Original Article

Beneficial Antipsychotic Effects of Omega-3 Fatty Acids Add-On Therapy for the Pharmacological Management of Patients With Schizophrenia

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Objective: It has been shown that serum and red blood cells' level of Omega-3 fatty acids are low in people with schizophrenia. Many studies have, therefore, attempted to explore the beneficial effects of these substances in the management of Schizophrenia. However, the outcomes of the previous studies have not been clear cut. The present study is an attempt to retest this hypothesis by eliminating some of the limitations of the previous studies.

Methods: In a prospective double blind placebo-controlled clinical trial, 85 inpatients with schizophrenia randomly assigned to either risperidone plus Omega-3 or risperidone plus placebo. After a washout period, 44 patients received 2-8 mg/day of risperidone plus placebo and 43 patients received risperidone plus 3 gr/day of Omega-3 for 6 weeks. The treatment effect was calculated by Friedman, Mann Whitney and t test. There were no significant differences between groups in age, sex, education, duration of illness and the number of previous hospitalizations.

Results: There were no statistically significant differences in the scores of Positive and Negative Syndrome Scale between two groups at weeks 0, 3 and 6 and for the whole duration of the study.

Conclusion: In our study, Omega-3 fatty acids had no superiority to placebo in reducing the positive and negative symptoms of schizophrenia. However, due to a short duration of our study, we recommend that more long term clinical trials are needed in order to develop a better understanding of the therapeutic effects of the Omega-3 fatty acids in the pharmacological management of schizophrenia.

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Introduction

Schizophrenia is one of the major psychiatric disorders with a lifetime prevalence of around 1%. It usually begins before the age of 25 years. Most patients will go through a deteriorative process and need lifetime therapy and support (1-3). However, current pharmacological therapies provide limited management options and leave many patients with residual symptoms and undesirable side effects. Therefore, new approaches are needed to overcome these shortcomings.

Currently, serotonin-dopamine antagonist drugs are the first choice for the pharmacological treatment of schizophrenia (4,5). However, the efficiency of new drugs and dietary supplements including Omega-3 fatty acids are being studied in the management of schizophrenia (6-10).

Towards the end of 1980s, it was found that plasma and red blood cells' concentrations of the Omega-3 fatty acids were low in patients diagnosed with schizophrenia. This resulted in the new ways of thinking that adding these substances to treatment regimen of patient with schizophrenia might be an effective strategy (11-13).

Oxidative neuronal destruction secondary to stressful events has multiple adverse effects on neuronal development (14). These include breakage of DNA, inactivation of proteins, changes in gene expression and removal of cellular wall fats (containing polyunsaturated fatty acids). The evidence for the role of these oxidative changes and resulting neuronal destruction in the pathogenesis of schizophrenia are increasing. Therefore, it is thought that the

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prescription of Omega-3 fatty acids or other antioxidants, especially in the early stages of the disease, when brain has a higher neuroplasticity, can be effective in the long-term management of Schizophrenia (15).

We found contradictory results while reviewing the literature concerning the effectiveness of Omega-3 fatty acids in the treatment of schizophrenia. One of the reasons for the discrepancies among the findings of the various studies was that while some studies were done in inpatient population the others were conducted in the community and therefore the control on dietary regimen was not robust. The other reasons were the inclusion of patients with psychotic disorders, other than schizophrenia, or those who were on different types of antipsychotic medication with different durations, or adding multiple antioxidants on the neuroleptic regimen (16-19). For example, Ross et al (2007) studied the effect of antioxidants on patients with schizophrenia (18). For a period of 4 months, they added one gram of Omega-3 fatty acids, 800 units of vitamin E and 1000 mg of vitamin c to the patients' original antipsychotic drug regimen. At the end of the study, they found that there was a significant improvement in negative and positive symptoms and a reduction in extrapyramidal side effects and akatisia (18).

