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Effect of omega-3 fatty acids versus 5-hydroxytryptophan as add on therapy to sertraline in controlling suicidal ideation in patients with depression: A comparative study

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Abstract
Background: Omega-3 fatty acids and 5-hydroxytryptophan have been gaining attention as promising alternative treatment for depressive illness. These agents are given as add on treatment to conventional antidepressant drugs. The present study was carried out to evaluate efficacy of omega-3 fatty acids versus 5-hydroxytryptophan as add on therapy in controlling suicidal ideation in depressive patients on sertraline.
Methods: This was a prospective, open label, randomized, parallel group study conducted in department of Psychiatry. Ninety treatment naïve patients (18-65 years age) were divided into 3 groups of 30 each. Group I: Sertraline, Group II: Sertraline plus omega-3 fatty acids, Group III: Sertraline plus 5-hydroxytryptophan. Suicidal ideations were assessed with Beck's scale for suicidal ideation (BSI) at weeks 0, 4 and 8. Data were analyzed using repeated measures ANOVA (SPSS version 20.0). Post hoc analysis was done using Bonferroni test.
Results: Baseline parameters in patients of all groups were comparable. Administration of sertraline resulted in reduction of Beck's scale for suicidal ideation scores as compared to baseline. Addition of omega-3 fatty acids and 5-hydroxytryptophan also showed reduction in BSI scores. Effect of sertraline monotherapy was more as compared to omega-3 fatty acids or 5-hydroxytryptophan as add on therapy, which was statistically significant (p value < 0.05).
Conclusion: sertraline monotherapy was better than both the add-on therapies.
Keywords: Omega-3 fatty acids, 5-hydoxytryptophan, depression, suicidal ideation

1. Introduction

Depressive illness is the most common type of psychiatric illness and globally more than 350 million people of all ages suffer from depression and is associated with significant social and functional impairment.[1] According to WHO, it is estimated that by the year 2020, depression will be the second leading cause of disability throughout the world, trailing behind ischemic heart disease.[2] The burden of depressive disorders is huge. Besides being rampant in the general population, it is also found with other co-morbid disorders, which further increases its burden. Depression has also been associated with increased risk for suicidal ideation. Around 1 million lives are lost every year due to depression according to WHO reports.[3] Major risk factors for suicidal ideation in patients with depressive illness include the sex of an individual, previous history of the illness, genetic predisposition/family history, and chronic or acute stress. The factors that make an individual prone to a depressive episode vary from person to person.[4]

According to a recent review, that the rate of recurrence of major depressive disorder treated in specialized mental health settings was very high (60% after 5 years, 67% after 10 years, and 85% after 15 years) but was significantly lower in the primary care population (35% after 15 years).[5] Depression may become a serious health condition, especially when long lasting and with moderate or severe intensity. It can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Suicide results in an estimated 1 million deaths every year.[3]

The impairment in central monoaminergic function was suggested to be the major cause underlying depressive disorder. The monoamine hypothesis of depression postulates that a functional deficiency of 5-hydroxytryptamine (serotonin) or noradrenaline in brain is the key to the pathology and/or behavioural manifestations associated with depression.[4] Many antidepressant drugs increase synaptic levels of serotonin, and some drugs also enhance the levels of two other neurotransmitters, norepinephrine and dopamine. The observation of this efficacy led to the monoamine hypothesis of depression, which postulates that the deficit of certain neurotransmitters is responsible for the corresponding features of depression.[5]

Sertraline is primarily a selective serotonin reuptake inhibitor (SSRI) and is also a dopamine reuptake inhibitor.[6] Sertraline is indicated for both severe depression and dysthymia, a milder and more chronic variety of depression. Sertraline had much lower rates of adverse effects than these TCAs, with the exception of nausea, which occurred more frequently with sertraline. Overall, sertraline appeared to be more effective than fluoxetine or nortriptyline in the older subgroup.[7]

Now-a-days, omega-3 polyunsaturated fatty acids have been gaining attention as a promising alternative treatment for mood disorders. The essential fatty acids in humans, docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA), are long-chain polyunsaturated fatty acids and must be obtained from diet.[8,9] Most of the studies have found beneficial effects of EPA/DHA combination in depressive illness.[10-12] Apart from antidepressant effects, omega-3 fatty acids have also been found to have broader therapeutic effects, including improvements in adverse impulse control, aggression and suicidal ideation.

