Assessing the Effectiveness of Add-on Therapy of Palmitoylethanolamide to Standard Therapy in Diabetic Peripheral Neuropathy

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Abstract

Background: Diabetic Peripheral Neuropathy (DPN) is a common yet challenging complication of diabetes, particularly in managing neuropathic pain. Palmitoylethanolamide (PEA), a naturally occurring nutraceutical from the ALIAmides group, has demonstrated potential for pain modulation, inflammation reduction, and improving quality of life.

Methods: A 9-month prospective observational study at PSG Hospital evaluated the impact of adding oral capsule PEA (708 mg in two divided doses) to standard therapy for DPN patients unresponsive to maximum tolerated dosages of Gabapentin, Pregabalin, amitriptyline, or duloxetine. The outcomes were the pain severity and quality of life. Pain was assessed using the Visual Analog Scale (VAS), sensitivity was evaluated via monofilament testing, and quality of life was measured using the American Chronic Pain Association (ACPA) Quality of Life Scale (QOLS).

Results: Sixty patients with DPN were treated with adjunctive PEA and monitored for 8 weeks. Pain scores decreased significantly (6.05±1.096 to 4.15±1.233 at 4 weeks and 3.57±1.155 at 8 weeks, $p<0.05$). Sensitivity improved via monofilament testing (7.12±1.58 to 9.43±0.78). Quality of life scores rose from 7.67 to 9.41 at 4 weeks and 9.68 at 8 weeks, indicating notable benefits.

Conclusion: PEA proved effective as a supplemental treatment for nonresponsive DPN patients, yielding significant reductions in pain, enhanced sensitivity, and better quality of life. Importantly, no side effects were reported, affirming its tolerability and safety.

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Keywords: Palmitoylethanolamide; Peripheral Neuropathy; Conventional Therapy; Neuroprotective Effect; Pain

Introduction

Diabetic Peripheral Neuropathy (DPN) is a peripheral neurodegenerative condition with an estimated 30% of this group negatively impacted, as it is the most frequent consequence of diabetes (1). Diabetic Neuropathy (DN) symptoms vary and rely on the nerve system affected (vegetative or peripheral sensory/motor) (2). Nerve pain includes electric shocks and stabbing episodes, unusual tingling or pins and needles, spontaneous burning, heightened pressure sensitivity, and pain triggered by pressure, brushing, or cold temperatures (3). In DPN, persistently elevated blood glucose levels harm small blood vessels, reducing the flow of nutrients and oxygen to the nerves (4). Foot ulcers form as a result of continuous injury to tiny nerve fibres (5). According to Yang et al., a recent study on a murine model of diabetes, changes in blood glucose levels weaken the myelin sheath and nerve fibres and cause inflammation, especially when it comes to an increase in pro-inflammatory cytokines like TNF-α, IL-6, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) (6). As a result, it has been shown that growing DPN severity is caused by a progressive loss of myelin sheath integrity (7). One of the main strategies for treating diabetic peripheral neuropathy

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(DPN) is to keep blood glucose levels under control. The main medications for treating neuropathic pain that are recommended by the Neuropathic Pain SIG (NeuPSIG), International Association for the Study of Pain (IASP), and the National Institute for Health and Care Excellence (NICE) guidelines are antidepressants (amitriptyline) and calcium channel α2-δ ligands (gabapentin, pregabalin). The preferred medications can be changed if the course of treatment is unsatisfactory or unsuccessful (8). Managing patient expectations in pain treatment is challenging due to modest relief expectations (30-50% reduction). Chronic pain can result from nervous system dysfunction, involving immune components like mast cells and microglia (9). PEA, a nutraceutical derived from sources like soy lecithin, has renewed attention for its effectiveness in treating pain and inflammation (10). PEA doesn't directly bind to typical cannabinoid receptors but boosts endocannabinoids indirectly by blocking their breakdown enzyme, elevating Endocannabinoid anandamide levels for enhanced pain relief. It also activates PPAR-α, TRPV1, and CB2-like receptors, enhancing analgesic effects (11). PEA is thought to primarily target peroxisome proliferator-activated receptor alpha (PPAR-α). This receptor modifies the gene networks responsible for controlling inflammation and discomfort (12). Likely by deactivating the NK-KB signalling pathway (11-14) PEA also binds to cannabinoid-like G protein-coupled receptors GPR55 and GPR119 (15). PEA has been shown in reports to have analgesic potential for DPN. PEA has also an entourage effect that might amplify the physiological effects of endogenous endocannabinoids like anandamide (N-arachidonoylethanolamine) (16).

