ORIGINAL ARTICLE

Does omega-3 supplement enhance the therapeutic results of methylphenidate in attention deficit hyperactivity disorder patients?

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Background: Although most of the ADHD (Attention Deficit Hyperactivity Disorder) patients respond to stimulant drugs very well, alternative drugs are required for non respondents. It has been revealed that subgroups of patients with ADHD have omega-3 fatty acid deficiency. So, the present study was planned to illustrate the effect of omega-3 supplementation, as an add-on to methylphenidate, on ADHD patients. **Materials and Methods:** In this double-blind RCT, ADHD children without any co morbidity, who had been diagnosed by a child and adolescent psychiatrist in child and adolescent university clinic, participated and were randomly divided into 2 groups. The experimental group methylphenidate plus omega-3 capsule (2000mg/d), while control group took methylphenidate plus placebo. Severity of ADHD symptoms were assessed by ADHD rating scale at the baseline and after 2, 4 and 8 weeks of treatment. **Results:** 69 patients (experimental = 36, control = 33) aged 7 to 15 participated. A significant reduction of both parent's and teacher's ADHD rating scale scores in both groups was observed. Bu t it couldn't show any difference between two groups. Difference score of parent's at baseline was 1.86+ (5/40), Pv 0.262, after 2 weeks -.70+ (4/30), Pv 0.668,4 weeks. 19+ (5/60), Pv 0.902 and 8 weeks. 30+ (4/42), Pv 0.845. Difference score of Teacher's at baseline was -1.56+ (3/45), Pv 0.541, after 2 weeks -.46+ (6/24), Pv 0.888, 4 weeks. 45+ (5/41), 0.868 and 8 weeks. 73+ (4/18), Pv 0.748. **Conclusion:** Omega-3 did not enhance the therapeutic results of methylphenidate in ADHD patients.

Key words: Attention deficit hyperactivity disorder, methylphenidate, omega-3

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common child psychiatric disorder,[1] involving about 3-7% of school children.[2] About 50% of referees to child and adolescent psychiatric clinics are suffering from ADHD.[3] As it is chronic, its familial and social consequences may persist into adulthood.[4]

The etiology of ADHD is multi-factorial and is probably caused by interactions between genes, gender and environmental factors.[5]

Psychostimulant medications continue to be a primary treatment modality for children with ADHD, suggests alterations in catecholaminergic – mainly dopaminergic and noradrenergic-transmitter functions markedly contribute to the symptoms of ADHD.[6]

However, some patients do not respond to stimulants and these medications have some significant side effects and limitations.[7]

Fatty acids play many critical roles in the developing and the adult central nervous systems. High polyunsaturated fatty acid (PUFA) intakes have been associated with reduced risks of neuropsychiatric disorders, in particular depression and neurodegenerative diseases.[8,9]

In the field of child psychopathology, the observation of a systematic association between ADHD symptoms and low PUFA status has led to the hypothesis that PUFAs are involved in the etiology of ADHD.[10-14]

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The fatty acids linoleic acid (18:3*n*-6, LA) and alpha-linolenic acid (18:3*n*-3, ALA) are called essential fatty acids (EFA) as they cannot be synthesized by the human body and therefore, have to be provided by the diet. The docosahexaenoic acid (22:6*n*-3, DHA) has an important structural role: It comprises 10% to 20% of human brain total fatty acid (FA) composition, and it is the most predominant *n*-3 fatty acid found in the brain.[15]

The eicosapentaenoic acid (20:5*n*-3, EPA) is also an *n*-3 long-chain fatty acid that is less abundant in neural (membrane) structures but has numerous roles in neural, enzymatic, and anti-inflammatory functions. In the *n*-6 family, arachidonic acid (20:4*n*-6, AA) is also an important structural lipid in the neural membranes. Gamma-linolenic acid (18:3*n*-6, GLA) and its metabolite the dihomogamma-linolenic acid (20:3*n*-6, DGLA) have anti-inflammatory properties, possibly functioning as protective agents against neurodegenerative diseases.[16]

Three studies in children[10-12] and one in adolescents[14] showed that ADHD participants had lower DHA concentrations in plasma and/or red blood cells compared to normal controls.

