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Palmitoylethanolamide (Levagen+) for acute menstrual pain: a randomized, crossover, double-blind, placebo-controlled trial

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ABSTRACT

Palmitoylethanolamide (PEA) is a well-tolerated compound effective in reducing pain. This randomized, double-blind, placebo-controlled crossover study investigated PEA for menstrual pain relief. Conducted in Australia from May to December 2023, the study included adults over 18. Participants consumed 300 mg of PEA or a placebo at menstrual pain onset. Pain scores were recorded on the numerical pain rating scale (NRS) every 30 minutes for up to 4 hours. If pain persisted, a second dose was permitted after 2-hours. The primary outcome measure was the reduction in acute menstrual pain scores from the NRS. Secondary outcome measures included the Treatment Satisfaction Questionnaire for Medication, rescue medication use and adverse events. Pain scores were analyzed using repeated measures analysis of variance. PEA resulted in a significant reduction in pain scores at 1 ($p = .045$), 1.5 ($p = .009$), 2 ($p = .015$) and 2.5 ($p = .039$) hours post dosage compared to placebo. No difference was seen for the Treatment Satisfaction Questionnaire for Medication, rescue medication used, or adverse events. This study demonstrates PEA supplementation is a safe and effective option for reducing menstrual pain compared to a placebo, with significant pain reduction observed at multiple time points post-dosage.

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Introduction

Menstrual pain, or primary dysmenorrhea (menstrual pain without any underlying pathology), is the most prevalent gynecological condition among women of reproductive age (Bernardi et al. 2017). The prevalence of dysmenorrhea is estimated to range from 45 to 95 percent, often resulting in restricted daily activity, work and school absenteeism, and significant personal distress (Iacovides, Avidon, and Baker 2015; Lefebvre et al. 2005; Proctor and Farquhar 2006). The pain typically begins with the onset of menstruation and arises from irregular uterine cramping, usually lasting between 8 and 72 hours (Bernardi et al. 2017; Iacovides, Avidon, and Baker 2015; Lefebvre et al. 2005; Proctor and Farquhar 2006). Despite its high prevalence and substantial impact on daily life, dysmenorrhea remains underdiagnosed and undertreated, largely due to its perception as a normal part of the menstrual cycle (Bernardi et al. 2017; Iacovides, Avidon, and Baker 2015).

The primary mechanisms underlying dysmenorrhea are not yet fully understood. However, the primary cause of painful symptoms is attributed to the excessive production of uterine prostaglandins, particularly prostaglandin F2-α (PGF2α) and prostaglandin E2 (PGE2), which peak during the initial days of menstruation (Bernardi et al. 2017). Elevated prostaglandin levels are directly linked to

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increased uterine tone, irregular high-amplitude myometrial contractions, and myometrial ischemia, which contribute to pain perception and heightened sensitivity of nerve endings (Bernardi et al. 2017; Iacovides, Avidon, and Baker 2015; Lefebvre et al. 2005).

Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, naproxen, and ibuprofen are the first-line treatment, inhibiting cyclooxygenase (COX) enzymes responsible for prostaglandin production (Bernardi et al. 2017). While effective for most women, frequent NSAID use can cause gastrointestinal issues (e.g., ulcers, bleeding) and systemic side effects like nausea, dizziness, and organ damage (Barcikowska et al. 2020; Lefebvre et al. 2005). Oral contraceptives and hormonal therapies are alternative treatments but lack robust efficacy evidence and have adverse effects (Barcikowska et al. 2020; Lefebvre et al. 2005). Additionally, 10–25 percent of women with dysmenorrhea do not respond to or cannot tolerate these options, highlighting the need for safer, more tolerable alternatives (Barcikowska et al. 2020; Lefebvre et al. 2005).

