

Role of vitamin D supplementation as adjunctive therapy to escitalopram in patients of major depressive disorder: a 8 week prospective, randomized, interventional, clinical study

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ABSTRACT

Background: Depression is a major public health problem and occurs in persons of all ages, and is associated with increased morbidity, soaring costs for treatment and reduced productivity and quality of life. Vitamin D is involved in numerous brain processes including neuroimmunomodulation, neuroprotection, neuroplasticity, regulation of neurotrophic factors, and making it biologically plausible to be associated with depression. Aim of the present study is to compare the therapeutic effects of vitamin D given along with escitalopram versus escitalopram given alone in patients with major depressive disorder.

Methods: In this prospective, randomized, interventional clinical study, 60 patients with a diagnosis of major depressive disorder based on ICD-10 criteria were randomly assigned into two groups, one group received 60000IU vitamin D3 weekly plus 10 mg escitalopram OD daily while the other group received escitalopram 10 mg OD daily alone for 8 weeks. Depression severity was assessed at 2-week intervals using the 24-item Hamilton Depression Rating Scale (HDRS). Serum 25(OH) vitamin D levels were measured in all the patients at baseline and after intervention.

Result: Fifty nine patients completed the trial. Depression severity based on HDRS decreased significantly after intervention, with a significant difference between the two groups. The vitamin D3+escitalopram combination was significantly better than escitalopram alone from the fourth week of treatment.

Conclusion: Role of vitamin D in mood disorder and its dietary supplementation is effective as an adjuvant treatment along with SSRIs in depressive disorders, especially in vitamin D deficient patients.

Keywords: Major depressive disorder, Selective serotonin reuptake inhibitor, Vitamin D3

INTRODUCTION

Depression is a major public health problem and associated with significant disability, mortality and healthcare costs. It is projected that depression will become leading cause of disease burden and morbidity by 2030.¹ Vitamin D is a unique neurosteroid hormone that may have an important role in the development of depression. Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been implicated in the pathophysiology of depression.²

Vitamin D also regulates serotonin synthesis via transcriptional activation of the tryptophan hydroxylase gene and impacts innate immunity and the production of pro inflammatory cytokines that in turn influence mood by activating the stress response. Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development making it biologically plausible that this vitamin might be associated with depression and that its supplementation might play an important part in the treatment of depression.²⁻⁵

Animal studies have confirmed the fundamental role of vitamin D in the development of the brain.⁶ Due to paucity of Indian data, we aimed to study the role of vitamin D3 as adjunctive therapy to escitalopram in patients of depression and to determine whether serum Cholecalciferol within the normal range could improve symptoms in such patients.

METHODS

A 8 weeks short term (March 2019 to April 2019) prospective, randomized, interventional, open label clinical study to evaluate the therapeutic effects of vitamin D as adjunctive therapy to escitalopram in patients with major depressive disorder was conducted in the Department of Pharmacology and Department of Psychiatry, FH Medical College and Hospital, Agra, Uttar Pradesh. Approval for the study was obtained from the Institutional Ethical Committee. Each subject signed an informed consent statement prior to participation and could withdraw without prejudice at any time.

Patients of age group 18-65 years and of both genders attending to psychiatry outpatient department during the study period diagnosed with first episode depression (drug naïve) as per criteria of the 10th edition of the International Classification of Diseases (ICD-10) along with hypovitaminosis D (< 25ng/ml) were included in the study. Exclusion criteria included patients with history of taking antidepressants and vitamin D supplements before commencement of study, suffering from suicidal thoughts, substance abuse, patients taking any other psychiatric drug, pregnant and lactating mothers and patients suffering from renal, hepatic and cardiovascular disorders. A total of 60 patients comprised of sample size and by simple randomization they were divided into two groups (Group A=30 & Group B=30). Group A (n=30) patients were given

escitalopram 10mg/daily orally along with vit. D3 60000 IU weekly orally for 2 months. While Group B (n=30) patients received only escitalopram 10mg/daily. No other psychiatric drug therapy was given to patients. Compliance was measured by counting escitalopram pills and measuring serum 25(OH) D.

Analysis was performed on the 59 patients who completed the study. One patient was lost to follow-up from the fifth week of treatment in group B while no patient was lost in group A. A complete preliminary clinical examination was conducted on all subjects included in the study to rule out any chronic ailments referred to in the exclusion criteria. Socio- demographic data regarding age, sex, rural/urban, educational status and socio economic background were recorded in the case report form. Body weight, BMI, HDRS score and serum 25(OH) D levels were also recorded at baseline. Patients were subsequently monitored and reassessed after 2, 4, 6 and 8 weeks. During each follow up visit HDRS score was evaluated and serum 25(OH)D3 levels were measured to compare with baseline values. Further, all adverse events at each visit or associated side effects during treatment were recorded in case report form. Statistical analysis of the data was performed by using the SPSS windows version 20. Mean values of change in HDRS score were compared between two groups by using unpaired 't' test.

