

Effects of Celecoxib on Electroconvulsive Therapy-Induced Cognitive Impairment in Patients With Major Depressive Disorder: A Pilot, Double-Blind, Placebo-Controlled Trial

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Abstract- Cognitive impairment, an important side effect of electroconvulsive therapy (ECT), may be related to the release of prostaglandins in the brain. Cyclooxygenase-2 (COX-2), constitutively expressed in the CNS, has a functional role in glutamate-mediated learning and memory. The goal of this pilot, double-blind, placebo-controlled trial was to evaluate the effects of the selective COX-2 inhibitor celecoxib on the adverse cognitive effects of ECT. Twenty patients diagnosed with the major depressive disorder for which ECT was indicated as a treatment for their current episode randomly received either celecoxib (200 mg orally twice a day, a total dose of 400 mg/day) or placebo. All patients underwent the same protocol for anesthesia and ECT procedures. The patients received celecoxib or the placebo for the whole period of ECT treatment, starting the day before ECT and continuing until the sixth (last) session of ECT. The Wechsler Mental Scale-III (WMS-III), the Mini-Mental Scale Examination (MMSE), and Stroop Color test were used to assess cognition before the first session and after the first, third and sixth sessions of ECT. Hamilton rating scale for depression was also used for the assessment of depression before and after the trial. Our data showed that celecoxib group did not have significant improvement in cognition based on WMS-III or MMSE scores. There was an improvement in the Stroop Color test but not statistically significant. Our results demonstrated that although celecoxib was well tolerated in patients undergoing ECT, it did not improve related cognitive impairment. Clinical trial registration number: IRCT201201247202N2. CNS, central nervous system; COX-2, Cyclooxygenase-2; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision; ECT, electroconvulsive therapy; ECS, electroconvulsive shocks; HAM-D, Hamilton rating scale for depression; LTP, long term potentiation; MDD, major depressive disorder; MMSE, Mini-Mental State Examination; NSAIDs, nonsteroidal anti-inflammatory drugs; WMS-III, Wechsler Memory Scale-III.

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Introduction

Electroconvulsive therapy (ECT) that induces artificial clinical seizures was first introduced as a treatment for schizophrenia in the 1930s, and soon after, it was considered as a highly effective treatment for major

depressive disorder (MDD) and a variety of other psychiatric disorders (1,2). There is a noteworthy volume of information in the literature concerning the effects of ECT on memory and cognition (3). A systematic review of the cognitive adverse effects of ECT has indicated memory impairment as a sub-acute side effect of ECT,

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which occurs within 24 hours to 2 weeks after the procedure (4). Anterograde, retrograde, and subjective memories are among the cognitive abilities that could be affected by ECT (2,4). Anterograde amnesia relates to impairment in the acquisition of new skills, whereas retrograde amnesia describes the loss of previously acquired memories (5). Reduction in the score of Mini-Mental State Examination (MMSE) and loss of recalling autobiographical memories are other types of cognitive impairments reported following ECT (6). ECT is associated with greater cognitive impairments when compared with sham ECT (anesthetizing the patient without applying electrodes and delivering electricity) (7).

There are some reported factors that are related to greater cognitive damage after ECT. For instance, if a patient is more disoriented during acute treatment, she/he is more likely to suffer retrograde amnesia. Moreover, the risk of ECT-induced memory loss increases when patients have pre-existing dementia or other neurological conditions (8). Older patients are more sensitive to adverse cognitive effects of ECT, and these effects last longer in the elderly (9). The molecular mechanisms of ECT-induced cognitive impairments have not been completely elucidated. Cholinergic, (10,11) glutamatergic (12), calcium channels (13), and glucocorticoid mechanisms are among the possibilities (14). Moreover, several studies have reported that electroconvulsive seizures are related to the release of prostaglandins in the brain; thus, ECT can influence inflammatory signaling pathways in the central nervous system (CNS) (15). Cyclooxygenase-2 (COX-2), constitutively expressed in the CNS, has a functional role in glutamate-mediated learning and memory (12,16). Furthermore, memory impairment after ECT may have resulted from glutamatergic excitotoxicity (12,17). An investigation on the saturation of long term potentiation (LTP) suggested COX-2 as one of the major cellular mechanisms that cause learning and memory impairment after repeated ECT (12). It was demonstrated that repeated electroconvulsive shocks (ECS) might induce and saturate LTP, which in turn results in a decreased potential and recruitment of LTP (12). According to these findings, interrupting the mechanisms that up-regulate LTP could protect against ECT-induced amnesia. The selective inhibition of COX-2, but not COX-1, may acutely prohibit the suppression of hippocampal LTP (18).

