International Journal of Health Sciences and Research
Vol.11; Issue: 1; January 2021
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

A Prospective, Randomized, Open Label Study to Assess the Role of Vitamin C as an Adjuvant to Paroxetine in Pharmacotherapy of Major Depressive Disorder

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ABSTRACT

Background: Oxidative stress has long been implicated as a cause for depression. Thus the present study was conducted with the aim of the study to evaluate the role of Vitamin C an antioxidant as an adjuvant to paroxetine in the pharmacotherapy of major depressive disorder.
Methods: This study was a prospective, interventional, randomized, parallel comparative and open label study. Sixty patients diagnosed as a case of major depressive disorder in accordance to ICD-10 criteria between the age group of 18-65 years of either sex were enrolled after taking a written informed consent. Group A (treatment) was given oral vitamin C 500 mg twice daily along with oral paroxetine, whereas group B (control) was given only oral paroxetine for the duration of 12 weeks.
Results: A highly significant ($p < 0.001$) reduction in Hamilton depression rating scale (HDRS) scores was observed in both the groups A and B individually. Clinical global impression (CGI) scale also shows highly significant ($p < 0.001$) reduction in the groups. A highly significant ($p < 0.001$) intergroup difference, with better results shown by group A was also observed.
Conclusions: Vitamin C supplementation was well tolerated and showed better outcomes when used as an adjuvant with paroxetine in comparison to standard paroxetine alone.

Keywords: Major depressive disorder, vitamin C, paroxetine, HDRS, CGI.

INTRODUCTION

First described as melancholia by Hippocrates, depression is an ailment of mind. Depression, the term, is derived from the Latin verb *deprimere* meaning "to press down". Although, melancholia was a broader term comprising fear, anger, obsessions, dejections and delusions, depression more or less concentrates on the mood and comes with an array of mental disorders dealing with different aspects of mental health. Depression may be considered as a modern disorder acquired with today's fast pace, highly competitive, stressful, and sedentary lifestyle while other factors such as environmental, genetic, and personality traits contribute to its etiology in some way or another.[1]

The current modalities for the pharmacotherapy of major depressive disorder comprise of selective serotonin reuptake inhibitors (SSRI) as first-line

drugs. Selective norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), and less commonly used monoamine oxidase inhibitors (MAOI) are other major groups of drugs used.[2] Even though SSRIs have revolutionized the pharmacotherapy of depression there is still a big gap to be filled due to high side-effects and 3 – 6 weeks delay in clinical benefits and lack of efficacy shown by many patients. Due to these reasons search for newer better treatments are still on. Several models support the evidence of involvement of monoamine transmission systems in depression and vitamin C has shown to act as a neuromodulator. Preclinical models showing antagonist effects of vitamin C at glutamatergic N-methyl-D-aspartate (NMDA) receptors also adds in support of vitamin C as an anti-depressant.[3]

Vitamin C has a primary antioxidant action in the central nervous system and helps maintain the functioning of several processes by scavenging reactive oxygen and nitrogen species.[4] Other than antioxidant effects, vitamin C also acts as a co-factor in the synthesis of various neurotransmitters particularly catechol-amines like dopamine and norepinephrine. It also facilitates the reaction by acting as co-substrate for the dopamine-β-monooxygenase enzyme which is the key enzyme in the process of conversion of dopamine to norepinephrine.[5,6] As norepinephrine has established role in pathophysiology of depression and more and more studies are supporting the theory of oxidative stress as being another culprit in this disease, vitamin C role in treatment of the same gets further support.

The present study was undertaken to explore adjunctive role of vitamin C when given along with paroxetine (SSRIs) in the treatment of major depressive disorder.

MATERIALS AND METHODS

This study was a prospective, interventional, randomized, parallel comparative 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 was 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 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 were 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 paroxetine like- thioridazine, pimozide, 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. Laboratory investigations (hemoglobin, TLC, DLC, FBS, LFT & RFT) were done and recorded on day 1 of study (baseline record) and were repeated at 12^{th} week of drug administration (end point record) on the days of their follow ups. The adverse effects reported by the patients were recorded. Each finding and lab results were duly filled in the preformed performa.

