

Palmitoylethanolamide-based nutraceutical Calmux® in preventive treatment of migraine

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ABSTRACT

Background: The aim of this study was to determine the efficacy and tolerability of treatment with a Palmitoylethanolamide (PEA)-based nutraceutical in patients with episodic migraine.

Methods: A pilot, prospective, open-label experimental study was designed in which patients with episodic migraine with and without aura seen in the general practice office of a tertiary centre during a period of 6 months were offered the possibility to participate. No control group was included. All included patients were treated with nutraceutical Calmux® taken every 12 h for 3 months. Monthly attack frequency, attack intensity, impact of migraine (HIT-6 and MIDAS scales) and quality of sleep at baseline and after 3 months of treatment were compared.

Results: Twenty-five patients (22 women and 3 men) were included, with a mean age of 36.3 ± 12 years. Headache days per month decreased from 10 ± 2.1 days to 6.6 ± 3.6 days ($p < 0.00001$). Days of analgesic use decreased from 9.2 ± 2.6 days to 4.1 ± 2.1 ($p < 0.0001$). None of the patients included suffered from adverse events attributable to treatment. Pain intensity showed a mean reduction of 3.1 points, from 8.1 at baseline to 5 at 3 months of treatment ($p < 0.005$).

Conclusions: PEA nutraceuticals could be useful in migraine prevention. Further studies are necessary, but we consider that PEA-based nutraceutical could be a new approach in the treatment of migraine patients.

1. Introduction

The estimated prevalence of migraine is 11.6%, with 11.4% in Europe and 16.4% in Central and South America [1]. Migraine has a clear female predominance, with an approximate ratio of 2:1, and it is associated with a negative impact on the quality of life and functionality of those who suffer from it, being considered among the top 20 causes of disability in the adult population by the World Health Organisation. Despite the significant loss of quality of life and decrease in work performance and productivity, it remains underdiagnosed and undertreated [2]. Different classes of oral medications are used for migraine prevention; most frequently used are antiepileptic drugs, antidepressants, betablockers, calcium channel antagonists and serotonin antagonists. These preventive pharmacological treatments for migraine are non-specific drugs, with a high rate of therapeutic failure, that can be as high as 67% [3]. Moreover, all these medications are associated with several side effects [4]. Betablockers can produce bradycardia, fatigue, hypotension, sexual dysfunction and depression. Anticonvulsants are associated with asthenia, dizziness, somnolence, difficulty with memory

and concentration and fatigue. Antidepressants can cause dry mouth, blurry vision, somnolence, constipation, weight gain and urinary retention. And calcium channel antagonist may induce weight gain, somnolence, dizziness and depression [5]. For all these reasons, it remains a priority to find therapeutic alternatives that allow migraine patients to improve without the appearance of undesirable adverse effects.

Calmux® is a nutraceutical marketed in Spain to treat pain and inflammation. It is composed of PEA (400 mg), Scutellaria (400 mg), Boswellia (250 mg) and Harpago (200 mg), and its recommended dose is one capsule twice a day.

Palmitoylethanolamide (PEA), an amide formed by ethanolamine and palmitic acid, is an endogenous lipid that modulates pain and inflammation through an action that has been shown in different studies to be effective in different pain disorders and has an excellent tolerability profile [6–8]. Lo Verme et al. identified the peroxisome proliferator-activated receptor (PPAR) alpha as the receptor mediating the anti-inflammatory actions of PEA [9]. As has been reported, the PPAR-alpha and PPAR-beta/delta levels are significantly higher during

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the migraine attack than during the headache free period and there is also difference between patients with migraine and healthy controls, suggesting that PPARs are involved in the pathogenesis of migraine [10]. Furthermore, PEA has been shown to downmodulate mast cell activation and, applied exogenously has demonstrated anti-inflammatory effect in mast cell-mediated experimental models of acute and chronic neurogenic inflammation [11]. Thus, different anti-inflammatory mechanisms have been identified that could have a beneficial effect specifically in the treatment of migraine. The usefulness of PEA in the preventive treatment of nummular headache was suggested by Chirchiglia et al. [12]. Papetti et al. reported the efficacy and low rate of adverse events of preventive treatment with PEA in a pediatric population of patients with migraine [13]. Chirchiglia et al. studied efficacy and safety of treatment with ultramicrosized PEA for 3 months in patients with migraine with aura, and observed a reduction in days with headache, but they did not assess the impact of migraine in quality of life of patients [14]. For these reasons we consider that a pilot study exploring tolerability, efficacy, and impact in quality of life of a PEA-based treatment in adults with migraine could bring an alternative way to treat these patients.