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide with endocannabinoid-like properties, belonging to the N-acylethanolamine family (Lang-Illievich et al. 2022; Rankin and Fowler 2020). Identified in the 1990s for its anti-inflammatory effects, PEA reduces interleukin levels, downregulates mast cell activity at inflammation sites, and inhibits NF-κB pathways via PPAR-α engagement, suppressing NLRP3 inflammasome activation in a concentration-dependent manner (Deshmukh et al. 2021; Rankin and Fowler 2020; Scuteri et al. 2022). These mechanisms help limit cytokine release from macrophages, highlighting PEA's anti-inflammatory potential (Deshmukh et al. 2021).

Given PEAs well documented analgesic properties, PEA offers a promising alternative for menstrual pain treatment due to its good tolerability and safety profile (Deshmukh et al. 2021). Studies have demonstrated PEA's efficacy in managing pain associated with conditions like endometriosis, neuropathy, musculoskeletal pain, and palliative care (Cobellis et al. 2011; D'Amico et al. 2020; Davis et al. 2019; Giugliano et al. 2013; Scuteri et al. 2022). For instance, Giugliano et al. (2013) found that daily supplementation with 800 mg PEA and 80 mg transpolydatin for 90 days significantly reduced endometriosis-related pain (Giugliano et al. 2013). Similarly, Cobellis et al. (2011) reported that the same regimen over three months significantly decreased dysmenorrhea, dyspareunia, and pelvic pain compared to placebo (Cobellis et al. 2011).

To date, no double-blind clinical studies have examined the use of a singular dose of PEA for menstrual pain, highlighting the need for further research. While existing studies suggest PEA's potential effectiveness, its specific impact on menstrual pain remains unconfirmed. This study aimed to evaluate PEA's effectiveness compared to a placebo in alleviating acute menstrual pain in healthy females, hypothesizing that PEA supplementation would significantly reduce pain severity compared to a placebo.

Materials and methods

Study design

This was a 16-week, randomized, double-blind, placebo-controlled, crossover clinical trial utilizing an active group (Levagen+) and placebo group [microcrystalline cellulose (MCC)]. The study was conducted in Australia between May and December 2023.

Study population

Participants were recruited from an existing participant database and via social media outlets (e.g., Facebook adverts) from across Australia. Interested individuals were provided with the participant information sheet and a minimum 24 hours later, conducted screening against the inclusion and exclusion criteria (detailed below) via a telehealth consultation.

Eighty (80) menstruating females aged 18 years and older self-reporting mild to moderate menstruating cramp pain (caused by primary dysmenorrhea) were enrolled in this study. Participants were included in the study if they were able to provide informed consent and agreed not to take other supplements or medications for menstrual pain during a menstrual event. Participants were also required to have a regular menstrual cycle (28 days ±7 days) and period, a self-reported history of menstrual cramp pain occurring during four of the past six menstrual cycles and typically requiring at least one dose of an OTC analgesic medication (such as naproxen, aspirin, ibuprofen or acetaminophen) taken on at least 1 day of a menstrual cycle for effective pain relief.

Exclusion criteria included any known secondary causes for dysmenorrhea (i.e. endometriosis, adenomyosis, uterine fibroids or infection) as previously diagnosed by their doctor, any known bleeding disorders, recent surgery, or concurrent blood thinning treatment. Participants with an unstable or serious illness (e.g., kidney, liver, heart conditions, diabetes, lung conditions, chronic asthma, diagnosed psychological or mood disorder) were excluded. Patients with a known current malignancy (excluding BCC) or have received chemotherapy or radiotherapy treatment for malignancy within the previous 2 years, currently taking Warfarin, Heparin, Dalteparin, Enoxaparin or other anticoagulation therapy were excluded. Pregnant or lactating women, active smokers, nicotine use or drug (prescription or illegal substances) abusers, chronic past and/or current alcohol users (>14 alcoholic drinks week) were excluded. Participants who were allergic or hypersensitive to any of the ingredients in active or placebo formula or participated in any other clinical trial during the past 1 month were excluded. If any participant was consuming a supplement or medication that would result in their exclusion, there was a minimum 4-week washout period required prior to re-applying for entry into the study.

