Inflammopharmacology
https://doi.org/10.1007/s10787-019-00582-9

ORIGINAL ARTICLE

A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis

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Received: 30 November 2018 / Accepted: 6 March 2019

Abstract

Background The aim of the study was to assess the safety, tolerability and efficacy of palmitoylethanolamide (PEA) when dosed at 300 mg and 600 mg per day on symptoms of knee osteoarthritis.

Methods This was a single site, comparative, double-blind placebo controlled study in adults with mild to moderate knee osteoarthritis with 111 participants randomized to receive 300 mg PEA, 600 mg PEA or placebo each day, in divided doses b.i.d, for 8 weeks. The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The secondary outcomes were the Numerical Rating Scales (NRS) for pain, the Depression Anxiety Stress Scale (DASS), the Perceived Stress Scale (PSS), the Pittsburg Sleep Quality Index (PSQI), the Short Form Health Survey (SF-36), the use of rescue pain medication and clinical safety assessment.

Results There was a significant reduction in the total WOMAC score in the 300 mg PEA ($p=0.0372$) and the 600 mg PEA ($p=0.0012$) groups, the WOMAC pain score (300 mg PEA, $p=0.0074$; 600 mg PEA, $p=<0.001$), the WOMAC stiffness score (PEA 300 mg, $p<0.0490$; 600 mg PEA, $p=0.001$) and in the WOMAC function score in the 600 mg PEA group ($p=0.033$) compared to placebo. The NRS pain evaluations for "worst pain" and "least pain" were significantly reduced in the 300 mg PEA group ($p<0.001$, $p=0.005$) and the 600 mg PEA group ($p<0.001$, $p<0.001$) compared to placebo. There was a significant reduction in anxiety (DASS) in both active treatment groups (300 mg PEA, $p=0.042$; 600 mg PEA group ($p=0.043$) compared to placebo. There were no changes in the clinical markers and the product was well tolerated.

Conclusions The study demonstrated that palmitoylethanolamide may be a novel treatment for attenuating pain and reducing other associated symptoms of knee osteoarthritis. Further studies on the pharmacological basis of this anti-inflammatory effect are now required.

Keywords Inflammation · Osteoarthritis · Pain · Palmitoylethanolamide · *N*-acylethanolamines

Introduction

Osteoarthritis (OA) is one of the most common degenerative and progressive joint diseases caused by the breakdown of articular cartilage and remodeling of joint tissues driven by inflammatory mediators (Loeser et al. 2012; Alshami 2014). The chondrocytes, which are responsible for the turnover of extracellular matrix components of the articular cartilage, are unable to maintain balance between synthesis and degradation (Man and Mologhianu 2014). Apart from these characteristics, common pathological features of OA include thickening of the subchondral bone, osteophyte formation, synovial inflammation, ligament degeneration and joint capsule hypertrophy (Chen et al. 2017). The condition is associated with pain, stiffness and disability, with

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Published online: 29 March 2019

the disease worsening as it progresses and therefore subsequently reducing quality of life (Zhang et al. 2016). Since the mechanisms behind OA cause and progression are poorly understood, management of OA involves pain control (e.g., oral/topical non-steroidal anti-inflammatory drugs), weight control, exercise therapy, prevention of complications such as muscle atrophy or joint deformities and maintenance of functional status and quality of life (Mora et al. 2018; Zhang et al. 2008).

Interestingly, the degree of joint pain does not always correlate with the extent of joint damage or the presence of active inflammation (Park et al. 2010; Hochman et al. 2010). Studies have shown the presence of chronic low-grade inflammation and oxidative stress in patients with OA, primarily with natural immune mechanisms (Chen et al. 2017; Mora et al. 2018). These studies show that long term use of drugs are not able to reduce OA pain beyond minimal clinically important levels (Bijordal et al. 2007) and, as it is an ongoing disease that does not resolve, it is now recognized that it is associated with chronic pain (Neogi 2013). Furthermore, knee OA patients have reported feelings of burning, tingling and numbness, with additional symptoms suggesting the presence of neuropathic pain (Hochman et al. 2010; Neogi 2013). Increasing evidence has shown that neuro-inflammation plays a key role in pain progression which is sustained by an imbalance within pro-inflammatory and pro-resolving mediators (Paladini et al. 2016).

N-acylethanolamines (NAEs) are a family of endogenous bioactive lipids that regulate multiple processes including pain and inflammation (Alhouayek and Muccioli 2014). One of the most widely studied NAEs is the analgesic endocannabinoid compound, palmitoylethanolamide (PEA). Previous research has demonstrated the effectiveness of PEA on conditions characterized by chronic and/or neurological pain (Skaper et al. 2014; Woodhams et al. 2015; Petrosino and Di Marzo 2017). The major focus on mechanisms of actions of PEA has been on the analgesic (Calignano et al. 1998), anti-inflammatory (Mazzari et al. 1996) and neuroprotective effects (Lambert et al. 2001).

