

**Vitamin C as an adjuvant for treating major depressive disorder, a randomized placebo-
controlled clinical trial**

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Oral vitamin C in major depressive disorder

Vitamin C as an adjuvant for treating major depressive disorder, a randomized placebo-controlled clinical trial

Abstract

Background: Major depressive disorder (MDD) is a multifactorial disease that can affect patient's quality of life. Low intake of nutrients and antioxidants have been proposed to be 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 major depressive disorder.

Methods: This study was a double-blind randomized clinical trial that was conducted on 88 MDD patients referred to psychiatric clinics of the Yazd University of Medical Sciences. Patients were randomly received vitamin C (n=44) or placebo (n=44) for 2 months. Demographic characteristics including gender, age, marital status, level of education, occupation and duration of disease were collected. The Hamilton depression questionnaire was filled for the patients at baseline, and 1 and 2-month follow ups. Data analysis was performed using the SPSS version 18 software.

Results: Out of 88 examined patients, 41 (46.6%) were male and 47 (53.4%) were female. The groups did not differ in gender ($p=0.285$), marital status ($p=0.813$), occupation ($p=0.875$), education level ($p=0.679$), age ($p=0.345$), and depression duration ($p=0.728$). No significant between group difference was found in mean depression score between baseline ($p=0.628$) and one month after treatment ($p=0.534$). The mean depression score was significantly higher in the placebo group compared to the vitamin C group two months after treatment ($p=0.030$).

Conclusion: Adding vitamin C to the standard treatment was effective in improving mood in MDD patients. Therefore, adding vitamin C to standard MDD treatment is recommended.

Keywords: major depressive disorder, ascorbic acid, clinical trial

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Background

Major depressive disorder is a psychiatric illness that imposes a high cost on the patient and society (Collins et al. 2011; Kessler et al. 2003). According to DSM-5, major depressive disorder is a syndrome with persistent and pervasive symptoms of low mood or lack of pleasure with a set of symptoms including sleep, appetite, energy level, concentration of psychomotor activity and their continuation for at least two weeks. Suicidal thoughts and behavior are one of the worrying symptoms of major depression, which is the third leading cause of death in people aged 15 to 24 and the fourth leading cause of premature death and disability (Aleman and Denys 2014; American Psychiatric Association and American Psychiatric Association 2013; Coppen and Bailey 2000).

According to the estimates, this disease is expected to become the most common disease in the world by 2020. According to the national study of diseases and injuries in Iran, depression is the third health problem of the country. The lifetime prevalence of major depressive disorder is estimated at 5-17%, and the American Psychiatric Association states that the 12-month prevalence rate of major depressive disorder in the United States is about 7%. The prevalence of major depression in Iran is estimated at 25% (Griffiths et al. 2014).

Major depression has a multifactorial etiology caused by biological, genetic, psychological and environmental factors. Studies conducted in the last decade have shown that major depression is related to the imbalance of neurotransmitters such as serotonin, dopamine, noradrenaline, and glutamate of the central nervous system, disruption of the hypothalamus, pituitary-adrenal system, disruption of the regulation of inflammatory pathways, oxidative damage, reduction of antioxidant levels, and mitochondrial disorders. This is confirmed by reducing the plasma concentration of important antioxidants and reducing the enzymatic activity of oxidants such as glutamine peroxidase. Nutrition, sleep and physical activity are three important factors that play an important role in the etiology of the development and treatment of depression (Leonard and Maes 2012; Lopresti et al. 2013; Maletic et al. 2007).

Today, the deficiency or prescription of certain foods has been proposed as the underlying factors or the treatment of depression, for example, reducing fat consumption with the aim of reducing

plasma cholesterol can increase depression (Muldoon et al. 1990). Kalmin and colleagues reported that cognitive impairment, which is itself a part of psychiatric problems, can be prevented or delayed by increasing the intake of antioxidants such as vitamin E, C, and beta-carotene. Oxidative stress is the main cause of degeneration in some neurological diseases, depression, anxiety and Alzheimer's; In fact, oxidative stress is caused by an imbalance between the production of reactive oxygen species and the ability of the biological system to detoxify these active mediators (Ferdowsi et al. 2015).

