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Effect of Palmitoylethanolamide on Visual Field Damage Progression in Normal Tension Glaucoma Patients: Results of an Open-Label Six-Month Follow-Up

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ABSTRACT The purpose of this study is to assess the effect of palmitoylethanolamide (PEA) oral administration on intraocular pressure (IOP) and visual field damage progression in normal-tension glaucoma (NTG) patients. Thirty-two consecutive patients affected by NTG were enrolled and randomized in a 1:1 ratio to receive PEA treatment (group A) or no treatment (group B). Group A patients took ultramicronized 300 mg PEA tablets two times per day for six months. Best-corrected visual acuity (BCVA), IOP, and visual field test were evaluated at baseline and at the end of the six-month follow-up. No significant differences in clinical parameters between the two groups were observed at baseline. At six months, group A patients showed significant IOP reduction (from 14.4 ± 3.2 mm Hg to 11.1 ± 4.3 mm Hg, $p < 0.01$). No statistically significant changes were seen in BCVA in either group. Visual field parameters significantly diminished in patients receiving PEA compared to baseline values (-7.65 ± 6.55 dB vs. -4.55 ± 5.31 dB, $p < 0.001$; 5.21 ± 4.08 dB vs. 3.81 ± 3.02 dB, $p < 0.02$; mean deviation [MD] and pattern standard deviation [PSD] respectively), while no significant changes were seen in group B. A generalized linear model demonstrated that the final IOP, MD, and PSD was affected only by the systemic PEA treatment ($p < 0.01$ each) and not affected by demographic or clinical characteristic between the groups. Hence, systemic administration of PEA reduces IOP and improves visual field indices in individuals affected by NTG. Neither ocular nor systemic side effects were recorded during the study period.

KEY WORDS: • ***glaucoma progression*** • ***intraocular pressure*** • ***normal tension glaucoma*** • ***palmitoylethanolamide*** • ***visual field***

INTRODUCTION

THE EXPRESSION ''GLAUCOMA'' includes various ocular conditions involving progressive optic nerve damage associated with loss of visual function and, frequently, with elevated intraocular pressure (IOP).[1] Normal-tension glaucoma (NTG) is a unique condition in which optic nerve damage and vision loss occur despite normal pressure inside the eye. However, the benefit of IOP-lowering treatment influences all the different conditions included in glaucoma, being excellent in patients with angle-closure glaucoma, good in primary open-angle glaucoma, and relatively modest in NTG patients.[2] NTG would have no fundamental difference from ordinary chronic primary open-angle glaucoma, except that the etiologic trigger or pathogenic process is accelerated at a lower level of IOP.[3] Evidence from clinical studies shows that circulatory abnormalities, including low blood pressure, nocturnal hypotension, and unstable mean ocular perfusion pressure, may be involved in the pathogenesis of NTG.[4–7] The IOP increase (mechanic stress) and unstable blood flow (ischemic stress) lead to activation of glial cells as a nonspecific response to stress.[2] In the optic nerve head, the most important glial cells are astrocytes. Astrocytes respond to all forms of central nervous system (CNS) insults by a process commonly referred to as reactive astrogliosis.[8] Several factors are implicated in astroglial activation and optic nerve degeneration pertaining to glaucoma, among these peptides such as endothelin-1, cytokines such as tumor necrosis factor alpha and the transforming growth factor beta superfamily, oxidative stress, advanced glycation end products, and trophic factors seem to be the most important.[9] The activation of astrocytes alters the local microenvironment in the optic nerve head, upregulating proteins and increasing glutamate efflux from astrocytes with cell death of neurons due to excitotoxicity and a consequent loss of retinal ganglion cells.[9–11] These structural changes are usually accompanied by functional modifications, revealed by standard automated perimetry (SAP), which ultimately are responsible of a significant reduction in quality of life.

