sachiko K, Koji Sh, Jun N. Successful treatment for obsessive-compulsive disorder with addition of low-dose risperidone to fluvoxemine. Psychiatry and Clinical Neuro Seicence, 2006; 60: 389-93.
8. Yun Jung C. Efficacy of treatments for patients with obsessive-compulsive disorder. Journal of the American academy of nurse practitioners, 2009; 21: 207-213.
9. Christopher M, Neill E, Gregory H, Suzanne W, Lawrence H. A double blind, placebo controlled study of risperidone addition in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Arch Gen Psychiatry, 2000; 57: 794-801.
10. Horcajadas F, Soto J, Contalapiedra G, Colvin R, Morales J, Salgado M. Effectiveness and tolerability of addition of risperidone in obsessive-compulsive disorder with poor response to serotonine reuptake inhibitors. Actas Esp Psigquiat, 2006; 34: 147-152.
11. Lykouras L, Alevizos B, Michalopoulou P, Rabavias A. Obsessive-compulsive symptoms induced by atypical antipsychoties. Progress in neuro-psychopharmacology & biological psychiatry, 2003; 27: 333-346.
12. Sadock BJ, Saock VL, Rviz P. Comprehensive text book of psychiatry. 9th edition, 2009; Chapter 14: 1906-14.
13. Ramasubbu R, Ravindron A, Lapierre Y. Serotonine and dopamine antagonism in obsessive- compulsive disorder: Effect of atypical antipychotic drugs. Phermacopsychiatry, 2000; 33: 236-38.
14. Kapur S, Zipursky RB, Remington G, Jones C, Dasilva J, Wilson A, Houle S. 5HT2 and D2 receptor occupancy of Olanzapin in schizophrenia: A PET investigation. AM J Psychiatry, 1998; 155: 921-28.
15. Storch E, Murphy T, Adkins J, Lewin A, Geffken G, Johns N, et al. The children's Yale-Brown obsessive-compulsive scale. Psychometric, 2006; 20(8): 1055-70.
16. Fati L. The comparison of the efficacy of exposure with response prevention, clomipramine, and combination of two methods in the treatment of obsessive-compulsive disorder. Thesis for MS degree, Psychiatric Institute of Tehran, Iran University of Medical Sciences, 1991, Tehran, Iran.

9/2/2013