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# Research Paper: Effects of Celecoxib Adjunct to Selective Serotonin Reuptake Inhibitors on Obsessive-Compulsive Disorder

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## ABSTRACT

**Introduction:** Inflammatory processes in the brain play an important role in the etiopathogenesis of Obsessive-Compulsive Disorder (OCD). Cyclooxygenase inhibitors, such as celecoxib reduce the production of proinflammatory cytokines. This double-blind study aimed to investigate the effects of adding celecoxib to Selective Serotonin Reuptake Inhibitors (SSRIs)on treating OCD.

**Methods:** Sixty patients who met the diagnosis criteria for OCD based on the Diagnostic and Statistical Manual of Mental Disorders -Fourth Edition- Text Revision (DSM-IV-TR) were recruited in the present study. Two psychiatrists independently confirmed the diagnosis by performing structured interviews. The study participants included 23 patients who received SSRIs and celecoxib (400 mg twice daily) and 22 patients in the control group that received SSRIs and placebo. Moreover, at baseline, in weeks 4, 8, and 12, the explored patients were assessed by a psychiatrist using the Yale-Brown Obsessive-Compulsive Scale (Y-BCOS).

**Results:** A significant difference was observed in the change of scores on the Y-BOCS in week 12, compared with the onset of the study between the study groups (t= -8.976, df=38, P=0.001). There was a significant difference between the study groups in obsession (F= 49.19, df= 1, P≤0.001), compulsion (F= 13.78, df= 1, P= 0.001), and OCD (F= 57.25, df= 1, P≤0.001), i.e., higher in the celecoxib group.

**Conclusion:** This study showed that adjuvant treatment with celecoxib can further improve the symptoms of OCD in individuals receiving SSRIs.

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## Highlights

- Adjuvant treatment with celecoxib can improve the obsession symptoms of OCD.
- Adjuvant treatment with celecoxib can improve the compulsion symptoms of OCD.
- Adjuvant treatment with celecoxib can be safe and with no significant side effects.

## Plain Language Summary

Obsessive-Compulsive Disorder (OCD) is more complicated by neurological diseases. Several reports showed potential role of inflammation in this psychiatric condition .the current study aims to evaluate the effects of celecoxib as an anti-inflammatory drug .the results showed the clinical effect of celecoxib, is significant in the treatment and can improve the obsession and compulsion symptoms of OCD.

## 1. Introduction

Several reports addressed the potential role of proinflammatory cytokines in the development of major psychiatric disorders, including schizophrenia, bipolar disorder, autism spectrum disorders, Alzheimer's disease, as well as Obsessive-Compulsive Disorder (OCD) (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013; Réus et al., 2015; Young, Bruno, & Pomara, 2014).

OCD is more complicated by neurological diseases, such as Sydenham butter, Huntington's disease, and Parkinson's disease; all of which interfere with basal ganglia. Similarities between Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) and OCD also provided evidence for a common etiologic mechanism for these diseases (Morer, Lázaro, Sabater, Massana, Castro, & Graus, 2008). By studying 21 patients, 91.3% of patients with OCD presented CSF anti-basal ganglia and anti-thalamic autoantibodies (Bhattacharyya et al., 2009). In this disease, the role of inflammation is hypothesized to be mediated by the increase of glutamate in the brain (Nicholson et al., 2012; Rotge et al., 2009). It also increases oxidative

Stress (Salim, Chugh, & Asghar, 2012). Several human studies signified the role of cox2 inhibitors in improving psychiatric symptoms, including OCD (Keller et al., 2013). Based on studies, anti-inflammatory agents, like celecoxib were effective in treating schizophrenia (Akhondzadeh et al., 2007), autism, and major depressive disorder (Akhondzadeh et al., 2009). This study was performed based on the hypothesis that antiinflammatory agents are also effective in treating OCD (Asadabadi et al., 2013; Shalbafan et al., 2019).