Since the prevention and treatment of depression has a significant effect on reducing the total health and treatment costs. For this purpose, the effect and importance of one of the ways of prevention and treatment; This means that the use of supplements becomes evident during this period. Fortunately, vitamin C is a water-soluble vitamin and a large amount of it is usually excreted through urine, so vitamin C poisoning rarely occurs.

Symptoms related to vitamin C poisoning include hot flushes and restlessness, headache, stomach discomfort, abdominal muscle cramps, diarrhea, nausea, indigestion, skin rashes, and tooth enamel damage (Katzung et al. 1998).

The present study was conducted with the aim of investigating the effect of adding oral vitamin C to the standard treatment of major depressive disorder in patients referred to the clinics of Shahid Sadoughi University of Medical Sciences in Yazd in 2018-2019.

Materials and Methods

This study was a randomized clinical trial; All patients with major depression admitted to university clinics in Yazd in 2018-2019 were considered as the research population. The sampling method in this study was easy and accessible, and the patients were included in the study in the order of the time they visited the clinic, if they met the entry conditions. The required sample size for the study using the sample size estimation formula to compare averages and considering the confidence level ($Z_{1-95\%}$, $a/2=1.96$, $Z_{1-b}=0.84$) and (test power 80%), the standard deviation of the score Depression, which is estimated as 1.17 and was estimated based on Jokar's study of 44 patients in each group [39]

$$2(z_{1-a/2} + z_{1-b})^2(S)^2$$

$$N = \frac{2(z_{1-a/2} + z_{1-b})^2(S)^2}{(d)^2}$$

$$(d)^2$$

After approving the project and obtaining permission from the honorable vice president of research and ethics committee, the researchers refer to the psychiatric clinics affiliated to Shahid Sadoughi University of Medical Sciences. Patients who were diagnosed with major depression based on 5 DSM by a psychiatrist were included in the study. At first, the patients were evaluated with the demographic form and Hamilton's test. Sampling was done in an easy way. The criteria for entering the study are at least 18 years of age, no drug use and no illness, no major changes in diet in the last few months, the ability to speak Persian, at least reading and writing literacy, a high level of consciousness (GCS=15) and suitable conditions. To complete the questionnaire without verbal and hearing problems in such a way that they are able to communicate. Not taking antioxidants one month before entering the study, not having underlying diseases such as cardiovascular, pulmonary diabetes, cancer, and willingness to participate in the research. Exclusion criteria include refusing to continue participating in the drug sensitivity study, suffering from comorbid disorders, depression, and major psychiatric disorders. With systemic medical diseases, written and informed consent was obtained from all research samples to participate in the study. The data collection tool was a two-part questionnaire that included a demographic questionnaire and Hamilton's depression questionnaire.

The first part was a demographic questionnaire that included my gender, marital status, education level, nationality, employment insurance, duration of illness, current treatment and medications, consumption, family history. The second part was the Hamilton Depression Questionnaire, which was completed before and after the start of the intervention (1 month later and after the end of 2 months, this questionnaire was completed by a psychiatric assistant in the clinic environment).

The depression rating scale (HAM-D7) was created by Hamilton (1960), which consists of 21 questions in 7 items and is used to measure the severity of depression in depressed people. It is

one of the clinical evaluation scales for measuring depression, Gharaii B, Mehryar A, Mehrabi F reported the reliability coefficient of this scale with the Hamilton Anxiety Rating Scale using the test-retest method as 0.85 and 0.89 (Sahraian et al. 2015).

After evaluating Hamilton's questionnaire before treatment in the examined patients, all patients were treated with S-citalopram tablets (dose 10 mg daily) manufactured by Daru Farah Company as standard treatment. Numbers from 1 to 88 were written on top of the questionnaire, and then the questionnaires were given to the statistical consultant, and he divided the patients into two groups of 44 people based on the numbers written in the questionnaire and using a table of random numbers. The patients in the first group were treated with pills. Vitamin C from Daro Farah Company (500 mg twice a day) and the second group were treated with a placebo (which was completely similar in appearance to vitamin C tablets and was given to the patients twice a day like vitamin C). Medicines were given to the patients by the therapist, but the questionnaires were completed by the interviewer, who was not aware of the division of the groups). Then the patients were examined by phone one month and two months after the treatment and Hamilton's questionnaire was asked to the patients by the interviewer.

