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Acute and chronic effects of electroconvulsive treatment on oxidative parameters in schizophrenia patients

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ABSTRACT

Electroconvulsive therapy (ECT) is an effective treatment alternative for schizophrenia. Previous studies have already indicated the possible effects of oxidative stress in this disorder. However, there have been no previous studies evaluating the effects of ECT on the oxidative stress in these patients. We therefore aimed to investigate the acute and chronic effects of ECT on serum levels of oxidant and antioxidant molecules in schizophrenia patients (n = 28). The serum MDA and CAT levels of the patients with schizophrenia were higher than that of the controls before ECT (n = 20) but there was no significant difference in the serum NO and GSH levels of the patient groups compared to the controls. We found that the NO levels of the patients were higher than the controls in the group experiencing their first episode but not in the chronic group. There was a significant clinical improvement in the patients in terms of BPRS, SANS and SAPS reduction after the 9th ECT, but not the 1st ECT. Serum MDA levels were significantly reduced compared to the baseline after the 9th ECT session although there was no significant difference after the 1st session. Separate evaluation of the patient groups revealed that the significant MDA decrease following ECT was in the patients experiencing their first episode and not in the chronic group. No significant difference was noted in the serum levels of other oxidant and antioxidant molecules after either the 1st or 9th ECT session. These results suggest that ECT does not produce any negative effect on oxidative stress in patients with schizophrenia.

1. Introduction

Electroconvulsive therapy (ECT) is defined as a medical procedure in which a brief application of an electrical stimulus is used to produce a generalized seizure under controlled conditions. Despite the development of psychopharmacology, ECT is still used for psychiatric disorders, namely depressive disorders and schizophrenia (American Psychiatric Association, 1990; Fink, 2001; Taylor, 2007). However, its efficacy in schizophrenia has not been clearly demonstrated. Although a large number of hypotheses have been proposed, the exact mechanism of the therapeutic or adverse effects of ECT is yet to be established. Most of the studies investigating the mechanisms of ECT in the past 20 years have focused on biological theories (Cooper et al., 1990; Newman et al., 1998).

Reactive oxygen species (ROS) are continuously produced as a result of metabolic activities in the body and exert several physiological and pathological effects via many different mechanisms (Halliwell and Gutteridge, 2000). Under normal circumstances, ROS are eliminated by cellular enzymatic [superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT)] and non-enzymatic [glutathione (GSH) and uric acid] antioxidant defenses. If ROS are not effectively eliminated, they can cause oxidative cell injury, i.e., peroxidation of cell membrane phospholipids, proteins (receptors and enzymes) and DNA (Mahadik et al., 2001). The brain has comparatively greater vulnerability to oxidative damage as a result of the relatively low levels of antioxidants, high levels of polyunsaturated fatty acids and increased need of oxygen (Sultana et al., 2008).

There is increasing evidence suggesting the involvement of free radical-mediated neuronal dysfunction in schizophrenia (Fendri et al., 2006; Mahadik and Mukherjee, 1996; Ng et al., 2008; Reddy et al., 2003; Yao et al., 1999, 2000, 2004). The end products of lipid peroxidation, particularly malondialdehyde (MDA), have been widely used as indices of oxidative stress in clinical studies (Lepping et al., 2011). Elevated levels of MDA have been shown in the plasma, erythrocytes, leukocytes and platelets of patients with schizophrenia

Abbreviations: ANOVA, analysis of variance; BPRS, Brief Psychiatric Rating Scale; CAT, catalase; ECT, electroconvulsive therapy; ECS, electroconvulsive shock; GSH, glutathione; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; NO, nitric oxide; ROS, reactive oxygen species; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative symptoms; SOD, superoxide dismutase; SPSS, Statistical Program for Social Sciences.