Therefore, we sought to evaluate the effects of the selective COX-2 inhibitor celecoxib on cognitive impairment related to ECT in patients with MDD. To our

knowledge, no placebo-controlled human studies have been done on this subject up to date. Therefore, we conducted the present double-blind, placebo-controlled trial of celecoxib in patients diagnosed with MDD undergoing ECT. Our hypothesis was that celecoxib might have protective/improving effects against ECT-related cognitive impairment in MDD patients.

Materials and Methods

Study design

This prospective, double-blind, placebo-controlled clinical trial was registered at www.irct.ir with an identifier number of IRCT201201247202N2. Ethical committee approval was obtained from the Tehran University of Medical Sciences (TUMS) before starting the study as per the provision of the Helsinki declaration (2000).

The study setting was the psychiatry department of Roozbeh Hospital, affiliated with TUMS, Tehran, Iran. This is a well-known academic center for the treatment of psychiatric patients in Iran. The criteria for inclusion in the study were a comprehensive psychiatric evaluation in which patients between 20 to 75 years of age met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) criteria for MDD for which ECT was indicated as a treatment for their current episode and was admitted to the hospital between August 2010 and January 2012. The severity of the participant's depression was also determined using the Hamilton Depression Rating Scale (HAM-D). The HAM-D is the most widely used physician-administered rating scale for depression. The scale summarizes 17 individual scores to provide a total score that indicates the severity of depression (19). HAM-D was assessed in study participants before and after the trial. All study participants signed consent forms after the study procedures were explained.

The exclusion criteria included the history of drug abuse, irritable bowel syndrome, diabetes mellitus, renal or hepatic impairment, unstable vascular aneurysm, intracranial hemorrhage or stroke, severe pulmonary conditions, hearing or verbal disorders. Pregnant or lactating women, patients receiving corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs), and those who had received ECT within the previous two months were also excluded from the trial. Additionally, the presence of psychotic features or delirium, a category above the American Society of Anesthesiologists class III (ASA class III) were among exclusion criteria .

ECT protocols

Patients underwent a total of 6 ECT sessions every 48 hours, the duration between the first ECT and the fourth ECT was 12 days. They received bilateral ECT by using ThymatronDGx (Somatics INC). All ECT procedures were performed between 7:30 to 9 A.M at Roozbeh hospital. Patients were fasting for at least 8 hours before the ECT procedure. During each ECT procedure, patients were administered 0.5 mg atropine followed by 2-3 mg/kg thiopental intravenously (i.v.); succinylcholine (0.5 mg/kg) was administered as a muscle relaxant after the induction of anesthesia. The stimulus intensity was determined by a dose titration procedure (starting at 25.2 millicoulomb), and the seizure threshold was identified in the first session (20,21). Patients' ventilation was supported using 100% oxygen by a bag and mask until the resumption of patients' breath. Electrocardiogram, arterial oxygen saturation (pulse oximetry), noninvasive blood pressure, and heart rate of the patients were monitored continuously during the procedure.

Randomization and treatment

Twenty patients with MDD fulfilled the criteria and completed the study (10 female, ten male; mean [\pm S.D.] age, 34.25 \pm 10.18 years). The study participants, who were admitted to receive ECT, were randomized by the research executive manager (one of the investigators) based on a table of random numbers. Accordingly, patients were given celecoxib (200 mg orally twice a day, a total dose of 400 mg per day) or placebo beginning the day before the first session of ECT until the sixth session of ECT. The study patients, the anesthesiologist, the nursing staff, and the rater of the scales were all blind to the intervention allocation status (Figure 1).

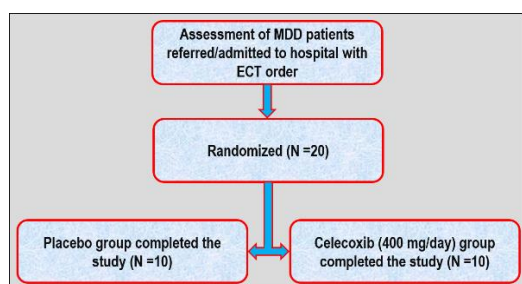


Figure 1. Flowchart of study

Assessments

The cognitive assessment of the subjects was done 24 hours before the first ECT session and 24 hours after the

first, third, and sixth sessions of ECT. The MMSE, the 17-item version of the Hamilton rating scale for depression (HAM-D), Stroop Color test, and Persian standardized Wechsler Memory Scale-III (WMS-III) subsets (logical memory, digit span, and associate learning) (22) were assessed. Cognitive assessment and checking the adverse effects were carried out by staff who were blinded to the patients' treatment assignments. Cognitive improvement was defined based on changes in the scores of MMSE and WMS-III (logical memory, digit span, and associate learning) and reduction of errors in the Stroop Color test. Side effects and tolerability were reported by direct inquiry.

