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Omega-3 supplementation in children with ADHD and intractable epilepsy

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ABSTRACT

Background: Omega-3 may have a role in the treatment of drug- resistant epilepsy.
Objectives: To evaluate omega-3 supplementation in seizure control in children with attention deficit hyperactivity disorder (ADHD) and intractable epilepsy.
Patients and Methods: Sixty children with ADHD and intractable epilepsy were enrolled. They were randomly assigned in a double-blind fashion in a 1:1 ratio into the omega-3 supplementation group or the placebo group in addition to risperidone and antiepileptic drugs. All patients were assessed for the frequency and severity of the epileptic attacks at baseline, monthly, and at 6 months from the beginning of the study; 30 children received omega-3 and the other 30 children received placebo.
Results: At baseline, the median number of seizures per month was 5 in both groups. After one month, this median decreased to 3 and became 2 after two months of supplementation with omega-3 in the supplementation group while it remained 5 in the control group. After 3 months and till the end of the study, this median decreased to 0 while it remained 5 in the control group throughout the study period.

Children who were supplemented with omega-3 showed a significant decrease in the monthly frequency of seizure attacks after six months of supplementation compared to the baseline before supplementation ($P < 0.05$) There was no significant decrease in the severity of the seizures attacks among our patients with omega-3 supplementation ($P > 0.05$).
Conclusion: Omega 3 may help in achieving good seizure control in children with ADHD and intractable epilepsy.

1. Introduction

Epilepsy and attention-deficit/hyperactivity disorder (ADHD) are common neurological disorders in childhood. ADHD is a heterogeneous neurodevelopmental disorder determined by genetic, environmental, psychosocial, and familial factors. ADHD is characterized by hyperactivity, impulsivity, and lack of attention [1]. The prevalence of ADHD is 3–7% worldwide but differs according to age and sex. The onset of ADHD is mainly in school-aged children but can persist into adulthood. Boys are more likely to develop AHDH than girls [2]. Epilepsy is defined by the occurrence of two or more unprovoked, non-febrile seizures. It affects up to 1% of children and adolescents. The relationship between epilepsy and ADHD is still poorly understood [3]. Previous studies in children with epilepsy found a 2.5 to 5.5-fold-increased risk of ADHD compared to controls [3,4]. Early age of onset, poor seizure control, and use of multiple anti-seizure medications, however, is reported in children with epilepsy and intellectual disability that have high rates of the combined and hyperactive/impulsive types of ADHD [5]. Children with epilepsy have a significant risk for problems with attention and/or ADHD with a prevalence of 30% to 40%. Inattention is more common than hyperactivity and impulsivity. Additional neurological dysfunction and intractable seizures are major risk factors [6]. Intractable epilepsy is defined as persistent

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seizures despite the proper use of 2 or more maximally tolerated AEDs (antiepileptic drugs) with proper selection, optimum serum drug level, and good compliance) [7].

Although the link between nutrients and ADHD and epilepsy is still a matter of debate, the role of dietary supplements in the prevention and treatment of various clinical manifestations of ADHD and epilepsy has been a topic of recent interest.

Omega-3 contains many polyunsaturated fatty acids namely alphalinolenic (ALA), eicosapentaenoic (EPA), docosahexaenoic (DHA), stearidonic acid, eicosatetraenoic acid, docosapentaenoic acid (n-3DPA), tetracosapentaenoic acid, and tetracosahexaenoic acid [8]. ALA is the only "essential" omega-3 PUFA, as human beings can synthesize EPA, n-3DPA and DHA from ALA [9].

Omega-3 FAs may have many benefits in heath and disease. They improve triglyceride levels and capacitance of blood vessels. Also, they have anti-inflammatory and anti-obesity properties for children and adolescents [10]. It was reported that omega-3 FAs may improve lipid profiles and cardiovascular functions in children and adolescents [11].