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(Dakhale et al., 2004; Dietrich-Muszalska et al., 2005; Herken et al., 2001a; Khan et al., 2002; Kuloglu et al., 2002; Padurariu et al., 2010; Petronijević et al., 2003; Wood et al., 2009). Increased plasma levels of oxidants including nitrite (Zoroglu et al., 2002), nitric oxide and lipid peroxide (Li et al., 2006) were also reported in schizophrenia patients. Changes occur in the antioxidant defense status to cope with the oxidative stress caused by free radicals (Akyol et al., 2002; Ben Othmen et al., 2008; Herken et al., 2001a; Vaiva et al., 1994; Yao et al., 1998; Yao et al., 1999). Many studies conducted in patients with schizophrenia have shown a significant decrease in antioxidant enzyme levels (Padurariu et al., 2010; Raffa et al., 2009; Wood et al., 2009).

Previous studies conducted on experimental animals have reported that epileptic seizures lead to an increase in oxidative stress (Patel, 2004). On the other hand, there are very few studies investigating the putative role of oxidative stress after electroconvulsive shock (ECS)-induced convulsions. ECS, the animal equivalent of ECT, has been shown to have many effects on oxidative parameters in various regions of the rat brain (Barichello et al., 2004; Feier et al., 2006; Jornada et al., 2007; Kreisman et al., 1983; Zupan et al., 2008). To the best of our knowledge, only one study has evaluated the effects of ECT on oxidative stress in humans (Virit et al., 2010). In that particular study conducted in patients with depression, ECT was shown to reduce the antioxidant (SOD levels) capacity (Virit et al., 2010). However, no study to date has evaluated the effects of ECT on oxidative stress in patients with schizophrenia.

Epileptic (Patel, 2004) and ECT-induced seizures (Virit et al., 2010) can alter the blood levels of oxidants and antioxidants. These alterations may be associated with the therapeutic and adverse effects of ECT in schizophrenia. The aim of the present study was to evaluate the levels of some peripheral oxidant (NO and MDA, lipid peroxidation marker) and antioxidant species (GSH and CAT) before and after ECT in patients with schizophrenia and to compare these levels to that of age- and gender-matched healthy control subjects.

2. Methods

2.1. Subjects

The present study was performed in the Department of Psychiatry of Inonu University Faculty of Medicine. Thirty patients aged between 18 and 60 years diagnosed with schizophrenia according to the Turkish version of the Structured Clinical Interview for the DSM-IV (SCID-IV) (Corapcioglu et al., 1999) and 20 healthy age- and gender-matched control subjects were included in the present study. The age range was kept wide and we included both first episode and chronic patients in the study. The aim was to see how ECT affected oxidative stress parameters in both groups to enable a comparison. A complete medical history was obtained and physical examination and laboratory tests were performed in all subjects. Exclusion criteria included the presence of severe organic disorders, seizure disorders, history of head injury with loss of consciousness, alcohol and other substance dependence (except for smoking), and the use of vitamin supplements within the 6 months prior to the study. Disease severity was evaluated using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983a) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983b). Age- and gender-matched healthy volunteers comprising the control group were recruited from the hospital staff. The control group subjects were evaluated by a senior psychiatrist to confirm that they did not have any Axis I psychiatric disorder or first-degree relatives with a psychiatric disorder. None of the subjects included in the study had a history of head trauma, major medical or endocrine disorder, a history of any neurological problem or lifetime history of alcohol or drug dependence.