Materials and Methods

The current study is a double blind placebo-controlled clinical trial, which was originally going to be conducted on 106 inpatients with a diagnosis of schizophrenia (Ibn E Sina hospital, Mashhad, Iran). The diagnosis was confirmed by two psychiatrists using DSM- IV- TR criteria independently. We excluded those on depot antipsychotic medication and also those with substance dependency and medical illness during the last 2 weeks prior to the start of the study.

However, 20 patients discharged themselves against the medical advice and thus were excluded from the study. Another patient was also excluded, because he had treatment resistant schizophrenia. Therefore, current study was finally conducted on 85 consenting inpatients.

Using table of random numbers, patients were randomly allocated into 2 groups receiving either Omega-3 or placebo. At the beginning, a psychologist completed a Positive and Negative Symptoms Scale (PANSS) (20) for each patient. This was repeated in the following third and sixth weeks. Abnormal Involuntary Movement Scale (AIMS), for the assessment of drug side effects, was also completed by a psychiatric resident in the third and sixth weeks. The only antipsychotic drug used in the two groups was risperidone with a daily dosage of 2-8 mg.

Omega-3 fatty acids and placebo were started with the dosage of 1 pearl on the first day. They were similar in taste, color and shape (yellow transparent pearls) and increased to 3 pearls a day by the third days. This regimen was followed through for the next 6 weeks. 1 gram pearl of Omega-3 fatty acids contained 2000 mg of fish oil, 360 mg of eicosapentaenoic (EPA) acid and 240 mg of docosahexaenoic acid (DHA).

The PRN (as needed) oral lorazepam with the maximum daily dosage of 4 mg and PRN biperiden with a maximum daily dosage of 6 mg were respectively used in the case of anxiety and extrapyramidal side effects.

The psychologist and the psychiatrist who assessed the patients were blind to the treatment groups, so were the treating psychiatrist and the patients.

We used SPSS package for statistical analysis. The chi-square test, fisher exact test and independent t-test were used for evaluating the homogeneity of qualitative and quantitative variables in the two groups respectively. PANSS scores were compared in the two groups at 0, 3 and 6 weeks time after treatment via repeated measuring and between the two groups via the independent t-test. P value of equal or below 0.05 was considered as significant.

Results

The age average in the Omega-3 group was 37.38±6.2 years. It was 39.03±7.12 years in the placebo group. There was no statistically significant difference between the two groups as regards the age (p= 0.48).

Out of 85 patients, 76 were male (39 were in the Omega-3 group and 37 in the placebo group). 9 patients were female (3 in the Omega-3 group and 6 in the placebo group). The fisher exact test showed that there was homogeneity between the two groups regarding the gender difference (p=0.25).

Fifteen and a half percent of the patients were illiterate, 28.6% had primary education, 28.6% had secondary school education and 27.4% of the patients had high school or university education (p=0.38). In our study 10 patients reported a positive family history of schizophrenia (p=0.50).

The average number of previous hospitalizations in the Omega-3 group was 6.35±3.62 times and in the placebo group was 6.62±3.65 times (p=0.73). The average age of the first hospitalization in the Omega-3 and the control groups was at 25.69±10.04 and 26.66±7.37 years old respectively (p=0.61). The average illness duration in the Omega-3 group was 14.15±8.3 years and in the placebo group was 15.76±8.67 years (p=0.39).

The changes in the score of PANSS subscales (positive and negative symptoms, the general psychopathology, formal thought disorder, agitation and suspiciousness) in the both groups were studied at weeks 0, 3 and 6. The repeated measures of PANSS scores showed that there was not any significant differences in PANSS scores among the case and the control groups in subscales of general psychopathology at 0, 3 and 6 weeks after treatment (p>0.1) (Tables 1 and 2).

The changes of the depression scores during the 3 stages of assessment were not significant in the Omega-3 group (p=0.146).

Using t-test, no statistically significant difference was found in any of the PANSS scores at weeks 0, 3 and 6 after treatment between the Omega-3 and the placebo groups (p>0.1) except for the general psychopathology score that was high in the Omega-3 group in week 3 (p=0.04) (Table 3-5).

