Improving the Response Rate in Migraine Headache Attacks

This article at a glance

- This study addressed the potential effectiveness of daily EPA/DHA for migraine headaches in adults with chronic migraine also taking low-dose amitriptyline, a drug used for migraine prevention.
- Participants taking both EPA/DHA and amitriptyline for 2 months reported a major reduction in the frequency of headache attacks.
- The results of this study warrant new studies to confirm the significant effect of the EPA/DHA intervention.
Migraine is one of the most common disorders of the central nervous system. Migraine manifests most typically as recurrent headaches that can last from ~4 hours to three days. Migraine headaches are disabling for many people: it has been estimated that some 10% of adults worldwide have migraine, and this may account for 1.3% of all years of life lost to disability worldwide. Several drugs are available to treat migraine, which act to acutely abort the pain, or are used prophylactically to reduce the frequency and duration of migraine attacks. In some countries, the prevalence of migraine is particularly high, for example in Brazil 15.3% of adults have been reported to be affected. The public health impact of migraine is however, not strongly emphasized, with poor recognition and marked under-diagnosis and under-treatment. In only 12% of countries worldwide are headache disorders included in an annual health-reporting system. Self-treatment of headaches is performed by half of the affected individuals globally. Further attention to migraine diagnosis, and improvements in safe and effective approaches to prevent and treat the disorder are clearly needed.

One area of research on migraine has addressed the question if omega-3 long-chain polyunsaturated fatty acids (omega-3 LCPUFA) may play a role in modulating the frequency and severity of migraine. The rationale is that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce serotonin (5-hydroxytryptamine) release from platelets and modulate vasodilation, two processes that have been associated with the etiology of migraine headaches. Furthermore, omega-3 LCPUFA may regulate peri-vascular
inflammation, another process implicated in migraine. Furthermore, a lower intake of both EPA and DHA is furthermore associated with a higher frequency of migraine headache attacks. However, at present the totality of evidence concerning the dietary or supplemental intake of omega-3 LCPUFA in migraine prevention is conflicting and insufficient to support or refute their use.

Specific limitations in studies on migraine prevention need to be taken into account. A marked placebo effect is observed in trials that assess migraine prophylaxis using drugs, even under randomized, controlled and blinded conditions. In clinical trials that assess the effect of migraine prophylactic drugs, one-third to a half of the patient population studied respond to placebo. Response is usually defined as a reduction of at least 50% in the monthly frequency of migraine headaches. For example, amitriptyline is a tricyclic anti-depressant drug that is used as first-choice treatment for migraine prophylaxis, but its response rate is only about 20% higher than placebo. The choice of the control oil used in the control treatment is also very important, to rule out an effect of the control treatment itself (for example, olive oil intake may have a beneficial effect on migraine headaches). Study design and co-medication should be carefully controlled.

Important progress in the understanding of possible links between migraine and polyunsaturated fatty acids has come from the recent demonstration that increases in dietary omega-3 LCPUFA intake, and the consequent improvement in tissue levels, in combination with a decrease in dietary intake of omega-6 LCPUFA and tissue arachidonic acid levels, can effectively lower migraine symptoms. A dietary
intervention that increases omega-3 and reduces omega-6 LCPUFA intake significantly reduced headache frequency and duration, promoted the formation of endogenous antinociceptive (pain-reducing) lipid mediators, and improved the quality of life in patients with severe migraine. Modulation of the descending nociceptive control pathways was already recognized as an important mode of therapeutic action of drugs used for migraine prophylaxis. The analgesic activity of EPA and DHA is mediated in part through specific epoxide derivatives that can be produced from these fatty acids endogenously. How EPA/DHA intake may interact with current pharmacological prophylaxis of migraine and could modulate headache symptoms had not been studied.

A recent randomized controlled trial has investigated the potential relative benefit of oral EPA/DHA supplementation for migraine prevention in patients also taking amitryptiline. The study was performed by de Almeida Soares and colleagues in the Center of Neurology and Headache of Piauí, Botica Pharmacies, Santo Agostinho College, and the Department of Neurology, Universidade Federal do Piauí, all in Teresina, Brazil. The researchers were experienced in attending to patients with migraine, and stated their interest in assessing the use of certain types of foods in helping alleviate the frequency of headache attacks. Against this background, in this study they specifically determined the potential benefit of supplementation with omega-3 LCPUFA for migraine prevention.

Sixty chronic migraine patients with daily headaches were randomly assigned to two study groups. The recruited patient group consisted of a convenience sample, i.e. 60

Although relatively small, this is the first randomized controlled intervention study to explore the potential benefit of the omega-3 long-chain polyunsaturated fatty acids EPA and DHA for migraine in adults also taking a low dose of amitriptyline, a drug used to prevent headache attacks.
patients that were first seen at the migraine center and were diagnosed with chronic migraine were included in the study. Diagnosis was made according to the criteria of the International Classification of Headache Disorders. All participants were prescribed a relatively low dose of amitriptyline (10 mg/day). The omega-3 group received 800 mg EPA and 700 mg DHA daily, as a microencapsulated powder formulation taken with a glass of water, divided over a twice daily intake before meals. The control group received the same powdered formulation containing starch. The organoleptic properties of the supplements were identical, employing the same flavoring, sweetener and dye. The intervention was carried out for 60 days after which the patients were re-evaluated. Nine patients dropped out during the study.