Clinical studies have demonstrated that PEA has been effective in treating neuralgia (Calabro and Bramanti 2017), lumbosciatica (Canteri et al. 2010; Dominguez et al. 2012), carpel tunnel syndrome (Conigliaro et al. 2011), lumbar stenosis (Desio 2011), pudendal nerve entrapment (Calabro and Brananti 2017) and nonsurgical lumbar radiculopathies (Chirchiglia et al. 2018). There are promising results for the use of PEA for pain associated with multiple sclerosis (Hesselink and Kopsky 2015), as an adjunct therapy in Parkinson's disease (Brotini et al. 2017) and pain associated with diabetic neuropathy (Assini et al. 2010; Schifilliti et al. 2014). PEA has also been shown to be an effective analgesic, when used in combination with stilbene polydatin, for endometriosis (Cobellis et al. 2011; Giugliano et al. 2013) and as an analgesic for post-operative pain (Bacci et al. 2011). Furthermore, the pain-relieving effect of PEA was demonstrated in two separate cohorts of patients suffering from chronic pain caused by different aetiopathogeneses, including osteoarthritis, nerve root compression, post-herpetic neuralgia, diabetic polyneuropathy, pain associated with induced neuropathy, among others. These results suggest that the therapeutic effect of PEA is independent of pain aetiopathogenesis (Gatti et al. 2012; Keppel Hesselink and Hekker 2012). Preliminary support for PEA as a treatment for joint disease-related pain was demonstrated in a comparative study, albeit the lack of a placebo arm, showing that PEA was more effective than ibuprofen for pain relief in temporomandibular joint (TMJ) osteoarthritis (Marini et al. 2012). The aim of the study was to investigate the safety, tolerability and efficacy of two doses of PEA on symptoms of knee osteoarthritis.

Methods

Trial design

This was a single-site, comparative, double-blind, randomized placebo controlled clinical trial of 8 weeks duration assessing the efficacy of PEA 300 mg/day (A300), PEA 600 mg/day (A600) and placebo on quality of life, symptoms associated with mild to moderate osteoarthritis and clinical markers. It was conducted between March 2016 and March 2018 in Brisbane, Australia.

Participant recruitment

Participants were aged between 38 and 76 years old, and medically diagnosed with osteoarthritis in either one or bilateral knees. The study population included 111 men and women participants, recruited through the local public media. After preliminary screening via telephone, participants were required to attend a pre-trial interview and provide written informed consent. Initial health assessment included lifestyle questions, current medications, medical history and a physical examination.

Inclusion and exclusion criteria

Participants were required to have a minimum pain level of 4 on the NRS, to abstain from all osteoarthritis medication (pharmaceutical and natural therapies) and use only paracetamol as the rescue medication (with the use recorded in the participant daily diary). Potential participants were excluded if they had any other forms of arthritis including rheumatoid arthritis or osteoporosis, or had significant joint injury within last 6 months, or if they had been using

pharmaceutical drugs (such as nonsteroidal anti-inflammatory drugs) and/or natural therapies (such as fish oil, glucosamine, chondroitin and green-lipped mussel) to manage their symptoms of knee osteoarthritis within the last 30 days, or had a BMI > 35. Women were excluded if they were pregnant or breast-feeding. Potential participants were also excluded if they had uncontrolled diabetes, high cholesterol, hypertension, were receiving anti-coagulation therapy, had a history of cerebrovascular accidents, stroke, or transient ischemia, had a major depressive disorder, had experienced unintended weight loss of more than 15% of body weight in the last 6 months or had an active substance abuse (alcohol or drug dependency).

Interventions

The investigational products were manufactured by Nutra Manufacturing Inc., Greenville, South Carolina, USA. The palmitoylethanolamide powder Levagen® was provided by Gencor Pacific, 21-E, Elegance Court, Hillgrove Village, Discovery Bay, Hong Kong. Participants received one of three interventions: orally dosed PEA 300 mg/day (in 150 mg capsules taken twice daily); orally dosed PEA 600 mg/day (in 300 mg capsules taken twice daily) or inert matched placebo capsules containing maltodextrin (also taken twice a day). The participants were instructed to take a capsule with breakfast and a capsule with dinner for 8 weeks.

Randomisation and blinding

Randomisation of the products was performed independently of the investigators using Random Allocation Software, version 1.0, May 2004. The investigational products were delivered to the investigators in trial product containers that were identical in function and appearance, marked from 001 to 120. Once enrolled in the trial, participants were randomly allocated to the next available number in the sequence and had equal chance of being in either the A300 group, the A600 group or the placebo group. Investigators were blinded to the randomization and therefore blinded to which participants were allocated to each of the three arms. Participants were monitored for compliance with the protocol by a combination of interviews (on day 2, week 1, week 4 and week 8) as well as a the use of a participant diary recording daily medication, daily rescue medication, changes in health/medication and any adverse reactions. The treatment doses taken were also assessed by number of returned capsules at completion of study.

Outcomes

The primary hypothesis was that the investigational product (PEA) was efficacious in the management of pain, stiffness and function associated with knee osteoarthritis in the left or right knee, using doses of 300 mg/day and 600 mg/day compared to a control (placebo), as measured by the WOMAC. The WOMAC consists of three subdomains; pain (6 questions), stiffness (2 questions) and function (12 questions) (Bellamy et al. 1988). Participants completed the questionnaire at baseline, day 2 and week 1 (pain subdomain only), and at week 4 and week 8.

Knee pain intensity was assessed by the Numerical Rating Scale (NRS), an 11-point, 0–10 numeric pain scale with 0 representing "no pain" and 10 representing "worst pain you can imagine". It is recognized that those with symptomatic osteoarthritis find a single pain point inadequate for assessing pain due to fluctuations and complexities in pain within each day (Hawker et al. 2011). Therefore, the worst pain, least pain and pain range was assessed, using the question "What was your worst level of pain yesterday and least level of pain yesterday in the 24 h from midnight to midnight", assessed at baseline, day 2, week 1, week 4 and week 8. The use of rescue medication (paracetamol) for each of week was calculated from the participant daily diary.

The following quality of life assessments were also completed at baseline and week 8. The Depression Anxiety Stress Scales (DASS) is a quantitative measure of distress along the 3 axes of depression, anxiety and stress. The questions (7 in each category) are summed to provide a level of distress; Depression: normal (0–4), mild (5–6), moderate (7–10), severe (11–13), extremely severe (> 14); Anxiety: normal (0–3), mild (4–5), moderate (6–7), severe (8–9), extremely severe (> 10); and Stress: normal (0–7), mild (8–9), moderate (10–12), severe (13–16), extremely severe (> 17) (Ng et al. 2007).