Assessment scale:

Hamilton Depression Rating Scale (HDRS) and Clinical Global Impression – illness severity (CGI – S) scale was assessed at baseline and then every 4^{th}, 8^{th} and 12^{th} 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. The 17 items consists of depressed mood, feelings of guilt, suicide, insomnia-early, insomnia-middle, insomnia-late, work & 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.

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. Each component is rated

separately on every interaction and the CGI – I scores generally tracks with the CGI – S.

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, 4^{th}, 8^{th} and 12^{th} week and represented in the form of graph. All the quantitative data were expressed as mean ± SD for each variable. The baseline parameters (such as haemoglobin, TLC, DLC, FBS, LFT and RFT) of all the patients in two groups were analysed by unpaired student "t" test. 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

Table 1 shows the socio-demographic division of the patients participated in this study amongst the two groups A and B. In this study there were slight female predominance seen along with urban dominance of participants. Married patients make up the majority of the study participants population.

Table 1: Socio-demographic distribution in the study groups.

Demographic characteristics		Group A	Group B	Total
Age (mean±SD)		39.36±13.12	39.73±11.12	60
Gender	Male	15	13	28
	Female	15	17	32
Nativity	Urban	18	20	38
	Rural	12	10	22
Literacy	Illiterate	07	01	08
	Primary school	07	08	15
	Secondary school	10	15	25
	College and above	06	06	12
Employment status	Employed	13	15	28
	Unemployed	17	15	32
Marital status	Single	07	05	12
	Married	22	22	44
	Widow	00	02	02
	Divorced	01	01	02

Table 2 shows the study parameters of both groups at baseline (mean±SD) were comparable with statistically insignificant difference between two groups (p > 0.05). (TLC – total leucocyte count, DLC – differential leucocyte count, FBS – fasting blood sugar, AST – aspartate transaminase, ALT – alanine transaminase, HDRS – Hamilton depression rating scale, CGI-S – clinical global impressions-illness severity)

Table 2: Baseline parameters of study groups

Parameters		Group A	Group B	P value
Haemoglobin (mg/dL)		13.13±1.48	14.01±1.45	0.36
TLC (cell/mm^3)		7150±1892.41	7153±1504.41	0.98
DLC (%)	Neutrophils	63.66±6.94	62.46±7.13	0.52
	Lymphocytes	32.3±7.24	33.5±6.09	0.46
	Monocytes	2.46±1.73	2.1±1.51	0.39
	Eosinophils	1.5±0.93	1.3±0.75	0.36
	Basophils	0.56±0.77	0.43±0.62	0.47
FBS (mg/dL)		94±11	89.16±11	0.14
AST (units/L)		21.23±8.71	22.13±9.56	0.73
ALT (units/L)		30.17±15.13	28.23±8.06	0.46
Serum creatinine (mg/dL)		0.9±0.2	0.96±0.18	0.18
Blood urea (mg/dL)		17.04±5.6	15.19±5.3	0.13
Serum vitamin C (µmol/L)		14.69±11.42	14.97±13.4	0.92
HDRS		24.93±9.93	21.33±7.94	0.16
CGI - S		5.13±1.11	4.76±1.13	0.29

Figure 1 shows highly significant ($p < 0.001$) reduction in scores of Hamilton depression rating scale (HDRS) at week 4 in group A and statistically significant ($p < 0.05$) reduction in group B. Further highly significant ($p < 0.001$) reduction is seen in both groups A and B at week 8 and 12. A highly significant ($p < 0.001$) differences was seen in HDRS scores of groups A and B at week 12.

