

# Effect of vitamin C upon Selective Serotonin Reuptake Inhibitors (SSRIs) treated Obsessive Compulsive Disorder Patients: A randomized controlled clinical trial in Bangladesh

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## Abstract:

**Objective:** To assess the efficacy of vitamin C as an adjunct to Selective Serotonin Reuptake Inhibitors (SSRIs) in treating OCD patients.

**Design:** Single-blind randomized controlled trial.

**Study eligibility:** Randomly selected 96 OCD patients diagnosed by the psychiatric consultants following the DSM-5 criteria of both sexes aged 18 years and above were initially enrolled; finally, 83 completed the study. The study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh, from March 2018 to February 2019.

**Interventions:** After obtaining written informed consent, participants were randomly divided into group A (control group) and group B (intervention group). A baseline recording of the body's endogenous antioxidant markers (plasma vitamin C and erythrocyte glutathione levels), oxidative stress marker (plasma malondialdehyde), and Yale-Brown score of OCD by Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) were measured in both groups. The control group (n=40) received oral SSRIs daily for eight weeks, while the intervention group (n=56) received the SSRIs plus oral vitamin C (500 mg twelve hourly) daily for the same duration. The biochemical parameters and the Y-BOCS score of OCD of both groups were obtained after eight weeks, and the result was analyzed and compared.

**Main outcome measures:** The outcomes were levels of plasma vitamin C, erythrocyte (RBC) glutathione and plasma malondialdehyde, and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).

**Result:** Baseline recordings suggest significantly ( $p < 0.05$ ) lower levels of plasma vitamin C and RBC glutathione concentrations and non-significant ( $p > 0.05$ ) higher levels of plasma MDA concentrations in both groups. After eight weeks of intervention with vitamin C plus SSRIs, plasma vitamin C and RBC glutathione levels were significantly ( $p < 0.001$ ) increased more in the intervention group compared to the control group (97.26% vs 44.44% and 57% vs 44.16%, respectively). On the other hand, plasma MDA concentrations and the mean Y-BOCS score were reduced more in the intervention group compared to their counterpart (48.15% vs 37.74% and 29.69% vs 21.74%;  $p < 0.001$ ).

**Conclusion:** The result showed that vitamin C adjunct to SSRIs in OCD patients had significantly improved vitamin C and RBC glutathione concentrations, while the plasma MDA level and the Y-BOCS score were decreased in the intervention group. Treatment with vitamin C leads to a more significant improvement in OCD symptoms.

**Trial registration:** Registered with Clinical Trials. Gov (NCT03754647).

**Keywords:** Obsessive compulsive disorder; OCD; SSRIs; vitamin C, OCD Treatment.

## Introduction

Obsessive Compulsive Disorder (OCD) is the fourth most common mental disorder globally, with a prevalence of 2-3% in the general population characterized by persistent and unwanted intrusive thoughts, images, and urges (obsessions) and repetitive behaviours or mental acts (compulsion) and can cause pervasive impairments during the day to day performances of a person.<sup>1</sup> In Bangladesh, its prevalence is about 0.5% of the population<sup>2</sup>, and among children, the prevalence is 2%.<sup>3</sup> Intervention studies have observed that Quality Of Life (QOL) was severely impaired in OCD patients compared to the general population.<sup>4</sup> A person's personal, familial and social life ultimately may destroy to

such a severe point that normal functioning and daily performances may become partially or totally deranged.<sup>5, 6</sup> Society and the country suffer a lot if the number of such patients keeps increasing.<sup>7, 8</sup>

The aetiology of various neuropsychiatric conditions, including obsessive-compulsive disorder, has been linked to oxidative stress.<sup>4, 9</sup> Disruptions in the equilibrium between free radical generation and CNS antioxidant defences may cause tissue damage and affect the functions of the central nervous system. Recent researchers have indicated increasing levels of free radical-induced injury to the brain tissue due to oxidative stress in OCD patients.<sup>10, 11</sup> Malondialdehyde (MDA) is the major end product of oxidative stress and the resultant product

of lipid peroxidation.<sup>12</sup> Free radical metabolism is more active in OCD, which starts a vicious cycle that enhances deleterious effects upon the antioxidant defence systems of the CNS. MDA levels in individuals with OCD were found to be significantly higher than in healthy control participants.<sup>13-15</sup> Glutathione (GSH), a cysteine-containing tripeptide, is considered to be a powerful, versatile, and one of the most important endogenous antioxidants which constitute a first-line defence against oxidative stress<sup>15</sup> and prevents free radical-induced cellular damage.<sup>16</sup> A recent study has revealed that in the lower posterior cingulate cortex, glutathione levels become lower in obsessive-compulsive disorder.<sup>17</sup> GSH reduces hydrogen peroxide radical generation by inhibiting hypochlorous acid generation and hydroxyl radical formation.<sup>18</sup> So, glutathione may be considered as an important biomarker to assess antioxidant protection against reactive oxygen substances.<sup>19</sup>

