Effect of Adjunctive Celecoxib on BDNF in Manic Patients Undergoing Electroconvulsive Therapy: a Randomized Double Blind Controlled Trial

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Key words
- bipolar disorder
- electroconvulsive therapy (ECT)
- bipolar disorder treatment

Abstract

Introduction: The possible effect of inflammatory factors on decreasing BDNF has been proposed in the literature. There is conflicting evidence regarding association between BDNF level alteration and treatment response in depressive patients undergoing electroconvulsive therapy (ECT). This study investigated the effects of celecoxib in manic patients undergoing ECT on treatment response and BDNF levels.

Methods: This randomized, double-blind, clinical trial included 35 manic patients who received either celecoxib (200 mg twice daily) or placebo, from one day before the 1st ECT session throughout the 6th session. BDNF levels were measured at baseline, 1st, 3rd and 6th ECT sessions. Young mania rating scale was used to assess treatment response.

Results: Adding celecoxib was not associated with a significant rise in BDNF levels following ECT. No difference was noted between groups in terms of treatment response. No significant association was found between changes in BDNF levels and patients' responses.

Discussion: Adjuvant celecoxib did not significantly affect the BDNF level or the treatment response following ECT in manic patients.

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Introduction

Bipolar disorder (BD) is a prevalent, chronic psychiatric disorder with a complex genetic and neurochemical etiology [1–4]. Alteration of multiple neurotrophic/growth factors [1] along with impairments in synaptic plasticity [5] and cell survival [6] have been detected in patients diagnosed with BD [6] and attributed to the alterations of neurotrophins [5].

Brain-derived neurotrophic factor (BDNF) is the most widely expressed [5] neurotrophin in the brain [3], particularly, in the hippocampus and cerebral cortex [7]. BDNF, a nerve growth factors [8], affects serotoninergic [2,6] dopaminergic [2] and glutamatergic systems [2,6] and plays an important role in neuronal connectivity, neuroplasticity [2,6] and neuronal survival [2,3,5–7] by stimulating receptors containing "intrinsic tyrosine kinase activity" [8]. Sartorius et al. provided evidence for correlation between serum and brain BDNF levels in a rat model of ECT [9]. Pillai et al. reported a correlation between the peripheral levels of BDNF with its cerebrospinal fluid concentration during the 1st episode psychosis [10]. On the contrary, Béjot et al. reported that serum or plasma levels of BDNF did not change in a rat model of stroke despite a significant increase in brain BDNF [11]. It should be noted that the mentioned studies were performed under different settings. BDNF has been studied in different neuropsychiatric disorders including BD [3,6,12]. Patients with BD seem to have lower serum BDNF concentrations in the depressive and manic phases than in the euthymic status. BDNF levels have also been reported to be negatively correlated with the severity of mood episode [13]. There is conflicting data regarding the direction of BDNF changes in different mood status [7]. BDNF has been suggested as a potential biomarker for differentiating unipolar from bipolar depression and also as a predictor of treatment response [4]. Despite very little data in this area, increases in BDNF levels have been suggested to be associated with responses to ECT in refractory depressed patients [14]. To our knowledge, only one study has been published regarding BDNF levels in manic patients following ECT. However, changes in BDNF levels were not found to be associated with clinical response [15]. A similar finding was noted in another study in patients with refractory schizophrenia undergoing ECT [16].

Adjunctive celecoxib, a cyclooxygenase II inhibitor, has been studied in different psychiatric disorders and on the inflammatory mediators with varying results [17–25]. Funakoshi-Tago et al. found that celecoxib can strongly inhibit TNFα-induced transcriptional activity and DNA-binding activity of NF-kB [26]. The activation of NF-kB signaling pathways is responsible for the effects of IL-1 on neurogenesis. Moreover, blockade of IL-1 can reverse the decreasing effect of this cytokine on BDNF production in chronic stress [27]. The present study was primarily aimed to assess the effects of adjuvant celecoxib on BDNF levels in BD patients undergoing ECT. Finding any association between this intervention and alteration in treatment response was another objective of this study.