PEA is additionally believed to have a separate endocannabinoid signalling system that doesn't have the negative effects of exogenous endocannabinoids (17). An initial meta-analysis across various chronic neuropathic pain conditions, including DPN, found PEA to gradually alleviate pain, suggesting that PEA could be a promising and innovative therapeutic approach for addressing chronic and neuropathic pain linked to neuroinflammation (18). DPN is a chronic complication of diabetes, often associated with significant pain and neuroinflammation, leading to reduced quality of life. Current standard therapies for neuropathic pain offer limited relief and may require additional medications for adequate pain management. PEA has demonstrated analgesic and neuroprotective properties, primarily through PPAR-α-mediated mechanisms, reducing microglial and mast cell activity. Its potential to decrease the need for rescue medications and provide a novel therapeutic strategy for chronic neuropathic pain and neuroinflammation warrants further exploration. Adding PEA to standard therapy could offer enhanced symptom control and improved outcomes for DPN patients. This study aimed to assess the effectiveness of PEA as an add-on therapy to the standard treatment in managing pain and neuroinflammation in patients with DPN.

Methods

We carried up a prospective observational study from June 2023 to March 2024 at the general medicine department of PSG Hospital in Coimbatore, Tamil Nadu, India. The study was approved by the Institutional Review Board at the Institutional Human Ethics Committee (PSG/IHEC//2023/Appr/FB/058, dated 10 Nov 2023) and carried out in accordance with the Helsinki Declaration

Study participants

The study subjects were carefully selected based on inclusion criteria. Patients above 18 years and with a history of type 2 diabetes mellitus diagnosed with DPN and were not responsive to standard therapy with maximum tolerated dosage (i.e., Gabapentin, 1200–3600 mg/day, pregabalin 300-600mg/day, amitriptyline 25–150 mg once daily, or twice as much in two doses, duloxetine 60-120 mg/day) were included. The oral capsule of PEA (708 mg/day in two divided doses) was initiated as add-on therapy and continued for 8 weeks of treatment. Patients with nondiabetic neuropathy, pregnant or lactating women, adolescents, the elderly, and patients with diabetic foot ulcers and uraemia were excluded from the study.

Sample size calculation

Based on the previous PSG hospital admission of patients with diabetic peripheral neuropathy, the sample size was determined using the Cochrane Equation (N = Z2*p*q/e2, where e = 0.05 (margin error), Z = 1.96 @95% (confidence interval), q = 1-p, and p = population proportion). A sample size of 66 was used.

Study Procedure

The first step in this study was to screen patients based on inclusion and exclusion criteria. Following selection, study participants' agreement was acquired following a thorough explanation. The demographic details (Age, sex, comorbidities, medical history, medication history, Diabetic parameters) were collected from their respective patient files and recorded. Diabetic markers including HbA1c, fasting blood sugar (FBS), and postprandial blood sugar (PPBS) were the primary diagnostic tests performed. Diabetic markers including HbA1c, FBS, and PPBS were the primary diagnostic tests performed. The visual analogue scale (VAS) score was used to assess

neuropathic pain in patients. The VAS score ranging from 0-10 measures minor, moderate, and intense pain. At the baseline, fourth, and eighth weeks of treatment, the pain intensity (Visual Analogue Scale (VAS)), the monofilament score, and the QOLS were determined.

Assessment of study outcomes

Pain Scoring

VAS has been utilized for assessing abstract concepts like pain, quality of life, and anxiety. It's a straight line with no pain at one end and the worst pain imaginable at the other representing the VAS for pain. A patient indicates where on the line their level of pain corresponds. It could assist in determining the appropriate dosage of painkillers. The scoring ranges from 0-10 from no pain of range (0-3), mild pain of range (3-5), moderate pain (5-7), and severe pain (7-10) in the pain scale. Its widespread utilization offers a valuable understanding of pain perception and treatment effectiveness.

Sensitivity testing using monofilament scoring

A tiny strand of nylon joined to a plastic base is called a monofilament. This is used by the clinician to assess loss of sensation in the foot. A monofilament weighing 10 grams/5.07 on the scale is employed to determine whether the protective sensation is present or absent during sensitivity testing. The monofilament score is recorded using 10gm/5.07 monofilament that exerts 10 gm of pressure at 5.07 of the thickness measured at five spots in each foot of patients during treatment. The monofilament score is recorded using 10gm/5.07 monofilament that exerts 10 gm of pressure at 5.07 of the thickness measured at five spots in each foot of patients during treatment. The monofilament should be placed 90 degrees to the skin surface and released in a controlled manner. For every test, it should be applied, held, then released after 1-2 seconds. The monofilament should buckle when applied and held at a distance of approximately 1 cm from the horizontal. It cannot slip or "wiggle" while being kept in position. When applied and held the monofilament should buckle at about 1 cm from the horizontal.