Vitamin C (ascorbic acid) is an essential vitamin for the healthy functioning of the central nervous system, as well as its role as the brain's primary antioxidant in preventing free radical-induced brain damage.<sup>20,21</sup> Chakraborty and colleagues found that the newly diagnosed, drug-naïve patients with OCD had a higher level of thiobarbituric acid reacting substances and lower ascorbate (vitamin C) levels.<sup>22</sup> Vitamin C plays this protective function in the brain by modulating neurotransmitter activity, reducing cortisol activity, preventing stress-induced oxidative damage, and exerting other antioxidant defences in the brain.<sup>23</sup> It was thought that antidepressant drugs had demonstrated some capability to improve the anti-oxidative systems.<sup>24</sup> Since vitamin C is thought to be an ample antioxidant in the brain, adjunct therapy with it may provide extraprotection.<sup>25,26</sup> Previous studies have suggested that Vitamin C treatment could ameliorate neuropathological alterations and memory impairments due to neurodegenerative changes exposed to a neurotoxic substance like aluminium or colchicine.<sup>27,28</sup> According to recent research, vitamin C supplementation reduced average mood disturbances in hospitalized patients by 35%.<sup>29</sup> Therefore vitamin C has become a nutrient of interest as adjuvant therapy for managing depressive

symptoms.<sup>30-32</sup> Again, it was observed that the Beck Depression Inventory score was significantly reduced in male shift workers administered with vitamin alone and in combination with omega-3 fatty acids.<sup>33</sup>

In human studies, vitamin C was given at a dosage of 1000 mg/day (500 mg twice daily), indicating that people with psychiatric disorders often need larger doses of vitamin C to alleviate symptoms.<sup>34,35</sup> It appeared to the present researchers that raising plasma vitamin C levels in children and adolescents on antidepressants may assist in alleviating depressive symptoms.<sup>36</sup> It was assumed that with 500 to 1000 mg/day of vitamin C given to patients of OCD whose plasma vitamin C levels are lower than normal may potentiate the efficacy of SSRIs. However, the question arises if vitamin C administration in adjunctive with SSRI produces better alleviation than SSRI alone in patients suffering from OCD. However, the role of ascorbic acid (vitamin C) in the pathological conditions of OCD has yet to be thoroughly investigated, especially in Bangladesh. Therefore, the present study was an endeavour to observe the status of oxidative stress while simultaneously assessing the antioxidant defence mechanisms of the CNS. Thus, this study was conducted to assess the effects of concurrent administration of vitamin C and SSRI with SSRI alone in OCD patients.

## Methodology

### Study design and participants

The current study was a randomized controlled trial conducted at the Department of Pharmacology and the Department of Psychiatry of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March 2018 to February 2019. The research protocol was reviewed and approved by the Institutional Review Board of BSMMU on 14<sup>th</sup> March 2018 (approval number BSMMU/2018/3110). This study was also registered on ClinicalTrials.gov (NCT03754647). Although every precaution was taken to look after and monitor the participants in case of any complications arising, participants were asked to report any adverse effects of the medication given during the study period, and the researchers were ready to arrange for treatments if necessary. The complete anonymity of the participants was strictly maintained. Keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects, all the study subjects were informed verbally in an easy, reasonable local language (Bangla) about the study design, the purpose of the study, and their right to withdraw themselves from the intervention procedure at any stage of the research for any reason.

