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ORIGINAL ARTICLE

Palmitoylethanolamide Effects on Intraocular Pressure After Nd:YAG Laser Iridotomy: An Experimental Clinical Study

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Abstract

Purpose: The purpose of this article was to evaluate whether the anti-inflammatory agent palmitoylethanolamide (PEA) can counteract the increase of intraocular pressure (IOP) that may occur after neodymium-doped: yttrium aluminum garnet (Nd:YAG) laser iridotomy.
Methods: Fifteen patients underwent bilateral laser iridotomy (Visulas YAG III Laser; Zeiss) for the prevention of primary closed-angle glaucoma. The IOP was measured at the beginning of the study (t–1), after 15 days of pretreatment with placebo or PEA (t0), and at 15, 30, and 120 min after the iridotomy (t1, t2, t3). The pretreatment consisted of 2 tablets of placebo or PEA per day for 15 days.
Results: The t-test did not show a significant difference between the preoperative mean values of IOP $t-1$ and t0 in both the pretreatments. Analysis of variance/Tukey's test pointed out a significant increase of the postoperative IOP values in placebo pretreated patients ($P \leq 0.05$), but not in those who were pretreated with PEA. The trend analysis confirmed the significant positive trend in placebo pretreatment. The parallelism test between the 2 regressions showed a significant difference for the slopes ($P = 0.022$) and not for the intercepts ($P = 0.520$).
Conclusions: PEA can counteract the increase of IOP that occurs after iridotomy. It is likely that PEA controls the inflammatory process after iridotomy.

Introduction

Several authors[1–4] described the incidence and seriousness of complications after Argon or Q-switched neodymium-doped: yttrium aluminum garnet (Nd:YAG) laser iridotomy, especially in those patients presenting with narrow iridocorneal angles or closed-angle glaucoma. An immediate postsurgical intraocular pressure (IOP) rise of 6 mmHg or more was, in fact, noticed in 42% of the eyes undergoing the treatment, and in 28% of the patients a higher rise was recorded (≥40 mmHg) when compared with the presurgery IOP level.[1–4] It was demonstrated that these acute IOP rises might damage the optic nerve in susceptible eyes.[5] Numerous researchers have used different presurgical pharmacological treatments to decrease the IOP rise by means of topical and/or systemic therapy. These include beta blockers,[6–8] pilocarpine,[9] clonidine,[10] dorzolamide,[11] iopidine,[12] corticosteroids,[13] nonsteroidal anti-inflammatory agents,[14,15] and carbonic anhydrase inhibitors.[16] The majority of these systemic treatments did not have the desirable therapeutic effects except for oral carbonic anhydrase inhibitors that are capable of preventing pressure rises in the treated patients.[16] Cabonic anhydrase inhibitors are not always well tolerated by the patients[17,18] and the topic treatments do not always decrease the IOP enough. Moreover, all the authors agreed that an increase in the postsurgical IOP can be dangerous in glaucomatous patients.[10]

Recent studies have emphasized the anti-inflammatory function of an endogenous molecule belonging to the group of fatty acid ethanolamides known as palmitoylethanolamide (PEA).

This molecule has been found in leukocytes and in stimulated macrophages,[19,20] in inflamed or stressed skin cells,[21,22] in experimental studies on the cortical neurons,[23] and more recently, in the cerebral cortex of mice subjected to focal ischemia.[24] PEA is the product of a natural fatty acid, palmitic acid (C16:0), in which the carboxylic function forms an amide through the combination with the primary amine, ethanolamine.[25,26] It is a natural molecule and was originally isolated from soy lecithin[27] and eventually found in the majority of mammal tissues.[28] As it does not directly interact with the cannabinoid receptors (CB_1 and CB_2), it cannot be considered an endocannabinoid. However, it has been widely demonstrated that PEA is synthesized and released after cellular damage, performing an anti-inflammatory action.[19–22]

In the wake of these data, our research team wanted to investigate the effects of PEA during Nd:YAG laser

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iridotomy considering that, after surgery, an inflammatory process occurs in several structures of the anterior chamber, with an IOP rise. The aim of this study was to demonstrate the modulatory effect of PEA on the postsurgical IOP rise.

