

Proof-of-Principle, Open-Label Prospective Cohort Trial of a Novel Nutraceutical for the Prevention of Refractory Migraine

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Received date: August 19, 2015; Accepted date: October 26, 2015; Published date: October 30, 2015

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Abstract

Objective: To estimate the possible effectiveness of a novel nutraceutical for the prevention of attacks of migraine.

Materials and methods: Six months open-label “proof-of-principle” prospective cohort trial in 15 consecutive patients with refractory migraine using a novel nutraceutical.

Results: Five patients were considered non-responders. In the 10 responders the mean number of episodes decreased from 12.3 (SD: 6.6) in the 6 months before treatment to 3.6 (SD: 3.2) during treatment ($p=0.002$), the mean duration of attacks decreased from 1.75 (SD: 0.63) days to 0.95 (SD: 0.44) days ($P=0.016$), and the total number of days with migraine per month decreased from mean 3.13 (SD: 1.42) to 0.54 (SD: 0.52) ($P=0.002$), corresponding to a diminution of 74%. Comparison of responders and non-responders revealed patients with 21 or more attacks in the 6 months before treatment not to improve.

Conclusion: This preliminary trial suggests the intake of the novel nutraceutical to significantly reduce the burden of migraine in two thirds of patients with refractory disease, particularly in subgroups with 21 or less episodes in 6 months.

Key words:

Migraine; Nutraceutical; Prevention

Introduction

It is estimated that approximately 17% of women and 6% of men suffer from migraine, but only 12% of them take migraine-preventing medication, though another 17% use medications with potential anti-migraine effects for other medical reasons [1]. First line preventive medicinal treatments are beta-blockers, tricyclic antidepressants, calcium channel blockers, anticonvulsants, and less commonly ergot-alkaloids and the derivative methysergide. However, a number of patients fail to respond to these “standard” preventive treatments and are considered refractory [2]. Rational combination therapy [3], treatment of co-morbidities, avoidance of modifiable risk factors, and the use of non-pharmaceutical food supplements have been recommended [4-10], while medication overuse should be discouraged [11,12].

Many theories attempt to explain the pathophysiology of migraine. Most recently the role of calcitonin gene-related peptide (CGRP) has become the focus of research. This peptide is a potent vasodilator and can function in the transmission of pain. Its implication in the pathogenesis of migraine [13] may lead to the development of antagonists that may be used as new therapeutic agents for migraine [14]. At the other hand, proton ((1)H) and phosphorus ((31)P) magnetic resonance spectroscopy has revealed major reduction of high-energy phosphates production in the occipital lobe of migraine-

without-aura patients [15-17], suggesting the presence of a mitochondrial component in the pathophysiology. The latter findings corroborate the hypothesis of Burnstock [18] on the importance of purinergic signalling in the brain [19,20] and its deregulation in the pathophysiology of migraine.

Many patients suffering from migraine use triptanes to suppress acute migraine attacks. These vasoconstrictors affect muscle energy metabolism and reduce mitochondria function, explaining their side-effects [21]. Hence, the American migraine prevalence and prevention (AMPP) study has identified important unmet medical needs in current migraine management [22].

More than a decade ago we have introduced a nutraceutical food supplement for the treatment of infertile men with asthenozoospermia that enhances energy production by the sperm mitochondria [23]. Later we successfully prescribed a similar product to patients with chronic fatigue syndrome/myalgic encephalopathy [24]. Several patients spontaneously reported a reduction of the number of migraine attacks, their duration and intensity during intake of the nutraceutical. Therefore, we undertook a proof-of-principle prospective trial to assess the possible benefit of the nutraceutical food supplementation in patients primarily consulting for refractory migraine.

Materials and Methods

Fifteen consecutive patients, 13 women and two men (father and son) consulting at the private clinic of each one of the co-authors were included in this open-label, prospective cohort trial. They presented

with refractory migraine of at least 6 months duration. The mean age at intake was 41.3 years (SD 10.4 years, range between 24 and 59 years). After history taking and thorough investigation and treatment of comorbidity, the patients were invited to participate in the trial and received add-on treatment with a nutraceutical food supplement containing balanced amounts of vitamins B6, B9 and B12, pine bark extract, astaxanthin from *Haematococcus pluvialis*, the extract of *Lepidium meyenii* (Maca), l-acetyl carnitine, ubiquinone Q10, zinc picolinate and selenomethionine (Improve®, Nutriphyt, Oostkamp, Belgium)(formulation in annex), and fish oil rich in docosahexaenoic acid (DHA; 22:6ω3) and eicosapentaenoic acid (EPA; 20:5ω3) (Omarin®, Nutriphyt, Oostkamp, Belgium). The patients were requested to return for control and follow-up visits after 3 and 6 months of treatment.

