

Stereopsis evaluation in patients under pharmacological treatment for presbyopia

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Abstract

Objective: Stereopsis is the binocular perception of depth, which has been associated to the improvement in near visual acuity. Presbyopia is the progressive weakening of accommodation, which could be modulated by an eye-drop pharmacological treatment (Benozzi's method). The purpose of this work was to evaluate stereopsis in patients treated with Benozzi's method for presbyopia.

Methods: A non-randomized case-series prospective study was developed. Twenty emmetropic patients were included, in the range from 40 to 55 years old. Different parameters were measured, such as spherical equivalent refraction (SE), uncorrected and corrected distance and near visual acuity (UDVA-CDVA/UNVA-CNVA), ocular motility and stereopsis. Measurements were performed in three situations: at baseline, with optical correction (eyeglasses) and, after 30 minutes of treatment (eye-drops instillation).

Results: The mean SE refraction in the right eye was 0.34 ± 0.32 D and in the left eye it was 0.23 ± 0.22 D. Orthophoria was found in 85% of patients while 15% had exophoria. The mean UNVA was 0.197 ± 0.02 LogMAR; with optical correction achieved J1 (0 LogMAR) and after treatment, the mean UNVA was 0.02 ± 0.06 LogMAR (18 cases with J1 and 2 with J2). Pre-treatment mean stereopsis was 200.5 ± 190.85 s of arc, which improved to 52.5 ± 19.70 s of arc ($p < 0.0018$) after the op-

tic correction and to 58 ± 22.38 s of arc ($p < 0.002$) after pharmacological treatment. Both methods exhibited similar results by Titmus stereoscopic tests showing no statistically significant difference ($p > 0.41$).

Conclusions: This study demonstrates that pharmacological treatment for presbyopia not only re-established near and distance visual acuity but restored stereopsis.

Keywords: Stereopsis, presbyopia, pharmacological treatment, stereoacuity.

Evaluación de la estereopsis de pacientes en tratamiento farmacológico de la presbicia

Resumen

Objetivo: La estereopsis es la percepción binocular de profundidad que está asociada a la mejoría de la visión cercana. El objetivo del presente trabajo fue evaluar la estereopsis en los pacientes tratados con el Método Benozzi, que es un tratamiento farmacológico para la presbicia.

Métodos: Se desarrolló un estudio prospectivo, no randomizado, de una serie de casos en 20 pacientes emétopes de 40 a 55 años. Se evaluaron: equivalente esférico (ES), agudeza visual (AV) de lejos y cerca, con y sin corrección, motilidad ocular y estereopsis. Se realizaron las mediciones sin y con corrección óptica de cerca y 30 minutos luego de realizar el tratamiento.

Resultados: El valor medio del ES fue de $0.34 \pm 0.32D$ en ojos derechos y de $0.23 \pm 0.22D$ en ojos izquierdos. El 15% presentaba exoforia y se encontró ortoforia en el resto. El valor medio de la AV cercana s/c fue de 0.197 ± 0.02 LogMAR y de 0.02 ± 0.06 LogMAR (18 casos con J1 y dos con J2) con tratamiento. Con el uso de anteojos todos obtuvieron J1 (0 LogMAR). El valor medio de la estereopsis antes del tratamiento fue de $200,5 \pm 190,85$ s de arco, que mejoró luego de la corrección óptica a $52,5 \pm 19,70$ s de arco ($p < 0.0018$), y luego del tratamiento con Método Benozzi a $58 \pm 22,38$ s de arco ($p < 0.002$). La estereopsis no mostró diferencias estadísticamente significativas entre los anteojos y el tratamiento ($p > 0.41$).

Conclusiones: Este estudio demuestra que el tratamiento farmacológico para la presbicia no sólo mejora la visión de cerca, mientras mantiene la visión de lejos, sino que también mejora la estereopsis.

Palabras clave: estereopsis, presbicia, tratamiento farmacológico.

Avaliação da estereopsia de pacientes em tratamento farmacológico da presbiopia

Resumo

Objetivo: A estereopsia é a percepção binocular de profundidade que está associada com a melhoria da visão de perto. O objetivo do presente trabalho foi avaliar a estereopsia nos pacientes tratados com o Método Benozzi, que é um tratamento farmacológico para a presbiopia.