Over the past two decades, psychiatric research addressed an association between OCD and streptococcal disease, and autoimmune diseases. Moreover, Tumor Necrosis Factor-alpha (TNF-a) polymorphism was also associated with the severity of OCD symptoms (Kawikova et al., 2007; Martino, Dale, Gilbert, Giovannoni, & Leckman, 2009). Furthermore, inflammatory processes, such as chronic infections and immune response may play a crucial role in the pathogenesis of OCD; accordingly, OCD can be triggered by acute streptococcal infection (Murphy & Pichichero, 2002). A similar disease with OCD is the Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) syndrome, i.e., considerably expanded in previous years (Kurlan, 1998; Swedo et al., 1997). The main symptom of PANDAS is obsessive-compulsive behavior similar to those found in OCD (Perlmutter et al., 1999). Its mechanism remains unexplained; however, there might be some connections between infection and obsessive-compulsive behavior (Greenberg, Murphy, & Swedo, 1998), especially with streptococcal antibodies that may cause reactions in brain cells (Müller et al., 2001).

Inflammatory processes play an important role in the etiopathogenesis of OCD (Müller & Ackenheil, 1998). Therefore, the role of anti-inflammatory agents in OCD treatment is of significance. In line with previous studies that cyclooxygenase-2 inhibitors reduced the production of inflammatory cytokines (Akhondzadeh et al., 2009), the current study aimed to evaluate the effects of celecoxib on OCD treatment. Celecoxib was selected for this study, as it is a Non-Steroidal Anti-Inflammatory Drug (NSAID), i.e.,

believed to selectively inhibit prostaglandin synthesis, primarily via COX-2, and because it does not inhibit COX-1.

## 2. Methods

This 12-week, placebo-controlled trial was performed in the Outpatient Specialty Clinic of Ibn-e-Sina Hospital affiliated with the Mashhad University of Medical Sciences, Iran, from March 2014 to August 2014.

Patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for OCD were included in this research. The diagnosis was confirmed by a psychiatrist based on a structured interview and with a score of ≥21 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). The patients received no Selective Serotonin Reuptake Inhibitor (SSRI) 4 weeks before entering the study. Patients who had streptococcal infections over the 4 weeks were excluded from this study. Furthermore, patients who met the criteria of intellectual disabilities, bipolar I or bipolar II disorders, substance dependence or abuse, personality disorders, a mental disorder due to general medical conditions, and any history of gastrointestinal discomfort were excluded from this study. Pregnant women were also excluded.

This study was approved by the Institutional Review Board of Mashhad University of Medical Sciences. The study participants provided an informed consent form and were aware that could discontinue cooperation with the research project as desired. The trial was performed per the Declaration of Helsinki and subsequent revisions (Chan et al., 2013). The trial was registered in Iran (Code: IRCT201512235280N21).

The selected patients were divided into two groups by random computer-generated numbers with a 1:1 allocation ratio of medication and placebo. The examined patients were randomly given SSRI plus celecoxib 400 mg/day (200 mg bid) (morning & evening) or SSRI plus placebo for a 12-week, double-blind, placebo in a controlled study. Drugs in both groups were the same in shape, size, and color. Three patients withdraw from the study (one in the celecoxib group & two in the placebo group).

The study subjects were evaluated at the beginning of the study, as well as weeks 4, 8, and 12 using the Y-BOCS. The questionnaires were completed by a trained psychiatric assistant. Throughout the study, the individual who administered the medications, the researcher, and patients were blinded to assignments. If there was a>35% reduction in Y-BOCS scores, compared to the baseline, it was considered as a complete response to treatment. Values between 25% and 35% were considered as a partial response and a <25% reduction in Y-BOCS scores, compared to the baseline, was considered non-response to treatment (Goodman et al., 1989).

