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# THE EFFECT OF VITAMIN D SUPPLEMENTATION WITH SERTRALINE IN PATIENTS OF MAJOR DEPRESSIVE DISORDER: A 12 WEEKS PROSPECTIVE INTERVENTIONAL STUDY

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**ABSTRACT** Depression is a major public health problem and associated with significant disability, mortality and healthcare costs. Vitamin D is a unique neurosteroid hormone that may have an important role in the development of depression.

A 12 weeks short term prospective, randomized, interventional, open label clinical study was conducted to evaluate the therapeutic effects of vitamin D as adjunctive therapy to sertraline in patients with major depressive disorder. A total of 60 patients comprised of sample size and by simple randomization they were divided into two groups (groupA=30 & group B=30). Group A (n=30) patients were given sertraline 50mg/daily orally along with vit. D 60000 IU weekly orally for 3months. While group B (n=30) patients received only sertraline 50mg/daily. Depression severity was assessed at 3, 6, 9 and 12 weeks using the 24-item Hamilton Depression Rating Scale. We find that vitamin D is safe and effective as an adjunctive treatment to Sertraline in major depressive disorder

**KEYWORDS :**

## 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]

Vit D also regulates serotonin synthesis via transcriptional activation of the tryptophan hydroxylase 2 gene [3] and impacts innate immunity and the production of proinflammatory cytokines that in turn influence mood by activating the stress response[4]. Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development [5] 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.

Animal studies have confirmed the fundamental role of vitamin D in the development of the brain[6]. To our knowledge no interventional study in India have evaluated the role of Vit D with sertraline in major depressive disorders.

The aim of the present study is to establish the adjuvant role of vitamin D with sertraline in patients of depression and to determine whether serum Cholecalciferol within the normal range could improve symptom in such patients.

## MATERIAL AND METHODS

A 12 weeks short term (Oct 2018 to Dec 2018) prospective, randomized, interventional, open label clinical study to evaluate the therapeutic effects of vitamin D as adjunctive therapy to sertraline in patients with major depressive disorder was conducted in the Department of Pharmacology and Department of Psychiatry, S. N. Medical College and Hospital, Agra, Uttar Pradesh. Approval for the study protocol 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) falling under the group (F32) as per criteria of the 10th edition of the International Classification of Diseases (ICD-10) along with hypovitaminosis D( <12ng/ml) were included in the study. Exclusion criteria included patients with history of taking antidepressants or vitamin D supplements before commencement of study, suffering from suicidal thoughts, substance abuse, patients taking any other psychiatric drug, pregnant and lactating mothers, 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 (groupA=30 & group B=30). Group A (n=30) patients were given sertraline 50mg/daily orally along with vit. D 60000 IU weekly orally for 3months. While group B (n=30) patients received only sertraline 50mg/daily. No other psychiatric drug therapy was given to patients. Compliance was measured by counting sertraline pills and measuring serum 25(OH) D.

Depression severity was assessed at 3, 6, 9 and 12 weeks using the 24-item Hamilton Depression Rating Scale. 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, socio-economic status, family history etc were recorded in the case report form. HDRS score and serum 25(OH) D levels were also recorded at baseline.

Patients were subsequently monitored and reassessed after 3, 6, 9 and 12weeks. During each follow up visit HDRS score was evaluated and serum 25(OH) D 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 Table1.Female patients suffering with depression along with hypovitaminosis D were more as compared to males. Most of the depressive patients belonged to rural background and were illiterate having low socioeconomic status.

**Table1: Demographic Details of Both The Groups**

| Parameters | Group A (n=30) | Group B (n=30) | Chi square value | P value |
|---|---|---|---|---|
| Male / Female | 6/24 | 4/26 | 0.5669 | 0.45 |
| Urban / Rural | 11/19 | 11/19 | 0.2971 | 0.59 |
| Literate /Illiterate | 13/17 | 13/17 | 0.0673 | 0.79 |
| Low socioeconomic status/middle class | 18/12 | 15/15 | 0.6061 | 0.43 |

Comparison of baseline values is shown in Table 2. There was no significant differences between the two groups with regard to age, body weight, body mass index (BMI), serum 25(OH)D and HDRS

score. Moreover, the BMI did not change significantly during the intervention period ($p > 0.05$).

**Table2: Baseline Parameters of Both The Groups**

| Parameters | Group A | Group B | t value | P value |
|---|---|---|---|---|
| Age (years) | 34.45±5.65 | 34.78±6.78 | 1.036 | 0.8474 |
| Body weight (kg) | 71.35 ± 5.31 | 73.65 ± 5.33 | 1.8378 | 0.07 |
| BMI (kg/m²) | 26.12 ± 2.13 | 26.92 ± 3.58 | 0.9768 | 0.299 |
| Serum 25(OH)D (ng/dl) | 12.15 ± 1.78 | 10.16 ± 2.99 | 1.4983 | 0.13 |
| HDRS Score | 30.31 ± 7.33 | 31.65 ± 7.35 | 0.798 | 0.45 |

Comparative evaluation of the HDRS score between the two groups is shown in Table3. The serum 25(OH)D increased significantly in the Sertraline + vitamin D group from 11.65 ± 1.78 to 40.85 ± 10.14 ($p < 0.001$). Values at weeks 3, 6, 9 and 12 showed that the vitamin D–Sertraline combination was significantly better than sertraline alone from the fourth week of treatment (p=0.0007).

**Table3: Comparison Of HDRS Score Between The Two Groups**

| | 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:

Our study is a randomized, placebo-controlled 12 weeks trial designed to determine the effects of vitamin D supplementation in patients with major depressive disorder, and we find that vitamin D is safe and effective as an adjunctive treatment to Sertraline in major depressive disorder.

We find few studies[7,8] investigating the association between depression and vitamin D deficiency, but no randomised controlled trial that can show beneficial effect of vitamin D with Sertraline in mood disorders.

In a recent open trial, it was shown that a single 300,000 IU dose of vitamin D could decrease depression severity in elderly patients with major depression.[9] In another 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 vitamin D have a lower risk of depression.[13] However, these findings are difficult to interpret, as reduced vitamin D could be a consequence of depressive behaviors. 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 mechanism 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, acetylcholinesterase, 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.

In conclusion we can correlate role of vitamin D in mood disorder and its dietary supplementation is effective as an adjuvant treatment along with sertraline 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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