After collecting the study data, it was entered into the computer and analyzed by SPSS version 18 software. Descriptive data were presented in the form of average percentage and standard deviation in the form of graphs and tables. Data analysis was performed using Chi-square statistical tests (to compare qualitative data between two groups), T-test (to compare quantitative data between two groups). In all the tests, values of $P > 0.05$ were considered significant.

Inclusion criteria

The criteria for entering the study are at least 18 years of age, no drug use and no medical illness, no major changes in diet in the last few months, the ability to speak Persian, at least literate in reading and writing, with a high level of consciousness (CCS=15) The suitable conditions for completing the questionnaire were having no speech and hearing problems in such a way that they are able to communicate, not taking antioxidants one month before entering the study, not having underlying diseases such as diabetes, cardiovascular, lung, cancer, and willingness to participate in the research.

Exclusion criteria

Exclusion criteria included refusing to continue participating in the drug sensitivity study, suffering from comorbid depression disorders, suffering from major psychiatric disorders, or suffering from systemic medical diseases.

Ethical considerations

- (1) obtaining written informed consent from patients to participate in the study
- (2) The optionality of the participation of samples in the research
- (3) All research objectives were explained to the patients.
- (4) The samples in question will be given the necessary assurance information regarding confidentiality.
- (5) Ethical principles should be considered in writing materials and using scientific books and resources.
- (6) In the implementation of this research, no additional costs were imposed on the patients.
- (7) This study was started after the approval of the Ethics Committee of the Faculty of Medicine of Shahid **Sadoughi** University of Medical Sciences in Yazd and receiving the ethics code number 1399.291.IR.SSU.MEDICINE.REC. **IRCT registration number: IRCT20130311012782N56**
- (8) Occurrence of drug side effects is one of the ethical issues in this plan, about which the patients are educated, and in case of any side effects, the necessary treatment is done for the patient, and if necessary, the drug is discontinued and the patient is excluded from the study.

Results

This study aimed to determine the effect of adding oral vitamin C to the standard treatment of major depressive disorder on 88 patients with MDD in two groups of 44 people (vitamin C and placebo). Out of the 70 examined patients, 41 (46.6%) were male and 47 (53.4%) were female. The average age of the studied patients was 34.46 ± 11.12 years and the average duration of depression was 10.45 ± 4.69 months.

The results of the study on the frequency distribution of the gender of the patients in the two investigated groups showed that out of 44 patients in the vitamin C group, 18 (40.9%) were male and 26 (59.1%) were female. The results showed that there is no statistically significant difference between the gender distribution of the patients in the two investigated groups ($P\text{-value}>0.05$).

The results of the study on the frequency of occupation of the patients in the two investigated groups showed that 11 (25%) of the 44 patients in the vitamin C group had a job, 12 (27.3%) were employed, and 21 (47.7%) were housewives. The results of the following table were statistically analyzed using the Chi-Square test, and the results showed that there is no statistically significant difference between the frequency distribution of patients' occupations in the two investigated groups ($P\text{-value}>0.05$).

The results of the study about the average score of depression before treatment in the two investigated groups are shown in Table 1. The analysis of Table 8 using T-test showed that there is no statistically significant difference between the average depression scores before treatment in the two groups under investigation.

Table 1: The average score of depression before treatment in the two studied groups

The results of the study about the average score of depression 1 and 2 after treatment in the two groups under investigation are shown in Table 2. The analysis of Table 9 using the T-test showed that there is a statistically significant difference between the average depression score two months

after the treatment in the two groups under investigation; so that the average depression score two days after the treatment in the group treated with vitamin C was significantly lower than the group treated with placebo; In other words, 2 months after treatment, patients treated with vitamin C had less depression and more recovery than patients treated with placebo. Also, according to the results, no statistically significant difference was found between the average depression scores one month after the treatment in the two groups.