Long chain (LC) PUFA, (ARA) and (DHA) are major structural components of brain cells. Also, they are highly concentrated in the brain and are vital for neurological development and proper mental health [8,12].

DHA should be considered as a semi-essential nutrient as the amount of DHA that is synthesized from ALA is not adequate [9,13]. The essential fatty acids, ALA and LA, are only found in trace amounts in brain phospholipids and EPA (precursor to DHA) is found mainly in phosphatidylinositol (PI) [14].

They share in many physiological processes in the brain like synaptic integrity, synaptic neurotransmission, and involvement in the catecholamines metabolic pathways, production of phospholipids in neuronal membranes, as well as the fluidity and permeability of the neuronal membrane [15,16]. Previous studies in children with ADHD showed low concentrations of these essential fatty acids in patients' plasma compared to the control group, highlighting the potential benefits of omega-3 FAs in improving the clinical symptoms of ADHD [17-20]. Also, Dietary supplementation with omega-3 fatty acids led to a decrease in inflammatory mediators and oxidative stress biomarkers [21]. Omega-3 FAs may inhibit neuronal excitability and may have anticonvulsant effects with a potential role in the treatment of refractory seizure [15]. Most clinical trials have shown an inverse association between omega-3 supplementation and frequency and severity of seizure [22-25]. However, in some studies these effects were not observed [26,27].

We aimed to answer the clinical question whether or not previous AEDs with combination of omega-3 and risperidone is more efficient than previous AEDs with risperidone alone in decrease of seizures monthly frequency and severity of children with intractable epilepsy and ADHD.

2. Patients and methods

This prospective case- control interventional clinical trial with a registration number of NCT01931587 was conducted in 60 children with ADHD and intractable epilepsy. However, 6 children did not return after 4 weeks and did not complete the study.

The study was conducted in the period from January 2019 to June 2020 after written informed consent. Children with ADHD and intractable epilepsy were enrolled from the pediatric neuropsychiatric outpatient clinic, Al Hada and Taif military hospitals, Saudi Arabia. There were 31 males and 23 females with ages ranging from 7 to 14 years (mean 9.6 +/− 2.5 years). Sample size was based on Z formula and a confidence interval of 95% with 80% power type one error of 5%, and an effect size (difference in frequency of good response between the two groups) of 30% based on result of our pilot study, was assessed in 30 children in each group [28].

Our strategy to calculate and behave with lost to follow up participants was to restrict analysis to those with full outcome information (complete case analysis).

An independent research board of faculty of medicine, Taif University had reviewed and approved the study protocol before the study was conducted (approval no. R2178562). All ethical guidelines on the 1964 Declaration of Helsinki and its later amendments were considered. ADHD was diagnosed by pediatric psychiatrist using the Statistical Manual of Mental Disorders Diagnostic criteria, 5th Edition (DSM-V) through a face-to-face interview for the child and his parents with at least score of 20 in ADHD diagnostic rating scale [29]. Intractable epilepsy was identified based on the definition of the International League against Epilepsy [30].

Exclusion criteria were: Other neuropsychiatric disorders, progressive neurologic disease, mental disorders not concordant with ADHD, development of status epilepticus during the study, administration of any kind of supplement in the previous 3 months, Liver disease with impaired liver function tests, renal disease with a rise of at least 50% in serum creatinine or impaired creatinine clearance, allergy to omega-3 or risperidone, any change in antiepileptic drugs regimen, and poor compliance.

Children with ADHD and intractable epilepsy were randomly assigned in a double-blind fashion in a 1:1 ratio into omega-3 supplementation group or the placebo group by permuted-block randomization.

Group 1 included 30 children with ADHD and intractable epilepsy on AEDs and risperidone who received supplementation of omega-3 as an adjuvant therapy to the standard treatment.

Group II included 30 children with ADHD and intractable epilepsy on AEDs and risperidone who received the standard treatment and placebo without supplementation of omega-3.

