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Effects of Omega-3 Supplement in the Treatment of Patients with Bipolar I Disorder

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ABSTRACT

Background: Fatty acids play various physiological roles in the organism; they are crucial for the structure of cell membranes, metabolic processes, transmission of nerve impulses and brain functions. In recent years, particular attention has been paid to the rich sources of omega-3 for the treatment of many diseases, especially mental illnesses. The present study aimed to investigate the effects of omega-3 supplement in the treatment of patients with bipolar I disorder (BID).

Methods: In this double-blind clinical trial, 100 patients suffering from BIDs were randomly divided into two, i.e. control ($n = 50$) and experimental ($n = 50$) groups. In addition to the other standard treatments, 1000 mg of omega-3 supplement was given to the experimental group on daily basis for 3 months and placebo was given to the control group. The Young Mania Rating Scale was completed for both groups before and after the intervention. Afterward, data were analyzed using paired *t*-test, independent *t*-test, and Chi-square test.

Results: Before intervention, mean severity of mania in the experimental group (23.50 ± 7.02) and control group (23.70 ± 8.09) was not significant ($P \leq 0.89$). The difference after the intervention in the experimental group (10.64 ± 3.3) and control group (20.12 ± 6.78) was significant ($P < 0.01$). The mean intensity of mania before (23.50 ± 7.02) and after (10.64 ± 3.3) intervention reported to be significant at $P < 0.05$.

Conclusions: Since omega-3 supplement was effective for the treatment of BID, it is suggested to use omega-3 supplements as an adjuvant therapy along with the other pharmacotherapies.

Keywords: Bipolar I disorder, omega-3 supplement, treatment

INTRODUCTION

Bipolar I disorder (BID) is one of the psychiatric disorders that is characterized by mood changes and frequent periods of depression and mania.[1]

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Bipolar mood disorder is commonly prevalent, such that lifetime prevalence of BID is reported to be 2.4%.[2] It may be seen in all people of the world and in any race and any socioeconomic levels. Bipolar disorder is known as the sixth worldwide cause of disability in young adults in the world.[3-5]

Bipolar disorder causes inability, disability, and discomfort for the patient and his/her family sufficiently. Severe

symptoms can lead to hospitalization and relapse in patients with disease and social effects; including extravagant, reckless sexual behavior, destructive behavior, and agitation due to numerous injuries, including personal, psychological, familial, economic, and employment.[6]

One important problem in Iran is delay between symptoms onset and refer to mental health service. Hosseini *et al*. (2014) concluded that early onset of depression can be the cause to delay to refer to mental health service, especially psychiatrists. That can make some complications such as substance use, commit suicide, and interpersonal relationship problems.[7]

According to the high prevalence of bipolar disorder in Iran and in other countries, prevalence of patients and family, and social cost and complications of the disease, its prevention and treatment are considered to be a priority for healthcare.[8-12]

From supplements effective in bipolar disorder, omega-3 has been discussed in immunotherapy or combination therapy.[13-15]

Epidemiological and biochemical studies demonstrate convincing evidence regarding the relationship between bipolar disorder and reduced consumption of omega-3. In general, low levels of omega-3 in the blood and brain tissue after death have been found in patients with bipolar disorder. There is no clear explanation yet, but lack of omega-3 consumption is the preventable risk factor for recurrent mood disorder.[16]

In a study by McNamara in the United States of America, the relationship of omega-3 fatty acids with mood disorders and their effects on the prevention and treatment of these disorders were studied. The results showed that omega-3 can contribute to reduce the symptoms of these patients and reducing their suicide rates.[17]

Balanzá-Martínez *et al*. studied the background of therapeutic effects of omega-3 fatty acids in the patients with bipolar disorder in Spain, and the results demonstrated the effective role of omega-3 in treating bipolar disorder.[18]

Safa *et al*. studied the therapeutic effect of omega-3 along with fluvoxamine and fluvoxamine only on BID patients in Iran. The results indicated that in comparison to treated group, fluvoxamine alone was effective in reducing the mean score of depression and depressive symptom.[19]

Objectives

BID is a common and debilitating disorder in which several aspects of personal, social, and occupational life, and interpersonal relationships of patients were affected. Therefore, the present study was carried out to investigate the effects of omega-3 supplement in the treatment of patients with BID.

