http://jbcp.shahed.ac.ir 10.22070/jbcp.2019.3616.1104

Open Access Research Article

Journal of Basic and Clinical Pathophysiology
Print ISSN: 2322-1895, **Online ISSN:** 2345-4334
Vol.7, No.1, March 2019

A Semiannual Publication of
Shahed University Press

The effect of ascorbic acid as a supplementary treatment with risperidone in controlling the symptoms of schizophrenia: A double-blind, placebo-controlled clinical trial

Moahammadreza Khodaie, Neda Alibeigi, Venous Gholamreza Mirzaei*

Department of Psychiatry, University of Welfare and Research Sciences, Tehran, Iran

Abstract

Background and Objective: Considering the hypothesis of the effects of the use of antioxidants such as ascorbic acid on the improvement of oxidative stress induced by schizophrenia, the present study was designed to investigate the effect of ascorbic acid as an adjunctive therapy with risperidone in controlling the symptoms of schizophrenia.

Materials and Methods: This randomized clinical trial was conducted on patients with schizophrenia admitted to Tehran's Razi hospital of psychiatry in 2018. The patients were divided into control and intervention groups. The group treated with ascorbic acid received this drug daily at 500 mg twice daily and the placebo group received a similar drug, similar to ascorbic acid, at the same rate for 4 months. The PANSS (Positive & Negative Symptom Scale) questionnaire was used to determine the status of the positive and negative symptoms and the SCORS (Schizophrenia Cognition Rating Scale) questionnaire was used to determine the cognitive status at the end of weeks 8 and 16 when entering the study. Data were analyzed using paired t-test and Wilcoxon in SPSS 20 software.

Results: The effect of ascorbic acid on the positive and negative symptoms of patients at the 8th and 16th weeks showed that after eight weeks of treatment, among the positive symptoms, conceptual disorganization, excitement, hostility and grandiosity, among the negative symptoms, blunted affect has had a significant improvement relative to before intervention. After 16 weeks of treatment, except difficulty in abstract thinking, all of the symptoms showed a significant improvement compared with the symptoms of the patients before the study. Compared to ascorbic acid, the effect of placebo on all of the positive and negative symptoms and other symptoms in most cases was not significant. Regarding the effect of ascorbic acid on the cognitive symptoms of patients in the 8th and 16th week, there was no significant difference in the few numbers of cognitive symptoms in the eighth week, although after eight weeks, overall cognitive symptoms were significantly improved ($p<0.05$). In addition, after 16 weeks of treatment, almost all of the parameters of the cognitive symptoms and the total of cognitive symptoms were significantly improved compared to the pre-intervention ($p<0.01$). Compared to ascorbic acid, the effect of placebo on cognitive symptoms in most cases was not significant ($P >0.05$).

Conclusion: The results of this study showed that ascorbic acid, having its antioxidant effects after sixteen weeks of treatment, reduced the patients' positive and negative symptoms and their cognitive symptoms. Compared to ascorbic acid, the effect of placebo on cognitive symptoms and positive and negative symptoms was not significant in most cases.

Key words: Schizophrenia, Ascorbic acid, Risperidone, Positive & negative symptom, Cognitive symptoms

1. Introduction

Schizophrenia is one of the main psychiatric disorders that affects one percent of the human population. This disease presents itself as two categories of symptoms: Positive symptoms include hallucination, delusions, disturbed thoughts and behavior, and negative symptoms including low affection and poor speech, impotence and imperfection in targeted behavior, which are the main causes of the inability of these patients. (1,2). One of

Revised: November 2018**, Accepted:** February 2019, **Available online:** March 2019
Corresponding Author: Venous Gholamreza Mirzaei **Email:** venous_m11@yahoo.com

the etiologies presented in this disease is oxidative stress. The human brain has unmatched phospholipids, such as linoleic acid, which are susceptible to oxidative stress and play an important role in transmitting the neural signal. Destruction of linoleic acid may result in changes in the neurotransmitter messaging and eventually in the classification of information in schizophrenic patients (3-7). Studies have shown that treatment with antipsychotics reduces the damage caused by free radicals in patients with schizophrenia (8). On the other hand, oxidative stress is associated with the pathophysiology of many psychiatric disorders, including schizophrenia, and should be considered as one of the therapeutic approaches in these diseases (9). Biochemicals are important indicators of oxidative stress, increased levels of malondialdehyde, nitrite, nitrate and decreased activity of antioxidant defense system such as superoxide dismutase (10-12), among which one of the final products of lipid peroxidation reaction In the malondialdehyde brain, which is a sensitive and specific criterion for auto-oxidation of lipid, and in conditions of increasing or decreasing inhibition of free radicals, an imbalance state occurs in the expression of peroxidase, which is the basis of the pathogenesis of acute and chronic cerebral diseases. (13). Studies in patients with schizophrenia have shown that antioxidant systems play a role in the incidence of schizophrenia. Generally, in these patients, antioxidant activity decreases (14), in addition, in these patients, levels of malondialdehyde in plasma, erythrocytes, leukocytes and platelets increased (14-16).

