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Original Article

Effect of Olanzapine and Risperidone on Oxidative Stress in Schizophrenia Patients

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Oxidative stress has been suggested to contribute to the pathophysiology of schizophrenia. Increased oxidative stress is the result of either an increased production of free radicals or a depletion of the endogenous antioxidants. However, whether this imbalance of oxidant-antioxidant status in schizophrenia is integral to disease itself or the effect of antipsychotic drugs is not clearly understood. The present study was undertaken to evaluate the effect of olanzapine and risperidone on oxidative stress, and anti oxidant status. A total of 179 patients were enrolled, and 93 of them completed the study. Malondialdehyde (MDA) and reduced glutathione (GSH) were measured for oxidative stress assessment. Plasma levels of ascorbic acid (vitamin C) and α-tocopherol (vitamin E) were measured for anti-oxidant status evaluation. All patients were studied at baseline, and after 3 months treatment with olanzapine or risperidone. 30 apparently healthy people were taken as control. The schizophrenia group presented higher levels of oxidative stress than the control group, as revealed by elevated quantities of the pro-oxidant MDA, and decreased levels of the antioxidants GSH, plasma α-tocopherol and ascorbic acid ($P < 0.01$). After 3 months in both olanzapine and risperidone treated groups MDA levels were reduced significantly ($P < 0.01$). However, levels of erythrocyte GSH, plasma vitamin E, and vitamin C were increased significantly ($P < 0.01$). Therefore, atypical antipsychotics like olanzapine and risperidone improved the antioxidant status which might play a role in the improvement of schizophrenia symptoms.

Keywords: Schizophrenia, oxidative stress, antioxidants, olanzapine, risperidone

The incidence of psychotic illness is increasing in general population. Among those schizophrenia is the most common which is a chronic, severe disabling psychiatric illness. The World Health Organization reported a worldwide prevalence of about 0.7% for schizophrenia in 2011 with about 24 million people suffering from with the disease.

Over the past years, several researches have been conducted to identify the aetipathogenesis of schizophrenia. Different neuro-developmental, structural, and behavioral abnormalities are associated with schizophrenia. It has been suggested that such abnormalities might be originated from malfunctioning genes. Non genetic factors such as ethnicity, drug or alcohol abuse, life-style, medications, pre-natal and neonatal infections, maternal malnutrition, complication during birth,

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and many other factors may play an important role in disease etiopathogenesis (1). Accumulating evidence suggests that these factors increase the possibility of oxidative stress and damage to the brain by inducing cellular metabolic stress (2). Oxidative stress has been proposed to be common to several psychiatric disorders (3). Oxidative stress is a condition where there is imbalance between generation of reactive oxygen species (ROS), and antioxidant defenses in favor of the former. Free radicals are highly reactive chemical species generated during normal metabolic processes (4). Neuronal membranes can be altered by free radicals through lipid peroxidation, leading to functional alterations and even cell death (5). However; oxyradicals have a very short life span and usually are inactivated or scavenged by antioxidants before they can induce damage to lipids, proteins or nucleic acids. The human body has complex antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These enzymes block the initiation of reactive species chain reactions (6).

The non-enzymatic antioxidants are compounds like glutathione (GSH), vitamin E, vitamin C and β-carotene, which react with reactive species and thereby prevent the propagation of chain reactions (7). Cellular levels of antioxidants respond to levels of oxyradicals, which enables cells to defend against increased oxyradicals production (8). Cellular antioxidants act in combination (9). α-tocopherol is a chain breaking antioxidant that act by neutralizing a free radical, and gets converted into α-tocopheroxyl radical by ascorbic acid (10). If produced in excess or not removed effectively by antioxidants, oxyradicals result in cellular damage. Dehydroascorbic acid formed in this reaction can be reconverted back to ascorbic acid by reduced GSH (11).Therefore, it is important that sufficient amounts of α-tocopherol, reduced ascorbic acid, and reduced GSH be present within the cell so as to provide protection against oxidative injury.

Free radicals and ROS play a number of significant and diverse roles in neurodegenerative diseases, including schizophrenia (12). The brain and nervous system are particularly prone to free radical damage (13). The brain has a high rate of oxidative metabolic activity, high oxygen consumption, and low levels of protective antioxidant enzymes. The high proportion of readily oxidizable membrane polyunsaturated fatty acids (PUFAs) makes it more exposed to oxidative stress (8). There are strong evidence that oxygen free radicals may play an important role in the pathophysiology of schizo-phrenia (14, 15). Estimating the levels of reactive oxidative products provides a useful strategy to determine the impact of oxidative stress. Lipid peroxidation is often assayed by measuring thiobabituric acid reactive substances (TBARS). The end products of lipid peroxidation, especially malondialdehyde (MDA) assessment have been the most widely used indice of oxidative stress in clinical studies (16, 17). Studies performed in schizophrenia patients have generally suggested a compromised antioxidant system, and increased levels of lipid peroxidation products. Many researchers have found a significant increase in plasma MDA levels in patients with schizophrenia (18, 19).

