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THE ROLE OF FLUOXETINE THERAPY IN CHANGING THE PLASMA LEVELS OF 8-ISO-PROSTAGLANDIN F2 (8-ISO-PGF2) IN PATIENTS WITH MAJOR DEPRESSION

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ABSTRACT

Major depression, one of the types of psychiatric disorders, can be described by disruption in mood-adjustments, behavioral activities and associated with low esteem or worthlessness or feeling of no happiness in the activities which were previously interesting and pleasurable, lasting for at least two weeks with intermittent symptom-free episodes. It is found to be comparatively more among females and presents as early as around mid to late 20s. Major depression can be due to genetic, familial, immunological; infectious or noninfectious causes which ultimately culminates in oxidative stress. Oxidative stress is imbalance between oxidative injury and the antioxidant defense mechanisms which can be analyzed by either increased levels of metabolites of oxidative injury or reduced levels of antioxidants. Oxidative stress causes production of reactive oxygen species which results in peroxidation of lipids and 8-iso-PGF2α is one of the products of lipid production. Drug of choice for the treatment of major depression is fluoxetine which decreases the oxidative stress-induced damage and causes subsequent restoration of antioxidant function. Increased levels of plasma 8-iso prostaglandins F 2α (8-iso-PGF 2α) can be assessed by Enzyme-linked Immunosorbent Assay (ELISA) method and can be compared in the newly diagnosed drug naïve major depression patients and after eight-week fluoxetine therapy. Very few studies have been done in the past for the estimation of plasma 8-iso-PGF2α levels in major depression patients and none was done to compare the levels before starting and after completion of eight-week fluoxetine therapy. The current study has been done to estimate the oxidative stress by analyzing plasma 8-iso-PGF2α levels in newly diagnosed drug-naive cases and after fluoxetine course for eight-weeks in the same patients and it shows decrease in the levels of plasma 8-iso-PGF2α in major depression patients following eight-week fluoxetine therapy.

1. INTRODUCTION

Major depression, one of the varieties of psychiatric disorder, can be identified by disruption of mood-adjustments, behavioral activities and presence of low esteem or worthlessness or feeling of no happiness in previously interesting and pleasurable activities; continuously lasting for atleast two weeks.[1-2] The prevalence of depression was found to be higher in the females than the males and the mean age of earliest identification of the disorder was found to be between mid to late 20s.[3-4]

The etiological factors responsible for progression of the disease could be genetic, familial, immunological; infectious causes like herpes virus, Human Immunodeficiency Virus **(HIV)**, Borna virus or non-infectious causes such as Alzheimer's disease, autoimmune diseases and multiple sclerosis etc. which lead to oxidative stress.[5-7]

Oxidative stress can be defined as disparity between oxidative injury and the defense mechanisms against the same and assessed by either elevated levels of metabolites of oxidative injury or diminished levels of antioxidants.[8] Reactive oxygen species and reactive nitrogen species (**ROS** and **RNS**, respectively) are free radicals, synthesized during oxidative stress and have propensity to damage carbohydrates, nucleic acids, proteins, and lipids.[9-10] Oxidative stress causes peroxidation of lipids and 8-iso prostaglandins $F_{2\alpha}$ **(8-iso-PGF2α)** is an important metabolite produced as a result of lipid peroxidation.[11] Fluoxetine is the drug used in the treatment of major depression, responsible for reduction in oxidative stress-induced damage and resultant restoration of anti-oxidant activity.[12]

Elevated levels of plasma 8-iso-$PGF_{2\alpha}$ can be quantitatively assessed by Enzyme-linked Immunosorbent Assay **(ELISA)** method and can be compared in the newly diagnosed drug naïve major depression patients and after eight-week fluoxetine therapy. Among the major depression patients, the analysis of plasma 8-iso-PGF2α levels has been done on very few occasions but none of them consisted of

comparison of the plasma 8-iso-PGF2α levels in drug naïve major depression patients and after completing eight-week fluoxetine therapy. This study was done to evaluate the oxidative stress by comparing the plasma levels of 8-iso-PGF2α in the newly diagnosed drug-naive cases and among the same patients after completion of fluoxetine therapy for eight-weeks.

2. MATERIALS AND METHODS

The prospective clinical study was performed from October 2016 to March 2018 in the department of anatomy in collaboration with the department of psychiatry and biochemistry in one of the premier post graduate medical institute in southern part of India. The required permission was obtained from the Postgraduate Research Monitoring Committee **(PGRMC)** and Institute Ethics Committee **(IEC)** – Human Studies, of the institute, respectively.