Ascorbic acid is inherently an organic compound with antioxidant properties. Ascorbic acid is a form of vitamin C. Ascorbic acid is produced in plants and animals from glucose (17). All animals either make it or feed it. Ascorbic acid usually acts as an antioxidant (18). Typically reacts with oxidants of active oxygen species, such as hydroxyl radicals composed of hydrogen peroxide. These radicals, by interacting with nucleic acids, proteins and fats, damage animals and plants at the molecular level and initiate chain reactions. Ascorbic acid can end this radical chain reaction of electron transfer (19-22).

Ascorbic acid is present in a large number of fruits and vegetables such as citrus, cantaloupe, melons, cherries, kiwi, mangoes, pineapples, strawberries, tomatoes and watermelons. Vegetables such as broccoli, cauliflower, cabbage, green pepper and red and potatoes are better sources of vitamin C than fruits (17). Vitamin C deficiency can be detected in both clinical and laboratory methods. Clinical symptoms include follicular hyperkeratosis, spotting bleeding, swelling and gingival bleeding, and joint pain. Its labyrinth is also a low concentration of vitamins in the blood, plasma, and white blood cells (18). The results of the studies have shown that vitamin C levels of fasting plasma and urinary excretion of vitamin C six hours after the test of ascorbic acid in patients with schizophrenia is significantly lower than that of the control group, and patients with schizophrenia need higher levels of vitamin C To the daily needs of healthy people (22).

Considering the hypothesis of the effects of the use of antioxidants such as ascorbic acid on the improvement of oxidative stress induced by schizophrenia (23-35), the present study was designed to investigate the effect of ascorbic acid as an adjunctive therapy with risperidone in controlling the symptoms of schizophrenia.

2. Materials and Methods

2.1. Study Population

This double blind randomized clinical trial was conducted on patients with schizophrenia admitted to Tehran's Razi Hospital of Psychiatry in 2018. 18-45 years old patients with schizophrenia who had been diagnosed with DSM-V criteria for at least one year and were treated with risperidone during this period have been enrolled. People with various types of mood disorders such as bipolar disorder and depression, neurological disorders such as Parkinson's, patients with mental retardation or blindness and deafness, patients with substance abuse 6 months before the study, and patients who did not agree to participate in the study have been excluded. Then, the samples were randomly assigned to the two groups treated with ascorbic acid and placebo by using a randomized table and observing the synchronization between age and sex parameters and, of course, dosage of risperidone.

2.2. Intervention

The patients were divided into control and intervention groups. In the beginning of the intervention, the medication and placebo were encoded in two separate boxes available to the researcher. Then the code of each drug package was covered with a label and randomly assigned to the intervention or control group. At the end of the intervention, the label was removed from the drug boxes and it was determined on the basis of the intervention that the patient received the medication and which placebo was received. The group treated with ascorbic acid received this drug daily at 500 mg twice daily and the placebo group received a similar drug, similar to ascorbic acid, at the same rate for 4 months (25, 28). Proposals The study was approved by the Council of Theses of the University of Social Welfare and Rehabilitation Sciences and the researchers adhered to all the principles of the

protocols and guidelines recommended by the Helsinki regarding the observance of ethics in the research.

2.3. Outcome

The PANSS (Positive & Negative Symptom Scale) questionnaire was used to determine the status of the positive and negative symptoms and the SCORS (Schizophrenia Cognition Rating Scale) questionnaire was used to determine the cognitive status at the end of the week 8 and 16 when entering the study (25, 28, 30, 34). In addition, at the same time, patients were asked questions about side effects and the checklist was completed (28). The PANSS test is designed to evaluate the dimensions and typology of the schizophrenia phenomenon and has 30 questions that assesses the patient's positive and negative symptoms based on semi-structured clinical interviews. There are also three questions for assessing the probability of aggression. Each question was answered in a seven-point Likert scale, from lack of sign to over-severity (36). In order to assess the cognitive problems of patients with schizophrenia, a SCoRS questionnaire was used in this study. In this questionnaire, 20 questions of scoring, memory, memory, language production, inference, problem solving, motor skills, and social cognition are scored (37).

2.4. Statistical Analysis

Data were entered into SPSS version 20 software. In descriptive analyzes, frequency, frequency, mean, and standard deviation were used. Paired t-test or non-parametric Wilcoxon test was used in the statistical population according to the distribution of samples. Chi-square test was used to compare qualitative variables. ANCOVA test was used to change the co-variate variable in the two groups at the beginning of the study and the significance level for all samples was considered as $P < 0.05$.