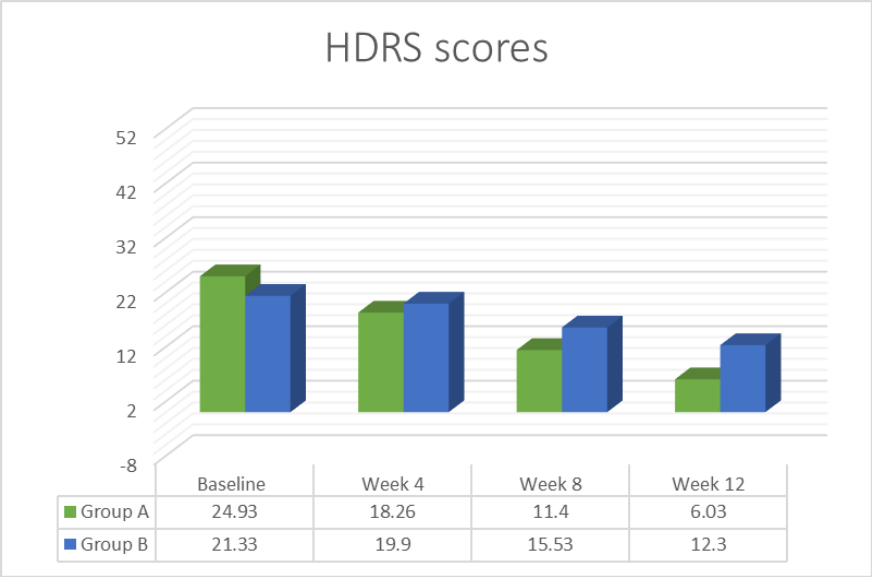

Figure 1: Comparative change in HDRS score during study duration in study groups.

Figure 2 shows highly significant ($p < 0.001$) reduction in scores of Clinical Global Impression – illness severity (CGI – S) at week 4 in group A and statistically significant ($p < 0.05$) reduction in group B. Further highly significant ($p < 0.001$) reduction is seen in both groups A and B at week 8 and 12. A highly significant ($p < 0.001$) differences was seen in CGI – S scores of groups A and B at week 12.

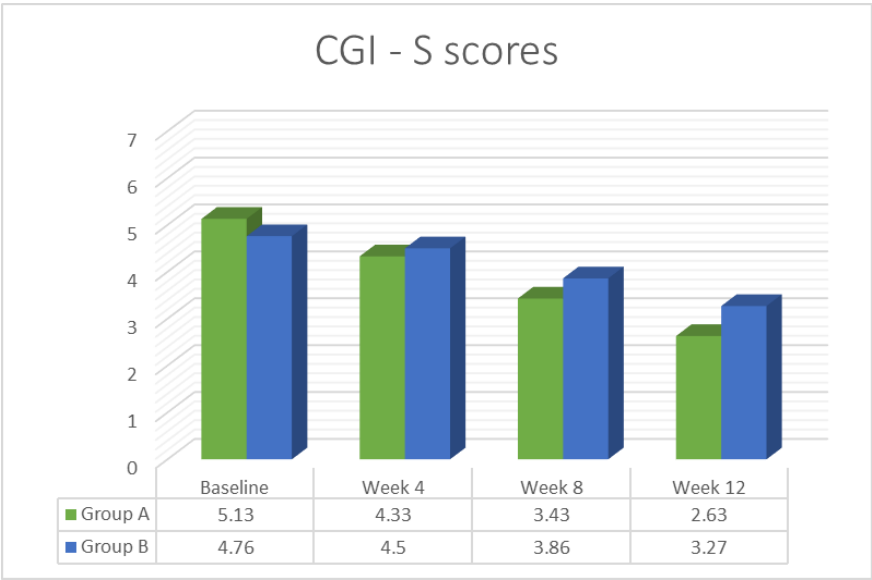

Figure 2: Comparative change in CGI – S score during study duration in study groups.

Figure 3 shows statistically significant ($p < 0.05$) reduction in scores of Clinical Global Impression – global improvement (CGI – I) at week 8 in groups A and B. Further highly significant ($p < 0.001$) reduction is seen in both groups A and B at week 8 and 12. A highly significant ($p < 0.001$) differences was seen in CGI – I scores of groups A and B at week 12. Note :

CGI – I is applicable from first follow up onwards.