Studies have been conducted about the effect of omega-3 and omega -6 supplements to improve ADHD symptoms. However, the results have been inconsistent and there are a lot of contradictions.[13,17-27]

Arnold and his colleagues conducted two studies with major limitations that failed to show supplementation with *n*-6 fatty acids had a positive or negative impact on behaviors in ADHD children.[21,22]

Two intervention studies were performed, supplementing ADHD children with DHA alone or with DHA-EPA with a high ratio in favor of DHA: Neither found any positive effect on behavior or cognition.[19]

However, the evidence is too limited to conclude to any positive effect on cognitive abilities that are usually impaired in ADHD children. The results obtained to date suggest that supplementation with a combination of LCPUFA *n*-3 and *n*-6 fatty acids is most promising, but results remain overall too inconsistent to conclude whether long-chain *n*-3 and *n*-6 fatty acids supplementation is beneficial enough to develop public health recommendations.

In fact, this theme requires more researches. So, the present study was planned to illustrate the effect of Omega-3, as a supplement, which is added to metylphenidate to improve ADHD symptoms. As a result, researchers are looking for alternative and supplementary drugs.

MATERIALS AND METHODS

This was an eight-week, randomized clinical trial carried out on ADHD children referred to outpatient child and adolescent psychiatry clinic at Dr. Sheikh pediatric hospital, Mashhad city in northeastern Iran during 2007.

75 child and adolescents (aged 7-15) with diagnosis of ADHD were enrolled. At the time of admission all the patients met the full criteria for ADHD [based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revised (DSMIV-TR)]. Diagnosis was based on an independent interview with the parents and pro-bands by board-certified child and adolescent psychiatrists. Demographic information was obtained by interviewing the patients and their primary caregivers. Parents were asked to rate the severity of the DSM-IV-TR ADHD symptoms that their children displayed at home. To be included in this study, patients were required to have total and/or subscale scores on Attention - Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for patient›s age and gender.[28]

Patients with co morbid psychiatric diagnose (such as depression and anxiety) a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I); any evidence of suicide risk and mental retardation (I.Q.b70) were excluded.

Additional exclusion criteria were hypertension, hypotension. With history of serious organic problems (such as mental retardation, visual and hearing problems, seizure, head trauma, severe medical situations and substance abuse in the current 6 months) and who were already under treatment, were excluded from the study.

All subjects and their parents or legal guardian (advocate) gave written informed consent for participation. The study was conducted in accordance with the ethical standards of the investigative site's institutional review board was approved by the Institutional Review Board (IRB) of Mashhad University of Medical Sciences.

Subjects could withdraw any time during the study (if the patients or their legal advocate no longer wanted to continue).

After meeting all the inclusion and exclusion criteria, patients were simply randomized to two groups in a 1:1 ratio using a computer-generated code. The experimental group were prescribed methylphenidate plus omega-3, while control group methylphenidate plus placebo. Medications were prescribed in a double-blind manner. Specifically, all investigational staff

members who performed efficacy and tolerability rating scales were blind to the patient treatment group.

The initial dose of methylphenidate (product of Novartis) was 2.5 to 5 mg/day and it was increased 2.5 to 5 mg weekly, to attain a final dose of 1 mg/kg (maximum dose = 60 mg/day) in 2 or 3 divided doses. Omega-3 (product of Novartis) was prescribed as two 1000-miligram capsules (containing 240 mg of DHA and 360 mg of EPA) per day in two divided doses. They were encapsulated in a without tast and smell form. Placebo was given as capsules same as the omega-3.

Two psychiatrists who were not blind to the treatment status of patients and who did not perform efficacy or tolerability ratings monitored the clinical signs, symptoms, and adverse effects of treatments and adjusted the dose of medication.

The principal measure of outcome was the Parent and Teacher ADHD Rating Scale-IV that has been used extensively in Iran in school-age children and provides valid measures of behavioral abnormality and attention.[28-30]

Severity of ADHD symptoms was assessed by parent's and teacher's versions of ADHD rating scale at the baseline and after second, fourth and eighth weeks of intervention.