In group, I, one capsule of oral omega-3 daily and 0.5 mg of risperidone divided into two equal doses with previous AEDs and in group II, one oral capsule of placebo daily and 0.5 mg of risperidone divided into two equal doses with previous AEDs, were given. The drug's use was continued for 6 months and the children were followed up monthly for 6 consecutive months.

Based on randomization, omega-3 or placebo should be taken daily for 6 months by patients added to risperidone and AEDs. Both omega-3 and placebo were identical in appearance to guarantee proper blinding during the study.

The capsule of omega-3 that used in our study was fish oil (Omega-3) from 21st Century Co, the USA that each capsule contains 1000 mg of omega 3 fish oil, 180 mg of eicosapentaenoic acid and 120 mg docosahexaenoic acids.

The placebo capsule that used in our study was mixed oils (palm olein 70%, rapeseed oil 15%, and sunflower oil 15%).

Adherence to omega-3 supplementation and risperidone was assessed by counting the remaining capsules. Patients were considered compliant if they consumed >80% of supplements. Response to omega-3 supplementation to AEDs and risperidone was assessed during follow up visits in the outpatient clinic according to seizure frequency and severity of the epileptic seizures that were done prior to starting the intervention, monthly, and at the end of the study.

In patients, seizure frequency was assessed by recording the number of attacks per month through a diary given to their parents who had to register the number of seizure attacks on daily basis.

Seizure severity was evaluated using National Hospital Seizure Severity Scale (NHS3), which contains seven factors related to seizure and generates a score from 1 to 27 [31]. The scale was administered during an interview with the parents or a seizure witness. Scores on the NHS3 in the intervention and placebo groups were

compared prior to the study, monthly, and 6 months after the start of supplementation of omega 3 or placebo.

3. Outcome measures

Primary outcomes included monthly frequency of seizure and seizure severity scale scores and response to omega-3 supplementation compared before and after 6 months of treatment. Secondary outcome was clinical side effects.

3.1. Statistical analysis

Data were analyzed using SPSS version 16.0 (Chicago, IL, USA). Quantitative data are presented as means ± standard deviation. Chi-square test was used to compare categorical data. All variables were assessed for normality by Kolmogorov–Smirnov test. Student *t*-test was used to compare quantitative variables. P-value < 0.05 was considered significant.

4. Results

This study was conducted on 60 children with ADHD and intractable epilepsy. Eighty patients were initially screened for study inclusion and 20 did not meet the entry criteria. Out of the 60 included patients, 54 participants had completed the study. The attrition rates between the two groups of this study (4 (13.3%) in the intervention group and 2 (6.6%) in the placebo group, P = 0.09) did not reach statistical significance (Fig. 1).

Adherence in the remained participants was 100%. Sixty children were included in our study with loss of 6 children during the study period. Finally, 54 children completed the study. They were 31 boys and 23 girls with a mean age of 9.6 +/− 2.5. They included 26 children in the group of omega-3 supplementation and 28 children in the control group (Fig. 1).

All the patients were followed up in the outpatient clinic on monthly basis till the end of the study. During follow up, a seizure diary was determined to find out the frequency of monthly seizures and their score in the NHS3. There were no statistically significant differences between the 2 groups regarding clinical characteristics (Table 1). At baseline, One month before omega-3 supplementation, the median number of seizures per month was determined in the supplementation and placebo groups. The median was 5 in both groups. After one month, this median decreased to 3 and became 2 after two months of supplementation with omega-3 in the supplementation group while it remained 5 in the control group. After 3 months, this median decreased to 0 and was maintained at 0 thereafter while it remained 5 in the control group throughout the study period. In our study, the number of epileptic attacks decreased significantly and dramatically: 15 out of the 30 children in the intervention arm became seizure-free after 6 months of supplementation, while10 patients were having only a few seizure attacks per month (1–3) and finally, only one child continued to have 5 + seizure attacks per month, although 20 patients had been in this category before starting the intervention. Therefore, children with ADHD and intractable epilepsy who were supplemented with omega-3 showed a statistically significant decrease in the monthly frequency of seizure attacks after 6 months of omega-3 supplementation compared to baseline before supplementation (P < 0.05) (Table 2).