Métodos: Desenvolveu-se um estudo prospectivo, não randomizado, de uma série de casos em 20 pacientes emétopes de 40 a 55 anos. Avaliaram-se: equivalente esférico (ES), acuidade visual (AV) de longe e perto, com e sem correção, motilidade ocular e estereopsia. Realizaram-se as medições sem e com correção óptica de perto e 30 minutos logo de realizar o tratamento.

Resultados: O valor médio do ES foi de $0.34 \pm 0.32D$ em olhos direitos e de $0.23 \pm 0.22D$ em olhos esquerdos. 15% apresentava exoforia e se encontrou ortoforia no resto. O valor médio da AV próxima s/c foi de 0.197 ± 0.02 LogMAR e de 0.02 ± 0.06 LogMAR (18 casos com J1 e dois com J2) com tratamento. Com o uso de óculos todos obtiveram J1 (0 LogMAR). O valor médio da estereopsia antes do tratamento foi de $200,5 \pm 190,85$ s de arco, que melhorou logo da correção óptica a $52,5 \pm 19,70$ s de arco ($p < 0.0018$), e logo do tratamento com Método Benozzi a $58 \pm 22,38$ s de arco ($p < 0.002$). A estereopsia não mostrou diferenças estatisticamente significativas entre os óculos e o tratamento ($p > 0.41$).

Conclusões: Este estudo demonstra que o tratamento farmacológico para a presbiopia não melhora apenas a visão de perto, enquanto mantém a visão de longe, mas também melhora a estereopsia.

Palavras chave: estereopsia, presbiopia, tratamento farmacológico.

Introduction

With aging decrease visual performance, as happens with the “presbyopia”, which is the progressive weakening of accommodation resulting in loss of the visual ability to focus on objects situated at different distances¹. As presbyopia, other ocular functions deteriorate with aging like stereopsis. Stereopsis is the binocular perception of depth and it has been disclosed to improve with better near visual acuity². Moreover, with concerns to its functional significance, it has been reported to be a significant risk factor for self-reported visual disability with aging³. Good stereoacuity impact the performance on certain motor necessary for ordinary tasks that implicate precise manipulation of objects within near range as threading a needle⁴. In concern to the affection of stereopsis in the large disparity range, is important to support depth judgments at distances up to 200m as⁵, manage through the environment, up and down stairs and obstacle prevention⁶.

Actually, presbyopia treatments have inherence 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 treatment⁷⁻⁸. Corneal refractive surgery includes monovision or multifocality created by excimer ablation, conductive keratoplasty, and diverse inlays. Other surgical correction can be intraocular lens replacement using either monofocal implants for monovision, multifocal lenses, accommodative implants, and extended depth of focus lenses (EDOF)⁹.

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 diclofenac¹. Pilocarpine, as a parasympathetic agonist, produces a spasmodic contraction of the ciliary muscle and miosis¹⁰. Diclofenac is a non-steroid anti-inflammatory drug (NSAID). This combination of NSAIDs and parasympathetic agonists permits the decrease in the intensity of the contraction of the ciliary muscle and the pupil, changing the shape and

position of the lens obtaining focus at all distances restoring accommodation¹¹.

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

Materials and methods

Study design

A non-randomized case-series prospective study was developed, including 20 patients with presbyopia treated with pharmacological treatment for presbyopia “Método Benozzi”, from March to June 2019. The study was performed following the tenets of Helsinki, in a private ophthalmology clinic (Centro de Investigación Avanzada de la Presbicia) in Buenos Aires city, Argentina. An informed consent was obtained from every patient. The present study protocol was evaluated and approved by the Ethical Committee of the Argentinian Presbyopia Society (0001/2019).

Exclusion and inclusion criteria, parameters to evaluate and statistics.

All patients were studied following a complete ophthalmic baseline assessment. The examination scheme included uncorrected distance visual acuity (UDVA), uncorrected near visual acuity (UNVA), corrected distance visual acuity (CDVA), and corrected near visual acuity (CNVA), ocular motility and stereopsis. Stereopsis was assessed at baseline, with optical correction with eyeglasses and for last, with the pharmacological treatment for presbyopia 30 minutes after the instillation of the eye-drops.