Study procedure

The study was a telehealth-based study, with no face-to-face interaction with participants. All communication between investigators and participants was by phone (primary contact method), e-mail, and text message (used for reminders). Eligible participants passed screening and provided their written consent to participate in the study. Once participants completed baseline measures (self-reported height and weight) participants were posted their trial product. The trial products were randomized into blocks of 4 (2 active and 2 placebo) products (e.g., ABAB, AABB, ABBA, etc.). Randomization was performed using Random Allocation Software (Sealedenvelope.com.au) by an individual not involved in the trial to ensure both participants and investigators were blinded to the allocation.

Participants were directed to take their trial product in numerical order as listed on the bottles (i.e., 1, 2, 3, 4) with water. Each randomized bottle of trial product contained enough trial product (2 capsules) for a single menstrual pain event. Each capsule of the active product consisted of 350 mg of Levagen+ (containing no less than 300 mg of PEA; supplied by Gencor Pacific Ltd) and each capsule of the placebo consisted of 350 mg of microcrystalline cellulose.

Participants were able to record up to 4 menstrual pain events (in numerical order of product bottles) over 16 weeks (which ever occurred first). A menstrual pain episode was considered any day during menstruation where the participant had a qualifying menstrual pain score of at least 5 on the numerical pain rating scale (NRS) where 0 is no pain and 10 is the worst pain experienced. Once the qualifying pain score of 5 was reached, participants consumed 1 capsule from their appropriate trial product bottle (i.e., bottle 1 for their first recorded pain even through to bottle 4 for their fourth recorded pain event) with water. After taking the study product dose (1 capsule), participants completed the NRS every 30 minutes for 2 hours [or until the pain resolved (score of 0 on the NRS)]. If pain was still reported 2 hours post initial dose, a second dose (1 capsule) was taken with water. After taking the second dose, participants continued to complete the NRS every 30 minutes for a further 2-hours [or until the pain resolved (score of 0 on the NRS)]. All data was collected using an

e-diary system, where participants were able to login to a secure site using their participants identification number to record all their data. No identifiable data was collected via this portal, nor was any data saved on the website. Rather the system automatically linked the recorded data to the participants profile and saved it on a secure server (Dropbox for business).

At any time during the 4-hours of recording, rescue medication was permitted to be taken but had to be recorded and could result in data being excluded from analysis. Rescue medication was able to be taken without the need for recording any time after the 4-hour recording was completed. After each pain event, participants completed a Treatment Satisfaction Questionnaire for Medication (TSQM) to evaluate their overall satisfaction with the effectiveness of the study product 12 to 24 hours after its administration.

It was not expected that any product related adverse events would occur during this study, given the low, single dose design combined with the excellent safety profile of Levagen+. Any adverse events were expected to be mild gastrointestinal related issues with fast resolution. In the event of an adverse event, the participant was to report to the trial coordinators to discuss management of the adverse event and suitability to continue in the trial.

Outcome measures

The primary outcome measure for this study was a reduction in acute menstrual pain severity as measured using the NRS. Secondary outcome measures included effectiveness of the treatment questionnaire (TSQM), rescue medication use and adverse events. Participants were also asked to complete an exit telehealth consultation to answer a brief questionnaire about their study experience and report the number of capsules remaining upon completion of the trial.