For quantifying the antioxidative defense in schizophrenia, antioxidant enzymes such as SOD, GPx, and CAT are most commonly measured, along with vitamin E and vitamin C levels. The changes reported about the activities of antioxidant enzymes are controversial in schizophrenia patients (19-21). GSH is the brain's dominant antioxidant implicated in the pathophysiology of schizophrenia (22). There is 27% reduction in the cerebrospinal fluid (CSF) levels of GSH, and 41% reduction in the postmortem CSF of schizophrenic patients (23, 24). A significant decrease was reported in the blood levels of total GSH in schizophrenia patients in comparison with control subjects (13).

The mainstay of treatment of schizophrenia is antipsychotic medications of which the first generation drugs primarily act by suppressing the

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dopaminergic receptor activity. At the beginning of 1990s, a new generation of antipsychotic drugs like atypical antipsychotics was introduced. In comparison with the first generation or typical antipsychotics, atypical antipsychotics exhibit better efficacy in treating both negative and positive symptoms of schizophrenia, and a superior safety profile regarding adverse events as extrapyramidal symptoms (25). The antipsychotic effects of second generation is attributed to their action on serotonin receptors rather than dopaminergic receptors. Typical antipsychotics bind D_2 receptor 50 times more avidly than D_1 or D_3 receptors (26). There are also controversies regarding the oxidative stress status in patients treated with typical vs atypical antipsychotics. Some researchers reported that chronic administration of typical antipsychotic haloperidol but none atypical antipsychotics like risperidone, clozapine or olanzapine induces oxidative stress by decreasing the activity of antioxidant enzymes, causing membrane lipid peroxidation (27). However, there are also studies which demonstrated a decreased level of lipid peroxidation in the cerebral cortex after chronic administration of haloperidol. Lipid peroxidation was found to be significantly higher after treatment with typical antipsychotics (28), whereas atypical antipsychotics improved oxidative damage markers such as TBARS (29).

The aim of the present study was to evaluate the oxidative stress, and the status of protective antioxidants under stress condition due to schizophrenia. We measured the plasma levels of stress markers like MDA and GSH in red blood cells (RBCs), and evaluated the antioxidant status by determining plasma levels of vitamin C and vitamin E. We also determined the alteration of these markers in patients on treatment with atypical antipsychotics, olanzapine and risperidone.

Materials and methods

Patients

The study was carried out in Department of Pharmacology and Department of Psychiatry of BSMMU during September 2013 to January 2015. Samples were collected up to November 2014. Patients with schizophrenia attending the outpatient department or admitted in the inpatient department of psychiatry, BSMMU were recruited in the study. A total of 179 patients fulfilling the inclusion criteria were enrolled by non-probability sampling. Of them, 93 completed the study, where 43 were in olanzapine, and 50 were in risperidone treatement. Patients were above 18 years, from either sex, and were diagnosed by psychiatrists of BSMMU according to DSM-5 criteria. 30 apparently healthy age and sex matched controls that came for routine checkup, were included from outpatient department. The ethical issue was reviewed and approved by the Institutional Review Board (IRB) of BSMMU and informed consent was obtained from all subjects, guardians and families of the subjects as circumstances demanded.

Patients who received antipsychotic drugs within the last 30 days, or took vitamin E, vitamin C for the last 3 months, or had serious cognitive deficit that causes disturbance of communication, or had serious infection or terminal illness were excluded from the study:

Study design

Schizophrenia patients were divided into two groups: risperidone treated group (n= 50) received risperidone at a dose of 4-16 mg/day orally, and olanzapine treated group (n=43) received olanzapine tablets at a dose of 5-20 mg/day orally for a period of 3 months. The whole study consisted of 2 visits: a baseline, and a follow up visit after 3 months of treatment. At baseline visit, blood was collected for MDA, GSH, vitamin C, and vitamin E levels assessment. All patients received standard routine medical care throughout the study. Regularity of drug intake was ensured over telephone, and with patient's compliance sheet. After 3 months of treatment, blood was collected for biochemical parameters measurement. In control group, blood collection was performed only once

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after overnight fasting to measure the biochemical parameters.

