ROLE OF ASCORBIC ACID IN IMPROVING MOOD IN PATIENTS WITH DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: To find out the effect of ascorbic acid in improving mood in patients undergoing treatment for depression.

Methodology: A randomized control trial was conducted at Department of Psychiatry, Mercy Teaching Hospital, Peshawar, involving 102 subjects equally divided into two groups: interventional (IG) and control (CG). The IG received antidepressants (+ Psychological support) and daily Ascorbic Acid 500 mg, while the CG received antidepressants (+ Psychological support). Plasma ascorbic acid levels were carried out in addition to Hamilton Depression Rating Scale (HAM-D). Data analysis was performed using SPSS 26 and paired sample t test was used as the test of significance. This trial was registered at Australian New Zealand Clinical Trial Registry (ACTRN12624000525583).

Results: The baseline HAM-D score for the overall sample was 21.81±6.16 and ascorbic acid level of 1.27±0.45, approaching the lower limit of the normal range. Following a three-month treatment, the mean HAM-D score was 13.39±7.39 (p=0.000), and ascorbic acid level of 1.97±0.69 (p=0.000). In the IG, baseline values were 20.92±6.49 for HAM-D and 1.32±0.48 for ascorbic acid, and the end-study values were 14.35±8.29 for HAM-D and 1.94±0.65 for ascorbic acid, with a significant p-value of 0.000. Similarly, at baseline, the HAM D-CG value was 23.14±5.68 and ascorbic acid value was 1.25±0.41, which was 12.53±6.46 for HAM-D and 1.99±0.74 for ascorbic acid at end-study, with a significant p-value of 0.000 for both.

Conclusion: Combination of ascorbic acid and antidepressants (+ Psychological support) showed a similar level of effectiveness compared to the use of antidepressants (+ Psychological support).

Keywords: Ascorbic Acid; Depression; Hamilton Depression Rating Scale (HAM-D); Antidepressants.

INTRODUCTION

Depression stands out as the predominant factor contributing to years spent with disability.[1] Despite its prevalence, there is limited knowledge regarding the underlying causes, hindering the ability to shape informed treatment strategies.[2] The monoamine hypothesis has been the prevailing theory for nearly five decades, suggesting that major depressive disorder results from a deficit in monoamine neurotransmitters. Despite utilizing various monoamine-focused treatments to address depressive symptoms, the rates of remission remain notably low, often falling below 60%, as noted by Berton and Nestler.[3] Observations from clinical reports highlight significant connections between stressors, particularly those of prolonged duration, and the onset of various diseases, primarily through cellular oxidative stress.[4] Therefore, the administration of antioxidant supplements may prove beneficial in addressing certain diseases associated with oxidative stress.[5,6] This underscores the necessity for new drug classes. Consequently, there is a crucial need to investigate preventive measures and address modifiable risk factors for depression. Research has shown a connection between a lack of ascorbate and heightened depressive symptoms, suggesting that ascorbate may contribute to the regulation of mood.[7] Despite the numerous therapeutic choices for managing depression, merely 30% of patients attain remission, even when receiving appropriate antidepressant treatments and psychiatric monitoring. Additionally, a frequent occurrence is a decline in therapeutic effectiveness with each successive treatment, leading to treatment-resistance.[8]

The effectiveness of ascorbic acid in treating depressive disorders has been seen in a patient over a 14-day period.[9] Clinical evidence suggests a potential connection between the deficiency of ascorbic acid and depressive symptoms; however, the underlying mechanism remains less understood.

Depression, a widespread and impactful medical condition, is fortunately manageable; nevertheless, a significant proportion of patients do not exhibit positive responses to current medications. This lack of responsiveness is partly linked to an incomplete comprehension of the molecular circuits that form the basis of depression.[10]

The emotional state of mind is considered to be regulated by micronutrient levels, given the capacity of nutrients in brain organization and activities. The purpose of the present study was to analyze the association between ascorbic status and mood situation in individuals diagnosed with depression. This research focuses attention on the remarkable ability of ascorbic acid advancing to advance innovative treatment approaches for depression.

METHODOLOGY

This randomized control trial was conducted at Department of Psychiatry and Behavioural Sciences, Mercy Teaching Hospital, Peshawar, involving 102 subjects equally divided into two groups: interventional (IG) and control (CG). The study got approval from the Advanced Studies and Review Board and ethical committee of Khyber Medical University, Peshawar. The interventional group received conventional treatment (antidepressants ± psychological support) along with Ascorbic Acid 500mg daily for three months, whereas the control group received only conventional treatment (antidepressants ± psychological support). Adhering to aseptic protocols, approximately 5 ml of blood was drawn through venepuncture from the peripheral vein, utilizing a disposable syringe from patients of both groups. The Hamilton Rating Scale for Depression (HAM-D) served as the primary assessment tool to gauge the severity of depression.

Medication adherence was inquired about by the patients and/or caregivers, and assessments were conducted at baseline and after twelve weeks. The study's protocol adhered to the "Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines" (Figure 1).