Participants of both sexes aged 18 years and above who were diagnosed as patients of OCD by the psychiatric consultants of the Department of Psychiatry, BSMMU, following the DSM-5 criteria, were included in the study.<sup>37</sup> However, patients receiving antidepressants and/or psychotherapy within the last two months, users of any antioxidant vitamins, i.e., vitamin A (retinol), vitamin C (ascorbic acid), or vitamin E (cholecalciferol), which could interfere with the concentration of endogenous antioxidant estimation were

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excluded from the study. The sample size was estimated at 53 in each group,

considering  $Z\alpha = 1.96$  at 5% level of significance and  $Z\beta = 0.85$  at 80% power.<sup>22</sup> Considering a dropout rate of 10%, the sample size was calculated as 58 in each group. However, out of 116 participants, only 96 met the inclusion criteria and were enrolled in the study.

### Procedure

The study consisted of two visits, a baseline visit and a follow-up visit after eight weeks. A semi-structured questionnaire was used to get socio-demographic and other relevant information. At baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scoring was done for all participants using a structured questionnaire to assess the degree of OCD. A Bangla-validated version of the Y-BOCS scale was used.<sup>38</sup> Blood was collected to estimate plasma vitamin C, RBC glutathione, and MDA levels. Assurance was provided that the experiment included only collecting 5 ml of blood from the antecubital vein with a complete aseptic procedure and as minor inconvenience as possible and could be stopped at any objection. The process took approximately 45 minutes for each patient. After collecting samples,

participants were divided randomly into group A (controlgroup) and group B (intervention group).

Group A consisted of 40 participants who received SSRIs only (Fluoxetine 20-80 mg/ Escitalopram 10-20 mg/ Sertraline 50-200 mg/ Fluvoxamine 50-300 mg/ Citalopram 20-40 mg). Group B consisted of 56 participants who received oral vitamin C (500 mg twice daily) along with SSRIs at their recommended dosages. The specific SSRI and dosage for the particular OCD patients were selected by the senior Psychiatrist or Professor of the Psychiatry department of BSMMU. Both groups received the medicines for eight weeks, and after then, parameters were assessed. Results were recorded in separate result sheets. Comparisons between groups were made at baseline, follow-up, and within groups before and after drug intervention. Data were analysed by Microsoft Office Excel and IBM SPSS version 22. The level of significance was set at a p-value less than 0.05.

### Results

After 8 weeks, 32 patients from control group and 51 patients from intervention group completed the study. Analysis was done according to per protocol principle.

**Table1 Baseline Characteristics of participants**

	Control group (n=32)	Intervention group (n=51)	Total (n=83)
<b>Mean age in years (min-max)</b>	26±7.9 (18-47)	26±5.7(18-40)	26±6.8 (18-47)
<b>Sex</b>			
Male	22(69%)	38(74.5%)	60(72%)
Female	10(31%)	13(25.5%)	23(28%)
<b>Marital status</b>			
Married	11(34%)	15(29%)	26(31%)
Unmarried	21(66%)	36(71%)	57(69%)
<b>Occupational status</b>			
Unemployed	4(12.5%)	7(14%)	11(13%)
Employed	16(50%)	31(61%)	47(57%)
Student	12(37.5%)	13(25%)	25(30%)
<b>Positive family history</b>			
Present	11(34%)	19(37.3%)	30(36%)
Absent	21(66%)	32(62.7%)	53(64%)
<b>Educational status</b>			
Primary	1(3%)	3(6%)	4(5%)
Secondary	12(38%)	20(39%)	32(38%)
Graduate and above	19(59%)	28(55%)	47(57%)
<b>Residence</b>			
Rural	8(25%)	18(35%)	26(31%)
Urban	24(75%)	33(65%)	57(68%)

The Study participants were male predominant (72%), higher educated (57%), unmarried (69%), and hailed from urban areas (68%) with a mean age of 26 years (table 1). However, only one-third of the participants had a positive family history of OCD in both groups.

**Table 2: Changes in plasma vitamin C, RBC glutathione, malondialdehyde, and Y-BOCS score at baseline and After eight weeks in the control and intervention group**