Methods

Patients and protocol

The research was carried out by analyzing a sample of 15 patients with a family history of glaucoma, in whom a reduced depth of the anterior chamber in both eyes had been diagnosed. There were 5 males and 10 females with an average age of 66.13 ± 12.43 years (range: 87–47 years). Eligibility was determined through a detailed medical and ocular history and a comprehensive eye exam. All subjects were free of ocular or systemic disease, including age-related macular degeneration, diabetes, multiple sclerosis, myopia, previous intraocular surgery, or trauma. The eye examination included the best-corrected visual acuity (BCVA) for far and near vision, slit-lamp biomicroscopy, IOP measurements with Goldmann applanation tonometry at 4 different times, corneal pachymetry, gonioscopy, dilated fundus examination, horizontal cup-disc (C/D) ratio evaluation, visual field on the 30-2 threshold SITA standard program, visual field on the frequency-doubling technology 30-2 threshold program Matrix Humphrey (Carl Zeiss Meditec, Inc.), and pattern electroretinogram on the optoelectronic stimulator Vision Monitor MonPack 120 by Metrovision (Pérenchies, France).[29]

The inclusion criteria were:

- Refraction values from +1 to +4 dioptres (D) sphere and up to ±2D cylinder;
- BCVA for far distance ranging between 8/10 and 10/10 (logMAR 0.14 to −0.3);
- Normal corneal pachimetry (540–620 μm);
- Horizontal C/D ratio of 0.4 to 0.7 at slit-lamp examination.

These patients had to undergo a bilateral prophylactic iridotomy to prevent primary closed-angle glaucoma. The eyes were randomly selected and the study was single masked. This was a 2-phase surgery. In fact, the eyes were separately treated with an interval of 20 days between the 2 surgeries, and the second operation occurred only if the first one had been successful. Before the surgery, the patient was subjected to 15 days of "placebo" pretreatment. For the second eye, 15 days of pretreatment with "PEA" (Visimast 300 mg, Epitech Group Srl) was done. During the pretreatment with both the PEA and placebo, 2 tablets a day were administered to the patients. In both phases, the following measurement protocol of IOP was followed:

(1) At the beginning of the study (IOPt-1);
(2) After 15 days of pretreatment with "placebo" or "PEA" (IOPt0), before the surgery began;
(3) At 15, 30, and 120 min (IOPt1, IOPt2, IOPt3), after the end of surgery.

The collected data during the placebo and PEA pretreatment configured a case–control study.

The research followed the tenets of the Declaration of Helsinki. All of the patients had given informed consent. The research was approved by the Committee on Faculty Ethics.

Iridotomy surgery

The iridotomy surgery was performed using the pulsing *Visulas YAG III Laser* (Carl Zeiss Meditec, Inc). With the 1064 nm laser wavelength, a maximum temperature of 40°C, and a setting on a wave train III with a starting potency of 2.5 mJ, luminous intensities of 10^{10} W/cm^2 (for the duration of a few nanoseconds) to 10^{11} W/cm^2 (for the duration of a few picoseconds) can be reached, generating electric fields of 10^6–10^7 V/cm. Ossibuprocaine chlorohydrate (Novesina, Novartis Pharma SpA) 0.4% individually packaged was used as the anesthetic presurgically and for the tonometry.

Statistics

The IOP values, expressed in mmHg, were subjected to different methods of univariate statistical analysis:

1. Methods of univariate descriptive statistic of the central location (AVS mean, M) and dispersion (standard deviation).
2. Univariate statistical comparison of sample means [Student's *t*-test and analysis of variance (ANOVA)/Tukey's test].
3. Univariate statistical comparison of sample trends (parallel test to compare 2 regressions), when requested.

These analyses were performed by means of 2 statistical packages, SPSS 13.0 and Primer for Windows, respectively. The statistical significance of the comparison was attested to a probability value of $P \leq 0.05$.

To apply the univariate statistical comparison methods, the following logic-demonstrative criteria were carried out:

- The presurgery average values of IOPt-1 and IOPt0 were compared by the *t*-test to ascertain that the "placebo" or "PEA" had no effect on the presurgical IOP;
- The postsurgery average values of IOPt1, IOPt2, and IOPt3 were compared by the ANOVA/Tukey's test to ascertain the significant effect of the "placebo" and "PEA" pretreatments on the postsurgical IOP;
- The trends of the postsurgical values of IOPt1, IOPt2, and IOPt3 with respect to IOPt0 have been compared through the parallel test comparison between 2 regressions, to ascertain whether or not a significant difference in behavior of the "placebo" and "PEA" pretreatment existed.

Results

Descriptive statistical analysis

The results of the statistical analyses are reported in Table 1.

These data will be better understood by following the statistical path by which they were compared.

Figure 1 shows the results of the statistical comparisons, given by the *t*-test, of the average presurgery IOPt-1 and IOPt0 values in the "placebo" and "PEA" pretreatments: univaried comparative statistical analysis by Student's *t*-test. From the nonsignificance of the statistical comparisons, it can be clearly deduced that there has not been any remarkable effect of "placebo" or "PEA" pretreatment on the presurgical IOP.