Statistical analysis

Sample size was calculated using G*power (v3.1) to detect a 30 percent reduction in NRS (Numerical Rating Scale) scores in the active treatment group compared to placebo, with a power of 0.95 and an α error probability of 0.05. The effects size (d = 0.44) was derived by assessing data from both menstrual pain and PEA studies of a similar design (where pain is an outcome measure) (Artukoglu et al. 2017; Briskey et al. 2024; Giugliano et al. 2013; Stochino Loi et al. 2019). A baseline NRS of 5 was set for both groups (as per the protocol) with post intervention NRS scores of 4.5 ± 2.5 (placebo) and 3.4 ± 2.5 (active treatment) established from the existing literature and our previous work on PEA (Briskey et al. 2024). This calculation indicated that at least 58 participants would be required for a crossover design. To account for an anticipated dropout rate of 30 percent, 80 participants were enrolled.

Statistical analyses were conducted using IBM SPSS Statistics (version 27). Continuous data were checked for normality using the Shapiro-Wilk test and visually assessed through Q-Q plots. Changes in pain scores over time were analyzed using repeated measures analysis of variance (RMANOVA), with time and treatment condition (active vs. placebo) as within-subject factors in the crossover design.

For post-hoc comparisons, paired t-tests were used to evaluate differences between time points within each treatment condition. Between-group differences at each time point were analyzed using independent t-tests.

Categorical data, including responder rates (e.g., percentage of participants reporting ≥50 percent pain reduction), were analyzed using chi-square tests.

Missing data were handled using a mixed-effects model for RMANOVA to ensure robustness against dropouts. All tests were two-tailed, with statistical significance set at $p < .05$.

Ethical considerations

All participants provided written informed consent prior to commencing the study. This study was conducted in compliance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice and the Therapeutic Goods Administration. Ethical approval was obtained from the National Institute of Integrative Medicine (NIIM), an NHMRC accredited Human Research and Ethics Committee (approval number: 0113E_2022). This clinical trial was registered on the ANZCTR (registration number: NCT05810116).

Results

80 participants were enrolled in the study, with 73 participants recording at least one menstrual pain event. Of the 7 withdrawals, 6 were lost to follow-up without recording any menstrual pain events, and 1 was dropped due to noncompliance without recording a menstrual pain event (Figure 1). There was no significant difference between groups for adverse event occurrence ($p = .49$). During the study, a total of eight adverse events from 6 participants were recorded following the consumption of the trial product. Of the eight events recorded, six were not immediately reported to investigators and only detected at to the final exit questionnaire, of which three were from one participant (3 × increased menstrual bleeding). Of the eight adverse events recorded, five adverse events were following the consumption of the Levagen+ product (lower back pain, brain fog/sleepiness, dry mouth and 2 × increased menstrual bleeding) and three were following consumption of the placebo product (hot