5-Hydroxytryptophan (5-HTP) and L-tryptophan are amino acid precursors required for serotonin synthesis and have been extensively evaluated for their antidepressant action.[13] Administration of 5-HTP alone depletes catecholamines (dopamine, norepinephrine and epinephrine). When dopamine depletion is great enough, 5-HTP will no longer function.[14] This mandates that 5-HTP should be administered as adjuvant therapy along with established anti-depressant treatment. Many studies have been shown that 5-hydroxytryptophan and omega-3 fatty acids augment the efficacy of antidepressant medication.[15,16] There is dearth of literature on 5-hydoxytryptophan and omega-3 fatty acids as anti-depressants in Indian context. Hence, the present study was carried out to evaluate efficacy of omega-3 fatty acids versus 5-hydroxytryptophan as add on therapy in controlling suicidal ideation in depressive patients on sertraline.

2. Methods

A prospective, open label, randomized, comparative clinical study was conducted by the Departments of Pharmacology and Psychiatry, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. It was conducted from October 2014 to August 2015, for a period of 8 weeks for each patient and carried out as per the guidelines of GCP and declaration of Helsinki. Ethical approval was taken prior to the study from Institutional Review Board (No.AC/IRBl14102 Dated: 30.09.2014), PGIMS, Rohtak. Ninety patients of either sex were screened and divided in three groups randomly of 30 each as per the inclusion and exclusion criteria for the study.

Patients were selected based on the following inclusion criteria:

1. Patient presenting with ICD-10 depressive episode for the first time.
2. HAM-D score of 15 or more on 17 item version.
3. Age between 18 and 65 years.
4. Patient or his/her relative willing to give written informed consent prior to enrolment in the study.

Patients with psychotic symptoms or history of any other organic brain disease, patient needing any other psychiatric drug other than sertraline, patient with history of any known adverse effect due to sertraline and pregnant women and lactating mothers were excluded.

Ninety newly diagnosed cases of depressive episode as per ICD-10 Classification of mental disorders: diagnostic criteria for research, fulfilling the inclusion and exclusion criteria were included in the study. The purpose of the study was explained to patients and written informed consents were taken from all the patients and their relatives to participate in the study. The details of all the participants were recorded in the specially designed case record format. At the beginning of the study, all the subjects had undergone a complete physical and mental status examination as given in the case record format.

2.1 Drug treatment: The eligible patients after screening were randomly allocated to three treatment groups. Each study group consisted of 30 patients and received one of the following treatments orally:

Group A: Sertraline 50 mg tab once daily.
Group B: Sertraline 50 mg tab once daily plus omega-3 fatty acids 1 gm cap per day.
Group C: Sertraline 50 mg tab once daily plus 5-hydroxytryptophan 100 mg tab per day in two divided doses.

Suicidal ideations at the time of enrolment were assessed with Beck's scale for suicidal ideation (BSI).[17,18] Improvement after drug treatment was subsequently evaluated at 4 and 8 weeks interval from the day of 1st assessment using the same tool only. Patients developing intolerable side effects at any time during period of study were excluded from study and were put on escape treatment.

2.2 Escape treatment: A provision was made for escape treatment to those patients whose symptoms were not adequately controlled with any of the adjuvant therapy. Those patients were treated as per the standard treatment guidelines and were dropped from the study.

2.3 Statistical analysis: The data collected were expressed as Mean±S.D. Statistical Package for Social Sciences (SPSS) version 20.0 was used for analysis of data collected. Intergroup statistical analysis was done with one way ANOVA and intragroup analysis was done with repeated measures ANOVA. Post hoc test was carried out using Bonferroni test wherever applicable. A p-value <0.05 was considered as statistically significant.

3. Results

A total of 141 patients with clinical diagnosis of moderate depressive illness were screened for this study. Out of these, 38 patients were excluded as they did not match the predefined inclusion criteria – 9 patients had HDRS [19,20] score less than 15 at the time of enrolment, 11 patients were not willing to give consent, 7 were pregnant ladies, 3 were lactating mothers, 6 patients were found to be less than 18 years of age and 2 were more than 65 years of age. Out of the 103 eligible patients only 90 patients completed the study and the rest 13 were lost to follow up (Flow chart). The eligible patients were randomly allocated in three groups - Group A received sertraline 50 mg once daily, Group B received sertraline 50 mg once daily plus omega-3 fatty acids 1 gm per day and Group C received sertraline 50 mg once daily plus 5-hydroxytryptophan 100 mg per day in two divided doses. The baseline demographic characteristics and clinical scores of the study population are shown in Table 1.

