Stereopsis Restoration in Patients Under Pharmacological Treatment for Presbyopia

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Abstract

**Background:** Presbyopia is the physiologically normal age-related progressive weakening of accommodation resulting in the loss of the visual ability to focus on objects situated at different distances. Stereopsis is the binocular perception of depth and it improve with better near visual acuity. Presbyopia treatments have influence on stereopsis. The pharmacological treatment consists of topical daily eye-drops in both eyes with a combination of pilocarpine and diclofenac, restoring accommodation and preserving binocularity. The aim of this study was to evaluate stereopsis in patients treated with the pharmacological treatment and to compare with optical correction.

**Methods:** Twenty emmetropic patients, between 40 to 55 years old were studied by testing far and near visual acuity and stereopsis (Titmus Stereo Optical test) at baseline; optical correction with eyeglasses and, after instillation of eye-drops.

**Results:** At baseline the median of stereopsis was 120 (80-350) s of arc, which improved to 40 (40-75) s of arc (p<0.0001) after the optical correction procedure and to 40 (40-80) s of arc (p<0.0001) after pharmacological treatment.

**Conclusions:** Both methods exhibited similar results showing no statistically significant difference. These observations demonstrate that the pharmacological treatment for presbyopia not only reestablished near and distance visual acuity but also restored stereopsis.

**Keywords:** Stereopsis. Presbyopia. Pharmacological treatment for presbyopia. Stereoacuity

**Abbreviations:** EDOF - extended depth of focus, NSAID - non-steroid anti-inflammatory drug, D – diopters, UDVA - uncorrected distance visual acuity, UNVA - uncorrected near visual acuity, CDVA - corrected distance visual acuity, CNVA - uncorrected near visual acuity, J – Jaeger, S of arc – seconds of arc

1. INTRODUCTION

Presbyopia is the progressive weakening of the accommodation, resulting in the loss of the visual ability to focus on objects situated at different distances [1][2].

As presbyopia, other ocular functions deteriorate with aging like stereopsis. Stereopsis is the binocular perception of depth that exists only in some higher animals and in humans. This visual ability to perceive the world in three dimensions is through information of monocular cues such as perspective, size, superposition, motion parallax, accommodation, and haze; and binocular cues as binocular disparity. Disparity happens when the two images fall on non corresponding parts of the two retinas. Stereopsis has been disclosed to improve with better near visual acuity [3]. Moreover, with concerns to functional significance of stereopsis, the deterioration of it has been reported to be a significant risk factor for self reported visual disability with aging [4]. Good stereoacuity impact the performance on certain motor abilities necessary for ordinary tasks that require precise manipulation of objects within a near range such as threading a needle [5]. In concern to the effect of stereopsis regarding large disparity range, it is important to maintain depth judgments at distances up to 200m [6] such as, management of the environment, climbing up and down stairs and obstacle prevention [7].
Nowadays, presbyopia treatments have influence on stereopsis. Within the plethora of treatments for presbyopia there are different strategies that could involve spectacles, contact lenses, surgical correction, and the innovative pharmacological treatment [8][9].

Corneal refractive surgery includes monovision or multifocality created by excimer ablation, conductive keratoplasty, and diverse inlays. Other surgical correction could be an intraocular lens replacement using either monofocal implants for monovision, multifocal lenses, accommodative implants, and extended depth of focus lenses (EDOF) [10].

The pharmacological treatment (Benozzi’s Method®: patents US 8,524,758 B2 and EP1,938,839 B1 among others) consists of topical daily eyedrops in both eyes with a combination of pilocarpine and diclofenac [1]. Pilocarpine, as a parasympathetic agonist, produces a spasmodic contraction of the ciliary muscle and miosis [11].

Diclofenac is a non-steroid anti-inflammatory drug (NSAID). This combination of NSAIDs and parasympathetic agonists enables the intensity decrease of the contraction of the ciliary muscle and the pupil, changing the shape and position of the lens obtaining focus at all distances and consequently restoring accommodation [12]. This promising new way to treat presbyopia, the Benozzi Method, allows the rehabilitation of accommodation by physiologically stimulating the ciliary muscle using the combinations adjusted according to the specific needs and characteristics of each patient. Thus, presbyopic patients are able to focus naturally at all distances, as long as they continue treatment or until the lens loses its properties [12].

Eye glasses are the classic method to treat presbyopia, as it is known that they maintain binocularity and stereopsis. Taking into account that the pharmacological treatment restores accommodation and preserves binocularity, the aim of this study was to evaluate stereopsis in patients treated with the pharmacological treatment for presbyopia.

