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ORIGINAL ARTICLE

Supplementation With Omega-3 Polyunsaturated Fatty Acids in the Management of Recurrent Migraines in Adolescents

ZEEV HAREL, M.D., GENEROSO GASCON, M.D., SUZANNE RIGGS, M.D., ROSALIND VAZ, M.D., WILLIAM BROWN, M.D., AND GERALD EXIL, M.D.

Purpose: **To examine whether dietary supplementation with fish oil rich in very long-chain n-3 polyunsaturated fatty acids might reduce frequency and severity of migraines in adolescents.**

Methods: **Twenty-seven adolescents suffering from frequent migraines for at least 1 year (mean 4 ± 1 years since migraine onset) participated in a randomized, double-blind, cross-over study consisting of 2 months of fish oil, 1-month washout period, and 2 months of placebo (olive oil). Participants self-assessed severity and duration of headache episodes (7-point faces and 10-point visual analog pain scales, 5-point frequency and severity rating scale) throughout the study. At the end of every 2-month treatment period, participants rated the effectiveness of treatment on a 7-point Likert scale (1,"not effective, not worthwhile"; 4,"moderately effective, moderately worthwhile"; 7, "totally effective, totally worthwhile"). A score of ≥ 4 on the Likert scale was considered as improvement.**

Results: **Twenty-three adolescents (16 girls, 7 boys, 18 Whites, 3 Hispanics, 1 African-American, 1 Cape Verdean, mean age 15 ± 1 years) completed the study. Compared with frequency of headaches before the study (31 ± 4 episodes/2 months), there was a significant ($p <$ .0001) reduction in headache frequency during fish oil treatment (4 ± 1 episodes/2 months) and during placebo (olive oil) treatment (4 ± 1 episodes/2 months) but no significant (NS) difference between treatments. Likewise, self-assessment on a 7-point faces pain scale revealed a significant reduction in headache severity during fish oil treatment (2.9 ± 0.5, $p = .01$) and during placebo (olive oil) treatment (3.5 ± 0.4, $<p = .03$), compared with headache severity before study (5.0 ± 0.3) and no significant difference between treatments. Patients' ratings of treatments revealed that 87% experienced reduction in headache frequency, 74% experienced reduction in headache duration, and 83% experienced reduction in headache severity during treatment with fish oil, compared with 78% who experienced reduction in headache frequency, 70% who experienced reduction in headache duration, and 65% who experienced reduction in headache severity during treatment with placebo (olive oil, NS). About 91% stated that they would recommend fish oil to friends or relatives with headaches vs. 91% who would recommend placebo (olive oil, NS).**

Conclusions: **Patients experienced a similar reduction in frequency, duration, and severity of headaches during treatment with fish oil and during treatment with olive oil. Although there was no significant difference between treatments, the marked improvement from baseline experienced by the patients suggests that the effect should not be dismissed as simply a placebo effect. In fact, results of this preliminary study suggest that both fish oil and olive oil may be beneficial in the treatment of recurrent migraines in adolescents. Further studies are warranted to compare each of these treatments with other interventions. © *Society for Adolescent Medicine, 2002***

From the Divisions of Adolescent Medicine (Z.H., S.R., R.V.) and Pediatric Neurology (G.G., W.B., G.E.), Hasbro Children's Hospital, Providence, Rhode Island; and Department of Pediatrics, Brown University, Providence, Rhode Island (Z.H., G.G., S.R., R.V., W.B., G.E.).

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Address correspondence to: Zeev Harel, M.D., Division of Adolescent Medicine, Hasbro Children's Hospital, 593 Eddy Street, Providence, Rhode Island 02903. E-mail: zharel@lifespan.org.

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Recurrent headaches are a frequent complaint throughout adolescence and may impair the quality of life and the daily activities of the teenager [1]. The management of recurrent migraines in adolescents has consisted mainly of prophylactic medications and behavioral treatments [2,3]. However, inconsistent results have been obtained with these interventions [2,3], emphasizing the need for developing new treatments to alleviate migraines in adolescents.