Each patient received ECT under general anesthesia three times a week for a total of 9 sessions. Premedication included intravenous administration of atropine sulfate (0.5 mg), propofol (1.0 mg/kg), and succinylcholine (0.5 mg/kg). ECT was performed between 9:00 and 11:00 a.m. after an overnight fast. The patients received bilateral ECT using a Thymatron TM DG (Somatics, Inc., Lake Bluff, IL, USA) device with standard settings and a bipolar brief pulse square wave. Two stimulus electrodes were placed over the left and right frontotemporal scalp. ECT conditions were the same for all patients (maximum charge delivered, 504 mC; current, 0.9 A; frequency, 10–70 Hz; pulse width, 0.5 ms; maximum duration, 8 s). During ECT, the motor convulsions (using the cuff method), electroencephalogram, induced tachycardia, and, if necessary, electromyogram were monitored. ECT was added to the treatment of chronic patients on antipsychotics and the medication was continued throughout the ECT period. A trial of antipsychotic medication was made for at least one week in patients who had experienced their first episode and those that also required ECT were included in the study. Antipsychotic medication was also continued throughout the ECT period in these patients who had experienced their first episode. All pre- and post-ECT oxidative parameter measurements were therefore made while the patient was on medication. Antipsychotics used in the study population included risperidone (n = 10), olanzapine (n = 10), quetiapine (n = 4), and haloperidol (n = 4).

The present study was carried out in accordance with the Declaration of Helsinki guidelines and was approved by the Local Ethics Committee. All participants were informed about the study protocol and provided written informed consent prior to the study.

2.2. Biochemical analyses

Venous blood samples (baseline and following the 1st and 9th ECT sessions) were collected from the schizophrenia patients as well as healthy controls into heparinized tubes in the morning, between 7:00 and 10:00 a.m., following 12 h of fasting and tobacco abstinence. Erythrocytes and plasma were separated by centrifugation at 4000 rpm for 10 min, and plasma samples were then labeled and stored at −80 °C until analysis. The biochemical assays were performed while being blinded to the available clinical information throughout the investigations.

All chemicals were obtained from Sigma. Routine biochemical analyses were carried out using an autoanalyser and commercial kits from Olympus (Olympus AU 600, Japan). Plasma levels of MDA were determined according to the method of Mihara and Uchiyama (1978). 3 mL of 1% phosphoric acid solution was added into 0.5 mL of plasma pipetted into a tube together with 1 mL of 0.6% thiobarbituric acid solution. The mixture was heated in boiling water for 45 min. After cooling, 4 mL of n-butanol was added and the absorbance was measured in a spectrophotometer (Ultraspec Plus, Pharmacia LKB Biochrom, UK) at wavelengths of 535 and 525 nm. The difference between the absorbances at 535 and 525 nm was used to calculate the thiobarbituric acid-reactive substances of lipid peroxidation. A standard curve was plotted using 1,1,3,3-tetramethoxypropane as a standard, and the results were expressed as nmol/L.

The method developed by Fairbanks and Klee (1986), based on the reaction of sulfhydryl groups with Ellman's reagent, was used for the measurement of GSH. Absorbances of the samples were multiplied by the factor obtained from the standard curve and GSH activity was calculated as μmol/L. The plasma level of NO was determined by the method of Cortas and Wakid (1990), based on the spectrophotometric measurement of the colored complex produced by the interaction of NO formed in the environment as a result of nitric oxide synthase activity with Griess reagent. NO activity was expressed as μmol/L.

The activity of CAT enzyme was determined according to the method of Aebi (1974). The principle of the assay is based on the determination of the rate constant (s^{-1} k) or the H_2O_2 decomposition rate at 240 nm. The results were expressed as U/g Hb.

2.3. Statistical analyses

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS, Inc. Chicago, IL, USA) version 13.0. Demographic and clinical variables between groups were compared using the independent sample t-test. We used the one-way analysis of variance (ANOVA) test with post-hoc Bonferroni correction to compare the oxidative parameters of the patient and control groups. Repeated measures ANOVA was used to compare pre- and post-treatment oxidant–antioxidant levels of the patients. Repeated measures ANOVA was performed with treatment phases (3 phases as baseline, after the 1st ECT session, and after the 9th ECT session) as a within-subject factor. Pearson's correlation test was used to evaluate the relationship between the oxidant–antioxidant levels and demographic and clinical data. A p value <0.05 was considered statistically significant.