3. Results

Twenty patients (45.5%) were male and 24 patients (54.5%) were female. There was no statistically significant difference in sex between two groups of ascorbic acid and placebo based on the results of chi square ($P = 0.69$). Also, 13 patients (29.5%) were married and 31 patients (70.5%) were single. According to Chi-square test, there was no significant difference in the marital status between the two groups of ascorbic acid and placebo ($P=0.41$. (In addition, the mean age of the patients was 35.47 ± 12.44 years. The youngest patient was 21 years old and the oldest was 45 years old. Based on independent t-test, there was no significant difference in age between the two groups of ascorbic acid and placebo ($P=0.51$). The results of the demographic variables of patients showed that the matching of patients in terms of demographic variables was successful ($P<0.53$). Examining the side effects of treatment in the study groups showed that none of the patients experienced nausea, vomiting, cutaneous rash, diarrhea, and other cases that were the most commonly suspected poisoning event.

The effect of ascorbic acid on the positive and negative symptoms of patients in the 8th and 16th weeks showed that after eight weeks of treatment, among the positive symptoms, conceptual disorganisation, excitement, hostility and grandiosity, among the negative symptoms, blunted affect has had a significant improvement over before intervention. After 16 weeks of treatment, except difficulty in abstract thinking, all of the symptoms showed a significant improvement compared with the symptoms of the patients before the study (Table 1). Compared to ascorbic acid, the effect of placebo on all of the positive and negative symptoms and other symptoms in most cases was not significant (Table 2).

Regarding the effect of ascorbic acid on the cognitive symptoms of patients in the 8th and 16th week, there was no significant difference in the few numbers of cognitive symptoms in the eighth week, although after eight weeks, overall cognitive symptoms were improved significantly ($P <0.05$). In addition, after 16 weeks of treatment, almost all of the parameters of the cognitive symptoms and the total of cognitive symptoms were significantly improved compared to the pre-intervention ($P <0.01$). (Table 3).

Compared to ascorbic acid, the effect of placebo on cognitive symptoms in most cases was not significant ($P >0.05$). (Table 4).

Table 1. The effect of ascorbic acid plus risperidone on positive and negative symptoms of patients after 8 and 16 weeks of treatment regarding patients' condition before intervention

PANSS	Before Intervention	After 8 weeks	P value	After 16 weeks	P value
P1 Delusions	3.67±1.4	3/31±1/9	0/08	2/7±1/8	*0/01
P2 Conceptual disorganisation	2/79±0/8	2/06±0/9	*0/009	1/89±0/8	*0/003
P3 Hallucinatory behavior	3/1±1/8	2/7±1/4	0/07	2/4±1/3	*0/009
P4 Excitement	2/51±1/2	1/79±0/9	*0/003	1/67±1/6	*0/001
P5 Grandiosity	2/87±1/2	1/68±1/1	*0/001	1/44±1/8	*<0/001
P6 Suspiciousness/persecution	3/1±1/5	2/8±0/9	0/06	2/6±0/7	*0/03
P7 Hostility	2/18±1/3	1/6±0/9	*0/02	1/3±0/6	*0/003
N1 Blunted affect	2/6±1/5	1/97±1/3	*0/03	1/67±1/3	*0/003
N2 Emotional withdrawal	2/8±1/7	2/4±1/2	0/06	2/4±1/2	*0/02
N3 Poor rapport	2/67±1/5	2/3±1/2	0/08	2/1±1/2	* 0/04
N4 Passive/apathetic social withdrawal	2/8±1/6	2/6±1/1	0/5	2/1±1/8	* 0/04
N5 Difficulty in abstract thinking	3/2±1/1	2/8±1/1	0/2	2/6±1/5	0/07
N6 Lack of spontaneity& flow of conversation	3/2±1/1	2/9±1/2	0/06	2/7±1/2	* 0/05
N7 Stereotyped thinking	2/9±1/8	2/45±1/3	0/09	2/3±1/3	*0/07
G1 Somatic concern	2/05±1	1/7±1/1	0/3	1/6±1/3	0/07
G2 Anxiety	2/1±1	1/65±0/9	*0/04	1/53±0/7	*0/03
G3 Guilt feelings	1/9±0/9	1/56±0/6	*0/03	1/54±0/6	*0/03
G4 Tension	2/3±1/1	1/4±1/7	0/06	1/3±1/1	*0/004
G5 Mannerisms & posturing	3/6±1/1	2/8±1/3	*0/03	2/9±1/9	*0/04
G6 Depression	2/01±1/4	1/6±0/6	*0/03	1/4±0/9	*0/001
G7 Motor retardation	2/87±1/5	2/19±1/4	*0/006	2/21±1/8	*0/008
G8 Uncooperativeness	2/86±1/7	1/93±0/8	*0/008	1/68±1/8	*0/005
G9 Unusual thought content	3/1±1/4	2/06±0/7	*0/03	2/03±0/9	*0/03
G10 Disorientation	2/54±1/4	1/87±0/9	0/1	1/59±1/9	0/08
G11 Poor attention	3/01±1/3	2/53±1/3	*0/001	2/57±1/8	*0/001
G12 Lack of judgment & insight	3/01±1/2	2/67±0/8	*0/04	2/41±0/5	*0/03
G13 Disturbance of volition	1/9±1/1	1/4±0/8	*0/03	1/5±1/5	*0/03
G14 Poor impulse control	2/05±1/1	1/46±0/6	*0/003	1/51±0/9	*0/003
G15 Preoccupation	2/9±1/3	2/47±0/9	0/09	2/31±1/4	*0/048
G16 Active social avoidance	3±1/7	2/7±1/3	0/07	2/51±1/3	0/04
Total	86/3±18/9	73/2±15/8	*0/008	65/1±18/7	*0/003

