Research Article

Role of vitamin B supplementation with Fluoxetine in treatment of depression: A randomized controlled clinical trial

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Abstract

Objective: To explore the change in antidepressant efficacy of Fluoxetine with vitamin B supplementation. **Methods :** The present study is a Single Centre, Open Label, Active Controlled, Parallel, and Single Period 8- Week study of 53 patients. Patients are divided in to two groups Fluoxetine alone group which contain 26 patients and Fluoxetine plus vitamin B group which contain 27 patients, after recruitment they were followed up and assessed for CG Impression & on HDRS score and for objective assessment. The primary outcome was observed by improvement in HDRS scores. Response to treatment, and Reduction in HDRS score is analyzed by Un- paired t test. **Results**: In study subjects clinically significant improvement was observed in fluoxetine plus neurotropic vitamins group as compared to fluoxetine alone group. However statistical analysis shows different results, unpaired t test when applied for the comparison of outcome in the two related samples, the t observed = 4.000. The t observed value falls out of the acceptance region t reference = 1.717. Therefore the null hypothesis stands valid. **Conclusion:** Fluoxetine plus vitamin B supplementation is not superior to Fluoxetine alone, for moderate to severe cases of mental depression without psychotic symptoms.

Key words: Vitamin B, Fluoxetine, HDRS - Hamilton depression rating score.

Introduction

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration [1]. The worldwide prevalence of clinical depression in the general population is estimated between 3 to 10%, and is increased among individuals with chronic disorders, ranging from 22 to 46% [2]. Prevalence of depression in Indian population is exactly not known but various studies done on Indian population which demonstrate the prevalence of depression in community samples and the prevalence rates have varied from 1.7 to 74 per thousand population [3,4]. Reddy and Chandrasekhar carried out a meta-analysis, which included 13 studies on epidemiology of psychiatric disorders which include 33572 subjects from the community and reported prevalence of depression to be 7.9 to 8.9 per thousand population and the prevalence rates were nearly twice in the urban areas [3]. The findings with regard to prevalence in urban population are in line with the findings of a survey done on the entire adult population of an industrial township, which showed that the prevalence rate for depression to be 19.4 per thousand [5].

Clinical guidelines recommend the use of SSRIs as first-line treatment [6]. Remission rates in the acute phase of treatment are 30-40% and an overall 30% show poor response to anti-depressant monotherapy [7-9]. In such cases, addressing other co-morbid conditions is suggested in addition to upgrading or augmenting anti-depressant doses [6].

Various biological factors play a role in the aetiology of depression [10-12] and vitamin B12 deficiency is one such biological factor [13-14]. There is evidence of

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vitamin B12 deficiency in 5% to 10% of the Dutch population [15], and it is clear from the literature that poor vitamin B12 status is accompanied by an increased prevalence of depressive and other neuropsychiatric disorders [13,16-21].

Vitamin B12 plays an important role in DNA synthesis and neurological function. Its deficiency is associated with hematological, neurological and psychiatric manifestations of which the latter includes irritability, personality change, depression, dementia and rarely, psychosis [22]. Recent literature has identified the links between this vitamin deficiency and depression. High B12 levels in serum are associated with good treatment response; high homocysteine levels which are common in folate / B12 deficiency and in those suffering from depression are associated with poor response to anti depressant treatment [23-25].

B-vitamins including B6 and B12 have known to be important for essential functioning of the one-carbon metabolism in the biosynthesis of monoamine neurotransmitters including serotonin, dopamine, norepinephrine, and epinephrine, all of which are known to affect mood and cognition [26-28].

Role of vitamin B supplementation along with fluoxetine in depression is well known as written in previous text but only a few studies are available to explain this, especially in developing countries like India . Therefore to explore the effect of vitamin B supplementation in depression we planned a randomized controlled study in Indian population.

Material & Methods

This was a Single Centre, Open Label, Active Controlled, Parallel, and Single Period 8- Week study to explore whether Fluoxetine plus vitamins B supplementation , has a better efficacy as compared to Fluoxetine alone.

Subjects & Interventions: Patients was enrolled from outpatient clinics of the department of Psychiatry at MGM medical college and MY hospital Indore. The study subjects were newly diagnosed cases of depression, diagnosed at the Psychiatry OPD, further assessed on the ICD – 10 Criteria [29] & the Hamilton depression rating score for severity of Mental Depression [30-31].

The subjects having moderate to severe depression as per ICD- 10 criteria and having a HDRS ≥ 14, while satisfying the inclusion and exclusion criteria were included in the study.

The recruitment was open ended, initially in the fluoxetine alone arm and later in the fluoxetine plus vitamin B arm, after recruitment they were followed up and assessed for CG Impression & on HDRS and for objective assessment. 53 patients satisfying the inclusion criteria are included in study. Patients are divided in to two groups, Fluoxetine alone group which contain 26 patients and Fluoxetine plus vitamin B group which contain 27 patients.

Additionally, on each follow up they were subjected to General Physical examination followed by Clinical examination and assessment of adverse drug reactions, Compliance with medication and vital parameters of the study.

In our study we use Fluoxetine hydrochloride equivalent to Fluoxetine IP – 20 mg oral capsules once daily to be taken with food. Vitamin B supplementation we used in our study is, NEUROBION FORTE tablets which contains vitamin B1, vit B2, vit B3, vit B6 and vit B12.

Inclusion Criteria

Patient 18 to 65 yrs old with newly diagnosed depression (PSYCHIATRIST'S DIAGNOSIS), moderate to severe on ICD – 10 scale, with a HDRS score ≥ 14, of over 2 weeks duration .

Exclusion Criteria

Patients with following features were excluded.