3. Results

Thirty patients and 20 healthy control subjects were included in the present study. However, two patients were excluded from the study due to the cardiac adverse effects that developed during ECT treatment and the results of 28 patients were analyzed. Demographic and clinical characteristics of the schizophrenia patients and healthy controls are summarized in Table 1. The mean age was 30.29 ± 7.58 years in the patient group (15 males and 13 females), and 29.53 ± 9.66 years in the control group (10 males and 10 females). There was no significant difference between patients and controls in terms of age ($t=0.288$, $p=0.775$), gender ($p=0.807$) and smoking rates ($p=0.922$) (Table 1).

According to the independent sample t-test, there was no significant difference between the patients and controls in terms of baseline NO ($t=1.704$, $p=0.095$) and GSH ($t=0.612$, $p=0.544$) levels. However, the patients had significantly higher MDA ($t=4.930$, $p=0.000$) and CAT levels ($t=5.330$, $p=0.000$) than the controls at baseline (Table 2).

There was no significant difference between female and male subjects in terms of the four oxidant–antioxidant parameters in the control group. The serum levels of the four oxidant–antioxidant parameters also did not differ between female and male subjects in the patient group.

In the present study, patients were grouped as those with new-onset schizophrenia (i.e., first episode patients who did not receive any prior treatment) and those with chronic schizophrenia. The first-episode patients, chronic schizophrenia patients and controls were also compared using ANOVA. There was no significant difference between these three groups in terms of age ($F=2.127$, $df=2$, $p=0.131$). A significant difference was noted in terms of serum NO levels between the three groups ($F=3.919$, $df=2$, $p=0.027$). According to the post-hoc Bonferroni analysis, the NO level was significantly higher in the first-episode patients than in the controls ($p=0.030$); however, there was no significant difference between the patients with chronic schizophrenia and the controls ($p=1.000$). There was no significant difference between the NO levels of first-episode patients and patients with chronic schizophrenia ($p=0.083$). A significant difference was noted in terms of the serum MDA levels between the three groups ($F=15.306$, $df=2$, $p=0.000$). According to the post-hoc Bonferroni analysis, the MDA levels of the first-episode patients and the patients with chronic schizophrenia were significantly higher than that of the controls ($p=0.000$ and $p=0.007$, respectively). The MDA levels of the first-episode patients were significantly higher than that of the patients with chronic schizophrenia ($p=0.046$). There was no significant difference between these three groups in terms of serum GSH levels ($F=1.559$, $df=2$, $p=0.222$). A significant difference was noted in terms of the serum CAT levels between the three groups ($F=14.845$, $df=2$, $p=0.000$). According to the post-hoc Bonferroni analysis, the CAT levels of the first-episode patients and the patients with chronic schizophrenia were significantly higher than that of the controls ($p=0.000$ for each). There was no significant difference between the first-episode patients and chronic schizophrenia patients in terms of the serum CAT levels ($p=1.000$) (Table 3).

In order to evaluate the effects of ECT on serum oxidant–antioxidant parameters in the patients, the repeated measures ANOVA test was performed to compare baseline values with the values measured after the 1st ECT session and those measured after the 9th ECT session. No significant change was noted in serum NO levels ($F=0.008$, $df=2$, $p=0.992$) but the MDA levels were significantly reduced ($F=5.817$, $df=2$, $p=0.005$). According to the post-hoc Bonferroni analysis, no significant change was observed in the MDA levels after the 1st session of ECT as compared to the baseline ($p=1.000$). However, the MDA levels were significantly reduced after the 9th session of ECT as compared to the baseline ($p=0.032$). There was no significant change in the serum GSH ($F=0.301$, $df=2$, $p=0.741$) or CAT ($F=0.736$, $df=2$, $p=0.505$) levels after ECT (Table 2).

