

DOI: <https://dx.doi.org/10.18203/2319-2003.ijbcp20211023>

Original Research Article

Major depressive disorder: association with vitamin C levels and role of vitamin C supplementation in pharmacotherapy

Kohima Aggarwal¹, Navyug Raj Singh^{1*}, Neeru Bala², Manjit Singh²

¹Department of Pharmacology, ²Department of Psychiatry, Government Medical College, Amritsar, Punjab, India

Received: 03 February 2021

Accepted: 05 March 2021

***Correspondence:**

Dr. Navyug Raj Singh,

Email: navyug69@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Oxidative stress has a well-documented role in pathophysiology of depression. Decrease in levels of vitamin C, an antioxidant, has also been reported in major depressive patients. This study was conducted to assess the association of vitamin C deficiency with major depressive disorder and any change in clinical response to antidepressant therapy with vitamin C co-administration vis-a-vis baseline vitamin C level status.

Methods: This study was a prospective, interventional, parallel, randomized and open label study. Sixty patients diagnosed as a case of major depressive disorder in accordance to ICD-10 criteria were enrolled after taking a written informed consent. Two clinical scales namely Hamilton depression rating scale (HDRS) and clinical global impression-illness severity (CGI-S) scale were used for assessment and monitoring.

Results: Vitamin C deficient subjects had relatively severe disease as assessed by HDRS and CGI-S scales. A highly significant ($p < 0.001$) reduction was observed in HDRS and CGI-S scores in vitamin C deficient and insufficient groups with supplementation. A statistically insignificant ($p > 0.05$) reduction was seen in HDRS and CGI-I scores in vitamin C sufficient group while also showing a comparatively milder disease.

Conclusions: Vitamin C deficiency was found to have a direct relation with severity of illness, as those patients who had insufficient and sufficient vitamin C levels at recruitment were found to exhibit milder symptoms compared to those who were vitamin C deficient. With treatment, greater improvement was observed in those patients who were deficient at the outset.

Keywords: CGI, Depression, HDRS, Vitamin C deficiency

INTRODUCTION

Depression, even though known since ancient times may be considered as a modern disorder acquired with today's fast pace, highly competitive, stressful, and sedentary lifestyle as supported by the high prevalence seen with social network era. While other factors such as environmental, genetic, and personality traits contribute to its etiology in some way or another.¹⁻³ Depression is more syndromal than medical, possessing a cluster of symptoms and signs which reflect common pathophysiology responsible for them. It is not yet fully understood but various theories have been proposed by many individual researchers over the years.⁴

While understanding the pathophysiology of depression in humans the most common neurotransmitters implicated in the process of establishment of depression is serotonin.⁵ With more research it has been found that three neurotransmitters and their mutual balance is considered the cause for depression rather than just serotonergic depletion. Thus dopamine, serotonin and norepinephrine are responsible for different symptoms of depression.⁶ Pharmacotherapy of depression chiefly focuses on serotonin and norepinephrine neurotransmitters along with dopamine modulation reserved for resistant cases of major depressive disorders. SSRI as a monotherapy is considered first-line therapy for clinical management of depression nowadays.⁷ Even after showing better efficacy than other

groups of antidepressant drugs, sometimes not all patients get benefitted from SSRIs alone and at other times the side-effects makes it hard to continue the patients on similar regimen.

Therefore, search of a newer better class of drugs or adjuvant drugs to increase efficacy of existing drugs are on. Recent studies have shown that an increase in oxidative stress as well as an imbalance between oxidants and anti-oxidant radicals leading to macromolecular damage, also have some major role in pathophysiology of depression. This can be attributed to that fact that decrease in antioxidants are a frequent finding in depression.⁸ Oxidative stress consists of damage to tissue leading to cell death because of reactive oxygen species and other free radicals generated during aerobic metabolism. 8-OHdG is an oxidized derivative of deoxyguanosine and is a marker for DNA lesion. F2-isoprostanes is an oxidized derivative of arachidonic acid, and is useful to assess oxidative stress in vivo and is a marker of lipid peroxidation in particular. It has been implicated that a clear increase in these markers is seen in patients suffering from major depressive disorder.⁹