The MMSE is a 12-item test that can be reliably and repeatedly used to screen and monitor cognitive dysfunction in patients undergoing ECT (6,23,24). The highest score in MMSE is 30, with the inversely related to cognitive abnormality. Scores lower than 23 usually indicate some degree of cognitive impairment. The WMS-III has been designed to assess different memory functions in patients between 16-90-year-old with three subscales of logical memory, digit span, and associate learning. (25-27) Higher scores in this test represent a better cognitive function. The Stroop Color Test also assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus (28,29).

Statistical analysis

Results are reported as mean \pm S.D. Data were analyzed using the Statistical Package for the Social Sciences version 19 (IBM SPSS-19). A mixed-design analysis of variance model was employed to examine the between-condition (i.e., celecoxib vs. placebo) differences in repeated measures of depression and neuropsychological scores. Evaluation session (time) was the within-subject factor and condition group (i.e., celecoxib vs. placebo) was the between-subjects factor; the interaction between the treatment group and evaluation session was also included in the model. The violation of equality of covariance matrices and violation of sphericity assumption was verified. In case of the significance of Mauchly's test for sphericity, significance levels of each factor and their interaction was estimated using Greenhouse-Geisser correction. All analyses used the two-tailed significance criteria of $P < 0.05$.

Table 1. Demographic and illness characteristics for patients receiving placebo or celecoxib.

| Demographics | Celecoxib group (n = 10) | | Placebo group (n=10) | | t (df) | P |
|---|--------------------------|-------|----------------------|--------|---------------|------|
| | Mean | S.D. | Mean | S.D. | | |
| Age | 32.50 | 11.74 | 36 | 8.628 | 0.57 (18) | 0.46 |
| Education (years) | 8.90 | 3.40 | 6.80 | 3.800 | 0.76 (18) | 0.21 |
| Age on disease onset | 28.40 | 11.50 | 29.80 | 11.300 | 0.27 (18) | 0.78 |
| Number of hospitalization | 1.56 | 1.23 | 0.70 | 0.94 | 1.7 (18) | 0.11 |
| | N | % | N | % | χ^2 (df) | P |
| Gender (female) | 6 | 60 | 4 | 40 | 0.8 (1) | 0.37 |
| Marital status | | | | | 2.1 (2) | 0.35 |
| Single | 4 | 40 | 3 | 30 | | |
| Married | 4 | 40 | 2 | 20 | | |
| Divorced | 2 | 20 | 5 | 50 | | |
| Unemployed | 6 | 60 | 6 | 60 | 0 (1) | 1.00 |
| Adverse effects | 2 | 20 | 1 | 10 | 0.28 (1) | 0.59 |
| Family history of psychiatric disorders | 30 | 3 | 4 | 0.4 | 0.1 (1) | 0.76 |

Results

Twenty eligible patients (undergoing ECT therapy) completed the study. Ten patients were assigned to the celecoxib group, and ten patients were assigned to the placebo group. Celecoxib was well tolerated, and no patients withdrew from the study. The demographic characteristic of patients is shown in table 1. There were no significant differences between patients in the duration of depression and the number of previous episodes or comorbid disorders at baseline. Likewise, a comparison of demographic features did not show a significant difference between the two groups. Side effects were generally mild and transient and included stomach upset headache, heartburn, and nausea.