The effects of ECT on study parameters in the first-episode patients were re-analyzed using repeated measures ANOVA. No significant effect of ECT was noted on NO levels in the first-episode patients ($F=1.409$, $df=2$, $p=0.268$). However, ECT was found to reduce the MDA levels in the first-episode patients more prominently ($F=8.386$, $df=2$, $p=0.002$). According to the post-hoc Bonferroni analysis, there was no significant change in the serum MDA level after the 1st ECT session (26.33 ± 6.16) as compared to the baseline (25.49 ± 6.59) in the first-episode patients ($p=1.000$), while a significant decrease was observed in the MDA level after the 9th ECT session (19.13 ± 5.17) when a curative effect was also observed ($p=0.042$). No significant effect of ECT was noted in the first-episode patients on GSH ($F=2.885$, $df=2$, $p=0.079$) and CAT levels ($F=1.178$, $df=2$, $p=0.328$). No significant effect of ECT was noted on any of the parameters in patients with chronic schizophrenia [NO, ($F=1.005$, $df=2$, $p=0.377$); MDA, ($F=0.805$, $df=2$, $p=0.456$); GSH, ($F=0.221$, $df=2$, $p=0.803$); CAT, ($F=0.309$, $df=2$, $p=0.736$)].

According to the repeated measures ANOVA test results, ECT was significantly effective on clinical disease severity measured by BPRS ($F=257.473$, $df=2$, $p=0.000$), SANS ($F=152.770$, $df=2$, $p=0.000$) and SAPS ($F=252.045$, $df=2$, $p=0.000$). According to the post-hoc

Table 1
Demographic characteristics of patients and controls.

	Patients (n = 28)	Controls (n = 20)	p
Age, years, (mean ± SD)	30.3 ± 7.6	29.5 ± 9.7	0.775
Gender, M/F, (n/n)	15/13	10/10	0.807
Smoking, +/−, (n/n)	13/15	9/11	0.922

Abbreviations: SD, standard deviation; M, male; F, female.

Table 2
Laboratory results of controls and patients before and after electroconvulsive therapy.

	Controls	Patients		
		Before ECT	After the 1st ECT	After the 9th ECT
NO, nmol/L	3.61 ± 0.54	3.98 ± 0.96	3.96 ± 0.83	3.96 ± 0.83
MDA, nmol/L	15.41 ± 4.16	22.56 ± 5.88	22.46 ± 6.52	18.99 ± 5.76
GSH, μmol/L	7.98 ± 0.42	8.10 ± 0.95	8.20 ± 0.92	8.02 ± 0.96
CAT, U/g Hb	2.66 ± 1.41	4.73 ± 1.20	4.41 ± 1.15	4.55 ± 1.30
SANS	–	80.68 ± 10.66	73.50 ± 13.23	30.54 ± 10.76
SAPS	–	78.75 ± 7.25	71.50 ± 9.85	23.21 ± 12.42
BPRS	–	65.14 ± 6.93	61.11 ± 8.53	20.89 ± 8.64

Data are presented as mean ± standard deviation.
Abbreviations: ECT, electroconvulsive therapy; NO, nitric oxide; MDA, malondialdehyde; GSH, glutathione; CAT, catalase; SANS, Scale for the Assessment of Negative symptoms; SAPS, Scale for the Assessment of Positive Symptoms; BPRS, Brief Psychiatric Rating Scale.

Table 3
Laboratory results of patients and controls.

	Controls (n = 20) Mean ± SD	Patients with new-onset schizophrenia (n = 11) Mean ± SD	Patients with chronic schizophrenia (n = 17) Mean ± SD
NO, nmol/L	3.61 ± 0.54	4.40 ± 1.03	3.71 ± 0.83
MDA, nmol/L	15.41 ± 4.16	25.49 ± 6.59	20.65 ± 4.62
GSH, μmol/L	7.98 ± 0.42	8.40 ± 0.99	7.91 ± 0.89
CAT, U/g Hb	2.66 ± 1.41	4.86 ± 1.41	4.65 ± 1.07

Abbreviations: SD, standard deviation; NO, nitric oxide; MDA, malondialdehyde; GSH, glutathione; CAT, catalase.