The adverse effects were monitored throughout the study; they were assessed using a checklist administered by a resident psychiatrist at baseline and 4, 8, and 12 weeks after the onset of treatment. A two-way Repeated-Measures Analysis of Variance (RP-ANOVA) (treatment × time interaction) was used to analyze the obtained data. The study groups, as a between-subjects factor (group) and 12 weekly measurements during treatment as the within-subjects factor (time) were considered; this was performed for Y-BOCS total scores. The research groups at baseline were compared to each other and the outcome of the two groups at 4, 8, and 12 weeks from the onset of the trial was also compared with an Unpaired Student's t-test. We then calculated the mean and standard deviation scores. The collected data were analyzed in SPSS. We also employed Chicago IL for comparing demographic data and the Fisher's Exact test (two-sided) to measure the frequency of adverse effects between the study groups. All statistical tests were considered statistically significant at P≤0.05.

## 3. Results

Initially, 60 patients were enrolled in the study; of whom, 5 did not meet the inclusion criteria and 10 patients met exclusion criteria. Thus, 45 patients were randomly assigned to the celecoxib (n=23) and placebo (n=22) groups.

There was no significant difference in demographic information between the research groups (Table 1). Moreover, 40 patients continued the study for 12 weeks, and 5 patients left the study. Three patients left the study in the test group for unclear reasons. A patient in the placebo group left the study due to reduced libido and the other patient because of moving to another city (Figure 1).

There was no significant difference between the study groups on the Hamilton Depression Rating Scale at baseline (t=0.47, df=38, P=0.74). The difference between the applied interventions was significant at the endpoint (week 12) (t=-6.56, df=38, P<0.001). The Mean±SD changes at the endpoint, compared to baseline were equal to -20.50±0.46 for the celecoxib and -8.00±0.69 for the placebo groups. A significant difference was observed in the change of scores of the Y-BOCS. In week 12, compared with the baseline between the research groups (t=-8.976, df= 38, P<0.001).

**Table 1.** Comparing the characteristics of the examined patients

| Variables | SSRI+Celecoxib Group | SSRI+Placebo Group | P |
|---|---|---|---|
| Gender | Female :17<br>Male :3 | Female :16<br>Male :4 | 0.99 |
| Age, y (Mean±SD) | 34.90±9.50 | 36.20±9.28 | 0.73 |
| Marital status | Married:14<br>Single:6 | Married:13<br>Single:7 | 0.99 |
| Duration of disorder (y) (Mean±SD) | 9.1±7.84 | 8.45±8.17 | 0.70 |
| Number of episodes (Mean±SD) | 1.75±0.78 | 1.90±1.07 | 0.13 |
| Medications history | Fluoxetine: 4; citalopram: 7; Sertraline: 9 | Fluoxetine: 7; citalopram: 9; Sertraline: 4 | 0.29 |
| Past psychiatric history | Yes:4 No:16 | Yes:5 No:15 | 0.99 |
| Family history | Yes:9 No:11 | Yes:11<br>No:9 | 0.75 |
| History of admission for OCD | Yes:2 No:18 | Yes:2 No:18 | 0.99 |

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There was a significant difference between the applied pharmacotherapies respecting the between-subjects factor (Greenhouse–Geisser correction; df=1, F=9.291, P=0.004). The effect of the provided pharmacotherapies was not similar between the study groups over time (groups-by-time interaction, Greenhouse–Geisser correction, F=3.97, df=1, P=0.053).