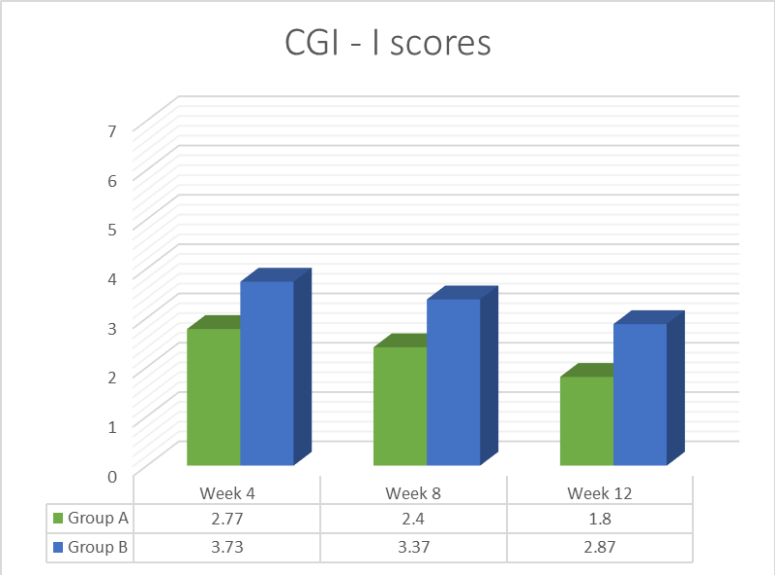

Figure 3: Comparative change in CGI – I score during study duration in study groups.

DISCUSSION

Depression is a syndromal disorder characterise by behavioural symptoms in the form of instability of mood, unprovoked anger, hopelessness, feeling of doom and lose of interest in activities previously perceived to be pleasurable. Decades of research done for the better understanding of its pathophysiology supports theory of serotonergic imbalance above other imbalance neurotransmitter theories like dopaminergic and noradrenergic, thus justifying the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression. But due to individualized symptoms and lack of proper understanding of the pathophysiology of this disorder, not every patient experiences the desired benefits from SSRIs monotherapy. Therefore, the search for various add on therapies and adjunctive treatment has been going on for the last decade.

In this prospective, interventional, randomized, parallel comparative, and open label study, the adjunctive effect of vitamin C with paroxetine have been studied in patients with major depressive disorder. Sixty patients between the ages of 18 – 65 of either sex suffering from the major depressive disorder diagnosed in accordance to ICD-10 criteria were recruited in the study and were randomized into two groups of thirty patients each. Group A was given oral vitamin C (500 mg) twice daily along with oral paroxetine (up to 50 mg/day), whereas group B received only oral paroxetine (up to 50 mg/day) for 12 weeks.

The mean age of the study subjects in two groups was comparable (Table 1). Most of them were middle aged a trend seen in other studies on depression like Stephanie M. Gorka et al. in 2019 in U.S.A. and Gemma Lewis et al. in 2019 in UK.[7,8] There was a slight overall female predominance (53.33%) compared to males (46.67%) recruited in the study (Table 1). Variable reports are there as far as gender preponderance is concerned. A female predominance is seen with the patient group in the epidemiology of this disorder as supported by study done by Colleen E Carney et al. in 2017 in Toronto with 107 participants with 68% of them being female, whereas a slight gender difference with male predominance is seen in an open non-comparative study done by H R Chaudhry et al. in Pakistan and a study done in 2009 by Jared P. Dempsey.[9,10,11] Nativity of the patients in this present study were predominantly urban (63.33%) (Table 1), which differs from an epidemiology study done by Subramani Poongothai et al. in

2017, where higher predominance is seen in rural areas (61.4%).[12]

In this study, patients with secondary school (41.67%) education and unemployed status (53.33%) makes up the majority (Table 1). This pattern of distribution has also been reported by other authors. In a randomized, double blind, placebo controlled trial conducted by Emma del Carmen Macías-Cortés et al. in 2015 in Mexico shows maximum participants with secondary school education (80%) and unemployed (61%)[13], and in a pilot study done by Gretchen A. Brenes et al. in 2007, it was 83% with secondary school education.[14] However, it differs from a study done by Gemma Lewis et al. in 2019 in UK, where the employed patients were more making up 66% of total and another study done by Karen A. Ertel et al. in 2011 in U.S.A. shows 67.33% employed patients amongst recruited.[8,15] Marital status of the patients in this study shows predominance of married patients (73.33%) (Table 1). Similar findings are seen in an Indian cross-sectional study conducted by A. P. Rajkumar et al. in 2009 by 51.4% and in a study done by Karen A. Ertel et al. in 2011 in U.S.A. by 60%.[15,16]

Baseline biochemical investigations seen in this study shows a homogenous population randomly distributed between both the groups A and B with statistically insignificant difference ($p > 0.05$) (Table 2). At the end of the study, these parameters remain within the normal range in both the groups and no statistically significant difference is observed ($p > 0.05$).