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances using 19 individual questions that are used to generate seven domain scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction with the sum of scores giving a total global score (Buysse et al. 1989).

Stress levels were assessed using the Perceived Stress Scale (PSS) which measures the degree of stress in a person's life. There are ten questions that ask how unpredictable, uncontrollable, and overloaded respondents find their lives and direct queries about current levels of experienced stress. Participants respond to each question on a 4-point scale of "how often" with 0 being "never" to 4 being "very often", to determine if a person is classified as experiencing low, moderate or high stress (Levenstein et al. 1993).

The Short Form Health Survey (SF-36) is a set of generic, coherent, and easily administered quality-of-life measures. It describes the impact of the disease in terms of patient-centered outcomes rather than the biological or disease-centered outcomes perceived by clinicians. It assesses eight areas of health, ranging from those related to limitations in physical activities caused by disease to general perceptions of vitality and health (Ware and Sherbourne 1992). Participants completed the questionnaire at baseline, at week 4 and week 8.

The haematological and biochemical parameters and the non-specific inflammatory markers, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed at baseline and week 8 for safety evaluation of the investigative treatment. The blood specimens were collected and analyzed by Queensland Medical Laboratories (QML). Additional safety were evaluated through interviews and the participant daily diary, with adverse events defined as any untoward event occurring during the trial regardless of whether it was considered medication related.

Statistical methods

Sample size and analysis

Sample size was calculated on the primary outcome, the WOMAC total score. Based on a power of 80%, a sample size of 35 participants in each of the three arms was required, with 120 participants recruited to account for potential withdrawals. SPSS software was used for statistical analysis. Statistical significance was set as a P value < 0.05 (two-tailed). A modified intent to treat (ITT) approach was used for data analysis of the primary outcome, where all patients who were randomized to receive treatment and completed baseline assessments (including clinical markers) were included in the analysis. Health parameters (age, weight, height, BMI and blood pressure) and clinical markers were assessed for differences between groups at baseline and week 8 by ANOVA. The WOMAC, the NPS and pain scores were analyzed using repeated measures ANOVA with post hoc between group multiple comparisons.

Human Research Ethics Approval

The study was carried out according to the principles expressed in the Declaration of Helsinki and was approved by the Queensland Clinical Trial Network Human Research Ethics Committee (QCTN). No: 2014001, 5th June 2015. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) No: 12615000149561.

Results

Participant demographics

Initially, 188 potential participants completed screening, 119 attended baseline clinic interviews, with 111 people enrolling in the study and completing baseline assessments; A300 group $n=36$; A600 group, $n=35$; and placebo group, $n=40$. There were 11 withdrawals after the 4-week assessment as follows: A300 group ($n=4$): personal reasons (1), diverticulitis flare-up (1), damaged knee required surgery (1), stomach upset (1); A600 group ($n=2$): personal reasons (1), dizziness (1); in the placebo group ($n=5$): personal reasons (3), diverticulitis flare-up (1), stomach upset (1) (Fig. 1).

Gender participation was approximately in proportion in each treatment group with no significant differences for health parameters; in particular weight, body mass index (BMI), blood pressure and lifestyle factors. However, there were a higher number of cigarette smokers in the placebo group. All participants in the study presented with osteoarthritis in one or bilateral knees. Those with osteoarthritis in bilateral knees assessed either the right or left knee when completing the WOMAC and NPR assessments. The treatment groups were similar in the WOMAC scores and pain scores at baseline (Table 1). The three groups had similar scores for depression (corresponding to feeling mildly depressed), anxiety (corresponding to feeling moderately anxious) and stress (corresponding to feeling mildly stressed) as measured by the DASS. The results for the quality of life questionnaires SF-36 and PQSI were also similar in all treatment groups.

Effect of treatment with PEA on symptoms of knee osteoarthritis

Assessment of WOMAC

The WOMAC total score was similar at baseline for the treatment arms. There was a reduction in WOMAC total score in all three groups at 4 weeks; A300 group (reducing from 41.2 to 27.7), A600 group (from 43.2 to 25.4) and the placebo group (from 42.8 to 32.0), with further reductions in the A300 group (to 23.9) and the A600 group (to 20.0) but not the placebo group (to 32.0) by week 8. The WOMAC total score for both the active treatment groups significantly reduced compared to placebo at week 8; A300 group ($p=0.037$) A600 group ($p=0.001$).

There was a gradual reduction in the WOMAC pain score in all three groups reported at week 1 and then at 4 weeks; A300 group (reducing from 8.9 to 7.2 to 7.0), A600 group (from 9.2 to 7.0 to 6.2) and the placebo group (from