Figure 2 synoptically reports the results of the univariate statistical comparison analysis by ANOVA/Tukey's test of

Table 1. Intraocular Pressure Values (mmHg) Measured at Different Moments (t–1, t0, t1, t2, t3) in the Presence of "Placebo" and "PEA" Pretreatments

	IOP (mmHg)[a]				
Pretreatment	*t* – 1	*t*0	*t*1	*t*2	*t*3
Placebo	16,133 ± 1,246	16,200 ± 1,014	19,667 ± 1,952	21,600 ± 2,694	22,600 ± 2,720
PEA	16,600 ± 3,158	15,000 ± 2,752	14,933 ± 2,789	15,467 ± 2,416	15,600 ± 2,324

[a]Values are expressed as means ± standard deviation.
IOP, intraocular pressure; PEA, palmitoylethanolamide.

the postsurgery IOPt1, IOPt2, and IOPt3 average values versus presurgery IOPt0.

From the significance of the comparisons of each pretreatment, it is evident that the postsurgical behavior of IOP has a different trend in those patients pretreated with "placebo" or "PEA."

In the "placebo" pretreatment, the IOP shows a significant postsurgical rise, which culminates at *t*3, but is already manifested from *t*1. In "PEA" pretreatment, instead, no significant postsurgical IOP rise was noticed.

From Table 1, it can be deduced that in the "placebo" treatment the postsurgical IOP reached, at its maximum in *t*3, an average value of 22.60 ± 2.72 mmHg, compared with a starting value of 16.13 ± 1.25 mmHg, showing an average rise of 6.47 ± 1.47 mmHg. On the contrary, in the "PEA" pretreatment, postsurgical IOP reached, at its maximum in *t*3, an average value of 15.60 ± 2.32 mmHg, compared with a starting value of 16.60 ± 3.16 mmHg, showing an average decrease of 1 ± 0.83 mmHg. Univaried comparative statistical analysis was done by comparing the average values of the postsurgical IOP in patients treated with "PEA" compared with those of the "placebo" pretreatments.

Figure 3 reports the postsurgical IOP trend in the "placebo" and "PEA" pretreatments. From the slope of the pertinent regression lines, it can be noticed how these lines splay noticeably, the former showing a progressive rise and the latter substantially remaining on the starting level.

Table 2 reports the results of the parallel test confronting the intercepts (a) and the slopes (inclinations b) of the regression lines expressed by the following equation: $Y = a + b*X$, where Y = IOP is the dependent variable and X = measurement time (t0, t1, t2, t3) is the independent variable.

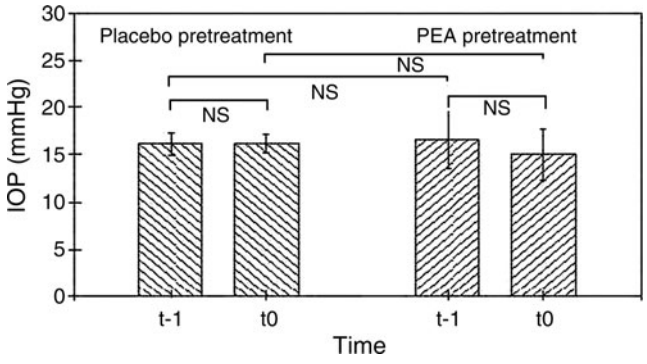

FIG. 1. Bar chart showing the statistical comparison by *t*-test of the average presurgery IOP values (mmHg), measured at the moments *t*–1 and *t*0, in the "placebo" and "PEA" pretreatments. NS, nonstatistically significant difference; IOP, intraocular pressure; PEA, palmitoylethanolamide.

From the significance of the *t* values of all of the regression curves, it can be clearly deduced that a significant positive trend of the IOP values, related to the postsurgical moments *t*1, *t*2, and *t*3, is present only in the "placebo" pretreatment.

From the significance of *t* in the statistical comparison between the intercepts (a) of the 2 regression lines, it is deduced that there is no significant difference in the presurgical IOP (*t*0) of the "placebo" and "PEA" pretreatments.

From the significance of *t* in the statistical comparison between the slopes (b), the difference in trend of the postsurgical IOP in the "placebo" and "PEA" pretreatments is evident. This different trend is due to the fact that with a "placebo" pretreatment the postsurgical IOP shows a progressive rise, which is not found in a "PEA" pretreatment. To ascertain this statement, Fig. 4 shows the comparison, by