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Palmitoylethanolamide (PEA), a naturally occurring amide of ethanolamide and palmitic acid, is a lipid messenger that mimics several endocannabinoid (eCB) driven actions, even though it does not bind to cannabinoid receptors. Since the 1990s, interest has surged again due to the discovery of its effects in many different animal paradigms. It is classified as a food for medical purposes or as a diet supplement in various countries of Europe.[12] Converging evidence indicates that PEA binds with relatively high affinity to peroxisome proliferator-activated receptor (PPAR), and they are now recognized among their physiological ligands.[13] In the brain, these receptors have been implicated in neural cell differentiation and death, as well as in inflammation and neurodegeneration.[14] In the eye, the role of PPAR ligands in protecting retinal ganglion cells against glutamate insult has also been ascertained.[15] High vitreous levels of glutamate have been documented in glaucoma, and the major causes of cell death from glutamate are the influx of calcium into cells and the generation of free radicals.[16]

On the basis of these considerations, the present study was designed to assess the effect of PEA oral administration on visual field damage progression in normal tension glaucoma patients through an open label six-month follow-up.

PATIENTS AND METHODS

Thirty-two consecutive patients (12:20, male:female; mean age 53.72 years; range 31–67 years) affected by NTG were enrolled in this prospective, comparative clinical trial held between January 2012 and January 2013 at the Chair of Ophthalmology, Department of Medicine and Health Sciences, University of Molise, Italy. The study was performed in accordance with good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board approved the study protocol. All participants provided written informed consent after receiving a detailed description of the procedure to be used and the nature of the study.

All patients were treated in both eyes with latanoprost eye drops once daily for at least three months; patients under other topical medications hemodynamically active were not included in the study.[17] Included patients were randomly divided into two groups: 16 patients (6:10, male:female) were assigned to the PEA treatment group, and 16 to the control (nontreatment) group. All subjects underwent a full medical and ocular history and a detailed ocular examination, including best corrected visual acuity (BCVA), IOP measurement, Humphrey visual field (HVF) test, red-free disc photo, stereo disc photo, optical coherence tomography (OCT) examination, gonioscopy, slit-lamp examination, fundus examination, and 24 h ambulatory blood pressure (BP) monitoring. Inclusion criteria were patients with a diagnosis of NTG, defined as optic disc abnormalities consistent with glaucomatous optic neuropathy with visual field loss. Glaucomatous optic disc abnormality was defined as neuroretinal rim thinning, notching, excavation, or a retinal nerve fiber layer (RNFL) defect. Glaucomatous visual field loss was defined as a pattern standard deviation outside 95% normal limits or a Glaucoma Hemifield Test result that was not within normal limits and abnormally high sensitivity, confirmed with two or more consecutive visual field tests. Other inclusion criteria were: (1) IOP of 18 mmHg or less without topical hypotensive therapy (average of the two highest values recorded during diurnal measurements, made from 8:00 a.m. to 6:00 p.m., every two hours by Goldmann applanation tonometer); (2) aged 18 years or older; (3) logarithm of the minimal angle of resolution (logMAR) BCVA of 0.70 or better; (4) progression of anatomic and functional damage as determined by computerized perimetry and serial stereophotographs of the optic nerve head; (5) no history of amblyopia; (6) no history of ocular disease or previous eye surgery responsible for vision changes that confound recognition of a test result solely due to glaucoma. Exclusion criteria were: (1) active ocular disease; (2) use of other ocular medications or therapies that might have a substantial effect on IOP; (3) history of ocular surgery; (4) use of other similar systemic medications (*e.g.*, ergoloid mesylate derivative); (5) vasoactive systemic therapies (Ca-antagonists, oral beta-blocker, *etc.*) and current tobacco smoker; and (6) pregnancy or lactation. Eyes with glaucomatous visual field defects were defined as those that met two of the following criteria, as confirmed by more than two reliable consecutive tests, in addition to compatibility with optic nerve appearance: (1) a cluster of three points with a probability of $<5\%$ on a pattern deviation (PD) map in at least one hemifield and including at least one point with a probability of $<1\%$ or a cluster of two points with a probability of $<1\%$; (2) a Glaucoma Hemifield Test (GHT) result outside normal limits; and (3) a pattern standard deviation (PSD) outside 95% of the normal limit. Reliable visual field assessment was defined as a visual field test with a false-positive error $<15\%$, a false-negative error $<15\%$, and a fixation loss $<20\%$. The first perimetric result was excluded from analysis to obviate learning effects.[7]

The product used in the study was ultramicronized PEA (Visimast 300®; Medivis Srl, Catania, Italy). The palmitoylethanolamide was provided in the form of tablets; each tablet contained 300 mg PEA. The subjects were instructed to take one tablet after breakfast and dinner, for a total of two tablets daily for six months. Patients were surveyed using a questionnaire to assess the duration of actual intakes of PEA for the treatment duration analysis.