Biochemical analyzes

With all aseptic precaution 5 ml blood were collected by venepuncture from the antecubital vein, and kept in 1 x 5 ml K_3EDTA (anticoagulant) containing test tube. Plasma was separated by centrifugation (3,500 rpm for 10 min), and stored for further use.

For erythrocyte hemolysate preparation, plasma and buffy coat were separated from the top. The packed RBCs were washed thrice with five volumes of cold 0.9% saline by centrifugation at 3,500 rpm for 10 min. The packed cells were suspended in five volumes of deionized distilled water at 4 °C for 24 h to lyse RBCs. Then suspension was then centrifuged at 3,500 rpm for 10 min to collect RBCs lysate.

Plasma MDA level was estimated by UV-180 spectrophotometer (Shimadzu, Japan) by thiobarbituric acid (TBA) reaction method of Yagi (30). Estimation of erythrocyte GSH level was based on the method of Ellman (31). Estimation of plasma vitamin C level was performed by the method of Rahman et al. (32), and vitamin E level was assessed by the method of Baker and Frank (33).

Statistical analysis

Data were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences) version 16.0. Unpaired and paired sample t-test was used to compare the continuous data between and within groups, respectively. The level of significance was set at 5% and $P< 0.05$ was considered significant.

Results

According to Table 1, before treatment with antipsychotic drugs, MDA level was significantly higher in study group in comparison with control group, while GSH, vitamin E, and vitamin C levels were significantly lower in study group in comparison with control group.

Table 2 reveals that in olanzapine treated group, MDA level was significantly reduced after 3 months of drug treatment, while GSH level increased significantly. The antioxidant vitamins such as vitamin E and vitamin C levels were also increased significantly after 3 months of drug treatment.

Table 3 reveals that in the risperidone treated group MDA level was reduced significantly after 3 months of drug treatment, while GSH level was increased significantly. The antioxidant vitamins E and C levels were also increased significantly after 3 months.

Figures 1-4 represent the variations of plasma MDA, erythrocytes GSH, plasma vitamin E, and plasma vitamin C levels in schizophrenia and control subjects during the treatment period.

Table 1. Oxidative stress markers at baseline

Oxidative stress markers	Groups		P-value
	Case (n=93)	Control (n=30)	
Plasma MDA (µmol/L)	6.3±0.5	2.1±0.5	0.0001
Erythrocyte GSH (mg/gm of Hb)	0.6±0.2	2.1±0.5	0.0001
Plasma vitamin E (mg/L)	4.3±0.6	7.3±0.7	0.0001
Plasma vitamin C (µmol/L)	30.6±8.3	78.7±10.9	0.0001

Data were analyzed using Unpaired t-Test and were presented as mean±SD.

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Table 2. Oxidative stress markers in olanzepine treated group after 3 months

Oxidative stress markers	Olanzapine (n=43)		P-value
	Baseline	At 3 months	
Plasma MDA (µmol/L)	6.3±0.5	2.8±0.3	0.0001
Erythrocyte GSH (mg/gm of Hb)	0.5±0.1	1.1±0.3	0.0001
Plasma vitamin E (mg/L)	4.4±0.6	6.5±0.6	0.0001
Plasma vitamin C (µmol/L)	30.9±8.7	59.9±10.7	0.0001

Data were analyzed using Paired t-Test, and were presented as mean ± SD.

Table 3. Oxidative stress markers in risperidone treated group after 3 months

Oxidative stress markers	Risperidone (n=50)		P-value
	Baseline	At 3 months	
Plasma MDA (µmol/L)	6.4±0.5	3.0±0.4	0.0001
Erythrocyte GSH (mg/gm of Hb)	0.6±0.2	1.5±0.4	0.0001
Plasma vitamin E (mg/L)	4.2±0.6	6.1±0.7	0.0001
Plasma vitamin C (µmol/L)	30.4±8.1	61.3±10.4	0.0001

Data were analyzed using Paired t-Test, and were presented as mean ± SD.

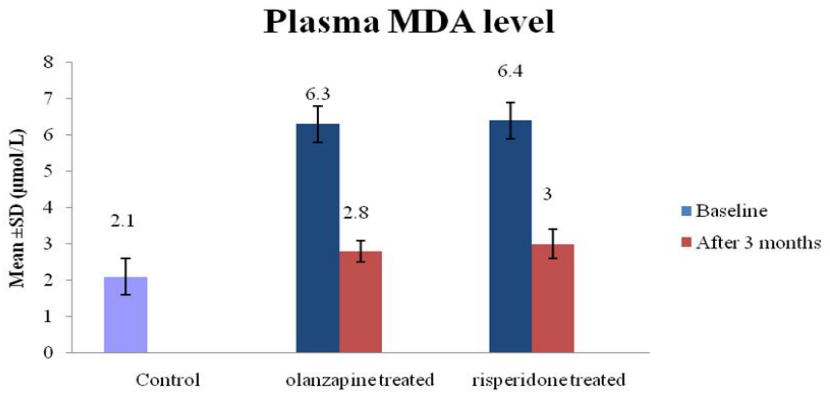


Figure 1. Plasma MDA levels. Plasma MDA levels were higher in schizophrenia patients in comparison with controls, but decreased after 3 months treatment with either olanzapine or risperidone.