The study group for the study consisted of eighty drug naïve patients belonging to 18-50 years age, newly diagnosed with major depression as per DSM 5 criteria attending the Psychiatry Outpatient Department of the institute. Pregnant women, diabetics, hypertensive, cancer patients or those with any genetic disease were not included for the study.

2.1 Sample size calculation

Open Epi programme 9 open sources Epidemiology statistics for Public Health version 3.01 formula for comparing two means with an expected difference in plasma 8-iso-PGF2α level 29.05 was used for calculating the sample size.[13] An assumption of an alpha error of 0.05 and power 90% was the foundation for the calculation. Considering the analysis in the subgroup and 10% dropouts, 80 newly diagnosed major depression patients were recruited for the study.

2.2 Blood collection and estimation of plasma F2-isoprosatne

2 ml of peripheral venous blood was withdrawn under strict aseptic precautions after explaining the procedure and obtaining the written consent from parents/ legally accepted representative (LAR). The collected sample was added to 2 ml of histopaque (lymphocyte separation media) in a centrifuge tube without allowing mixing of the two followed by centrifugation at 1500 rpm for half an hour. As a result of centrifugation, red blood corpuscles (RBCs) occupied the bottom, histopaque in the lower layer, a buffy coat containing lymphocytes was in the middle layer and the topmost layer consisted of plasma. After isolating the lymphocytes, the top layer consisting of plasma was taken in microvial and stored at -80^{0}C temperature. Estimation of 8-iso-PGF2α was done in the Department of Biochemistry utilizing **8-iso-PGF2α ELISA kit** of Bioassay Technology Laboratory **(Figure. 1)**.