Table 2. The Effect of placebo plus risperidone on positive and negative symptoms of patients after 8 and 16 weeks of treatment regarding patients' condition before intervention

PANSS	Before Intervention	After 8 weeks	P value	After 16 weeks	P value
P1 Delusions	3/5±1/4	3/4±1/7	0/6	3/01±1/4	0/09
P2 Conceptual disorganisation	2/86±0/8	2/59±0/8	0/1	2/51±0/8	0/1
P3 Hallucinatory behavior	3/3±1/3	2/9±1/4	0/09	2/4±1/4	*0/04
P4 Excitement	2/9±1/2	2/6±1/9	0/08	2/34±1/1	0/05
P5 Grandiosity	2/68±1/3	2/53±1/1	0/1	2/44±1/1	0/09
P6 Suspiciousness/persecution	3/18±1/3	2/9±0/9	0/09	2/6±1/3	0/07
P7 Hostility	2/18±2/1	1/8±0/7	*0/04	1/7±1/1	*0/03
N1 Blunted affect	2/4±1/3	2/1±1/3	0/2	2/01±0/7	0/1
N2 Emotional withdrawal	2/78±1/3	2/6±1/3	0/1	2/43±1/1	0/09
N3 Poor rapport	2/67±1/3	2/5±1/2	0/3	2/4±1/7	0/2
N4 Passive/apathetic social withdrawal	2/8±1/6	2/5±1/1	0/4	2/5±0/9	0/4
N5 Difficulty in abstract thinking	3/2±1/1	2/8±1/1	0/2	2/6±1/8	0/1
N6 Lack of spontaneity& flow of conversation	3/1±1/1	2/9±1/2	0/1	2/9±1/8	0/2
N7 Stereotyped thinking	2/8±1/8	2/31±1/4	0/08	2/41±1/4	0/09
G1 Somatic concern	1/9±1	1/7±1/8	0/3	1/6±0/8	0/1
G2 Anxiety	2/1±1/1	1/87±0/9	0/2	1/61±0/7	0/1
G3 Guilt feelings	1/9±0/9	1/61±1/1	0/09	1/45±1/2	0/07
G4 Tension	2/4±1/1	1/7±1/3	0/1	1/7±1/1	0/1
G5 Mannerisms & posturing	2/9±1/4	2/6±1/3	0/2	2/4±1/7	0/1
G6 Depression	2/31±0/9	1/81±0/9	0/09	1/78±1/2	0/09
G7 Motor retardation	2/64±1/5	2/31±1/4	0/08	2/21±1/1	0/07
G8 Uncooperativeness	2/5±1/7	1/98±0/9	0/1	2/1±0/9	0/2
G9 Unusual thought content	2/8±1/1	2/01±1/2	0/09	2/21±1/1	*0/04
G10 Disorientation	2/67±1/1	1/96±0/9	0/3	1/9±1/3	0/2
G11 Poor attention	3/01±1/3	2/87±1/3	0/2	2/69±1/3	0/2
G12 Lack of judgment & insight	2/91±1/2	2/78±1/2	0/5	2/3±1/8	0/1
G13 Disturbance of volition	1/87±1/1	1/6±1/3	0/1	1/6±1/3	0/1
G14 Poor impulse control	2/01±1/1	1/78±0/6	0/08	1/71±1/6	0/07
G15 Preoccupation	2/8±1/1	2/6±0/9	0/2	2/4±0/9	0/1
G16 Active social avoidance	3/01±1/7	2/9±1/3	0/4	2/9±0/8	0/4
Total	82/3±15/9	76/1±18/1	0/1	73/5±16/9	0/08

Table 3. The Effect of ascorbic Acid plus risperidone on cognitive symptoms of patients after 8 and 16 weeks of treatment regarding patients' condition before intervention