Boswellia serrata is a medium-sized shrub whose resin contains up to 12 types of acids, 6 of which have an inhibitory action on enzymes involved in inflammation: α - and β -boswellic acids, acetylated α - and β -boswellic acids, 11-keto- β -boswellic acid and 3-O-acetyl-11-keto- β -boswellic acid [15]. The anti-inflammatory action of boswellic acids is caused by different mechanism of actions, mainly the inhibition of leukotriene synthesis and, to a lesser extent, prostaglandin synthesis and inhibition of the complement system. Scutellaria Baicalensis is an herbal extract that has shown anti-inflammatory effect; its mechanism of action includes inhibition of cyclooxygenase (COX-2), contributing to a decrease in prostaglandin synthesis, thus developing a systemic anti-inflammatory function [16]. Harpagophytum procumbens is an herbal extract, whose main compounds are iridoid glycosides, such as harpagoside, harpagide and procumbide; Harpagophytum has been largely used for anti-inflammatory and analgesic purposes for osteo-articular disorders [17]. Anti-inflammatory effect of Harpagophytum has been related to the inhibition of the synthesis of pro-inflammatory cytokines and decrease in COX-2 levels [18].

The aim of this study was to determine the efficacy and tolerability of treatment with a combination of 400 mg PEA + 400 mg Scutellaria + 250 mg Boswellia + 200 mg Harpago (Calmux®) twice a day in patients with episodic migraine.

2. Methods

2.1. Study design

We performed a pilot, prospective open-label study from January 2021 to June 2021 in patients seen in the general practice office in Hospital Universitario de Gran Canaria Dr. Negrin, a tertiary centre covering the population of the northern area of the island of Gran Canaria.

An initial sample size of 25 participants was estimated as the initial phase of this pilot study. The formula for comparing two averages was used for the calculation of this sample size: $N = [2(Z_{\alpha} + Z_{\beta})^2 * S^2] / d^2$, where N is the sample size, Z is the value corresponding to desired risk, S is the variance of the quantitative variable that has the reference group and d is the minimum value of the difference to be detected.

2.2. Inclusion and exclusion criteria

Inclusion criteria.

- 1) Diagnosis of episodic migraine (with or without aura) according to IHS-3 criteria.

- 2) More than 3 migraine attacks or more than 6 headache days per month.
- 3) Age over 18 years.

Exclusion criteria.

- 1) Current treatment with other preventive drugs.
- 2) IHS-3 criteria for headache with analgesia abuse are met.
- 3) Patients refusing to participate in the study.

2.3. Intervention

All included patients were treated with a formulation consisting of 200 mg PEA + 200 mg Scutellaria + 125 mg Boswellia + 100 mg Harpago taken every 12 h for 3 months.

Patients included were allowed to use analgesic treatment with non-steroidal anti-inflammatory drugs or triptans if needed. No other preventive treatments were allowed during the participation in the study.

Three visits were performed: a baseline inclusion visit (V1), a second visit 4 ± 1 week after the baseline visit (V2) and a third visit 12 ± 2 weeks after the baseline visit (V3).

At the baseline visit, the following variables were collected: age, sex, profession, employment status, medical and surgical history, with special interest in the presence of anxiety, depression, fibromyalgia or other chronic pain disorders, treatments that the patient was taking at the time of the visit for any previous process, type of migraine: with or without aura, number of days per month with headache in the previous 3 months, number of days per month taking any analgesic for headache in the previous 3 months, number of days visiting the emergency department due to headache in the previous 3 months, migraine-related quality of life using the MIDAS questionnaire, impact of migraine on their life using the HIT-6 questionnaire, presence of symptoms of depression, anxiety or stress using the DAS-21 questionnaire, sleep quality using the Pittsburgh sleep questionnaire.