The frequency of attacks of migraine was recorded as well as their duration. The average burden of migraine per month was calculated by multiplying the number of attacks with their duration in each one of the six months observation period, divided by 6.

Statistics were performed with the MedCalc statistical programme (MedCalc, Ostend, Belgium) [25]. Since the number of observations was low and the distribution of the results was not Normal for all variables, both parametric tests (mean and standard deviation) and non-parametrical tests (median and 95% confidence intervals) were applied. The non-parametrical Wilcoxon test for paired observations was used to calculate the statistical significance of changes during treatment. Also the receiver operating characteristic (ROC) curve was plotted and analysed in order to assess the clinical usefulness of treatment (Area under the Curve), and to identify the criterion value optimally differentiating between patients who did or did not benefit from treatment [26].

Results

In the majority of patients the migraine occurred without aura, and it was triggered by hormonal events, namely the menstrual period (6

out of 13 women), or by sleep deprivation (3 cases), or by loud noise (2 cases), or by specific food ingredients (2 cases). Several patients presented significant comorbidity including Bechterew’s disease, so-called chronic Lyme’s disease, neuralgia of the major occipital nerve (Arnold), irritable bowel syndrome, insulin resistance, hyperparathyroidism, or chronic fatigue syndrome.

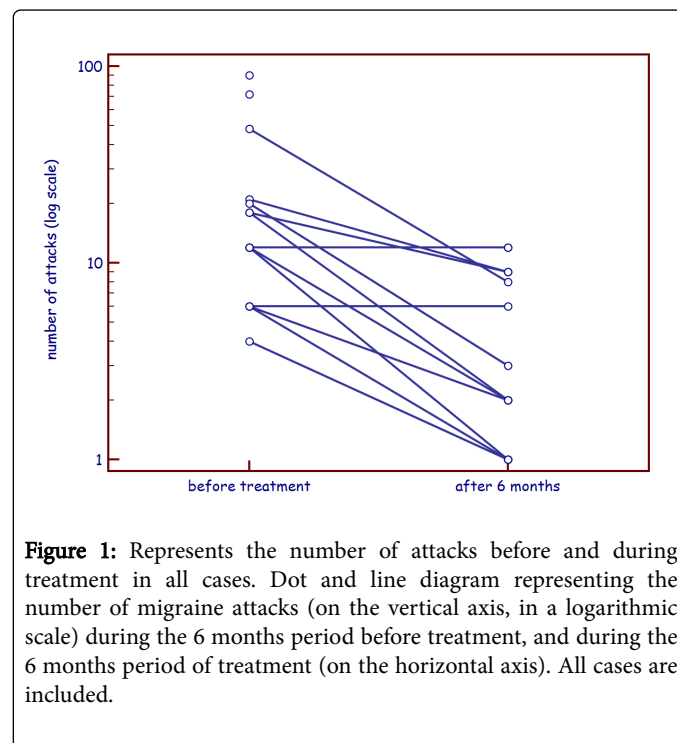


Figure 1: Represents the number of attacks before and during treatment in all cases. Dot and line diagram representing the number of migraine attacks (on the vertical axis, in a logarithmic scale) during the 6 months period before treatment, and during the 6 months period of treatment (on the horizontal axis). All cases are included.

	Number of cases	Number of attacks	Duration of attacks	Burden per month
		Mean (SD) Median (95% CI)	Mean (SD) Median (95% CI)	Mean (SD) Median (95% CI)
Before treatment All cases	15	23.8 (25.7)* 12.0 (7.6-38;0)	1.61 (0.77)** 1.5 (1.0-2.0)	4.06 (2.84)* 3.0 (2.0-5.6)
During treatment All cases	13	5.2 (4.3)* 3.0 (2.7-7.8)	1.15 (0.68)** 1.0 (0.8-1.2)	1.2 (1.66)* 0.5 (0.3-1.5)
Before treatment Responders	10	12.3 (6.26) 12.0 (6.0-19.0)	1.75 (0.63) 2.0 (1.0-2.0)	313 (1.42) 3.0 (2.0-4.3)
During treatment Responders	10	3.6 (3.2) 2.0 (1.0-7.6)	0.95 (0.44) 1.0 (0.5-1.0)	0.54 (0.52) 0.3 (0.2-1.0)

Table 1: Treatment results. *P=0.002; **P=0.016. Number of attacks is the total number of migraine attacks that have occurred in a 6 months period. The data “during treatment all cases” include the patients who were not lost to follow-up only. Duration of attacks is the average duration of attacks in a 6 months period (in days). Burden per month: number of attacks × duration of attacks averaged per month (in days).

Two patients dropped out, and are considered failures of treatment or non-responders. Of the remaining 13 patients, 3 did not present any improvement and are also considered non-responders.