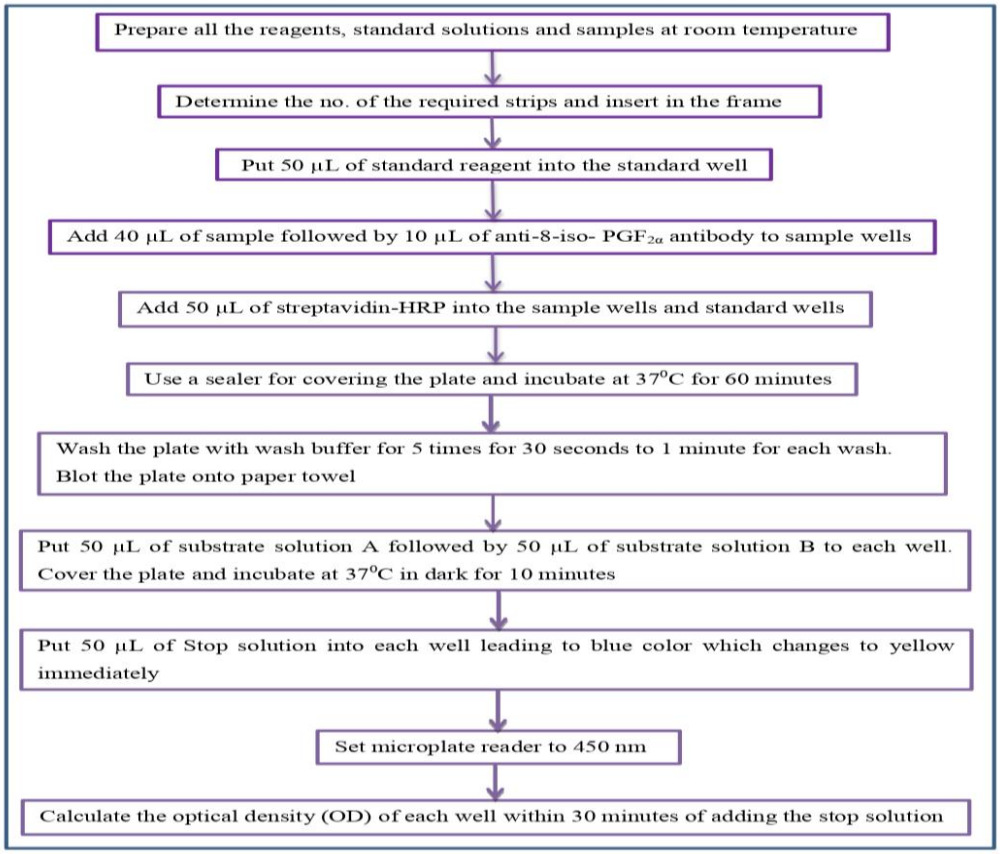
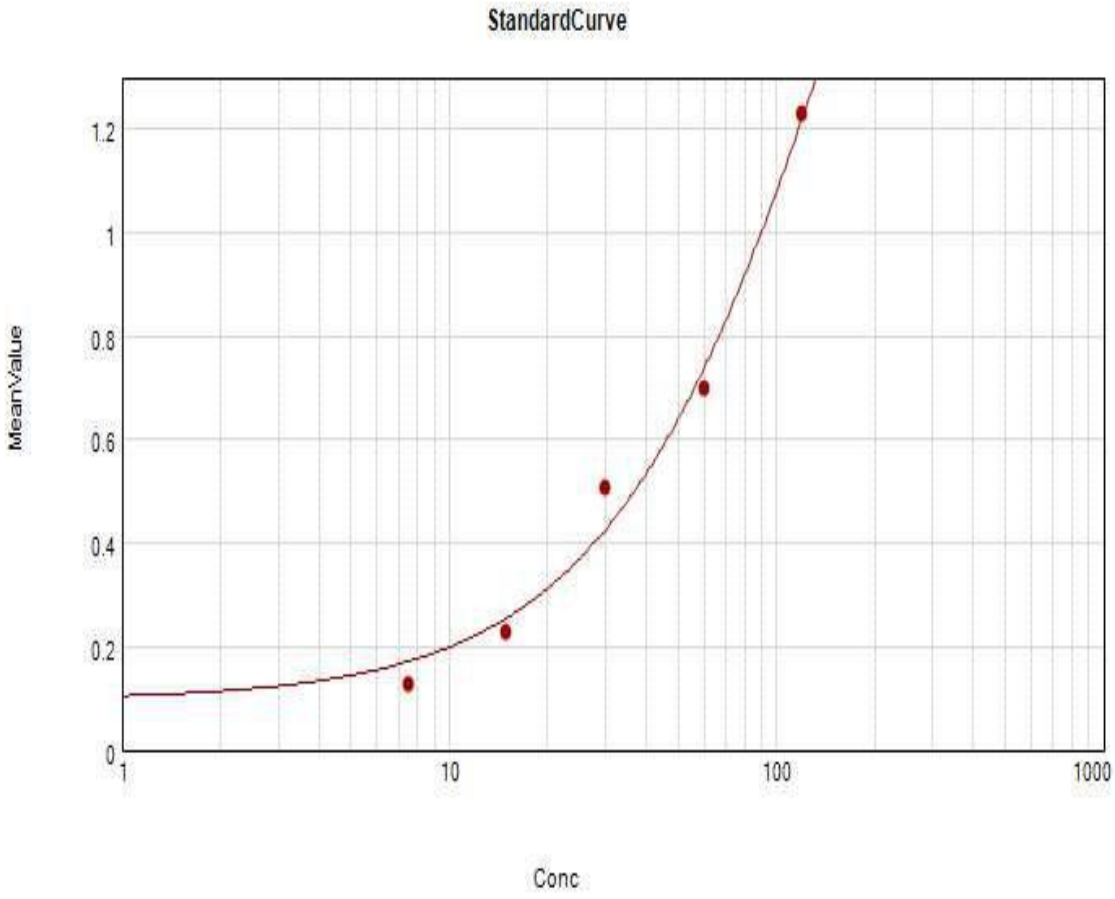


Figure 1: Flow chart showing the steps required for 8-iso-PGF2α estimation using.

ELISA chart

The calorimetric method using BT LABS Human 8-iso prostaglandin F2α ELISA kit (96 wells) was utilized to analyze the levels of 8-iso-PGF2α among the plasma samples of 80 major depression patients before starting and after completing the eight-week fluoxetine therapy. The results were obtained through an ELISA reader. The first six wells were used as standard. The accuracy of the standards showed a positive linear curve fit with a significant R^2 value of .987 (almost approaching 1) **(Figure 2 and 3)**.



Curve Fit Results ▲

Curve Fit : 4-Parameter $y = D + \frac{A - D}{1 + \left(\frac{x}{C}\right)^B}$

	Parameter	Estimated Value	Std. Error	Confidence Interval
Std R^2 = 0.987 EC50 = 191.2	A	0.097	0.073	[-0.216, 0.411]
	B	1.139	0.620	[-1.529, 3.806]
	C	191.2	464.3	[-1807, 2189]
	D	3.138	4.884	[-17.88, 24.15]

Figure 2: Standard curve obtained by using BT LABS 8isoPGF2α ELISA kit in samples before starting the treatment.