2. MATERIALS AND METHODS

2.1. Patients

This prospective study comprised 20 patients from the “Centro de Investigación Avanzada de la Presbicia”, Buenos Aires, Argentina. The study was evaluated and approved by the Ethics Committee of the Presbyopia Argentinian Society, and written consent was obtained from all individuals.

Inclusion criteria were patients between 40 to 55 years old, who also had healthy eyes with a demonstrated loss of accommodative function. Participants had a spherical equivalent between ± 0.75 dioptres (D), and uncorrected distance visual acuity (UDVA) equal to or better than 20/40 (0.3 LogMAR) in each eye. Patients were excluded from this study if they were pregnant or breast feeding, had previous ocular surgeries like laser vision correction, or had a history of ophthalmological diseases.

All patients were studied following and examination scheme performed in each patient under the same conditions and by the same physician. The examination scheme included monocular uncorrected distance visual acuity (UDVA), monocular uncorrected near visual acuity (UNVA), monocular corrected distance visual acuity (CDVA), and monocular corrected near visual acuity (CNVA). Standard Snellen projector Chart was used to evaluate distance visual acuity and Jaeger (J) Eye Chart at 40 cm of the eyes of the patient for near visual acuity assessment. Also ocular motility was evaluated through cover- uncover test. Stereopsis was assessed at baseline (T₀), using optical correction with eyeglasses (T₁) and for last, with one drop of the pharmacological treatment for presbyopia (T₂) (Figure 1).

2.2. Ocular Motility: Cover-Uncover Test

The monocular cover-uncover test is essential for detecting the presence of a heterophoria or heterotropia. The examiner observes carefully for any movement in the noncovered eye as the other eye is covered. In the instance of a phoria, the uncovered eye does not move however the eye that is cover will deviate when occluded and return to a straight position when the occluder is removed. The deviation that occurs during the test is a outcome of interruption of binocular vision. Some patients may have straight eyes and start out with a heterophoria prior to the cover-uncover test, however, after extended testing— and therefore persistent interruption of binocular vision— dissociation into a evident heterotropia can appear.
2.3. Stereopsis Test

The stereoacuity under natural light was evaluated using the Titmus Stereopsis Test (Stereo Optical Co., Chicago, IL, USA) as shown in Figure 2. When testing, subjects viewed the images through polarizing spectacles with 40 cm distance and held perpendicular to the visual axis. This assessment was done confirming that the subject is truly seeing the target circle standing out and then repeating the procedure with the page inverted to reverse the disparity to avoid the use of monocular cues. In this manner, the subject perceives the target circle behind, rather than in front of the page [13]. The booklet comprises of a large-disparity fly, three series of animals, and nine sets of circles. The fly and the series of circles are used in adults meanwhile the series of animal are usually used for children. The fly was shown first to determine the presence of gross stereopsis. If a positive response was given, the series of circles test continued to stipulate a finely graded sequence for critical testing. Four circles comprised each circle set, and only one of them seems to be closer to the patients than others (three dimensions). A total of 9 levels, ranging from 40 to 800 seconds of arc, are applied in circle test. With the decrease of the degree of crossed disparity, the difficulty level in stereopsis increases. Stereoacuity is recorded with the most difficult level achieved by patients.

Figure 2. Titmus Stereopsis Test - Stereo Optical Co., Chicago, IL, USA

The Titmus Stereopsis Test evaluates stereopsis. A total of 9 levels, ranging from 40 to 800 seconds of arc, are applied in circle test. With the decrease of the degree of crossed disparity, the difficulty level in stereopsis increases. Stereoacuity is recorded with the most difficult level achieved by patients.

2.4. Statistical Analysis

Quantitative data is presented as mean ± standard deviation. Clinical data were checked for normal distribution using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The differences of means were analyzed using paired sample t test for normal data and Wilcoxon test as non-parametric test. As data were not normally distributed, they were plotted as median and 25th/75th percentiles. A value of p <0.05 was considered statistically significant in all tests.
Statistics were calculated using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA.

3. RESULTS AND DISCUSSION

20 presbyopic patients were studied, of whom 9 were women and 11 men. The mean age was 49.7 ± 4.1 years. All patients were emmetropic with spherical equivalent refraction in the right eye 0.34 ± 0.32D and in the left eye 0.23 ± 0.22D. In relation to the cover-uncover test, 85% of patients presented no phoria while 15% had exophoria (Table 1).