SCORS	Before Intervention	After 8 weeks	P value	After 16 weeks	P value
Remember people	2/81±0/9	2/45±1/4	0/09	2/01±1/4	*0/03
Remember the places	2/8±0/7	2/42±1/6	0/1	2/15±1/6	*0/04
Follow the TV program	2/89±1/3	2/63±0/7	0/3	2/33±0/6	0/09
Remember the location of objects	2/1±1/4	1/65±1/1	*0/04	1/55±1/2	*0/03
Remember the routine	2/8±1/4	2/04±0/9	*0/03	2/01±0/8	*0/03
Learn how to use new gadgets	2/73±0/8	2/34±1/4	0/75	2/14±1/1	0/2
Establish information and instructions	2/5±0/6	2/13±0/6	0/2	1/98±1/1	0/08
Remember your speech	2/71±0/4	2/01±1/8	*0/04	1/89±1/8	*0/03
Account and money book	2/9±0/8	2/6±1/1	0/06	2/3±1/3	*0/02
Correct conversation and speech	2/04±0/8	1/4±0/8	*0/03	1/4±0/8	*0/03
Focus on reading the text	3/2±0/8	2/65±0/7	0/09	2/31±0/9	*0/009
Getting to know everyday things	2/9±0/9	2/3±0/9	*0/04	2/2±0/8	*0/04
Keep focus	2/9±0/9	2/6±1/4	0/1	2/1±1/4	0/05
Learn new content	2/87±0/8	2/54±1/6	0/06	2/31±1/6	*0/03
Talking with the right speed	2/51±0/9	2/36±1/1	0/5	2/1±1/1	0/08
Doing things at the right speed	2/87±1/9	2/71±1/1	0/6	2/16±1/8	0/09
Manage changes in the everyday life plan	3/1±1/1	2/7±0/6	0/06	2/7±0/6	*0/008
Understanding the order of individuals	2/2±1/8	1/7±0/7	*0/04	1/7±0/7	*0/006
Detect people's feelings about issues	2/21±0/8	1/98±0/7	0/09	1/98±0/7	*0/04
Follow the conversations in the crowd	2/84±0/6	2/71±0/9	0/2	2/41±1/7	0/09
Total	50/5±17/2	44/3±115	*0/02	41/9±16/9	*0/009
General assessment	5/63±1/8	4/91±2/2	*0/04	3/9±2/1	*0/009
General change of individual problems	-	3/98±1/6	-	5/01±1/4	-

Table 4. The effect of placebo plus risperidone on cognitive symptoms of patients after 8 and 16 weeks of treatment regarding patients' condition before intervention

SCORS	Before Intervention	After 8 weeks	P value	After 16 weeks	P value
Remember people	2/81±0/9	2/55±1/1	0/1	2/81±0/9	0/1
Remember the places	2/8±0/7	2/57±1/5	0/2	2/8±0/7	0/1
Follow the TV program	2/89±1/3	2/63±0/7	0/3	2/89±1/3	0/09
Remember the location of objects	2/1±1/4	1/78±1/1	0/09	2/1±1/4	0/09
Remember the routine	2/8±1/4	2/6±1/6	0/4	2/8±1/4	*0/04
Learn how to use new gadgets	2/6±1/1	2/39±1/1	0/5	2/6±1/1	0/1
Establish information and instructions	2/5±0/6	2/09±0/9	0/2	2/5±0/6	0/09
Remember your speech	2/6±0/9	2/31±1/4	0/3	2/6±0/9	0/08
Account and money book	2/7±0/9	2/4±1/1	0/5	2/7±0/9	0/1
Correct conversation and speech	2/31±1/1	1/9±0/8	0/1	2/31±1/1	*0/03
Focus on reading the text	3/1±0/8	2/7±1/4	0/1	3/1±0/8	*0/03
Getting to know everyday things	2/9±1/2	2/7±1/3	0/4	2/9±1/2	0/1
Keep focus	2/8±0/9	2/53±1/1	0/1	2/8±0/9	*0/04
Learn new content	2/91±1/5	2/61±1/4	0/09	2/91±1/5	*0/02
Talking with the right speed	2/61±1/3	2/46±1/2	0/8	2/61±1/3	0/6
Doing things at the right speed	2/71±1/3	2/56±1/1	0/6	2/71±1/3	0/4
Manage changes in the everyday life plan	2/9±1/3	2/5±0/5	0/1	2/9±1/3	0/1
Understanding the order of individuals	2/32±1/5	1/9±0/7	0/1	2/32±1/5	0/09
Detect people's feelings about issues	2/11±0/7	1/81±0/7	0/3	2/11±0/7	0/3
Follow the conversations in the crowd	2/79±0/6	2/71±0/9	0/9	2/79±0/6	0/7
Total	51/3±11/2	49/3±13/7	0/2	51/3±11/2	0/1
General assessment	5/11±1/2	4/91±2/2	0/3	5/11±1/2	0/2
General change of individual problems	-	2/32±1/9	-	-	-