Materials and Methods

This randomized, double-blind, clinical trial, registered at the Iranian Registry of Clinical Trials (IRCT) under IRCT2014011 77202N7, was conducted at a university-affiliated psychiatric hospital in Tehran. In-patients between 17 to 65 years old in acute phase of mania based on the DSM-IV-TR criteria entered this study. Subjects who were eligible and ordered to receive at least 3 ECT therapies were randomly assigned to 2 groups using a table of random numbers. Patients in group 1 received 200 mg celecoxib before starting ECT and then 200 mg twice daily up to the initiation of the 6th ECT session. Patients in group 2 received inert placebo capsules with the same schedule. Informed consent was signed by patients' legal guardians. Patients were excluded if they suffered any inflammatory conditions, renal or hepatic failure, heart failure, recent gastrointestinal bleeding or active peptic ulcer and those on NSAIDs or corticosteroids. Patients who received ECT during 2 months prior to the initiation of the study, pregnant and lactating women were also excluded from this trial.

Procedures

Bilateral ECT, using brief pulse Thymatron® DGx (Somatics, LLC) equipment, was performed 3 times a week when patients were fasting for at least 8 h and voided prior to the procedure. Patients were routinely monitored for seizure duration and hemodynamic status. Seizure duration was assessed using the cuff method. If seizures lasted < 15 s, ECT was repeated with 50% increase in the electrical dose. Patients' ventilation was supported throughout the procedure and continued until patients' full recovery. Blood samples were obtained from patients at baseline; the sampling was repeated 5–6 h after the 1st, the 3rd and the 6th ECT sessions. After centrifuging the samples, they were kept frozen at −70 °C until the time of the analyses. BDNF concentrations were measured using sandwich enzyme-linked immunosorbent assay (RayBio® Human BDNF ELISA Kit, RayBiotech, Inc) according to the package insert instructions.

The Young Mania Rating Scale (YMRS) was applied at baseline and after the 3rd and the 6th ECT sessions. Response to treatment was defined as 50% decline in baseline YMRS scores. Patients with YMRS scores of < 12 at the last observation were considered to be in remission. When the assessments of the 6th ECT sessions were not available, the values recorded at the 3rd ECT sessions were considered for the analysis.

Statistical analysis

Mean (SD, range) and frequency (percentage) was reported to describe the study data. Independent sample t-test and Chi-square test were performed to compare continuous and categorical variables, respectively. Welch F-ratio statistics and Games-Howell post-hoc test were used to test the relation between baseline BDNF and disease duration. Pearson correlation was used to estimate the correlation between variables. In order to compensate for missing data, adjusted BDNF levels for baseline values were compared between the 2 groups by analysis of covariance (ANCOVA). The generalized estimating equation (GEE) approach with an autoregressive correlation matrix was used to compare the repeated BDNF measures between the 2 groups while controlling for the time of measurement. Correlation between repeated measures of BDNF and YMRS scores was estimated by the GEE approach. $P < 0.05$ was defined as a statistically significant difference. Logistic regression was used to assess the association between BDNF level alteration and treatment responses.

Results

260 patients were screened as potential candidates to enter the study. The flow chart of this study is shown in **Fig. 1**. The celecoxib group included 16 and placebo group included 19 qualified patients. Patients' characteristics are shown in **Table 1**. Most patients received different combinations of psychotropics. Patients' baseline characteristics were not significantly different as presented in **Table 1**. The median numbers of psychiatric hospital admissions in the celecoxib and placebo groups were 2 and 4, respectively.

The BDNF levels at different assessment times are shown in **Table 2** and **Fig. 2**. Complete data of BDNF measurements was available for more than 80% of the patients. This study noted that the baseline serum BDNF levels in patients were not significantly related to age ($P = 0.602$), sex ($P = 0.320$), number of psychiatric hospitalizations ($P = 0.347$) and education ($P = 0.566$). It was also noted that a longer duration of the disease was associated with lower baseline BDNF levels. Mean BDNF levels were 539.14, 363.57, or 208.48 ng/ml when disease duration was < 5 years, between 5 to 10 years and > 10 years, respectively ($P = 0.05$). A statistically significant difference was noted by Post hoc analysis when comparing patients suffering psychiatric disorders for > 10 years to those with disease durations of < 5 years ($P = 0.013$). The baseline values of BDNF were found to be significantly different between the placebo and the celecoxib group ($P = 0.032$). When BDNF levels were adjusted for baseline values, the P values for differences between the 2 groups at the 1st, 3rd and the 6th assessment points were 0.325, 0.062 and 0.441, respectively. Despite higher serum BDNF levels in the celecoxib group, GEE did not show a significant difference between the 2 groups when adjusted for time and baseline BDNF levels ($P = 0.065$, $\beta = 128.73$, SE: 69.83). The baseline BDNF levels did not have any effect on consecutive BDNF concentrations when controlling for the time of assessment and the assigned group ($P = 0.084$, $\beta = 0.198$, SE: 0.115).

