

# The effects of sodium valproate with fish oil supplementation or alone in migraine prevention: A randomized single-blind clinical trial

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## Keywords

Fish Oil, Migraine, Sodium Valproate, Pain

## Abstract

**Background:** Omega-3 polyunsaturated fatty acids (PUFA) have beneficial effects on both specific and non-specific inflammatory reactions. The aim of this study was to evaluate the effect of dietary supplementation with fish oil in migraine prevention.

**Methods:** A 12-week, randomized, single-blind clinical trial was conducted from October 2008 to June 2009. A total of 67 patients (52 women, 15 men) with migraine headache were randomly allocated to 2 groups. In the first group, 38 patients (30 females with a mean age of  $35 \pm 9$  year) received 400 mg/day sodium valproate. In the second group, 29 patients (22 females with a mean age of  $36 \pm 9$  years) received sodium valproate 400 mg daily plus fish oil supplementation (180 mg). Response to the treatment was assessed at 0, 1, 2, and 3 months after start of the therapy.

**Results:** A significant decrease in duration, monthly frequency, and severity of headache after month 1, 2, and 3

in comparison with month 0 occurred in both groups. There was a significant reduction in headache severity ( $P = 0.046$ ) and frequency ( $P = 0.044$ ) in the group with fish oil supplementation after month 1 in comparison with sodium valproate alone. In contrast, there was no significant difference between two treatment groups in duration of the headache after month 1. Mean intensity, mean duration and mean frequency of the attacks after month 2 and 3 were not significantly different between the two groups.

**Conclusion:** This study demonstrated that sodium valproate plus fish oil supplementation significantly reduces migraine headache more than sodium valproate alone but only at the beginning of the treatment.

## Introduction

The management of recurrent migraines has consisted mainly of prophylactic medications and behavioral treatments. However, the results are not entirely satisfactory and side effects are a major problem with prophylactic drug treatment.<sup>1,2</sup>

Migraine is thought to have a polygenetic and

multifactorial etiology.<sup>3</sup> Neurogenic and perivascular inflammation has been implicated in pathophysiology of migraine.<sup>4</sup> The eicosanoids, prostaglandins (PGs) and leukotrienes (LTs), cyclooxygenase and lipoxygenase pathway products, are inflammatory mediators involved in the pathogenesis of headaches.<sup>5-7</sup>

Polyunsaturated fatty acids (PUFA), which represent approximately 30% of intracellular fatty acids, are essential dietary components not synthesized by humans. The fatty acid composition of inflammatory and immune cells alters according to the fatty acid composition of the diet. In particular, the proportion of different types of polyunsaturated fatty acids ( $\omega$ -3,  $\omega$ -6 PUFA) in these cells is changed, and this presents a relation between dietary PUFA intake, inflammation, and immunity.<sup>1,8</sup>

Among the fatty acids, the omega-3 PUFA acquires the most potent immunomodulatory activities. Among the omega-3 PUFA, those from fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are more biologically potent than other components. They are structurally and functionally distinct from the  $\omega$ -6 PUFA.<sup>9,10</sup>

The specific fatty acids, EPA and DHA, are homologues of the  $\omega$ -6 fatty acid, arachidonic acid and contend with  $\omega$ -6 PUFAs for the production of PGs and LTs.<sup>11</sup> Typically, human inflammatory cells contain high proportions of the  $\omega$ -6 PUFA arachidonic acid and low proportions of  $\omega$ -3 PUFA.

At sufficiently high intakes, long-chain n-3 PUFAs, as found in oily fish and fish oils, arachidonic acid replace by EPA in inflammatory cell membranes. This change leads to decreased production of arachidonic acid-derived mediators. This response alone is a potentially beneficial anti-inflammatory effect of  $\omega$ -3 PUFA.