1. Patients age between 40 to 55 years old; 2. Refractive errors were measured (auto-refractometer; Nidek ARK700K) and patients were excluded if one of the eyes has a cycloplegic spherical refraction greater than -0.50 D or 1.0

D and/or with cylinder refraction higher than 1.0 D; 3. The uncorrected distance visual acuity (UDVA) was measured with Snellen charts and converted to the logarithm of the minimum angle of resolution (logMAR) and uncorrected near visual acuity (UNVA) was measured with reading chart at 45 cm distance (objectively measured), with Jaeger (J) standard notation (from J1 to J8). If binocular UDVA was lower than 20/40, patients were excluded; 4. Patients with amblyopia, history of any kind of glaucoma, pseudophakia, macular disease or any retinal disorder, or had a history of ophthalmological diseases were also excluded.

Stereopsis test

The stereoacuity under natural light was evaluated using the Titmus Stereopsis Test (Stereo Optical Co., Chicago, IL, USA). When testing, subjects viewed the images through polarizing spectacles with 40 cm distance and held perpendicular to the visual axis. 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. Each circle set are comprised by 4 circles, and only one of them seems to be closer to subjects than others (3D). 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.

Statistical analysis

Quantitative data are presented as mean \pm standard deviation. Differences of means were analyzed using paired sample t test. A value of $p < 0.05$ was considered statistically significant in all tests. Statistics were calculated using was performed using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California, USA.

Results

20 presbyopic patients were studied, of whom 9 were women and 11 men. The mean age was 49.7 ± 4.1 years. They were all emmetropic patients with spherical equivalent refraction in the right eye $0.34 \pm 0.32D$ and in the left eye $0.23 \pm 0.22D$. In relation to ocular motility, 85% of patients (17 cases) had orthophoria while 15% (3 cases) had exophoria.

Figure 1 shows distance visual acuity with and without treatment. Considering that the patients included in the study were emmetropic they presented a very good UDVA of 0.019 ± 0.01 LogMAR. All the patients reached CDVA of 0 LogMAR (20/20 Snellen) both when treated with optical correction with eyeglasses and with pharmacological treatment.

In figure 2, near visual acuity with and without treatment is observed. The mean UNVA was 0.197 ± 0.02 LogMAR without treatment. All the patients with optical treatment achieved a CNVA of J1 (0.0 LogMAR) whereas when treated with the pharmacological treatment, all the patients achieved 0.02 ± 0.06 LogMAR (18 cases with J1 and 2 with J2).

Stereopsis testing, as measured by Titmus stereoscopic tests, is shown in figure 3. Pre-treatment mean stereopsis was $200.5 \pm 190.85s$ of arc which improved to 58 ± 22.38 s of arc ($p < 0.002$) after pharmacological treatment (Figure 3A) and to 52.5 ± 19.70 s of arc ($p < 0.0018$) after the optical correction procedure (Figure 3B). Both methods exhibited similar results by Titmus stereoscopic tests showing no statistically significant difference ($p > 0.41$).

Discussion

Stereopsis is developed from the early infancy and is gradually lost as accommodation decreases. The reduced level of stereopsis has a substantial impact on visuomotor tasks and difficulties in locomoting safely, among others. The present study demonstrates in 20 emmetropic presbyopic patients that pharmacological treatment for presbyopia restored near and distance visual

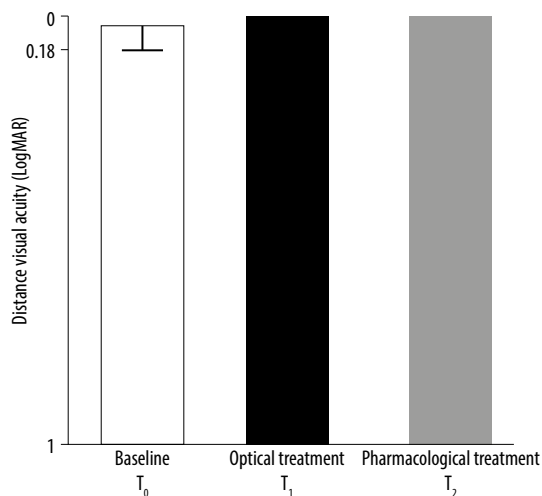


Figure 1. Distance visual acuity with and without treatment. Baseline (T₀) uncorrected distance visual acuity, with eyeglasses (T₁) and with pharmacological treatment (T₂).