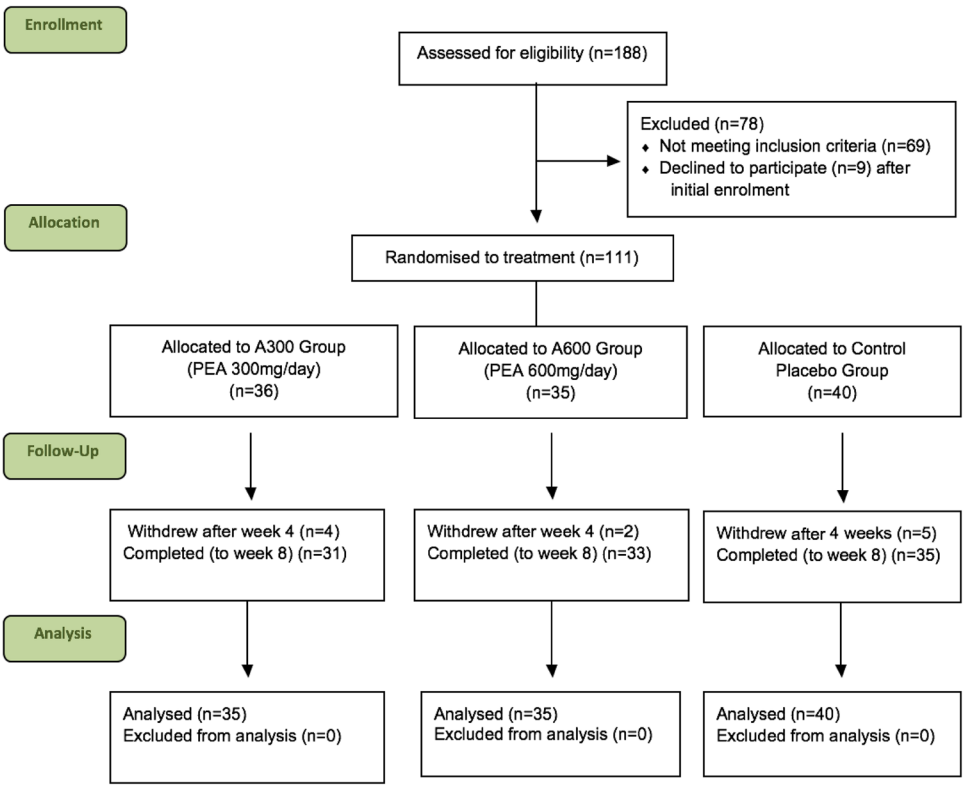

Fig. 1 Flowchart of participant progress

Table 1 Baseline demographics of study participants

	PEA (300 mg/day)	PEA (600 mg/day)	Placebo
Age (mean ± SD)	57 ± 11	58 ± 11	55 ± 11
Number of males	16	18	18
Number of females	20	17	22
Total number of participants	36	35	40
Body weight (mean ± SD)	79	81	81
Body mass index (BMI) (mean ± SD)	26	27	27
Systolic blood pressure	126	126	127
Diastolic blood pressure	81	85	85
Drink coffee (*n*, %)	24	34	38
Drink alcohol (*n*, %)	31	25	32
Smoke cigarettes (*n*)	2	1	9
Non-sedentary lifestyle	25	30	26
OA right knee assessment (present bilaterally)	13 (6)	15 (8)	16 (3)
OA left knee assessment (if present bilaterally)	24 (14)	20 (12)	24 (11)
OA in bilateral knees	20	20	14

9.0 to 7.8 to 7.4), with further reductions in the A300 group (to 4.5) and the A600 group (to 3.9) but not the placebo group (to 6.8) by week 8. The WOMAC pain score for both active treatment groups significantly reduced, A300 group ($p = 0.007$; A600 group ($p < 0.001$), compared to the placebo group at week 8.

There was a similar trend with a reduction in WOMAC stiffness scores for all treatment arms from baseline to week 4; A300 group, 4.2 to 2.7; A600 group, 4.1 to 2.2; and placebo group, 4.3 to 3.0. By week 8, however, there were further statistically significant reductions in the A300 group compared to the placebo group (reduced to 2.4 compared to 3.2; $p = 0.049$) and in the A600 group compared

to the placebo group (reduced to 1.9 compared to 3.2; $p = 0.001$).

The WOMAC function subdomain was similar at baseline for all treatment arms with a similar reduction observed in all treatment arms from baseline to week 4; A300 group, 28.1 to 19.3; A600 group, 30.2 to 17.6; and placebo group, 29.1 to 22.1. By week 8, there were further reductions in the A300 group although not significantly different to the placebo group (17.7 and 22.2 respectively; $p = 0.075$). However, by week 8, there was a statistically significant reduction in the A600 group compared to the placebo group (scores of 14.2 and 22.2 respectively; $p = 0.003$) (Fig. 2).

Assessment of Pain Levels and Use of Rescue Medication

Participants assessed knee pain using the NRS at baseline, week 1, week 4 and week 8. There was no difference for either "worst pain yesterday" or "least pain yesterday" or the range of pain between the groups at baseline. In the A300 group, the "worst" pain score reduced by 19.1% at week 1, by 32.2% at week 4 and by 40% at week 8. Similarly, the "worst" pain score for the A600 group reduced by 21.5% at week 1, by 32.2% at week 4 and by 49.5% at week 8. The placebo group reported minor reductions in pain of 7.9% (week 1) and 12.7% (week 4), returning to baseline scores by week 8. There was a significant reduction in "worst pain" scores in favour of both the A300 group and A600 group compared to placebo group at week 8 ($p < 0.001$, $p < 0.001$ respectively). These results were reflected in the "least" pain scores. The "least pain" levels were similar at baseline with active treatment groups reporting a gradual significant reduction over the subsequent study time points; A300 group; $p = 0.005$; A600 group, $p < 0.001$) compared to placebo. With the complexities in pain presentation, the "daily pain range" (between the worst and least pain) was also calculated. Interestingly, the range of pain reduced by only 10% in the placebo group at all time points. However, the range of pain was significantly reduced in the A300 group from 4.3 to 3.9 (9.3% reduction) at week 1, to 2.8 (34.9% reduction) at week 4 and maintained this level of pain reduction at week 8 ($p < 0.001$). The A600 group also reported a significant reduction in pain from 4.0 to 3.1 (22.5%) at week 1, a further reduction to 2.4 (40.0%) at week 4 which was still maintained at week 8 ($p < 0.001$) compared to placebo (Fig. 3).

