Symptomatic Control of Presbyopia through Pharmacological Ciliary Body Stimulation

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Abstract

Purpose: The aim of this paper is to investigate the feasibility in term of safety and potential efficacy of a new drug combination for binocular use as an on invasive pharmacological solution for addressing presbyopia.

Methods: Fourteen emmetropes presbyopic subjects (28 eyes) were given in each eye only one drop of the preparation under study. Uncorrected visual acuity for distance and for near, refraction for far and near, best corrected visual acuity, best corrected far-near visual acuity, photopic and scotopic pupil size, Schirmer Test, Endothelial Cell Count, Intraocular Pressure, keratometry, pachymetry and Anterior Chamber Depth were taken prior to the administration of the eye drops, and then 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 1 week and 1 month post-administration prospectively in each eye and binocularly.

Results: The results showed near uncorrected visual acuity improved by about 2 to 3 lines in each eye and binocularly from baseline. No patient had a loss in uncorrected far vision in each eye and binocularly. Refractive measurements in this study showed there was a maximum myopic shift of just 0.5 D that progressively reduces and disappears at 4 hours.

Conclusion: The new topical drug treatment analyzed herein, significantly improves near vision without affecting far vision. This binocular pharmacologic treatment of presbyopia has the rationale to ameliorate reading vision for presbyopes with the advantages of anon-monovision therapy. A randomized controlled double-masked clinical trial with a new treatment schedule is ongoing in our institution.

Keywords: Accommodation; Ocular; Administration; Ophthalmic; Drug Therapy; Combination; Presbyopia; Vision; Binocular

Introduction

Presbyopia, due to the progressive age-related accommodative loss, begins to affect near visual tasks around 40 years and is associated with substantial, negative effects on vision-targeted health-related quality of life [1]. In the 2015, more than 2.5 billion people in the world aged 40 years or older and in light of the growing and ageing global population, in the next years presbyopia will affect even more people [2]. Pathophysiology of presbyopia still remains poorly understood thus the correction of presbyopia and the restoration of accommodation are the final frontier of ophthalmology. In the last decade surgical correction for presbyopia improved but still presents some limitations, thus an increasing interest about non-surgical treatments is growing up recently [3]. Topical treatment of presbyopia is an attractive approach which, if available and effective, would be the choice for many patients. The few topical treatments for presbyopia currently under study claim to work on different aspects of the accommodative process but each one of these approaches may present some disadvantages [4–7]. The topical treatment presented here in contains a parasympathetic, an NSAID, two alpha-agonist agents and an...
anti-cholinesterase agent administered bilaterally and promises to ameliorate the symptoms of presbyopia through the pharmacological stimulation of iris and ciliary muscle minimizing the drawbacks associated with a pure parasympathetic action. The purpose of this report is to inform about the initial outcomes obtained in a pilot investigation with a new drug combination for binocular use in presbyopic patients.

**Methods**

This pilot study was begun after approval was obtained from the Clinic’s Ethics Committee of Fundación Oftalmológica Vejaranoin Popayán Colombia. Each participant gave written informed consent, and the study followed the tenets of the Declaration of Helsinki. The pharmacological stimulation protocol was developed and submitted for patent in 10 countries by Dr. Vejarano who had been using his own product satisfactory since five and a half years ago (July 2010) [8]. Fourteen presbyopic subjects (28 eyes), 9 naturally emmetropes and 5 stable emmetropes post-LASIK surgery, with an average age of 48.21 years (range, 41 - 55 years) participated in this study. Participants were volunteers randomly selected. Presbyopia was considered to be present if patient needs to use a lens ≥ +1.00 D to read a print size of Jaeger 0.8. Each subject was given in each eye only one drop of the ophthalmic formulation containing Pilocarpine, Phenylephrine, Polyethylene glycol, Naphenacon, Pheniramine and Naphazoline. All the drugs administered in this study are Food and Drug Administration-approved and have been used for years as safe and effective to treat ocular pathologies. Various ophthalmologic measurements were taken prior to the administration of the eye drops, and then 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 1 week and 1 month post-administration in each eye and binocularly. The measurements performed include uncorrected visual acuity (UCVA) for distance and for near, refraction for far and near, best corrected visual acuity (BCVA), best corrected far near visual acuity (BCFVNA), photopic and scotopic pupil size, Schirmer Test, Endothelial Cell Count (ECC), Intraocular Pressure (IOP), keratometry, pachymetry and Anterior Chamber Depth (ACD). Distance visual acuity was measured at 40-cms using handheld Snellen projector chart with Jaeger notation with always the same luminosity. Pupil diameter was measured using Optical Biometer AL-scan (Nidek Co., LTD, Japan), Pentacam (Oculus Optikgeräte GmbH, Germany) and Auto Ref/Keratometer (Nidek Co., LTD, Japan). ECC was measured using Cell Check clinical specular microscope (Könö Medical Inc., Japan). IOP was measured with Goldmann applanation tonometer AT-900 (Haag-Streit AG, Switzerland) and Pascal dynamic contour tonometer (Ziemer Ophthalmic Systems AG, Switzerland). Keratometry was measured using Auto Ref/Keratometer (Nidek Co., LTD, Japan). Pachymetry and ACD were measured with Pentacam (Oculus GmbH, Germany). Inclusion criteria admitted patients aged between 40 and 65 years, emmetropic (cycloplegic spherical equivalent, ± 0.50 D; astigmatism, ≤ 0.50 D), with binocular uncorrected distance visual acuity of at least 20/25 in both eyes without additional ocular or systemic pathology. None of the patients included in the study had received previously any chronic mydriatic or myotic therapy. During the study, the subjects were closely monitored and regularly asked to report the grade of satisfaction and any kind of adverse effects; although this pilot study was designed to assess the feasibility use of a single drop in each eye, the topical formulation is intended to be used twice daily, once in the morning and once in the afternoon before to start to work or to use the near vision. Due to data characteristics, a Friedman test was run to determine if there were differences in the different variables during the study period (from 30 minutes to one month) in the analyzed eyes. Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons (SPSS, 2015) to compare post-instillation data with baseline.