	At baseline (Mean ± SD)	After eight weeks (Mean ± SD)	% change	Difference between group	P value (95% CI)
Plasma Vitamin C (milligram/decilitre)					
Control group(n=32)	0.342 ±0.042	0.494 ±0.038	44.44%↑	52.82%	<0.001(0.13to0.17)
Intervention group(n=51)	0.328 ±0.046	0.647±0.082	97.26%↑		<0.001(0.29to0.35)
RBC Glutathione (milligram/gramofhaemoglobin)					
Control group	1.97±0.15	2.84±0.24	44.16%↑	12.84%	<0.001(0.77to0.97)
Intervention group	2.00±0.09	3.14±0.25	57%↑		<0.001(1.07to1.21)
Plasma Malondialdehyde (micromole/litre)					
Control group	5.29±0.37	4.14±0.41	21.74%↓	7.95%	<0.001(-1.35to-0.95)
Intervention group	5.22±0.31	3.67±0.17	29.69%↓		<0.001(-1.65to-1.45)
Y-BOCS score					
Control group	22.84 ±4.50	14.22 ±3.39	37.74%↓	10.41%	<0.001(-10.61to-6.63)
Intervention group	23.47 ±2.85	12.17 ±3.20	48.15%↓		<0.001(-12.49to-10.11)

↑=Increase, ↓=Decrease

The mean baseline levels of plasma vitamin C, RBC glutathione, plasma MDA and Y-BOCS scores of group A and group B were almost similar. However, it was observed that after eight weeks, the mean plasma vitamin C and RBC glutathione concentrations were significantly elevated ( $p < 0.001$ , t-test), where plasma MDA concentrations and Y-BOCS score were significantly decreased ( $p < 0.001$ , t-test) in both groups (table 2).

The differences were also statistically significant ( $p < 0.001$ , t-test) between the two groups. However, after calculating the percentage of change from baseline to eight weeks of two groups, the intervention group had a higher percentage of change than the control group in the level of vitamin C, RBC glutathione and MDA concentrations and Y-BOCS score. Therefore, the elevation of plasma vitamin C and RBC glutathione concentrations and reduction of plasma MDA concentrations and Y-BOCS score after eight weeks of vitamin C (500mg twice daily) administration in the intervention group was found to be higher than in the control group.

### Discussion

Attempts to cure or ameliorate anxiety-related CNS disease and Obsessive Compulsive Disorder (OCD) by administering medicines, nutrients, or micronutrients have been ongoing for several years.<sup>39,40</sup> Vitamin C (sometimes called the 'Final antioxidant' in the CNS) counteracts the CNS oxidants production in association with other CNS antioxidants.<sup>41</sup> It is still uncertain whether oxidants are directly responsible for the neural damage implicated in OCD or whether OCD is directly liable for neuronal injury and resultant products of oxidation.<sup>14,22</sup> Regardless of the cause of the neural damage implicated in OCD, antidepressants have been the drug of

choice in treating these patients for many years, though the precise cause of OCD is still unknown. However, the role of vitamin C or ascorbate in the CNS has been overwhelming in recent research on CNS diseases, including OCD.<sup>25,42</sup>

The control and intervention groups of the current study had similar mean vitamin C concentrations (0.342 vs 0.328mg/dL) at baseline, which were lower than those of healthy normal individuals.

Previous research has also observed lower vitamin C concentrations in OCD patients.<sup>42,43</sup> The lower vitamin C concentrations in the present study and some previous studies support the assumption that the levels of vitamin C in OCD patients are depleted in attempts to detoxify the oxidants, which are produced in increased amounts as a result of increased lipid peroxidation in brain tissues of OCD patients.<sup>44,45</sup> This study found that the mean differences in plasma vitamin C levels at follow-up between the two groups were statistically significant ( $p < 0.001$ ) and suggested more significant improvement in the intervention group compared to the control group. From the viewpoint of the present researchers, the improvements in OCD symptoms were due to the administration of exogenous vitamin C along with SSRI in the OCD patients and are indicative of a significant antioxidant effect exerted by the vitamin C in CNS in addition to the antioxidant effects offered by the SSRI (SSRI has some anti oxidant effect as well). In previous research conducted with OCD patients, a significant improvement in OCD patients after a 12-week therapy with Fluoxetine and the oxidative stress indicator (serum Thiobarbituric Acid Reacting Substances) appeared to be significantly ( $p < 0.001$ ) decreased, while the antioxidant parameter (plasma ascorbate) was significantly ( $p < 0.001$ ) increased.<sup>22</sup> The researchers

speculate that the antioxidant property of Fluoxetine is operative so that the other antioxidant vitamin C is spared to exert its detoxification effects upon the oxidants production. This observation also follows that of Chakraborty et al.<sup>22</sup> Moreover, the history of suicidal thoughts has been linked to a deficiency in antioxidant vitamins and carotenoids.<sup>46</sup> This evidence again supports the assumption that depression and OCD have an inverse relationship with serum and CNS antioxidant levels. It is because the antioxidant property of vitamin C remains operative active in the observations of the present study to offer additional support to the SSRIs (which exerted their anti-OCD and antioxidant effect simultaneously) so that the OCD patients benefit.

