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Efficacy of Palmitoylethanolamide (Levagen+™) Compared to Ibuprofen for Reducing Headache Pain Severity and Duration in Healthy Adults: A Double-Blind, Parallel, Randomized Clinical Trial

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Abstract

Background: Palmitoylethanolamide (PEA) has shown promise as an analgesic for those with chronic pain pathologies. With recently increased bioavailability, PEA may also be a treatment for acute pain presentations such as tension-type headaches. **Aim:** To assess the efficacy of a bioavailable PEA formulation (Levagen+™) for reducing the severity and duration of acute episodes of tension-type headaches when compared to a standard treatment, nonsteroidal anti-inflammatory drug (NSAID) (the comparator). **Methods:** The study was a double-blind, randomized, single site, comparator controlled clinical study, with the cohort consisting of otherwise healthy adults, aged between 18 and 71, who experienced regular tension-type headaches. 94 adults experiencing headaches were randomised to receive either PEA (n = 47) or Ibuprofen comparator (n = 47). Upon headache onset, participants consumed their allocated product, recorded pain levels using a visual analogue scale (VAS) and continued to log their pain scores at 30-minute intervals for up to 4-hours. **Results:** Eighty-six participants (44 active treatment and 42 comparator) recorded at least one headache with a total of 271 tension-type headaches recorded (120 active treatment and 151 comparator). Most headaches were reduced in both treatment arms by 2 hours and almost all by 4 hours; 90% in the PEA group, and 97% in comparator group, $p > 0.5$. For moderate at onset headaches, the comparator group had a greater percentage of pain-free

events at 2-hours. However, the time taken to resolve severe headaches was significantly lower in the PEA group than the comparator group ($p < 0.05$). **Conclusions:** These results place PEA as a potential treatment option for tension-type headaches.

Keywords

PEA, Palmitoylethanolamide, Headaches, Levagen, LipiSperse

1. Introduction

Headaches are broadly separated into two categories: primary and secondary. Primary includes tension-type headaches, migraines and cluster headaches while secondary refers to headaches caused by infection, injury or tumour [1] [2] [3]. The pathophysiology of primary headaches is a complex process involving neuronal dysfunction [2] [4], activation of pain pathways [4], upregulation of inflammatory processes in vascular structures [2] [5] [6], sensitization to pain stimuli [5] and musculoskeletal abnormalities [7]. Treatment for headaches usually incorporates over the counter pain relieving medication and lifestyle management [1] [2] [3].

The primary treatment for headaches is pharmaceuticals such as Ibuprofen and aspirin [1] [2]. Prolonged use of these medications has been shown to lead to potential adverse health outcomes including gastrointestinal upset [8] [9] and cardiovascular [8] [9], renal and hepatic effects [8]. Additionally, tolerance to some medications can occur [10], which can increase the incidence of medication over-use headaches (MOH) [11]. These reasons identify the need for other treatment options with a good safety and tolerability profiles.

Palmitoylethanolamide (PEA) is a locally acting endogenous fatty acid derivative that is ubiquitously expressed in body tissues including the brain [12] [13]. PEA is produced on-demand from cell membranes as a protective response to noxious stimuli [14] [15]. PEA's analgesic and anti-inflammatory effects have been documented for over 50 years [14] and confirmed in several chronic pain studies [7] [9] [15] [16] [17] [18]. Along with down-regulating multiple proinflammatory and nociceptive pathways [19], PEA is known to inhibit mast and glial cell activity [9] [20], both of which are involved in the pathogenesis of pain and inflammation [9] [18].

PEA is of particular interest as a treatment for chronic tension-type headaches. Research has demonstrated that PEA is safe and well tolerated when taken daily (from 300 mg to up to 1200 mg per day) for management of chronic pain conditions [13]. Previously, pilot studies have found that ultra-micronized PEA improved the frequency, duration, and severity of migraine headaches as either a standalone treatment or in combination with standard NSAIDs [15] [16]. While PEA has been previously compared to Ibuprofen for treating osteoarthritis symptoms [9], this is the first study to compare PEA to an Ibuprofen comparator for

headache treatment.

The aim of this study was to assess the efficacy of a bioavailable PEA formulation utilising LipiSperse® dispersion technology (Levagen+™) compared to a traditional therapy, Ibuprofen, in reducing the pain/severity and duration of tension-type headaches. We hypothesize that PEA supplementation will reduce the perceived pain/severity and duration of headaches comparatively to that of Ibuprofen.