At baseline and at the end of follow-up (six months later), the following parameters were evaluated: BCVA (early treatment diabetic retinopathy study chart [ETDRS] at 4 m); IOP with the patient in a sitting position at the slit lamp—the means of three consecutive readings—and central corneal thickness (Canon TX-20P fully automatic noncontact tonometer; Canon, Inc., Tokyo, Japan); visual field test (automatic computerized perimetry 24-2 SITA standard test, Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA, USA); and red-free disc photo, stereo disc photo, and OCT (Heidelberg Engineering GmbH, Heidelberg, Germany). Central corneal thickness measurement and 24 h ambulatory BP monitoring were performed at the beginning and end of the study period.

Table 1. Demographics and Clinical Characteristics of Patients with Normal Tension Glaucoma at Study Entry

Characteristic	*Value*
Number of patients	32
Gender (male:female)	12:20
Mean age (range)	53.72 years (31–67 years)
IOP	14.4 ± 3.2 mm Hg
Central corneal thickness	546 ± 24 μm
Best corrected visual acuity (BCVA)	0.08 ± 0.01 logMAR
Systolic blood pressure	112.7 ± 7.4 mm Hg
Diastolic blood pressure	68.4 ± 5.2 mm Hg
Heart rate	63.3 ± 8.2 beats/min

IOP, intraocular pressure; logMAR, logarithm of the minimal angle of resolution.

Patients were asked to complete an adverse events questionnaire for the entire follow-up period to monitor ocular and nonocular adverse events. This form was collected at each visit, and additional comments regarding treatment and adverse events were encouraged from each subject.

Analyses of the data were carried out using SPSS v8 (SPSS, Inc., Chicago, IL, USA) statistical packages. The performer of statistical analyses was masked, and in cases of bilateral NTG, only one eye, randomly chosen, was considered. Baseline demographic and clinical parameters between groups were compared using one-way analysis of variance (ANOVA). Paired *t*-tests compared differences before and after medication with baseline values within groups. In addition, a generalized linear model was used to assess the relationship between final IOP, mean deviation (MD), and PSD and multiple variables. A p-value < 0.05 was considered statistically significant. The sample size calculation was based on the assumption that a difference in mean defect at visual field test (MD) of 1.5 dB is clinically relevant. At least 16 eyes were needed, given $\alpha = 0.05$, $1 - \beta = 0.90$, and standard deviation (SD) = 1.5 dB.

RESULTS

A total of 32 patients were investigated of which 12 were men and 20 were women. The mean age was 53.72 years (range 31–67 years). Demographic and clinical characteristic of recruited patients at study entry are summarized in Table 1. Patients were randomly divided into two groups: 16 patients (6:10, male:female) received PEA (group A, treated patients), whereas the remaining 16 patients (6:10, male:female) represented the control (group B, nontreated patients). Group A patients took two PEA tablets daily (after breakfast and dinner), for the entire follow-up period (six months). At baseline, there were no significant differences in demographic characteristics and clinical parameters between the two groups, as assessed by paired *t*-test. All patients finished the study. PEA treatment reduced IOP significantly. At baseline, the mean IOP ± SD was 14.4 ± 3.2 mm Hg. Six months later, the mean IOP significantly decreased to 11.1 ± 4.3 mm Hg ($p < 0.01$) in patients receiving PEA, whereas it did not change significantly in controls (14.2 ± 3.6 mm Hg, not significant [n.s.]). The mean IOP reduction was about 2.2 mm Hg (about 17%). PEA administration did not induce significant modifications in SBP, DPB, or HR when compared with the respective baseline values (SBP = 111.3 ± 6.9 mm Hg vs. 101.7 ± 4.5 mm Hg and 115.3 ± 6.9 mm Hg vs. 110.9 ± 6.5 mm Hg, n.s.; DBP = 66.8 ± 6.3 mm Hg vs. 65.2 ± 5.4 mm Hg and 65.2 ± 7.8 mm Hg vs. 64.7 ± 6.9 mm Hg, n.s.; HR = 61.1 ± 5.1 beats/min vs. 58.4 ± 6.2 beats/min and 63.1 ± 6.1 beats/min vs. 59.9 ± 5.7 beats/min, n.s.; Table 2).