Neurogenic and perivascular inflammation has been implicated in the pathophysiology of migraine [4]. The eicosanoids prostaglandins (PGs) and leukotrienes (LTs), cyclooxygenase and lipoxygenase pathway products, are inflammatory mediators involved in the pathogenesis of headaches [5–12]. High intake of omega-6-polyunsaturated fatty acids (n-6 PUFAs) in the Western diet results in the predominance of these n-6 PUFAs in cell wall phospholipids [13,14]. Following a change in brain serotonin levels, these n-6 PUFAs, particularly arachidonic acid, are released, and a cascade of potent PGs (from the second series) and LTs (from the fourth series) build-up is initiated in the brain [11]. *In vitro* data suggest that PGs such as PG E_2 are involved in neurogenic inflammation and may facilitate nociceptor excitation [15]. *In vivo* data suggest that the brain neurovascular inflammatory response mediated by PGs and LTs produces headaches and other symptoms such as nausea and vomiting [11]. PGs and thromboxane of the second series, cyclooxygenase metabolites of arachidonic acid, are potent inflammatory mediators, which are increased in patients with migraines [8,9,11]. Cyclooxygenase inhibitors, anti-inflammatory medications such as naproxen sodium [16], ibuprofen [17], and tolfenamic acid [18] as well as inhibition of thromboxane synthetase [19] have been shown to shorten the duration and reduce the severity of acute headache attacks, providing further evidence for the participation of eicosanoids in the pathogenesis of headaches. Potent LTs of the fourth series, lipoxygenase metabolites of arachidonic acid, are also felt to play an important part in generating headaches and associated symptoms [5–7,10,11]. LTs have been implicated in the pathogenesis of headache [6], and plasma LT levels are elevated during headache attacks [10].

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) compete with n-6 PUFAs for the production of PGs and LTs at incorporation into cell wall phospholipids and at the enzyme (such as delta-6 desaturase) level [20–22]. Omega 3-fatty acids are polyunsaturated fatty acids in which the first double bond, closest to the methyl end, occurs between the third and fourth carbon atoms. Linolenic acid (LNA; C18:3 n-3), the essential n-3 PUFA, is found primarily in vegetable oil products, meat, walnuts, beans, and vegetables such as purslane, broccoli, and spinach [23]. After ingestion, human cells have the capacity to desaturate and elongate LNA to the very long chain (VLC) n-3 PUFA, eicosapentaenoic acid (EPA; C20:5 n-3), and docosahexaenoic acid (DHA; C22:6 n-3). Limited dietary supply of LNA and limited ability of the body to produce EPA and DHA from LNA have prompted a recommendation to increase direct consumption of VLC n-3 PUFA, which are found mainly in seafood [13]. Increase in n-3 PUFA dietary intake leads to incorporation of more n-3 PUFAs into tissue and vascular phospholipids [20–22] and to reduced formation of potent eicosanoids (20–22,24). Supplementation with n-3 PUFA has been shown in previous studies to attenuate various inflammatory processes and pain [13,25]. This beneficial effect of n-3 PUFA dietary supplementation likely results from a decrease in the production of potent PGs from the second series and LTs from the fourth series and from an increase in the build-up of less potent PGs from the third series and LTs from the fifth series [13,26]. The objective of the present study was to examine the effect of dietary supplementation with VLC n-3 PUFA in the management of recurrent migraines in adolescents.