Bonferroni analysis, the BPRS score was noted to be significantly reduced after the 9th ECT ($p = 0.000$) while no change in the BPRS score was found after the 1st ECT ($p = 0.154$) as compared to the baseline. The SANS and SAPS scores were also found to be significantly reduced after the 9th ECT session as compared to the baseline ($p = 0.000$ for each).

According to the Pearson correlation analysis, no significant correlation was found between baseline disease severity scores (measured by the BPRS, SANS and SAPS) and baseline oxidant–antioxidant parameters.

4. Discussion

This is the first study evaluating the effects of ECT on oxidative parameters in patients with schizophrenia to the best of our knowledge. We first compared the serum oxidant–antioxidant levels of patients with schizophrenia compared with that of controls. The effects of ECT on oxidative parameters were then investigated in the patient groups.

In the present study, the baseline serum MDA and CAT levels of the schizophrenia patients were significantly higher than that of the controls. MDA and CAT levels were higher than in the control group in both the chronic patients and first-episode patients. The MDA levels of the patients with new-onset schizophrenia were significantly higher than that of the patients with chronic schizophrenia. The baseline NO levels were significantly higher in the patients with new-onset schizophrenia compared to the controls, while the NO levels of patients with chronic schizophrenia were similar to that of the controls. There was no significant difference between the patients with new-onset schizophrenia or chronic schizophrenia and controls in terms of the serum GSH level. Moreover, the use of ECT resulted in significant clinical improvement of disease severity in the patients and also led to a significant decrease of the MDA levels. No significant effects of ECT were observed on other oxidant and antioxidant parameters.

The high serum NO levels noted in patients with new-onset schizophrenia in the present study were consistent with those reported in previous studies (Li et al., 2006; Taneli et al., 2004; Zhang et al., 2010; Zoroglu et al., 2002). In addition to evidence regarding the high circulating levels of NO, significantly increased levels of NO metabolites have also been shown in the red blood cells of patients with schizophrenia compared with control subjects (Herken et al., 2001b). Taneli et al. (2004) reported that antipsychotic treatment led to a decrease in NO levels, although this was not significant. Similarly, the serum NO levels of the patients with chronic schizophrenia under drug treatment in the present study were lower than the treatment-naive patients with new-onset schizophrenia, although this was not significant. Thus, the lack of a significant difference between the serum NO levels of patients with chronic schizophrenia and controls may be attributed to the effects of antipsychotic treatment.

MDA levels are measured as an indicator of lipid peroxidation in oxidative stress studies. The serum MDA levels of the patients with new-onset schizophrenia and those with chronic schizophrenia were higher than that of the controls in our study. Elevated levels of MDA have been shown in the plasma, erythrocytes, leukocytes and platelets of patients with schizophrenia (Dakhale et al., 2004; Dietrich-Muszalska et al., 2005; Herken et al., 2001b; Khan et al., 2002; Kuloglu et al., 2002; Padurariu et al., 2010; Petronijević et al., 2003; Wood et al., 2009). In the present study, the MDA levels in patients with chronic schizophrenia under antipsychotic treatment were found to be significantly lower than in treatment-naive patients with new-onset schizophrenia, but they were still significantly higher than in the control subjects. Antipsychotic treatment has been shown to reduce MDA levels in patients with schizophrenia in previous studies (Al-Chalabi et al., 2009; Dakhale et al., 2004). Our results indicating high MDA levels in schizophrenia patients and relatively lower MDA levels in chronic schizophrenia patients under antipsychotic treatment support previous findings.