Thus, long-chain  $\omega$ -3 PUFAs act their anti-inflammatory role directly (by inhibiting arachidonic acid metabolism) and indirectly (e.g., by altering the expression of inflammatory genes through effects on transcription factor activation).<sup>12</sup> Several studies have shown that  $\omega$ -3 fatty acids are required for the optimal functioning of the nervous system. Additionally,  $\omega$ -3 PUFA have beneficial effects on both specific and non-specific inflammatory reactions and the production of cytokines; this led them to be tried therapeutically in several immunological and inflammatory processes.<sup>1,12</sup>

There have been a number of clinical trials assessing the benefits of dietary supplementation with fish oils in several inflammatory and autoimmune diseases in humans, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis and migraine headaches. The clinical efficacy of fish oil was shown in rheumatoid arthritis and heart disease but it was weak in inflammatory bowel diseases, asthma and

migraine.<sup>12,13</sup> Data about migraine is inconsistent, therefore, better designed, and larger trials are required to assess the therapeutic potential of long-chain n-3 PUFAs in migraines. The aim of this study was to evaluate the effect of fish oil as a supplement that was added to sodium valproate in the treatment of migraine.

## Materials and Methods

This study was a 12-week, randomized single-blind clinical trial to evaluate the effect of fish oil in the prophylactic treatment of migraine headaches.

Consecutive patients who sought treatment for migraine headache were evaluated in neurology clinic of Noor Hospital affiliated to Isfahan University of Medical Sciences, Iran, between October 2008 and June 2009.

The migraine headache was defined according to International Headache Society (IHS) criteria.<sup>14</sup> Eligibility criteria were as follows: (1) migraine without aura for at least 3 months before study and a frequency of 3 or more headache attacks per month during the past 3 months; (2) no concurrent treatment; (3) no serious concomitant medical problems, such as history of renal stones, cardiac disease, liver disease, or malignancy; (4) not currently lactating or pregnant; and (5) available for follow-up for 6 months. Patients with neurological diseases or taking any prophylactic treatment for headache at the moment of our observation were also excluded. Local ethical committee approval was granted, and the nature of the trial and possible side effects of the drugs was explained to the patient. After a detailed discussion with neurologist, patients made a final decision and each patient signed an informed consent.

Fish oil was prepared as soft gel capsules. Each 1-g  $\omega$ -3 capsule consisted of EPA (180 mg) and DHA (120 mg). Sodium valproate (NaV) 400 mg daily for a total of 3 months was also used as a main drug in two groups.

A total of 130 participants (32 males, 98 females) were assigned randomly and equally to one of the two treatment groups. The first treatment group received NaV 400 mg daily for 3 months. The second group received fish oil 2 capsules per day added to NaV (400 mg daily) for 3 months.

All patients had a pretreatment evaluation that consisted of demographic data and frequency, severity and duration of migraine headache and previous treatments. During the study period, patients were asked to decrease taking analgesic, and in any case not to take it more than once a day.

The trial was single blinded and physicians were not aware of the treatment type that patient received. Patients were evaluated at baseline, 1, 2 and 3 months after the start of the therapy to evaluate the

compliance of the patients and efficacy parameters. A 10-point visual analog scale (VAS) evaluated the severity of headache (with 0 indicating no pain and 10 indicating "the worst pain imaginable"). Patients' age, gender, severity of headache, frequency of headache per month, duration of headache, name and dosage of drugs used were determined before and after 1, 2 and 3 months of treatment.

The results were analyzed by SPSS for Windows version 15 (SPSS Inc, Chicago, IL, USA). The results were reported as the mean  $\pm$  SD. The variables were compared between groups by Student's t test or with Mann-Whitney U test or Fisher's exact test, as appropriate.

## Results

One hundred and thirty patients agreed to participate in the study. All subjects reported frequent headaches occurring at least 3 months before the study entry with a frequency of 3 or more headache attacks per month during the past 3 months. Sixty seven patients (52 women, 15 men) were included in the final analysis. Fifty three patients dropped out of the study, 4 because of pregnancy, the others because of failure to comply, or unable to follow. The mean age of patients was 35.3  $\pm$  9.6 years, ranged from 14 to 50 years (mean  $\pm$  SD).