Quality of life analysis

The ACPA's QOLS was used to measure quality of life. The QOLS was determined at baseline, 4th, and 8th weeks of treatment by interviewing patients with 10 questions on the scale and scoring 0-10. Here 0 indicates non-functionality, a score of 5 represents struggle but fulfilling home responsibilities and a score of 10 represents normal Quality of life.

Statistical analysis

Software for statistical analysis, SPSS version 29, was used. The pain scores before and after therapy were compared using a paired T-test and correlation.

Results

Sixty patients unresponsive to conventional therapy added with PEA of both genders (23 males and 37 females), with a mean age of 59.92±12.5 years, were recruited in the study. The mean BMI was 28.45 ± 3.91kg/m2. The study patients were suffering from a comorbid condition such as hypertension, dyslipidaemia, obesity and coronary artery disease (CAD), and acute cerebral venous thrombosis (CVT). Among the comorbid conditions, obesity was more frequent (50%) followed by dyslipidaemia (16.6%), CAD (3.33%), and CVT (1.66%). Out of 60 patients 12 patients (20%) were on Pregabalin, 5 patients (8.33%) on amitriptyline, 11 patients (18.33%) on gabapentin, 8 patients (13.33%%) on Pregabalin + Amitriptyline, and 12 patients (20%) on Pregabalin + gabapentin + amitriptyline. Pain assessment showed that 25% (n=25) were in grade I and 75% (n=45) in grade II of pain (VAS). The frequency of pain categories showed a significant difference between baseline and eight weeks of treatment. The frequency of mild pain was 25% at baseline and 70% at eight weeks. The frequency of moderate pain was 75% at baseline and 18.3% at eight weeks. No patients experienced severe pain during treatment (Table 1).

Table 1. Pain intensity and sensitivity testing in the treatment group

Assessment		Score Range	PEA*	
			Baseline (%)	8th Week (%)
Pain Intensity	No pain	0-3	0	11.6
	Mild pain	3- 5	25	70
	Moderate pain	5-7	75	18.3
	Severe pain	7-10	0	0
Monofilament	Abnormal sensation	0-4	20	5
	Low sensation	4-7	35	25
	Normal Sensation	7-10	45	70

* PEA; Palmitoylethanolamide

The effectiveness of PEA on pain reduction was analysed by paired t-test and calculatet P-values were not less than 0.05 at a 95% confidence range for statistical significance. Among 60 subjects the mean pain score at the baseline was 6.05±1.096, which dropped to 4.15±1.233 after 4 weeks and then to 3.57±1.155 in 8 weeks, representing a 50% reduction in pain.

For the monofilament test, each foot had five locations, categorizing sensitivity into low sensitive (4-7) and abnormally sensitive (0-4), which accounted for 20% at baseline and 5% at the eighth week. The difference in monofilament test scores at three-time points was statistically significant ($p<0.05$) at a 95% confidence interval. The mean of the score was 7.12±1.58 initially and rose to 8.78 ±1.2 at four weeks and further to 9.43± 0.78 at eight weeks. The results revealed a significant difference in the mean QOLS (7.67 at baseline, 9.41 at 4 weeks, and 9.68 at 8 weeks) (Table 2).

Table 2. The mean difference in pain score (VAS), monofilament test score, and quality of life score before, 4 weeks, and 8 weeks after treatment

Outcome	Baseline	4 weeks	Change at 4 weeks	8 weeks	Change at 8weeks	P value
VAS*	6.05±1.096	4.15±1.233	-1.9	3.57 ±1.155	-2.48	0.001
Monofilament Score	7.12±1.58	8.7±1.2	+1.05	9.43±0.78	+2.31	0.001
Quality of life score	7.67±9.1	9.41±0.69	+1.74	9.68±0.49	+2.01	0.001

VAS: visual analogue scale

Our study revealed a correlation between the diabetic parameters and pain and monofilament scores in the 4th and 8th weeks (Table 3). The FBS, PPBS, and Hba1c vs pain correlation coefficient was found to be strongly positive 0.193*, 0.249* for 4 and 8 weeks. A negative correlation of -0.027*, and -0.061* was observed when comparing monofilament score vs BMI.