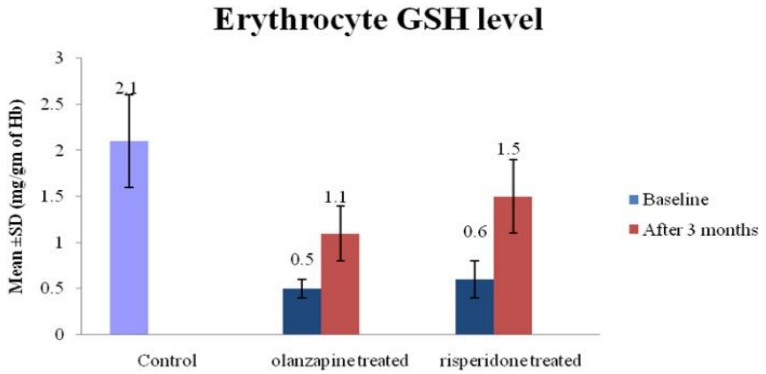


Figure 2. Erythrocytes GSH levels. Erythrocytes GSH levels were lower in schizophrenia patients in comparison with controls, but increased after 3 months treatment with either olanzapine or risperidone.

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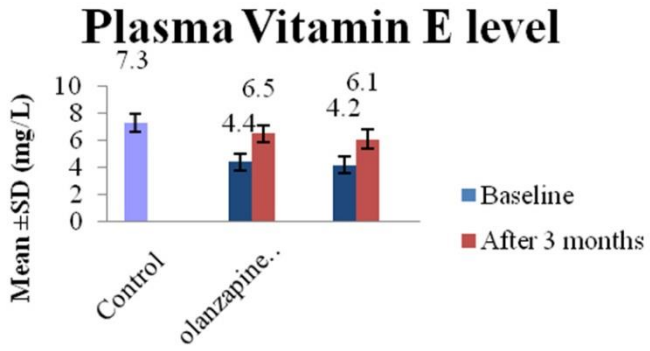


Figure 3. Plasma vitamin E levels. Plasma vitamin E levels were lower in schizophrenia patients in comparison with controls, but increased after 3 months treatment with either olanzapine or risperidone.

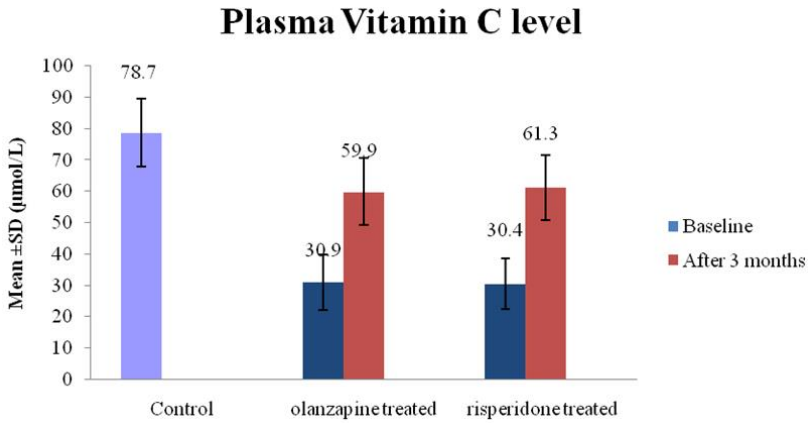


Figure 4. Plasma vitamin C levels. Plasma vitamin C levels were lower in schizophrenia patients in comparison with controls, but increased after 3 months treatment with either olanzapine or risperidone.

Discussion

A growing body of evidence suggests that oxidative stress is involved in the pathophysiology of schizophrenia. However, many of the results regarding oxidative stress and antioxidant status in this disease are contrasting. In the present study, examination of oxidative stress status revealed that the MDA level, an indicator of oxidative stress, was significantly higher ($P< 0.05$) in schizophrenia patients as compared to control subjects. We also assessed the antioxidant status by measuring GSH level in erythrocytes, and non enzymatic antioxidants plasma vitamin E and C levels. We found a significantly lower ($P< 0.05$) level of GSH in schizophrenia patients compared to control group. Vitamin E and C levels were also significantly lower ($P< 0.05$) in patients in comparison to control group.