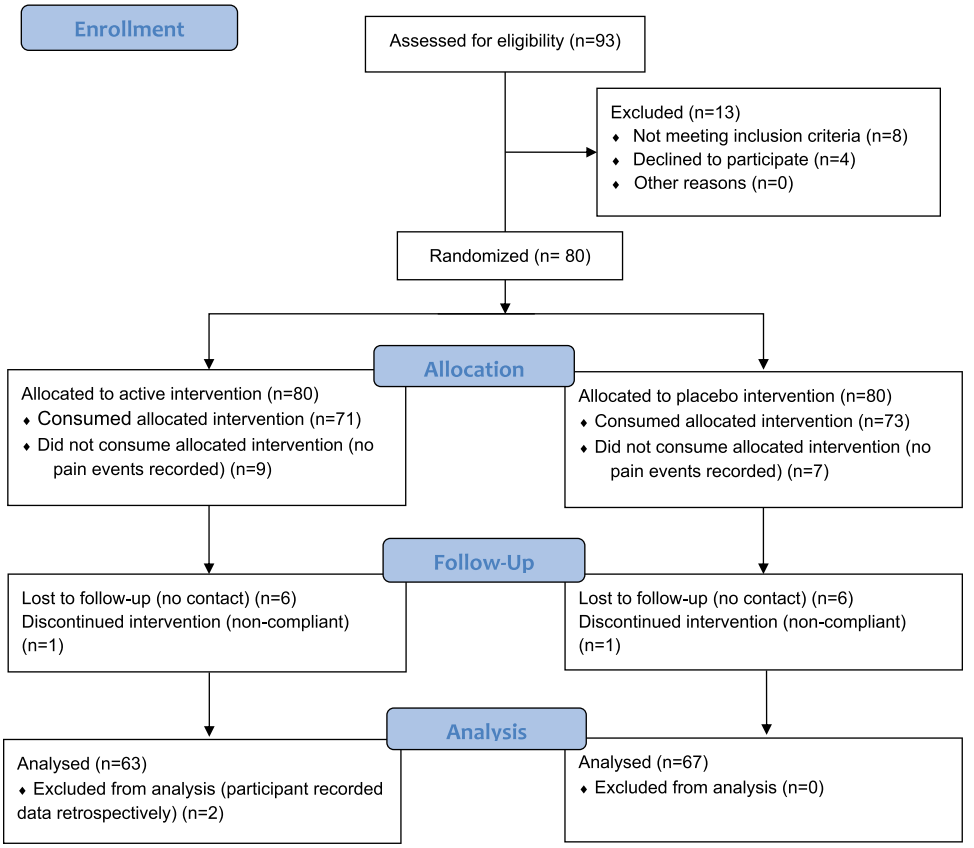

Figure 1. Consort guideline flow chart. The numbers presented are the number of participants, not the number of pain events recorded. Each participant was able to record up to 2 pain events for each intervention in a randomized crossover manor.

Table 1. Demographics of participants reporting a menstrual pain event.

	Levagen+	Placebo
Age (years)	31.4 (8.3)	31.2 (8.3)
Weight (kg)	69.7 (14.5)	70.0 (15.0)
Height (m)	1.7 (0.1)	1.7 (0.1)
BMI (kg/m^2)	25.5 (5.5)	25.7 (5.5)

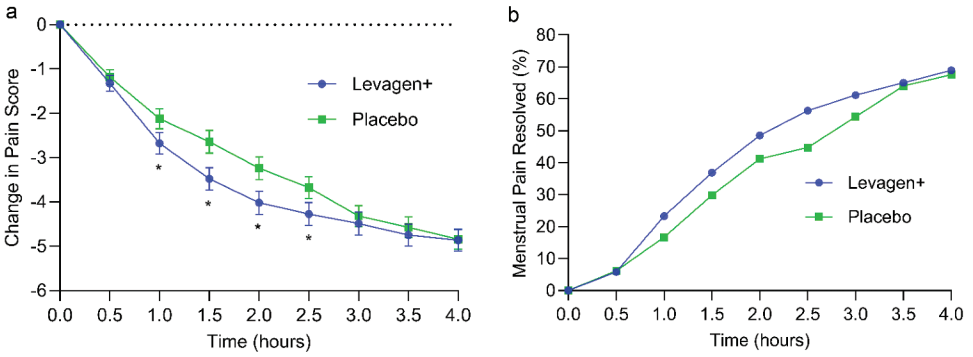

Figure 2. Effectiveness of Levagen+ at reducing pain. (a) Reduction in pain scores from baseline over 4 hours post treatment, (b) Number of menstrual pain events resolved over 4 hours post treatment. *significant difference between groups at $p < .05$. Data is presented as mean ± SEM where available.

flushes, headache and fatigue and increased menstrual bleeding). As the adverse events experienced were unable to be attributed to other causes, and were unusual for the participants, it was not possible to completely rule out the possibility that the effects were due to the trial products.

Participants in this study were relatively young and within the healthy BMI range (Table 1). On average, each participant recorded 3.4 menstrual pain events, with 248 total events recorded (121 active, 127 placebo). Of the 248 events recorded, there were 31 (18 active and 13 placebo) pain events reported for which pain-relief medication was taken within 4 hours of taking the trial product and were therefore excluded from analysis. There was no significant difference between groups for rescue medication use ($p = .34$). The remaining 217 episodes (103 active, 114 placebo) where participants did not report taking any rescue medication within 4-hours of dosing were analyzed and presented below.