We could not find any statistically significant difference between PANSS scores of the Omega-3 and the placebo groups for the whole duration of the study (Mann Whitney test) (Table 6).

During the course of the study 6 patients developed extra pyramidal side effects and 3 patients had gastrointestinal side effects. Since the severity of the symptoms was mild, they were not excluded from the study. One patient in the Omega-3 group developed tardive dyskinesia from the outset, but the severity of this side effect did not change much during the course of study.

Table 1: the mean scores of PANSS subscales in week 0, 3 and 6 in Omega-3 group

PANSS	Week 0		Week 3		Week 6		Analysis	
	Mean	SD	Mean	SD	Mean	SD	χ^2	P
Positive symptoms	50.42	7.56	45.17	9.80	39.40	7.25	21.891	0.001
Negative symptoms	47.97	8.06	42.85	9.26	37.20	6.80	10.52	0.005
General psychopathology	51.11	8.47	45.85	10.11	38.77	7.70	25.72	0.001
Anergy	51.88	9.60	43.65	7.62	39.28	7.32	16.43	0.001
Thought disorder	46.57	6.24	42.28	7.78	38.17	5.54	29.11	0.001
Activation	52.91	7.33	48.37	8.36	44.45	7.26	22.11	0.001
Suspiciousness	53.17	8.99	49.71	8.91	43.25	6.50	20.246	0.001
Depression	49.60	6.60	49.22	6.73	45.62	6.58	3.84	0.146

Table 2: the mean scores of PANSS subscales in week 0, 3 and 6 in placebo group

PANSS	Week 0		Week 3		Week 6		Analysis	
	Mean	SD	Mean	SD	Mean	SD	χ^2	P
Positive symptoms	49.00	7.68	44.52	6.01	39.04	6.50	31.363	0.001
Negative symptoms	46.83	8.05	42.61	8.57	38.61	8.97	18.859	0.001
General psychopathology	50.95	9.00	42.54	7.91	39.02	8.10	32.112	0.001
Anergy	48.8	8.86	45.64	8.82	41.28	9.12	22.268	0.001
Thought disorder	46.90	5.88	42.50	5.88	39.52	5.85	26.129	0.001
Activation	50.90	8.22	46.85	6.74	44.57	5.95	10.671	0.005
Suspiciousness	51.09	8.88	48.11	7.29	42.88	6.10	27.69	0.001
Depression	51.38	7.28	46.95	6.73	44.80	5.88	9.69	0.008

Table 3: the mean scores of PANSS subscales at week 0 in both Omega-3 and placebo groups

PANSS	Omega-3 group		Placebo group		Analysis	
	Mean	SD	Mean	SD	t	p
Positive symptoms	51.02	7.85	49.09	7.61	1.150	0.025
Negative symptoms	48.30	8.16	46.90	7.97	0.801	0.42
General psychopathology	52.38	9.04	51.02	8.91	0.697	0.48
Anergy	52.42	9.76	49.16	8.79	1.621	0.1
Thought disorder	47.64	6.93	47.00	5.84	0.642	0.64
Activation	53.21	8.89	51.11	8.24	1.240	0.21
Suspiciousness	53.54	8.89	51.11	8.77	1.268	0.20
Depression	50.36	6.84	51.46	7.21	0.726	0.47

Table 4: the mean scores of PANSS subscales at week 3 in both Omega-3 and placebo groups

PANSS	Omega-3 group		Placebo group		Analysis	
	Mean	SD	Mean	SD	t	p
Positive symptoms	46.14	9.90	44.32	7.05	0.974	0.33
Negative symptoms	43.36	9.14	42.58	8.47	0.408	0.68
General psychopathology	46.46	9.82	42.60	7.83	1.995	0.04
Anergy	44.96	7.97	45.60	8.71	0.358	0.72
Thought disorder	43.12	7.85	42.39	5.85	0.482	0.63
Activation	48.97	8.33	46.88	6.66	1.274	0.20
Suspiciousness	50.56	9.03	47.90	7.33	1.481	0.14
Depression	49.46	6.55	46.88	6.67	1.786	0.07