Methods

Subjects and Procedures

Boys and girls, aged 12 to 21 years, who fulfilled criteria for chronic migraines [27–29] were offered the opportunity to participate in the study. Adolescents were recruited from Divisions of Adolescent Medicine and Pediatric Neurology and through advertisements in a local city newspaper. The adolescents completed written informed consent prior to enrollment in the study. Parental consent was obtained for patients under 18 years of age. Information was gathered about patients' headaches and dietary intake. A general physical examination, including a neurologic examination, was performed, and a diagnosis of headache type was made according to Inter-

national Headache Society criteria [27–29]. A normal neurologic examination was required for enrollment in the study. Adolescents who were on prophylactic migraine treatment with medications such as propranolol, divalproex sodium, or amitriptyline and wished to continue with their treatment were allowed to participate, and those on preventive treatment with daily anti-inflammatory medication (such as naproxen) were excluded. Also excluded were patients with hypertension or seizure disorder.

In this double-blind cross-over study, subjects were randomly assigned to one of two groups: Group I subjects (14 patients) took two capsules per day of a marine n-3 ethyl ester concentrate for the first 2 months. This preparation has been reported to be well-absorbed from the human gastrointestinal tract [30]. Each 1-g n-3 ethyl ester concentrate soft gel capsule consisted of EPA (378 mg), DHA (249 mg), and tocopherol (2 mg). This dose is considered to be an appropriate supplementation dose in humans [13], and the 2-month treatment period allows optimal incorporation of the n-3 fatty acids in the phospholipids of the cell membranes [31]. The subjects in group II (13 patients) received two capsules of placebo per day for the first 2 months. Each 1-g soft gel placebo capsule contained olive oil ethyl ester concentrate including oleic acid (691 mg), palmitic acid (106 mg), linoleic acid (62 mg), and tocopherol (2 mg). Both the n-3 ethyl ester concentrate and the placebo olive ethyl ester concentrate were obtained from the National Institutes of Health Fish Oil Test Materials Program [32]. Olive ethyl ester concentrate was selected from among the three placebo treatments offered by this program. The other two placebo possibilities (corn oil ethyl ester, safflower ethyl ester) contained 50% or more of linoleic acid (n-6 PUFA) and were deemed unhealthy to use in this migraine-prone patient population. Following 1 month of washout period, participants from group I crossed over to placebo, and participants from group II switched to the marine concentrate for an additional 2 months of treatment. Randomization schedules and patient assignments were prepared by Rhode Island Hospital Pharmacy and sealed until the end of the study. The study was approved by the Institutional Review Board of Rhode Island Hospital.

Headache Assessment

Throughout the study, patients kept records of their headache episodes. In the event of headaches, participants were instructed to use their abortive pain medication while continuing with the experimental protocol. At the end of any headache attack or on the day following the attack, the participants were asked to self-assess the severity of their headaches and the duration of their pain and associated symptoms. The self-assessment of the headaches included: (a) 10-point visual analog pain scale; (b) 7-point faces pain scale; and (c) 5-point frequency and severity rating scale. In addition to pain, other symptoms such as nausea, vomiting, loss of appetite, sensitivity to light and/or noise, fatigue, nervousness, and dizziness were reported on the 5-point frequency and severity scale. Score on this scale was calculated as the sum of the products of frequency and severity ratings of each of the symptoms. Participants were also asked to document any pain medication they consumed during the headache attack.

At the end of each study experimental period, the adolescents handed in their headache episodes record; capsule counts were done; blood pressure, weight, and height were obtained; and body mass index (in kg/m^2), was calculated. The participants were then asked to rate the effectiveness of treatment (in writing) on a 7-point Likert scale (1, "not effective, not worthwhile"; 4, "moderately effective, moderately worthwhile"; 7, "totally effective, totally worthwhile"). A score of ≥ 4 on the Likert scale was considered as improvement. The adolescents were also asked to fill out the medical outcomes study survey for headache patients [33].

Lipid Profile

A blood sample (after overnight fasting) for measurement of lipid profile was obtained at the end of each study experimental period. Serum cholesterol concentrations were measured by a colorimetric method using Vitros CHOL Slides (Ortho-Clinical Diagnostics, Rochester, NY). Serum high-density lipoprotein (HDL) cholesterol concentrations were measured by a colorimetric method using Vitros Magnetic HDL Cholesterol Reagent and Vitros CHOL Slides (Ortho-Clinical Diagnostics). Serum triglyceride concentrations were measured by a colorimetric method using TRIG Ektachem Clinical Chemistry Slides (Johnson & Johnson Clinical Diagnostics, Rochester, NY). Serum low-density lipoprotein (LDL) cholesterol concentrations were calculated as total cholesterol-(triglicerides/5)-HDL cholesterol.