Sixty seven patients who completed the treatment were available for follow-up after 1, 2 and 3 months. At baseline, NaV group had slightly more frequency of headache and lower duration of migraine than fish oil

plus NaV group. The two groups were generally well matched at baseline with regard to age, gender and other migraine characteristics (Table 1).

A significant decrease in the duration, monthly frequency, and severity of headache after the first, second, and third month compared to baseline occurred in both groups (Table 2). There was a significant reduction in headache severity ( $P = 0.046$ ) and headache frequency ( $P = 0.044$ ) in NaV plus fish oil in comparison to NaV group after the first month. In contrast, no significant difference between the two treatment groups was detected in duration after first month. Correspondingly, mean severity, mean duration and mean frequency of the attacks after second and third month were not significantly different between the two groups (Table 2).

## Discussion

In the present study, patients suffering from migraine headaches experienced a significant reduction in frequency, duration, and severity of headaches during the first, second, and third month of treatment in both treatment groups, NaV alone and NaV plus fish oil. In comparison between the two groups, only a significant more reduction in severity and frequency was seen after first month treatment in NaV plus fish oil group. It suggests more rapid effect of supplementary fish oil in reducing the severity and frequency of headache in first month, but in contrast, this rapid effect does

**Table 1.** Characteristics of patients by treatment group at baseline

Characteristics	Sodium valproate N = 38	Sodium valproate plus fish oil N=29	P-value
Age (years)	34.6 (9.5)	36.3 (9.6)	0.518
Male/female	8/30	7/22	0.429
Severity of migraine headache	7.6 $\pm$ 1.8	7.9 $\pm$ 1.9	0.092
Duration of migraine headache	13.3 $\pm$ 13.2	16.7 $\pm$ 17.6	0.891
Frequency of migraine headache	15.4 $\pm$ 16.0	13.7 $\pm$ 15.1	0.06

**Table 2.** Comparison of headache severity, duration, and frequency in migraine patients before and after treatment with sodium valproate alone or sodium valproate plus fish oil

Treatment groups	Headache severity (VAS) Mean (SD)	Headache duration (hours) Mean (SD)	Headache frequency per months Mean (SD)
Sodium Valproate			
Baseline	7.6 (1.8)	13.3 (13.2)	15.4 (16.0)
After therapy			
month 1	3.9 (2.4)	6.3 (11.0)	5.4 (7.7)
month 2	4.0 (3.2)	7.6 (10.2)	6.3 (7.9)
month 3	4.0 (2.5)	7.8 (7.6)	4.9 (6.4)
Sodium Valproate plus Fish oil			
Baseline	7.9 (1.9)	16.7 (17.6)	13.7 (15.1)
After therapy			
month 1	2.9 (2.3)	5.9 (8.1)	2.4 (2.2)
month 2	3.6 (2.6)	10.0 (12.5)	3.0 (2.0)
month 3	4.6 (3.0)	7.5 (7.9)	4.8 (7.5)

not continue in other months. The significant increase in severity and duration after third month compared to the first month by fish oil added on NaV raises the possibility that patients benefited from fish oil administration in the first month but it seems that taking more medications during the second and third month did not have additional benefit for them. Therefore, it appears that the anti-inflammatory effect of fish oil does not continue for long time.

In 1985 and 1986, two double-blind cross-over studies, with a small number (5/15) of patients showed a decrease in migraine attack frequency with the use of a product rich in  $\omega$ -3 PUFA. This product was a kind of oil from fish flesh containing 30%  $\omega$ -3 PUFA (EPA, 18% and DHA, 12%).<sup>15,16</sup> A parallel design was conducted by Pradalier et al. in 2001.<sup>1</sup> In this double-blind placebo study, the dose of 6 g a day was chosen with this product and they used migraine attack frequency as the main parameter. This 6-month study failed to show a significant difference in frequency of headache compared to placebo and they did not find the positive results demonstrated on a small number of patients by the two previous studies.<sup>1</sup> Another study was a small double-blind crossover study of 27 adolescents over 5 months that subjects took two capsules per day of a marine  $\omega$ -3 ethyl ester concentrate for 2 months. Each 1-g n-3 ethyl ester concentrate soft gel capsule consisted of EPA (378

mg), DHA (249 mg), and tocopherol (2 mg).<sup>17</sup> This study showed no difference between fish oil supplementation and "placebo supplementation" with olive oil.