No significant differences were found between the groups with respect to gender distribution or age (~35 years). In both groups, approximately twice as many women than men were present, in line with the higher prevalence of migraine in women. No other anthropometric details were collected at baseline. The patients maintained a headache diary during the study period, allowing to record the frequency (number of days with headache) and severity (scoring of 1 to 10 on a visual-analogue scale, with 1 being absence of pain, and 10 very strong pain) of headache attacks. At study onset, there were no significant differences between the two groups with respect to headache characteristics: i) the time of onset of migraine symptoms prior to study enrollment (the majority of individuals had been having migraine for more than 10 years), ii) the duration of headache attacks (the majority reported attacks lasting between 4 and 72 hours), iii) pain location (two-thirds had unilateral migraine, i.e. pain on one side of the head), iv) the pain character (most patients reported pulsating pain), v) the headache worsening with physical
activity (more than half of participants confirmed it), vi) the presence of aura (about 10% of patients), or vii) the presence of other symptoms that frequently accompany migraine.

A comparison of headache characteristics reported during the two months revealed that a significantly greater reduction in the frequency of headache attacks had occurred in the omega-3 plus amitriptyline group (n=27 individuals) compared to the control amitriptyline-only group (n=24). In both groups, nearly all patients displayed some level of improvement in the number of days with headache. The response rate in the supplemental EPA/DHA plus amitriptyline group was 81.5%, i.e. a large majority of chronic migraine patients taking EPA/DHA and low-dose amitriptyline reported a more than 50% improvement in the frequency of attacks compared to the beginning of the study. In the control group the response rate was 12.5%.

People reporting headache attacks during 5 or fewer days a month made up two-thirds of the omega-3 plus amitriptyline group compared to one-third of the individuals receiving amitriptyline only. The duration of headaches was also significantly improved: individuals taking EPA/DHA reported a marked reduction in the number of days with headache for two days or longer, and twice as many people with headaches lasting one day compared to the control group.

This study suggests that on a background of prophylactic intervention with amitriptyline, the supplemental intake of EPA/DHA may be highly beneficial to chronic migraine patients, in reducing both the frequency and duration of migraine headaches. The study was
relatively small, and the results should be confirmed in larger patient groups. Although the study had collected data on migraine headache severity, no results were reported on this. Neither were detailed characteristics of the headaches, as recorded at baseline, reported at the end of the study. The study report was not very clear in its presentation of the results, somewhat affecting the general positive message about the suggested benefits that the study uncovered.

It is unclear if the reported benefits would extend to all patients with migraine. The study subjects were furthermore identified by convenience sampling, and not randomly from a larger group of migraine patients. The predominance of female patients is in line with the higher prevalence of migraine in women, in general and in Brazil. The results in men and women were not reported separately though, and would be of interest to examine. It is unlikely that EPA/DHA supplementation would cause harm, but will probably help a substantial portion of people suffering chronic migraine headaches. There was no mention of dietary assessment, which would be important to better understand the relative improvements that can be achieved by EPA/DHA supplementation.

Gaining improved appreciation of the benefit that omega-3 LCPUFA supplementation could offer in terms of added efficacy to the current preventive migraine medications, could be an interesting objective of future studies and provide valuable treatment approaches for migraine patients. For example, in a small study on childhood migraine the daily supplementation with 1 gram EPA/DHA added to an already efficacious dose of valproate did not provide a further reduction in headache frequency or severity, compared to that achieved with valproate alone. On the other hand, a small daily supplemental dose of fish oil has been shown to provide a reduction in migraine headache frequency and severity within
1 month of treatment with valproate in adults (although the added benefit compared to valproate alone disappeared after 1 month). Amitriptyline treatment in the present study was associated with a response rate of 12.5%, which is within the efficacy range of the placebo response rate. EPA/DHA supplementation improved the response rate to 81.5%, suggesting that a true prophylactic effect might be attributed to these fatty acids. The current study used a relatively low dose of amitriptyline, suggesting that the add-on prophylaxis with EPA/DHA is highly efficacious.

While the use of controlled diets in the prevention of migraine is supported by evidence, a need for larger trials in the field is recognized. Increased omega-3 LCPUFA intake is easily achieved either by ingesting more EPA/DHA-rich foods, mainly fish, or by supplementation, and has a high safety margin, but further substantiation of the new findings is needed in order to develop practical recommendations, in particular with respect to concurrent migraine medication and the totality of dietary PUFA intake. Working towards this substantiation could be a worthwhile goal that may possibly help many people suffering from migraine.


Worth Noting


Queiroz LP, Silva AA. The prevalence and impact of headache in Brazil. Headache 2015;55(S1):32-38. [Link]


Tajmirria M, Soheilipour M, Basiri K, Shaygannejad V, Ghorbani A, Saadatnia M. The effects of sodium valproate with fish oil supplementation or alone in migraine prevention: A