The effect of the treatment on pain was also assessed by calculating the number of participants that reported no pain or "0″ pain for "least pain" at each time point. For the A300 group, the number of participants reporting no pain increased during the study (baseline, $n = 8$; week 1, $n = 15$; week 4, $n = 17$; and week 8, $n = 21$). A similar trend was observed for the A600 group (baseline, $n = 9$; week 1, $n = 14$); week 4, $n = 23$; and week 8, $n = 24$). In the placebo group, there was minimal variation in the number of people

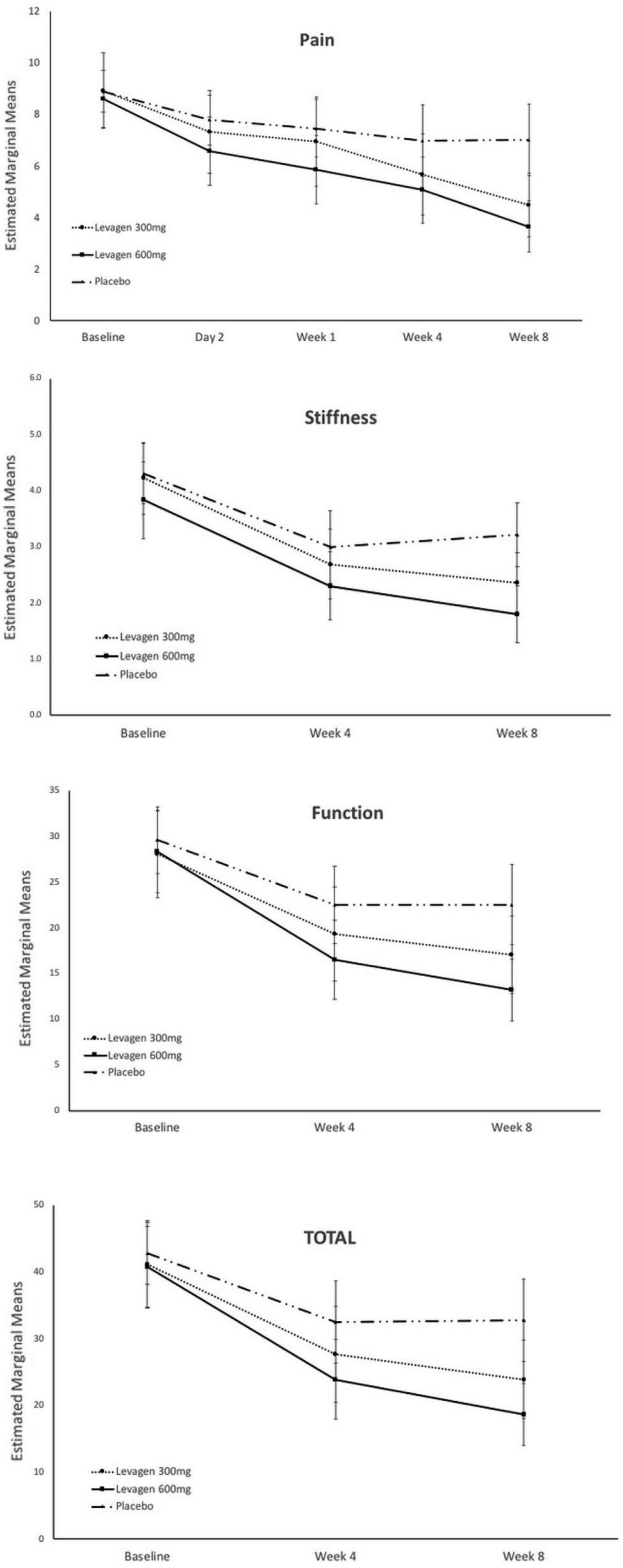

Fig. 2 WOMAC Total and sub-domain scores for PEA (300 mg/day), PEA (600 mg/day) and placebo at baseline, week 4 and week 8

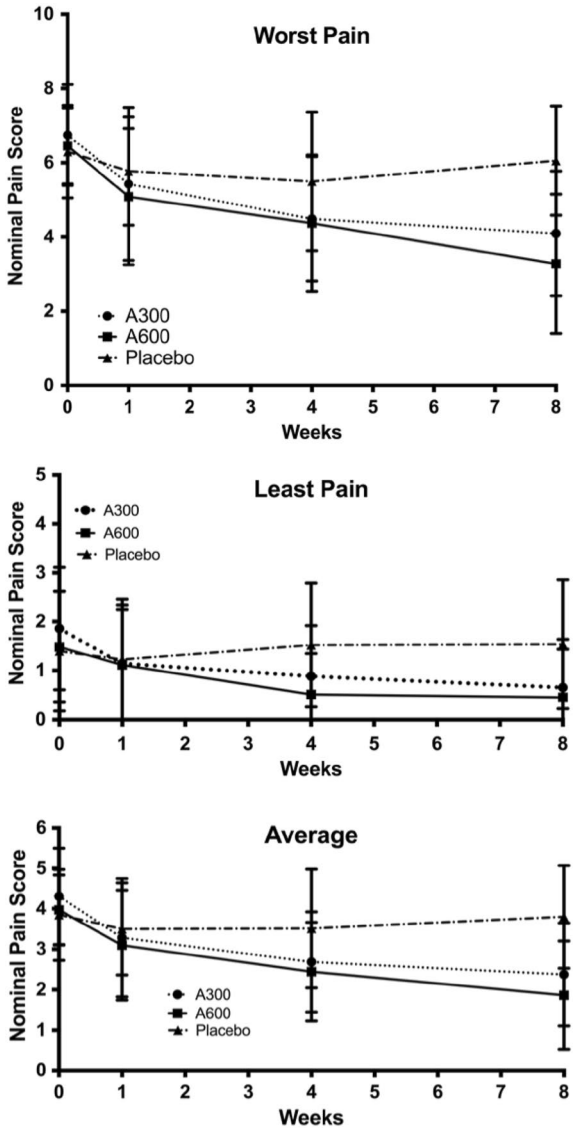

Fig. 3 Pain scores for PEA (300 mg/day), PEA (600 mg/day) and placebo at baseline, week 1, week 4 and week 8