RESULTS

Demographic details of the enrolled patients are shown in the Table 1. Females suffering with depression were more as compared to males. Most of the depressive patients belonged to rural background and were illiterate having low socioeconomic status. There was no statistically significant difference between the two groups ($p>0.05$), thus the groups were comparable.

Table 1: Demographic Details of Both the Groups.

Parameters	Group A (n=30)	Group B (n=30)	Chi square value	P value
Male/Female	5/25	3/27	0.5769	0.44
Urban/Rural	12/18	10/20	0.2871	0.59
Literate/Illiterate	14/16	13/17	0.0673	0.79
Low socioeconomic status/middle class	18/12	15/15	0.6061	0.43

Table 2: Baseline Parameters of Both the Groups.

Parameters	Group A	Group B	t value	P value
Age (years)	40.45±5.65	39.78±6.78	0.0759	0.67
Body weight (kg)	68.35±4.31	69.65±2.33	0.2653	0.79
BMI (kg/m ²)	25.32±2.33	26.12±3.78	0.1802	0.85
Serum 25(OH)D (ng/dl)	20.65±1.78	19.66±2.99	1.5583	0.63
HDRS Score	30.31±7.33	31.65±7.35	0.798	0.45

Comparison of baseline values is shown in Table 2. There were no significant differences between the two groups with regard to age, body weight, body mass index (BMI), serum 25(OH)D3 and HDRS score ($p>0.05$). Moreover, the BMI did not change significantly during the intervention period ($p>0.05$). Comparative evaluation of the HDRS score between the two groups is shown in Table

3. The serum 25(OH)D increased significantly in the Escitalopram+vitamin D3 group (A) from 20.65 ± 1.78 to 40.85 ± 5.14 ($p<0.001$). HDRS score values at weeks 2, 4, 6 and 8 showed that the vitamin D3-Escitalopram combination was significantly better than escitalopram alone from the fourth week of treatment ($p=0.0007$).

Table 3: Comparison of HDRS Score Between the Two Groups.

HDRS Score	Group A	Group B	t value	P value
Baseline	30.21±7.33	31.65±7.35	0.7598	0.45
2 weeks	27.43±4.60	27.23±4.60	1.6843	0.097
4 weeks	19.43±4.76	23.35±3.69	3.564	0.0007
6 weeks	15.67±4.27	20.00±2.37	4.4904	0.0001
8 weeks	11.48±4.65	18.25±3.17	6.5889	0.0001

DISCUSSION

The present study is a randomized, interventional, 8 weeks trial designed to determine the effects of vitamin D3 supplementation in patients with major depressive disorder, and we find that vitamin D3 is safe and effective as an adjunctive treatment to Escitalopram in major depressive disorder.

While there are few studies investigating the association between depression and vitamin D deficiency, but there is paucity of randomized controlled trial that can show beneficial effect of vitamin D3 with Escitalopram in mood disorders.^{7,8} In another open trial, it was shown that a single 300,000 IU dose of vitamin D3 could decrease depression severity in elderly patients with major depression.⁹ While other trial in older women has shown that a single annual dose of 500,000 IU of vitamin D3 for 3-5 years had no benefit on mood.¹⁰

Some Studies showed that serum levels of 25-hydroxy-vitamin D3 in patients with mental disorders are significantly lower compared with healthy controls.^{11,12} Clinical studies show that people with high levels of vitaminD3 have a lower risk of depression.¹³ However; these findings are difficult to interpret, as reduced vitamin D could be a consequence of depressive behaviours. Vitamin D supplementation has been shown to relieve depressive symptoms in patients with low levels.¹⁴ It is important to note that these studies evaluated the effects of vitamin D supplementation alone, not compared with antidepressants.

The exact mechanism of how vitamin D is associated with depression is unclear. A number of mechanisms may involve in association of depression and low level of vitamin D. These include the vitamin D receptor and 1-alpha-hydroxylase and vitamin D pathway components in neural differentiation, neuron function, neurotransmitter

synthesis and inhibition of apoptosis and regulation of cell membrane formation.^{15,16}

25-hydroxy-vitamin D3 can affect nerve growth factor, acetyl cholinesterase, tryptophan, testosterone, thyroid hormone and tyrosine hydroxylase messenger RNA synthesis, which are associated with depression.¹⁷ The classic monoamine neurotransmitter hypothesis suggests depression is associated with 5-HT, dopamine (DA) and norepinephrine (NE). It has been demonstrated that the expression of genes involved in the transfer of vitamin D affects nerves and stimulates the release of tyrosine hydroxylase, which plays a role in catecholamine biosynthesis.¹⁸ Vitamin D also improved the activity of glutathione in the cerebral cortex and striatum, and increased glutamate cysteine ligase (GCLM), glutathione reductase, which improved glutathione synthesis and played an important role in anti-oxidation.¹⁹ Thus vitamin D improves depression via suppressing antioxidant injury.

CONCLUSION

Authors can correlate role of vitamin D in mood disorder and its dietary supplementation is effective as an adjuvant treatment along with escitalopram in mood disorders, especially in vitamin D deficient patients. Vitamin D supplementation may be the most convenient and low-cost treatment method to improve the quality of life.

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