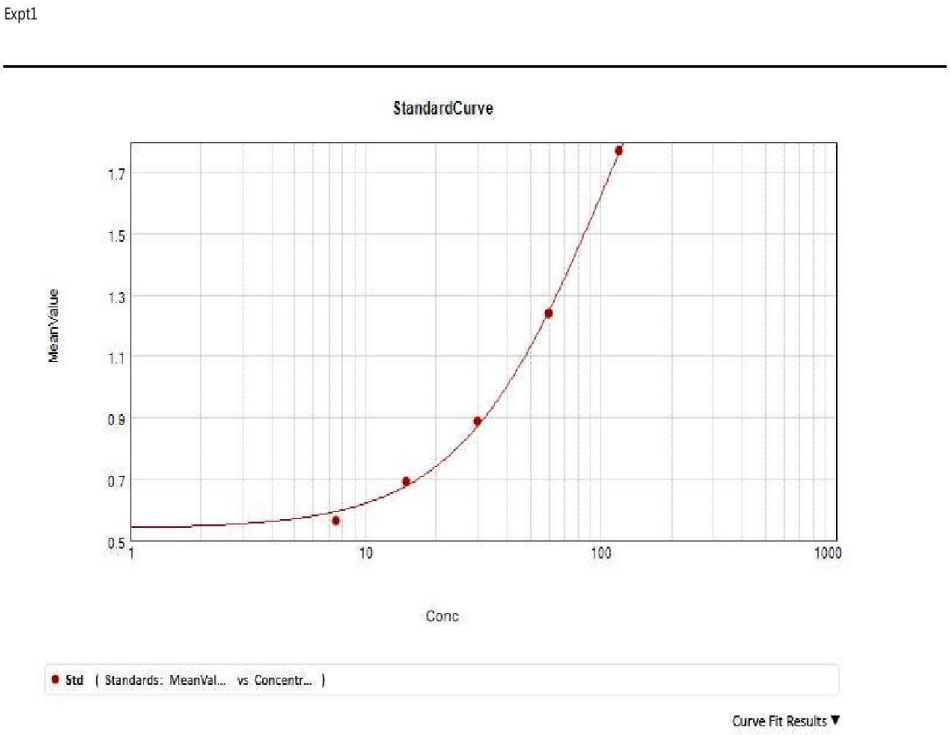
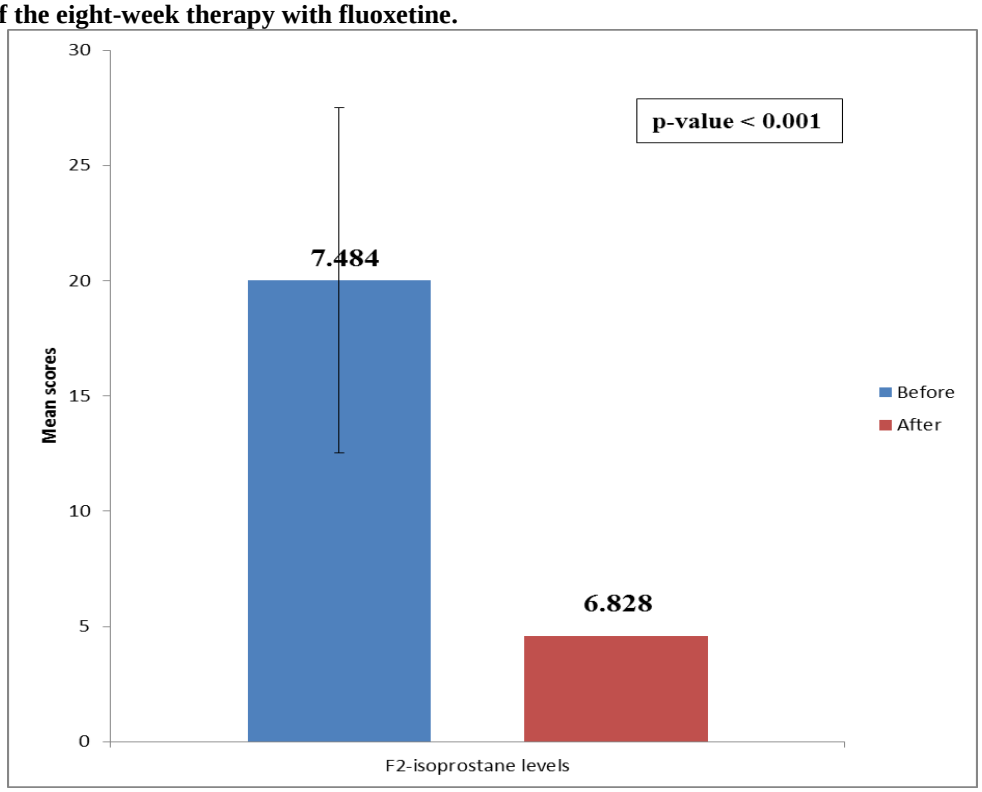


Figure 3: Standard curve obtained by using BT LABS 8isoPGF2α ELISA kit in samples before after completing the treatment.