2. Materials and Methods

2.1. Participants

94 healthy males and females aged over 18 years and experiencing at least two headache episodes per month were recruited Australia wide to remotely participate in the study. Participants were randomized into the study in a 1:1 ratio to the PEA or comparator group. Inclusion criteria included participants with no history or evidence of clinically significant medical conditions including but not limited to, cardiovascular, neurological, psychiatric, renal, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled in addition to access to a computer or smart phone for completing online questionnaires and events. Participants were excluded if they had long term use of medications (unless for a controlled medical condition), malignancy or treatment for malignancy within the previous two years, chronic past and/or current alcohol use (>14 alcoholic drinks per week). Other exclusion criteria included smokers, females not currently using a prescribed form of contraception (*i.e.* oral contraception pill, birth control implant e.g. implanon). Participants that were allergic or hypersensitive to any of the ingredients in the active or ibuprofen formula as well as females who were pregnant or breastfeeding were also excluded. Recruitment concluded when the target sample size was reached.

This study was conducted in compliance with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and was conducted in accordance with ethical approval from Bellberry Limited (approval number 2017-05-397-A-3); an NHMRC accredited Human Research and Ethics Committee and registered on the ANZCTR (ACTRN12618000294257). All participants were evaluated for eligibility and provided informed consent prior to commencing the study. This study was conducted between May 2019 and June 2020.

2.2. Treatment

The active treatment was provided by Gencor Pacific Ltd. (Discovery Bay, Hong Kong) as a finished product consisting of a combination of a proprietary formulation of PEA with the bioavailability enhancement technology LipiSperse® [Pharmako Biotechnologies Pty. Ltd. (Sydney, Australia)] and sold under the brand name Levagen+™. Each 525 mg dose of Levagen+ contained 450 mg of

PEA and ~75 mg of LipiSperse [which contains excipients polyglycerol polyricinoleate (E476), coconut oil fractionated, lime oil, olive oil, lecithin (sunflower and/or oat) (E322), silica (E551), vitamin E], taken at the first onset of headache symptoms. The comparator was 400 mg of Ibuprofen in matching capsules. The capsules were packaged in high-density polyethylene (HDPE) bottles with a HDPE tamper tell lid. The packaging, labelling and dosage administration of the comparator was the same as the active treatment.

Participants randomized to the treatment group (PEA; n = 47), or the comparator group (Ibuprofen; n = 47). Product allocation was conducted via Random Allocation Software (sealedenvelope.com) through a block randomisation list. All randomisation and product allocation procedures were conducted by someone independent to the study. Study investigators, participants and statistical analysis individuals were all blinded to the random allocation of the study products. Both the PEA and comparator products were housed in trial product containers that were identical in function and appearance.

Enrolment in this study was for a maximum of 4-months. During enrolment, participants were provided with enough product to record data for a maximum of five different headache episodes. At the first onset of headache symptoms, participants logged into a secure online portal to record their perceived pain (VAS) and consume their trial product. Through the online portal, participants could also record any rescue medication use and adverse events. Headache pain (VAS) was recorded every 30 minutes until pain subsided or for a maximum of 4-hours (whichever occurred first). A headache was considered resolved and event recording stopped when a VAS score of zero was recorded.

2.3. Outcomes

The primary outcome for this study was reduction in pain/severity as assessed by VAS for pain over the 4-hours from symptom onset. Secondary outcomes included time required for resolution of headache (*i.e.*, time from dose to return to a VAS score 0), proportion of participants reporting resolution at 2- and 4-hours and change in pain relief medication used during each headache episode. Product tolerability was assessed after each acute headache episode using the gastrointestinal tolerance questionnaire and adverse effect reporting. All adverse events, either spontaneously reported by the participant or noticed by the medical supervisor were recorded for the entire study duration.

2.4. Statistical Analysis

Sample size calculations predetermined that at least 35 participants were required for each group to detect a reduction of at least 25% in VAS pain score from supplementation (effect size of 0.8 with power at 0.85 and $\alpha = 0.05$).

2.5. Statistical Tests

Participants reporting rescue medication use within the first 2-hours of symp-

tom onset were excluded from analysis. Analysis was conducted using either R (reference) using a range of native statistical functions and in some cases functions from the packages tidyverse, dplyr and ggplot. Slope analysis and some graphing were completed in Microsoft Excel. This was completed for all primary and secondary outcomes. All results were first tested for normality before any other test was conducted. Based on the distribution of the data, the appropriate statistical tests were used. Differences between groups were assessed using independent t-tests and covariates were accounted for with an ANCOVA. If rescue treatment was used, that event will be given the maximum (most severe) score for that episode. In addition to this, the two groups were compared (t-test) for rescue treatment use as a means of further testing the efficacy of the treatment. A significant difference between groups was considered at a level of $p < 0.05$.