Following the onset of menstrual pain, supplementation with Levagen+ significantly reduced reported menstrual pain at 1.0, 1.5 and 2-hours post treatment compared to the placebo (Figure 2a, Table 2). At 2-hours post initial dose, 120 of the 217 menstrual pain episodes reported remained unresolved and required a second dose of the investigational product (Figure 2b, Table 3). After the second dose (at 2-hours), there was a further significant difference in pain seen at 2.5 hours (Figure 2a, Table 2).

Table 2. Menstrual pain scores.

Time (hours)	Levagen+	Placebo	Difference	*p*-value
0	6.2 ± 1.1	6.3 ± 1.1	0.1	.417
0.5	4.9 ± 1.9	5.1 ± 2.2	0.2	.276
1.0	3.5 ± 2.4*	4.1 ± 2.6	0.6*	.045*
1.5	2.7 ± 2.5*	3.6 ± 2.8	0.9*	.009*
2.0	2.2 ± 2.6*	3.0 ± 2.9	0.8*	.015*
2.5	2.0 ± 2.5*	2.6 ± 2.7	0.6*	.039*
3.0	1.7 ± 2.4	1.9 ± 2.5	0.2	.277
3.5	1.5 ± 2.3	1.7 ± 2.5	0.2	.263
4.0	1.4 ± 2.2	1.4 ± 2.3	0	.432

*Significant difference $p < .05$, values are mean ± SD.

Table 3. Menstrual pain episode resolution at 2-hours post initial dose.

	Resolved [n (%)]	Not Resolved [n (%)]	*p*-value[a]
Levagen+	50 (48.5)	53 (51.5)	.34
Placebo	47 (41.2)	67 (58.8)	

[a]*p*-value represents Fisher's exact value.

Following initial supplementation there was a steady increase in the number of participants reporting their menstrual pain being resolved (pain score of 0) at each reporting time point (Figure 2b). There was no significant difference between groups at any time point for the number of resolutions, with the 2.5-hour point trending toward significance ($p = .1$).

There was no difference between groups for any of the individual questions or total section scores from the TSQM. Due to the low number of reported side effects ($n = 8$), analysis of the data for this section of the TSQM could not be conducted.

Discussion

This study evaluated the efficacy of Palmitoylethanolamide (PEA; Levagen+) in reducing acute menstrual pain in healthy women. The findings indicate that Levagen+ significantly reduced pain scores compared to placebo at 1.0, 1.5, 2.0, and 2.5 hours post-dose, with a pain reduction of approximately 25 percent by 2.5 hours compared to the placebo group. Importantly, no differences in adverse events were observed between the groups, confirming the safety profile of PEA.

At three hours post consumption, the significant difference in pain scores between groups was no longer evident, with both groups reporting equivalent pain scores by the end of the study (4-hours). The lack of effect beyond the three-hour mark is likely attributed to the natural progression of menstrual pain relief over time. This is supported by the fact two-thirds of participants in both groups reporting their menstrual pain as resolved after 4-hours.

This trial contributes novel evidence regarding the acute use of PEA for menstrual pain. Unlike previous studies employing prolonged dosing regimens, this study demonstrated efficacy using a single-dose approach, enhancing its applicability for managing acute pain episodes. The results support Levagen+ as a viable alternative to traditional treatments such as NSAIDs, particularly for individuals seeking options with a favorable side effect profile. Furthermore, the absence of significant rescue medication use in both groups suggests that PEA may provide sufficient pain relief to reduce dependency on conventional analgesics.