The present study found higher plasma Malondialdehyde (MDA) levels at baseline in both the control and intervention groups. However, the MDA level difference between the two groups was not statistically significant ( $p > 0.05$ ). These indicate that free radical-induced CNS injury in OCD patients due to oxidative stress was of similar magnitude at base line in OCD patients of the present study.

These observations align with previous studies that have shown greater levels of MDA in OCD patients.<sup>4, 15</sup> This observation of higher levels of MDA in OCD patients at baseline suggests an elevation in lipid peroxidation occurring in the brain of OCD patients. The result is strengthened by the fact that the mean levels of plasma MDA became significantly decreased ( $p < 0.001$ ) in the intervention group ( $3.67 \pm 0.17 \mu\text{mol/L}$ ) compared to those in the control group ( $4.14 \pm 0.41 \mu\text{mol/L}$ ) after supplementation of vitamin C. The antioxidant effects of the administered vitamin C could effectively counteract the oxidants, due to which the plasma MDA levels in the vitamin C plus SSRI-treated group were significantly lowered compared to those in the control group.

No significant difference between the two groups at baseline mean RBC glutathione concentration was found in the present study. The lower levels of RBC glutathione in OCD patients at baseline support the assumptions that the defence systems against oxidative stress in the brain utilize glutathione as an antioxidant, due to which the plasma GSH levels in OCD patients of both groups A and B did not differ from each other at baseline. However, after eight weeks of vitamin C supplementation in group B OCD patients, the plasma GSH levels attained higher levels in the intervention group. These observations by the present researchers are similar to those of other studies conducted on both children and adult OCD patients.<sup>41,31,5,22</sup> A previous study obtained a significantly lower Posterior Cingulate Cortex Glutathione/Creatinine ratio in OCD patients compared to controls.<sup>17</sup> In the present experiment, after eight weeks, the RBC glutathione concentration in the intervention group was higher than the control group, and the difference was statistically significant ( $p < 0.001$ ) between the two groups.

In this study, the correlation between Y-BOCS score, plasma vitamin C, and MDA levels was negative, whereas a positive correlation was found between Y-BOCS score and RBC glutathione level after eight weeks of administration of vitamin C along with SSRI. The present researchers were

interested in exploring the relationship between clinical improvements of OCD patients and oxidative stress markers. At baseline, the difference in mean Y-BOCS score between the control group and intervention group was not statistically significant ( $p > 0.05$ ), which was no wonder as both groups suffered from OCD under similar conditions. However, after eight weeks of intervention with vitamin C administration at follow-up, the difference in Y-BOCS score between the control group and the intervention group was statistically significant ( $p < 0.05$ ) and indicates that the antioxidant effect of vitamin C could effectively improve the Y-BOCS score. It was also observed that the percentage changes in the Y-BOCS score decreased after eight weeks in the intervention group (48.15%). A decrease of 48.15% in the Y-BOCS value indicates a significant improvement in OCD patients of the intervention group (group B), as has been described by previous researchers.<sup>22</sup> Therefore, an interesting observation of the present research is that the synergistic effects between ascorbic acid and SSRIs could be a worthy recommendation for improving the effects of conventional pharmacotherapy (SSRIs) offered for OCD patients. However, the research's main limitation is that it is a single-blind study conducted at a single centre with a short duration of treatment. Also, confounding factors could not be avoided, and the structured clinical interview for DSM-5 (SCID) was not applied for diagnosis.

## Conclusions

It is evident from this study that orally administered vitamin C as an adjunct to SSRI in the treatment of OCD patients significantly improves the biomarkers and reduces the symptoms of OCD in comparison to SSRI alone. Due to the absence of substantial side effects and its inexpensive cost, vitamin C will be a better therapeutic adjuvant when used with SSRI in OCD patients. However, a double-blind, multicentre, placebo-controlled clinical trial with vitamin C as an adjunct to SSRIs for a long duration in OCD patients is recommended for future researchers to support evidence of the present study.

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