Catalase and GSH are the major antioxidant parameters used in previous oxidative stress studies conducted in patients with schizophrenia. In our study, the serum CAT level was found to be higher in the patients with new-onset schizophrenia and in patients with chronic schizophrenia as compared to the controls. In a previous study, CAT activity was found to be increased in disorganized (148%), paranoid (147%), and residual (165%) schizophrenia patients compared to the control subjects (Herken et al., 2001a). Our findings were consistent with the previous results suggesting increased CAT activity in patients with schizophrenia (Herken et al., 2001a). This increased CAT activity can be considered as a compensation mechanism to eliminate high levels of free radicals in these patients.

Glutathione, which is the major antioxidant system in the brain, plays a key role against oxidative stress. Decreased GSH levels have been found in vivo in the cerebrospinal fluid and medial prefrontal cortex of schizophrenia patients (Do et al., 2000; Matsuzawa et al., 2008) and postmortem in caudate nucleus (Yao et al., 2006). However, Terpstra et al. (2003) reported that the levels of GSH in the anterior cingulate cortex did not differ between patients with schizophrenia and control subjects. The serum GSH levels of the patients were similar to that of the controls in the present study. A recent meta-analysis revealed that there was no significant relationship between GSH activity and schizophrenia (Zhang et al., 2010).

One of our major findings was that there was no significant gender-related difference in the levels of oxidant and antioxidant parameters in either the patients or controls.

Similar to previous findings, our results also revealed that levels of the oxidant molecules NO and MDA increased in patients with schizophrenia. However, this study indicates that there is less tendency for oxidant molecules to increase in patients on long-term antipsychotic medication. It is therefore possible that antipsychotics prevent the increase of oxidative parameters such as NO and MDA. The role of antioxidants and especially CAT in sweeping oxidant molecules is known. It can be suggested that the antioxidant CAT level may also increase to compensate the increase in oxidant molecules.

One of our main objectives was to investigate the acute and chronic effects of ECT on oxidative parameters. Animal studies have shown that epileptic seizures result in free radical production and oxidative damage to cellular proteins, lipids, and DNA (Patel, 2002, 2004). The role of ROS in both the acute and chronic period of drug-induced status epilepticus has also been studied previously (Dal-Pizzol et al., 2000). However, the results of the present study were different from those reported

previously. The present study revealed that ECT performed in schizophrenia patients and the epileptic seizures induced by this procedure did not have any negative effects on oxidative stress parameters during either the acute or chronic period. No significant difference was noted in any of the oxidative parameters during the acute period following a single ECT performed in the patients. The treatment response after nine sessions of ECT was accompanied by a decrease in the serum MDA level, a lipid peroxidation marker, in contrast to what was expected. This beneficial effect of ECT in contrast to epileptic seizures is interesting. ECT may be decreasing MDA levels with a mechanism different than found in epileptic seizures. The lack of a change in any oxidative parameter following a single ECT administration also supports the notion that ECT may be affecting oxidant parameters in a way different than seen with epileptic seizures. The improvement in clinical parameters after 9 ECT sessions and the lack of a negative change in oxidant parameters together with the beneficial effect in the form of decreased MDA levels may be explained by a therapeutic effect of ECT. However, the most important limitation of this study is the measurement of oxidative parameters in the peripheral blood. It is not clear to what extent peripheral blood values reflect the oxidative changes in the brain. It is also not possible to measure cerebral oxidative changes in human studies at present. Our values may therefore reflect the cerebral or peripheral effects of ECT. The reason for the lack of an increase in oxidative stress following the epileptic seizures induced by ECT could be the controlled conditions used in contrast to actual epileptic seizures. Peripheral muscle contractions are largely prevented with medication (succinylcholine) in ECT-induced epileptic seizures. The patients were also anesthetized and ensured adequate oxygenation. It is therefore possible that ECT under these conditions does not lead to detrimental effects on oxidative stress parameters.