ADHD rating scale consists of 18 questions about ADHD symptoms which are answered in 4 levels of severity.[28] The minimum score of 20 on the teacher and parent ADHD rating scale was required for entry into the study. This score was selected based on previous studies.[28-30]

Statistical analysis

It was estimated that 35 patients in each group would be sufficient to detect a mean difference of 8 between groups (change in ADHD Rating Scale total score from baseline to the endpoint), based on a standard deviation of 13. This means the difference is detectable with a power of 90%, given a significance level of 5% using a two-sided *t* test. Efficacy analyses were performed in the intent-to-treat population, which was defined as subjects who took study medication and had at least one post baseline efficacy measure. Statistical analyses include chi2 or Fisher exact analyses and *t* tests to compare demographic and baseline clinical variables between treatment groups, independent sample T-test used for between two-group comparisons and paired sample T-test for within-group comparisons.

RESULTS

Out of 75 ADHD patients participated, 6 patients (4 patients in placebo group and 2 in omega group) of them gave up the study. In 5 cases, parents gave up the study because of personal reasons and only 1 patient left the study because of side effects of omega-3 supplement, including nausea, vomiting and abdominal pain. The research ran with 69 participants. They were 55 male and 14 female ADHD patients aged 7-15. Mean age was 8.7 ± 1.7 years. In attentive, hyperactive and mixed types of ADHD consisted of 15, 26 and 28 patients respectively. Experimental and control groups included 36 (29 males and 7 females) and 33 (26 males and 7 females) patients respectively. Experimental group consisted of 10 in attentive, 12 hyperactive and 14 mixed type patients. Control group included 5 in attentive, 14 hyperactive and 14 mixed type patients.

ADHD rating scale scores had a normal distribution. Paired *t* test showed a significant reduction of both parent's and teacher's ADHD rating scale scores during 8 weeks of experiment in both experimental and control groups [Table 1] and [Figure 1]. However, independent *t* test

Table 1: Parent and teacher ADHD rating scale in clinical trial of stimulant plus omega 3 and placebo in the treatment of patients with attention deficit hyperactivity disorder at the baseline (0) and after 2, 4 and 8 weeks of experiment

	Omega3 adjusted mean (SD) change statistical in score from baseline	pv	Placebo adjusted mean (SD) change statistical in score from baseline	pv
Parent ADHD rating scale				
Week 0-2	4.91±(3/98)	0.000	7.48±(3/91)	0.000
Week 0-4	9.66±(4/80)	0.000	5.31±(5/44)	0.000
Week 0-8	12.44±(5/34)	0.000	14.00±(5/40)	0.000
Teacher ADHD rating scale				
Week 0-2	5.600±(3/66)	0.000	5.45±(6/19)	0.001
Week 0-4	11.429±(9/16)	0.001	7.66±(4/72)	0.000
Week 0-8	6.75±(2.75)	0.035	11.76±(9/55)	0.000

ADHD= Attention deficit hyperactivity disorder

Table 2: Difference between experimental and control groups in term of ADHD rating scale scores at the baseline and after 2, 4 and 8 weeks of experiment

	Adjusted mean differences	*T*	pv
Parent ADHD rating scale			
Week 0	1.86±(5/40)	1.131	0.262
Week 2	-0.70±(4/30)	-0.431	0.668
Week 4	0.19+(5/60)	0.123	0.902
Week 8	0.30+(4/42)	0.197	0.845
Teacher ADHD rating scale			
Week 0	−1.56±(3/45)	−0.617	0.541
Week 2	−0.46±(6/24)	−0.142	0.888
Week 4	0.45±(5/41)	0.168	0.868
Week 8	0.73±(4/18)	0.326	0.748