No statistically significant changes were seen in BCVA (PEA group: 0.08 ± 0.09 logMAR vs. 0.07 ± 0.10 logMAR, n.s.; control group: 0.08 ± 0.12 logMAR vs. 0.07 ± 0.11 logMAR, n.s.). Visual field parameters (MD and PSD) significantly diminished in patients receiving PEA when compared with the baseline values (MD baseline vs. MD after PEA = −7.65 ± 6.55 dB vs. −4.55 ± 5.31 dB, $p < 0.001$; PSD baseline vs. PSD after PEA = 5.21 ± 4.08 dB vs. 3.81 ± 3.02 dB, $p < 0.02$). In the control group, these parameters did not vary significantly (MD baseline vs. MD six months later = −6.87 ± 4.96 dB vs. −7.88 ± 5.05, n.s.; PSD baseline vs. PSD six months later = 4.35 ± 3.69 dB vs. 5.67 ± 4.66, n.s.), although in the control group a trend toward a further deterioration of these visual field indices was noted (Table 3). Neither ocular nor systemic side effects were recorded during the study period (six months).

Lastly, to describe the linear association between the final IOP, MD, and PSD and a set of exploratory variables, including the PEA treatment, age, SBP, DBP, and HR, a generalized linear model was developed by stepwise method. Our result demonstrated that the final IOP, MD, and PSD was affected only by the systemic PEA treatment ($p < 0.01$ for each of the three variables) and not affected by different demographic (age, $p = 0.376$) or clinical characteristic between the groups (SBP, $p = 0.866$; DBP, $p = 0.453$; and HR, $p = 0.282$).

Table 2. Intraocular Pressure and Arterial Pressure Variations Induced by Palmitoylethanolamide Treatment

	Group A (treated)			*Group B (controls)*		
Variables	*Baseline*	*Follow-up*	p	*Baseline*	*Follow-up*	p
IOP (mmHg)	13.3 ± 3.8	11.1 ± 4.3	< 0.01	14.5 ± 3.8	14.2 ± 3.6	0.975
SBP (mmHg)	111.3 ± 6.9	101.7 ± 4.5	0.543	115.3 ± 6.9	110.9 ± 6.5	0.654
DBP (mmHg)	66.8 ± 6.3	65.2 ± 5.4	0.455	65.2 ± 7.8	64.7 ± 6.9	0.345
HR (beats/min)	61.1 ± 5.1	58.4 ± 6.2	0.358	63.1 ± 6.1	59.9 ± 5.7	0.249

Values are mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used for statistical analysis.
SBP, systolic arterial pressure; DBP, diastolic arterial pressure HR, heart rate.

Table 3. Best Corrected Visual Acuity and Variations of Visual Field Indices Induced by Palmitoylethanolamide Treatment

	Group A (treated)			*Group B (controls)*		
Variables	*Baseline*	*Follow-up*	p	*Baseline*	*Follow-up*	p
Mean BCVA (logMAR)	0.08 ± 0.09	0.07 ± 0.10	0.654	0.08 ± 0.12	0.07 ± 0.11	0.596
MD (dB)	−7.65 ± 6.55	−4.55 ± 5.31	< 0.001	−6.87 ± 4.96	−7.88 ± 5.05	0.345
PSD (dB)	5.21 ± 4.08	3.81 ± 3.02	< 0.02	4.35 ± 3.69	5.67 ± 4.66	0.453

Values are mean ± SD. A paired sample *t*-test was used for statistical analysis.
MD, mean deviation; PSD, pattern standard deviation.