**Results**

Table 1 summarizes descriptive data for some variables of particular interest. Figures 1-4 show time trends for each variable showing significant changes from 30 min to 1 month. Pairwise comparison (Bonferroni correction) is represented for each value compared with pre, reported only when significant (*). Statistical differences were found in the evolution for photopic pupil diameter ($\chi^2(8) = 68.581$, $p < .001$), scotopic pupil diameter ($\chi^2(8) = 30.856$, $p < .001$), intraocular pressure ($\chi^2(8) = 52.507$, $p < .001$), best corrected far near visual acuity ($\chi^2(8) = 22.467$, $p < .004$), binocular best corrected far near visual acuity ($\chi^2(8) = 61.685$, $p < .001$), far uncorrected visual acuity ($\chi^2(8) = 20.358$, $p < .009$), near uncorrected visual acuity ($\chi^2(8) = 95.324$, $p < .001$), binocular near uncorrected visual acuity ($\chi^2(8) = 101.205$, $p < .001$), binocular far uncorrected visual acuity ($\chi^2(8) = 37.989$, $p < .001$), spherical equivalent ($\chi^2(8) = 118.524$, $p < .001$) and...
best near addition ($\chi^2(8) = 25.213, p < .001$). However, clinically relevant improve in time trends have been only observed in binocular near uncorrected visual acuity until 5 hours (Figure 2c), near uncorrected visual acuity until 5 hours (Figure 3b) and spherical equivalent until 3 hours (Figure 4b). Notably binocular (Figure 2a) and monocular (Figure 3a) far uncorrected visual acuity didn’t show clinically relevant changes. Pupil diameter appeared significantly increased in photopic conditions only until the first hour and it appeared significantly decreased in scotopic condition only between 4 and 5 hours after instillation of the topical treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>M ± SD</th>
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<tr>
<td>Best corrected far-near visual acuity (Jaeger)</td>
<td>4.81 ± 2.75</td>
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<td>Best near addition (D)</td>
<td>1.85 ± 0.55</td>
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<tr>
<td>Binocular best corrected far-near visual acuity (Jaeger)</td>
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<td>Binocular far uncorrected visual acuity (LogMAR)</td>
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<td>Binocular near uncorrected visual acuity (Jaeger)</td>
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<td>Intraocular pressure (mmHg)</td>
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<tr>
<td>Near uncorrected visual acuity (Jaeger)</td>
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<td>Photopic pupil diameter (mm)</td>
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<td>Scotopic pupil diameter (mm)</td>
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<tr>
<td>Spherical equivalent (D)</td>
<td>0.32 ± 0.55</td>
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**Table 1:** Mean and standard deviation data before the instillation of the eye drops for each variable that presents significant statistical changes after the instillation.

![Figure 1](image1.png)

**Figure 1:** Time trends for best near addition (a), monocular (b) and binocular (c) best corrected far-near visual acuity from 30 min to 1 month. Asterisks show only significant differences for a value compared with PRE.

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Figure 2: Time trends for binocular far uncorrected visual acuity (a) defocus equivalent (b) and binocular near uncorrected visual acuity (c) from 30 min to 1 month. Asterisks show only significant differences for a value compared with PRE.

Figure 3: Time trends for monocular far (a) and near (b) uncorrected visual acuity and intraocular pressure(c) from 30 min to 1 month. Asterisks show only significant differences for a value compared with PRE.