Previous animal studies have shown that ECS has some beneficial effects on oxidative stress parameters in various brain regions of rats. Barichello et al. (2004) demonstrated a decrease in lipid peroxidation in the hippocampus, cerebellum, and striatum after a single electroconvulsive shock or multiple ECS. They have also demonstrated an increase in CAT and SOD activities at different time points after single and multiple ECS administration (Barichello et al., 2004). It is possible that the MDA levels that decreased with ECT in our study reflect the cerebral levels. In addition to the outcomes presented in animal studies, our results provide additional data supporting the theory that ECT-induced seizures have positive rather than negative effects on oxidative stress parameters in humans. Another explanation of the oxidative stress-decreasing effect of ECT is a general feeling of wellness in the patient following this treatment leading to healthier habits (such as better sleep or nutrition).

Animal studies have not demonstrated a beneficial effect of ECT on cerebral oxidative stress parameters. Jornada et al. (2007) demonstrated no alteration in lipid peroxidation and protein damage in the four parameters studied immediately following and 48 h and 7 days after a final maintenance ECS. Another study reported unchanged levels of lipid peroxidation in the hippocampus and cerebellum but significant increases in SOD and GSH-Px activities. No significant change was noted in the levels of lipid peroxidation markers and SOD and GSH-Px activities in the pons/medulla region (Zupan et al., 2008). These animal studies did not include any effect of a disorder such as schizophrenia or a preliminary state that could cause stress in the animal brain. Actually the ECS itself was used as the stress factor. The animals were also not ensured adequate oxygenation during the ECS application. This may have increased the oxidative stress and the compensatory antioxidant levels in the animals. The ECT used on humans is to correct the pathology and takes place under controlled conditions. An alternative explanation may be different central and peripheral effects of ECT. Studies on animals take measurements directly from brain tissue. Our measurements were from the peripheral blood, and peripheral effects may have affected our results. This study indicates that ECT does not increase oxidative stress in the peripheral blood when performed under controlled conditions using anesthesia. Another explanation for the decreased MDA levels may be the use of antipsychotics together with the ECT of all patients. Previous studies have shown decreased MDA levels with antipsychotic usage (Al-Chalabi et al., 2009; Dakhale et al., 2004). Chronic patients suffered milder oxidative stress as they had used antipsychotics for a long time. Patients who had used antipsychotics for a much shorter period had higher MDA and NO levels. This indicates that the antipsychotics used in our patients had a marked effect in decreasing oxidative stress.

To the best of our knowledge, the only study directly evaluating the effects of ECT on oxidative parameters in humans was conducted in patients with depression (Virit et al., 2010). In that particular study involving 16 patients without a control group, no significant change in the MDA and NO levels were noted after ECT, while a significant reduction was found in the SOD levels (Virit et al., 2010). Similarly, we did not find a significant change in NO levels after ECT in the present study but we did not evaluate SOD activity. Virit et al. (2010) reported that ECT did not lead to a significant change in MDA levels. However, a significant decrease in MDA levels after ECT was noted in the present study. The small number of patients in the Virit et al. study may have led to these contradicting results. Other studies on the effect of ECT on oxidative stress parameters may shed light on the subject.

There are several limitations of our study. We combined the use of antipsychotics with ECT, and these drugs may therefore have affected the blood levels of oxidant–antioxidant parameters. The assessment of peripheral oxidant–antioxidant molecules may also not adequately reflect their central activity. Finally, our sample size may be considered relatively small as we grouped together patients with new-onset and chronic schizophrenia. These preliminary findings will therefore need to be confirmed in large-scale studies.

5. Conclusions

In conclusion, these results indicate that ECT leads to a significant decrease in MDA levels with significant clinical improvement in disease severity in schizophrenia patients. However, it does not produce any negative effect on the other oxidant and antioxidant parameters in these patients. Our findings suggest that ECT is a safe treatment alternative in terms of oxidative stress for patients with schizophrenia. Future studies on a larger scale may provide further insight to the effects of ECT on oxidative stress in psychiatric patients.

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