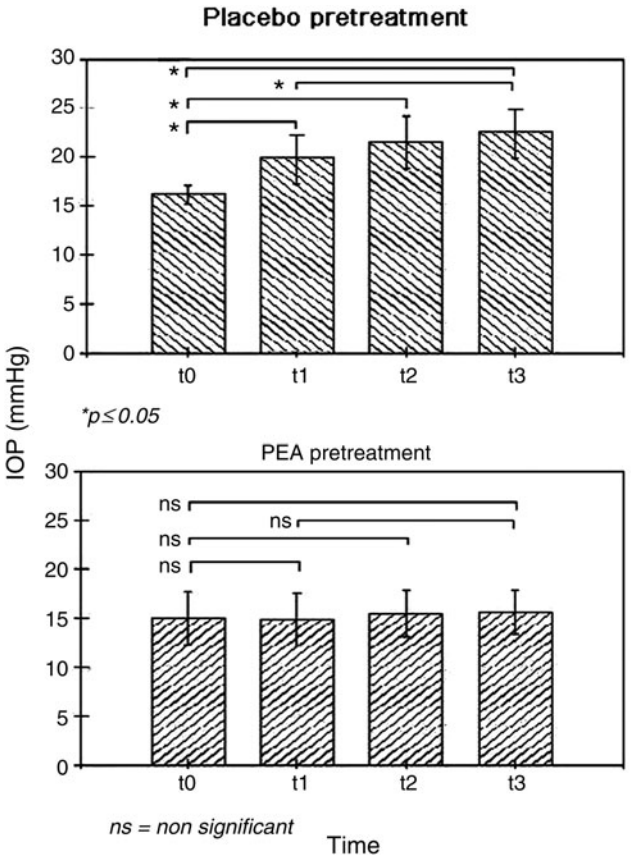

FIG. 2. Bar charts representing the univariate statistical comparison analysis by analysis of variance/Tukey's test among the postsurgical IOP average values (at *t*1, *t*2, and *t*3) and the presurgical IOP (*t*0).

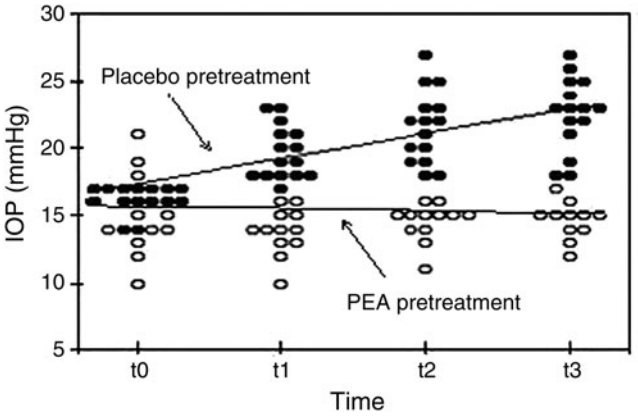

FIG. 3. Graphic representation of the regression lines related to postsurgical IOP trend in the "placebo" (filled circles) and "PEA" (open circles) pretreatments. The former shows a progressive rise and the latter substantially remains on the starting level.

t-test, of the postsurgical IOP values in both the "placebo" and "PEA" pretreatments.

From the significance of the statistical time-qualified comparisons it is deduced that, in every postsurgical moment, the IOP of the "placebo" pretreatment is significantly higher than that of the "PEA" pretreatment. It confirms that there is no trend in the postsurgical IOP with a "PEA" pretreatment, because the IOP is not subjected to a rise in the different postiridotomy times, as, instead, happens for IOP in a "placebo" pretreatment.

Discussion

The objective of this study was to ascertain whether PEA could block the IOP rise in patients who had to undergo an iridotomy for the prevention of primary closed-angle glaucoma. It is well known that the Visulas YAG III laser, used in the present study to perform the iridotomy, acts with a photomechanical effect rather than with a photothermal one. The electric fields produced are comparable to the ionization energy of molecules and a high free electron density is generated within the area. For this reason the electrical fields cause a breakdown in the material, with the formation of microplasma. The shockwave associated with the rapid expansion of the microplasma creates a mechanical break in these regions in which the pressure rise is greater than the tissue force of cohesion. It is therefore believed that the Nd:YAG laser might induce an oxidative stress condition and thus the formation of free oxygen radicals as reactive oxygen species (ROS). Later, these radicals might, directly or indirectly, disrupt the integrity of the blood–ocular barrier. Directly, the ROS might cause the lipid peroxidation of the cell membrane and this would subsequently damage the membranes themselves. Indirectly, it may be due to the activation of the metalloproteinases, which wear out the extracellular matrix with loss of the tight junction proteins.[30–32]

As for the hypertonic effects following trabeculoplasty, iridotomy, or capsulotomy, their mechanisms are not yet very well known. It is thought that the rise in IOP could be due to a direct or indirect shock in the uvea, causing prostaglandin (PG) synthesis, which breaks down the blood–ophthalmic barrier (blood-aqueous), causing myosis and an IOP rise.[33–35] It is known that the trabecular meshwork cells are capable of synthesizing PG, thus influencing the resistance to the out flow of aqueous humor.[36,37] On the basis of the theory of the inflammatory state as the main cause of the acute postsurgery IOP elevation, several anti-inflammatory drugs have been unsuccessfully used, for instance, corticosteroids[13] and nonsteroidal anti-inflammatory drugs.[14,15]