The complete dataset contained five records that were incomplete (only a starting headache intensity was recorded). These were removed from the dataset prior to analysis. The VAS data were in most cases not normally distributed, and a range of transformations failed to render most of the subsets normal. Mann-Whitney U tests were therefore used to analyze continuous-variable differences (*i.e.* numerical analyses of reported VAS changes) between groups for the metrics reported here. For categorical variables (such as proportion of headaches resolved or reduced from a higher severity category to a lesser one), differences were analyzed with Fisher's Exact test for one-dimensional tests and Mantel-Cochran-Haentzel Chi-squared tests for two-dimensional analysis, as shown in Results.

Thresholds of VAS values of >65 = severe, 30 - 65 = moderate, and 1 - 29 = mild was established for categorical analysis (as per HIS protocol) of reduction in pain following treatment.

3. Results

Both the PEA and comparator groups were normally distributed with no significant differences between groups at baseline (Table 1). 94 participants enrolled in the study, of which 86 recorded at least one headache, with a total of 269 headaches recorded (Table 1; Figure 1). There were fewer headache events recorded by the PEA group compared to the comparator group, which was not significant. Differences in headaches recorded did not unbalance any statistical test performed.

No significant differences were found for visual analogue scale (VAS) for pain scores at the onset of headache between groups ($p \sim 0.10$) (Table 2). There was no significant difference between groups for severity of headache at onset (Table 2).

The comparator group had a greater percentage of pain free events ($p < 0.05$) at 2-hours for moderate at onset headaches compared to the PEA group (Table 3). Headaches that were mild at onset were not statistically analyzed due to the small sample size (comparator n = 14, PEA n = 12).

Table 1. Baseline characteristics.

	Comparator	PEA
Participants (n)	47	47
Male/Female (%)	12/88	14/86
Participants Reporting Headaches (n)	42	44
Age (years)	43.3 (15.1)	39.0 (11.1)
Headaches per participant (n)	3.6 (1.5)	2.7 (1.4)
Headaches per month (n)	9.9	7.9

Results are mean (SD); PEA = palmitoylethanolamide; SD = standard deviation.

Table 2. Baseline headache severity.

	Comparator	PEA
Total headache observations (n)	149	120
Mild at onset (n)	14	12
Moderate at onset (n)	68	66
Severe at onset (n)	67	42
VAS score [n (SD)]	59.64 (18.4)	56.68 (17.9)

PEA = palmitoylethanolamide; VAS = Visual Analogue Scale; SD = Standard deviation.

Table 3. Headaches pain free at two hours.

	Comparator	PEA
Mild headaches resolved (%)	79	42
Moderate headaches resolved (%)	65*	42
Severe headaches resolved (%)	49	45

*significant difference between groups $p < 0.05$; PEA = palmitoylethanolamide.

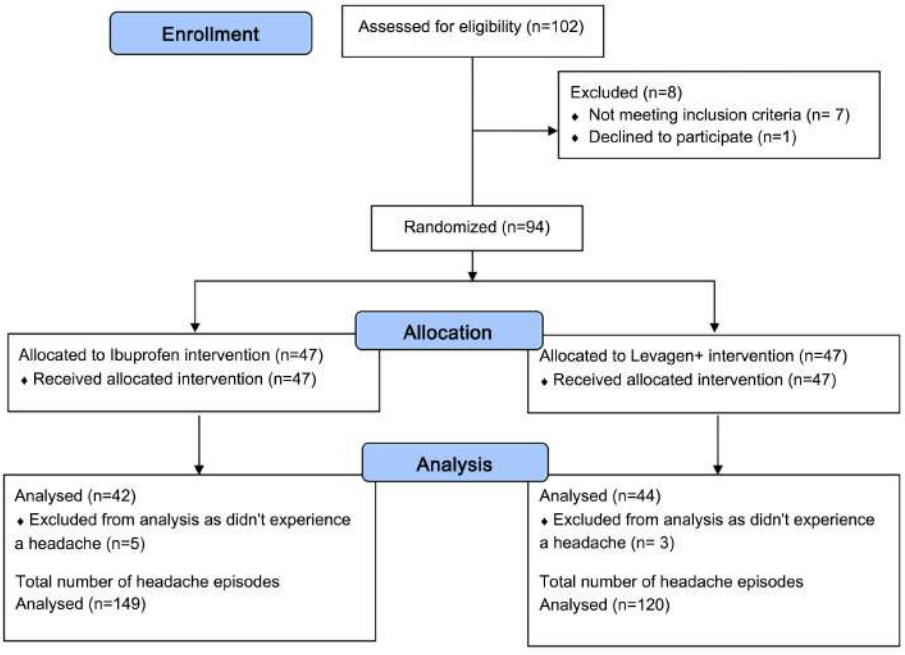

Figure 1. Participant flow diagram.