The YMRS scores are presented in **Table 2** and **Fig. 3**. The baseline YMRS scores were not significantly different between the 2 groups. This score was significantly lower in men than in women (27.54 vs. 36.63 respectively, $P = 0.009$), but was not significantly lower in older patients ($r = -0.222$, $P = 0.257$). Baseline

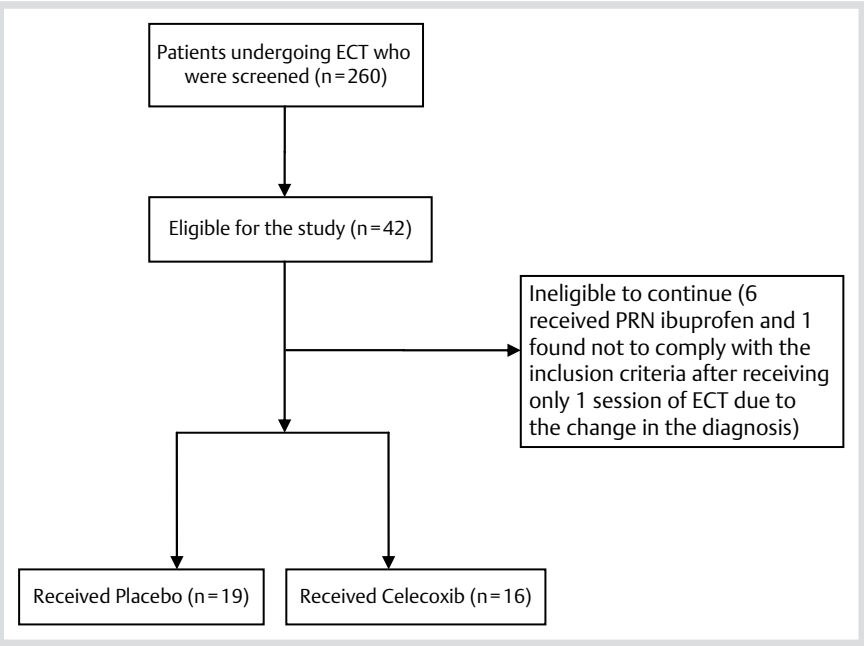

Fig. 1 The flowchart of the study.

	Celecoxib (n = 16)	Placebo (n = 19)	P value
Sex Male/Female	8/8	8/11	0.640
Age, mean ± SD (range)	32.53 ± 8.11 (19–46)	31.89 ± 9.56 (17–52)	0.908
Education			0.089
< Diploma	10	6	
Diploma or higher	6	12	
NA	0	1	
Number of psychiatric admission(s), mean ± SD (range)	2.75 ± 1.48 (1–6)	4.59 ± 3.62 (1–16)	0.069
Presence of psychotic feature	10	10	0.557
Duration of the psychiatric disease			0.600
< 5 years	2	6	
5–10 years	7	4	
> 10 years	5	7	
NA	2	2	
Psychotropic drug			–
Li	3	7	
Valproate	6	4	
Carbamazepine	0	1	
Topiramate	0	1	
Antipsychotics	14	14	
Benzodiazepines	11	13	

NA: not available (missing data)

Table 1 Baseline data of participants in the study.

	Celecoxib	Placebo	P value
Baseline Serum BDNF (μg/dL)	240 ± 207.32	460.22 ± 312.27	0.032
Serum BDNF (μg/dL) after 1st ECT	541.23 ± 325.42	507.75 ± 279.86	0.944
Serum BDNF (μg/dL) after 3rd ECT	501.11 ± 319.62	313.96 ± 305.11	0.100
Serum BDNF (μg/dL) after 6th ECT	441.84 ± 319.96	321.55 ± 287.65	0.160
Baseline YMRS	32.71 ± 9.35 (15–47)	31.91 ± 10.19 (11–54)	0.832
YMRS after 3rd ECT	19.00 ± 10.94	17.13 ± 11.49	0.684
YMRS after 6th ECT	11.11 ± 9.45	15.83 ± 13.24	0.397

Data are presented as mean ± SD (range)

P values are adjusted for baseline from univariate ANCOVA

Table 2 Serum BDNF levels and YMRS scores in different assessments.

