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Title: Efficacy of the Addition of Celecoxib to Selective Serotonin Reuptake Inhibitors in Treating Obsessive-Compulsive Disorder: A Double-Blind Clinical Trial Study

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**Purpose of the study**

Inflammatory processes in the brain play an important role in 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 efficacy of the addition of Celecoxib to selective serotonin reuptake inhibitors in treating Obsessive–Compulsive Disorder (OCD)

**Methods**

Sixty patients who met the criteria for OCD based on diagnostic and statistical manual of mental disorders –fourth edition- text revision (DSM-IV-TR) were recruited in the study. Two psychiatrists independently confirmed the diagnosis by structured interview. The 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. At the beginning of the study, in weeks four, eight and 12, the 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 Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) in week 12 compared with the onset of the study in two groups (t: 8.976, df: 38, P: 0.001). There was a significant difference between two groups in obsession (F: 49.19, df: 1, P ≤ 0.001) and compulsion (F: 13.78, df: 1, P: 0.001), and in obsessive compulsive disorder (F: 57.25, df: 1, P ≤ 0.001) which was higher in Celecoxib group.
Conclusion

This study showed that adjuvant treatment with celecoxib can further improve symptoms of OCD in individuals who are under treatment with SSRIs.

Keywords

Celecoxib; Clinical Trial; SSRI; Obsessive–Compulsive Disorder
INTRODUCTION

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

This disorder is more complicated by neurological diseases such as Sydenham butter, Huntington’s and Parkinson's disease, all of which interfere with basal ganglia. Similarities between Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) and OCD also provides evidence for a common etiologic mechanism for these two diseases (Morer et al., 2008). By studying 21 patients, 91.3% of patients with OCD had CSF anti-basal ganglia and anti-thalamic autoantibodies (Rhattacharyya 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 have shown the role of cox2 inhibitor in improving psychiatric symptoms, including obsessive compulsive disorder (Keller et al., 2013). Based on current studies, anti-inflammatory agents such as celecoxib have been effective in schizophrenia (Akhondzadeh et al., 2007), autism and major depression (Akhondzadeh et al., 2009). This study was performed based on the hypothesis that anti-inflammatory agents are also effective in the treatment of obsessive-compulsive disorder. (Asadabadi et al., 2013; Mohammadreza Shalbafan et al., 2019)

Over the past two decades, psychiatric research has shown that OCD is associated with streptococcal disease and autoimmune diseases, and recently tumor necrosis factor alpha (TNF-a) polymorphism is also associated with the severity of obsessive-compulsive symptoms (Kawikova et al., 2007, Martino, Dale, Gilbert, Giovannoni, & Leckman, 2009). According to the recent studies, inflammatory processes such as chronic infections and
immune response may play a crucial role in the pathogenesis of OCD, and this disorder can be triggered by acute streptococcal infection (Murphy & Pichichero, 2002). A similar disease with OCD is the pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) syndrome, which has expanded considerably 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 has not yet been explained although, 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 (Norbert Müller et al., 2001).

Inflammatory processes play an important role in the etiopathogenesis of OCD (Norbert Müller & Ackenheil, 1998). Therefore, the role of anti-inflammatory agents in OCD treatment is importance. In line with previous studies, that Cyclooxygenase-2 inhibitors reduced production of inflammatory cytokines (Akhondzadeh et al., 2009); the current study aims to evaluate the effects of celecoxib on OCD treatment. Celecoxib was selected for this study, because it is a non-steroidal anti-inflammatory drug (NSAID) that is believed to selectively inhibit prostaglandin synthesis, primarily via COX-2, and because it does not inhibit COX-1.

Materials and Methods:
This study is a 12-week, placebo-controlled trial in the Outpatient Specialty Clinic of Ibn-e-Sina Hospital [Mashhad University of Medical Sciences, Iran] during March 2014 to August 2014.

Participants
Patients who met Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for OCD were included. The diagnosis was confirmed by a psychiatrist based on structured interview and with the minimum score of 21 or higher on the Yale–Brown Obsessive–
Compulsive Scale (Y-BOCS). The patients did not receive any SSRIs four weeks prior to entering the study. Patients who had streptococcal infections over the course of the four-week period were excluded. Also, patients who met the criteria of mental retardation, bipolar I or bipolar II disorder, substance dependence or abuse, personality disorders, mental disorder due to general medical condition, and any history of gastrointestinal discomfort were excluded. Pregnant women were also excluded.