RESULTS

Plasma 8-iso-PGF2α levels in major depression patients had skewness of 0.013 and 1.228 before starting and after completion of the eight-week therapy with fluoxetine, respectively. Plasma 8-iso-PGF2α levels before the treatment followed Gaussian pattern hence the measures of central tendency were expressed as mean±standard deviation but there was Non-Gaussian pattern of distribution among the cases after the treatment, so the measures of central tendency were expressed as median with interquartile range (IQR) varying between 25^{th} to 75^{th} percentiles. The mean value of plasma 8-iso-PGF2α levels for cases before the treatment (20.013 ±7.484) was more as compared to the median value of plasma 8-iso-PGF2α levels for cases after the treatment [4.599 (6.828)] and the difference between the two values was statistically significant (p-value <.001**)** as shown in **Table 1**.

Table 1: Comparison of plasma F2-isoprostane levels in major depression patients Before starting and after completion of the eight-week therapy with fluoxetine.



Since there was Gaussian (Normal) pattern of distribution before starting and Non-Gaussian (non-Normal) pattern of distribution after completion of the treatment, the Wilcoxon signed rank sum Test was used to find the strength of significance between the plasma 8-iso-PGF2α levels in both scenarios. Also, the difference in the plasma 8-iso-PGF2α levels between the cases before starting and after completion of the eight-week therapy with fluoxetine was statistically significant.

DISCUSSION

The role of fluoxetine in influencing the antioxidant defenses and peroxidation of the lipids in the major depression patients was explained by Galecki et al. by estimating SOD1 and CAT, MDA and HDRS scores.[14] The effects of fluoxetine as well as citalopram on lipid peroxidation, SOD activity and ascorbic acid concentrations among cases and controls were studied by Khanzode et al., before starting and after concluding the treatment.[15] Plasma 8-iso-$PGF_{2\alpha}$ was product of peroxidation of lipids used in the current study and the levels of the same were significantly reduced in the plasma after conclusion of the treatment.

Lindqvist et al. studied the levels of markers indicating oxidative stress (e.g. 8-iso-$PGF_{2\alpha}$, 8-OHdG) in major depression patients and healthy subjects, and assessed the association among the markers and response to the treatment in the patients.[16] The differences between the plasma levels of 8-iso-PGF2α and 8-OHdG were found to be statistically significant in the individuals having major depression than the healthy ones. Among the major depression patients, the plasma levels of 8-iso-PGF2α were considerably more in the treatment non-responders at time of commencement of the treatment ($p = 0.006$), and after conclusion of eight-week therapy ($p = 0.031$). The levels of 8-OHdG after the eight-week therapy in the treatment non-responders ($p = 0.021$) were significantly elevated, but among the treatment responders after the requisite therapy there was a noteworthy reduction in the quantities of IL-6 ($p = 0.019$). The levels of markers of oxidative stress (e.g., 8-iso-$PGF_{2\alpha}$, 8-OHdG) and inflammation (e.g., IL-6) are influenced by antidepressant treatment.[7] In the present study the levels of 8-iso-PGF2α in the plasma were significantly lower in the cases after eight-week of fluoxetine treatment ($p<0.001$). The levels of 8-iso-PGF2α in the plasma were increased in the cases as compared to the controls. After treatment, since oxidative stress was arrested so there was decrease in the levels of 8-iso-PGF2α in the plasma but the excretion of 8-iso-PGF2α in urine was increased.[16,17-18] In the current study, the levels of 8-iso-PGF2α in the plasma were reduced after completion of the treatment and the reduction was statistically significant.

CONCLUSION

The levels of plasma 8-iso-PGF2α among the major depression patients were reduced after completion of eight-week fluoxetine therapy suggesting the antioxidant role of the drug along with its therapeutic effect in the treatment of major depression.

Contributors

Dr Rajeev Panwar (RP) brought up the idea; identified and sorted the suitable articles among peer reviewed literature, obtained the relevant data after doing the required procedures, penned the initial draft of the manuscript and completed the data analysis. Dr. M. Sivakumar (MS) was instrumental in giving input while writing the final draft of the manuscript. RP and MS did the final proof reading.

Conflict of interest

No conflict of interest was reported by either the first author or the rest of the co-authors.

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