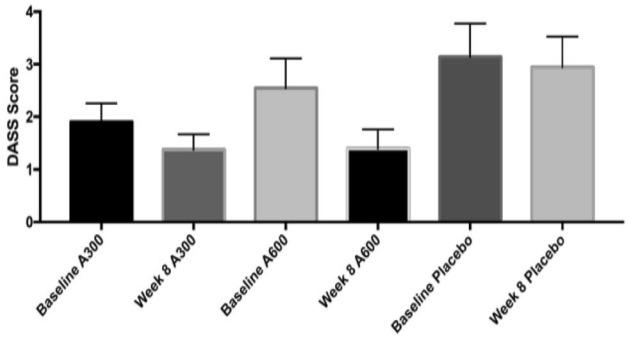

Fig. 4 DASS Anxiety domain score for PEA (300 mg/day), PEA (600 mg/day) and placebo at baseline, week 1, week 4 and week 8

reporting no pain in 24 h assessment period (baseline, $n=13$; week 1, $n=14$; week 4, $n=11$; week 8, $n=11$).

Participants recorded the use of rescue medication (paracetamol) in the participant daily diary. The doses were calculated as doses per week (with one dose equivalent to 200 mg of paracetamol). The use of rescue medication was minimal so interpretation of the results is difficult but the results are supportive of the observed WOMAC and NRS results. In the A300 group, 9 participants used rescue medication (average of 1.9 doses per week) and this reduced to 5 people in week 8 (average of 0.5 doses per week). In the A600 group, 8 participants used rescue medication (average of 1.4 doses per week) and this reduced to 4 participants by week 8 (average of 1.2 doses per week). In the placebo group, 9 participants recorded using rescue medication (average of 3.0 doses per week) and all 9 participants continued to maintain this level of rescue medication for pain relief (2.8 doses per week) (Fig. 3).

Assessment of other Quality of Life questionnaires

There was a significant difference in the anxiety score of the DASS in favor of the A300 group compared to placebo ($p=0.042$) and the A600 group compared to placebo ($p=0.043$) at week 8 (Fig. 4). There were no differences in the depression score or stress levels as assessed by the DASS or the PSI, in the treatment groups at 8 weeks. Furthermore, sleep quality as assessed by the PSQI and SF-36 subdomains did not differ significantly from baseline results for all treatment groups.

Assessment of Clinical Markers and Safety

The haematological and biochemical parameters were in the healthy reference range for all groups at baseline and remained stable over the 8 weeks. (Tables 2 and 3). The inflammatory markers, ESR and CRP also remained at similar levels between the treatment groups at baseline and at week 8. There were no serious adverse effects reported by the study participants.

Discussion

The results of this study demonstrated that PEA was effective for attenuating pain and reducing the associated symptoms of knee OA and was accompanied by a reduction in anxiety, over an 8 week treatment period. This is the first

Table 2 Biochemical parameters for PEA (300 mg/day), PEA (600 mg/day) and placebo at baseline, and week 8

Test (reference range)	PEA 300 mg/day baseline	PEA 600 mg/day baseline	Placebo baseline	PEA 300 mg/day week 8	PEA 600 mg/day week 8	Placebo week 8
Sodium (137–147 × mmol/L)	141 ± 2	141 ± 2	141 ± 2	140 ± 2	141 ± 2	141 ± 2
Potassium (3.5–5.0 × mmol/L)	4.5 ± 0.6	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	4.3 ± 0.3
Chloride (96–109 × mmol/L)	104 ± 2	104 ± 2	104 ± 2	104 ± 2	104 ± 2	104 ± 2
Bicarbonate (25–33 × mmol/L)	28 ± 2	28 ± 3	28 ± 2	28 ± 2	27 ± 3	28 ± 2
Glucose (3.0–7.7 × mmol/L)	5.3 ± 0.8	5.2 ± 0.8	5.1 ± 0.7	5.2 ± 0.6	5.3 ± 0.9	5.2 ± 0.5
Creatinine (40–110 × umol/L)	67 ± 13	73 ± 13	72 ± 16	64 ± 13	73 ± 14	72 ± 17
eGFR (over 59 × mL/min)	87 ± 6	85 ± 8	86 ± 7	89 ± 4	85 ± 8	86 ± 8
Uric acid (0.14–0.35 × mmol/L)	0.31 ± 0.1	0.35 ± 0.1	0.34 ± 0.1	0.32 ± 0.1	0.35 ± 0.1	0.35 ± 0.1
Total bilirubin (2–20 × umol/L)	9 ± 3	10 ± 3	9 ± 3	11 ± 3	10 ± 3	10 ± 4
Alkaline phosphatase (30–115 × U/L)	65 ± 15	66 ± 19	69 ± 17	62 ± 13	69 ± 23	68 ± 17
GGT (0–45 U/L)	36 ± 56	54 ± 50	28 ± 14	35 ± 63	56 ± 50	27 ± 40
Alanine aminotransferase (0–45 U/L)	32 ± 20	38 ± 39	25 ± 12	29 ± 15	33 ± 30	26 ± 11
Aspartate aminotransferase (0–41 U/L)	27 ± 14	29 ± 16	25 ± 8	27 ± 10	28 ± 13	25 ± 10
Lactate dehydrogenase (80–250 U/L)	175 ± 27	171 ± 29	170 ± 25	171 ± 27	174 ± 32	168 ± 28
Calcium (2.25–2.65 × mmol/L)	2.36 ± 0.22	2.34 ± 0.08	2.35 ± 0.07	2.34 ± 0.16	2.30 ± 0.08	2.34 ± 0.07
Phosphate (0.8–1.5 × mmol/L)	1.1 ± 0.2	1.01 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	1.3 ± 0.2	1.0 ± 0.2
Protein (60–82 × g/L)	70 ± 4	70 ± 3	70 ± 3	69 ± 4	70 ± 3	69 ± 5
Albumin (35–50 × g/L)	40 ± 3	41 ± 2	41 ± 2	40 ± 2	40 ± 8	41 ± 5
Globulins (20–40 × g/L)	28 ± 3	29 ± 3	29 ± 4	29 ± 3	28 ± 3	29 ± 4
Cholesterol (3.6–6.9 × mmol/L)	5.6 ± 1.1	5.8 ± 1.1	5.4 ± 1.0	5.6 ± 1.2	5.8 ± 1.1	5.3 ± 1.0
Triglycerides (0.3–4.0 × mmol/L)	1.3 ± 1.1	1.6 ± 1.0	1.5 ± 1.2	1.2 ± 1.4	1.4 ± 0.9	1.5 ± 0.8
Erythrocyte sedimentation rate (1-30 mm/h)	7.6 ± 6.2	6.5 ± 5.3	10.6 ± 9.9	7.4 ± 7.3	7.1 ± 5.7	9.0 ± 8.2
C-reactive protein (0-6 mg/L)	5.7 ± 2.8	5.2 ± 0.66	6.5 ± 3.0	5.8 ± 1.9	5.6 ± 1.6	5.8 ± 2.0