The results are listed in Table 1. There is a highly significant reduction of the number and duration of migraine attacks during treatment, both in the total population, and evidently in the

responders. On an average the burden of migraine in the responders was reduced by 74% (Figure 1).

The mean number of attacks in the period before treatment was significantly higher in the non-responder (46.8, SD: 35.1) than in the responders (12.3, SD: 6.6) ($P=0.002$), whereas the mean duration of the attacks was similar (1.35, SD: 0.40 days in non-responders, compared to 1.75, SD: 0.2 days in responders, $P=0.26$). In the ROC curve analysis of the responders compared to non-responders, the area under the curve was 0.80 ($P=0.021$), with sensitivity 100, specificity 60 at criterion value of 21 migraine attacks during the 6 months before treatment. None of the patients with number of attacks exceeding the criterion value benefited from treatment.

Discussion

Several publications have reported a favorable effect of nutraceutical food supplementation on the severity of migraine. In the present approach we have aimed at activating the mitochondrial function and increasing the generation of adenosine triphosphate (ATP) by giving carnitine. The nutraceutical formulation also included the anti-oxidant carotenoid Astaxanthin and the oxido-reductase ubiquinone Q10. The pro-anthocyanidine in pine bark extract exerted a predominantly anti-inflammatory activity. *Lepidium* extract (Maca) was added because of its phyto-adaptogenic effect increasing the production of the protective heat shock protein HSP72 in response to stress. The combination of Vitamins B6, B9 and B12 reduced the homocysteine concentration [27-29] which has been related to migraine. Zinc-picolinate plays a pivotal role in immunity and inflammation [30] and as modulatory factor of brain function [31], whereas selenium-methionine may add an epigenetic effect reducing DNA-methylation [29,33]. In addition, the long-chain poly-unsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) were given, since these provide the substrate for the Krebs metabolic cycle in the mitochondria generating ATP (adenosine triphosphate). This unique combination of ingredients was proven to be well-tolerated and not to cause any side effects.

All patients received treatment of their co-morbidity before initiation of the trial, whenever possible. One third of the patients did not report any favourable effect of the nutraceutical, with the number, duration and severity of migraine attacks remaining unchanged. These patients had a higher frequency of attacks than those who did respond to treatment. In fact, the food supplementation failed to exert any beneficial effect in a subgroup of patients with more than 21 attacks in the six months preceding inclusion in the trial. This confirms the findings of the American Migraine Prevalence and Prevention Study in patients with high-frequency migraine [22], and may suggest that the pathophysiological mechanisms could be different in these patients. In two thirds of the cases the nutraceutical intake was associated with a significant decrease of the number and duration of migraine attacks over the 6 months treatment period, reducing the burden on well-being caused by the disease.

This is an open-label prospective trial in a limited number of patients with migraine attacks refractory to classical treatment modalities. The number of cases is small because of the preliminary character of the trial, which aimed at proof-of-principle at the one hand, and the stringent criteria for the selection of patients included at the other hand [2]. However, the small number of cases should raise caution regarding the generalisation of the conclusions, and it seems indicated to start a double-blind, preferentially multi-centre, trial on a

larger number of patients. This novel nutraceutical having no side-effects, it could be safely tested as add-on therapy.

Annex

Formulation of nutraceutical

Astaxanthin: 1.5 mg; Acetyl-L-carnitine: 100 mg; Ubiquinone Q10: 25 mg; Zinc-picolinate: 7.5 mg; Selenium-methionine: 50 µg; Vitamin B6 (pyridoxine): 3 mg; Vitamin B9 (folic acid): 200 µg; Vitamin B12 (cobalamin): 1.5 µg; Pine bark extract: 35 mg; *Lepidium meyenii* (Maca): 250 mg; per tablet (Belgian patent # 1021188).

Dosage=1 tablet, together with 1000 mg fish oil (DHA, EPA) twice per day.

Clinical Implications

A novel nutraceutical food supplement given to patients suffering from refractory migraine was successful in decreasing the number and duration of attacks in two third of cases, particularly among those with less than 21 attacks in 6 months. Since this supplement did not cause any side effects it may be considered as add-on treatment, though further trials are needed.

- patients suffering from refractory migraine with frequency of less than 21 attacks in 6 months commonly benefit from add-on nutraceutical food supplementation
- in these patients a novel nutraceutical reduces the burden of migraine with 74%
- the nutraceutical has no side effects and does not interfere with medication
- a double-blind trial using the nutraceutical as add-on therapy is warranted

Conflict of Interest

The first author is holder of the patent of the nutraceutical. The second author declares no conflict of interest.

Acknowledgment

The authors thank Mr. Gabriel Devriendt (Nutriphyt ltd, Oostkamp, Belgium) for providing the material for the clinical trial.

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