In a similar study, assessment of oxidative stress showed that the MDA level was significantly elevated in schizophrenia patients compared to control subjects ranging in age from 18 to 60 years (34). Issa et al. measured MDA, GSH, and vitamin C levels in sera of 70 schizophrenic patients and 30 healthy individuals, where a significant elevation ($P<0.005$) in MDA level of schizophrenia patients was observed in comparison with the control group (35). In contrast, GSH, SOD and vitamin C values showed a significant decrease in sera ($P< 0.005$) of schizophrenia patients when compared with those of control group. A significant decrease in the RBC total GSH levels was also reportd previously in schizophrenia patients in comparison with controls (13). In another study, plasma levels of MDA in schizophrenia patients were found to be increased three to four fold compared to normal controls (8). The finding of an elevation in plasma levels of MDA is consistent with the majority of studies of schizophrenia patients with increased lipid

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peroxides (12, 36). However, some other studies have reported no significant difference in lipid peroxides between patients and controls (37).

The raised level of MDA in our study indicates a high oxidative stress in schizophrenia patients, and this may promote many pathophysiological changes in those patients. A high level of MDA is a sign of peroxidative injury to membrane phospholipids. The raised levels of MDA could be attributed to a rise in generation of ROS owing to the high rate of oxidative damage process that occurs in those patients.

It has been anticipated that antioxidant defense mechanisms could be impaired in patients with schizophrenia with alteration in antioxidant status leading to lipid peroxidation (12, 38). Vitamin C and E act as radical scavenging antioxidants, and suppress lipid peroxidation (39). In the present study, a significant reduction ($P< 0.05$) in erythrocytes GSH, plasma vitamin E and C levels was found in schizophrenia patients compared to control group. Our results of decreased GSH and vitamin C are consistent with the hypothesis which suggests that there is deficiency in the amounts of antioxidants in patients with schizophrenia which was put forward by Zhang et al. (40). Vitamin C serves as an essential defense line against dopamine induced neurogenerative processes (41). It reacts with activated oxygen species and prevents conversion of ferric to ferrous ions responsible for facilitating the generation of hydroxyl radicals (42). As most of the vitamin C is utilized for scavenging free radicals, and inhibiting lipid peroxidation, levels of vitamin C may be decreased in such patients (43).

The levels of vitamin E, the most potent lipid bound chain breaking antioxidant in serum was found to be significantly lower in schizophrenia patients as compared to controls (44). This report is consistent with our results of decreased vitamin E level in schizophrenia patients. This decrease may probably be contributed to the increased consumption of vitamin E for free radical neutralization, and its conversion to α-tocopheroxyl radical (45).

There are also controversies regarding the oxidative stress status in patients treated with typical vs atypical antipsychotics. It has been proposed that GSH deficit in schizophrenia may be associated with dopamine-induced oxidative stress (46). Antipsychotic drugs are known to block dopamine receptors, and consequently may result in increased levels of GSH. In our study following 3 months treatment with both olanzapine and risperidone there was significant reduction ($P< 0.05$) in MDA levels, and significant increase in erythrocytes GSH and plasma vitamin E and C levels in schizophrenia patients. However, the improvement in MDA and vitamin E levels was better in olanzapine treated group than risperidone group ($P= 0.009$ and $P= 0.011$, respectively). Some authors reported that chronic administration of typical antipsychotic haloperidol, but none of some atypical antipsy-chotics like risperidone, clozapine or olanzapine induced oxidative stress by decreasing the activity of antioxidant enzymes, and causing membrane lipid peroxidation (27). Studies show that atypical antipsychotics may improve oxidative status, increase antioxidant levels, and decrease oxidative stress markers such as TBARS (47). Dakhale et al. showed that the serum MDA and SOD levels were decreased significantly in schizophrenia patients after 8 weeks of treatment with atypical antipsychotics (29). At the same time levels of plasma vitamin C was increased significantly after same duration of treatment compared to baseline levels. In another study, serum total antioxidant status was shown to be decreased by olanzapine treatment in schizophrenia patients (48). However, other studies that included the individual antioxidant system gave controversial results (29).

It is evident from the present study that olanzapine and risperidone increase the level of antioxidants like GSH, vitamin C, and vitamin E, and reduce the oxidative stress by decreasing MDA levels. They might have an influence on improving

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the symptoms of schizophrenia through decreasing the oxidative stress. The present findings need to be further explored through a broad based study.

Conflict of interest

The authors declare that they have no competing interest.

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