For those reporting headache resolution (*i.e.* pain free), there was no difference for resolution time between groups for all headache events (Figure 2). Mean resolution time for severe headaches was significantly reduced for the PEA (95.5 minutes) group compared with the Comparator (116.9 minutes) group ($p < 0.05$; Figure 2). There was no significant difference in mean resolution time for moderate headaches between groups (Table 4).

The majority of headaches were reduced in both treatment groups by 2 hours and almost all by 4 hours (Table 5). There was no significant difference for VAS pain score reduction (PSR) between groups for all headache events or headache severity subgroups (Table 6, Figure 3).

Rescue medication use was significantly greater overall for the PEA group compared with the Comparator group ($p < 0.01$; Table 7). Rescue medication use was significantly less in the comparator group for the moderate headache categories ($p < 0.05$) with no difference in the mild or severe categories (Table 7).

There were no serious treatment related adverse events reported in this study. The incidence of mild gastrointestinal symptoms was similar in both groups (~12%).

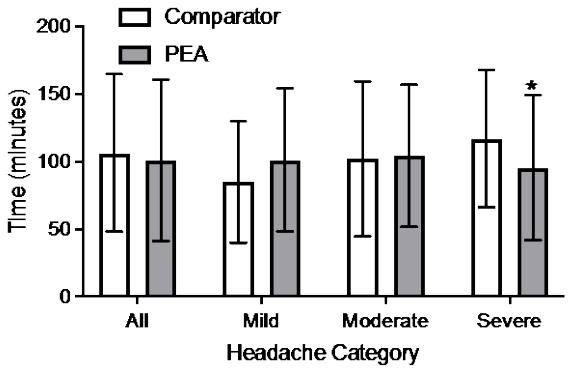

Figure 2. Mean resolution time for headaches not requiring rescue medication.

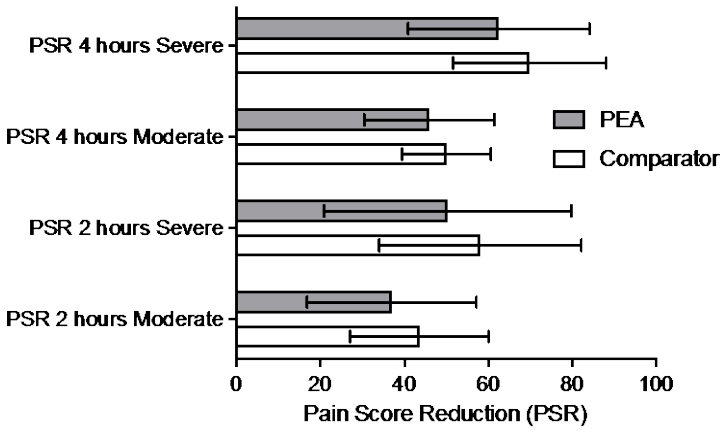

Figure 3. VAS PSR 2 and 4 hours after headache onset for moderate and severe headaches.

Table 4. Resolution time of headaches.

	Comparator	PEA
All headache events (min)	106.3 (58.2)	101.0 (59.7)
Mild headache events (min)	85.0 (44.9)	101.3 (53.0)
Moderate headache events (min)	102.0 (57.2)	104.2 (52.6)
Severe headache events (min)	116.9 (50.9)	95.5 (53.7)*

Results are presented as mean (SD); PEA = palmitoylethanolamide; * P < 0.05.

Table 5. Proportion of headaches categorically reduced at 2 and 4 hours.

	Comparator	PEA
Headaches reduced at two hours^ (%)	81.5	72
Headaches reduced at four hours^ (%)	97.6	90

^ excludes headaches that were mild at onset; PEA = palmitoylethanolamide.

Table 6. Reduction in VAS pain score 2 and 4 hours after treatment for headache subtypes.

	Comparator	PEA
Moderate 2 hours	43.6 (16.5)	37.0 (20.2)
Severe 2 hours	58.1 (24.1)	50.3 (29.5)
Moderate 4 hours	50.0 (10.6)	45.9 (15.5)
Severe 4 hours	69.8 (18.5)	62.5 (21.6)

Data presented as mean (SD); PEA = palmitoylethanolamide.

Table 7. Rescue medication use. Percent of participants from all headaches reported and for each subgroup category of headache reporting rescue medication use.

