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Vitamin C Supplementation as an Adjuvant Therapy for Major Depressive Disorder: A Randomized Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Major depressive disorder (MDD) is a multifactorial disease that can affect patient's quality of life. Low intake of nutrients and antioxidants has been linked to depression. The present study was conducted with the aim of investigating the effect of adding oral vitamin C to the standard treatment of patients with MDD. **Methods:** This randomized, double-blind placebo-controlled clinical trial was conducted on 88 MDD patients referred to psychiatric clinics of the Yazd University of Medical Sciences. Patients were randomly assigned into two groups of vitamin C (500 mg twice a day, n=44) and placebo (n=44) for 8 weeks. Also, The Hamilton depression questionnaire was employed at the baseline, and after 4 and 8-week follow up. Data analysis was performed using the SPSS version 18 software. **Results:** Out of 88 examined patients, no significant difference was detected regarding mean depression scores at the beginning of the study and also after 4 weeks of treatment (P=0.62 and P= 0.53, respectively). However, people in the vitamin C group revealed a significant improvement in average depression scores compared to those in the placebo group after 8 weeks (P=0.03). **Conclusion:** The results of the current investigation indicated that vitamin C may act as an effective adjuvant therapy for the treatment of patients suffering from MDD. Future studies are necessary in order to confirm the findings of this study.

Introduction

Major depressive disorder (MDD) is a psychiatric illness which is the third leading cause of death in people aged 15-24 and the fourth leading cause of premature death and disability, worldwide (Aleman and Denys, 2014, American Psychiatric Association, 2013, Coppen and Bailey, 2000). According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), MDD is a syndrome with a cluster of persistent and pervasive psychiatric disorders including suicidal thoughts, low mood, and lack of effective psychomotor activities, such as pleasure, sleep, appetite, energy level, and concentration (Griffiths *et al.*, 2014, Keltner and Steel, 2019). Recent studies

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have shown that dysregulation of body's inflammatory pathways and elevation of oxidative stress, together with the lower plasma concentration of important antioxidants, are strongly related to the etiology of MDD (Leonard and Maes, 2012, Lopresti *et al.*, 2013, Maletic *et al.*, 2007). It has been documented that oxidative stress can be a pathologic cause for some neuropsychiatric diseases such as schizophrenia and MDD (Bilici *et al.*, 2001, Bouayed *et al.*, 2009, Valko *et al.*, 2007). The potential vulnerability of brain to antioxidant imbalances through oxygen consumption and lipid rich constructs suggests that oxidative damage might have a role in depression disorders and elevated anxiety levels (Bouayed *et al.*, 2009). It has also been reported that stress itself causes neurotoxic damage through reactive radical species, and in this way, could affect synaptic plasticity and dendritic morphology (Zaidi and Banu, 2004).

Since these illnesses have exhibited detrimental effects on human general health, proper investigations regarding modifiable mediators such as dietary antioxidants seem to be a high priority (Sherafatmanesh *et al.*, 2024). Vitamin C (ascorbic acid) is known as a water-soluble antioxidant that could be helpful in reducing oxidative stress indirectly via restoring the reduced form of vitamin E and thus supporting its antioxidant activity (Mazloom *et al.*, 2013, Sherafatmanesh *et al.*, 2019). According to the previous investigations, patients with MDD had significantly lower levels of vitamin C (Khanzode *et al.*, 2003) compared to healthy individuals. Hence, it was hypothesized that improvement of oxidative stress by adding oral vitamin C to the standard treatment might affect depression score in patients with MDD in Yazd, Iran.

Materials and Methods

Study design and participants

The present randomized, double-blind placebo-controlled clinical trial was conducted on 88 individuals with an established diagnosis of MDD (based on DSM-5 criteria) who referred to psychiatric clinics of Yazd University of Medical Sciences, Yazd, Iran, during 2018-2019. The sample size was calculated based on the earlier study (Griffiths *et al.*, 2014) with the type I error of 5% (α=0.05, 95 % confidence interval (CI)), type II error of 20% (β=0.2, power of 80%). The inclusion criteria of the current investigation were as follows: People who were at least 18 years old, having no drug addiction, no major changes in diet in the last few months, not taking antioxidants supplements at least one month before entering the study, not having underlying diseases such as diabetes, cardiovascular, lung, cancer, and willingness to participate in the research.

At first, all patients were treated with S-citalopram tablets (10 mg daily) as the standard treatment. Then, participants were randomly assigned into two equal groups (44 participants in each group) by block randomization with a fixed block size of eight for 8 weeks as follows:

Vitamin C group (CG): Received vitamin C tablets (500 mg twice a day).

Placebo group (PG): Received one placebo tablets (twice a day).

The selected dose of vitamin C was according to the earlier investigations associated with the least health adverse effects. All S-citalopram, vitamin C, and placebo tablets were prepared by Fara Daru Fanavar Mehr Pharmaceutical Company, Tehran, Iran and prescribed to the patients by the therapist. The placebo tablets had the same appearance of size, shape, and color in comparison to vitamin C tablets. Compliance with the consumption of the tablets was assessed each week via phone call interviews. Moreover, participants' physical activity was evaluated using an international physical activity questionnaire (IPAQ) (Hallal and Victora, 2004). Besides, the authors requested not to alter their physical activity and eating habits. The participants' average amount of dietary vitamin C was considered to be 80 mg/day and patients were asked to limit the consumption of orange, kiwi, cabbage, sweet pepper, and grapefruit during the investigation. The randomization procedure was performed under supervision of a skilled clinician. The randomization sequence concealment sustained until the end of the trial.