At visit 2, the following variables were collected: presence of adverse effects of any kind, number of days per month with migraine in the previous month, number of days per month with headache in the previous month, number of days per month taking any analgesic for headache in the previous month, number of days visiting the emergency department due to headache in the previous month.

The following variables were collected at visit 3: number of days per month with migraine in the previous 3 months, number of days per month with headache in the previous 3 months, number of days per month taking any analgesic for headache in the previous 3 months, number of days visiting the emergency department due to headache in the previous 3 months, migraine-related quality of life using the MIDAS questionnaire, impact of migraine on your life using the HIT-6 questionnaire, presence of symptoms of depression, anxiety or stress using the DAS-21 questionnaire, sleep quality using the Pittsburgh sleep questionnaire.

The categorical variables were summarized in frequencies and percentages, while the numerical ones in averages and standard deviations (SD) or in medians and interquartile ranges (IQR), depending on whether or not the normality assumptions were given. The percentages were compared with the chi-square test; means, to the t-test; and medians with Wilcoxon test and Mann-Whitney U test for independent data. Data analysis was performed using the SPSS version 19 statistical package.

2.4. Ethical aspects

The study design was approved by the Clinical Research Ethics Committee of the Fernando Pessoa Canarias University (Code: 2020-07-06; approved on 10th October 2020).

The researcher explained to each participant the nature of the study, its purposes, its procedures, its estimated duration, the potential risks

and benefits derived from participation in the study, as well as any inconvenience that the study might entail. Each participant was advised that their participation in the study was voluntary and that they could leave the study at any time, without affecting their subsequent medical treatment or their relationship with their treating physician.

Each participant was given a patient information sheet before dating and signing the informed consent form.

3. Results

Twenty-five patients (22 women and 3 men) were included, with a mean age of 36.3 ± 12 years. Table 1 shows the baseline characteristics of the study participants. The population included 88% female and 12% male. Of all patients included, 80% had a diagnosis of episodic migraine without aura and 20% had a diagnosis of episodic migraine with aura. All patients included received Calmux® for three months. None of them left the study before the end of the study.

Thirty-six percent of the included patients ($n = 9$) had a $> 50\%$ reduction in the number of headache days after 3 months of treatment.

The number of days with headache per month after 3 months of treatment decreased from 10 ± 2.1 days to 6.6 ± 3.6 days ($p < 0.0001$), which meant a 33% reduction (Fig. 1). The number of days of analgesic use decreased from 9.2 ± 2.6 days to 4.1 ± 2.1 ($p < 0.0001$), which meant a 55.4% reduction.

When assessing the influence of treatment on the MIDAS scores, the number of patients with severe disability decreased from 64% to 28% ($p = 0.04$). Also, on the HIT-6 scale, there was a 50% reduction in patients reporting moderate or severe headache-related impact ($p = 0.08$), as shown in Fig. 2. On the MIDAS pain intensity question, there was a mean reduction of 3.1 points from 8.1 at baseline to 5 at 3 months of treatment ($p < 0.005$).

When analysing the Pittsburgh sleep quality questionnaire scores, no differences were found between the baseline visit and the visit after 3 months of treatment, remaining at a total of 4.

Thirty-six percent ($n = 9$) and 40% ($n = 10$) of participants reported feeling much better or a little better, respectively, on the patient's impression of global improvement scale score. Twenty-four percent ($n = 6$) reported no change after 3 months of treatment.

In terms of the occurrence of adverse effects, no medication-attributable effects were reported in any of the study participants, and none of the patients included abandoned the study.

After completion of the study period, 36% ($n = 9$) remained on monotherapy, 36% ($n = 9$) added a conventional preventive treatment and 28% replaced the study treatment with a conventional preventive.

■ V1 ■ V2

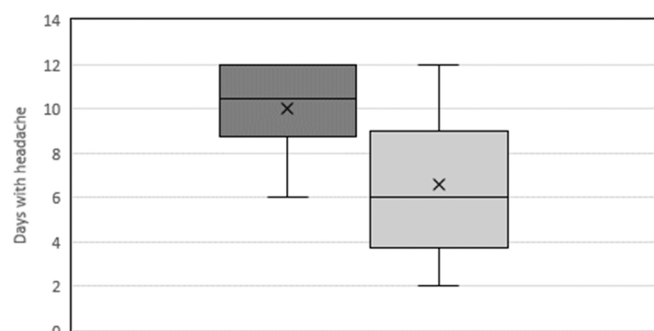


Fig. 1. Reduction in the number of days with headache after 3 months of treatment.