There was a significant difference between the interventions in the frequency of responses(P≤0.001). In the

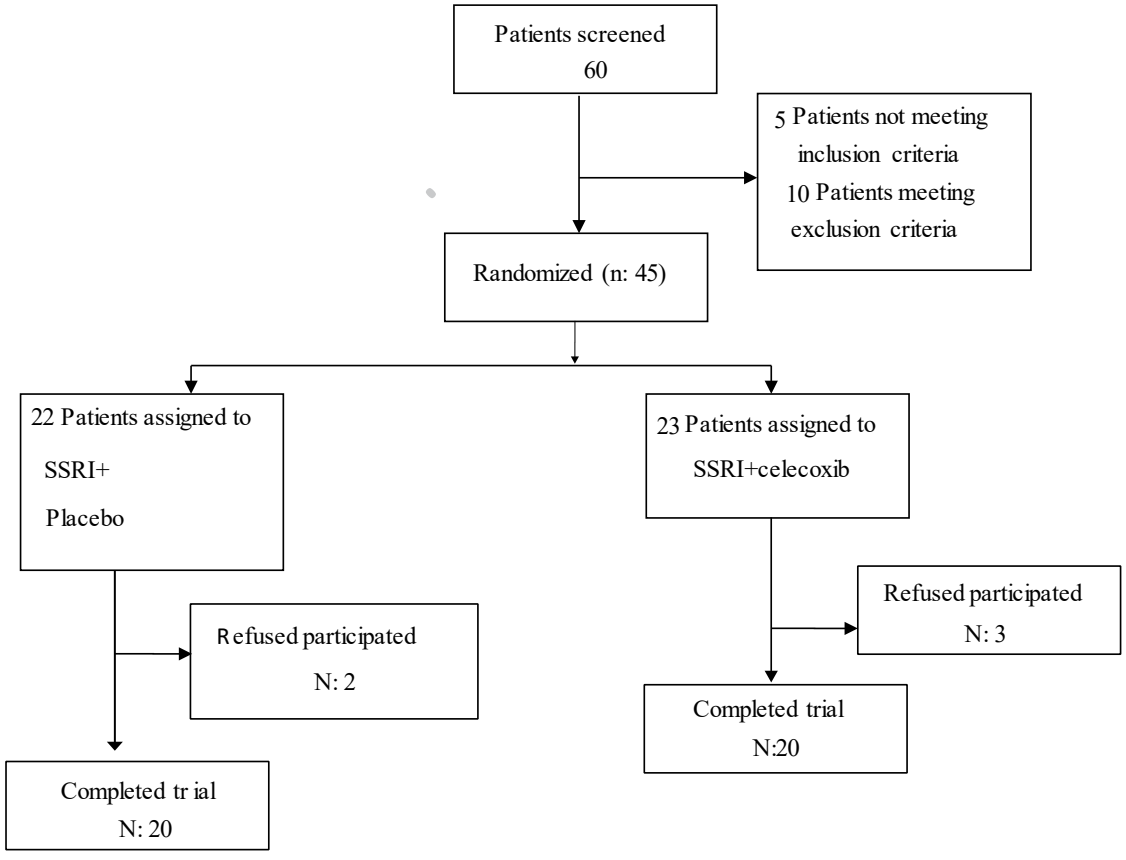


**Figure 1.** CONSORT diagram showing the disposition of all subjects screened for the study

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**Table 2.** The clinical complications and adverse effects in the study groups

| Variabels | No.(%) | | P |
|---|---|---|---|
| | SSRI+Celecoxib Group | SSRI+Placebo Group | |
| Headache | 2(10) | 3(15) | 0.98 |
| GI disturbance | 4(20) | 2(10) | 0.66 |
| Decrease or increase appetite | 2(10) | 2(10) | 0.99 |
| Other (Anxiety, Sexual dysfunction) | 2(10) | 1(5) | 0.98 |
| Respiratory | 1(5) | 1(5) | 0.99 |

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patient group, 95%(19) had full response and 5%(1) had no response; however, in the placebo group 5%(1) had full response, 35%(7) partial response, and 60%(12) no response. There was a significant difference between the study groups in obsession (F=49.19, df=1, P<0.001) (Figure 2) and compulsion (F=13.78, df=1, P:0.001) (Figure 3) as well as OCD (F=57.25, df=1, P<0.001) (Figure 4). The improvement in the intervention group was higher, relative to the placebo group.