A significant role of the association of oxidative stress with major depressive disorder has been established. Thus, the pharmacological approach in treatment has changed its focus to effective utilization of antioxidants which can protect the macromolecules from the damage. Amongst the array of anti-oxidants available to us, vitamin C has a pivotal role as studies have shown a decrease in its level in depressive patients.¹⁰

This study was conducted to evaluate the role of vitamin C as an adjuvant in major depressive patients who are vitamin C deficient and insufficient in comparison to those who had sufficient levels.

METHODS

This study was a prospective, interventional, parallel, comparative, randomized and open label study, conducted in the Department of Pharmacology, Government Medical College, Amritsar in collaboration with Department of Psychiatry, Guru Nanak Dev Hospital, Amritsar. This study was registered prospectively with Clinical Trials Registry- India (CTRI) with reference number-CTRI/2019/06/019598.

Study design and participants

The study was comprised of 60 diagnosed cases of major depressive disorder defined according to ICD-10, of either sex, between the age group of 18-65 years who fulfilled the inclusion criteria in the outpatient department (OPD) of Department of Psychiatry at Guru Nanak Dev hospital attached to Government Medical College, Amritsar. Patients were randomly divided into 2 groups of equal distribution, one group received paroxetine (up to 50 mg/day) along with vitamin C (1000 mg/day) in two equal

divided doses and the other group received paroxetine (up to 50 mg/day) only, which acted as a control for the duration of 12 weeks. Benzodiazepines were added as and when required for symptoms like sleep disturbance and anxiety. Randomization was carried out with the help of free computer-generated randomization software. An informed consent was taken from all the patients enrolled after explaining the study particulars in easily understandable vernacular language.

The study was conducted in accordance to good clinical practice and approval of Institutional Ethics Committee (No.019/TH/D-26/2018 Batch) was taken before the start of the study.

Inclusion criteria

The inclusion criteria for the study was the following-patients of either sex between the ages of 18-65 years, diagnosed cases of major depressive disorder according to ICD-10 visiting psychiatry OPD, who were willing to join the study after giving the informed consent.

Exclusion criteria

The exclusion criteria for the study was the following-patients with any organic cause of depression, any major comorbidities like cardiovascular, renal and hepatic diseases and any other psychiatric comorbidities. Special physiological conditions like pregnancy, and lactation were excluded. Patient not willing to give consent for the study.

Patients using drugs that may interact with vitamin C like-bishydroxycoumarin and with prooxetine like- thioridazine, pimozone, tamoxifen, warfarin, NSAIDs, alcohol, tryptophan, monoamine oxidase inhibitors like- linezolid and intravenous methylene blue, triptans, lithium, fentanyl, tramadol, cimetidine, other SSRIs and SNRIs, phenobarbital, phenytoin, imipramine, risperidone and any other potential drug interaction.

Methodology

After noting demographic details of patients, they were subjected to detailed history taking, asking specifically about any past and family psychiatric history, addiction history and sleep pattern. Recording of baseline vitals and general physical examination were done. The adverse effects reported by the patients were recorded. Each finding and lab results were duly filled in the preformed performa. For assessment of serum vitamin C levels- blood sample (at least 2 ml) was taken maintaining aseptic conditions using a disposable syringe from peripheral vein in the vacuum gel clot tube, and then was transported in blood transport box with 4 ice packs maintaining the temperature at +20°C. Precaution was taken to avoid haemolysis of whole blood sample. The serum sample thus obtained were then analysed using high-performance liquid chromatography (HPLC).