Table 2: The average score of depression 1 and 2 months after treatment in the two studied groups

Time	Group		P-value
	Vitamin C	Placebo	
1 month after treatment	1.43±15.56	1.62±15.36	0.534
2 month after treatment	2.1±10.36	2.78±11.40	0.030

Discussion

Major depressive disorder is one of the most common psychiatric diseases that reduces the patient's quality of life (1). This disease is a multifactorial disease caused by biological, environmental and genetic factors. Among the environmental factors influencing the occurrence of depression, we can mention nutritional factors, insufficient sleep and limited physical activity (9). Today, the lack of some food items has been proposed as underlying factors in the occurrence of depression. Oxidative stress is the main cause of degeneration in some neurological diseases such as depression, anxiety and Alzheimer's; In fact, oxidative stress is caused by an imbalance between

the production of reactive oxygen species and the ability of the biological system to detoxify these active mediators (11).

Recent studies have reported the role of oxidative stress in mental disorders, it has been shown that poor antioxidant status is associated with the risk of depression. As a result, antioxidants (as inhibitors of oxidative stress) are among the nutritional factors whose deficiency can be effective in the occurrence of depression (Salim 2014). Eating diets rich in antioxidants, including a large amount of fruits and vegetables, is also associated with a reduced risk of mental disorders (Gomez-Pinilla and Nguyen 2012). For example, it has been shown that the consumption of antioxidants in fruits and vegetables in elderly people leads to a reduction in risk. On the other hand, the frequency of fried food consumption was associated with depressive symptoms in a Japanese population (Payne et al. 2012).

The results of our study showed that there was no statistically significant difference between the average depression score before treatment ($p=0.628$) and one month after treatment ($p=0.534$) in the two groups under investigation. However, a statistically significant difference was found between the average depression score two months after treatment in the two investigated groups ($p=0.628$), so that the average depression scores two months after treatment in the group treated with vitamin C was significantly lower than the group treated with placebo.

Kalmin and his colleagues reported in a study that cognitive disorders, which are part of psychiatric problems, can be prevented or delayed by increasing the intake of antioxidants such as vitamin C and E (11). The study of Khajeh Nasiri, Omar and Gautam also showed that taking vitamin C with other supplements reduces the depression score (Amr et al. 2013; Gautam et al. 2012; Khajehnasiri et al. 2013). A study was conducted in 2013 by Amr et al. on children with major depression. This double-blind clinical trial study on 24 people in two groups including: the case group (12 people) receiving fluoxetine (20-20 mg per day) along with vitamin C (1000 mg per day) and the control group ($N=12$) and They received fluoxetine (20-20 mg per day) along with placebo.

Both groups showed significant scores in the children's depression rating scale. The average score of the depression questionnaire of the patients treated with fluoxetine vitamin C decreased significantly during six months, and the symptoms of depression were significantly reduced

compared to the fluoxetine plus placebo group. The obtained results indicate that vitamin C can be an effective factor in the treatment of children with major depression (Amr et al. 2013).

The results of another study conducted by Anitra et al. aimed at investigating the effect of kiwi (a food with high vitamin C, about 100 mg of vitamin C) on the mood of young adult men before and after 6 weeks of kiwi consumption (half a kiwi to two kiwis daily in the form of 2 groups) was conducted using the profile of mood states. It showed that there was no difference in mood in the group that consumed half a kiwi daily, but in the group that consumed two kiwis daily, the level of depression was significantly lower. There was no effect on the mood score of the participants according to the previous history of mood disorder was not found in the two groups. The results of this study showed that consuming kiwi fruit as a substance rich in vitamin C can improve mood in young men(Carr et al. 2013).

The mechanisms through which dietary antioxidants may be effective in reducing the risk of depression are not well identified. Oxidative stress and subsequent neuroinflammation are among the important factors in psychiatric disorders (Bouayed 2010), so dietary antioxidants can protect against nerve damage caused by oxidative stress, changes in synaptic molecules, and may improve depression and anxiety(Ng et al. 2008). Additionally, dietary antioxidants can protect against mitochondrial damage that is common among patients with psychiatric disorders(Leonard and Maes 2012).

