Celecoxib as an Adjuvant to Fluvoxamine in Moderate to Severe Obsessive-compulsive Disorder: A Double-blind, Placebo-controlled, Randomized Trial

Authors

Affiliations
Affiliation addresses are listed at the end of the article

Key words
- anti-inflammatory agents
- celecoxib
- cyclooxygenase-2 inhibitors
- obsessive-compulsive disorder

Abstract

Introduction: A growing body of evidence implicates inflammatory cascades in the pathophysiology of obsessive-compulsive disorder (OCD), making this pathway a target for development of novel treatments.

Methods: 50 outpatients with moderate to severe OCD participated in the trial, and underwent 10 weeks of treatment with either celecoxib (200mg twice daily) or placebo as an adjuvant to fluvoxamine. Participants were investigated using Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The main outcome measure was to assess the efficacy of celecoxib in improving the OCD symptoms.

Results: General linear model repeated measures demonstrated significant effect for time×treatment interaction on the Y-BOCS total scores [F (1.38, 66.34) = 6.91, p = 0.005]. Kaplan-Meier estimation with log-rank test demonstrated significantly more rapid response in the celecoxib group than the placebo group (p < 0.001). There was no significant difference in adverse event frequencies between the groups.

Discussion: The results of the current study suggest that celecoxib could be a tolerable and effective adjunctive treatment for more rapid and more satisfying improvements in OCD symptoms.

Introduction

Obsessive-compulsive disorder (OCD) is a relatively common psychological disorder with a reported lifetime prevalence of 1–3% in the general population [1]. Currently, selective serotonin reuptake inhibitors (SSRIs) and/or cognitive-behavioral therapy, particularly exposure and response prevention (ERP), are first-line medications of choice in patients with mild to moderate OCD [2, 3]. Unfortunately, SSRIs usually reduce the severity of OCD symptoms by as little as 20–30% [4] and only 40–60% of OCD patients achieve satisfactory results [5–7]. Hence, an increasing number of studies have focused on the development of augmentative agents in the management of OCD [1]. There is a growing body of evidence indicating the probable role of inflammatory processes and immune dysregulation in the etiopathogenesis of OCD. OCD has been reported to be associated with autoimmune disorders triggered by inflammatory processes such as streptococcal infections [8].

Obsessive-compulsive behavior is also the main characteristic feature of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) syndrome. Etiopathogenesis and symptom exacerbation of PANDAS have been attributed to an inappropriate immune response to streptococcal infection resulting in its central nervous system manifestations, which include OCD and tics [9]. Interestingly, while immunomodulatory therapeutic modalities including plasma exchange and intravenous immunoglobulin therapy have shown somewhat promising results in improving neuropsychiatric symptoms of PANDAS [10], there is no conclusive evidence for the probable beneficial role of antibiotics in reducing PANDAS symptoms [11] that would further indicate the role of autoimmunity in the etiopathogenesis of PANDAS. The role of autoimmune responses in the etiopathogenesis of OCD may also be supported by a decrease in the number of regulatory T cells as well as mild dysregulation of other inflammatory cell types in blood samples of OCD patients compared to age- and sex-matched healthy controls [12].

* The first two authors contributed equally to this work.
Along with OCD, the findings of numerous studies also suggested the role of proinflammatory cytokines in the etiopathogenesis of several neuropsychiatric disorders including schizophrenia, bipolar disorder and major depressive disorder [13]. Furthermore, investigation of the therapeutic opportunities provided by this thesis has resulted in several studies on the treatment of neuropsychiatric disorders with promising results [14,15]. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) and selective inhibitor of cyclooxygenase-2 (COX-2), a known promoter of both inflammation and pain. COX-2 inhibitors have been proven to be beneficial in prevention of glutamate-mediated neuronal death and suppression of proinflammatory cytokines [16,17]. Celecoxib also has the advantage of reduced gastrointestinal complications compared to other NSAIDs. Based on the currently available data, we hypothesized that the anti-inflammatory effects of celecoxib may be beneficial in the medication management of OCD. The present 10-week, double-blind, placebo-controlled trial aimed to evaluate the safety and efficacy of adjunctive therapy with celecoxib in improving the clinical symptoms of moderate to severe OCD.