Procedure

For test samples: The human blood sample was withdrawn and plasma was collected by centrifugation at 4000 rpm for 10 minutes. Then, the supernatant was collected and acetonitrile was added in equal amounts to that of plasma for deproteinization. The system was further vortexed for 2 minutes and kept aside for 15 minutes. After 15 minutes, the plasma was again centrifuged at 4000 rpm for 10 minutes to remove the precipitates. The supernatant was collected, filtered through a 0.2 µm filter and subjected to HPLC analysis.

For standard curve: The human blood sample was withdrawn and plasma was collected by centrifugation at 4000 rpm for 10 minutes. Then, the supernatant was collected and acetonitrile was added in equal amounts to that of plasma for deproteinization. The system was further vortexed for 2 minutes and kept aside for 15 minutes. After 15 minutes, the plasma was again centrifuged at 4000 rpm for 10 minutes to remove the precipitates. The supernatant was collected, and filtered through a 0.2 µm filter.

Accurately weighed 10 mg of ascorbic acid was transferred in 10 ml volumetric flask and volume makeup was done to 10 mL to make 1 mg/ml stock solution. Further, dilutions of 25, 50, 100, 200, and 300 µg/ml were made from the above stock solution. Each dilution 1 ml was mixed with 100 µl of plasma and subjected to HPLC analysis. The AUC for each dilution obtained was plotted against concentration to make the calibration curve of carboplatin in plasma.

Mobile phase: 1% Formic acid:acetonitrile:methanol in ratio 2.5:50:47.5 ml. The flow rate was kept at 1.4 ml/minute.

Stationary phase: RASIL C18 100A, 250 mm, 46 mm, 5 µm

Lambda max: The maximum wavelength at which the sample was analysed was 245 nm.

Assessment scale

Hamilton depression rating scale (HDRS) and clinical global impression-illness severity (CGI-S) scale was assessed at baseline and then every 4th, 8th and 12th week on follow ups. CGI-I (global improvement) was assessed on first follow up (week 4) and then on every follow up till end of the study (week 12).

HDRS is one of the most widely used measures of severity of depression done clinically by using 17-item questionnaire originated in 1960 and treated as gold standard. The 17 items consist of depressed mood, feelings of guilt, suicide, insomnia-early, insomnia-middle, insomnia-late, work and activities, retardation, agitation, anxiety-psychic, anxiety-somatic, somatic symptoms- GI, somatic symptoms, genital symptoms, hypochondria,

weight loss either A or B and insight. Scoring is done based on severity of symptoms where 0 being no symptoms. Eight item has maximum scoring till 2 those are- insomnia early, insomnia middle, insomnia late, somatic symptoms-gastrointestinal, somatic symptoms-general, genital symptoms, loss of weight, and insight. Nine items has maximum scoring till 4 those are- depressed mood, feeling of guilt, suicide, work and activities, retardation, agitation, anxiety-psychic, anxiety-somatic and hypochondrias. Thus the total score adds up to be 52. Based on final score the overall severity of depression is measured as, 10-13 is mild, 13-17 is moderate and more than 17 is severe depression.¹¹⁻¹³

CGI is brief scale for assessment of clinician's view of the patient's global functioning prior to and after starting a certain medication. It consists of CGI-S (illness severity) and CGI-I (global improvement) after treatment from observer's point of view based on his clinical experience and based on these the efficacy index is obtained. Both questions carry a rating of 0-7, where 0 is not assessed, 1 is normal, 2 is borderline mentally ill, 3 is mildly ill, 4 is moderately ill, 5 is markedly ill, 6 is severely ill and 7 is among the most extremely ill for the CGI-S scale and where 0 is not assessed, 1 is very much improved, 2 is much improved, 3 is minimally improved, 4 is no change, 5 is minimally worse, 6 is much worse and 7 is very much worse for the CGI-I scale. It correlates well with longer more tedious rating instruments used in psychiatric illnesses such as Hamilton depression rating scale. Each component is rated separately on every interaction and the CGI-I scores generally tracks with the CGI-S.^{14,15}

Statistical analysis

The efficacy and safety data were collected and recorded for each patient. Analysis was done on the basis of data obtained from patients who completed 12 weeks of study phase. Data generated from study was tabulated with respect to all the parameters at baseline, 4th, 8th and 12th week and represented in the form of graph. All the quantitative data were expressed as mean±SD for each variable. The serum vitamin C level, HDRS and CGI scores were analysed using unpaired student "t" test for intergroup comparison. Paired student "t" test was used for analysis of change from baseline to 12 weeks. A 'p' value of <0.05 was taken as statistically significant, and that of <0.001 as highly significant.

