An Investigation in Change of Depth of Focus with Constriction of the Pupil.

«Διερεύνηση της αύξησης του βάθους όρασης με τη μύση της κόρης»

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June 2020

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Abstract

The onset of presbyopia at the age of 40 and the continual decline in the amplitude of accommodation until the age of 55 has always led mid-age people to face several problems regarding tasks that acquire working at near distances. Although treating presbyopia has always been an epicenter of clinical studies with numerous approaches, new actions in the scientific community aim to make the “old” eye young again. Therefore, barring traditional approaches in correcting presbyopia, such as spectacles, contact lenses and surgical techniques, a new viewpoint has gained interest which indicates the use of a commercially ophthalmic miotic drug in order to increase Depth-of-Focus (DOF) by decreasing the pupil size. As pupil size is responsible for the amount of light entering the eye, it is also highly relevant to the potential success of many methods for improving the vision of presbyopes.

The work conducted in this thesis is a pilot study, in which a drop of 1% pilocarpine (miotic drug) was used in the non-dominant eye of 10 presbyopic subjects who underwent a range of measurements to assess any advantages in visual performance monocularly, and binocularly. Near and distance Visual Acuity (using logMAR charts), defocus curves (using a Landolt C optotype) and reading performance (reading acuity and reading speed) were evaluated, before and after instillation of pilocarpine, to determine if there were any benefitable changes throughout this process. Furthermore, Near Activity Visual Questionnaire (NAVQ) was used to subjectively asses participants’ satisfaction concerning near activity during the study.

Reducing pupil diameter, using 1% pilocarpine in the non-dominant eye, showed a minor, non-statistically significant, improvement in near acuity, while keeping good distance visual acuity. Defocus curves showed some enhancement of DOF, by improving acuity for specific near vergences. Furthermore, a significant improvement in some reading performance metrics was found after pilocarpine instillation, especially for binocular reading speed.

Taking into account the outcome of this work, there are positive signs that the current approach may be of importance for future applications and further research in the correction of presbyopia, specifically in early presbyopes.

Keywords: depth of focus, presbyopia, pupil size, reading performance, pilocarpine

Περίληψη

Η έναρξη της πρεσβυωπίας στην ηλικία των 40 ετών και η συνεχής μείωση του εύρους προσαρμογής έως την ηλικία των 55 ετών δημιουργούσαν ενίοτε στα άτομα μεσαίας ηλικίας πολλά προβλήματα σχετικά με καθημερινές ενασχολήσεις που απαιτούν εργασία σε κοντινές αποστάσεις. Παρόλο που η θεραπεία της πρεσβυωπίας υπήρξε ανέκαθεν επίκεντρο κλινικών μελετών μέσω πολλών προσεγγίσεων, νέες δράσεις στην επιστημονική κοινότητα έχουν ως στόχο να κάνουν το «παλιό» μάτι νέο ξανά. Επομένως, εκτός τις παραδοσιακές προσεγγίσεις για τη διόρθωση της πρεσβυωπίας, όπως γυαλιά, φακοί επαφής και χειρουργικές τεχνικές, μια νέα προσέγγιση αφορά τη χρήση οφθαλμικών σταγόνων (πιλοκαρπίνη) με σκοπό να μειωθεί η διάμετρος της κόρης έτσι ώστε να επιτευχθεί αύξηση του βάθους εστίασης (Depth-of-Focus, DOF). Καθώς το μέγεθος της κόρης είναι υπεύθυνο για την ποσότητα φωτός που εισέρχεται στο μάτι, παίζει σημαντικό ρόλο την πιθανή επιτυχία πολλών μεθόδων που χρησιμοποιούνται σήμερα για τη βελτίωση της όρασης των πρεσβυώπων.

Η παρούσα εργασία, που πραγματοποιήθηκε στα πλαίσια του μεταπτυχιακού προγράμματος «Οπτική και Όραση», αποτελεί μια κλινική μελέτη, όπου χρησιμοποιήθηκε μια σταγόνα 1% πιλοκαρπίνης στο μη κυρίαρχο οφθαλμό 10 πρεσβυώπων οι οποίοι υπεβλήθησαν σε διάφορες μετρήσεις αξιολόγησης της όρασής τους πριν και μετά την ενστάλαξη πιλοκαρπίνης. Οι μετρήσεις αυτές αφορούσαν την καταγραφή της οπτικής οξύτητας μακριά και κοντά με χρήση πινάκων logMAR, την επίδραση της θόλωσης στην οξύτητα (defocus curves) με τη χρήση οπτότυπου Landolt C, και την αξιολόγηση της επίδοσης ανάγνωσης (οξύτητα και ταχύτητα ανάγνωσης), πριν και μετά την ενστάλαξη της πιλοκαρπίνης για να προσδιοριστεί εάν υπήρχαν ωφέλιμες αλλαγές στην κοντινή όραση. Επιπλέον, χρησιμοποιήθηκε ειδικά διαμορφωμένο ερωτηματολόγιο Near Activity Visual Questionnaire (NAVQ) για να υπολογίσει υποκειμενικά την ικανοποίηση των συμμετεχόντων σχετικά με την κοντινή τους όραση κατά τη διάρκεια της μελέτης.