Figure 1: Outline of result

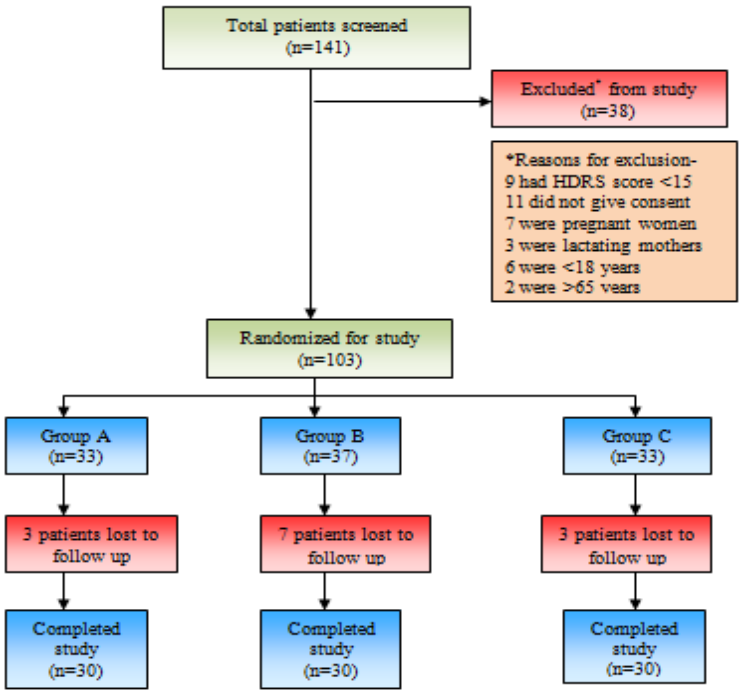

Table 1: Socio-demographic parameters of the three study groups

	Group A (n=30)	**Group B (n=30)**	**Group C (n=30)**
Gender N(%)			
Male	13(43.3%)	15(50.0%)	14(46.7%)
Female	17(56.7%)	15(50.0%)	16(53.3%)
Age group N(%)			
11-20 yrs	5(16.7%)	6(20.0%)	4(13.3%)
21-30 yrs	10(33.3%)	12(40.0%)	13(43.3%)
31-40 yrs	8(26.7%)	5(16.7%)	8(26.7%)
41-50 yrs	5(16.7%)	5(16.7%)	4(13.3%)
>50 yrs	2(6.7%)	2(6.7%)	1(3.3%)
Age in years (Mean±S.D.)	32.87 ±10.22	31.50 ±10.59	31.23 ±09.10
Education N(%)			
Literate	27(90.00%)	28(93.3%)	29(96.7%)
Illiterate	3(10.00%)	2(6.7%)	1(3.3%)
Occupation N(%)			
Employed	9(30.0%)	12(40.0%)	8(26.7%)
Housewife	12(40.0%)	7(23.3%)	11(36.7%)
Student	7(23.3%)	7(23.3%)	7(23.3%)
Unemployed	2(6.7%)	4(13.3%)	4(13.3%)
Retired	0	0	0
Comorbidities present N(%)			
Diabetes	3(10.00%)	4(13.3%)	1(3.3%)
Hypertension	2(6.7%)	3(10.00%)	1(3.3%)

Table 2: Comparison of BSI scores of the three groups at different time points

	Group A	Group B	Group C	F value (One way ANOVA)	p value
Week 0	15.13±3.52	14.10±4.01	13.60±4.42	1.131	0.327[#]
Week 4	11.30±2.61	10.50±2.86	10.07±3.13	0.852	0.430[#]
Week 8	6.00±1.82	5.60±2.33	5.93±2.26	0.299	0.742[#]
F value (Repeated measures ANOVA)	365.185	372.049	217.369		
p value	<0.001	<0.001	<0.001		

All values are expressed as Mean ± S.D.
[#]p value > 0.05 (non-significant)

Table 2 and Figure 2 show the BSI scores (Mean ± S.D.) of the three study groups at different time points of assessment. At week 0, mean values of BSI scores of group A, B and C were 15.13±3.52, 14.10±4.01, and 13.60±4.42. At week 4, mean values of BSI scores of group A, B and C were 11.30±2.61, 10.50±2.86, and 10.07±3.13. At week 8, mean values of BSI scores of group A, B and C were 6.00±1.82, 5.60±2.33, and 5.93±2.26. It can be seen that there were no significant difference between any two groups at a given time point of assessment as depicted by one way ANOVA (F=1.131, p=0.327; F=0.852, p=0.430; F=.299, p=0.742). However, on repeated measures ANOVA each group showed that there were significant changes in BSI scores of the three study groups at different time points of assessment (p<0.001).