METHODS

Study design

This was a double-blind random clinical trial with control group (placebo). The diagram of the study is presented in Figure 1. The statistical population consisted of all patients with BID who referred to Farabi Hospital of Kermanshah city in 2014. Inclusion criteria were existence of BID in the mania period or combination state according to the diagnosis of psychiatric based on the DSM IV-TR measures, patient and his supervisor's consent to participate in the study, and to be under the treatment of lithium and olanzapine. Exclusion criteria were the mentally retarded patients who based on the clinical diagnosis, had an intelligence quotient lower than 70 using intelligence test, patients with pervasive developmental disorders based on the patient's case history and clinical diagnosis, patients who require electroconvulsive therapy (ECT is now more commonly used for patients with resistance to those treatments, except in the case of life-threatening illness due to inanition, severe suicidal symptoms, or catatonia) or other treatments (such as other mood stabilizers except for lithium or the other anti-psychotics except for olanzapine) because of the severity of their symptoms according to the clinical diagnosis performed by the psychiatric, substance abuse, or dependence for at least 3 months before the study, pregnancy, risk of suicide, possibility of harming others, and patients who suffer from the severe side effects of consuming omega-3 supplements such as bruising and bleeding as a result of increased bleeding time. These patients were selected by the available sampling methods.

The minimum sample size was 43 patients, but this number was increased to 50 patients in each group to increase accuracy and because of the possibility of exclusion.

Sufficient description regarding the study was given to the patients and their families before the intervention, and the informed consent form approved by the Ethics Committee of Kermanshah University of Medical Sciences was taken from the legal guardians of the patients. Furthermore, this research was registered on the Iranian Registry of Clinical Trials with the code of H2013112414333 IRCT (www.irct.ir). At first and after completing patients' demographic information form, they were randomly put into one of the omega-3 and placebo groups. In the experimental group, patients received 1000 mg supplement capsules containing omega-3, made by nichers' factors in the USA on a daily basis for 3 months. Placebo was used in the control group. Patients were given one placebo capsule on a daily basis for 3 months. To study the effects of this intervention and to compare the treatment results of the two groups, all patients were clinically interviewed at the beginning and ending of the intervention by the psychiatric collaborator expert who had no information

regarding the treatment groups. In addition, all patients were educated about confounding factors such as physical exercise, insomnia, and consuming foods that have a higher amount of omega-3 and other factors. Afterward, Young Mania Rating Scale was used to evaluate the patients' status before and after the intervention. Statistical Package for Social Sciences (SPSS) version 20.0. (IBM Corporation) for windows paired t-test (for comparing data before and after treatment), independent *t*-test, and Chi-square test were used.

Instrument

Young Mania Rating Scale

This test is one of the most important rating measures for evaluating mania symptoms.[20] This scale has 11 items, which is completed based on the patients' subjective report by regarding their clinical status over the past 48 h. These 11 items are increased mood, increased energy and locomotor activity, sexual desire status, sleeping, excitability, rate and amount of speech, language, and thought disorder, thought content, destructive and aggressive behavior, appearance, and attitude. Likert scale for rating severity of each item was determined from 0 to 4 and in some cases 0–8 points. Maximum score for this test is 60. This test has been normalized within the population of Iranian patients by Dr. Barakatain *et al*., in which reliability coefficient for Cronbach's alpha was 0.72 for the patients group, 0.63 for the normal group, and 0.96 for reliability of the evaluators of the patients group. In addition, based on the above-mentioned study, cutoff point was 17.14%, sensitivity was 98.4%, and property was 98.4%.[21]

RESULTS

The studied sample included 100 patients with BID who were randomly divided into two equal groups (50 subjects in each group). There were 25 females and 25 males in the experimental group and 26 males and 24 females in the control group. Mean age for the experimental group was 36.8 ± 11 and 39 ± 11 in the control group. Thus, these two groups did not have any significant differences in this respect ($P > 0.05$).