Table 3. Effect of treatment on glucose metabolism for treatment group at baseline, 4 and 8 weeks

Parameters	Baseline	4 Weeks	8 Weeks	P Value
FBS	149±55.1	135±42.5	128±30.8	0.056
PPBS	219±75.8	208±37.7	174.2±33.55	0.001
HbA1c	8.5±1.6	7.6±1.4	7.3±1.20	0.035

FBS: fasting blood sugar, PPBS: postprandial blood sugar, HbA1c: glycosylated haemoglobin

Discussion

Findings from the research showed that, when tested over eight weeks, for mild to moderate neuropathic pain in non-responding individuals with diabetic peripheral neuropathy, the PEA formulation proved safe, efficacious, and neuroprotective. Similar findings demonstrate that after 4 weeks, 600 mg of a micronized, non-emulsified PEA considerably reduced pain by about 50%. After 30 and 60 days, there was also a notable decrease in neuropathic pain related to DPN (19). Furthermore, following 40 days of treatment, a greater dose of 1200 mg/day of the micronized (non-emulsified) PEA significantly decreased diabetic and traumatic chronic neuropathic pain (20). In the case series when PEA was used in combination with standard analgesics, PEAs tolerability was excellent in all patients. PEA has shown encouraging outcomes in some clinical trials where the compound's safety and efficacy were assessed (21). The results of the research by Lang et.al indicated that PEA possesses clinically significant analgesic effects affecting pain modulation through both central and peripheral mechanisms (22).

In this study, the efficacy of PEA was evaluated by comparing pain levels at baseline and 8 weeks. A notable reduction in pain was observed, with 50% pain decreasing from a baseline to 8 weeks. This finding was similar to the Chaurasia et.al study which compared the efficacy of PEA over the placebo group with a significant reduction in pain symptoms in neuropathic pain after 7 weeks (49 days) with a mean reduction from 7.1 to 2.1(23).

Monofilament scoring was performed to assess foot sensation and nerve damage extent. PEA supplementation notably enhanced monofilament scores, indicating improved sensation in patients. A study by Zang et.al, in 2018 concluded that the efficacy of 3-, 4-, and 10-site Semmes-Weinstein monofilament evaluation (SWME) testing for the detection of diabetic peripheral neuropathy did not change significantly. To screen for DN, three sites on each foot may be subjected to SWME testing (24).

Quality of life was assessed using the QOLS by the American Chronic Pain Association, which scores daily activities on a scale from 0 to 10. Results showed a notable improvement in the quality of life of patients. This indicates that PEA has a positive impact on the quality of life for patients with DPN and chronic pain, potentially by reducing pain levels and enhancing day-to-day functioning. There was no study reported with similar scale.

In this study, similar to Pickering et al., study, PEA was given in addition to other oral hypoglycaemic medications in a randomized trial to highlight its effectiveness as a stand-alone therapy as well as supplemental painkillers. When studied over an 8-week period versus placebo, the results suggested that PEA was safe, acceptable, and effective as an analgesic for mild to moderate pain associated with diabetic peripheral neuropathy. It also highlighted the possibility that larger studies may be conducted to determine whether glycaemic levels affected PEA's effectiveness (25).

This study observed correlations between FBS, PPBS, HbA1c vs Pain. We observed reduction in blood glucose level after PEA administration indicating that lower levels of these parameters may lead to reduced pain. Administration of PEA resulted in decreased blood glucose levels, suggesting a potential link between managing diabetes and alleviating peripheral neuropathic pain. Pickering et al., invited further investigation to provide a more thorough understanding of the direct relationship between PEA and lowering diabetes markers. According to animal studies, blood glucose levels that are both high and fluctuating may also impair the myelin sheath around nerve fibres (26).

The absence of side effects underscores the safety of PEA. Over 20 effective clinical trials using PEA have been reported and thoroughly analyzed, with approximately 2000 persons treated. There have not been any noteworthy adverse effects or harmful drug-drug interactions recorded.

In a meta-analysis of pooled data patients of both sexes who experienced chronic pain linked to a range of medical disorders responded well to PEA treatment. This finding is consistent with the theory that PEA regulates processes shared by various disorders linked to neuropathic or chronic pain (18). Our study's strength lays its focus on patients unresponsive to conventional neuropathic drugs, where PEA effectively reduced pain within four weeks. To learn more about the connection between blood glucose levels and PEA's efficacy, larger cohort studies are necessary.

Conclusion

This work highlights the effectiveness of PEA as a supplemental treatment for noncompliant patients receiving the maximum tolerated dose of conventional DPN treatment (i.e., Gabapentin (1200–3600 mg, divided into three doses daily), pregabalin (300-600mg in two divided doses), amitriptyline (25–150 mg once daily, or twice as much in two doses), and duloxetine (60–120 mg once daily or in two divided doses per day)). Within four weeks, patients experienced a significant reduction in pain scores, improved foot sensitivity, and enhanced quality of life. Despite the valuable insights gained, this study has several limitations. Firstly, it is a one-arm study without a comparison group, which limits the ability to draw direct comparisons between different treatment groups. Additionally, the lack of random sampling introduces the potential for selection bias, which may affect the generalizability of the results. These factors should be considered when interpreting the findings of this study.

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Conflicts of Interest

The authors declare no competing interests regarding the publication of this manuscript. Any assistance from AI in the study conduct and manuscript writing has been acknowledged and declared.

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