The Effect of Sertraline on Oxidative Stress in Patients with Depression

Rahma Ahmad Saadaldin Alkasso1, Kassim Salih Abdullah Al Neaimy2

Abstract

Background: There is effect of sertraline on oxidative stress in patients with depression.

Objective: To assess the oxidative stress and total antioxidant capacity in patients with depression, and evaluate the effect of antidepressant (sertraline) on the oxidative stress and total antioxidant status.

Design: Comparative case-series study.

Setting: The study was conducted in consultatory clinic outpatient departments of psychiatry physicians.

Methodology: The study period between Nov.1st, 2020 and April.1st, 2021. Thirty female patients newly diagnosed with depression and thirty, sex and age-matched healthy volunteers as control group were participated in the study. Malondialdehyde (MDA) and total antioxidant status (T-AOC) were measured control group and also measured in patients with depression before and after taking sertraline therapy for two months duration.

Results: Depressed patients have higher MDA values than that of the control group (9.191 ± 2.796 and 3.21 ± 0.94 nmol/ml respectively) (P-value = 0.001) and lower level of T-AOC (9.44 ± 3.210 U/ml) in depressed patients than that of control group (11.26 ± 2.98 U/ml) P-value = 0.027)

MDA values of newly diagnosed patients(9.191 ± 2.796 nmol/ml) were significantly higher than that of patients taking sertraline treatment for 2 months (6.123 ± 1.889 nmol/ml) (p<0.001). The T-AOC values of newly diagnosed patients (9.444 ± 3.210 U/ml) were significantly lower than that of patients taking sertraline treatment for 2 months (10.142 ± 2.362 U/ml) (p<0.122).

1 Bachelor of Science in Pharmacy
2 Ph.D / Mosul University, College of Medicine / Department of Pharmacology / E-mail:abdullahkassim@yahoo.com / Mobile: 009647701676407
Conclusion: The present study demonstrated that depressed patients have increased level of malondialdehyde and decreased level of total antioxidants capacity than the control group while depressed patients treated with sertraline for two months have decreased level of MDA and increased levels of T-AOC than their levels before treatment. This result may give a new insight that sertraline may exhibit its effect in the management of depression by acting as an antioxidant.

Keywords: Depression, Oxidative Stress, Sertraline.

Introduction:

Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one discrete depressive episode lasting at least 2 weeks and involving clear-cut changes in mood, interests and pleasure, changes in cognition and vegetative symptoms (Otte, et al., 2016). It can occur at any age from childhood to late life and is a tremendous cost to society as this disorder causes severe distress and disruption of life and, if left untreated, can be fatal (Bondy, 2002). Currently affecting around 300 million people worldwide and with 5%–17% of the population suffering from the disorder at least once in their lifetime (World Health Assembly, 2012).

The underlying pathophysiology of major depressive disorder has not been clearly defined (Namkung et al., 2018). Evidence from a large amount of research suggests that 5-hydroxytryptamine (5HT) systems in the central nervous system (CNS) play essential part in depression. Serotonergic neuron activity is lower in depressed patients, according to postmortem, CSF, and neuroendocrine researches (Mann et al., 1996; Drevets et al., 1999).

The role of CNS 5-HT activity in the pathophysiology of major depressive disorder is suggested by the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs). Research findings imply a role for neuronal receptor regulation, intracellular signaling, and gene expression over time, in addition to enhanced neurotransmitter availability (Yohn et al., 2017).

Major depression is associated with lowered antioxidant concentrations and increased oxidative stress levels as well (Hovatta et al., 2010; Leonard and Maes, 2012; Scapagnini et al., 2012; Galecki, 2014). Oxidative stress has been defined as the imbalance of pro-oxidant/antioxidant forces in favor of the former (Ibrahim et al., 2008). Oxidative stress also can be caused by either an increase in the production of ROS and free radicals (FR) or a decrease in the antioxidant defense system (Trevisan et al., 2001).

However, in high concentrations, reactive oxygen species lead to damage of components of the cell, including proteins (enzymes, receptors), lipids, and DNA, which consequently may lead to apoptosis.

The mechanisms by which oxidative stress may be related to depressive symptoms are yet to be elucidated, although it has been noted that the brain is particularly vulnerable to oxidative damage due to high oxygen utilization and subsequent generation of free radical by-products, relatively weak antioxidant defenses, and the risk for oxidative cellular injury and necrosis (Ng et al., 2008).

Major depressive disorder may be associated with changes in oxidative stress markers and that antidepressant agents may increase antioxidant defenses. It is possible that augmentation of antioxidant defenses may be one of the mechanisms underlying the neuroprotective effects of antidepressants observed in the treatment of MDD (Behr et al., 2012).