Regarding marital status, most patients with BID were celibate such that thirty subjects of the control group (60%) and 28 subjects of the experimental group (56%) were single. There was not any significant difference between these two groups regarding marital status ($P > 0.05$).

Regarding education status, eight subjects of the experimental group were illiterate, 14 subjects had elementary education, nine subjects had secondary education, 14 subjects had diploma, and five subjects were higher than diploma. In the control group, 12 subjects were illiterate, ten subjects had elementary education, 11 subjects had secondary education, 11 subjects had diploma, and six subjects were higher than diploma. Therefore, there was not any significant difference between these two groups ($P > 0.05$).

Mean age for onset of bipolar disorder was 36.6 ± 9.7 for both control and experimental groups. This mean age was 24.3 ± 7.6 for the experimental group and 29.9 ± 9.7 for control group. Statistically, there was a significant difference between these two groups ($P < 0.01$).

Regarding disease duration variable for BID, there was not significant statistical difference between control and experimental groups ($P > 0.05$). Mean disease suffering duration was 12.8 ± 8.8 for the experimental group and 10.8 ± 8.6 for the control group. Overall, mean disease duration was 11.8 ± 8.2 for both groups. In addition, the mean frequency of relapses for bipolar disorder was 3.68 ± 3.2 for both groups. This number was 3.6 ± 3.4 for the experimental group and 3.4 ± 3 for the control group. Thus here too, there was not any significant difference between these two groups ($P > 0.05$) [Table 1].

Normal distribution of severity of mania was evaluated using Kolmogorov test and the result of Kolmogorov confirmed normal distribution of the variable ($P > 0.05$).

Comparison of the severity average of mania in the experimental and control groups was assessed by independent *t*-test before intervention. Results showed ($P = 0.89$) no statistical significant difference between the two groups. Furthermore, comparison of the severity of mania, after intervention, showed significant statistical difference ($P < 0.01$).

Comparison of the severity of mania in the control group before and after intervention by *t*-test showed no significant difference ($P = 0.64$). However, the difference in the experimental group showed a statistically significant difference between the mean severity of mania before and after intervention ($P < 0.01$) [Table 2].

DISCUSSION

The aim of the present study was to investigate the effects of omega-3 supplement in the treatment of patients with BID. The results of this study is consistent with the results of the previous studies that indicate the effectiveness of consuming omega-3 supplements for adjuvant therapy of patients suffering from bipolar disorder.[17-19]

Fatty acids play various physiological roles in the organisms; they are crucial for the structure of cell membranes, metabolic processes, transmission of nerve impulses and brain functions.[22] Omega-3 is influential for brain development, function of brain membrane enzymes, learning, and many other instances, and its deficiency is associated with many psychological disorders.[6,23-25]

Table 1: Comparison of average age, age of disease onset, disease duration, and relapse frequency in the experimental group and control group

Variables	Mean (SD)		Significance level
	Experimental group	Control group	
Age	36.8 (11)	39 (11)	0.06
Age of disease onset	24.3 (7.6)	29.9 (9.7)	0.01
Disease duration	12.8 (8.8)	10.8 (8.6)	0.22
Relapse frequency	3.6 (3.4)	3.4 (3)	0.09

SD=Standard deviation

Table 2: Severity of mania in control and experimental groups before and after the prescription of omega-3

Study stages	Severity of mania		Significance level
	Experimental group	Control group	
Before prescription of omega-3	23.50 (7.02)	23.70 (8.09)	0.89
After prescription of omega-3	10.64 (3.3)	20.12 (6.78)	0.01
Significance level	0.025	0.64	

Therefore, particular attention has been paid to the rich sources of omega-3 for the treatment of many diseases, especially mental illnesses in the recent years.

Since the present study was carried out among the patients with BID who were hospitalized in Farabi Hospital of Kermanshah city, generalization of results should be done with caution. It is suggested for further research to study the effectiveness of omega-3 supplement for the treatment of other mentally ill patients.