Table 5: the mean scores of PANSS subscales at week 6 in both Omega-3 and placebo groups

PANSS	Omega-3 group		Placebo group		Analysis	
	Mean	SD	Mean	SD	t	p
Positive symptoms	39.40	7.25	39.04	6.50	0.225	0.82
Negative symptoms	37.20	6.80	38.61	8.97	0.769	0.44
General psychopathology	38.77	7.70	39.02	8.10	0.139	0.89
Anergy	39.28	7.32	41.28	9.12	1.045	0.29
Thought disorder	37.17	5.54	39.52	5.85	1.034	0.30
Activation	44.45	7.26	44.57	5.95	0.076	0.94
Suspiciousness	43.25	6.50	42.88	6.10	0.261	0.79
Depression	45.62	6.58	44.80	5.88	0.576	0.56

Table 6: Improvement of PANSS scores in 2 groups at 6 weeks

PANSS	Omega-3 group		Placebo group		Analysis	
	Mean	SD	Mean	SD	z	p
Positive symptoms	11.02	9.84	9.95	9.03	0.574	0.56
Negative symptoms	10.77	11.41	8.21	11.49	1.16	0.24
General psychopathology	12.34	11.09	11.92	10.73	0.067	0.94
Anergy	12.60	13.43	8.00	11.92	1.65	0.98
Thought disorder	8.40	7.37	7.38	7.43	0.54	0.58
Activation	8.45	8.68	6.33	9.65	0.89	0.37
Suspiciousness	9.91	10.40	8.21	9.95	0.98	0.32
Depression	3.97	10.12	6.57	9.09	1.18	0.23

Discussion

Up to 2003, four placebo-controlled trials studied the beneficial effect of the Omega-3 fatty acids in the treatment of schizophrenia. Two of these studies found that the Omega-3 fatty acids were effective in reducing the positive and negative symptoms of the patients; however, the other two did not find such a result. Therefore, the therapeutic role of the Omega-3 fatty acids in the treatment of schizophrenia remained unclear (21,22).

Fenton et al. (2001) compared the effect of fatty acid EPA with placebo on 87 outpatients with schizophrenia and schizoaffective disorders (already on various antipsychotic medications) for 16 weeks (16). At weeks 0, 2, 4, 8, 12 and 16, the patients were assessed with respect to the presence of the positive and negative symptoms and movement disorders. They did

not report any significant improvement in the positive and negative symptoms, mood and cognition of the patient in neither group.

Similarly, in another study by Emsley et al., on 40 patients diagnosed with schizophrenia, no significant difference was reported in the positive and negative symptoms and side effects between the group receiving omega-3 and the group receiving placebo (23). However, 8 of their patients were on clozapine and their sample consisted of a younger age group (18-55 years old) (19).

It has also been shown that there is possibly an inverse relationship between response to the Omega-3 and the duration of treatment with antipsychotic medication; the shorter the patient on antipsychotic medication, the better response to the Omega-3 treatment (17).

In contrast to the aforementioned studies, we found a significant difference within each group as regards improvement of PANSS scores after adding the Omega-3 to previous antipsychotic regimen. However, the difference between the two groups was not significant in week 3 and 6, which might be explained by the short duration of our study.

Our study was conducted on the hospitalized patients, whose symptoms are usually more severe than those who live in the community. This, we believe, has resulted in not finding a significant beneficial effect from add-on Omega-3, as all our patients were chronically psychotic and on a long-term antipsychotic medication. Also, the duration of our study was too short to draw any robust conclusion regarding the beneficial effect of the Omega-3 in the management of schizophrenia.

In conclusion, we suggest that more longitudinal clinical trials are needed to have a better understanding of the therapeutic effects of antioxidant agents, including Omega-3 fatty acids as an adjunct therapy in the management of schizophrenia.

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