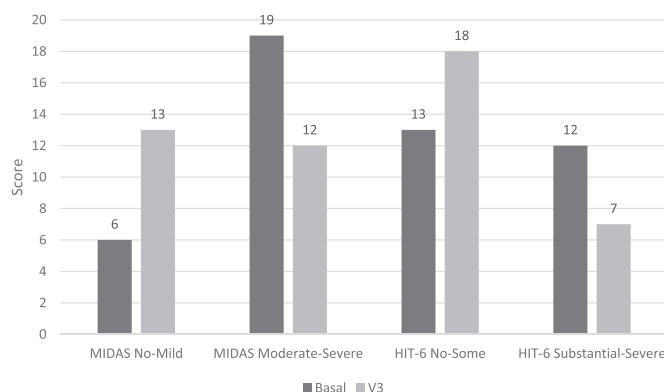


Fig. 2. MIDAS and HIT-6 scores after 3 months of treatment.

4. Discussion

Our study suggests that preventive treatment with PEA-based nutraceutical Calmux® is well tolerated and improves the frequency and intensity of migraine attacks, as well as disability related to migraine.

Preventive treatment of migraine is primarily aimed at reducing the frequency of attacks and making them milder and therefore easier to manage. The aim of preventive therapy is to reduce the frequency and severity of attacks by at least 50%, reduce dependence on acute medication, and improve the quality of life of people with migraine [19]. Although 38% of migraine patients could benefit from preventive therapies, it is estimated that only 11% currently receive them [2,19]. Thus, the Migraine Atlas, conducted by researchers at the University of Seville in 2018, found that 51.1% of people with migraine did not take any type of preventive medication and 47.8% of people with migraine who took preventive treatments stated that their efficacy was average [20]. In our study, 1 out of 3 patients treated had a reduction of more than 50% in days of pain, with a reduction of 3.37 days and 5.1 days in days per month with headache and with the need for analgesia, respectively. This indicates that PEA-based nutraceutical Calmux® could reduce the number of days with headache and the intensity of the crises, so that, although there are still days with pain, these are less intense and do not require analgesic treatment. This was reflected in the question regarding pain intensity on the MIDAS scale, which went from an average of 8.1 at the baseline visit to 5 after 3 months of treatment. At present, few studies have been published on PEA in the treatment of migraine. In a previous study, Chirchiglia et al. showed that treatment with 1200 mg of ultramicrosized PEA decreased number of days with headache from 3.1 ± 0.6 days/month to 2.0 ± 1 day/month ($p = 0.000$) in patients with migraine with aura. Reduction in pain intensity and duration was most evident at 60 days and was maintained

Table 1
Baseline characteristics of study participants.

Age	36,3 ± 12 years
Female sex (%)	22 (88%)
Type of migraine	
– Without aura	20 (80%)
– With aura	5 (20%)
Preventive treatments	
– Not current or previous (%)	17 (68%)
– Previous use only (%)	8 (32%)
– Current use (%)	0
History of previous preventive	
– Lack of efficacy	20
– Adverse effects	80
Migraine assessment in V1	
– Days of headache per month	10 ± 2,1 days
– Days of analgesic use	9,2 ± 2,6 days
– MIDAS Moderate-severe	19 (76%)
– MIDAS pain scale	8,1 ± 1
– HIT-6 major-severe	12 (48%)
– Pittsburgh Sleep Questionnaire	6,8 ± 2,9

until 90 days [14]. Recently, Papetti et al. published the results of a study in which they treated 70 paediatric patients with episodic migraine with 600 mg/day of PEA, comparing the frequency of onset of pain with the situation in the 3 months prior to treatment, and found that in 63% of cases the frequency of pain was reduced by more than 50%. In both studies, the tolerability of PEA was good [13].