This study was approved by the IRB of Mashhad University of Medical Sciences. Patients with an informed consent entered the study and stated that they could withdraw from the study at their will. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (Chan et al., 2013). The trial was registered in Iran: IRCT201512235280N21.

**Intervention**

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

**Measurements**

Patients were evaluated at the beginning of the study, week 4, 8, and 12 with the Y-BOCS. The questionnaires were completed by a trained psychiatric assistant. Throughout the study, the person who administered the medications, researcher, and patients were blinded to assignments. If there was more than 35% reduction in Y-BOCS scores compared to the baseline, it was considered as a complete response to treatment. Between 25% and 35%
considered as a partial response and less than 25% reduction in Y-BOCS scores compared to the baseline, was considered non-response to treatment (Goodman et al., 1989).

**Side effects**

Side effects were followed throughout the study and were assessed using a checklist administered by a resident psychiatrist at baseline and 4, 8, and 12 weeks after the onset of treatment.

**Statistical analysis**

A two-way Repeated Measures ANOVA (treatment × time interaction) was used. The two 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 two groups at baseline were compared to each other and the outcome of the two groups at 4, 8, and 12 weeks from the start of trial was also compared with an unpaired student’s T-test. We then calculated mean and standard deviation. Data was analyzed with the SPSS version 21. We also employed Chicago IL for comparing demographic data and the Fisher’s exact test (two-sided) to measure the frequency of side effects between the groups. All statistical tests were considered statistically significant upon P≤0.05.

**RESULTS**

**Demographic Data**

At first, 60 patients were enrolled in the study, of whom 5 did not meet inclusion criteria and 10 patients met exclusion criteria. Thus, 45 patients were randomly assigned; 23 were assigned to the celecoxib and 22 were assigned to the placebo group.

There was no significant difference in demographic information between the two groups (table 1). 40 patients continued studying for 12 weeks, and five patients left the study. Three patients left the study in the drug group for unclear reasons. A patient in the placebo group
left the study due to reduced libido and the other patient because of movement from a city to another city (Figure 1).

**Efficacy: SSRI +Celecoxib vs. SSRI + Placebo**

There was no significant difference between the two groups on the Hamilton Depression Rating Scale at the beginning of the study (t: 0.47, df: 38, P: 0.74). The difference between the two treatments was significant at the endpoint (week 12) (t:-6.56, df: 38, P<0.001). The changes at the endpoint compared to baseline were equal to -20.50±0.46 (mean±SD) for the celecoxib and to -8.00±0.69 for the placebo, respectively.

A significant difference was observed in the change of scores of the Y-BOCS in week 12 compared with the baseline in the two groups (t:-8.976, df: 38, P<0.001).

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

There was a significant difference between the two treatments in the percentage of responses: p value≤0.001. In the patient group, 95% (19) had full response and 5% (1) had no response, while 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 two treatments in both obsession (F:49.19, df:1, P<0.001) (figure 2) and compulsion (F:13.78, df:1, P:0.001) (figure 3) and in OCD (F: 57.25, df:1, P<0.001) (figure 4). The improvement in the intervention group was higher relative to the placebo group.
Effect size:

The effect size expressed by Cohen's, is 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 showed the Comparison between the mean dosage of drugs in the two groups, which was significant at p value: 0.000 (table 2). Mean and standard deviations of Dosage patients and placebo groups showed in table 3.

Side Effects

In this study, five categories of side effects were followed up in two groups and no significant difference was reported between the two groups (table 4).

Discussion

This is a novel study to investigate the effect of celecoxib on OCD patients as an adjuvant therapy.

This study demonstrated clinical effect of selective serotonin reuptake inhibitors (SSRIs) in keeping with anti-inflammatory agents such as celecoxib, although the effect of selective serotonin reuptake inhibitors is significant in the treatment (N Müller et al., 2006; Richelson, 1994). As the first study, based on our research, Sayyah et al. showed that celecoxib (400md/day) could reduce YBOC-S. Patients receiving fluoxetine and celecoxib had significantly less symptoms compared to fluoxetine and placebo. In their study, significant difference between two arms initiated from 2nd week, in the first evaluation, and continued to last evaluation at 8th week. In addition, they reported no severe adverse effect in celecoxib group (Sayyah, Boostani, Pakseresht, & Malayeri, 2011). Second investigation was conducted to compare efficacy of celecoxib (400mg/day) as adjuvant to fluvoxamine (200mg/day) with placebo plus fluvoxamine (200mg/day) for 10 weeks in OCD patients. The researchers also reported
that the patients in celecoxib arm responded more significantly than patients in placebo arm which was clearly seen in 4th and 10th weeks of follow up. (M Shalbafan et al., 2015). They did not report any severe or lasting adverse effect on celecoxib group. On the other hand, they suggested that celecoxib can be considered a choice to accelerate responding to SSRIs such as fluvoxamine.