In the study conducted by Juliet et al., which aimed to investigate the effect of a high dose of vitamin C on the mood of male students, using a mood profile questionnaire on 139 male students between the ages of 18 and 35, it was found that the average level of vitamin C in them, 48.2 umol/L and the average score of mood disorder in them was 25.5 (with a score range of 32 to 200). According to the analysis of Pearson's test, a significant inverse correlation ($r=-0.181$, $p<0.05$) was found between the plasma concentration of vitamin C and Kleber's mood disorder (based on the Mood Profile Questionnaire). These findings suggest that high vitamin C status may be associated with improved overall mood in young adult men(Pullar et al. 2018).

The results of the above studies were all consistent with the results of our study and proved the effect of vitamin C as an adjuvant drug in improving depression, but regarding the effect of vitamin

C on depression, it has been determined that this vitamin has antidepressant effects by changing brain serotonin levels (Lee et al. 2001). Antioxidant activities of ascorbic acid probably protect cell membrane lipoproteins from oxidative stress damage caused by free radicals. Vitamin C also acts as a neuromodulator of a number of transmitters(Harrison and May 2009).

But in some studies, the positive effect of vitamin C in improving depression was not proven. The results of Sahirian's study, which was conducted on 41 patients with major depression in the form of two groups (21 patients in the group receiving citalopram plus vitamin C and 22 patients in the control group and receiving citalopram plus placebo using Hamilton's questionnaire) showed that in During this experiment, the symptoms of depression decreased in both groups, but the difference between the two groups ($P=0.5$) as a result of taking vitamin C together with citalopram does not increase the effectiveness of citalopram in patients with major depressive disorder (13).

A study by Jokar et al aimed to investigate the effect of vitamin C on depression in 150 postmenopausal women. This double-blind clinical trial study was conducted on postmenopausal women in Hafez Shiraz Hospital. People were divided into two groups receiving vitamin C and placebo. The experimental group was for 6 months, they received 500 mg of vitamin C 2 times a day and the control group used the same method as the placebo. The findings showed that there was no significant difference between the two groups by comparing the depression score before and after the intervention (0.05). No significant difference was observed between the depression score before and after the intervention in the group receiving vitamin C ($P=0.365$) and in the placebo group ($P=0.215$) (Jokar and Farahi 2014).

Therefore, despite the fact that most of the studies have reported the consumption of vitamin C as an effective auxiliary factor in the treatment of depression and anxiety, the present study did not reach this conclusion. that increasing age itself can be an influencing factor on depression and can influence the results of the study, and secondly, the use of a different questionnaire from other studies (in this study, Beck's questionnaire was used, while in other studies, Hamilton's questionnaires and mood profiles were used.)

Conclusion

Considering that the average depression scores two months after the treatment in the group treated with vitamin C was significantly reduced compared to the placebo group, it can be concluded that adding vitamin C to the standard treatment of patients with major depressive disorder is effective in improving the mood of these patients. Therefore, adding vitamin C as an auxiliary drug to the treatment protocol of patients with major depressive disorder is recommended.

This study also had some limitations that should be considered. Among these limitations are the follow-up of patients for two months, the lack of examination of drug side effects in patients, the examination of the effect of only one dose of vitamin C on the depression score and the absence of examination of different doses of the drug, as well as the absence of examination of cognitive issues.

Considering that the results of this study showed that adding vitamin C to the standard treatment of depression is effective in improving patients with major depressive disorder, it is suggested that the use of vitamin C as an adjunctive treatment of depression (besides the standard treatment) should be considered. Also, considering the observation of the effect of vitamin C on the improvement of patients two months after treatment and no difference between the two groups in the one-month follow-up, it is suggested that the patients be followed up for a longer period of time in future studies. In addition, it is suggested that in future studies, the trend of depression score changes during the study period in the studied groups will be investigated and compared using the repeated measurements test.

Limitations:

the small sample size, short duration, the vitamin C status of subjects, dietary vitamin C of subjects, and the conditions which effect on vitamin c metabolism were among the limitations of this trial.

Declarations

Ethics approval and consent to participate

This study was started after the approval of the Ethics Committee of the Faculty of Medicine of Shahid Sadougi University of Medical Sciences in Yazd and receiving the ethics code number 1399.291.IR.SSU.MEDICINE.REC.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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