RESULTS

In this prospective, interventional, randomized, parallel comparative, and open label study, sixty patients were enrolled and were randomly divided into two groups A and B, which were comparable (p>0.05) with mean age 39.36±13.12 and 39.73±11.12 respectively.

Number of patients with various levels of vitamin C at baseline corresponding with depression severity accordingly to HDRS and CGI-S are shown in Figure 1.

Vitamin C deficient being <11 µmol/l and insufficient being 11-28 µmol/l with >28 µmol/l being sufficient levels.

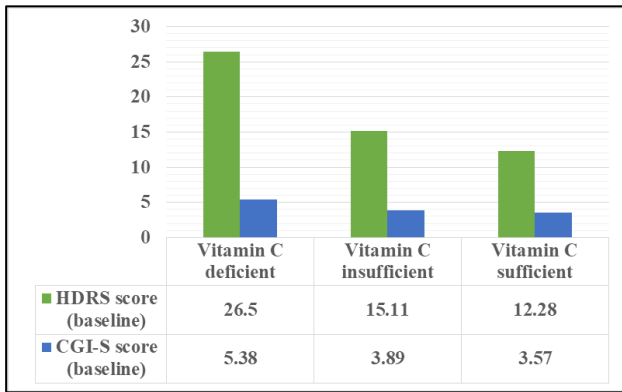


Figure 1: Baseline severity according to vitamin C deficiency status.

HDRS scores amongst the various levels of vitamin C shows different levels of improvement at the end of 12 weeks as shown in Table 1. A highly significant ($p < 0.001$) reduction in HDRS scores occurs in vitamin C deficient and insufficient groups, whereas a statistically insignificant ($p > 0.05$) reduction in HDRS scores was seen in vitamin C insufficient group. Even though vitamin C deficient group shows maximum severity at the beginning in comparison.

On the other hand, CGI-S scores shows significant improvement amongst all groups at the end of 12 weeks as shown in Table 2. A highly significant ($p < 0.001$) reduction in CGI-S scores occurs in vitamin C deficient and insufficient groups, whereas a statistically significant ($p < 0.05$) reduction in CGI-S scores was seen in vitamin C sufficient group. Again, vitamin C deficient group shows maximum severity of disease at the start of the study.

Table 1: Comparative change in HDRS scores according to deficiency status.

HDRS scores					
Vitamin C status	Baseline	Week 12	Mean change	% change	P value
Deficient (n=44)	26.5±8.3	9.84±3.53	-16.66	-62.86	<0.001
Insufficient (n=09)	15.11±1.27	7±3.87	-8.11	-53.67	<0.001
Sufficient (n=07)	12.28±0.75	7.71±3.86	-4.57	-37.21	0.06

Table 2: Comparative change in CGI-S scores according to deficiency status.

CGI-S scores					
Vitamin C status	Baseline	Week 12	Mean change	% change	P value
Deficient (n=44)	5.38±0.97	3.11±0.54	-2.27	-42.19	<0.001
Insufficient (n=09)	3.89±0.33	2.44±0.53	-1.45	-37.27	<0.001
Sufficient (n=07)	3.57±0.53	2.56±0.53	-1.01	-28.29	<0.05

Table 3: Comparative change in CGI-I scores in according to deficiency status.