The mean difference in HAM-D scores was compared between the two groups. The measure of full remission (HAM-D lower than 8) was differentiated between the interventional and control groups. Peripheral blood samples were collected from each patient, with a subsequent blood draw scheduled after 12 weeks of antidepressant treatment (± Psychological support). Laboratory investigations included the assessment of ascorbic acid levels by high performance liquid chromatography.

Statistical analysis was conducted using SPSS v.26. To assess the differences between the two groups, a paired sample t-test was used, considering a value of less than 0.05 as statistically significant.

This trial was registered at Australian New Zealand Clinical Trial Registry (ACTRN12624000525583).

RESULTS

Table 1 shows the distribution of sample by age and gender.

Table 2 displays the statistical analysis of baseline and end-study variables within the complete study population, consisting of the HAM-D scores and ascorbic acid levels, revealing that after a three month follow up, there was a significant improvement, p-value < 0.001 in the mean scores of both the variables (p-value = 0.000).

Table 3 compares the HAM-D scores and ascorbic acid levels of all interventional group patients, who have been prescribed antidepressants (+ Psychological support) plus Ascorbic acid at their first visit. The end-study HAM-D scores show a significantly improved status with a p-value of 0.000. The blood ascorbic acid level at baseline was closer to the lower limit i.e., 0.6mg/dl but the scores were increased at end-study, which was closer to the upper limit of normal levels i.e., 2mg/dl with a significant p-value of 0.000.

Table 4 compares the HAM-D scores and ascorbic acid levels of all control group patients, who have been prescribed antidepressants (+ Psychological support) at their first visit. The end-study HAM-D scores show a significantly improved status with a p-value of 0.000. The blood ascorbic acid level at baseline was closer to the lower limit i.e., 0.6mg/dl but the scores were increased at end-study, which was closer to the upper limit of normal levels i.e., 2mg/dl with a significant p-value of 0.000.

Table 5 compares the HAM-D scores and ascorbic acid levels of IG and CG after three month follow up. The depression score was improved in both groups as compared to the baseline; however, the p-value was non-significant (p=.298). Similarly, the ascorbic acid level in interventional group patients was comparatively less than ascorbic acid levels of control group patients, and there was no statistical difference in both the groups (p=.779).

DISCUSSION

The combined utilization of ascorbic acid and antidepressants demonstrated comparable efficacy when compared to the use of antidepressants alone. However, there is confirmation indicating a connection between ascorbic acid deficiency and adverse effects on mood and cognition. The blood levels of ascorbic acid linked to depression and cognitive impairment exceed those typically associated with clinical manifestations of scurvy.[11]

Table 1: Age and gender distribution (n=102)

Parameters	Age (in years)		Total	Gender		Total
	18-30	31-45		Males	Females	
Frequency	54	48	102	36	66	102
Percentage	52.9	47.1	100%	35.3	64.7	100%

Table 2: Paired sample statistics in complete sample (n=102)

Varaibales	Baseline	End-Study	t- value	p-value
HAM-D	21.81 + 6.16	13.39 + 7.39	8.28	0.000
Ascorbic Acid	1.27 + 0.45	1.97 + 0.69	-8.49	0.000

Table 3: Comparison of HAM-D score and ascorbic acid levels in the interventional group (n=51)

Variables	Baseline	End-Study	t-value	P-value
HAM-D score	20.92 + 6.49	14.35 + 8.29	3.90	0.000
Ascorbic acid levels	1.32 + 0.48	1.94 + 0.65	-5.95	0.000

Table 4: Comparison of HAM-D score and ascorbic acid levels in the control group (n=51)

Variables	Baseline	End-Study	t-value	p-value
HAM-D score	23.14 + 5.68	12.53 + 6.46	8.58	0.000
Ascorbic acid levels	1.25 + 0.41	1.99 + 0.74	-6.23	0.000

Table 5: Comparison of HAM-D scale and ascorbic acid levels in post-tests of both groups

Variables	End Study-IG	End Study-CG	t-value	p-value
HAM-D	14.35 + 8.29	12.53 + 6.46	1.05	0.298
Ascorbic acid levels	1.94 + 0.65	1.99 + 0.74	-0.28	0.779