Interestingly, the subjects reported dramatic decreases in headache frequency and severity with both compounds; the possibility of olive oil being an active component and was not proper placebo.<sup>17</sup>

Consequently, the result of studies was controversial and it needs more study with larger sample size to confirm the effect of fish oil in migraine headache.

This study had some limitations; the dose of fish oil that was used previously as a supplement was 3000-6000 mg per day but we used only 2 capsules per day of a product that consisted of EPA 180 mg and DHA 120 mg. Secondly, the number of study population was limited because of the difficulties in the follow up. Finally, we did not have an appropriate placebo group and as a consequence, the findings were single blinded.

In conclusion, this study demonstrated that sodium valproate with fish oil supplementation significantly reduces the frequency and severity of migraine headache better than sodium valproate alone in short term. However, this effect was disappeared after one month and did not continue for long term. To confirm this hypothesis, it is needed to do more study with larger sample size and long term follow up.

## References

- Pradalier A, Bakouche P, Baudesson G, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: a double-blind study versus placebo. *Cephalalgia* 2001; 2:818-22.
- Harel Z, Gascon G, Riggs S, et al. Supplementation with Omega-3 Polyunsaturated Fatty Acids in the Management of Recurrent Migraines in Adolescents. *Journal of Adolescent Health* 2002; 31:154-61.
- Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden and the need for preventive therapy. *Neurology* 2007; 68:343.
- Ferrari MD. Migraine. *Lancet* 1998; 351:1043-51.
- Ebersberger A, Averbek B, Messlinger K, et al. Release of substance P, calcitonin gene-related peptide and prostaglandinE2 from rat dura mater encephali following electrical and chemical stimulation in vitro. *Neuroscience* 1999; 89:901-7.
- Mezei Z, Kis B, Gecse A, et al. Platelet arachidonate cascade of migraineurs in the interictal phase. *Platelets* 2000; 11:222-5.
- Pradalier A. Immunologic aspects of migraine. In: Olesen J, Tfelt-Hansen P, Welch KM, editors. *The Headaches*. New York: Lippincott-Williams-Wilkins, 2000:277-82.
- Calder PC. Polyunsaturated fatty acids, inflammation, and immunity. *Lipids* 2001; 36:1007-24.
- Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr*. 2002; 21:495-505.
- Calder PC. Dietary modification of inflammation with lipids. *Proc Nutr Soc*. 2002; 61:345-5.
- Cleland LG, James MJ, Proudman SM. The role of fish oils in the treatment of rheumatoid arthritis. *Drugs*. 2003;63:845-53.
- Calder PC. N-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006; 83(6 Suppl):1505S-1519S.
- Gibson RA. The effect of diets containing fish and fish oils on disease risk factors in humans. *Aust N Z J Med*. 1988; 18:713-22.
- Headache Classification Committee of the International Headache Society. *The International Classification of Headache Disorders*. *Cephalalgia* 2004; 24:1.
- Mccarren T, Hitzemann R, Smith R, et al. Amelioration of severe migraine by  $\omega$ -3 fatty acids. *Clin Res*. 1985; 33:275A.
- Glueck CJ, McCarren T, Hitzemann R, et al. Amelioration of severe migraine with  $\omega$ -3 fatty acids: a double-blind, placebocontrolled clinical trial. *Clin Res*. 1986; 34:796A.
- Crawford P, Simmons M, Hoock J. Clinical inquiries. What dietary modifications are indicated for migraines? *J Fam Pract*. 2006; 55:62-3, 66.