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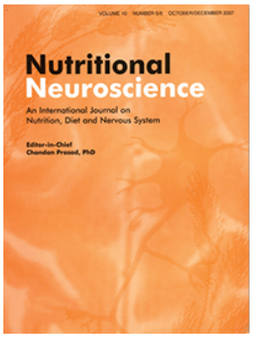

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A double- blind, randomized, and placebo-controlled clinical trial with omega-3 polyunsaturated fatty acids (OPFA ω-3) for the prevention of migraine in chronic migraine patients using amitriptyline

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Objective: To determine the prophylactic effect of OPFAω-3 in migraine.
Subjects and methods: This was a prospective, experimental, controlled, double-blind, and with comparison groups study. Sixty patients diagnosed with chronic migraine, according to the criteria of the International Classification of Headache Disorders, Third Edition (beta version) (ICHD-3β), were prophylactically treated with amitriptyline. They were divided into two equal groups: in group 1, prophylaxis was associated with OPFAω-3 and in group 2 with placebo. After 60 days, both groups were assessed by a second researcher.
Results: Of the 60 patients with chronic migraine, only 51 patients (15 men and 36 women) completed the treatment. The group that received OPFAω-3 consisted of 27 (52.9%) patients (six men and 21 women), while the control group was equal to 24 (47.1%) patients (nine men and 15 women). These differences were not significant ($\chi^2 = 1.428$; $P = 0.375$). In 66.7% (18/27) of the patients who used OPFAω-3, there was a reduction of more than 80.0% per month in the number of days of headache, while in the control group, the same improvement occurred in 33.3% (8/24) of patients. This difference was significant ($\chi^2 = 5.649$; $P = 0.036$).
Conclusions: Polyunsaturated omega 3 fatty acids (OPFAω-3) are useful for prophylaxis of migraine attacks.

Keywords: Fatty acids, Omega 3, Migraine, Prophylaxis

Introduction

Migraine is a chronic neurological disorder with a prevalence of 15.2% in Brazil.[1] It is defined as an abnormal neurovascular reaction that occurs in a genetically vulnerable organism. It externalizes itself clinically by recurrent attacks of headache and associated manifestations, depending on triggering factors.[2] This disorder reduces the quality of life of migraine patients, causing professional absenteeism and is associated with several co-morbidities.[3]

Several drugs are used in the prevention of headache attacks in migraine patients. However, there are other non-pharmacological treatments, including acupuncture, relaxation techniques, biofeedback, psychotherapy, and dietary therapy.[4–7]

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We believe that eating certain foods associated with drug therapy may help reduce the frequency of headache attacks.[8,9] Among these foods, we highlight the polyunsaturated omega 3 fatty acids (OPFAω-3) because they have an important action in the central nervous system by stimulating the synthesis of serotonin receptors and alleviating various inflammatory processes.[10]

Despite the relevance of the action of OPFAω-3 in the prevention of migraine, few experimental studies have been conducted to this purpose so far.[11–15] Our study is important because we evaluated the effectiveness of OPFAω-3 associated with drug prophylaxis in patients with chronic migraine.

Methods

Study design and patients

This was a prospective, experimental, controlled, double-blind, and with comparison groups study.

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The sample was convenience, thus not random, and consisted of the first 60 patients with chronic migraine according to the diagnostic criteria of International Classification of Headache Disorders, Third Edition (beta version) (ICHD-3β),[16] who were seen at a headache clinic, located in Teresina, Piauí, Brazil, from October to December 2015 and invited to participate in this research.

Inclusion and exclusion criteria

Patients aged between 18 and 50 years old, with daily headache, body mass index between 18 and 25 kg / m^2, and who agreed to submit to an interview, and in using the prescribed nutraceutical that would integrate the research, were included in the study. The study excluded patients, who reported other primary headache, concurrently or at different times, secondary headaches, associated diseases or medications that contraindicate the use of OPFAω-3, history of diet intolerance with OPFAω-3, using diet rich in polyunsaturated fatty acids during the research, and pregnant women.

Data collection

After filling the inclusion and exclusion criteria, a structured interview was conducted by the first researcher, based on a questionnaire to diagnose the migraine. Then, amitriptyline at a dose of 10 mg / day was administered to both groups, because this is a classic treatment for migraine and for ethical reasons we could not fail to treat these patients. To determine the effect of prophylactic OPFAω-3 in migraine, OPFAω-3 was administered to a group and placebo to the other group.