These findings are consistent with both previous studies. We used celecoxib at the same dose as previous trials (400mg/day) and the celecoxib group showed more improvement than the placebo group within 12 weeks of follow up. However, analysis showed that effect size of our intervention, celecoxib, in the 4th week was small and in the 8th and 12th weeks it was greater for total YBOC scale and both of its subgroups—obsession and compulsion. In addition, similar to one of the previous trials (M Shalbafan et al., 2015), number of responded patients in celecoxib group was significantly higher than placebo group. Inconsistent with these findings, in the above mentioned trial, the investigators reported that obsession symptoms demonstrated higher and faster reduction in comparison with compulsion, whereas compulsion subscale reduced more than both total scale and obsession subscale. In addition, the effect size on compulsion subscale is greater than other subscales of obsession and the total scale. It could be concluded as faster effect of celecoxib on compulsive symptoms.

Consistent with both the above mentioned trails, treatment with celecoxib 400 mg was well tolerated and showed minimal clinical adverse effects without any significant difference in both groups. No difference in clinical outcome was observed between the two groups in terms of patients’ clinical characteristics such as age, sex and disorder duration.

The mechanism of OCD is absolutely complicated. As we know, most investigated mechanism is dysregulation of serotonegic systems and almost all of the approved medications for this psychiatric condition are based on this mechanism (Fenske & Petersen,
However, response rate of patients to standard serotonergic medications is only 40-60% (Abudy, Juven-Wetzler, & Zohar, 2011). Therefore, researchers have recently focused on some other mechanisms to explain the etiology of OCD such as the role of glutamatergic (Arabzadeh et al., 2017; Esalatmanesh et al., 2016) and inflammatory (Krajčovičová & Meluš, 2014; Oken, 2001) systems. Dysregulation of inflammatory system has been considered the etiology of other psychiatric conditions such as depression (Akhondzadeh et al., 2009), autism (Asadabadi et al., 2013) and schizophrenia (Akhondzadeh et al., 2007), and celecoxib has been used in several trials as an anti-inflammatory (COX-2 inhibitor) agent with negligible gastrointestinal side effects (Gordo, Walker, Armada, & Zhou, 2017). In addition, some researchers evaluated cytokines level and concluded that 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 TNF-alpha levels in OCD patients in comparison with control group and reported that both of these cytokines were significantly higher in OCD patients (Konuk et al., 2007). In another study, it has been shown that celecoxib could decrease IL-6 level in depressed patients (Abassi, Hosseini, Modabbernia, Ashrafi, & Akhondzadeh, 2012). The role of cox-2 enzyme in the synthesis of prostaglandin E2 and the prostaglandin stimulating biosynthesis of pro-inflammatory cytokines such as 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, we can conclude that the effect of celecoxib on above mentioned cytokines and pro-inflammatory pathways may be a plausible explanation for an adjuvant therapy to SSRIs for the treatment of OCD.

The main advantage of this trial is its duration. However, there were several limitations for this study. The major limitation was variable type and dosage of SSRIs. It should be pointed
that small sample size, lack of categorization between types of OCD, and absence of the
evaluation of proinflammatory cytokines are some other limitations. These limitations should
be considered in the future investigations.

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Conflict of Interest:
▼The authors declare no conflict of interest.
References:


Murphy, M. L., & Pichichero, M. E. (2002). Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group
A streptococcal infection (PANDAS). Archives of pediatrics & adolescent medicine, 156(4), 356-361.


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

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

Figure 3. Mean±SD of the two protocols in Compulsive behaviour on Y-BOCS.

Figure 4. Mean±SD of the two protocols in Obsessive compulsive disorder on Y-BOCS.

Fig. 1. CONSORT diagram showing the disposition of all subjects screened for the study.
Figure 2. Mean of the two protocols in obsession though on Y-BOCS.
Figure 3. Mean of the two protocols in Compulsive behaviour on Y-BOCS.