At baseline, one month before omega-3 supplementation, the median score of the NHS3 was determined in the supplementation and placebo groups. The median score of the NHS3 was 12 and 11 in the supplementation and placebo groups respectively. After one month, this median decreased to 10 and became 9 after two months of supplementation with omega-3 in the supplementation group while it remained 11 in the control group. After 3 months, this median decreased to 9 and was maintained at 9 on the 4th, 5th, and 6th month of supplementation while it remained 11 in the control group throughout the study period. Therefore, children with ADHD and intractable epilepsy who were supplemented with omega-3 showed no statistically significant decrease in the monthly seizure severity NHS3 score after six months of omega-3 supplementation compared to the baseline before supplementation (P > 0.05) (Table 3).

By the end of this therapeutic trial, we found that all patients in the intervention group had NH3 scores between 1 and 18. However, the control group showed NH3 scores between 1 and 25. Although we reported changes in the NHS3 scores by the end of the therapeutic trial, these changes were statistically not significant, either between intervention cases and control or between the beginning and the end of the study (P > 0.05).

Among patients with omega-3 supplementation, we reported side effects in the form of sleepiness in 2 children, vomiting in 2 children, fishy taste in 3 children, and diarrhea in 2 children (34.6%). However, the control group showed 2 children with sleepiness, one child with constipation, and 2 children with vomiting (17.8%).

The frequency of adverse events was more significant in the intervention group than the control group (P = 0.4). However, all of these events are mild and tolerated.

5. Discussion

Epilepsy is one of the most prevalent neurologic conditions associated with ADHD in children with possible consequences of disability and mortality [32]. About 30% of children with epilepsy have refractory seizures despite the use of AEDs, and many patients developed adverse drug effects [23]. There is evidence from animal studies and clinical observations that supplementation with omega 3 fatty acids may be useful in the treatment of patients with epilepsy and it increases seizure threshold [23]. However, there is some controversy over the effectiveness of omega 3 fatty acids [33]. Therefore, the study was undertaken to ensure whether or not omega 3 supplementations would enhance seizure control in children with ADHD and intractable epilepsy.

To our knowledge, this is the first therapeutic trial that evaluated the impact of omega-3 supplementation -as adjuvant therapy to AEDs and risperidone in a dose of 1000 mg of omega 3 fish oil, 180 mg of eicosapentaenoic acid, and 120 mg docosahexaenoic acids daily for 6 months on seizure frequency and severity in children with ADHD and intractable epilepsy.

In our study, the number of epileptic attacks decreased significantly and dramatically: 15 out of the 30 children in the intervention arm became seizure-free after 6 months of supplementation, while10 patients were having only a few seizure attacks per month (1–3) and finally, only one child continued to have 5 + seizure attacks per month, although 20 patients had been in this category before starting the intervention.

As to the severity of seizure attacks, there was no significant decrease in the severity of the seizure attacks among our patients with omega-3 supplementation. The attacks that occurred were more or less as strong in the intervention group as in the control group. In agreement with our findings regarding seizure frequency, a clinical trial was conducted on 20 patients with intractable seizures to study the anticonvulsant effects of n-3 PUFAs. The study revealed a negative correlation between DHA and EPA plasma concentration and seizure frequency, duration, and severity [25]. In Alexandria, Egypt, a case-control study was conducted on 70 children with intractable epilepsy to evaluate the efficacy of omega-3 supplements like fish oil in decreasing the frequency and severity