Patients and Methods ▼

Trial design and setting

A single-center, 10-week, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in the outpatient clinics of Roozbeh Psychiatric Hospital (Tehran University of Medical Sciences, Tehran, Iran) from January 2014 to November 2014. Approval was obtained from the Institutional Review Board (IRB) of Tehran University of Medical Science (Grant No: 23218). The trial was performed according to the Declaration of Helsinki and its subsequent revisions. All patients signed an informed consent prior to study entry. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201312181556N56).

Participants

Men and women, aged between 18–60 years, with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥21 to have moderate to severe OCD, were eligible to take part in the study. Exclusion criteria were as follows: any other mental disorder on DSM-IV axis I, alcohol or substance (with the exception of nicotine) dependence, intelligence quotient < 70, any serious medical illness including cardiac, hepatic and renal disease, ingestion of any psychotropic medications during the last 6 weeks, pregnancy, breast feeding and rises in liver transaminase to 3 times the upper limit of normal or higher.

Interventions

Eligible participants were randomly assigned to receive either 200 mg celecoxib (celebrex, Pfizer, 200 mg capsule) twice daily or placebo in the same manner for 10 weeks. All patients, regardless of their treatment group, also received fluvoxamine 100 mg/day for the first 4 weeks of the study followed by 200 mg/day for the rest of the trial course.

Outcomes

All patients were assessed using Y-BOCS at baseline and weeks 4 and 10. A psychiatrist with good experience in implementing the Y-BOCS who had been involved in several clinical trials was in charge of rating the patients. The main outcome measure of this trial was evaluation of celecoxib efficacy in improvement of Y-BOCS total score compared to placebo using the general linear repeated measure model. Partial response and complete response were defined as 25% and 35% reduction in the Y-BOCS score, respectively. A Y-BOCS score < 16 was considered as remission. Adverse events were systematically evaluated at each time point.

Sample size

Assuming a difference of 4 on the Y-BOCS total score between the celecoxib group and the placebo group with a standard deviation (SD) of 4.5, a power of 80%, and a two-sided significance level of 5%, a sample size of 42 was needed. Considering a 20% attrition rate, a final sample size of 54 was planned.

Randomization, allocation, concealment and blinding

Generation of randomization codes was performed by a computerized random number generator (blocks of 4, allocation ratio 1:1). Concealment of allocation was performed using sequentially numbered and sealed packages. Separate people were responsible for random allocation and rating of the patients. The patients, research investigators, rater and the statistician were all blinded to the allocated treatment. Celecoxib and placebo capsules were completely identical in their shape, color, size, texture, and odor. The placebo rate anticipation was also assessed by the participants, and the rater at the study end.

Statistical analysis

All analyses were carried out according to the intention-to-treat principles with at least one post-baseline measurement. Continuous variables were reported as mean± standard deviation (SD) and categorical variables were reported as frequency (percentage). Baseline continuous variables were compared using an independent t-test. A general linear model repeated measure was used to evaluate time×treatment interaction considering the treatment group (celexib vs. placebo) as the between-subject factor and the study measurements as the within-subject factor (time). Greenhouse-Geisser adjustment in degrees of freedom was made if Mauchly’s test of sphericity was significant. An independent t-test and Cohen’s d effect size were used to compare score change from baseline to each time interval between the 2 study groups. Categorical variables were compared using chi-square test or Fisher’s exact test as appropriate. The time needed to respond to treatment was compared between the celecoxib and the placebo groups using Kaplan-Meier estimation with log-rank test. Statistical Package of Social Science Software (SPSS version 20, IBM Company, Armonk NY, USA) was used for statistical analysis and the graphs were drawn using SigmaPlot (version 12).