The present study was aimed to:
1. To assess the oxidative stress in patients with MDD by measurement malondialdehyde (MDA) which is often used as indicator of oxidative stress.
2. To assess the total antioxidant capacity in MDD patients
3. To evaluate the effect of antidepressant (sertraline) on the oxidative stress and total antioxidant capacity in patients with major depressive disorder.

Subjects and methods:

The present study had approval from the regional research committee of the College of Medicine, University of Mosul, Mosul, Iraq.

Thirty female patients, newly diagnosed with depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria from a psychiatric private clinic, with age range (20-70) years are recruited in the study. These patients who had not to use SSRIs therapy within the previous months started to receive Sertraline tablet 50 mg for two months duration. Another thirty healthy subjects, were considered as a control group.

The study was conducted in the consultatory clinic of psychiatry outpatient departments (private clinics of psychiatric physicians).

Pregnant and lactating women, patients with a comorbid condition affecting the immune system, including autoimmune or inflammatory disorders (e.g. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis), chronic infection (HIV, hepatitis B or C), cancer, corona virus infectious disease-2019 (Covid-19), people receiving trace elements or vitamin B-complex within one month before the study, smokers and alcohol drinking were excluded from the study.

The clinical and biochemical analysis include:

Weight was measured with light clothes by weighing scale.
Body mass index (BMI) was calculated according to the equation:

\[ \text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \]

(Leermarkers et al., 2000; Nuttall, 2015)

Biochemical analysis of malondialdehyde (MDA) a marker of oxidative stress and T-AOC were measured using Colorimetric Assay Kit Elabscience®. (USA).

Statistical analysis:

Dependent (paired) t-test and independent (unpaired) two sample student t-test were used to compare the result of various parameters among the studied groups. All values expressed as Mean ± SD and the P-value of <0.05 were considered to be statistically significant (Kirkwood, 1988).

Results:

The depressed patients and control groups were comparable in terms of age and BMI as shown by non statistically significant differences between the groups (P-value = 0.927, P-value = 0.415) respectively as shown in table (1).

Table (1): Comparison in personal characteristics between the depressed patients and control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Depressed women [n = 30] Mean ± SD</th>
<th>Control [n = 30] Mean ± SD</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.37 ± 15.28</td>
<td>43.03 ± 12.53</td>
<td>0.927</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.86 ± 4.61</td>
<td>28.96 ± 3.89</td>
<td>0.415</td>
</tr>
</tbody>
</table>

* Independent T-test of two means was used.

There are significant differences regarding MDA and non significant differences regarding T-AOC value as shown in table (2)

Table (2): Comparison in oxidative stress parameters between the depressed patients and control group.

<table>
<thead>
<tr>
<th>Oxidative stress parameters</th>
<th>Depressed women [n = 30] Mean ± SD</th>
<th>Control [n = 30] Mean ± SD</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/ml)</td>
<td>9.19 ± 2.796</td>
<td>3.21 ± 0.94</td>
<td>0.001</td>
</tr>
<tr>
<td>T-AOC (U/ml)</td>
<td>9.44 ± 3.210</td>
<td>11.26 ± 2.98</td>
<td>0.027</td>
</tr>
</tbody>
</table>

* Independent T-test of two means was used.
After two months of therapy, at the end of study, with antidepressant treatment. There was a significant differences (improvement) in mean serum concentration of MDA and, a non-
significant difference in T-AOC between before and after therapy (P. value =0.001 and 0.112 respectively) as shown in table (3).

Table (3): The effect of SSRI therapy on oxidative stress parameters of the depressed women after 2 months therapy, [n = 30].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before (n=30)</th>
<th>After (n=30)</th>
<th>% Improvement rate*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/ml)</td>
<td>9.191 ± 2.796</td>
<td>6.123 ± 1.889</td>
<td>33.4 %</td>
<td>0.001</td>
</tr>
<tr>
<td>T-AOC (U/ml)</td>
<td>9.444 ± 3.210</td>
<td>10.142 ± 2.362</td>
<td>-7.4 %</td>
<td>0.122</td>
</tr>
</tbody>
</table>

* % Improvement rate = [(before – after) / Before] × 100.

** Paired T-test of two means was used.

Discussion:

The pathophysiology of major depressive disorder (MDD) and its complexity is still not completely understood, however, there has been a lots of research further into link between depression and elevated oxidative stress (Palta et al., 2014).