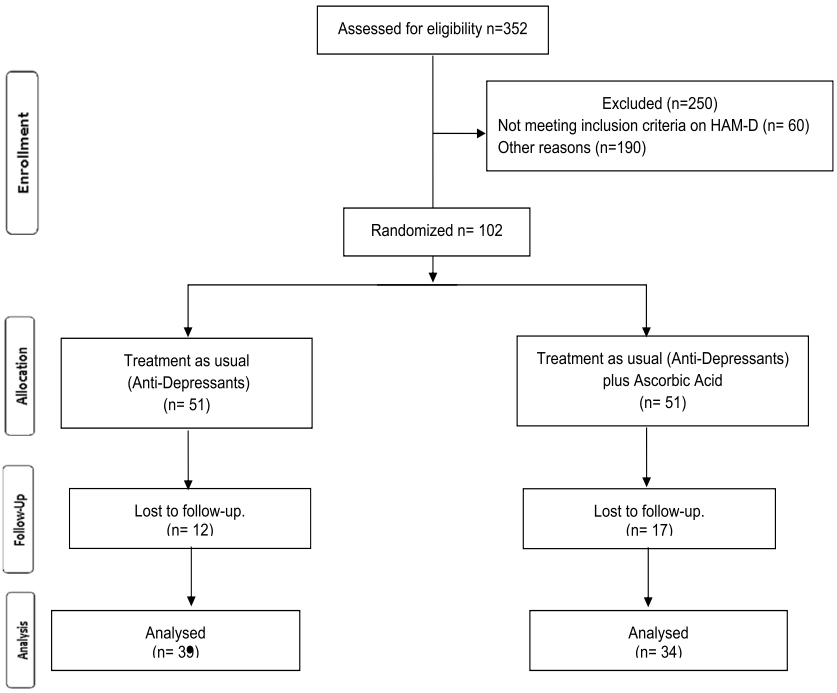

Figure 1: Flowchart depicting the patients' progression in this trial according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Depressive states are associated with a decline in plasma ascorbic acid levels, which is similar to the findings of our study.[12,13]

Sim et al conducted a randomized controlled trial (RCT) where they compared a placebo with ascorbic acid supplementation. The results revealed a significant increase in attention and work absorption with a distinct trend toward improvement in fatigue and comprehensive work engagement due to ascorbic acid supplementation. However, there was no observed effect on mood and serum concentrations of BDNF. Notably, in the Stroop color-word test, subjects receiving ascorbic acid supplementation exhibited better performance compared to those in the placebo group.[14]

Currently, there is experimental evidence suggesting the potential positive influence of dietary ascorbic acid intake on depression.[15] Dulabi et al discovered that ascorbic acid provides protection against weight gain and reduces both ghrelin-induced hyperphagia and depressive-like behavior induced by chronic social isolation stress in CIS rats.[16] Similarly, Fraga et al explored the potential of ascorbic acid to elicit a rapid antidepressant-like response in mice undergoing chronic corticosterone (CORT) administration.[17] Moreover, the results from a previous study suggest that ascorbic acid may impact anxiety-related behavior in social environments and stress-induced anorexia in SMP30/GNL knockout mice.[18] It is important to note that these findings are incongruent with our results.

The connection between ascorbic acid and depression was initially established through the observation of clinical manifestations resulting from a deficiency in ascorbic acid.[19] Several clinical studies have investigated ascorbic acid as a supplementary therapy for depression.[20, 21] The outcomes of studies investigating the impact of ascorbic acid on depression in both healthy individu-

als and those with certain medical conditions present conflicting results. In a randomized double-blind, placebo-controlled trial spanning 14 days and involving 42 healthy young adults, sustained-release ascorbic acid at a dose of 3,000 mg/day demonstrated an increase in mood. Additionally, ascorbic acid was observed to reduce subjective psychological stress.[21] Another randomized double-blind, placebo-controlled trial focused on depressed shift workers, where a daily dose of 500 mg of ascorbic acid significantly decreased depression severity ($p < 0.018$).[22] Another clinical trial that explored the efficacy of ascorbic acid as an adjunctive treatment for depression focused specifically on pediatric patients. The study involved 12 patients in the group receiving fluoxetine (10 to 20 mg/day) along with ascorbic acid (1,000mg/day), while a control group of 12 patients received fluoxetine (10 to 20 mg/day) along with a placebo. Over the course of three months, the depression scores, evaluated through the Children's Depression Rating Scale (CDRS), exhibited a more substantial decrease in the treatment group compared to the control group. However, within the same trial, the Clinical Global Impression (CGI) scale did not indicate the efficacy of ascorbic acid in treating patients with depression.[23] Several encouraging findings highlight the positive impact of ascorbic acid in animal models of depression. However, in a randomized, single-blind, placebo-controlled trial, the addition of ascorbic acid supplements did not lead to a reduction in depression among patients with type 2 diabetes.[24]

CONCLUSIONS

The findings of our study suggest that the combination of ascorbic acid and antidepressants (+ Psychological support) have a similar level of effectiveness compared to the use of antidepressants (+ Psychological support).

FUTURE IMPLICATIONS

The perspective for practicing ascorbic acid as an adjuvant treatment for depression manifests potential, but it comes with several challenges that need attention. Firstly, there is a considerable demand for new medications suitable for daily use. Secondly, research efforts should focus on uncovering the specific mechanisms by which ascorbic acid operates in clinical settings. Thirdly, additional investigations are necessary to comprehend the functions of ascorbic acid, particularly in identifying crucial pathophysiological dysfunctions associated with depressive conditions. Furthermore, extensive studies on the prolonged effects and safety profiles of ascorbic acid therapy, especially about multiple doses are imperative.

Future research on ascorbic acid should prioritize its pharmacology, determining optimal administration profiles for sustained therapeutic benefits by evaluating safety profiles in various dosage formulations, and identifying novel biomarkers to distinguish ascorbic acid responses within specific patient cohorts.

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Author's Contribution

SW conceived the idea and designed the study. MI helped in designing the study, data analysis and helped in the write up of the manuscript. SF and MI helped in the write up of the manuscript and supervised the study. All authors made substantial intellectual contributions to the study.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.