Results ▼

Participants and baseline characteristics

A total of 104 participants screened for eligibility criteria, among them 54 patients, were randomly assigned to receive either celecoxib plus fluvoxamine (n=27) or placebo plus fluvoxamine (n=25). 50 patients (25 in each group) had at least one post-baseline measurement and a similar number of study participants completed the trial (Fig. 1). Baseline characteristics of Shalbafan M et al. Celecoxib in OCD... Pharmacopsychiatry 2015; 48: 136–140
the patients were not significantly different between the groups (Table 1).

Outcome
Y-BOCS total score
General linear model repeated measures demonstrated significant effect for time × treatment interaction on Y-BOCS total score during the trial course [F(1.38, 66.34) = 6.91, p = 0.005] (Fig. 2a). At the study conclusion, remission achieved in 15 (60%) patients in the celecoxib group was compared with 8 (32%) patients in the placebo group (p < 0.047). Significantly, higher partial and complete response rates were also observed in the celecoxib group than the placebo group at the end of the trial (Table 2). An independent t-test demonstrated significantly greater reduction in Y-BOCS total score in the celecoxib group than the placebo group at weeks 4 and 10 (Table 3). Kaplan-Meier estimation showed that a shorter time was needed in the celecoxib group than the placebo group for partial response, p < 0.001.

Y-BOCS obsession subscale score
General linear model repeated measures demonstrated significant effect for time × treatment interaction on Y-BOCS obsession subscale scores during the trial course [F(1.44, 69.33) = 7.17, p = 0.004] (Fig. 2b). An independent t-test demonstrated significantly greater reduction in Y-BOCS obsession subscale scores in the celecoxib group than the placebo group at weeks 4 and 10 (Table 3).

Y-BOCS compulsion subscale score
General linear model repeated measures demonstrated significant effect for time × treatment interaction on Y-BOCS compulsion subscale scores during the trial course [F(1.35, 64.90) = 3.99, p = 0.038] (Fig. 2c). Independent t-test demonstrated significantly greater reduction in Y-BOCS compulsion subscale scores in the celecoxib group than the placebo group at week 10 (Table 3).

Adverse events
Frequency of adverse events did not differ significantly between treatment groups (Table 4). No serious adverse events or deaths occurred.

Blinding
The participants and the rater were unsure about the treatment allocation in more than 50% of the allocations.

Discussion
The results of the current study showed that the administration of celecoxib, as an adjuvant agent in addition to fluvoxamine, is significantly superior to fluvoxamine monotherapy in reducing both obsessive and compulsive symptoms and achieving a more rapid response to treatment in patients with moderate to severe OCD. The use of celecoxib also appeared to be safe and well tolerated in our study population and no clinically significant adverse effect was reported. The response to treatment in the placebo arm who received monotherapy with fluvoxamine was similar to the previous reports of treatment outcome with SRIs in OCD patients [4]. Fluvoxamine monotherapy resulted in about 30% reduction in OCD symptoms (9.4 points on Y-BOCS total score). Celecoxib plus fluvoxamine resulted in about 50% reduc-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Celecoxib group (n = 25)</th>
<th>Placebo group (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, years, mean ± SD</td>
<td>33.28 ± 8.64</td>
<td>31.16 ± 8.90</td>
<td>0.40</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>79.3 ± 11.2</td>
<td>78.1 ± 11.4</td>
<td>0.70</td>
</tr>
<tr>
<td>height (cm)</td>
<td>171.6 ± 14.3</td>
<td>172.8 ± 12.2</td>
<td>0.71</td>
</tr>
<tr>
<td>sex, female, n (%)</td>
<td>9 (36%)</td>
<td>10 (40%)</td>
<td>0.77</td>
</tr>
<tr>
<td>duration of the disease (years), mean ± SD</td>
<td>5.12 ± 2.87</td>
<td>6.40 ± 3.74</td>
<td>0.18</td>
</tr>
<tr>
<td>single: married</td>
<td>8 (32%): 17 (68%)</td>
<td>10 (40%): 15 (60%)</td>
<td>0.77</td>
</tr>
<tr>
<td>education</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>– primary or secondary school</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
<td></td>
</tr>
<tr>
<td>– diploma</td>
<td>13 (52%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>– university degree</td>
<td>4 (16%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS total score, mean ± SD</td>
<td>30.24 ± 3.87</td>
<td>29.48 ± 1.69</td>
<td>0.37</td>
</tr>
<tr>
<td>Y-BOCS obsession subscale, mean ± SD</td>
<td>16.20 ± 2.14</td>
<td>15.36 ± 1.35</td>
<td>0.10</td>
</tr>
<tr>
<td>Y-BOCS compulsion subscale, mean ± SD</td>
<td>14.04 ± 2.59</td>
<td>14.12 ± 1.01</td>
<td>0.89</td>
</tr>
<tr>
<td>baseline HDRS score, mean ± SD</td>
<td>7.24 ± 1.12</td>
<td>6.98 ± 1.48</td>
<td>0.48</td>
</tr>
<tr>
<td>medications history</td>
<td>Fluoxetine: 15; Clomipramine: 10; Fluvoxamine: 8</td>
<td>Fluoxetine: 16; Clomipramine: 12; Fluvoxamine: 10</td>
<td></td>
</tr>
</tbody>
</table>
tion in OCD symptoms (14.7 points on Y-BOCS total score) by the trial conclusion. Since baseline characteristics of patients in the 2 study groups did not differ significantly, it cannot explain the differences observed in the efficacy of fluvoxamine and placebo as adjuvant agents.