Table 2 shows the descriptive features of WMS-III, MMSE, and Stroop Color at baseline and after the 1st, 3rd, and sixth sessions of ECT, respectively. For WMS-III logical memory subscale, after Greenhouse–Geisser correction, the linear mixed model showed no significant change in logical memory scores ($F_{3,54} = 0.84, P = 0.45$) over the course of ECT treatment. The comparison of two treatment conditions does not show a significant between-condition difference for logical memory scores throughout all sessions ($F_{1,18} = 0.57, P = 0.46$) and no interaction between time and condition ($F_{3,54} = 0.20, P = 0.87$). For WMS-III digit span subscale, there was no evidence of the violation of the sphericity assumption. The linear mixed model showed no significant change in logical memory scores ($F_{3,54} = 1.56, P = 0.21$) over the course of ECT treatment. The comparison of two treatment conditions does not show a significant between-condition difference for digit span scores throughout all sessions ($F_{1,18} = 0.26, P = 0.61$) and no interaction between

time and condition ($F_{3,54} = 0.25, P = 0.72$). For WMS-III associate learning, after Greenhouse–Geisser correction, the linear mixed model showed a significant change in WMS-III scores ($F_{3,54} = 5.17, P = 0.009$) over the course of ECT treatment. The comparison of two treatment groups shows no significant between-condition difference for WMS-III associate learning scores throughout all sessions ($F_{1,18} = 1.79, P = 0.20$). However, after correction, the interaction between time and condition was not significant ($F_{3,54} = 0.62, P = 0.55$). For the Stroop Color outcome, there was no evidence of the violation of the sphericity assumption. The linear mixed model showed a significant change in Stroop Color scores ($F_{3,54} = 7.12, P = 0.001$) over the course of ECT treatment. The comparison of two treatment conditions does not show a significant between-condition difference for Stroop Color scores throughout all sessions ($F_{1,18} = 0.67, P = 0.80$) and no interaction between time and condition ($F_{3,54} = 0.29, P = 0.84$). For the MMSE outcome, after Greenhouse–Geisser correction, the linear mixed model showed no significant change in MMSE scores ($F_{3,54} = 1.46, P = 0.241$) over the course of ECT treatment. The comparison of two treatment conditions does not show a significant between-condition difference for MMSE scores throughout all sessions ($F_{1,18} = 0.51, P = 0.48$) and no interaction between time and condition ($F_{3,54} = 0.88, P = 0.67$). Finally, for the depression outcome, the linear mixed model showed a significant change in HAM-D scores ($F_{1,18} = 36.55, P = 0.001$) over the course of ECT treatment. The comparison of two treatment conditions does not show a significant between-condition difference for depression scores throughout all sessions ($F_{1,18} = 0.76, P = 0.39$) and no interaction between time and condition ($F_{1,18} = 0.18, P = 0.89$).

Table 2. Descriptive features of Wechsler Memory Scale version III (WMS-III), Mini-Mental State Examination (MMSE), and Stroop color at baseline (24 h prior first ECT), 24h after the first, the third, and the sixth (last) ECT session in both placebo and celecoxib groups. Hamilton depression scale (HAM-D) was assessed at baseline (24 h prior first ECT) and 24 hours after sixth (last) ECT

| | | Celecoxib group (n=10) | | Placebo group (n=10) | |
|------------------------|----------|------------------------|------|----------------------|------|
| | | Mean | S.D. | Mean | S.D. |
| WMS-Logical Memory | Baseline | 4.3 | 1.3 | 5.1 | 1.68 |
| | 1st ECT | 4.6 | 1.72 | 5.3 | 1.76 |
| | 3rd ECT | 5.2 | 1.36 | 5.4 | 2.2 |
| | 6th ECT | 4.9 | 1.34 | 5.6 | 2.32 |
| WMS- Digit Span | Baseline | 7.4 | 1.72 | 9 | 1 |
| | 1st ECT | 9 | 1.2 | 9.3 | 1.42 |
| | 3rd ECT | 8 | 2.2 | 8.9 | 2.34 |
| | 6th ECT | 8.8 | 2.04 | 7.9 | 2.52 |
| WMS-Associate Learning | Baseline | 11.8 | 2.04 | 12.9 | 2.14 |
| | 1st ECT | 12.1 | 3.5 | 13.8 | 2.6 |
| | 3rd ECT | 12.5 | 3.3 | 14.5 | 2.4 |
| | 6th ECT | 13 | 2.8 | 15.4 | 2.32 |
| Stroop Color | Baseline | 8.20 | 6.48 | 8.50 | 4.45 |
| | 1st ECT | 7.00 | 4.90 | 8.20 | 5.20 |
| | 3rd ECT | 6.00 | 4.06 | 6.50 | 4.67 |
| | 6th ECT | 6.00 | 5.16 | 6.30 | 6.20 |
| MMSE | Baseline | 26.80 | 2.57 | 26.50 | 3.14 |
| | 1st ECT | 27.40 | 1.84 | 26.10 | 3.31 |
| | 3rd ECT | 27.40 | 2.50 | 26.40 | 3.57 |
| | 6th ECT | 27.70 | 2.36 | 26.90 | 3.31 |
| HAM-D | Baseline | 22.30 | 3.20 | 24.30 | 4.40 |
| | 6th ECT | 15.60 | 7.85 | 17.30 | 4.90 |

Discussion

It is well established that ECT can provide rapid, significant improvement in severe symptoms of several psychiatric disorders, including MDD (30). A considerable number of patients undergoing ECT may experience various degrees of cognitive impairment (4). In the present double-blind, placebo-controlled clinical trial, we demonstrated that celecoxib (200 mg orally twice a day) is well tolerated in MDD patients undergoing ECT; however, it did not statistically improve the related cognitive function compared to the placebo group.