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Measurements

Hamilton Depression Questionnaire was employed in order to collect data regarding the participants' depression average score at the beginning of the study and after 4 and 8-week follow-ups. The validity and reliability of the mentioned depression rating scale have been evaluated in previous investigations (Reynolds and Kobak, 1995). This clinical evaluation scale consisted of 21 questions in 7 items which was specifically used to assess the severity of depression in depressed patients (Carrozzino *et al.*, 2020). In addition, the participants' demographic information, such as age, gender, marital status, education level, nationality, employment insurance, duration of illness, current medications, and family disease history were obtained by expert interviewers.

Ethical considerations

All research objectives were explained to the patients and then written consent forms were obtained. The method of this study was conducted according to the Declaration of Helsinki. It was also approved by the Ethics Committee on Human Experimentation of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.MEDICINE.REC.1399.291). Moreover, this trial was registered at the Iranian Registry of Clinical Trials (ID number: IRCT20130311012782N56).

Data analysis

All statistical analyses were carried out using the statistical package for social sciences (SPSS Inc, version 18.0). The Kolmogorov–Smirnov test was used regarding the normal distribution assessment of the data. In addition, independent samples t-test was employed to determine the differences between the study groups regarding the continuous variables. P-values<0.05 were also considered to be statistically significant.

Results

Out of the 88 examined patients, 41 (46.6%) were male and 47 (53.4%) were female. The mean age of the individuals was 34.46±11.12 years, and the mean duration of depression was 10.45±4.69 months. It is noteworthy to mention that there were no statistically significant differences among the general characteristics of the two study groups at the beginning of the study (all $P>0.05$). The mean of participants' depression scores at the beginning of the study in CG and PG was 17.34±1.23 and 17.20±1.39, respectively, which was not statistically significant ($P=0.62$). Although, as shows in **Table 1**, there was no statistically significant difference between CG and PG in terms of the mean depression score after 4 weeks ($P=0.53$), a considerable improvement was discovered in this mean of CG in comparison with the PG after 8 weeks of intervention ($P=0.03$)

Table 1. The comparison of mean (±SD) score of depression before and after 4 and 8 weeks follow-ups among the two study groups.

Follow-up	Vitamin C (n=44)	Placebo (n=44)	P-value[a]
After 4 weeks	15.56±1.43	15.36±1.62	0.53
After 8 weeks	10.36±2.10	11.40±2.78	0.03
P-value[b]	0.62	0.62	

[a]: Obtained from independent samples t-test; b: Paired t-test..

Discussion

Findings of the current investigation revealed that 8 weeks of vitamin C supplementation as an adjuvant therapy may play an important role in the attenuation of depression scores in patients suffering from MDD. MDD is one of the most common psychiatric diseases and reduces the patient's quality of life. In this regard, the oxidative stress has been reported to be the main cause of degeneration in some neurological disorders, such as depression, anxiety and Alzheimer's disease (Bouayed *et al.*, 2009). As a result, antioxidants (as inhibitors of oxidative stress) are among the important nutritional factors which can affect the occurrence of depression (Salim, 2014). For instance, it has been shown that the consumption of antioxidants in fruits and vegetables in elderly people may be accompanied by the lower risk of depression disorder (Payne *et al.*, 2012). Moreover, in one randomized double-

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blind, placebo-controlled 14-day trial, vitamin C supplementation leads to a significant reduction in scores of the Beck Depression scale (Brody, 2002). In agreement with the results of the present investigation, researchers in one study reported lower depression scores in children with MDD who were supplemented with vitamin C along with fluoxetine as the standard medication (Amr *et al.*, 2013). Similarly, in the study conducted by Pullar (Pullar *et al.*, 2018), a significant inverse correlation (r=-0.181, $P<0.05$) was found between plasma concentration of vitamin C and mood disorder score. However, the results of Sahraian's study showed that vitamin C supplementation along with citalopram did not improve the effectiveness of citalopram in patients with MDD (Sahraian *et al.*, 2015).

The mechanisms through which dietary antioxidants may be effective in reducing the risk of depression are not well identified. However, it has been determined that vitamin C has an antidepressant effect as a result of changing brain serotonin levels (Lee *et al.*, 2001). Antioxidant activities of vitamin C probably protect cell membrane lipoproteins from oxidative stress damage caused by free radicals (Harrison and May, 2009). Additionally, dietary antioxidants have been suggested to protect against neuroinflammation and mitochondrial damage which are common among patients with psychiatric disorders (Leonard and Maes, 2012, Ng *et al.*, 2008). Additionally, dietary antioxidants have been suggested to protect against mitochondrial damage which is common among patients with psychiatric disorders (Leonard and Maes, 2012).

The main limitations of this study were the lack of vitamin C assessments at baseline and at the end of the trial, a small sample size, and the short intervention period.

Conclusion

Findings of the present study indicated that vitamin C may act as an effective adjuvant therapy for treatment of patients suffering from MDD. Further investigations are needed to confirm the study results.

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None declared.

Authors' contributions

The study's conception and design were done by M Nadi Sakhvidi. and R Bidaki; analysis and interpretation of data were conducted by R Salehabadi and Z Salimi. R Salehabadi drafted the manuscript: R Bidaki, Z Salimi and M Nadi Sakhvidi did the critical revision of the manuscript for important intellectual content. All the authors read and approved the final manuscript.

Competing interests

The authors declared no conflict of interests.

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