The results of Stoll's study showed that there are tangible implications for understanding of the pathophysiological mechanisms of bipolar disorder and for development of future treatments. Biochemical studies on human white blood cells indicate that treatment with high-dose omega-3 causes internalization of these polyunsaturated combination into membrane phospholipids that is necessary for cell signaling.[9,16] Increasing the concentration of omega-3 fatty acids in phospholipid membranes of cells suppresses signals related to phosphatidylinositol transmission pathways.[9,16] The value of this mechanism is unknown. However, the accession of omega-3 polyunsaturated fatty acid into lipid bilayer membranes of cells changes the membrane physically and[17] probably these changes make phospholipid membranes resistant against hydrolysis by phospholipase enzymes. It may be the result of reducing the second messenger molecules, diacylglycerol and inositol triphosphate generation.

Epidemiologic data have linked the findings of the epidemiological studies that have shown the link

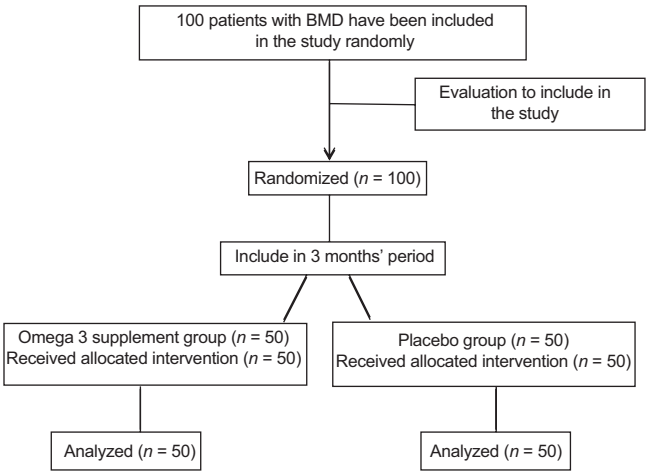

Figure 1: The process of entry into the study

between fish consumption and omega-3 absorption with national prevalence of depression, including postpartum depression, as well as bipolar disorder.[26] The amount of omega-3 fatty acids in plasma and red blood cells membrane is associated with severe depression.[27] Moreover, in addition, the ratio of omega-6 to omega-3 fatty acids (that are more common in our diet) in erythrocyte membranes is associated with depression.[28-30] Since omega-3 has a preventive role in coronary heart disease,[31] it can be justified that reduction of omega-3 is correlated with heart disease, cardiac mortality, and depression simultaneously. Consistent data show that omega-3 may have a preventive role against heart disease and mood disorders. Since atypical antipsychotic agents which are commonly used in the treatment of bipolar disorder are associated with an increased risk of diabetes, preventive effects of heart disease by omega-3 are significantly noticeable clinically.[14] In the double-blind, placebo-controlled, Stanley Bipolar Disorder Network trial, high-dose of eicosapentaenoic acid (EPA) was used as monotherapy and failed for the treatment of mood symptoms.[32] As well as, in a double-blind, placebo-controlled study of bipolar depression by applying 1 g or 2 g of ethyl-EPA as adjunctive treatment turned out that both doses are effective and tolerable for bipolar depression.[18]

CONCLUSIONS

The results of this study showed that supplements containing omega-3 are useful in the treatment of BID. The use of supplements containing omega-3 Along with other treatments is recommended based on the consideration of high prevalence of BID , the impossibility of making this substance in the human body, and the body's need for external supplements amount of this substance. In addition, it is recommended to measure the adequate blood levels of omega-3 consumption and absorption. As in previous similar studies, patients were

evaluated by the Young Mania Rating Scale weekly, so in future studies, patients should be evaluated on a weekly basis. At the end of the study, patients had normal mood and some of them had high mood and in none of them, depressive mood was not reported. While in our study YM was used to evaluate the subjects with normal and elevated mood, we recommend that researchers in future studies administer the different scales. Diet of patients must be totally under control and has to be similar.

Limitations are as follows; dissimilarity of diet, failure to measure blood levels of omega-3, and limited evaluation by YM only at the beginning and end of the study.

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Conflicts of interest

There are no conflicts of interest.

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