YMRS scores in patients < 30 years old were not significantly higher than those ≥ 30 years-old (34.91 vs. 29.14, P = 0.123). The baseline YMRS score was not found to be significantly related to the number of psychiatric hospital admissions (P = 0.533). Using GEE test showed that when adjusted for time and baseline, YMRS scores were not significantly different between the 2 groups (P = 0.435, β = − 1.64, SE: 2.10). The baseline YMRS scores significantly affected the scores of the consecutive evaluations

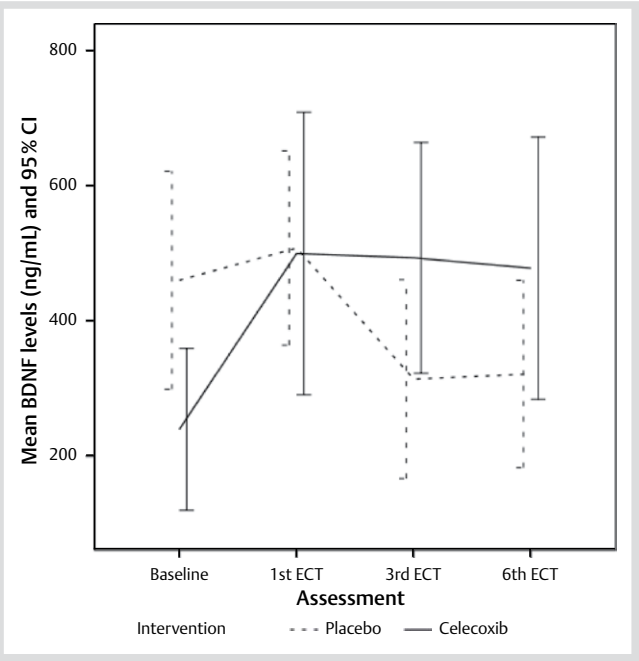

Fig. 2 The mean serum BDNF concentration with 95% CI at baseline and after the 1st, 3rd and 6th session of the ECT.

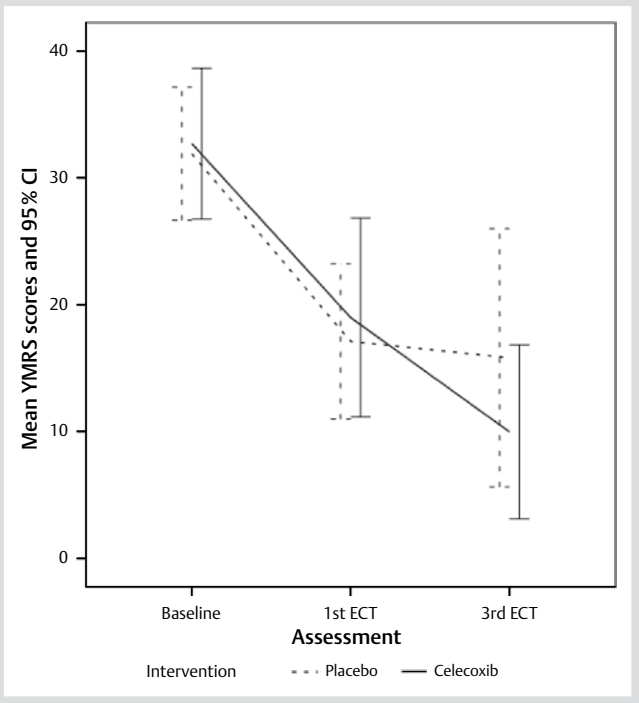

Fig. 3 The mean score of the young mania rating scale (YMRS) and 95% CI in baseline and after the 1st, 3rd and 6th session of the ECT.

when controlling for time of assessment and for assigned group ($P<0.001$, $\beta=0.74$, SE: 0.11). It was found that YMRS scores were significantly related to the baseline scores. This study found that the differences between YMRS scores at the 3rd and the 6th ECT sessions with the adjusted baseline scores in both groups were 0.726 and 0.420, respectively.

Numbers of responders were not significantly different in the 2 groups (7 in celecoxib group vs. 8 in the placebo group; $P=0.662$ in each group). Similarly, the numbers of the remitters between the 2 groups were not different (9 patients in each group; $P=0.306$). Additionally, no correlation was found between baseline YMRS scores and the baseline BDNF levels ($P=0.697$).