Both groups were re-evaluated by the second researcher, after 60 days of daily use of OPFAω-3 or placebo, according to the research protocol. The double-blind character was to restrict each of the examiners the information they generated and omit the patient knowledge of prescribed substances.

Every patient, regardless of the group, has filled the headache diary[17] to evaluate the frequency and intensity of pain. The frequency was determined by the number of days the patient complained of pain; and intensity through visual analogue scale (VAS), understood as a horizontal line of 10 cm, where the numbers 0 –10 are marked in ascending order from left to right. To facilitate understanding, these numbers were associated with verbal descriptors, where VAS equal to zero corresponds to the absence of pain; one to four, mild pain; five to seven, moderate pain; eight and nine, severe pain; and 10, very strong pain.

Procedure for the use of OPFAω-3 and placebo

OPFAω-3 was prepared as sachet, with standardized concentrations of 400 mg of eicosapentaenoic acid (EPA) and 350 mg of docosahexaenoic acid (DHA). It was administered daily to the group A where one was sachet diluted in 150 ml of water, twice a day, before meals, comprising a daily dose of 1.5 g.

The placebo administered to group B was also prepared as sachets and with the same organoleptic properties of the active substance, containing an inert substance, the starch. One sachet diluted in 150 ml of water, twice a day, before meals, was administered.

In order to maintain the same organoleptic properties in sachets administered, both in the OPFAω-3 and the placebo, we added flavoring (sucralose), sweetener (acesulfame), and dye (riboflavin) in the same proportion. These substances were used in low concentrations because they are only excipients.

In cases of intolerance to the use of these substances, such as, nausea or any adverse effect to amitriptyline, such as weight gain, dry mouth, constipation or drowsiness, and researchers were notified immediately and the subject was excluded from the search.

Statistical analysis

Once the information was organized in the database, the Epi Info™ 7, 7.1.5.0 version of 19 March 2015 for statistical analysis was used. The chi- square test with Yates correction for differences between averages of unpaired samples was used, assuming a significance level of 0.05.

Results

The sample consisted of 60 chronic migraine patients, presenting daily headache (19 men and 41 women) and was characterized by a mean age of 35.9 ± 8.7 years, ranging between 19 and 50 years. Throughout the study, nine patients gave up because of some adverse effects from the treatment.

Fifty-one patients completed the treatment, corresponding to 85.0% of the sample. The group that received OPFAω-3 consisted of 27 (52.9%) patients (six men and 21 women), while the control group had 24 (47.1%) patients (nine men and 15 women).

In both groups, there was a predominance of females and the ratio female/male to the group that used OPFAω-3 and the control group was equal to, respectively, 3.5:1 and 1.7:1. These differences were not significant ($\chi^2 = 1.428$; $P = 0.375$). The ages of the patients who used OPFAω-3 and the control group were, respectively, 36.9 ± 7.5 and 34.2 ± 9.9 years. These differences were not significant ($t_{mean} = -1.089$; $P = 0.286$) (Table 1).

In Table 2, we observe the headache characteristics used to diagnose 51 migraine patients. When considering all these characteristics, it was found that the two groups showed no statistical difference.

When we compared the initial frequency of headache with a frequency of 60 days after the intervention, it was found that the group that used OPFAω-3 decreased by more than 80.0% of the number of days

Table 1 Distribution of sex and age of the 27 chronic migraine patients using amitriptyline and OPFAω-3 and 24 using amitriptyline and placebo

Variables	Comparison groups		*P*-value
	Use of OPFAω-3	Control	
Sex			0.375*
Female (*n*; %)	21 (77.8)	15 (62.5)	
Male (*n*; %)	6 (22.2)	9 (37.5)	
Age (years)			0.286*
Mean (SD)	36.9 (7.5)	34.2 (9.9)	
CI 95%			
Variation	22–49	20–50	

Legend: OPFAω-3 – polyunsaturated omega 3 fatty acids.
**P*- values calculated using the chi-square test.

of headache per month (30 days versus ≤ 5 days) in 66.7% (18/27) of patients, whereas in the control group, the same improvement occurred in 33.3% (8/24) of patients. This difference was significant ($\chi^2 = 5.649$; $P = 0.036$), as shown in Table 3 and Fig. 1.