CGI - I scores					
Vitamin C status	Week 4	Week 12	Mean change	% change	P value
Deficient (n=44)	3.09±0.94	2.18±0.87	-0.91	-29.44	<0.001
Insufficient (n=09)	3.44±0.73	2.56±0.53	-0.88	-25.58	<0.05
Sufficient (n=07)	4±0.57	3±0.82	-1	-25	0.07

Lastly, CGI-I applicable from the first follow up i.e. 4th week shows different levels of improvement amongst the groups at the end of 12 weeks as shown in Table 3. A highly significant ($p < 0.001$) reduction in CGI-I scores occurs in vitamin C deficient group and a significant reduction ($p < 0.05$) occurs insufficient group, whereas a statistically insignificant ($p > 0.05$) reduction in CGI-I scores was seen in vitamin C sufficient group. Thus, even after having more severe disease to begin with, vitamin C deficient group shows better improvement in comparison to patients with less severe disease but with sufficient vitamin C levels.

DISCUSSION

In this prospective, interventional, randomized, parallel comparative, and open label study, the role of vitamin C as an adjuvant in major depressive patients who are vitamin C deficient in comparison to who has sufficient levels was being evaluated. Both group A and B were randomly distributed and were comparative in terms of age and baseline parameters to avoid selection bias.

Vitamin C levels show three cut offs. Levels >28 µmol/l are considered sufficient levels, <11 µmol/l as deficient

and 11-28 $\mu\text{mol/L}$ as insufficient.¹⁶ The prevalence of vitamin C deficiency was 73.33% (44 out of 60 subjects) in our study population out of which, 21 were recruited in group A and 23 in group B. 9 (6; 3) out of 60 (15%) patients were vitamin C insufficient, while remaining 7 (3; 4) out of 60 (11.67%) were vitamin C sufficient. Similar prevalence of 75% vitamin C deficiency was reported by a cross sectional study conducted by Chiplonkar et al on Western Indian population and prevalence of 73.9% of vitamin C deficiency in North Indian population was reported in a two centre population based study conducted by Ravindran et al, however, only 45.7% prevalence was reported for South Indian population.^{17,18} Much less prevalence was seen in American population as reported by Hampl et al in 2004 in a survey as 17% in males and 12% in females.¹⁹

HDRS scores reduction at the end of 12 weeks in vitamin C deficient (62.86%) and vitamin C insufficient (53.67%) patients was highly significant ($p < 0.001$). On the other hand, the HDRS reduction in vitamin C sufficient patients was statistically insignificant ($p = 0.06$) during same period. A highly significant ($p < 0.001$) reduction in CGI-S scores in vitamin C deficient (42.19%) and insufficient patients (37.27%) was also observed at the end of 12 weeks. A statistically significant ($p < 0.05$) CGI-S reduction (28.29%) is also shown by vitamin C sufficient patients. CGI-I scores were evaluated at week 4 i.e. first follow up in this present study and yielded a highly significant ($p < 0.001$) reduction by week 12 in vitamin C deficient patients (29.44%). Vitamin C insufficient patients also showed a statistically significant ($p < 0.05$) reduction (25.58%), whereas the vitamin C sufficient patients showed statistically insignificant ($p = 0.07$) reduction (25%). These results seem to suggest a milder disease in patients with sufficient vitamin C levels compared to those who were vitamin C deficient at recruitment. Gupta et al conducted a study in 2014 in Western Uttar Pradesh, India and concluded that depressed patients have vitamin C deficiency and can be benefitted by vitamin C supplementation.²⁰

A better clinical improvement, as reflected by assessment scales used in our study, was observed in those patients who were vitamin C deficient at the outset. Vitamin C supplementation with paroxetine was very well tolerated with no adverse effect reported by the treatment group during 12 weeks of study duration.

CONCLUSION

Present study concludes that vitamin C has adjuvant role in pharmacotherapy of major depressive disorder. Prevalence of vitamin C deficiency was found to be 73.33% in the study population with a direct relation with severity of illness, as those patients who had non-deficient vitamin C levels at recruitment were found to exhibit milder symptoms compared to those who were vitamin C deficient. With treatment, greater improvement was observed in those patients who were deficient at the outset.