Table 1. Demographic information of presbyopic patients

<table>
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<tr>
<th>Patient</th>
<th>Gender</th>
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<th>Spherical Equivalent</th>
<th>Phorias</th>
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All patients were assessed for monocular spherical equivalent and ocular motility. Figure 3 shows monocular distance visual acuity at baseline, with eyeglasses and one eye drop of the pharmacological treatment. Considering that the patients included in the study were emmetropic they presented a very good UDVA of 0.019 ± 0.01 LogMAR at baseline (T₀). All the patients reached CDVA of 0 LogMAR (20/20 Snellen) both when treated with optical correction (T₁) with eyeglasses and with pharmacological treatment (T₂).

Figure 3. Monocular Distance Visual Acuity at baseline (UDVA), with optical treatment and with pharmacological treatment (CDVA). The UDVA was 0.019 ± 0.01 LogMAR (T₀) and all the patients reached CDVA of 0 LogMAR (20/20 Snellen) both when treated with optical correction with eyeglasses (T₁) and with pharmacological treatment (T₂).
In Figure 4, monocular near visual acuity with and without treatment is observed. The mean UNVA was $0.197 \pm 0.02D$ without treatment ($T_0$). All the patients with the optical treatment ($T_1$) achieved a CNVA of J1 (0 LogMAR) whereas when treated with the pharmacological treatment ($T_2$), all the patients achieved J1 except 2 patients arrived at J2.

The mean UNVA was $0.197 \pm 0.02 D$ without treatment. Patients treated with both treatments achieved a CNVA similar to J1 (0 LogMAR) showed no significant differences ($p=0.25$).

Figure 4. Monocular Near Visual Acuity at baseline ($T_0$) (UNVA), with optical treatment ($T_1$) and with pharmacological treatment ($T_2$) (CDVA)

Stereopsis testing, as measured by Titmus stereoscopic tests, is shown in Figure 5. At baseline ($T_0$) the median of stereopsis was 120 (80-350) s of arc, which improved to 40 (40-75) s of arc ($p<0.0001$) after the optical correction procedure ($T_1$) (Figure 5A) and to 40 (40-80) s of arc ($p<0.0001$) after pharmacological treatment ($T_2$) (Figure 5B). Both methods exhibited similar results by Titmus stereoscopic tests showing no statistically significant difference ($p=0.0625$).

Figure 5. Stereopsis evaluation by Titmus Stereoscopic Test
A: Stereopsis was evaluated at baseline ($T_0$) and optical correction with eyeglasses ($T_1$). B: Stereopsis was evaluated at baseline ($T_0$) and after pharmacological treatment ($T_2$).

The present study demonstrates in twenty emmetropic presbyopic patients that pharmacological treatment for presbyopia restored near and distance visual acuity as well as optical treatment, which reached 20/20 and J1, respectively. The examination of the results of stereopsis indicated that all patients improved stereoacuity by both methods, showing no statistical differences between them.

In our investigation, we studied stereopsis by Titmus stereoscopic tests taking into account that patients involved are adults that could follow indications accurately. Titmus Test is convenient and accessible for any ophthalmologist to evaluate stereopsis. By using this test, the true perception of depth can be achieved not only by identifying a circle as different but also in addition by inverting the test to reverse the
disparity and ensuring that the stimulus changed from appearing in front of the page, to appear behind it. These precautions must be taken because it has been suggested that even if monocular cues are present in Titmus stereoscopic test, proper instructions by the examiners and the rigorous follow-up by the patients can minimize its effects to give a more accurate stereoacuity score [3,15].

Binocularity, stereopsis and accommodation are functions developed during childhood that decreases with aging. At birth, the visual system (included the components of the eye and the neural circuit patterns) is immature and during the first postnatal months begins its dynamic development [16,17]. In concern to stereopsis, it is not present at birth and progresses accordingly to the improvement of visual acuity [18]. The stereopsis development stage starts from around three months of age, with a rapid progression during the first year and improvement over the first five years of life where neural plasticity is in the apex [19]. The sensitive stage could extend to maturity, regarding that the neural plasticity decreased accordingly to growing up [16]. Accommodation in humans is achieved by ciliary muscle and iris sphincter contractions, convergence and variations in the shape and position of the lens [20]. When ciliary muscles contract during accommodative action they release tension on the zonules allowing the elastic lens capsule to reshape and change the dioptric power of the lens. The different subtypes of muscarinic receptors on the iris and ciliary muscle are responsible of the contractions when are stimulated by the cholinergic neurotransmitter, acetylcholine, by the generation of the structures movements and hence accommodation [21].