In our study, we also observed a 36% reduction in patients who reported moderate or severe disability on the MIDAS scale, and a 50% reduction in patients with a major or severe impact according to the HIT-6 scale. Both the reduction in the number of attacks and their lower intensity are factors that have a positive influence on the perception of quality of life and on the impact of migraine on the lives of migraine sufferers. We consider this is an interesting finding because the considerable impact of migraine on the individual and on society is well known, as it can limit work, family or social activities, as well and it can affect quality of life. Thus, the Migraine Atlas showed that almost 75% of migraine patients had moderate to very severe levels of disability as measured by MIDAS scale [20].

A very interesting finding is that none of the patients included in this study suffered adverse effects attributable to the drug, and none had discontinued treatment after 3 months of treatment. These results are in line with previous studies carried out to evaluate treatments with PEA, showing that PEA is well tolerated by the patients and tolerability profile is favourable. Another relevant factor in our study is that subjective perception of patients is favourable to treatment with the nutraceutical Calmox®, as reflected in the score on the patient's global impression of improvement scale, in which 1 out of 3 patients reported feeling much better, and 2 out of 3 reported having noticed some improvement.

Palmitoylethanolamide is an amide formed by ethanolamine and palmitic acid, which is part of the endogenous lipids that modulate pain and inflammation. Several studies have identified how the PPAR receptor alpha mediates the anti-inflammatory actions of this lipid amide [9]. In addition, PEA has shown direct action by inhibiting mast cells in their formation of pro-inflammatory substances. In turn, it acts on microglia by correcting the transmission of the pain impulse upstream to the CNS, where it also has a positive effect on CB1 and CB2 receptors in the neuron, modulating the pain processing response [9]. The efficacy of PEA in the treatment of pain has been demonstrated in several studies. In 2017, Artukoglu et al. conducted a meta-analysis of published work, including data from 10 studies collecting data from 786 cases and 512 controls. Although the studies were not homogeneous, it was concluded that PEA appeared to be effective in the treatment of chronic pain due to different substances, although the heterogeneity of the studies did not allow firm conclusions to be drawn [7]. Similar conclusions were reached by Gabriellsson et al. in a review of all clinical trials related to the treatment of pain with PEA [6]. In both studies, PEA showed an excellent tolerability profile, with almost no undesirable adverse effects reported, except for isolated cases of gastrointestinal discomfort [6,7]. Although migraine has a complex pathophysiology, involving structures of the central and peripheral nervous system, there is evidence to support the existence of inflammatory mechanisms in the genesis of migraine [21]. Thus, among the factors studied in recent years, PPAR receptors (peroxisome proliferation activation receptors) have been shown to be a promising target in the pathophysiology of migraine. There are three types of PPARs, alpha, beta/delta and gamma, each with different functions related to inflammatory and anti-inflammatory mechanisms. Thus, He-Min et al. showed that PPAR alpha and beta/delta levels were elevated in migraine patients during migraine attacks compared to inter-crisis periods and non-migraine controls, while PPAR gamma was decreased, suggesting a strong relationship between PPAR receptors and the genesis of migraine attacks [10]. On the other hand, De Icco et al. have recently shown how PEA may be involved in the ictal phase of migraine, probably by influencing spinal nociceptive sensitization [22].

We are aware of the limitations of this study. First, we designed an open-label study without a control group. This may have influenced the

perception of patients, who may be subject to a placebo effect, as well as the predisposition to take a treatment presented to them as a natural alternative. Second, the studied sample was small; a larger sample size would have allowed a more precise study of the effect on the reduction of pain days and analgesia use, as well as the impact on quality of life. On the other hand, it is likely that a larger sample size would have increased the rate of adverse events. Third, our follow-up was short, so we can not reach conclusions about the duration of the effect of treatment. However, we consider that the results, while not definitive, do allow us to assess the potential of PEA-based nutraceuticals in the preventive treatment of migraine. Our aim in this study is not to draw definitive conclusions about the efficacy of the nutraceutical Calmox® in the treatment of migraine, but rather to demonstrate a new approach that will make it possible to determine the future role of PEA in the treatment of migraine patients.

CRediT authorship contribution statement

Ayoze González Hernández: Conceptualization, Methodology, Validation, Formal analysis, investigation, Data management and Writing.

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