The mean differences of BDNF levels between the 3rd ECT treatment and baseline was 262.5±343.84 ng/ml in celecoxib and −166.5±425.93 in the placebo group. We did not find any interaction between the effect of group and the differences in BDNF with treatment response ($P=0.955$). Logistic regression showed that there was neither any association between the differences in BDNF levels and treatment response among all studied patients ($P=0.933$) nor within each group ($P=0.934$ for celecoxib; $P=0.839$ for placebo).

Discussion

This study evaluated the effect of adjunctive celecoxib on the serum BDNF levels and on treatment response in manic patients receiving ECT. The present study noted that the baseline serum BDNF levels were not affected by age and gender. Similarly, a meta-regression analysis on BDNF showed that the BDNF levels were not affected by age in manic patients [7]. One observational study also reported that BDNF plasma levels were not correlated with age or sex in both manic patients and in healthy controls [6]. Another study on an antidepressant-free population between 16 to 65 years of age showed similar findings [28]. Increasing age, in middle-aged and older women who were not receiving antidepressants, was reported to be significantly associated with lowering BDNF while this level stayed stable in men [29].

The present study shows the longer psychiatric illness is, the lower BDNF levels are. The BDNF levels of patients with <5 years of psychiatric disorders were found to be significantly different when compared with those who suffered their illnesses for >10 years. This finding is consistent with previous evidence that suggested BDNF levels were decreased in patients with prolonged diseases [30]. However, a discrepancy exists in this regard [12].

This study showed that there was a trend toward a significant rise ($P=0.065$) in BDNF levels with concurrent use of celecoxib with ECT. BDNF levels were found to be higher in the celecoxib group despite the fact that the baseline BDNF concentrations were significantly lower in the celecoxib group when compared with those in the placebo group. The difference between the baseline levels of BDNF in the 2 groups might have been responsible for not observing any statistically significant difference between the 2 groups.

It was previously proposed that the alterations in neurotrophins may occur partly in relationship with inflammatory molecules [31]. The authors of the present study initially hypothesized that probable change in the inflammatory markers following celecoxib administration may lead to the elevation of the BDNF levels. However, the results did not confirm that hypothesis.

The timing of sampling seems to play an important role in detecting the differences in BDNF levels. For instance, a study by Bocchio-Chiavetto et al. noted a significant rise in BDNF levels one month after the last ECT session despite the fact that no significant change in BDNF level was observed after the last ECT compared with the baseline level [32]. Fernandes et al. has suggested that the lack of increase in BDNF concentration after ECT might be attributed to the inadequate time needed for this biomarker to rise [33].

There are controversies about the impact of ECT on BDNF levels and its correlation with response to the treatment in the literature. Several studies have addressed this issue in patients with MDD while data regarding subjects suffering other psychiatric disorders including BD is very scarce in this area. Brunoni et al. performed a meta-analysis and concluded that BDNF would rise significantly following ECT in patients with depression. However, this increase was not found to be correlated with the treatment response [34]. Brunoni et al. conducted another meta-analysis including 19 studies in MDD patients. Patients included in 17 of these studies were receiving different antidepressants, and subjects in the other 2 studies underwent ECT. A significant increase in BDNF levels following treatment along with a significant improvement in depressive symptoms were reported in this meta-analysis [35].

It was previously noted that BDNF levels were increased in patients with acute mania who were receiving medications and not undergoing ECT [36]. On the contrary, our study did not note a significant change in the BDNF levels throughout the study. It is possible that the effect of ECT in manic patients on BDNF concentrations may differ from those suffering depressive disorders. Interestingly, a decrease in serum BDNF was noted in manic patients undergoing ECT in a recently published article [15].

The present trial did not find any significant effect for celecoxib when added to the routine ECT procedure in manic patients. The number of patients who responded to treatment and remitted did not differ significantly between the 2 groups. Moreover, our study did not find an association between responses to treatment with BDNF levels.

Conclusion

To the best of our knowledge, this was the first study that assesed the effect of adjunctive celecoxib on BDNF in manic patients undergoing ECT. No significant difference in alteration of BDNF levels was noted throughout the study. Additionally, response to treatment was not associated with any difference in BDNF levels from baseline. Alterations in YMRS scores were not found to be significantly different between the 2 groups of the study

Limitations

The limitations of this study included the short duration for following up patients and the small number of participants. It should be mentioned that the subjects in our study were receiving other psychotropics while on ECT which in turn can affect BDNF levels [3].

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Conflict of Interest

The authors declare no conflict of interest.

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