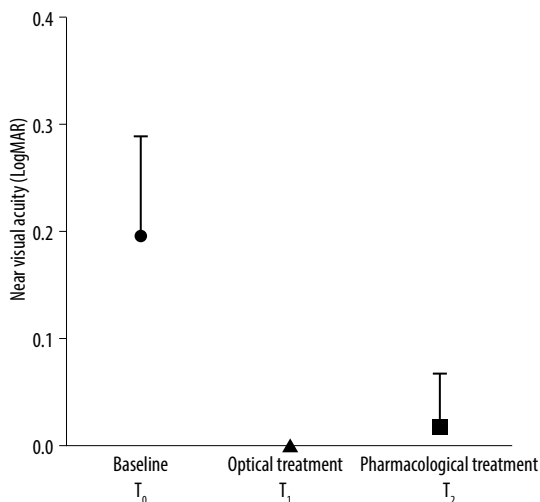


Figure 2. Near visual acuity with and without treatment. Baseline (T₀) uncorrected distance visual acuity, with eyeglasses (T₁) and with pharmacological treatment (T₂).

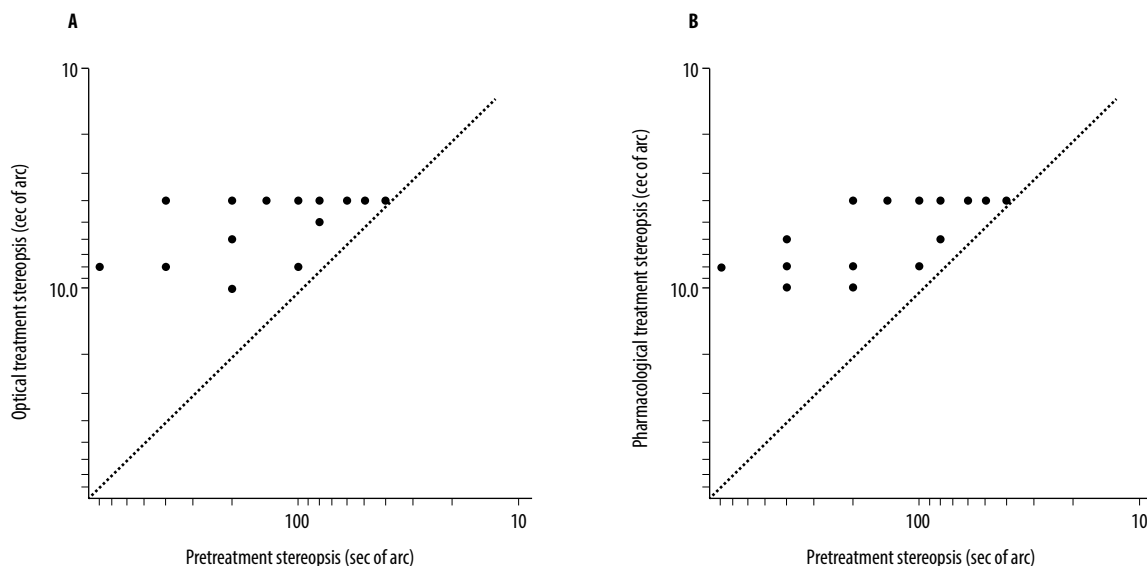


Figure 3. Stereopsis evaluation by Titmus Stereoscopic Test. A: Stereopsis was evaluated at baseline (T₀) and optical correction with eyeglasses (T₁). B: Stereopsis was evaluated at baseline (T₀) and after pharmacological treatment (T₂).

acuity reached 20/20 and J1, respectively, as well as optical treatment. Examination of the results of stereopsis by Titmus stereoscopic tests indicated that all patients improved stereoacuity by both methods showing no statistical differences between them.

At birth, the visual system (included the components of the eye and the neural circuit pat-

terns) is immature and during the first postnatal months begins its dynamic development. There are three critical stages in visual system maturity: development, sensitive and recovery, taking into account that the timing of each period depends on each specific visual function¹². In concern to stereopsis is not present at birth and progresses according visual acuity improves. Fox *et al.*

in 1980 reported that stereopsis emerges from 3.5 to 6 months from an investigation in infants based on attracting baby's attention through the apparent motion in visual space of a stereoscopic contour contained within a random-element stereogram¹³. Biagi *et al.* in 2015, provided the first maps of visual cortical function in human infants by functional magnetic resonance imaging (fMRI)¹⁴. The study lightened up that the associative regions of the cortex responsible for motion processing react similarly in 7-week-olds and adults. However, the development of functional connections between the associative areas and the primary visual cortex is not yet mature¹⁴. 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 apex¹⁵. The sensitive stage could extend to maturity, regarding that neural plasticity decreased according growing up¹².