ADHD= Attention deficit hyperactivity disorder

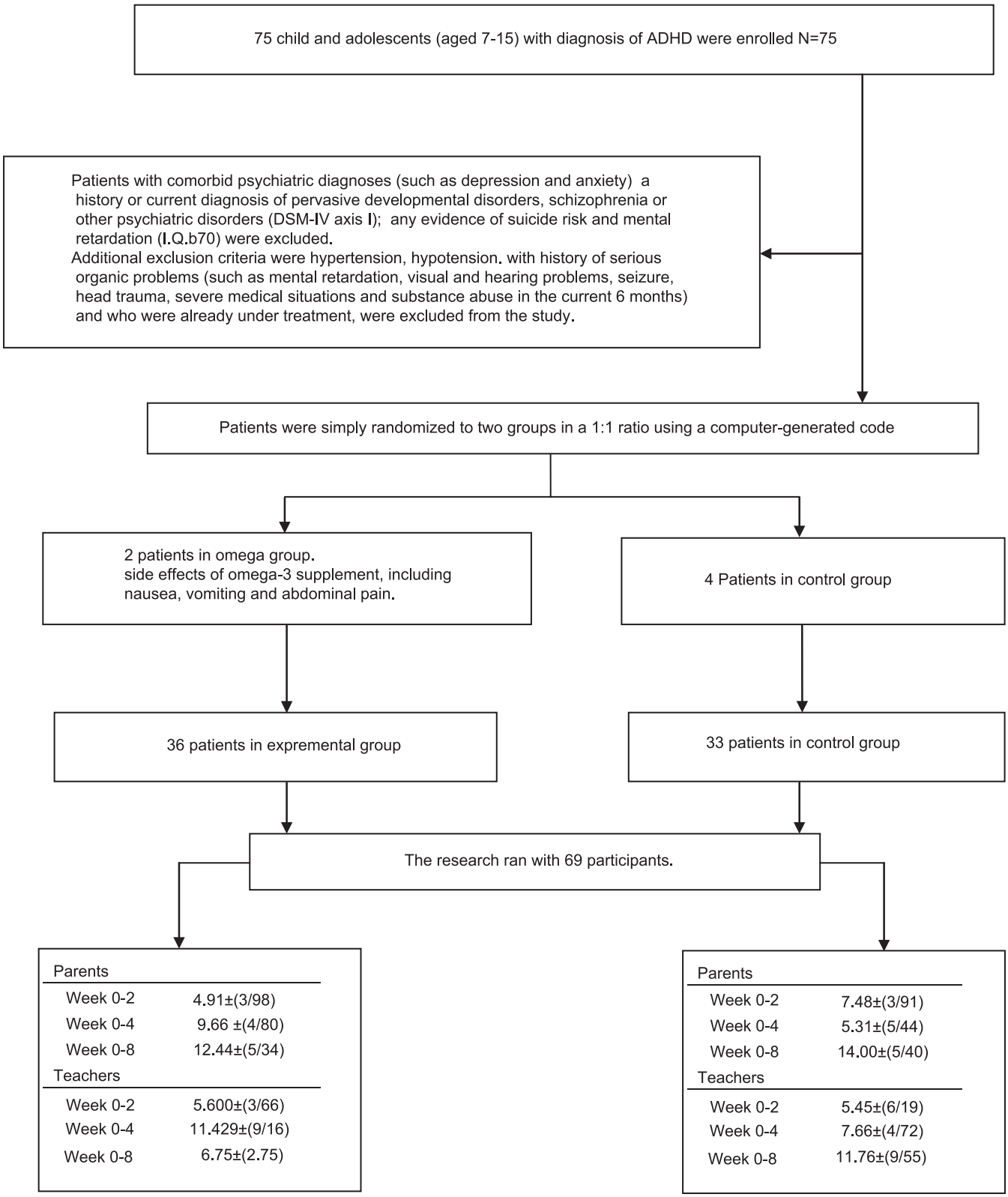

Chart 1: flow chart study.Presents the numbers of participants who were randomly assigned, received omega3 or placebo, and were analysed for the primary outcome

showed that difference between experimental and control groups in terms of parent's and teacher's ADHD rating scale scores was not significant at the baseline and second, fourth and eighth weeks [Table 2].