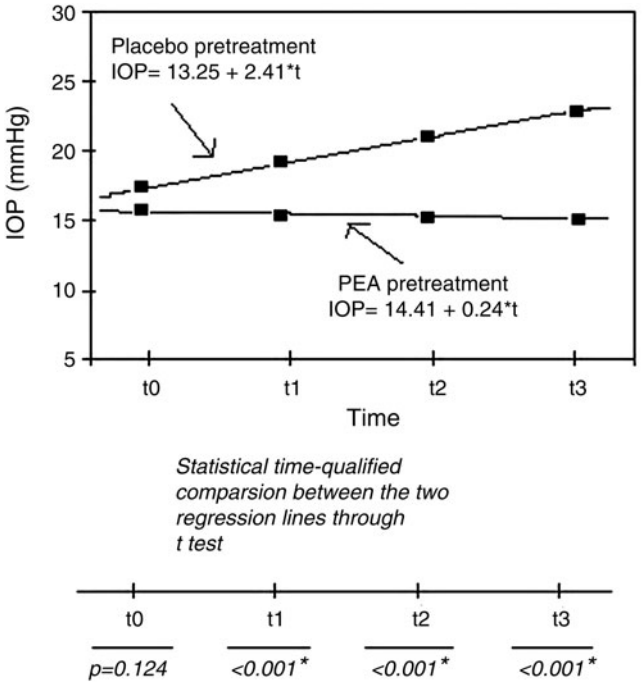

FIG. 4. Graphic representation of the regression lines related to the "placebo" and "PEA" pretreatments (up). Statistical time-qualified comparison between the 2 regression lines (down); *statistically significant.

Table 2. Comparison Between Two Regression Lines by Parallel Test Confronting the Intercepts (*a*) and the Slopes (inclinations *b*)

	Line 1	*Line 2*
Assessments	*Placebo pretreatment*	*PEA pretreatment*
Intercept (*a*)	13.25	14.41
ES intercept	1.62	0.32
Slope (*b*)	2.41	0.24
ES slope	0.59	0.09
Correlation coefficient (*r*)	0.94	0.89
T	4.07	2.71
P	>0.050[a]	0.110
Comparison between the intercepts (*a*):	$t=0.70$, $P=0.520$	
Comparison between the slopes (*b*):	$t=3.63$, $P=0.022$[a]	

From the significance of *t* in the statistical comparison between the intercepts (*a*) of the 2 regression lines, it is deduced that there is no significant difference in the presurgical IOP (*t*0) of the "placebo" and "PEA" pretreatments. From the significance of *t* in the statistical comparison between the slopes (*b*), the difference in trend of the postsurgical IOP with a progressive rise in "placebo" pretreatment is evident, which is not found in the "PEA" pretreatment.

[a]Statistically significant.

The maintenance of normal IOP after Nd:YAG laser iridotomy treatment because of the PEA could be explained by the fact that PEA is able to preserve the blood–ophthalmic barrier, carrying out an anti-inflammatory action that is probably mediated by a new class of nuclear receptors peroxime proliferator-activated receptors-alpha (PPAR-α).[38,39]

Some experiments have demonstrated the outstanding role of PPAR-α in controlling inflammatory responses. These studies have also shown that they are expressed on the surface of different cells within the immune system.[38] The tissue distribution of PPAR-α receptors in humans is in skeletal muscle, liver, heart, and kidney. On the contrary, a much lower concentration of these receptors can be found at the cerebral and pulmonary levels, although a higher concentration of these receptors at the central level has been found in recent studies.[40]

Research has shown that mice missing the gene codifying for PPAR-α had a prolonged inflammatory response.[41] Synthetic agonists of these receptors could cause anti-inflammatory effects in mice having, instead, the *ppar-α* gene.[39,42]

It has been observed that the anti-inflammatory effects are accompanied by a reduction in the expression of the inducible nitric oxide synthase, inducible cyclooxygenase, and several anti-inflammatory cytokines, such as interleukin-1β (IL-1β), PG (prostaglandin) E_2, and tumor necrosis factor α. This suggests a nuclear mechanism very similar to anti-inflammatory steroid drugs.[43]

Further, Poynter and Daynes[44] reported a decrease in IL-6 and PG, mediated by the reduction of the nuclear factor (NF)-κβ. PPAR-α agonists are probably able to increase the expression of the NF-κβ inhibitor (Iκβα), which blocks the activity of NF-κβ, thus inhibiting the production of proinflammatory molecules.[45] These results indicate that PEA can exert its anti-inflammatory action through its bond to PPAR-α receptors, thus acting as an agonist. Several studies, however, have shown that PEA can quickly reduce acute inflammation, suggesting also the existence of a nonnuclear mechanism of action.[39,46–48] Lo Verme et al.[39] state "Although the precise mechanism of PPAR-α anti-inflammation is unclear, the receptor has been linked to a non-genomic inhibition of the proinflammatory signaling pathways mediated by NF-κβ and activated protein-1. Thus, multiple lines of evidence suggest that PPAR-α receptors and their ligands are important modulators of the inflammatory process."