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Discussion

Several studies had been conducted to determine how much each factor involved in the accommodative process contributes to it [9-13]. The few topical treatments for presbyopia currently under study claim to work on different aspects of the accommodative process: involving monovision parasympathetic-mediated miosis and ciliary muscle stimulation; or targeting only the pupil sphincter muscle to achieve a pinhole effect; or softening the lens in order to restore its shape-changing ability [4-7]. Each one of these approaches may present some disadvantages. Pure parasympathetic treatments lead to a too small pupil diameter and to a myopic shift compromising far distance vision and they also cause several well-known adverse reactions due to the muscarinic stimulation of ciliary muscle and pupil sphincter [10]. Even if a lens-softening treatment would be safe, it might be less effective than expected because changes in mechanical properties seem to be less important in the advent and progression of presbyopia than changes in lens geometry [11]. A monovision treatment could reduce the visual performance in reduced light conditions compared to a binocular approach [13]. For this reason the treatment used in our pilot study is instilled in both eyes. Vejarano-patent pending eye drops would work both on stimulating the contraction of ciliary body and maintaining a physiological pupil diameter variation. In this condition, binocular treatment would avoid worsening of visual performance with reduced light and would allow a physiological image merging with clear focus at near, intermediate and distance. Pilocarpine provides both miosis and ciliary body contraction stimulating accommodation and may improve tear production stimulating lacrimal gland secretion [14]. Phenylephrine, Nepafenac and Pheniramine, in different ways and amounts each one, avoid an excess of pupil constriction and counteract ciliary muscle spasm and vascular congestion and hyperemia induced by pilocarpine [6,15-17]. Naphazoline empowers pilocarpine relaxing effect on dilator pupillae and relieves its side effects increasing acetylcholine release and reducing norepinephrine release [17]. Lubricant effect of polyethylene glycol improves the eye drops tolerance avoiding the burning typically from the most of the compounds. The findings of the synergistic effect between these molecules observed by Vejarano would permit to improve near vision preserving distance vision in all subjects. Synergism would reduce symptoms of headache and hyperemia allowing use of lower doses of miotics. In this study there was no evidence of tachyphylaxis. No ocular complications were detected in any treated

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eyes during the entire follow-up period. The results showed near uncorrected visual acuity (NUCVA) improved by about 2 to 3 lines in each eye and binocularity from a baseline mean of about J3.5 to about J1.5. No patient had a loss in UCVA at far in each eye and binocularly. Whereas other presbyopia drops improve near vision by causing an extreme miosis or amyoic shift that can reduce far vision, refractive measurements in this study showed there was a maximum myopic shift of just 0.5 D that progressively reduces and disappears after 3 hours. Pupil diameter was also measured and found to be mildly affected by the topical treatment, which is not fix allowing a "dynamic pseudoaccommodation". Moreover, the measurements showed that the treatment seemed to mitigate significant pupil enlargement under scotopic conditions as well as significant contraction in photopic conditions. Other assessments showed no clinical changes in tear film quality or quantity and endothelial cell count showing no adverse effects on the lacrimal film, corneal epithelium or endothelial cells. About IOP the study shows significant decrease of almost 2 mmHg after 5 hours. There is clinical evidence that the trabecular meshwork increase in stiffness with aging because of that, the glaucoma prevalence and incidence increase with age. With this daily movement of the scleral spur exists the possibility to avoid its rigidity, therefore the glaucoma incidence with aging.

Conclusion

This preparation improves 2-3 lines for near vision without affecting far vision. Action proved mostly accommodative with a new concept of dynamic pseudoaccommodation, this is a truly improved physiological accommodation. Binocular pharmacologic treatment of presbyopia with Vejarano-patent pending eye drops has the rationale to ameliorate reading vision for presbyopes with the advantages of a non-monovision therapy. This topical agent represents an on invasive solution for addressing presbyopia that we believe meets all of the criteria for an ideal treatment; despite the small number and the heterogeneity of the patients involved in this pilot study, findings looks very promising [18,19]. Further randomized controlled double-masked clinical trials will be conducted by our group to test the attractive Vejarano's eye drops to improve presbyopia.

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# Diameter Report

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**Name: Vejarano Felipe**

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Authorship
All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. This study is part of the final research work of Dr. Antonio Renna in the Specialization course: Clinical Methodology in Refractive, Cataract and Cornea Surgery of the Miguel Hernandez University, Spain, 2016.

Disclosures
Antonio Renna, Ernesto Dela Cruz and Jorge L. Alió declare that they have no conflict of interest. L. Felipe Vejarano is the inventor of the eye drops mentioned in this paper.

Compliance with ethics guidelines
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Key Summary Points

Why carry out this study?
- Presbyopia begins to affect near visual tasks around 40 years and is associated with substantial, negative effects on vision-targeted health-related quality of life.
- Topical treatment of presbyopia is an attractive approach which, if available and effective, would be the choice for many patients.

What was learned from the study?
- The new binocular topical drug treatment analyzed here in improves 2 - 3 lines for near vision without affecting far vision.
- This topical agent represents a noninvasive solution for addressing presbyopia that we believe meets all of the criteria for an ideal treatment.

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