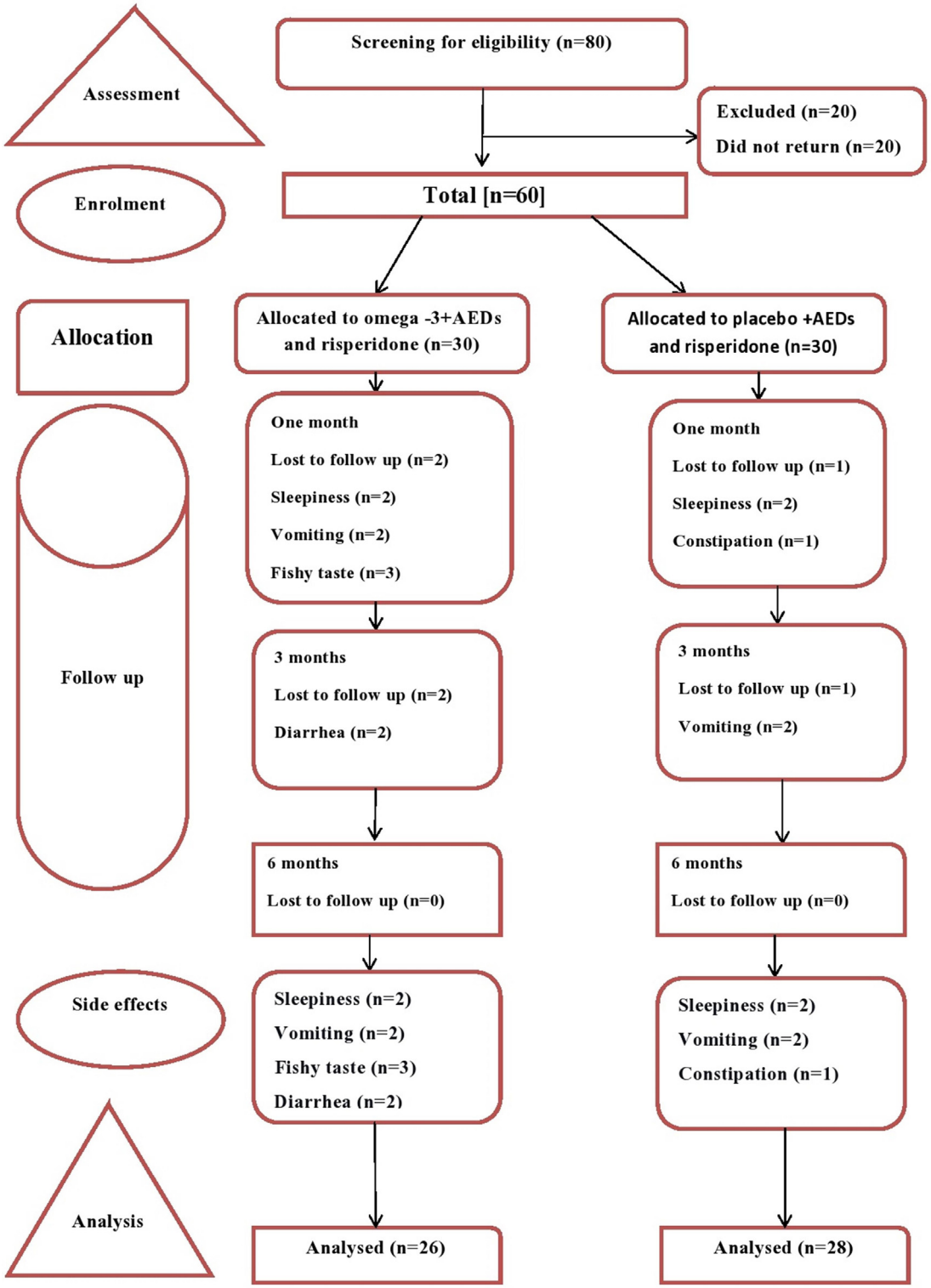

Fig. 1. Flowchart of ADHD and intractable epilepsy cohort.