DISCUSSION

Our findings suggest that systemic administration of PEA reduces IOP and improves visual field indices in individuals affected by NTG. In the PEA treatment group, at the end of follow-up, a significant IOP reduction was recorded, together with a recovery of MD and PSD. In the control group, the IOP did not vary from baseline, whereas and a slight deterioration of visual field indices occurred. The final IOP and visual field indices were affected only by PEA treatment and not by demographic or clinical factors of the groups in a generalized linear analysis. From these results, our study indicated that PEA might be effective for improving visual function in patients with NTG. PEA is a naturally occurring fatty acid amide, which, together with anandamide (AEA) and 2-arachidonoylglycerol, constitutes the eCB system. This endogenous system seems to exert an important role in endothelial protection, and has been found in different human systems, including the vascular system and ocular tissues.[18] PEA has been extensively studied for its anti-inflammatory, analgesic, anti-epileptic, and neuroprotective effects. It has also been reported to inhibit food intake, reduce gastrointestinal motility, counteract cancer cell proliferation, and protect the vascular endothelium in the ischemic heart.[12,19] PEA is present in several foods such as peanut oil, egg yolk, and soybean lecithin, as well as in mammalian blood.[20,21] The mechanisms by which PEA exerts its pharmacological properties remain mainly unknown. It is well documented that various cannabinoids are able to reduce IOP when administered orally, intravenously, or by inhalation,[22] and cannabinoid receptors, in particular CB1, play an important role in the regulation of IOP. The presence of CB1 receptors and an AEA-specific enzyme activity in the eye provided the context for a mechanism of action.[23,24] In glaucomatous patients, the levels of 2-arachidonylglycerol and PEA in the ciliary body are decreased, suggesting that both compounds may play a role in the regulation of IOP.[25,26] AEA activates CB1 receptors in the pigmented epithelium of the ciliary body, trabecular meshwork, Schlemm's canal, and ciliary muscle influencing the production and drainage of aqueous humor.[16] The cellular/molecular mechanisms responsible for the IOP-lowering effect of cannabinoids, rather than mediated by the CNS, are merely local, involving a direct effect on ciliary processes with a reduction of capillary pressure and secretion.[27,28] Moreover, cannabinoids may improve the uveoscleral outflow by dilating blood vessels of the anterior uvea,[21] most likely by induction of several outflow facilitating mediators of the prostanoids family.[29] Since PEA has no effect on CB1 or CB2 receptors, the effect of PEA could be mediated by an entourage effect, leading to an increase of the cannabinoid tone.[30] In fact, contrarily to eCBs, PEA administration does not induce either systemic (hypotension, tachycardia, euphoria, and dysphoria) or ocular (changes in pupil size, decreased tear production, and conjunctival hyperemia) side effects,[26] being effective and safe in reducing IOP. Although IOP reduction plays a pivotal role in the progression delay of NTG,[31,32] the therapeutic reduction does not stop the visual field damage progression in all NTG patients. Nevertheless, there is little doubt that other risk factors besides IOP are also involved, and among these, in NTG patients, blood flow is significantly reduced in various tissues of the eye. Blood flow reduction is more pronounced in NTG than in high tension glaucoma and, comparatively, more in patients with progressive types of glaucoma than those recorded in patients affected by more stable forms of glaucoma and, rather than to a systemic disorder such as arteriosclerosis, it may be due to a primary vascular dysregulation.[11,33,34] Dysfunction of regulation leads to an unstable ocular perfusion especially when IOP or blood pressure fluctuates. Insufficient autoregulation increases the risk for an unstable ocular perfusion, leading to an unstable oxygen supply with production of oxidative stress. The activation of the nearby astrocytes by mechanical or ischemic stress induces the production of nitric oxide (NO) excess, whose diffusion into the axons generates apoptosis.[35] In mammals, evidence suggests that glaucoma, through excitotoxicity, upregulates astrocytes proliferation, promoting a significant gliosis.[36] Scuderi *et al.*[12] recently demonstrated the ability of PEA to mitigate astrocyte activation, indicating that PEA is capable of neuronal protection toward neurodegenerative events. Although IOP lowering will continue to be the mainstay treatment even for NTG, non-IOP-lowering therapies to avoid further visual field damage progression have a certain appeal both for patients and for ophthalmologists. In fact, the absence of significant modification in systemic blood pressure and the lack of psychotropic effects after six months of treatment, the direct effect on IOP that is not much different from that of some ocular hypotensive drugs currently used (topical CAI, alpha agonists),[23,37] and the neuroprotective activity seem to indicate that PEA could represent a promising pharmacological tool in the treatment of NTG.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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