DISCUSSION

As it was expected, most of the patients were male, and the

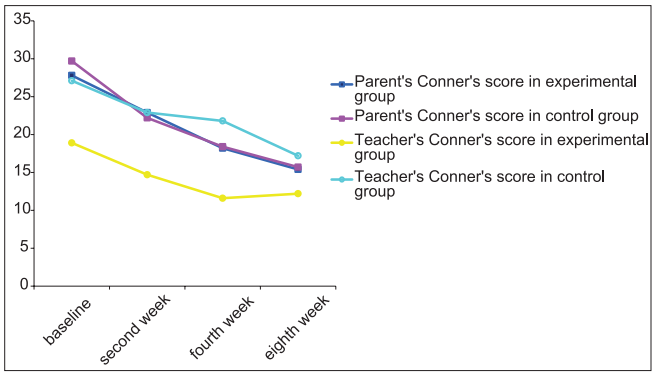

Figure 1: ADHD rating scale scores change in experimental and control groups during 8 weeks of study

most frequent subtype of ADHD was mixed type. Finally, both groups of patients have a significant improvement of ADHD symptoms during 8 weeks of treatment, but there was not a significant difference between two groups. This emphasizes that methylphenidate, as a stimulant drug, is quite effective on ADHD symptoms, but augment of omega-3 does not have a priority to placebo.

In prior researches, it has been shown that if children with ADHD received equivalent amount of omega-3 and omega-6 fatty acids in their diet, most of them had lower levels of omega-3 and a lower ratio of omega 3: Omega 6 fatty acids when compared with control subjects.[14,31] Even though researchers have shown that there is a significant relationship between omega-3 fatty acids deficiency and ADHD symptoms,[14,17,26,32,33] and omega-3 supplements have been capable to get an optimal plasma level in these patients,[19,20,34] there is a lot of debate about their effectiveness to reduce ADHD symptoms. Review studies have generally stated that open-label researches showed improvement of ADHD symptom by omega-3 supplements, but randomized controlled trials were often unsuccessful.[25,26,35] Inattentive subtypes of ADHD, patients with neuro developmental co morbidities, long term combination therapy of omega-3 and omega-6 fatty acids and simultaneously use of essential vitamins and minerals have tend to be more successful.[20,25,34-36] Also in some studies on effects of omega-3 supplements, ADHD symptoms improved only in one situation, at home or at school.[37,38] In most of the studies, omega-3 supplements have been used as an add-on to stimulant drugs that underestimates the effect of omega-3, in comparison with high efficiency of stimulants. But hopefully, an open-label study also has shown the significant improvement of ADHD symptoms by using omega-3 (ALA) and vitamin C supplements, without any stimulant drug.[20]

In some cases, omega-3 supplements also were efficient to reduce ADHD patients' disturbing behaviors, emotional problems and sleeping disorders.[13,36] Altogether, these benefits seem to be made because of changes in cell membrane composition, fluidity, receptors and enzymes, through altering the genes expression.[39]

In spite of these inspiring results, most of the double blind clinical trials, including the present study, did not consider omega-3 supplements prior to placebo to improve ADHD symptoms.[17-19] Thus, since omega-3 supplements have not been qualified as an evidence-based treatment,[35] the traditional stimulants seem to be the treatment of choice for ADHD patients. However, there appears to be at least a subgroup of ADHD patients who may have benefited with these supplements. But, we cannot predict the effectiveness of omega-3 supplements in ADHD patients, considering their symptoms of fatty acid deficiency, as they can be recognized only by blood assessments.[17]

Regarding the safety, tolerability, and some positive effects of omega-3 supplements in ADHD patients, that was shown in present study as well as the previous ones,[36,37] expanding our knowledge by conducting comprehensive studies with more samples and long-term treatments seem to be beneficial to resolve these contradictions. Also, as ADHD coexists with a wide range of psychiatric disorders affecting each other, exclusion of patients with co morbidities from this study may have affected the results and should be considered in the next studies in order to we can generalize the results to all ADHD patients.

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