Table 3 Haematological parameters for PEA (300 mg/day), PEA (600 mg/day) and placebo at baseline, and week 8

Test (reference range)	PEA 300 mg/day baseline	PEA 600 mg/day baseline	Placebo baseline	PEA 300 mg/day week 8	PEA 600 mg/day week 8	Placebo week 8
Hemoglobin (115–160 g/L)	139 ± 11	144 ± 12	142 ± 13	139 ± 11	144 ± 12	142 ± 13
Red cell count ($3.6–5.2 \times 10^{12}$/L)	4.6 ± 0.4	4.8 ± 0.4	4.6 ± 0.9	4.6 ± 0.4	4.8 ± 0.4	4.6 ± 0.9
Hematocrit (0.33–0.46)	0.42 ± 0.03	0.44 ± 0.03	0.57 ± 0.79	0.42 ± 0.03	0.44 ± 0.03	0.57 ± 0.79
Mean cell volume (80–98 fL)	91 ± 4	91 ± 4	92 ± 4	91 ± 4	91 ± 4	92 ± 4
Mean cell hemoglobin (27–35 pg)	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2	30 ± 2
Platelet count ($150–450 \times 10^9$/L)	256 ± 47	254 ± 58	279 ± 59	256 ± 47	254 ± 58	279 ± 59
White blood cells ($4.0–11.0 \times 10^9$/L)	6.2 ± 1.9	5.9 ± 1.4	8.4 ± 9.1	5.6 ± 1.6	5.6 ± 1.6	6.5 ± 1.5
Neutrophils ($2.0–7.5 \times 10^9$/L)	3.3 ± 1.0	3.1 ± 0.5	3.9 ± 1.9	3.3 ± 1.0	3.1 ± 0.5	3.9 ± 1.9
Lymphocytes ($1.1–4.0 \times 10^9$/L)	2.0 ± 0.5	2.0 ± 0.5	2.1 ± 0.7	2.0 ± 0.5	2.0 ± 0.5	2.1 ± 0.7
Monocytes ($0.2–1.0 \times 10^9$/L)	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2
Eosinophils ($0.04–0.40 \times 10^9$/L)	0.20 ± 0.1	0.25 ± 0.2	0.27 ± 0.3	0.20 ± 0.1	0.25 ± 0.2	0.27 ± 0.3
Basophils ($< 0.21 \times 10^9$/L)	0.04 ± 0.04	0.05 ± 0.03	0.06 ± 0.04	0.04 ± 0.04	0.05 ± 0.03	0.06 ± 0.04

human clinical study to demonstrate the effectiveness of PEA for knee joint osteoarthritic pain. The results support the previous study of 600 mg/day PEA on temporomandibular joint (TMJ) osteoarthritis over 2 weeks, where PEA elicited a similar progressive decrease of pain intensity, in comparison to ibuprofen which had a faster resolution of pain in the first week but no further decrease in the following week, demonstrating that the PEA effect was associated with a greater improvement in maximum mouth opening at treatment end, as compared to ibuprofen (Marini et al. 2012).

Previous clinical trials have focused on PEA for conditions of chronic neurological pain as a stand-alone treatment or adjunct to other medications. The therapeutic doses used in previous clinical studies are comparable to the doses used in the present study. For example, a 600mg/day dose of PEA was shown to be effective in the treatment of lumbosciatic pain (Dominguez et al. 2012). Higher doses of 1.2 g/day for 30 days have been shown to provide a significant improvement in neurophysiological parameters of carpal tunnel syndrome (Conigliaro et al. 2011) and reduce pain in diabetic patients with carpal tunnel syndrome (Assini et al. 2010). Interestingly, PEA has been shown to have an additive or synergic drug–drug effect when used with sub-therapeutic does of carbamazepine, pregabalin and oxycodone in treatment of chronic pain (Desio et al. 2011), and when used with thalidomide/bortezomib in multiple myeloma patients with painful neuropathy (Truini et al. 2011). Recently, a meta-analysis by Paladini and co-authors (2016) demonstrated that PEA-induced pain relief was not related to the etiopathogeneisis of chronic pain, was progressive and independent of age and gender.