Serum vitamin C levels in this study at baseline were comparable amongst both the groups A (14.69 ± 11.4 µmol/L) and group B (14.97 ± 13.4 µmol/L) (Table 2). Most of the patients had vitamin C levels lower than the normal range (>28 µmol/L). This trend has been reported by some other Indian studies on depressive disorder as well. Prerana Gupta et al. (10.23 µmol/L) and Mukesh Dherani et al. (13.7 ± 13.75 µmol/L) reported very low baseline serum vitamin C levels.[17,18] However, higher baseline serum vitamin C levels are reported in similar studies conducted in other regions like Libya by Suhera M Aburawi et al. (25.27 ± 1.53 µmol/L) and in New Zealand by Juliet M. Pullar et al. (58.2 ± 18.6 µmol/L).[19,20] Group A patients took vitamin C daily as an adjuvant to paroxetine, which was reflected in a highly significant ($p < 0.001$) increase by 288.43% in serum vitamin C levels at the end of 12 weeks. This is an indicator of a good compliance of prescription order by the patients during study period. The intergroup difference between the group A and B in serum vitamin C levels at the end of 12 weeks was highly significant ($p < 0.001$) with a mean difference of 41.97 ± 1.55 µmol/L.

Baseline HDRS scores were observed to be 24.93 ± 9.93 in group A and 21.33 ± 7.94 in group B whereas CGI – S scores were group A (5.13 ± 1.11) and group B (4.76 ± 1.13). Both the groups were statistically comparable ($p > 0.05$) thus insuring no selection bias in the process of recruitment. Baseline scores indicate severity of the disease at recruitment. The severity of depression amongst the study participants were comparable to other studies as conducted by Maurizio Fava et al. (22.8 ± 4.6) and Ali Sahraian et al. (21.4 ± 4.1).[21,22]

Group A showed a decrease by 26.75% in HDRS score at 4 weeks, 54.27% at 8 weeks and 75.81% at 12 weeks ($p < 0.001$). A similar trend was also observed in group B and HDRS score decreased by 6.7% ($p < 0.05$), 27.19% ($p < 0.001$) and 42.33% ($p < 0.001$) at 4^{th}, 8^{th} and 12^{th} weeks respectively (Figure 1). Group A thus recorded a greater comparative reduction in the HDRS score at all the three observation points. Statistically, the intergroup differences between group A and B in terms of reduction in total HDRS scores at week 12 was observed to be highly significant ($p < 0.001$) with a mean difference of 6.27 ± 0.09. Adjuvant vitamin C therapy, therefore, seems better in terms of achieving lower HDRS scores compared to paroxetine alone.

Suhera M Aburawi et al. in 2014 conducted a clinical study with a variety of antidepressants few of them being paroxetine, fluoxetine, clomipramine, etc. to evaluate vitamin C adjuvant role and showed the highly significant ($p < 0.001$) final HDRS score reduction in vitamin C group to be 5.46 ± 1.06 and Mostafa Amr et al. in 2013 conducted a pilot study in paediatric population with fluoxetine to assess role of vitamin C as adjuvant and showed the highly significant ($p < 0.001$) final reduction in Children's Depression Rating Scale (CDRS) paediatric equivalent of HDRS to be 9.0 ± 1.50 in vitamin C group, similar to our study (6.03 ± 1.96).[23,19] However, Ali Sahraian et al. in 2015 conducted a clinical trial with citalopram along with vitamin C v/s citalopram alone and showed the highly significant ($p < 0.001$) final HDRS score reduction in both groups but a statistically insignificant ($p > 0.05$) inter group difference concluding no adjuvant benefit of vitamin C with citalopram.[21] It is different though with studies done on other SSRIs like fluoxetine as referred above which show results similar to ours as regards HDRS score.