The effect size expressed by Cohen'd was as follows: 0.19-0: value absent or no effect size, 0.49-0.2: small effect size, 0.79-0.5: medium effect size, and >0.8: great effect size (Sullivan & Feinn, 2012).

Kruskal-Wallis test results indicated the comparison between the mean dosage of drugs in the study groups, i.e., significant at P=0.000 (Table 2). The Mean±SD dosage provided to the test and placebo groups is reported in Table 3. In this study, 5 categories of adverse effects were followed up in two groups and no significant difference was reported between the research groups in this respect (Table 4).

## 4. Discussion

This was a novel study to investigate the effects of celecoxib on OCD patients as adjuvant therapy. This study demonstrated the clinical effect of SSRIs in addition to anti-inflammatory agents, like celecoxib; however, the effect of SSRIs was significant in the treatment (Müller et al., 2006; Richelson, 1994). In line with our research, Sayyah et al. argued that celecoxib (400 md/day) could reduce YBOC-S scores. Patients receiving fluoxetine plus celecoxib experienced significantly fewer symptoms, compared to those under fluoxetine and placebo therapy. In their study, the significant difference between two arms initiated from the second week, in the first evaluation, and continued to last evaluation at the eighth week. Moreover, they reported no severe adverse effect in the celecoxib group (Sayyah, Boostani, Pakseresht, & Malayeri, 2011). Another investigation compared the efficacy of celecoxib (400 mg/day) adjuvant to fluvoxamine (200 mg/day) with placebo plus fluvoxamine (200 mg/day) for 10 weeks in OCD patients. The researchers also reported that the patients in the celecoxib arm responded more significantly than those in the placebo arm, i.e., detected in the fourth and 10th weeks of follow-up (Shalbafan et al., 2015). They reported no severe or lasting adverse effects in the celecoxib group. Furthermore, they suggested that celecoxib can be considered a choice to accelerate responding to SSRIs, like fluvoxamine.

These findings were consistent with both previous studies. We used celecoxib at the same dose as previous trials (400 mg/d); the celecoxib group revealed more improvement than the placebo group at a 12-week follow-up. However, data analysis indicated that the effect size

**Table 3.** Dosage in the patient and placebo groups

| Drugs | Mean±SD |
|---|---|
| Sertraline | Patient: 161.11±65.08<br>Placebo: 212±85.39 |
| Fluoxetine | Patient: 45.00±19.74<br>Placebo: 57.77±18.55 |
| Citalopram | Patient: 42.00±10.95<br>Placebo: 58.57±73.47 |

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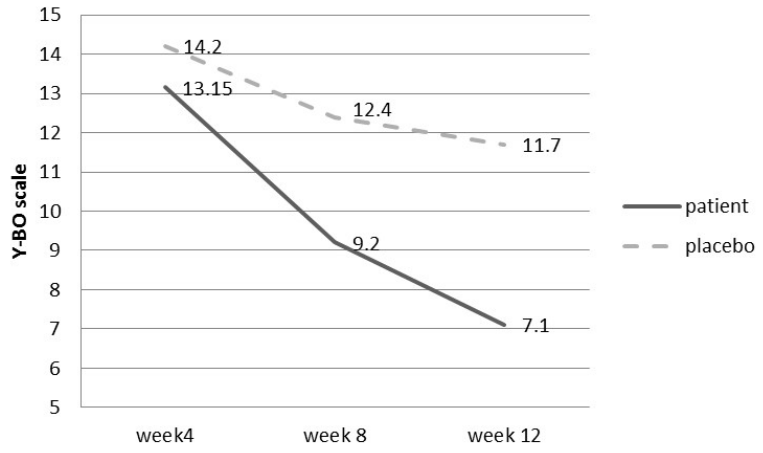