During the first years of childhood, the human being presents a maximum of 15 adaptive dioptries, however, for most visual tasks the need for accommodation is much lower [22].

Although the amplitude of accommodation decreases gradually until approximately 65 years, when it is almost completely lost, the deficit in most people seem to have a sudden onset and consequently presbyopia appears. According Helmholtz’s theory of accommodation [23], presbyopia is defined as the gradual loss of accommodation with aging consequential to the loss of elasticity of the lens capsule and substance.

Many strategies were developed to ameliorate presbyopia condition, although sacrificing binocularity. Monovision used for presbyopic correction is a well-established method with the non-dominant eye corrected for near vision and the dominant eye for distance vision. There are many ways to accomplish monovision, using contact lenses, laser in situ keratomileusis (LASIK) treatment of monovision (approved by FDA in 2007) [24], and using intraocular monocular implants. Nevertheless, the complex visual system is intended to make both eyes to work together to obtain information from the background. Human visual field overlaps in nearly 60 per cent and where a sacrifice of a greater peripheral vision is made in favor of information provided by binocular disparity, and this results in benefits to the functional ability [16].

When the retinal images formed on each eye disagree, stereopsis is affected and different approaches have been widely studied in the past. Former literature relates asymmetric changes in the contrast of the two retinal images to degradation of stereopsis [25]. Latest revisions have searched the role of aberrations, outside defocus and astigmatism when they are unequal in the two eyes, over stereopsis [26]. Monovision decreases contrast sensitivity, binocularity and stereopsis [24] that is why the selection of the patient is essential. Inappropriate patients reported include aviators, professional drivers, writers and those who spend all day on computers [24]. Binocular vision is fundamental for stereopsis and, applying monovision, stereopsis can be seriously compromised [27].

Regarding corneal inlay influence on stereopsis, it has not been widely studied [28]. However, the results of the experiment realized by Fernández et al. showed that a small aperture as a corneal inlay, can produce similar values of stereoacuity to those attained only under photopic conditions [27]. These results are not the same under scotopic situations.

It has also been shown that multifocality achieved through contact lenses, sophisticated spectacles, corneal correction or intraocular implants reduces stereoacuity, even though it is vaguely better than with monovision [29]. While technology is rapidly improving and there are very sophisticated lens options for presbyopes none offer the range and quality of vision achieved by a young eye with active accommodation [30].

Surgical corneal presbyopic correction attempts to create a bifocal cornea, nevertheless this procedure carries risks of scarring, night vision problems and vision loss [10], in addition to the loss of binocularity and stereopsis [24]. The same happens with lenticular procedures in addition to
the risks of night vision problems, glare, halos, and endophthalmitis [31]. Besides accommodating implants theoretically could have reduced effects on binocularity and stereopsis, all these procedures are quite invasive, which could be more appropriate for cataract patients [32].

Different treatments for presbyopia are available for varied types of patients and all of them have their advantages. The correct selection of patient is mandatory for a successful result. Emmetropic, presbyopic, between 40 to 55 years old patient is the ideal one for the pharmacological treatment suggested and evaluated in this study. Patients under the effect of one eye drop of the pharmacological treatment recovered monocular distance and near visual acuity, as proved in this study. Maintaining binocular vision is condition for stereopsis. Further, a reduced range of stereopsis has a negative influence on the ability to perform several tasks, and can lead to increase trouble relating in the real world. The decrease in stereovisual affects performance in complex spatial-motor activities, resulting in difficulties for tasks in ordinary life. The relevance of this results is that the pharmacological treatment is a possible new alternative to reestablish stereopsis as well as optical traditional treatment. With eyeglasses.

4. CONCLUSION

Stereopsis is developed from the early infancy and is gradually lost when accommodation decreases. The reduced level of stereopsis has a substantial impact on visuomotor tasks and difficulties in moving safely, among others. The pharmacological treatment proved to ameliorate stereopsis as well as the optical treatment taking into account that both methods conserve binocularity, necessarily condition for stereopsis, in contraposition with other strategies that correct presbyopia. Taken together, these observations demonstrate that the pharmacological treatment for presbyopia not only reestablished near and distance visual acuity but also restored stereopsis.

REFERENCES


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