Statistical Methods

Comparisons between and within groups were performed using Student's two-tailed *t*-test for paired

and unpaired data, and Chi-square analysis, as appropriate. Multiple regression analysis was used to examine associations of patients' ratings of treatment effectiveness with gender, years since onset of migraines, and family history of migraine. A type I error of $<.05$ was considered significant. For descriptive data, results are expressed as the mean ± standard error of the mean.

Results

Participants' Characteristics

Twenty-seven adolescents agreed to participate in the study, 19 girls and 8 boys, with a mean age of 15 ± 1 years. Ethnic distribution was composed of Whites (21 patients), Hispanics (4 patients), African-American (1 patient), and Cape Verdean (1 patient). All reported frequent headaches occurring more than once a week for more than 1 year (mean 4 ± 1 years since migraine onset). Twenty-five had migraine without aura, and two had migraine with aura. Twenty-three participants had a family history of migraine. Seventeen participants had undergone brain imaging tests (10 patients, magnetic resonance imaging; 6 patients, computed tomography; 1 patient, both magnetic resonance imaging and computed tomography), which were normal. Twelve participants had been on migraine prophylactic treatment in the past. Six participants continued with their headache prophylactic treatment during the study (two patients on amitriptyline, two patients on propranolol, one patient on divalproex sodium, and one patient on amitriptyline and divalproex sodium). All participants reported low fish consumption; 11% consumed fish once a week, 37% once a month, 33% rarely, and 19% never consumed fish. Throughout the study, no side effects of study medications were reported, and there was no significant change in participants' body mass index or blood pressure. A total of 23 adolescents (16 girls, 7 boys, 18 Whites, 3 Hispanics, 1 African-American, 1 Cape Verdean, mean age 15 ± 1 years) adhered to the entire 5-month study protocol and were included in the final analysis. Four patients dropped out of the study, one because of difficulty swallowing capsules, the other three because of failure to comply.

Self-Assessment of Headaches Throughout the Study

Compared with headache frequency before study, there was a significant reduction in the number of headache episodes both during treatment with fish oil and during treatment with placebo (olive oil), from a mean of 31 episodes per 2 months (approximately one episode every other day) before study to a mean of four episodes per 2 months (approximately one episode every 2 weeks) during study ($p < .0001$). However, there was no significant difference between the number of headache episodes during the 2 months of fish oil treatment (4 ± 1) and the number of headache episodes during the 2 months of placebo (olive oil) treatment (4 ± 1). Likewise, when assessing reported headache severity on the 7-point faces pain scale compared with ratings before study (5.0 ± 0.3), there was a significant reduction during both treatment with fish oil (2.9 ± 0.5, $p = .01$) and treatment with placebo (olive oil, 3.5 ± 0.4, $p = .03$) but no significant difference between the two treatments. On the 10-point pain visual analog scale, there was a significant reduction in severity ratings only during treatment with fish oil (4.0 ± 0.7, compared with 6.8 ± 0.4 before study, $p = .02$) and no significant difference between treatments. Assessment of headache severity and duration on the 5-point rating scale revealed a significant reduction during fish oil treatment only (score of 13 ± 4, compared with 22 ± 2 before study, $p = .04$) and no significant difference between treatments. While all patients reported abortive medication use at baseline, only 11 patients on fish oil treatment reported use of abortive pain medication during 80% of their headache episodes, and only 11 patients on olive oil treatment reported abortive medication use during 87% of their headache episodes with no statistical difference between treatments.