**Figure 2.** Mean of the two protocols in obsession though on the Y-BOCS

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of our intervention, celecoxib, in the fourth week was small; in the eighth and 12th weeks, it was greater for the total YBOC scale score and its subgroups, i.e., obsession and compulsion. Additionally, similar to one of the previous trials (Shalbafan et al., 2015), the number of responded patients in the celecoxib group was significantly higher than that in the placebo group. Inconsistent with these findings, in the above-mentioned trial, the investigators reported that obsession

symptoms demonstrated higher and faster reduction, compared with compulsion; however, compulsion subscale reduced more than the total scale and obsession subscale. Furthermore, the effect size on the compulsion subscale was greater than that in the other subscales of obsession and the total scale. It could be concluded as the faster effect of celecoxib on compulsive symptoms.

Consistent with the above-mentioned trials, treatment with celecoxib 400 mg was well tolerated. Moreover, it was associated with minimal clinical adverse effects without any significant difference between the study groups. No difference in clinical outcome was observed between the research groups concerning patients' clinical characteristics, such as age, gender, and disorder duration.

The mechanism of OCD is complicated. The most investigated mechanism is the dysregulation of serotonergic systems, and almost all of the approved medications for this psychiatric condition are based on this mechanism (Fenske & Petersen, 2015). However, the response rate of patients to standard serotonergic medications is only 4060% (Abudy, Juven-Wetzler, & Zohar, 2011). Therefore, researchers have recently focused on some other mechanisms to explain the etiology of OCD, such as the

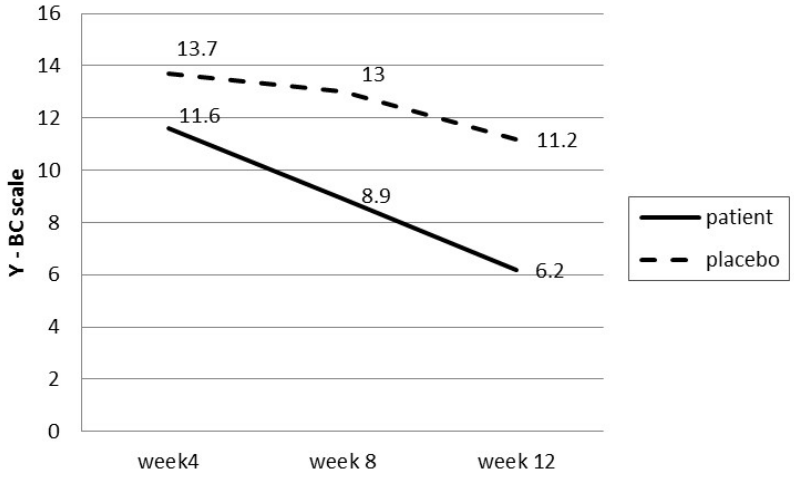


**Figure 3.** The mean score of the two protocols in compulsive behavior on the Y-BOCS

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P<0.05; NS: Not significant.