The observed analgesic effects of PEA may be explained by its ability to modulate inflammatory responses and reduce mast cell activity at the site of pain. PEA's engagement with the peroxisome proliferator-activated receptor-alpha (PPAR-α) pathway can suppress the release of pro-inflammatory cytokines, such as interleukins, while also downregulating nuclear factor-kappa B (NF-κB) activity. These mechanisms potentially attenuate prostaglandin-induced myometrial contractions, which are a primary cause of menstrual pain (Deshmukh et al. 2021; Rankin and Fowler 2020; Scuteri et al. 2022). The timing of the analgesic effect aligns with prior pharmacokinetic studies showing significant plasma levels of PEA approximately 45 minutes post-ingestion, peaking at 90 minutes (Briskey, Mallard, and Rao 2020). Therefore, it would be anticipated that the therapeutic/analgesic effects of PEA would start to occur approximately 60-minutes after consumption.

Previous studies in this area have shown 400 mg of PEA with 40 mg of polydatin administered twice daily for 90 days was able to relieve pain in patients presenting with an endometriosis-related pain in as little as 1-month (Indraccolo and Barbieri 2010). Similarly, a pilot study on endometriosis pain showed 400 mg of PEA plus 40 mg transpolydatin twice daily significantly reduced dysmenorrhea, dyspareunia, and pelvic pain compared to a placebo (Cobellis et al. 2011). A larger clinical study on primary dysmenorrhea showed 400 mg of PEA plus 40 mg transpolydatin reduced pelvic pain in 98.18 percent of participants compared to 56.36 percent in the placebo group (Tartaglia et al. 2015).

Similarly, a study on endometriosis showed 600 mg of PEA twice daily improvement pelvic pain, deep dyspareunia, dysmenorrhea, dyschezia, as well as in quality of life and psychological well-being (Stochino Loi et al. 2019). However, as the study by Tartaglia and colleagues was an open label study, a possible placebo effect needs to be considered. Despite this, the collective data to date supports the possibility that PEA is an option for helping reduce pain associated with menstruation and endometriosis.

A potential limitation to this study is that participants were permitted to use contraceptive while on the study (including hormonal contraceptives). This might pose a limitation because these medications can alter menstrual cycles and pain levels. Hormonal contraceptives often reduce prostaglandin production and suppress ovulation, both of which can decrease dysmenorrhea severity. This may have masked the effects of the investigational treatments or introduce variability in pain levels reported. However, including participants using hormonal contraceptives was not considered a limitation, as all participants had to reach a minimum pain level before consuming the trial product. And as the study outcomes were related to the reduction in pain from a set starting point, it can therefore be assumed that any effect observed in the alleviation of pain was likely due to the interventional product. By including people using hormonal and oral contraceptives it can be shown that PEA is effective across a diverse population. Additionally, as the study was a cross-over design, contraceptive use was evenly distributed between the treatment and placebo groups, therefore its impact is balanced, minimizing any potential bias.

Future research should explore prophylactic dosing strategies, as administering PEA at the onset of symptoms rather than at a predefined pain threshold may enhance its effectiveness. Additionally, studies comparing different dosages and formulations could identify an optimal regimen for achieving rapid and sustained pain relief. A PEA can remain in the system for several hours (Briskey, Mallard, and Rao 2020), a single 700 mg dose of Levagen+, may provide a better analgesic effect on an acute pain episode such as menstrual pain. The present study used a total daily dose of 600 mg of PEA (2 × 300 mg) per event, chosen because the formulation has been shown to have approximately twice the absorption of standard PEA formulations, despite being half the dose used in some studies (Briskey, Mallard, and Rao 2020). Another future direction would include larger sample sizes and extended follow-up periods to help clarify the long-term benefits and safety of PEA use.

Conclusion

Levagen+ represents a promising intervention for acute menstrual pain, offering effective and safe relief. Its ease of use and minimal side effects make it a valuable option for women seeking alternatives to NSAIDs. Further research on prophylactic dosing, optimized formulations, and comparative effectiveness with standard treatments will solidify its place in clinical practice and expand options for menstrual pain management.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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