CGI – S scores at the baseline was observed to be 5.13 ± 1.11 in group A and a highly significant ($p < 0.001$) reduction at week 4 (15.59%), at week 8 (33.14%) and at week 12 (48.73%) was observed. Group B also showed a significant ($p < 0.05$) reduction from the baseline (4.76 ± 1.13) at week 4 (5.46%) and a highly significant ($p < 0.001$) reduction at week 8 (18.91%) as well as at week 12 (31.30%) (Figure 2). The intergroup difference in terms of CGI – S scores reduction was observed to be highly significant ($p < 0.001$) with mean difference of 0.64 ± 0.03.

CGI – I scores are applicable from the first follow up onwards. CGI – I scores of group A at week 4 (1^{st} follow up) was observed to be 2.77 ± 0.81 and at week 8 a statistically significant ($p < 0.05$) reduction was observed (13.35%) and at week 12 a highly significant ($p < 0.001$) reduction (35.02%) was observed. In group B at week 4 score was 3.73 ± 0.74 and at week 8 significant ($p < 0.05$) reduction (14.21%) and at week 12 highly significant ($p < 0.001$) reduction (28.42%) was observed (Figure 3). At the end of 12 weeks, the intergroup differences was observed to be highly significant ($p < 0.001$) with mean difference of 1.07 ± 0.19.

None of the study reporting adjuvant role of vitamin C has used CGI scale except for Mostafa Amr et al. which was a small pilot study and has reported an insignificant ($p > 0.05$) decrease in CGI scores.[23] The validity of this scale (both CGI-S and CGI-I) however, has been confirmed by a number of other studies on antidepressants.

Suresh Durgam et al. in a phase 3, double blind, randomized, placebo controlled study done in 2018 with vilazodone in major depressive patients showed a highly significant ($p < 0.001$) reduction in CGI – S scores at end point (2.9 ± 1.2) and an open label, 52 week study conducted by Anita H Clayton et al. in 2014 with aripiprazole plus SSRI in major depressive patients showed CGI – S scores at the end of the study (2.2 ± 0.6), that is comparable with the present study (2.63 ± 0.49).[24,25]

A randomized, placebo controlled, double blind study conducted by Atul R Mahableshwarkar et al. in 2015 with vortioxetine in major depressive patients showed CGI – I scores reduction at week 8 to be 2.35 ± 0.09.[26] And in a double blind, randomized controlled trial conducted by George I. Papakostas et al. in 2018 CGI – I scores observed at week 8 and 12 were 2.19 ± 0.1 and 1.95 ± 0.1 respectively.[27] A phase III, multi-centre, randomized, double-blind, fluoxetine-referenced study conducted by Karen L. Weihs et al. in 2018 observed CGI – I scores at week 8 to be 2.13 ± 0.86.[28]

Our study thus reflects a clear advantage of using vitamin C as adjuvant with paroxetine showing an edge over control group consistently across all the three assessment scales used viz. HDRS, CGI – S and CGI – I. Vitamin C

supplementation with paroxetine was very well tolerated. It seems to enhance antidepressant efficacy of paroxetine without compromising its safety profile.

CONCLUSION

The effect of vitamin C as an adjuvant was studied in major depressive disorder patients who were on standard background therapy of paroxetine. It can be concluded that vitamin C supplementation was well tolerated and showed better clinical outcomes (in terms of reduction in HDRS & CGI scores) when used as an adjuvant in comparison to standard paroxetine alone.

With respect to the safety, both the groups were comparable. The study had few limitations with respect to sample size, being open label and single centric study. Further studies may be done to evaluate the adjuvant role of vitamin C with other anti-depressants.

ACKNOWLEDGEMENTS

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

DECLARATIONS

Funding: *No funding sources*
Conflict of interest: *None declared*
Ethical approval: *The study was approved by the Institutional Ethics Committee*

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How to cite this article: Aggarwal K, Singh NR, Bala N et.al. A prospective, randomized, open label study to assess the role of vitamin C as an adjuvant to paroxetine in pharmacotherapy of major depressive disorder. *Int J Health Sci Res.* 2021; 11(1): 163-173.

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