In Table 4, we have found that in the group that used OPFAω-3 there was an improvement of over 50.0 and 75.0% in, respectively, 81.5 and 85.2% of patients, while in the control group, this improvement was in, respectively, 12.5 and 62.5% of patients. This difference was significant ($\chi^2 = 5.577$; $P = 0.038$).

Discussion

In this study, two groups of volunteers diagnosed with chronic migraine were compared, through the use of nutraceutical and placebo, to evaluate the effect of OPFAω-3 in the prevention of attacks of headache. Therefore, in order to obtain valid and consistent data, a correct diagnosis was established for the research subjects, according to the ICHD-3β criteria.[16]

In addition, we opted for the description of the characteristics of pain and associated manifestations, as these variables are specific to migraine and may be used in the diagnosis of the sample, as demonstrated in this study.

The two comparison groups received OPFAω-3 and placebo and were prophylactically treated with the same drug. Amitriptyline was chosen because it is a well- known drug effective in the prevention of migraine. In addition, low doses prescribed contributed to the emergence of a few adverse effects.

Throughout the research, only nine patients dropped out of treatment because they presented some anticholinergic effects or antihistamines of amitriptyline (weight gain, dry mouth, constipation, or drowsiness)[18]or frequent nausea from the use of nutraceutical.

The dietary supplementation with OPFAω-3 did not exceed 1.5 g per day because doses above 3.0 g / day could lead to risks of bleeding and immune system depression.

When we start the prophylactic treatment of migraine, we must understand the different pathophysiological mechanisms of this disease. Among these mechanisms, we highlight the neurogenic and perivascular inflammation and vasodilation of the meningeal arteries.[19,20] According to several studies, the

Table 2 Distribution of headache characteristics in 27 chronic migraine patients using amitriptyline and OPFAω-3 and 24 using amitriptyline and placebo

Variables	Categories	Comparison groups		*P*-value
		Use of OPFAω-3 *n* (%)	Control *n* (%)	
Onset of pains (years)	<1	1 (3.7)	–	0.766*
	1–4	3 (11.1)	2 (8.3)	
	5–9	4 (14.8)	7 (29.2)	
	≥10	19 (70.4)	15 (62.5)	
Duration of headache attacks (hours)	<4	5 (18.5)	7 (29.2)	0.573†
	4 to 72	19 (70.4)	15 (62.5)	
	>72	3 (11.1)	2 (8.3)	
Pain location	Unilateral	18 (66.7)	14 (58.3)	0.746
	Bilateral	9 (33.3)	10 (41.7)	
Pain character	Pulsatile	21 (77.8)	17 (70.8)	0.806‡
	Dull or pressure	4 (14.8)	6 (25.0)	
	stabbing	2 (7.4)	1 (4.2)	
Worsening of headache with physical activity	No	9 (33.3)	10 (41.7)	0.746
	Yes	18 (66.7)	14 (58.3)	
Aura presence	No	24 (88.9)	22 (91.7)	0.890
	Yes	3 (11.1)	2 (8.3)	
Associated symptoms	Nausea, vomiting	15 (55.6)	12 (50.0)	0.594¶
	Photophobia and phonophobia	2 (7.4)	4 (16.7)	
	Nausea, vomiting, photophobia and phonophobia	10 (37.0)	8 (33.3)	

Legend: *P* values calculated using the chi-square test, comparing: *onset of pain <10 years versus onset of pain ≥10 years; †headache attacks lasting < 4 hours versus ≥ 4 hours; ‡pulsatile versus dull/pressure or stabbing; ¶nausea and vomiting versus photophobia and phonophobia /nausea, vomiting, photophobia, and phonophobia.

Table 3 Distribution of frequency of headache attacks in 27 chronic migraine patients using amitriptyline and OPFAω-3 and 24 using amitriptyline and placebo, after 60 days of treatment

Frequency of headache attacks (Days / month)	Comparison groups		*P*-value
	Use of OPFAω-3 *n* (%)	Control *n* (%)	
≤5	18 (66.7)	8 (33.3)	0.036
6–10	4 (14.8)	7 (29.2)	
11–15	2 (7.4)	4 (16.7)	
16–20	2 (7.4)	1 (4.2)	
21–25	–	2 (8.3)	
26–30	1 (3.7)	2 (8.3)	

Legend: *P*- values calculated using the chi-square test, comparing frequency of headache attacks ≤5 days per month versus frequency of headache attacks >5 days per month.

eicosanoid prostaglandins and leukotrienes are mediators of this inflammation and produce headache and other symptoms, such as nausea and vomiting.