Figure 2: BSI scores (Mean ±S.D.) of the three study groups

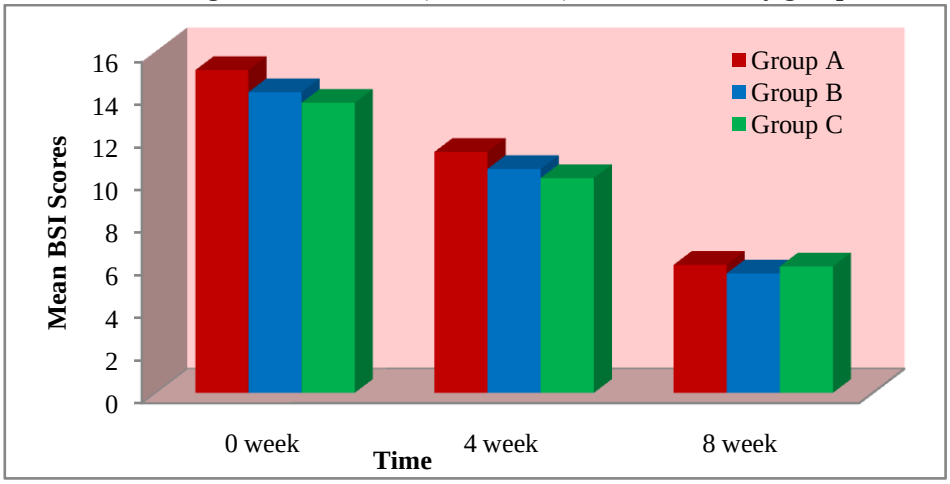

Table 3: Post hoc analysis of repeated measures ANOVA

Mean difference	Group A	Group B	Group C
Week 0-4	4.100*	3.600*	3.533*
Week 4-8	5.033*	4.900*	4.133*
Week 0-8	9.133*	8.500*	7.667*

*The mean difference is significant at p=0.01 level.

Table 3 shows post hoc analysis of repeated measures ANOVA. Bonferroni test was applied. The mean differences of BSI scores of group A at different time points were 4.100, 5.033 and 9.133 respectively. The mean differences of BSI scores of group B at different time points were 3.600, 4.900 and 8.500 respectively. The mean differences of BSI scores of group C at different time points were 3.533, 4.133 and 7.667 respectively. Bonferroni test depicts that there were significant differences in BSI scores of the three study groups at different time points of assessment (p<0.01).

4. Discussion

Regarding to BSI scores, comparison of score values at different time points in the three study drugs and post-hoc analysis (Table 2 and 3) show that greatest response was seen with group A followed by group B, and the least in group C. For group A, from a baseline BSI score of 15.13±3.52, it improved to 11.30±2.61 at 4 weeks and 6.00±1.82 at 8 weeks. Compared to the decrease in group A, the corresponding reduction in group B was less and variation across different time points was statistically significant. For group B, the baseline score was 14.10±4.01, at week 4, 10.50±2.86, whereas at week 8, the score was 5.60±2.33. Improvement of BSI score in group C was lesser as compared to group A and B (A>B>C). For group C, from a baseline score of 13.60±4.42, it became 10.07±3.13 at week 4 and 5.93±2.26 at week 8, which was lesser than that of improvement in group A and B. Intra-group variation of BSI scores at 0 week, 4 weeks and 8 weeks was highly statistically significant for all the 3 groups (<0.001), but inter-group comparison between the 3 treatment

groups did not reveal any significant difference at week 0, 4 and 8 (Table 2). Post hoc analysis (Table 3) depicts that there were significant differences in the BSI scores of the three study groups at any two time points assessment ($p<0.001$) and the maximum improvement in BSI scores were seen at week 8 with group A. These shows that regarding BSI scores, the maximum positive response was seen in group A (sertraline monotherapy group) followed by group B (sertraline in combination with omega-3 fatty acids) and the least improvement was seen with group C (sertraline in combination with 5-hydroxytryptophan).

Mechanisms through which omega-3 fatty acids may be efficacious are related to inflammatory processes that have been linked to depression. Omega-3 fatty acids appear to decrease the production of inflammatory eicosanoids from arachidonic acid. There is also an effect of omega-3 fatty acids on brain-derived neurotrophic factor, which encourages synaptic plasticity, provides neuroprotection, and enhances neurotransmission.

5. Conclusion

The sertraline monotherapy was better than add-on therapy in controlling suicidal ideation in patients with depression. Further studies with larger number of patients, longer duration with more follow-ups and also comparison with other conventional anti-depressants are mandated to reach any conclusion.

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