Studies on the pain experience of OA patients have shown that intermittent and constant pain have adverse effects on patient's mood, sociality and sleep (Neogi 2013; Alshami 2014). As a member of the endocannabinoidome family, PEA may have psychological modulating properties including regulation of depression, stress and anxiety (Stensson et al. 2018). The treatment with PEA significantly decreased levels of anxiety in this study. Interestingly, recent research demonstrated that antidepressants like imipramine and escitalopram can increase PEA levels in the brain (Smaga et al. 2014). Furthermore, the results of a small short-term study showed that PEA (dose of 1.2 g/day) used as adjunctive therapy to citalopram effectively improved symptoms of patients with major depressive disorder (Ghazizadeh-Hashemi et al. 2018). Recently, in an open labelled study, patients with carpal tunnel syndrome suffering from sleep disorders and painful symptoms reported that PEA (dose of 600 mg/day) provided an improvement in overall sleep quality with an increase of continuous sleep time and a reduction of sleep latency and disturbances as well as a significant mitigation of painful symptoms (Evangelista et al. 2018). To date, the current evidence suggests that the therapeutic effects of PEA on both the central and peripheral nervous system occur through synergistic interactions amongst several mechanisms (Petrosino and Di Marzo 2017). There were no changes in hematological parameters during the treatment period. This data is supported by multiple clinical trials on a variety of disease models (Petrosino and Di Marzo 2017). Furthermore, it has been shown that the anti-inflammatory effect of PEA (unlike other NAEs) does not undergo tolerance following repeated administration of high doses (Wise et al. 2008).

PEA has been shown to exert its anti-hyperalgesic effects by down-modulating several inflammatory mediators such as inflammatory cytokines, neutrophil infiltration, pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS), pro-inflammatory kinases such as mitogen-activated protein kinase (MAPK), neurotrophic factors such as nerve growth factor (NGF) and mast cell degranulation via the 'Autocoid Local Injury Antagonism' (ALIA) mechanism, inhibiting the release of histamine, PGD2 and TNF-α (Costa et al. 2008; Alhouayek and Muccioli 2014). Studies using animal models of chronic inflammation and chronic or neuropathic pain suggest that PEA can reduce the recruitment and activation of mast cells, the production of pro-inflammatory mediators, and endoneural edema, thus reducing both pain and inflammation while preserving peripheral nerve morphology (Bettoni et al. 2013). This is supported by evidence indicating a crucial role of the endocannabinoids in controlling neuronal excitability at the level of the spinal cord in a clinically relevant rat model of OA (Sagar et al. 2008).

PEA also affects endocannabinoid (eCB) signaling through peroxisome proliferator-activated receptor alpha (PPAR-α) activation (Petrosino and Di Marzo 2017; Guida et al. 2017). It does so by inducing the expression of anti-inflammatory proteins such as IκBα, which inhibits NF-κB translocation. This in turn suppresses the expression of pro-inflammatory proteins, such as TNF-α, which reduces the recruitment of immune cells (Alhouayek and Muccioli 2014). PEA is known to indirectly activate the cannabinoid receptor type 1 (CB1), cannabinoid receptor type 2 (CB2), transient receptor potential cation channel subfamily V member 1/vanilloid receptor 1 (TrpV1) and peroxisome proliferator-activated receptor gamma (PPAR-γ). It does so by preventing the FAAH mediated degradation of homologous cannabinoid, *N*-arachidonoylethanolamine/anandamide (AEA) that activates these receptors (Costa et al. 2008; Ho et al. 2008). CB1 and CB2 are two G-protein-coupled receptors (GPCRs) that have analgesic properties when activated. CB1 receptors are often expressed in the presynaptic terminals of the brain where they inhibit neurotransmitter release, in the peripheral nervous system and in the adipose tissue, skeletal muscle, bone, skin, heart, liver, reproductive organs and gastrointestinal system (Petrosino and Di Marzo 2017).

The strengths of the present study included the double-blind, placebo-controlled design, a population with mild to moderate OA, using PEA as a stand-alone treatment, with participants abstaining from all other anti-inflammatory drugs and natural treatments such as fish oils, glucosamine and chondroitin, and generally with a positive mental health and healthy sleep patterns. It had some limitations including a relatively small population size and short follow-up period and the proportion of male and females was not equal. It also

excluded the obese population which may influence the final dose required for therapeutic activity.

Current evidence suggests that the therapeutic effects of PEA on both the central and peripheral nervous system occur through synergistic interactions amongst several mechanisms. The results of this study support the concept that osteoarthritic pain has both nociceptive and neuropathic components and that PEA has potential as a novel and safe treatment for the management of osteoarthritic pain and associated symptoms. Furthermore, the effect of PEA in attenuating OA joint pain may also have significant effects on the intestinal microbiome by improving intestinal microbiome dysbiosis. Further studies on the pharmacological basis of this anti-inflammatory effect of PEA are now required.

Compliance with ethical standards

Conflict of interest Luis Vitetta has received National Institute of Complementary Medicine and National Health and Medical Research Council of Australia competitive funding and Industry support for research into nutraceuticals and herbal medicines. This research project was industry funded. None of the authors have a commercial interest in the investigative product. None of the authors have declared any conflict of interest.

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