	Comparator	PEA
Total incidence of rescue medication used (%)	9	23*
Mild at onset (%)	0	8
Moderate at onset (%)	9	24*
Severe at onset (%)	10	23

*p < 0.05.

4. Discussion

While no differences were observed between groups for participant characteristics, there was a higher ratio of females to males in both groups. This may be due to females being more prone to suffering from headaches [19] and therefore, more likely to enroll in the study than males. Other factors may include differences in genetic factors, sex hormone fluctuations, receptor binding, stress responsiveness and pain perception between males and females [19].

For total headache episodes, there was no difference between groups for reduction in pain (VAS) at onset of headache episodes (p = 0.10; **Table 2**). Pain

scores reduced by at least 85% of the starting pain score over four hours for both products. While the pathophysiology of tension-type headaches is unknown, it is proposed that the primary mechanism is sensitization of central and peripheral nervous systems involved in pain processing [5] [15] [16] [21] [22] [23]. Two key molecules identified in the development of pathological pain are mast and glial cells, which when activated, release a host of immune mediators that can sensitize nociceptors, thus reducing pain threshold [3] [5] [15] [16] [24] [25] [26] [27] [28]. PEA acts by down regulating mast cell degranulation at local sites and therefore exerts an antagonistic action against inflammation and pain receptor stimulation [9]. Further, PEA has been shown to have a dose-dependent analgesic action and is thought to be related to its ability to inhibit mast and glial cell activation [3] [15] [25]. Through suppressing immune modulators of pain, PEA may effectively target the root of pathological pain, instead of solely alleviating symptomatology [15] [16] [29]. At headache onset following pain receptor activation, PEA may help to target and downregulate mast cells associated with headache pain resulting in an alternative treatment to current first-line therapies such as NSAIDs [9] [30].

According to International Headache Society (IHS) guidelines [31], the primary measure for efficacy of treatment is the proportion of headache events pain free at two hours after treatment and before the use of any rescue medication [31]. When headaches were separated into severity classes (mild, moderate and severe), analysis identified that both products were effective at reducing pain scores over two and four hours. However, after 2-hours, the comparator was shown to reduce pain more effectively for moderate intensity headaches compared to PEA ($p < 0.05$).

When evaluating the mean resolution time of resolved headaches, it was shown that time taken for severe headache events to resolve following PEA (95.5 min) supplementation, was significantly less compared to the Comparator group (116.9 min). This result suggests PEA may be more effective against more severe headaches rather than mild or moderate headaches. It may therefore be that PEA may be a suitable for treating severe headaches and migraines rather than mild headache.

Pain and headache resolution data is supported by rescue medication use. Rescue medication use was significantly lower in the comparator group ($p < 0.05$) for total and moderate headache episodes. Therefore, the comparator, known to reduce tension headaches [32] [33], may be a better option for mild and moderate headaches, while PEA may be better suited to more severe headaches. However, one factor difficult to assess, is the mechanism/cause of the headache. Ibuprofen and PEA may both act better for headaches with a particular aetiology. Future studies would benefit by determining the aetiology of a person's headache and assessing the efficacy of the treatment on the different mechanisms.

This study showed good gastrointestinal tolerance for both treatment groups. The lack of side effects for both treatments may however be due to the periodic

use. Past studies reporting adverse effects associated with the use of Ibuprofen, are typically from long term use rather than that used here [34] [35].

A limitation of this study is that it relied on participants' perception of headache severity. Therefore, the subjective data collected could be influenced by environmental and psychological factors that impact the individual's pain threshold. However, without using highly expensive imaging technology there is no other means to obtain headache pain data. Future studies might benefit by including a cross-over design to account to the different levels of pain thresholds that may be experienced by different individuals.

Other future directions for PEA research may benefit from including participants experiencing migraines. This would enable the assessment of PEA as a potentially effective treatment of a more severe class of headache. Although limited in this study due to COVID-19, pathology would also provide valuable information to future studies. By looking at changes in pathology, it might help answer why PEA is more effective in some headaches and not others.

5. Conclusions

As far as we are aware, this is the first study to directly compare the efficacy of the PEA to a traditional NSAID, in improving primary headache symptoms. Overall, while the comparator was shown to result in less rescue medication used, PEA may be a viable option for treating headaches of moderate or severe intensity. PEA reduced headache pain at 2 and 4 hours to equivalent levels to the comparator. Furthermore, PEA was able to resolve severe headaches faster than the standard treatment.

The results of this study potentially make PEA a treatment option for acute headache episodes. However, this calls for further clinical studies comparing PEA to traditional analgesic treatments in different headache models including migraines. Additionally, long-term prospective studies could serve to give an accurate depiction of product efficacy and tolerability after prolonged usage.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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