Medical Outcomes Study Survey for Headache Patients

Assessment of quality of life and well-being of patients using the medical outcomes study survey revealed no significant difference between participants' response at the end of fish oil treatment (total score 96 ± 1) and their response at the end of placebo (olive oil) treatment (total score 95 ± 1).

Patients' Evaluation of Treatment at the End of Each 2-Month Treatment Period

When asked whether treatment was effective ("yes"/"no"), 83% of participants stated that their headaches had improved during treatment with fish oil, and 91% stated that their headaches had improved dur-

ing treatment with placebo (olive oil). When efficacy of treatment was rated on a 7-point Likert scale, 87% rated as 4 or higher the reduction in headache frequency with fish oil, versus 78% who rated as 4 or higher the reduction in headache frequency with placebo (olive oil, NS). Regarding the effect on headache severity, 83% rated fish oil as 4 or higher and 65% rated placebo (olive oil) as 4 or higher (NS). Regarding the effect on headache duration, 74% rated fish oil as 4 or higher and 70% rated placebo (olive oil) as 4 or higher (NS). No significant associations were found between patients' ratings and their gender, years since migraine onset, or a positive family history of migraine. When asked on a 7-point scale whether they would recommend study treatment to friends or relatives with frequent headaches, 91% of patients gave a score of 4 or higher to fish oil and 91% gave a score of 4 or higher to placebo (olive oil, NS).

Lipid Profiles

No significant differences between treatment with fish oil and treatment with placebo (olive oil) were noted in cholesterol (164 ± 6 vs. 163 ± 5 mg/dL, normal < 170 mg/dL), LDL cholesterol (100 ± 5 vs. 97 ± 5 mg/dL, normal < 110 mg/dL), HDL cholesterol (49 ± 3 vs. 49 ± 2 mg/dL, normal > 35 mg/dL), and triglyceride levels (73 ± 7 vs. 84 ± 7 mg/dL, normal <150 mg/dL), measured at the end of each of the two treatment periods.

Discussion

In the present study, adolescents suffering from recurrent migraine headaches experienced a significant reduction in frequency, duration, and severity of headaches during 2 months of treatment with fish oil and during 2 months of treatment with olive oil, which was intended as placebo. Although there was no significant difference between these treatments, the improvement from baseline experienced by the patients suggests that the effect should not be dismissed as simply a placebo effect, and raises the possibility that both fish oil and olive oil may be beneficial in the treatment of recurrent migraine headaches in adolescents.

Recent reports have suggested that increasing dietary intake of n-3 PUFA results in formation of less potent inflammatory mediators (PGs from the third series and LTs from the fifth series) and attenuates inflammatory processes that may affect adolescents. Supplementation with VLC n-3 PUFA was effective in alleviating symptoms of dysmenorrhea in adolescents [25], high dietary intake of VLC n-3 PUFA was associated with higher levels of pulmonary functions in patients with asthma [34], and dietary supplementation with VLC n-3 PUFA had a beneficial effect in patients with cystic fibrosis [35], inflammatory bowel diseases [36,37], and rheumatoid arthritis [38].

Similar to findings in these previous reports, we believe that the marked effect of supplementation with VLC n-3 PUFA in the present study may be because of a build-up of less potent PGs and LTs in the brain. With dietary enrichment with VLC n-3 PUFA, more VLC n-3 PUFAs are incorporated in brain cell wall phospholipids [39,40]. With a change in brain serotonin, more VLC n-3 PUFAs are released. As a result, there is a decrease in the production of potent PGs and thromboxane from the second series together with an increase in the production of less potent PGs and thromboxane from the third series, changes that lead to less cerebrovascular reactivity [41,42]. The production of the less potent LTs of the fifth series likely contributes to attenuation of the cerebral perivascular and neurogenic inflammatory process and to reduction in headache symptoms. In addition to the effect on PGs and LTs, n-3 PUFAs have been shown to suppress nitric oxide production [43], which is believed to play a role in generation of migraines [4,44]. Finally, both *in vitro* [45] and *in vivo* [46] studies have suggested a possible interaction between n-3 PUFAs and serotonin. It remains to be determined in future studies whether dietary supplementation with n-3 PUFAs can influence central nervous system levels of serotonin and its effects on neurons and blood vessels.