To our knowledge, this pilot trial is the first human study that examined the effect of celecoxib on ECT-induced cognitive impairment in MDD patients. The existing evidence in animal studies has demonstrated the effects of COX inhibitors on memory and cognition (12,31-33). The initial investigation by Rao *et al.*, (2002) revealed that 19-day treatment with the non-selective COX inhibitor indomethacin (4 mg/kg/day, oral) attenuated retrograde amnesia induced by two once-daily ECS treatments in rats (34). Considering the fact that COX-2 expression is up-regulated in the microglia of cognitive regions (e.g., hippocampus and cerebral cortex) in patients with Alzheimer's disease (35,36), it is

suggested that COX-2 inhibitors may be of therapeutic value in cognitive impairment (37). Selective COX-2 inhibitors have become more available in recent years due to their minimal gastrointestinal adverse effects compared with non-selective COX inhibitors. Accordingly, Andrade *et al.*, (2008) investigated the effects of 8-day oral administration of indomethacin (4 mg/kg/day), celecoxib (15 mg/kg/day), or placebo on ECT-induced retrograde amnesia in rats (12). They found that celecoxib but not indomethacin significantly protected against ECS-induced retrograde amnesia compared with the placebo group (12). In another study, the same group similarly found protective effects of celecoxib (15 mg/kg/day) against ECT-induced memory impairments when it was administered 18 days prior and during ECTs in Wistar rats (31). These pre-clinical data suggest that selective COX-2 inhibitors such as celecoxib could have beneficial effects in improving cognitive impairments induced by ECT.

The mechanisms underlying memory or cognitive impairment due to ECT has not been fully understood. Accumulating evidence suggests a role for glutamatergic neurotransmission in the pathophysiology of memory impairment related to ECT (17,38,39). Glutamatergic system is a key element of LTP and synaptic plasticity

involved in memory and cognitive function (40). Additionally, an investigation on the saturation of LTP suggested COX-2 as one of the major cellular mechanisms that cause learning and memory impairment after repeated ECT (12,31). The above study collected experimental pieces of evidence and demonstrated that repeated ECS might induce and saturate LTP, which in turn results in a decreased potential and recruitment of LTP. Thus, interrupting the mechanisms which up-regulate LTP could protect against ECT-induced amnesia. The selective inhibition of COX-2, but not COX-1, may acutely prohibit the suppression of hippocampal LTP (18), and thereby improving the cognitive function.

While results of clinical studies with COX-2 inhibitors in depression are still absent, clinical improvement of the depressive syndrome has been detected in patients who have been treated with rofecoxib (41). These initial clinical data suggest the therapeutic effects of the selective COX-2 inhibitors in psychiatric disorders, even though these effects should be confirmed in clinical studies on a larger number of MDD patients.

We originally hypothesized that celecoxib might reduce cognitive impairment caused by ECT. However, our data revealed that patients treated with celecoxib did not have any significant improvement in cognitive function as assessed by WMS-III, MMSE, and Stroop Color tests. This end result may be due to the small sample size of this study. Another possibility that the present study did not note much improvement in cognition after the addition of celecoxib to ECT may be due to the fact that the ECT procedure did not produce significant cognitive impairment in this small number of patients. It should be noted that geriatric patients or other patients with high-risk factors for cognitive impairment were not included in this study. Another possibility could be related to the dose of celecoxib (total 400 mg/day) used in this study, as it may have been a relatively low dose to effectively target the cognitive symptoms in these patients.

In summary, although the results of a present double-blind, placebo-controlled clinical trial suggested that celecoxib is well tolerated during ECT therapy in MDD patients, it did not reveal a significant improvement in the ECT-induced cognitive dysfunction in these patients. Further multi-center cohort studies with a larger number of MDD patients and perhaps higher doses of celecoxib are needed to verify the results of the current study.

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