4. Discussion

The results of this study showed that in the group of ascorbic acid plus risperidone, after eight weeks of treatment, there was a significant improvement in pre-interventional medications among the positive symptoms, , conceptual disorganisation, excitement, hostility and grandiosity, among the negative symptoms, blunted affect has had a significant improvement over before intervention. In addition, in this group after sixteen weeks of treatment, except for abstract thinking, all of the symptoms showed a significant improvement compared to the symptoms of the patients before the study. Compared to ascorbic acid, after eight and sixteen weeks of combined treatment with risperidone, the effect of placebo on the positive and negative symptoms in most cases was not significant. Results of the combined effect of Ascorbic acid and Risperidone on the cognitive symptoms of patients after eight weeks showed no significant difference in cognitive parameters, but in combination, ascorbic acid plus risperidone after eight weeks of treatment improved the cognitive symptoms of patients Meaningful. In addition, after 16 weeks of treatment, almost all of the parameters of cognitive symptoms and, of course, the total cognitive symptoms in this group, were significantly improved compared to the pre-intervention period. Compared to ascorbic acid, the effect of placebo and placebo on placebo on cognitive symptoms in patients showed that the effect of placebo on cognition after 8 and 16 weeks was not significant in most cases.

The effects of antioxidant agents, including vitamins, on the symptoms of schizophrenia have been studied in human and animal studies. In this regard, Magalhães and colleagues in 2016 in Brazil underwent a systematic review of the protocol of the Cochrane Institute on antioxidant treatment in schizophrenia in 22 clinical trials. The antioxidants studied in these studies included ginkbiluba, n-acetyl-cytene, allopurinol, dihydropieroestrour (DHEA), vitamin C, vitamin E, or selgilin. The short-term treatment outcome was an average of at least 20% improvement in the positive and negative symptoms of schizophrenia in the PANSS scale. Based on PANSS psychotic symptoms were significantly lower in antioxidants. In general, the study was not included in short-term treatment with complications. Side effects were also reported in these studies (24). Compared to the results of the Magalhães review study, our study did not show any significant side effects, and after eight and especially sixteen weeks, there was a significant improvement in the number of positive and negative symptoms based on the PANSS scale.

Bentsen and his colleagues in Norway in 2013 examined the effect of omega-3 fatty acids and vitamins E and C on the treatment of schizophrenia. Sixteen weeks of treatment with Ethyl-eicosapentaenoate significantly reduced PANSS score and psychotic symptoms, especially delusional symptoms. Gave In addition, treatment with two vitamins alone reduced the psychotic symptoms, especially the delusions. Adding vitamins to treatment with ethyl acycosupentaenoate has increased therapeutic effects (25). Compared with the results of Bentsen et al., Although symptoms of delirium and damage after 8 weeks had no significant difference with pre-intervention, but similar to the results of their study, positive and negative symptoms, the PANSS scores, including predisposing delusions and damage before the study Significant improvement.

In addition, Arvindakshan and colleagues in India in 2003 showed that significant improvement in the symptoms of the disease was observed based on the scores of the BPRS scales, the PANSS scale and the PANSS psychopathology scale, and the increase in the score for the quality of life scale (QOL) after administration 1g of Vitamin C after 4 months (34). Compared to the results of Arvindakshan et al., although our study did not examine quality of life, similar to the results of their study, auxiliary treatment with ascorbic acid improved PANSS scores and positive and negative symptoms.

It seems that in schizophrenic patients, levels of oxidizing agents are higher than those of healthy people, and the mechanism of probable effect of ascorbic acid on the improvement of symptoms in patients with schizophrenia is related to its antioxidant effects. In the study conducted by Salehi et al, it was concluded that antioxidant defense levels in schizophrenic patients decreases (38). In addition, Dadheech et al. showed that levels of α-tocopherol, total ascorbic acid, and glutathione in patients with schizophrenia decreased significantly compared to the control group. Additionally, in the chronic phase of schizophrenia, a significant increase in oxidative stress and antioxidant levels was observed in acute state. In this study, a significant increase in dehydroascorbic acid and decreased ascorbic acid resulted in decreased ascorbic acid activity and increased oxidative stress, indicating high levels of malondialdehyde in schizophrenic patients (31). The results of Dadheech and Salehi's study suggest that oxidative stress is involved in the pathophysiology of schizophrenia, and ascorbic acid, with its antioxidant properties, can play an important role in coping with oxidizing agents. In 2008, Hoffer concluded that there is evidence that high doses of antioxidant vitamins can improve metabolic abnormalities in some people who are at risk of developing it. Schizophrenia is one of these neurological diseases. Vitamin C treatment, including

vitamin C, can be promising in the treatment of this disease(27). The results of this study are also consistent with the results of our study.