In terms of safety, vitamin C was very well tolerated by the patients with no adverse event reported during the duration of the study. Thus based on results of present study we recommend vitamin C supplementation to major depressive patients at least with deficiency status.

ACKNOWLEDGEMENTS

We acknowledge the voluntary enrolment of study participants and their co-operation in the conduct of the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. *J Affect Disord.* 2012;140(3):205-14.
- Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. *BMC Psychiatr.* 2014;14:107.
- Horwitz AV. How an Age of anxiety became an age of depression. *Milbank Q.* 2010;88(1):112-38.
- Paykel ES. Basic concepts of depression. *Dialogues Clin Neurosci.* 2008;10(3):279-89.
- Cowen PJ, Browning M. What has serotonin to do with depression? *World Psychiatr.* 2015;14(2):158-60.
- Moret C, Briley M. The importance of norepinephrine in depression. *Neuropsychiatr Dis Treat.* 2011;7(Suppl 1):9-13.
- Undurraga J, Baldessarini RJ. Direct comparison of tricyclic and serotonin-reuptake inhibitor antidepressants in randomized head-to-head trials in acute major depression: systematic review and meta-analysis. *J Psychopharmacol Oxf Engl.* 2017;31(9):1184-9.
- Liu T, Zhong S, Liao X, Chen J, He T, Lai S, et al. A meta-analysis of oxidative stress markers in depression. *PLoS One.* 2015;10(10):e0138904.
- Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology.* 2015;51:164-75.
- Bajpai A, Verma AK, Srivastava M, Srivastava R. Oxidative stress and major depression. *J Clin Diagn Res JCDR.* 2014;8(12):CC04-7.
- Obeid S, Abi Elias Hallit C, Haddad C, Hany Z, Hallit S. Validation of the Hamilton depression rating scale (HDRS) and sociodemographic factors associated with Lebanese depressed patients. *L'Encephale.* 2018;44(5):397-402.
- Rohan KJ, Rough JN, Evans M, Ho SY, Meyerhoff J, Roberts LM, et al. A protocol for the hamilton rating scale for depression: item scoring rules, rater training,

- and outcome accuracy with data on its application in a clinical trial. *J Affect Disord.* 2016;200:111-8.
13. Worboys M. The Hamilton rating scale for depression: the making of a “gold standard” and the unmaking of a chronic illness, 1960-1980. *Chronic Illn.* 2013;9(3):202-19.
 14. Busner J, Targum SD. The clinical global impressions scale. *Psychiatr Edgmont.* 2007;4(7):28-37.
 15. Dunlop BW, Gray J, Rapaport MH. Transdiagnostic clinical global impression scoring for routine clinical settings. *Behav Sci.* 2017;7(3).
 16. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. *JAMA.* 1999;281(15):1415-23.
 17. Ravindran RD, Vashist P, Gupta KS, Young SI, Maraini G, Camparini M, et al. Prevalence and risk factors for vitamin C deficiency in North and South India: a two centre population based study in people aged 60 years and over. *PLoS One.* 2011;6(12).
 18. Chiplonkar SA, Agte VV, Mengale SS, Tarwadi KV. Are lifestyle factors good predictors of retinol and vitamin C deficiency in apparently healthy adults? *Eur J Clin Nutr.* 2002;56(2):96-104.
 19. Hampl JS, Taylor CA, Johnston CS. Vitamin C deficiency and depletion in the United States: The Third National Health and Nutrition Examination Survey, 1988 to 1994. *Am J Public Health.* 2004;94(5):870.
 20. Gupta P, Haria J. Relationship between depression and vitamin c status: a study on rural patients from Western Uttar Pradesh in India. *Int J Sci Stud.* 2014;1(4):37-9.

Cite this article as: Aggarwal K, Singh NR, Bala N, Singh M. Major depressive disorder: association with vitamin C levels and role of vitamin C supplementation in pharmacotherapy. *Int J Basic Clin Pharmacol* 2021;10:403-8.