Whatever the pharmacological mechanism, the results of our study and the data from literature suggest the use of PEA as a drug capable of regulating the acute inflammatory processes in the eye, at least after a Nd:YAG laser iridotomy. In addition, the local action of this drug may yield benefits in cases of ocular inflammation, because the PEA is devoid of central nervous system side effects.[49,50]

Unfortunately, the mechanism by which PEA acts remains unknown and some authors hypothesize that the selective PPAR-α agonist WY-14643, at high concentrations, may be proinflammatory and proangiogenic in a variety of human ocular cells. Therefore, they state that therapeutic applications of such agents in ophthalmology may be limited, but the authors conclude that additional studies are needed to further explore this issue, including using other selective PPAR-α agonistis.[51]

Nowadays, in most branches of medicine, the current thinking is to use the "disease-oriented" approach. This affects the actual or potential mechanisms of endogenous control depending on the disease and PEA assumes a special importance for its full potential, which is still under study.

We are going to continue our studies with this drug to determine whether its beneficial effects may be similar to those obtained at a lower dosage and administration for a shorter time of only a few days, because it can have both a genomic and nongenomic mechanism of action.[39,46–48]

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Author Disclosure Statement

The authors report no conflicts of interest.

References

1. Krupin, T., Stone, R.A., Cohen, B.H., Kolker, A.E., and Kass, M.A. Acute intraocular pressure response to argon laser iridotomy. *Ophthalmology* 92:922–926, 1985.
2. Robin, A.L., and Pollack, I.P. A comparison of neodymium: YAG and argon laser iridotomies. *Ophthalmology* 91:1011–1016, 1984.
3. Moster, M.R., Schwartz, L.W., Spaeth, G.L., Wilson, R.P., McAllister, J.A., and Poryzees, E.M. Laser iridectomy. A controlled study comparing argon and neodymium: YAG. *Ophthalmology* 93:20–24, 1986.
4. Schwartz, L.W., Moster, M.R., Spaeth, G.L., Wilson, R.P., and Poryzees, E. Neodymium-YAG laser iridectomies in glaucoma associated with closed or occludable angles. *Am. J. Ophthalmol.* 102:41–44, 1986.
5. Blackwell, C., Hirst, L.W., and Kinnas, S.J. Neodymium-YAG capsulotomy and potential blindness. *Am. J. Ophthalmol.* 98:521–522, 1984.
6. Cai, J.P., Cheng, J.W., Wei, R.L., Ma, X.Y., Jiang, F., Zhu, H., and Li, Y. Prophylactic use of timolol maleate to prevent intraocular pressure elevation after Nd-YAG laser posterior capsulotomy. *Int. Ophthalmol.* 28:19–22, 2008.
7. Peng, D.W. Prevention of IOP rise following laser iridectomy with topical timolol and indomethacin. *Zhonghua Yan Ke Za Zhi* 29:83–85, 1993.
8. Rakofsky, S., Koch, D.D., Faulkner, J.D., Terry, S.A., Mandell, A.I., Gross, R.L., Kelley, E.P., Iacono, T.L., and Lue, J. Levobunolol 0.5% and timolol 0.5% to prevent intraocular pressure elevation after neodymium: YAG laser posterior capsulotomy. *J. Cataract Refract. Surg.* 23:1075–1080, 1997.
9. Schrems, W., Eichelbrönner, O., and Krieglstein, G.K. The immediate IOP response of Nd-YAG-laser iridotomy and its prophylactic treatability. *Acta Ophthalmol. (Copenh.)* 62:673–680, 1984.
10. Kitazawa, Y., Sugiyama, K., and Taniguchi, T. The prevention of an acute rise in intraocular pressure following Q-switched Nd:YAG laser iridotomy with clonidine. *Graefes Arch. Clin. Exp. Ophthalmol.* 227:13–16, 1989.
11. Hartenbaum, D., Wilson, H., Maloney, S., Vacarelli, L., Orillac, R., and Sharpe, E. A randomized study of dorzolamide in the prevention of elevated intraocular pressure after anterior segment laser surgery. Dorzolamide Laser Study Group. *J. Glaucoma* 8:273–275, 1999.
12. Stîngu, C., Cristescu, A., Daˇraˇban, C., Ioniţaˇ, M., and Serghiescu, S. Iopidine in the control of intraocular pressure after glaucoma laser treatment. *Oftalmologia* 54:32–35, 2001.
13. Ruderman, J.M., Zweig, K.O., Wilensky, J.T., and Weinreb, R.N. Effects of corticosteroid pre-treatment on argon laser trabeculoplasty. *Am. J. Ophthalmol.* 96:84–89, 1983.
14. Weinreb, R.N., Robin, A.L., Baerveldt, G., Drake, M.V., Blumenthal, M., and Wilensky, J. Flurbiprofen pretreatment