In addition, Sivrioglu and colleagues showed that the positive and negative symptoms of patients and the overall assessment of psychiatric status in patients in referral follow-up was significantly lower than baseline after receiving 600 mg of omega-3 fatty acids, vitamin E 800 units and vitamin C 1g daily for 4 months. The level of superoxide dismutase was significantly lower at the end of the study. The results of this study showed the positive effects of vitamin C supplements on the positive and negative symptoms of schizophrenia as well as the severity of haloperidol side effects (28), which is in line with our study results.

The results of the study by Dakhale and colleagues concluded that oral vitamin C supplementation with atypical antipsychotics improves the oxidative stress and symptoms of patients, so both drugs can be used to treat schizophrenia (30). Compared to the results of the study, Dakhale et al. Although the scale of assessment of the symptoms of patients varied in our study, the results of our study were consistent with the overall improvement of the symptoms with their study results. In addition, in 2004, they investigated the effect of atypical antipsychotics on lipid peroxidation, superoxide dismutase (SOD) and ascorbic acid levels, and showed a significant increase in serum oxidant levels and a significant decrease in plasma ascorbic acid in schizophrenic patients. The findings of this study showed the role of free radicals in schizophrenia and its correction with atypical antipsychotics (32). In our study, the effects of ascorbic acid supplementation with an atypical antipsychotic, such as risperidone, were evaluated in a similar study to the results of this study.

Conclusion

The results of this study showed that ascorbic acid, having its antioxidant effects after sixteen weeks of treatment, reduced the patients' positive and negative symptoms and their cognitive symptoms. Compared to ascorbic acid, the effect of placebo on cognitive symptoms and positive and negative symptoms was not significant in most cases.

Conflict of interest

Authors of this manuscript have no conflicts of interest.

Acknowledgment

Current study was a part of the thesis by Dr. Venous Gholamreza Mirzaei submitted for fulfillment of the degree of Specialty in Psychiatry Medicine and was supported by University of Social Welfare and Rehabilitation Sciences in Tehran, Iran. The authors would like to express their appreciations to the Patients and staff in Razi Psychiatry hospital for their kindly help.

References

1. Bahmany N, Zandi Ghashghaee K, Khosravi S. A comparison between effectiveness of three types of music on memory activity and sustained attention in schizophrenic patients. Iranian South Medical Journal 2014; 17 (4) :706-715
2. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet 2016;388(10039):86-97.
3. Gold C, Heldat TO, Dahle T, et al. Music therapy for schizophrenia of schizophrenia - Like illnesses. The Cochrane Database of Systematic Reviews 2005; 18(2): 004025.
4. Rafiee Vardanjani L, Parvin N, Dehkordi SF, Shahinfard N, Morte S, Ansari Samani R. The effects of Portulaca oleracea L (purslane) on psychologic symptoms and malondialdehyde level in schizophrenic patients. The Scientific Journal of Kurdistan University of Medical Sciences 2013, 18(4): 28-34
5. Altuntas I, Aksoy H, Coskun I, Caykoylu A, Akcay F. Erythrocyte superoxide dismutaseand glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels inschizophrenic patients. Clinical Chemistry and Laboratory Medicine 2000;38:1277-82.
6. Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipidperoxidation and antioxidant enzyme levels in patients with schizophrenia and bipolardisorder. Cell Biochemistry and Function 2002;20:171-5.
7. Pavlović D, Tamburić V, Stojanović I, Kocić G, Jevtović T, Djordjević V. Oxidative stressas marker of positive symptoms in schizophrenia. Facta Universitatis Series: Medicine and Biology 2002;9:157-61.
8. Zhang XY, Tan YL, Cao LY, Wu GY, Xu Q, Shen Y, and et al. Antioxidant enzymes andlipid peroxidation in different forms of schizophrenia treated with typical and atypicalantipsychotics. Schizophrenia Research 2006;81:291-300.
9. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence baseand therapeutic implications. The International Journal of Neuropsychopharmacology 2008;11:851-76.
10. Ghosian Moghadam MH, Ansari I, Roghani M, Ghanem A, Mehdizade N. The Effect of Oral Administration of Hypericum Perforatum on Serum Glucose and Lipids, Hepatic Enzymes and Lipid Peroxidation in Streptozotocin-Induced Diabetic Rats. Galen Medical Journal 2017; 6(4):319-329.
11. Pazdro R, Burgess JR. The role of vitamin E and oxidative stress in diabetes complications. Mechanisms of Ageing and Development 2010;131:276-86.
12. Ghosian Moghaddam MH, Ansari I, Roghani M, Moradi M. The Effects of Origanum Majorana on Oxidative Stress and Histopathology of Renal Tissue among Streptozotocin-Induced Diabetic Rats. Thrita 2013; 2(3): 29-34.