The present study was carried out to assess the oxidant /antioxidant capacity in 30 depressed patients in comparison to another group apparently healthy individuals kept as a control group and to evaluate the effect of 2 months of therapy of selective serotonin reuptake inhibitors (Sertraline) on oxidative stress and antioxidant capacity in a sample consisting of 30 newly diagnosed female patients with depression. The oxidative stress of MDD patients had been accessed by measurement plasma levels of a byproduct of lipid peroxidation, i.e. malondialdehyde (MDA), the most commonly used indicator of oxidative stress, and the plasma antioxidant capacity was evaluated by measurement total antioxidant capacity (T-AOC).

The groups were matched concerning the number and their ages as well as body mass index (BMI) as confirmed statistically by the absence of significant differences between the studied groups. This matching of patients groups number, ages, and BMI may exclude any effect of these parameters on the results of the study. The removal of the age, number and BMI factors interference with results of clinical trials were done in the majority of other trials concerning the antioxidant field (Jimenez-Jimenez et al., 1998; Besler et al., 2002; Besler and Camogli, 2003; Miller et al., 2011).

In this study serum, MDA levels were found higher in depressed patients (9.19 ± 2.796 nmol/ml) than in the control
group (3.21 ± 0.94 nmol/ml), (P-value = 0.001).

T-AOC concentration was lower in MDD (9.44 ± 3.210 U/ml), in comparison to a control group (11.26 ± 2.98 U/ml), (P-value = 0.027).

Our results are in accordance with the results of some previous studies that compared the serum level of T-AOC and individual antioxidant enzymes in MDD patients.

Bajpai et al., (2014), found a significantly high level of MDA in the patients with major depression as compared to healthy controls.

In the same study Bajpai et al., (2014) assess the antioxidant status in these patients by measurement individual antioxidants. Serum levels of ascorbic acid and superoxide dismutase (SOD) were significantly below as compared to healthy controls (all P < 0.0001). Ceruloplasmin levels were also depressed in cases.

According to Galecki (2014), total glutathione, uric acid, and ascorbic acid levels decreased, whereas glutathione peroxidase (GPX) levels increased, malondialdehyde (MDA) levels increased, 8-hydroxy-deoxyguanosine levels increased, and nitrite and nitrate levels increased.

A meta-analysis of oxidative stress markers in depression had been done by Liu et al., (2015) during the period between 1990-2014, collected the studies that measured the oxidative stress markers in depressed patients (115 articles). The results of this meta-analysis showed that oxidative damage products, including red blood cell (RBC) malondialdehyde (MDA), serum MDA and 8-F2-isoprostanes levels were higher than controls (P<0.05).

T-AOC levels in the blood were lower in depressed patients than in controls (P<0.05), but they did not rise after antidepressant treatment. But it did not increase after antidepressant therapy this is in accordance with the results obtained in our study. After two months of therapy with antidepressant treatment (sertraline). There were obvious differences (improvement) in mean serum level of MDA and, a non-significant difference in T-AOC between before and after therapy (P-value = 0.001 and 0.112 respectively).

A meta-analysis was searched by Mazereeuw et al., (2015) for initial, peer-reviewed articles examining lipid peroxidation markers (malondialdehyde, lipid hydroperoxides, 4-hydroxynonenal, isoprostanes, and other lipid peroxidation markers) in patients with MDD and healthy controls, as well as the influence of antidepressant drugs on those markers in MDD patients. Lipid peroxidation markers were found to be considerably higher in depressed patients than in healthy controls.

Malondialdehyde is a marker for continuous oxidative stress processes, as
well as the synthesis of proinflammatory lipids generated from arachidonic acid metabolism, all of which are important in the pathophysiology of MDD (Dinan et al., 2009)

There is some evidence that the activation of immune cells is related to the overproduction of reactive oxygen species. Extensive production of ROS leads to lipid peroxidation in biological membranes and causes loss of fluidity in cell membranes, falls in membrane potential, and eventual rupture leading to release of cell and organelle contents (Estebauer et al., 1991).

Since alterations in phospholipids which are the structural components of a cell membrane in the brain may induce changes in membrane microviscosity and, consequently, in various neurotransmitter systems, which are regarded to be linked to serious depression's pathophysiology (Bilici et al., 2001)

This meta-analysis also discovered that antidepressant drug treatment is linked to a consistent reduction in lipid peroxidation markers across time. These findings back up the theory that oxidative stress, specifically lipid peroxidation, plays a role in MDD.

**Conclusions:**

Oxidative stress was enhanced in MDD patients as shown by a significant increased in MDA levels and decreased in T-AOC compared with control group. Also treatment with the antidepressant medicine sertraline resulted in a considerable reduction in MDA levels in the blood and a non-significant improvement in T-AOC, since SSRIs may provide new concept for treatment of depression.

**References:**


World Health Assembly (2012) Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level: *report by the Secretariat. World Health Organization.*