in argon laser trabeculoplasty for primary open-angle glaucoma. *Arch. Ophthalmol.* 102:1629–1632, 1984.
15. Pappas, H.R., Berry, D.P., Partamian, L., Hertzmark, E., and Epstein, D.L. Topical indomethacin therapy before argon laser trabeculoplasty. *Am. J. Ophthalmol.* 99:571–575, 1985.
16. Metcalfe, T.W., and Etchells, D.E. Prevention of the immediate intraocular pressure rise following argon laser trabeculoplasty. *Br. J. Ophthalmol.* 73:612–616, 1989.
17. Stewart, W.C., Halper, L.K., Johnson-Pratt, L., Polis, A., and Hartenbaum, D. Tolerability and efficacy of dorzolamide versus acetazolamide added to timolol. *J. Ocul. Pharmacol. Ther.* 18:211–220, 2002.
18. Reyes, E., Izquierdo, N.J., and Blasini, M. Adverse drugs reactions associated with glaucoma medications. *Bol. Asoc. Med. P. R.* 89:51–55, 1997.
19. Bisogno, T., Maurelli, S., Melck, D., De Petrocellis, L., and Di Marzo, V. Biosynthesis, uptake, and degradation of anandamide and palmitoylethanolamide in leukocytes. *J. Biol. Chem.* 272:3315–3323, 1997.
20. Di Marzo, V., De Petrocellis, L., Sepe, N., and Buono, A. Biosynthesis of anandamide and related acylethanolamides in mouse J774 macrophages and N18 neuroblastoma cells. *Biochem. J.* 316:977–984, 1996.
21. Berdyshev, E.V., Schmid, P.C., Dong, Z., and Schmid, H.H. Stress-induced generation of N-acylethanolamines in mouse epidermal JB6 P+ cells. *Biochem. J.* 346:369–374, 2000.
22. Hohmann, A.G. Spinal and peripheral mechanisms of cannabinoid antinociception: behavioral, neurophysiological and neuroanatomical perspectives. *Chem. Phys. Lipids* 121:173–190, 2002.
23. Cadas, H., Gaillet, S., Beltramo, M., Venance, L., and Piomelli, D. Biosynthesis of an endogenous cannabinoid precursor in neurons and its control by calcium and cAMP. *J. Neurosci.* 16:3934–3942, 1996.
24. Franklin, A., Parmentier-Batteur, S., Walter, L., Greenberg, D.A., and Stella, N. Palmitoylethanolamide increases after focal cerebral ischemia and potentiates microglial cell motility. *J. Neurosci.* 23:7767–7775, 2003.
25. Kuehl, F.A., Jacob, T.A., Ganley, O.H., Ormond, R.E., and Meisinger, M.A.P. The identification of N-(2-hydroxyethyl)-palmitamide as a naturally occurring anti-inflammatory agent. *J. Am. Chem. Soc.* 79:5577–5578, 1957.
26. Bachur, N.R., Masek, K., Melmon, K.L., and Udenfriend, S. Fatty acid amides of ethanolamine in mammalian tissues. *J. Biol. Chem.* 240:1019–1024, 1965.
27. Kuehl, F.A., Jacob, T.A., Ganley, O.H., Ormond, R.E., and Meisinger, M.A.P. The identification of N-(2-hydro-xyethyl)-palmitamide as a naturally occurring anti-inflammatory agent. *J. Am. Chem. Soc.* 79:5577–5578, 1957.
28. Lambert, D.M., Vandevoorde, S., Jonsson, K.O., and Fowler, C.J. The palmitoylethanolamide family: a new class of anti-inflammatory agents? *Curr. Med. Chem.* 9:663–674, 2002.
29. Nebbioso, M., De Gregorio, F., Prencipe, L., and Pecorella, I. Psychophysical and electrophysiological testing in Ocular Hypertension. *Optom. Vis. Sci.* 88:1–12, 2011.
30. Candelario-Jalil, E., Yang, Y., and Rosenberg, G.A. Diverse roles of matrix metalloproteinases and tissue inhibitors of metalloproteinases in neuroinflammation and cerebral ischemia. *Neuroscience* 158:983–994, 2009.
31. Bauer, A.T., Burgers, H.K., Rabie, T., and Marti, H.H. Matrix metalloproteinase-9 mediates hypoxia-induced vascular leakage in the brain via tight junction rearrangement. *J. Cereb. Blood Flow Metab.* 30:837–848, 2010.
32. Sandoval, K.E., and Witt, K.A. Blood-brain barrier tight junction permeability and ischemic stroke. *Neurobiol. Dis.* 32:200–219, 2008.
33. Waitzman, M.B. Possible new concepts relating prostaglandins to various ocular functions. *Surv. Ophthalmol.* 14:301–326, 1970.