* P < 0.05). NS, not significant
Figure 4. Mean of the two protocols in Obsessive compulsive disorder on Y-BOCS.

**Table 1. Comparing the Characteristics of patients in the two groups**

<table>
<thead>
<tr>
<th></th>
<th>SSRI+celecoxib group</th>
<th>SSRI+Placebo group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sex</strong></td>
<td>Female :17, Male :3</td>
<td>Female :16, Male :4</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>34.90±9.50</td>
<td>36.20±9.28</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td>Married:14, Single:6</td>
<td>Married:13, Single:7</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Duration of disorder (year)</strong></td>
<td>9.1±7.84</td>
<td>8.45±8.17</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Number of episode</strong></td>
<td>1.75±0.78</td>
<td>1.90±1.07</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Medications history</strong></td>
<td>Floxetine: 4; citalopram : 7; Sertraline: 9</td>
<td>Floxetine: 7; citalopram : 9; Sertraline: 4</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Past psychiatric history</strong></td>
<td>Yes:4, No:16</td>
<td>Yes:5, No:15</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Yes:9, No:11</td>
<td>Yes:11, No:9</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Table 2: Clinical complication and side effect in both group

<table>
<thead>
<tr>
<th></th>
<th>SSRI+celecoxib group</th>
<th>SSRI+Placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2(10%)</td>
<td>3(15%)</td>
<td>0.98</td>
</tr>
<tr>
<td>GI disturbance</td>
<td>4(20%)</td>
<td>2(10%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Decrease or increase</td>
<td>2(10%)</td>
<td>2(10%)</td>
<td>0.99</td>
</tr>
<tr>
<td>appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Anxiety, Sexual</td>
<td>2(10%)</td>
<td>1(5%)</td>
<td>0.98</td>
</tr>
<tr>
<td>dysfunction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1(5%)</td>
<td>1(5%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table 3: Mean and standard deviation of Dosage in patient and placebo groups

<table>
<thead>
<tr>
<th>Drugs</th>
<th>mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>sertraline</td>
<td>Patient:161.11±65.08</td>
</tr>
<tr>
<td></td>
<td>Placebo:212±85.39</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>Patient:45.00±19.74</td>
</tr>
<tr>
<td></td>
<td>Placebo:57.77±18.55</td>
</tr>
<tr>
<td>citalopram</td>
<td>Patient:42.00±10.95</td>
</tr>
<tr>
<td></td>
<td>Placebo:58.57±73.47</td>
</tr>
</tbody>
</table>
Table 4: effect size in both groups

<table>
<thead>
<tr>
<th>Y BOCS score</th>
<th>SSRI +Celecoxib</th>
<th>SSRI + Placebo</th>
<th>P value</th>
<th>Cohen' d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score (week4)</td>
<td>24.7±5.08</td>
<td>26.6±5.58</td>
<td>0.28</td>
<td>0.35</td>
</tr>
<tr>
<td>Total score (week8)</td>
<td>18.1±4.55</td>
<td>25.4±5.13</td>
<td>≤0.001</td>
<td>1.5</td>
</tr>
<tr>
<td>Total score(week12)</td>
<td>13.3±4.8</td>
<td>22.9±4.48</td>
<td>≤0.001</td>
<td>2.06</td>
</tr>
<tr>
<td>Obsession (week4)</td>
<td>13.15±2.9</td>
<td>12.9±3</td>
<td>0.79</td>
<td>0.08</td>
</tr>
<tr>
<td>Obsession (week8)</td>
<td>9.2±2.8</td>
<td>12.4±2.99</td>
<td>0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>Obsession (week12)</td>
<td>7.1±2.88</td>
<td>11.75±2.71</td>
<td>≤0.004</td>
<td>1.66</td>
</tr>
<tr>
<td>compulsion(week4)</td>
<td>11.6±3.25</td>
<td>13.7±3.09</td>
<td>0.04</td>
<td>0.66</td>
</tr>
<tr>
<td>compulsion (week8)</td>
<td>8.9±2.4</td>
<td>13±2.57</td>
<td>≤0.001</td>
<td>1.64</td>
</tr>
<tr>
<td>compulsion (week12)</td>
<td>6.2±2.41</td>
<td>11.75±2.71</td>
<td>≤0.001</td>
<td>2.16</td>
</tr>
</tbody>
</table>