• Those with psychotic symptoms. • Pregnant / lactating mother. • Had received any antidepressant/ fluoxetine in last 5 weeks. • In need of ECT.	• Untreated HTN , BP ≥ 150/90 • H/o of renal disease / cardiac disease / diabetes /liver disease • With contraindications to fluoxetine. • If subject was incapable of presenting him /her for adequate follow up.

End Point: Reduction in HDRS, to ≤ 10 at 8th - 10th week of follow up, was considered as a satisfactory End Point.

Data Analysis: The primary outcome was improvement in HDR scores. Response to treatment, Reduction in HDRS, is analyzed by Un- paired t test, applied between the two treatment groups. Categorical data is expressed as percentage with its 95% confidence interval. Significance is defined as a two tailed $p< 0.05$.

Ethical Approval: A study protocol was approved by the Ethics Review Committee of MGMC medical college and MY hospital Indore. After explaining the study procedure all patients signed an informed consent form.

Observations & Results

Table No 1: Age (in years, average) wise distribution of patients.

Criteria → Group ↓	Minimum-Maximum	Mean	Standard Deviation	Confidence Interval	P value
Fluoxetine	23- 56	39.66	9.83	20-59.4	**P<0.05**
Fluoxetine plus vitamins B	20-56	35.68	9.86	16-55.4	**P<0.05**

This table shows that the two groups had equal age distribution. The mean age for fluoxetine group is 39.66 where as mean age for fluoxetine and vitamin B group is 35.68.

Table No 2: Sex wise distribution of patients.

Criteria → Group↓	No. of males	No.of females	Ratio (M:F)
Fluoxetine	10	17	**1.0: 1.7**
Fluoxetine plus vitamin B	11	18	**1.0: 1.63**

In study subjects the two groups matched each others for their male to female participation to rule out gender influence/bias.

Table No 3: Hamilton Depression Rating Scores, through the course of study (Mean ±SEM).

At week/ weeks → Group ↓	0 week	2nd week	6th week	8th week
Fluoxetine	22.96 ± 4.9	18.53 ± 7.2	13.30 ± 4.4	6.47 ± 2.3
Fluoxetine plus vitamin B	20.92 ± 3.9	16.90 ± 6.9	10.81 ± 4.8	4.95 ± 1.8

There was sustained reduction in severity of depression in both the groups, based on HDRS assessment scale. The improvements in HDRS scores were consistent throughout the study.

Table No 4: Improvement in Hamilton Depression Rating Scores.

Criteria → Group ↓	Mean HDR Scores at week 0	Mean HDR Scores at week 8	Average improvement in terms of mean HDR Scores	% improvement in terms of mean HDR Scores	t value t reference = 1.717
Fluoxetine	22.96	6.47	16.49	71.8%	**t observed= 4.000**
Fluoxetine plus vitamin B	20.92	4.95	15.97	76.3%	

On statistical analysis, with the help the unpaired t test for the comparison of outcome in the two related samples, the t observed = 4.000. The t observed value falls out of the acceptance region t reference= 1.717. Therefore the null hypothesis stands valid.

Table No 5: Safety data (Adverse drug reactions observed).

Adverse drug reactions	Fluoxetine	Fluoxetine plus vitamin B
No. of subjects	26	27
Gastrointestinal disorders Abd discomfort/ cramps/diarrhoea	1(4.8%)	1(4.16%)
Anorexia	1(4.8%)	0
Psychiatric disorders Insomnia	3(14.4%)	0
Reproductive Systems disorders Sexual dysfunction	0	1(4.16%)
Skin and subcutaneous tissue disorders Skin Rash	0	1(4.16%)
CNS disorders Vertigo	1(4.8%)	3(12.48%)

Discussion

Mental Depression is among the 20 most common causes of morbidity and disability in India, leading to substantial decrease in quality of life and Productivity [32]. Drugs are in vogue to combat mental depression and to elevate mood through modulating the central synaptic neurotransmitter mechanism. The results of clinical study showed that the improvement observed in fluoxetine plus vitamin B group was better as compared to the group treated with fluoxetine alone. However statistical analysis shows different results, upaired t test when applied for the comparison of outcome in the two related samples, the t observed = 4.000. The t observed value falls out of the acceptance region t reference= 1.717. Therefore the null hypothesis stands valid. And it was concluded that, fluoxetine plus vitamin B supplementation is not better in comparison to fluoxetine alone statistically, for moderate to severe cases of mental depression without psychotic symptoms. This observation of the present study is not in conformity with the previous documentation by authors, like Roos D et al, who interpreted that the cerebral abnormalities are a result of vitamin B12 deficiency in gastrectomized patients [33]. Further it has been reported by Hvas AM et al that low plasma level of vitamin B6 was significantly associated with symptoms of depression [34]. Bell IR et al also observed that addition of B1, B2 & B6 to tricyclic antidepressants caused greater improvement in geriatric patients of depression [35].

Several studies have shown that low levels of vitamin B6 and B12 were also related to depressive disorders [36,37,38,39], however, some studies failed to show any relationship between vitamin B12 and depressive symptoms [40,41,42]. Similarly, high intakes of vitamins B6 and B12 have shown to be protective of depressive symptoms in a prospective study [43], but not in others [44, 45]. Thus, the controversial results remained to be elucidated in the future.

Conclusion

Vitamin B supplementation with fluoxetine, does not lead to statistically significant improvement in depressive symptoms in our study group. The possible reasons for non confirmotory results of the study are smaller sample size. Further studies are needed to investigate issues such as which patient groups would be suitable for vitamin and folic acid supplements, what is the proper duration of the therapy, the optimum dose, and the extent to which large doses of vitamins and folic acid supplements are safe. Future studies also need to examine vitamin levels in patients with severe or chronic depression.

Conflict of Interest: The authors declare that they have no conflict of interests.

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