34. Podos, S.M. Prostaglandins, nonsteroidal anti-inflammatory agents and eye disease. *Trans. Am. Ophthalmol. Soc.* 74:637–660, 1976.
35. Bhattacherjee, P., and Paterson, C.A. Further investigation into the ocular effects of prostaglandin E2, leukotriene B4 and formyl-methionyl-leucyl phenylalanine. *Exp. Eye Res.* 51:93–6, 1990.
36. Weinreb, R.N., Mitchell, M.D., and Polansky, J.R. Prostaglandin production by human trabecular cells: *in vitro* inhibition by dexamethasone. *Invest. Ophthalmol. Vis. Sci.* 24:1541–1545, 1983.
37. Weinreb, R.N., Ruderman, J., Juster, R., and Zweig, K. Immediate intraocular pressure response to argon laser trabeculoplasty. *Am. J. Ophthalmol.* 95:279–286, 1983.
38. Daynes, R.A., and Jones, D.C. Emerging roles of PPARs in inflammation and immunity. *Nat. Rev. Immunol.* 2:748–759, 2002.
39. Lo Verme, J., La Rana, G., Russo, R., Calignano, A., and Piomelli, D. The search for the palmitoylethanolamide receptor. *Life Sci.* 77:1685–1698, 2005.
40. Michalik, L., and Wahli, W. Peroxisome proliferator-activated receptors: three isotypes for a multitude of functions. *Curr. Opin. Biotechnol.* 10:564–570, 1999.
41. Devchand, P.R., Keller, H., Peters, J.M., Vazquez, M., Gonzalez, F.J., and Wahli, W. The PPAR alpha-leukotriene B4 pathway to inflammation control. *Nature* 384:39–43, 1996.
42. Chinetti, G., Fruchart, J.C., and Staels, B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. *Inflamm. Res.* 49:497–505, 2000.
43. Costa, B., Conti, S., Giagnoni, G., and Colleoni, M. Therapeutic effect of the endogenous fatty acid amide, palmitoylethanolamide, in rat acute inflammation: inhibition of nitric oxide and cyclo-oxygenase systems. *Br. J. Pharmacol.* 137:413–420, 2002.
44. Poynter, M., and Daynes, R. Peroxisome proliferator activated receptor alpha activation modulates cellular redox status, represses nuclear factor-kappaB signaling, and reduces inflammatory cytokine production in aging. *J. Biol. Chem.* 67:3488–3493, 1998.
45. Delerive, P., Gervois, P., Fruchart, J.C., and Staels, B. Induction of Ikappa B alpha expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator activated receptor-alpha activators. *J. Biol. Chem.* 275:36703–36707, 2000.
46. Conti, S., Costa, B., Colleoni, M., Parolaro, D., and Giagnoni, G. Antiinflammatory action of endocannabinoidi palmitoylethanolamide and the synthetic cannabinoid nabilone in a model of acute inflammation in the rat. *Br. J. Pharmacol.* 135:181–187, 2002.
47. Lo Verme, J.L., Fu, J., Astarita, G., La Rana, G., Rusoo, R., Calignao, A., and Piomelli, D. The nuclear receptor peroxisome proliferator-activated receptor-α mediates the anti-inflammatory actions of palmitoylethanolamide. *Mol. Pharmacol.* 67:15–19, 2005.
48. Fu, J., Gaetani, S., Oveisi, F., et al. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. *Nature* 425:90–93, 2003.
49. Ibrahim, M.M., Deng, H., Zvonok, A., Cockayne, D.A., Kwan, J., Mata, H.P., Vanderah, T.W., Lai, J., Porreca, F., Makriyannis, A., and Malan, T.P., Jr. Activation of CB2

cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. *Proc. Natl. Acad. Sci. U. S. A.* 100:10529–10533, 2003.
50. Helyes, Z., Nemeth, J., Than, M., Bolcskei, K., Pinter, E., and Szolcsanyi, J. Inhibitory effect of anandamide on resiniferatoxin-induced sensory neuropeptide release *in vivo* and neuropathic hyperalgesia in the rat. *Life Sci.* 73:2345–2353, 2003.
51. Zhang, J.Z., and Ward, K.W. WY-14643, a selective PPAR-α agonist, induces proinflammatory and proangiogenic responses in human ocular cells. *Int. J. Toxicol.* 29:496–504, 2010.

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