of refractory epileptic seizures. It was found that Omega-3 caused a significant reduction in seizure frequency but there was not any significant difference in the severity of seizures between cases and controls [34]. Besides, DeGiorgio et al. studied 24 patients with intractable epilepsy through a randomized placebo-controlled trial, to evaluate the efficacy of low-dose and high-dose fish oil versus placebo (corn oil, linoleic acid). They reported low-dose fish oil may reduce refractory seizures and improve the prognosis of patients with epilepsy [35]. However, Yuen et al. studied 10 patients with chronic epilepsy through a non-randomized open trial of eicosapentaenoic acid (EPA), an omega-3 fatty acid in a dose of 1000 mg daily 3 months. They reported a 12%-56% reduction in seizure frequency in 60% of patients and a marked reduction in seizure severity in only one patient [36]. The Efficacy of daily eicos-

Table 1
Clinical Characteristics of the study groups.

Data	Omega-3 supplemented group	Placebo group	Total	P-value
Age in years(Mean ± SD)	9.4 +/− 2.8	9.8 +/− 2.3	9.6 +/− 2.5	0.94
Weight in Kg	8.34 +/− 1.82	8.24 +/− 1.62	8.28 +/− 1.74	0.76
Sex				
Male	16	15	31	
Female	10	13	23	0.34
Seizure type				
Generalized	11	13	24	0.46
Partial	7	8	15	
Mixed	8	7	15	
Epilepsy classification				
Symptomatic	15	12	27	
Cryptogenic	7	9	16	0.23
Idiopathic	4	7	11	
Neurodevelopment				
Normal	11	13	24	0.18
Delay	15	15	30	

Table 2
Distribution of children with ADHD and intractable epilepsy according to the number of seizure attacks per month.

Children with ADHD and intractable epilepsy	Number of seizure attacks per month	Before intervention	after one month	after 2 month	after 3 month	After 4 month	After 5 month	After 6 month	P-value
Intervention group		No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	
	250	2 (6.6)	0 (0)	0 (0)	0(0)	0(0)	0 (0)	(0)0	
	70 -	3(10)	3(10.7)	2(7.2)	(0)0	(0)0	0 (0)	(0)0	
	50	(13.4)4	3(10.7)	(10.7)3	(7.7)2	(3.8)1	0 (0)	(0)0	
	-20	(10)3	2 (7.2)	(14.4)4	(3.8)1	(3.8)1	(3.8)1	(0)0	
	-5	(26.7)8	6 (21.4)	5(17.5)	(11.5)3	(7.7)2	(7.7)2	1(3.8)	
	-1	10(33.3)	12(42.8)	(21.4)6	(27)7	(27)7	(27)7	(38.5)10	
	0	0(0)	(7.2)2	8(28.8)	13(50)	(57.7)15	16 (61.5)	(57.7)15	
	Total	(100)30	(100)28	(100)28	(100)26	(100)26	(100)26	(100)26	
	Median	5	3	2	0	0	0	0	0.009
Control group									
	250	(3.3) 1	(3.4)1	(3.4)1	(0)0	(0)0	(0)0	(0)0	
	70 -	2(6.6)	(6.8)2	(6.8)2	(3.5)1	(3.5)1	(0)0	(0)0	
	50	4 (13.4)	(17.2)5	(17.2)5	(21.5)6	(17.5)5	(21.5)6	(21.5)6	
	-20	(16.7)5	(13.7)4	(20)6	(25)7	(21.5)6	(25)7	(25)7	0.76
	-5	(33.3)10	(27.5)8	(31)9	(21.5)6	(21.5)6	(21.5)6	(17.5)5	
	-1	8(26.7)	(31)9	(20)6	(25)7	(5.32)9	(28.5)8	(32.5)9	
	0	0(0)	(0)0	(0)0	(3.5)1	(3.5)1	(3.5)1	(3.5)1	
	Total	(100)30	(100)29	(100)29	(100)28	(100)28	(100)28	(100)28	
	Median	5	5	5	5	5	5	5	0.56
P*of Median		3.00	0.07	0.08	0	0.00	0.00	0.00	

Table 3
Distribution of children with ADHD and intractable epilepsy according to the seizure severity according to NHS3 scale.