The findings of the present study are consistent with the report of Sayyah et al. on augmentative treatment with celecoxib in patients with OCD. They investigated the efficacy of the same celecoxib dosage as an adjuvant therapy to fluoxetine in the management of OCD in an 8-week clinical trial [18]. They found that those in the celecoxib group showed a greater improvement of OCD symptoms compared to controls who received fluoxetine and placebo. The superior effect of celecoxib compared to placebo was observed as soon as 2 weeks after the initiation of therapy and was still significant at the study end at week 8. In agreement with their report, we found a significantly greater improvement of OCD symptoms in the first assessment after receiving medication for 4 weeks and the results were repeated at week 10. The beneficial effects of celecoxib in rapid reduction of obsessive and compulsive symptoms may be explained mainly by the role of COX-2 inhibitors in the suppression of inflamma-

### Table 3
Comparison of outcome indexes between the 2 groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Celecoxib group (n = 25)</th>
<th>Placebo group (n = 25)</th>
<th>P-value</th>
<th>power</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number (%) of PRs at week 4</td>
<td>9 (36%)</td>
<td>4 (16%)</td>
<td>0.10</td>
<td>0.25</td>
<td>2.95 (0.76–11.33)</td>
</tr>
<tr>
<td>number (%) of PRs at week 10</td>
<td>23 (92%)</td>
<td>10 (40%)</td>
<td>0.0001</td>
<td>0.97</td>
<td>17.25 (3.31–89.97)</td>
</tr>
<tr>
<td>number (%) of CRs at week 4</td>
<td>3 (12%)</td>
<td>4 (16%)</td>
<td>1.00</td>
<td>0.02</td>
<td>0.71 (0.14–3.58)</td>
</tr>
<tr>
<td>number (%) of CRs at week 10</td>
<td>22 (88%)</td>
<td>9 (36%)</td>
<td>0.0001</td>
<td>0.97</td>
<td>13.03 (3.03–55.95)</td>
</tr>
<tr>
<td>number (%) of remitters at week 4</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1.00</td>
<td>0.02</td>
<td>2.08 (0.17–24.61)</td>
</tr>
<tr>
<td>number (%) of remitters at week 10</td>
<td>15 (60%)</td>
<td>8 (32%)</td>
<td>0.047</td>
<td>0.39</td>
<td>3.18 (0.99–10.17)</td>
</tr>
</tbody>
</table>

CI, confidence interval; PR, partial responders; CR, complete responders
COX2 in CNS neural cells mediates

The authors declare no conflict of interest.

Acknowledgement

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Conflict of Interest

The authors declare no conflict of interest.