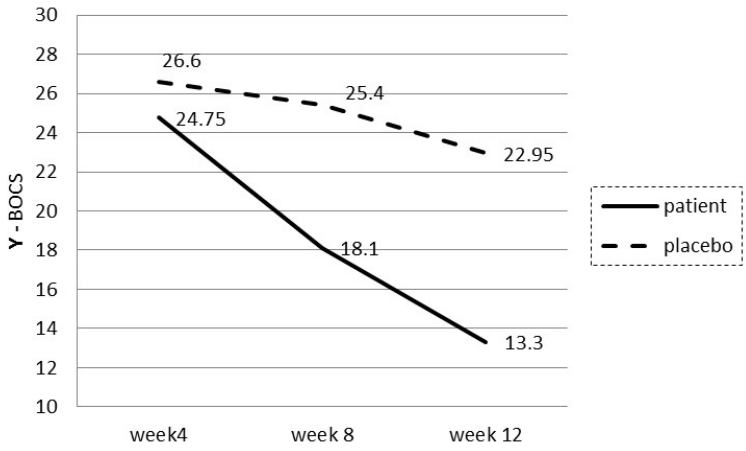


**Figure 4.** The mean value of the two protocols in obsessive-compulsive disorder on the Y-BOCS

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role of glutamatergic (Arabzadeh et al., 2017; Esalatmanesh et al., 2016) and inflammatory (Krajčovičová & Meluš, 2014; Oken, 2001) systems. The dysregulation of the inflammatory system was considered the etiology of other psychiatric conditions, like depression (Akhondzadeh et al., 2009), autism (Asadabadi et al., 2013), and schizophrenia (Akhondzadeh et al., 2007). Besides, celecoxib was used in several trials as an anti-inflammatory (COX-2 inhibitor) agent with negligible gastrointestinal adverse effects (Gordo, Walker, Armada, & Zhou, 2017). In addition, some researchers evaluated cytokines level and concluded that the dysregulation of cytokines is the main proinflammatory system involved in the pathogenesis of some psychiatric conditions (Benedetti et al., 2017; Ghafelehbashi, Pahlevan Kakhki, Kular, Moghbelinejad, & Ghafelehbashi, 2017). Interestingly, Konuk et al. evaluated IL-6 and TNFalpha levels in OCD patients, compared with the control group; they reported that both of these cytokines were significantly higher in OCD patients (Konuk et al., 2007). Another study reflected that celecoxib could decrease IL-6 levels in depressed patients (Abbasi, Hosseini, Modabbernia, Ashrafi, & Akhondzadeh, 2012). The role of the cox-2 enzyme in the synthesis of prostaglandin E2 and the prostaglandin stimulating biosynthesis of proinflammatory cytokines, like IL6 were investigated in previous studies (Akhondzadeh et al., 2007; Leonard & Myint, 2009; Miller, Maletic, & Raison, 2009; Muller & Schwarz, 2008; Simon et al., 2008). Therefore, the effect of celecoxib on the above-mentioned cytokines and pro-inflammatory

**Table 4.** The effect size in the research groups

| Y BOCS score | Mean±SD | | P | Cohen's d |
|---|---|---|---|---|
| | SSRI +Celecoxib | SSRI + Placebo | | |
| Total score (week 4) | 24.7±5.08 | 26.6±5.58 | 0.28 | 0.35 |
| Total score (week 8) | 18.1±4.55 | 25.4±5.13 | ≤0.001 | 1.5 |
| Total score (week 12) | 13.3±4.8 | 2.9±4.48 | ≤0.001 | 2.06 |
| Obsession (week 4) | 13.15±2.9 | 12.9±3 | 0.79 | 0.08 |
| Obsession (week 8) | 9.2±2.8 | 12.4±2.99 | 0.001 | 1.1 |
| Obsession (week 12) | 7.1±2.88 | 11.75±2.71 | ≤0.001 | 1.66 |
| Compulsion (week 4) | 11.6±3.25 | 13.7±3.09 | 0.04 | 0.66 |
| Compulsion (week 8) | 8.9±2.4 | 13±2.57 | ≤0.001 | 1.64 |
| Compulsion (week 12) | 6.2±2.41 | 11.75±2.71 | ≤0.001 | 2.16 |

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pathways may be a plausible explanation for adjuvant therapy to SSRIs for treating OCD. The main advantage of this trial was its duration. However, there were several limitations to this study. The major limitation was the variable type and dosage of SSRIs. The small sample size, lack of categorization between types of OCD, and absence of the evaluation of proinflammatory cytokines were some other limitations of this trial. These limitations should be considered in future investigations.

## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by the Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1393.198). All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information. They were free to leave the study whenever they wished, and if desired, the research results would be available to them. Written consent has been obtained from the subjects. Principles of the Helsinki Convention were also observed.

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### Authors' contributions

All authors equally contributed to preparing this article.

### Conflict of interest

The authors declared no conflicts of interest.

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