During the first years of childhood, the human being presents a maximum of 15 adaptive diopters, however, for most visual tasks the need for accommodation is much lower¹⁶. Although the amplitude of accommodation decreases gradually until approximately 65 years, when it is almost completely lost, the deficit in most people seems to have a sudden onset and presbyopia appears. According Helmholtz's theory of accommodation¹⁷, presbyopia is defined as the gradual loss of accommodation with aging consequential to loss of elasticity of the lens capsule and substance. Accommodation in humans is achieved by ciliary muscle and iris sphincter contractions, convergence and variations in the shape and position of the lens¹⁸. When ciliary muscles contract during accommodative action it 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 iris and ciliary muscle are stimulated by the cholinergic neurotransmitter, acetylcholine¹⁹.

The improvements in stereopsis for patients who underwent pharmacological treatment were significant, especially because other presbyopia treatments available to date have diminished stereopsis and binocularity in some degree²⁰.

Monovision used for presbyopic correction is a well-established method with one eye corrected for near vision and the other eye for distance vision. There are many ways to accomplished monovision, using contact lenses, laser *in situ* keratomeleusis (LASIK) treatment of monovision (approved by FDA in 2007)²⁰, and using intraocular monocular implants. The non-dominant eye is corrected for near vision and the dominant eye for distance vision. Nevertheless, the complex visual system is intended to consent 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 welfares to functional ability¹².

Monovision is in the edge of the brain to create stereopsis²¹. 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 stereopsis²². Latest revisions have searched the role of aberrations, outside defocus and astigmatism when they are unequal in the two eyes, over stereopsis²³.

Monovision intentionally decreases contrast sensitivity, binocularity and stereopsis²⁰ that is why the selection of the patient is essential. Inappropriate patients include aviators, professional drivers, writers and those who spend all day on computers²⁰. Binocular vision is fundamental for stereopsis and, applying monovision, stereopsis can be seriously compromised²⁴.

Regarding corneal inlay influence on stereopsis, it has not been widely studied²⁵ but the results of the experiment realized by Fernández *et al.* 2013 showed that a small aperture as a corneal inlay, can produce similar values of stereoacuity to those attained only under photopic conditions²⁴. These results are not the same under scotopic situations.

Has also been shown that multifocality achieved through contact lenses, sophisticated spectacles, corneal correction or intraocular implants reduces stereoacuity, although it is vaguely better than with monovision²⁶. 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 accommodation²⁷.

Surgical corneal presbyopic correction attempts to create a bifocal cornea, but this procedure carries risks of scarring, night vision problems and vision loss⁹, in addition to loss of binocularity and stereopsis²⁰. The same happens with lenticular procedures in addition to the risks of night vision problems, glare, halos, and endophthalmitis²⁸. Besides accommodating implants theoretically could have reduced effects on binocularity and stereopsis, all these procedures are quite invasive, they may be more appropriate for cataract patients²⁹.

Patients under pharmacological treatment recovered both distance and near visual acuity, as proved in this study. Maintaining binocular vision is essential for stereopsis. Moreover, we can observe improvement of stereopsis in the patients treated with the eye drop. This enhancement can be observed as long as the effect on visual acuity. Among the different treatments for presbyopia available, the relevance of the results is evaluated in relation to a range of outcomes, where optical treatment with eyeglasses and pharmacological treatment achieved to reestablish stereopsis. This point is essential when it is proven that a reduced range of stereopsis has a negative influence on the ability to perform several tasks, and can lead to an increase in trouble relating in the real world. The diminution in stereoacuity affects performance in complex spatial-motor activities, resulting in difficulties in ordinary life.

Conclusion

Finally, in a recent publication, the presented treatment has shown efficacy and safety in an eight-year retrospective study³⁰. In the present work, this pharmacological treatment proved to ameliorate stereopsis as well as optical treatment taking into account that both methods conserve binocularity, necessarily condition for stereopsis, in contraposition with other strategies that intend to correct presbyopia. Taken together, these observations demonstrate that pharmaco-

logical treatment for presbyopia not only reestablished near and distance visual acuity but restored stereopsis.

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