Children with ADHD and intractable epilepsy	Seizure severity as by NHS3 scale	Before intervention	after one month	after 2 month	after 3 month	After 4 month	After 5 month	After 6 month	P-value
Intervention group		No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	
	1-8	11(36.6)	11 (45.8)	5 (35.2)	4(40)	(41.6)5	4 (44.4)	3	
	9-16	12 (40)	10 (41.6)	6 (47)	(60)6	(58.3)7	5(55.6)	5	
	17-24	(23.3)7	3(12.5)	(17.6)3	0	0	0	0	
	Total	(100)30	24 (100)	(100)14	(100)10	(100)12	(100)9	8	
	Median	12	10	11	9	9	9	9	0.64
Control group									
	1-8	(30) 9	10	9		9		8	
	9-16	14 (46.6)	13	12		20			
	17-24	7(23.3)	6	6	6	6	6	6	
	Total	(100)30	29	27	27	27	27	27	
	Median	11	11	11	11	11	11	11	0.76
P*of Median		0.87	0.65	0.98	0.66	0.43	0.72	0.54	

apentaenoic acid (one gram) and docosahexaenoic acid (0.7 g) on 57 epileptic patients were evaluated by Yuen et al. for 12 weeks via randomized, placebo-controlled trial. They found a reduction in the seizure frequency over the first 6 weeks of treatment in the supplement group. However, this effect was not permanent [23]. A polyunsaturated fatty acid-enriched modified Atkins diet showed good results in the management of refractory seizures in a 7-year-old boy with Lennox-Gastaut syndrome without any reported side effects [37]. Schlanger et al. observed a significant reduction in frequency and severity of refractory seizures in 5

epileptic patients with central nervous system diseases treated with daily 3.5 g of omega-3 polyunsaturated fatty acids (omega-3 PUFA) for 6 months [38]. Our findings are in agreement with a recently published Iranian randomized, double-blind, placebo-controlled trial in which supplementation of omega 3 in a dose of 1000 mg of omega-3 fish oil, 180 mg of eicosapentaenoic acid, and 120 mg docosahexaenoic acids for 12 weeks as adjunctive therapy to AEDs and risperidone reduced seizure monthly frequency in children with ADHD and intractable epilepsy [39]. Essential fatty acids play a major role in the development and function of the central nervous system (CNS). Recently, omega-3 FAs are gaining interest in studies of CNS disorders including epilepsy, affective disorders, neuropsychiatric disorders, and cognitive decline [21]. The beneficial effects of omega-3 can be attributed to the elevation of seizure thresholds, alteration of ion channel activities, modification of electrical signal transduction, and dampening of inflammatory responses [15,21].

Our results showed that omega-3 was a safe supplement and no major side effects were observed in children with ADHD and intractable epilepsy. These findings are in agreement with other authors who reported the safety of omega-3 even in high doses [27,34,35]. We have some limitations in our study as we could not assess plasma levels of DHA and EPA in placebo- and Supplement-patients before and after treatment. Also, the small sample size was a limitation of our study.

6. Conclusion

We concluded that omega-3 administration has beneficial effects on the reduction of seizure frequency, but no effect on seizure severity, in children with intractable epilepsy and ADHD. Owing to their safety and benefits, supplementation with omega-3 FAs in these patients offers a promising complementary approach to standard therapy of AEDs and risperidone. Further randomized controlled placebo trials with a larger sample of patients and different preparations are required to establish the optimal doses and benefits of omega-3 in children with ADHD and intractable epilepsy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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