13. Stohs S. The role of free radicals in toxicity and disease. Journal of Basic and Clinical Physiology and Pharmacology 1995;6:205-28.
14. Raffa M, Mechri A, Othman LB, Fendri C, Gaha L, Kerkeni A. Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2009;33:1178-83.
15. Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2008;32:1677-81.
16. Magalhães PV, Dean O, Andreazza AC, Berk M, Kapczinski F. Antioxidant treatments for schizophrenia. Cochrane Database of Systematic Reviews 2016;2:CD008919.
17. Wang J, Zhang Z, Huang R. Regulation of ascorbic acid synthesis in plants. Plant Signaling & Behavior. 2013;8(6):e24536.
18. Weiss WP. A 100-Year Review: From ascorbic acid to zinc-Mineral and vitamin nutrition of dairy cows. Journal of Dairy Science 2017;100(12):10045-10060.
19. Grosso G, Bei R, Mistretta A, Marventano S, Calabrese G, Masuelli L, et al. Effects of vitamin C on health: a review of evidence. Frontiers in Bioscience (Landmark Ed) 2013;18:1017-29.
20. Pohanka M, Pejchal J, Snopkova S, Havlickova K, Karasova JZ, Bostik P, et al. Ascorbic acid: an old player with a broad impact on body physiology including oxidative stress suppression and immunomodulation: a review. Mini-Reviews in Medicinal Chemistry 2012;12(1):35-43.
21. Akram NA, Shafiq F, Ashraf M. Ascorbic Acid-A Potential Oxidant Scavenger and Its Role in Plant Development and Abiotic Stress Tolerance. Frontiers in Plant Science 2017;8:613.
22. Suboticanec K, Folnegović-Smalc V, Korbar M, Mestrović B, Buzina R. Vitamin C status in chronic schizophrenia. Biological Psychiatry 1990;28(11):959-66.
23. Damazio LS, Silveira FR, Canever L, Castro AA, Estrela JM, Budni J, et al. The preventive effects of ascorbic acid supplementation on locomotor and acetylcholinesterase activity in an animal model of schizophrenia induced by ketamine. The Anais da Academia Brasileira de Ciências 2017;89(2):1133-1141.
24. Magalhães PV, Dean O, Andreazza AC, Berk M, Kapczinski F. Antioxidant treatments for schizophrenia. The Cochrane Database of Systematic Reviews 2016;2:CD008919.
25. Bentsen H, Osnes K, Refsum H, Solberg DK, Bøhmer T. A randomized placebo-controlled trial of an omega-3 fatty acid and vitamins E+C in schizophrenia. Translational Psychiatry 2013;3(12):e335-.
26. Heiser P, Sommer O, Schmidt AJ, Clement HW, Hoinkes A, Hopt UT, et al. Effects of antipsychotics and vitamin C on the formation of reactive oxygen species. Journal of Psychopharmacology 2010;24(10):1499-504.
27. Hoffer LJ. Vitamin therapy in schizophrenia. The Israel Journal of Psychiatry and Related Sciences 2008;45(1):3-10.
28. Sivrioglu EY, Kirli S, Sipahioglu D, Gursoy B, Sarandöl E. The impact of omega-3 fatty acids, vitamins E and C supplementation on treatment outcome and side effects in schizophrenia patients treated with haloperidol: an open-label pilot study. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2007;31(7):1493-9.
29. Young J, McKinney SB, Ross BM, Wahle KW, Boyle SP. Biomarkers of oxidative stress in schizophrenic and control subjects. Prostaglandins Leukot Essent Fatty Acids 2007;76(2):73-85.
30. Dakhale GN, Khanzode SD, Khanzode SS, Saoji A. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. Psychopharmacology 2005;182(4):494-8.
31. Dadheech G, Mishra S, Gautam S, Sharma P. Oxidative stress, α-tocopherol, ascorbic acid and reduced glutathione status in schizophrenics. Indian Journal of Clinical Biochemistry 2006;21(2):34-38.
32. Dakhale G, Khanzode S, Khanzode S, Saoji A, Khobragade L, Turankar A. Oxidative damage and schizophrenia: the potential benefit by atypical antipsychotics. Neuropsychobiology 2004;49(4):205-9.
33. Castagné V, Rougemont M, Cuenod M, Do KQ. Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia. Neurobiology of Disease 2004;15(1):93-105.
34. Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophrenia Research 2003;62(3):195-204.
35. Michael N, Sourgens H, Arolt V, Erfurth A. Severe tardive dyskinesia in affective disorders: treatment with vitamin E and C. Neuropsychobiology 2002;46 Suppl 1:28-30.
36. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-76.
37. Mazhari S1, Ghafaree-Nejad AR2, Soleymani-Zade S3, Keefe RSE. Validation of the Persian version of the Schizophrenia Cognition Rating Scale (SCoRS) in patients with schizophrenia. Asian Journal of Psychiatry 2017;27:12-15.
38. Salehi B, Vakilian K, Ranjbar A. Relationship of Schizophrenia with Lipid Peroxidation, Total Serum Antioxidant Capacity and Thiol Groups. Iranian Journal of Psychiatry and Clinical Psychology 2008; 14 (2):140-145.