In an open-label, uncontrolled study, Wagner et al. [47] reported that dietary supplementation with 1800 mg/day of gamma-linolenic and alpha-linolenic acids reduced severity, frequency, and duration of migraine attacks. That study indicated that supplementation with linolenic acid, the essential n-3 PUFA, was also beneficial in the management of recurrent migraine headaches. However, because human cells have a limited capacity to desaturate and elongate linolenic acid to the VLC n-3 PUFA [13], dietary fish oil rich in VLC n-3 PUFA is 2.5 to 5 times more effective than alpha-linolenic acid in modulating eicosanoid metabolism and altering tissue phospholipid fatty acid composition [48]. Future studies are warranted to compare the effect of linolenic acid, the essential n-3 PUFA, with the effect of

VLC n-3 PUFA in the management of recurrent migraine headaches in adolescents.

Similarly intriguing is the improvement in headache frequency, severity, and duration during supplementation with olive oil, which served as a placebo in this study. Oleic acid, the main fatty acid of olive oil, can be converted *in vivo* to oleamide, a fatty-acid amide with measurable neurologic effects in animals, including modulation of several serotonin receptor subtypes [49]. In addition, the olive oil phenolic compounds inhibit leukotriene generation at the 5-lipoxygenase level [50,51]. Supplementation with olive oil leads to a reduction in vascular cell adhesion molecules that may also play a part in inflammatory processes [52]. Finally, a study by Navarro et al. [53] reported an increase in n-3 PUFA content of membrane phospholipids in various tissues including the brain in response to an olive oil diet, suggesting that an adequate intake of olive oil enhances incorporation of dietary n-3 PUFA in all cell and tissue lipids.

The present study has some limitations. The choice of placebo in clinical studies of fatty acids is difficult because placebo options consisting of supplementation with saturated fatty acids or n-6 PUFAs are considered unhealthy. In the present study, olive ethyl ester concentrate was selected as placebo over corn oil ethyl ester and safflower ethyl ester, the two other placebo options offered by the Fish Oil Test Materials Program because these two other placebo options contained 50% or more of linoleic acid (n-6 PUFA) [32]. As in our study, olive oil has been used as a placebo treatment in previous studies investigating the anti-inflammatory effects of VLC n-3 PUFA [54,55]. Similar to our findings, other studies have shown beneficial effects of treatment with olive oil in patients with cardiovascular disease [54] and rheumatoid arthritis [55], raising the possibility of an anti-inflammatory effect of olive oil. It is also possible that other study interactions, such as the requirement for maintenance of detailed headache logs and personal attention, have contributed to the reduction in headache frequency, duration, and severity observed in the present study. Although a placebo effect may be considered, it is worth noting that the response rate to placebo in other children and adult migraine prophylactic studies is about 20% to 30% [56,57], far less than the response to fish oil and olive oil observed in our study. In the present study, we employed a double-blind, cross-over design with 1 month of washout period. It might be that the effect of dietary supplementation with either VLC n-3 PUFA or olive oil lingers for more than 1 month. In future studies, it will therefore be important to prolong the washout period time using a cross-over design or to test the effect of fish oil and olive oil, compared with another placebo, using another method such as the cohort parallel design.

In conclusion, patients experienced a similar reduction in frequency, duration, and severity of headaches during treatment with fish oil and during treatment with olive oil. The marked improvement from baseline experienced by the patients suggests that the effect should not be dismissed as simply a placebo effect. In fact, results of this preliminary study suggest that both fish oil and olive oil may be beneficial in the treatment of recurrent migraines in adolescents. Further studies are warranted to compare each of these treatments with other interventions.

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