Prostaglandins and thromboxanes, arachidonic acid metabolites, and cyclooxygenase are potent mediators of inflammation and are higher in migraine patients. Therefore, anti-inflammatory drugs are used for treating migraine attacks and provide evidence for the involvement of eicosanoids in the pathogenesis of headaches.[14,21]

Several drugs are used in the prevention of headache attacks in migraine patients. However, there are other non-pharmacological treatments, including acupuncture, relaxation techniques, biofeedback, psychotherapy, and dietary therapy.[4–7]

In relation to dietary therapy, it has been observed that some functional foods have protective and preventive effects on various diseases.[22,23] Among these foods are the OPFAω-3, fats not synthesized by the human body, such as EPA, DHA, and docosapentaenoic that could help in reducing the frequency and intensity of headache attacks by stimulating the synthesis of serotonin receptors[24] and alleviating various inflammatory processes.[10,13–15,21,25] These fatty acids are present in greater quantities in deep water fish oils,

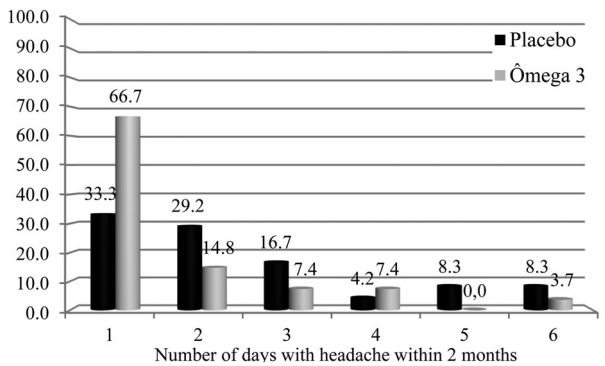

Figure 1 Distribution of frequency of headache attacks in 27 chronic migraine patients using amitriptyline and OPFAω-3 and 24 using amitriptyline and placebo, after 60 days of treatment.

Table 4 Distribution of frequency improvement of headache attacks in 27 chronic migraine patients using amitriptyline and OPFAω-3 and 24 using amitriptyline and placebo, after 60 days of treatment

Frequency improvement of headache attacks (%)	Comparison groups		*P*- value
	Use of OPFAω-3 *n* (%)	Control *n* (%)	
>50	22 (81.5)	3 (12.5)	0.038
>75	23 (85.2)	15 (62.5)	

such as salmon, tuna, mackerel, herring, cod, albacore, anchovy, dogfish, and sardines.[26,27]

In our study, most patients with chronic migraine who did dietary supplementation with OPFAω-3 by more than 80.0% the number of headache days per month, confirming that the functional nutrition is useful in patients with chronic pain.[11,12,28] Possibly, this beneficial effect of OPFAω-3 resulted in a decrease in the production of prostaglandins and leukotrienes[15,25] or a change in the release of serotonin by platelets.[9,24]

Amitriptyline was administered to both groups because this is a classic treatment for migraine and for ethical reasons we could not fail to treat these patients. Indeed, we believe that A OPFAω-3 was better than placebo. This significant difference observed in the group that used OPFAω-3 should be attributed to OPFAω-3. Regarding the low response (33%) for the group that used amitriptyline and placebo, it is possibly due to the small dosage of amitriptyline and treatment with monotherapy.

Other studies have also shown that there is a decrease in the frequency and intensity of migraine attacks with the use of products rich in OPFAω-3,[8,9,13,14] especially when OPFAω-3 is associated with OPFAω-6.[11]

This study was important because we evaluated the efficacy of dietary supplementation with OPFAω-3 associated with pharmacological prophylaxis in patients with chronic migraine.

Conclusions

Dietary supplementation with polyunsaturated omega 3 fatty acids OPFAω-3, associated with migraine prophylactic, may reduce the frequency and intensity of headache attacks in migraine patients.

Disclaimer statements

Contributors All authors contributed equally.

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Conflicts of interest None.

Ethics approval The study was approved by the Ethics in Research Involving Human Subjects Committee at the Santo Agostinho College, Brazil, protocol number 1.252.372 and the Presentation Certificate to Ethics Assessment, registry number 6835215.6.0000.5602, on September 30, 2015. All participants signed the informed consent form.

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