Η μείωση της διαμέτρου της κόρης με τη χρήση 1% πιλοκαρπίνης στον μη κυρίαρχο οφθαλμό, έδειξε μια μικρή, αλλά μη στατιστικά σημαντική, βελτίωση στην κοντινή οπτική οξύτητα, διατηρώντας παράλληλα καλή οξύτητα για μακριά. Οι defocus curves έδειξαν βελτίωση της οξύτητας σε συγκεκριμένες αποστάσεις. Επιπλέον, κάποια βελτίωση παρατηρήθηκε στις μετρήσεις απόδοσης ανάγνωσης, μετά την ενστάλαξη της πιλοκαρπίνης, ειδικά για τη διόφθαλμη ταχύτητα ανάγνωσης.

Λαμβάνοντας υπόψη το αποτέλεσμα αυτής της εργασίας, υπάρχουν θετικές ενδείξεις ότι η τρέχουσα προσέγγιση μπορεί να φανεί χρήσιμη σε μελλοντικές εφαρμογές και

περαιτέρω έρευνες για τη διόρθωση της πρεσβυωπίας, ειδικά στους νέους πρεσβύωπες.

Λέξεις-κλειδιά: βάθος εστίασης, πρεσβυωπία, μέγεθος κόρης, απόδοση ανάγνωσης, πιλοκαρπίνη

Acknowledgement

I would like to express my gratitude to my supervisor Sotiris Plainis for his generous support, his valuable and constructive suggestions during the planning and development of this research work. He never stopped encouraging me and always provided his professional guidance and useful recommendations on this project. He guided me effortlessly through this journey by being a great inspiration and making me feel confident.

I could not forget to thank my second supervisor Dr. Shehzad Naroo who was by side during my staying at Aston University for a 3-month period. His generosity, kindness and knowledge were given to me in the most appreciated way.

I would also like to extend my thanks to the staff of Optometry department at Aston University for their help in offering me the resources I needed in running the program.

Mashaaer Basheen, is another important component of this work. She helped me with the progress of the study and also by offering me her warm welcome in Aston. She proved to be an admirable professional and an amazing friend.

Finally, I would like to thank my family for always being by my side, supporting everything I do. They made everything possible.

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Chapter 1

Presbyopia – Treatment spectrum

1. Introduction

The gradual decline with age in the amplitude of accommodation of the crystalline lens has always presented problems in quality of life, leading to presbyopia at the age of mid 40s and almost the complete absence of active accommodation after the age of about 55 years. The symptoms of presbyopia begin around the age of 40 years old and one of the difficulties researchers are facing is that its pathophysiology remains poorly understood. The Helmholtz theory of accommodation is the most widely accepted proposed mechanism, which is based on the assumption that the change in the lens shape is due to the change in the ciliary muscle diameter. During accommodation, the ciliary muscle contracts, relaxing the tension on the zonular fibers, thus resulting in a reduced overall lens diameter. This relaxed zonular state allows the lens to obtain a more spherical shape, which leads to an overall increase in refractive power. There have been many other postulated theories of presbyopia to challenge Helmholtz's theory, yet not one has been universally accepted (Coleman DJ, 2001). Dysfunctional lens syndrome is a term that is gaining more popularity in use for patient education and satisfaction. It is a simple method to describe the continuum of progression associated with age related crystalline lens changes that can help patients achieve a better grasp of their presbyopia.

With a projected prevalence of 2.1 billion people affected worldwide by 2020, as found by Fricke et al., (FRICKE, 2018), and with lifespan getting longer, treatment spectrum of presbyopia has been evolving rapidly creating a huge market for a wide variety of appropriate non-invasive and surgical solutions (Pallikaris I. Plainis S & Charman WN, 2012). Surgical strategies for dealing with presbyopia may be extraocular (corneal or scleral) or intraocular (removal and replacement of the crystalline lens or some type of treatment on the crystalline lens itself). There are however a number of limitations and considerations that have put a barrier to the

widespread acceptance of surgical correction of presbyopia. Each surgical strategy presents its own unique set of advantages and disadvantages. For example, lens removal and replacement with an intraocular lens may not be preferable in a young patient with presbyopia without a refractive error. Similarly, treatment on the crystalline lens may not be a suitable choice for a patient with early signs of cataract (Gil-Cazorla R, 2016). Another innovating possible solution is to use liquid crystal contact lenses that can change focal power by applying a small electric field across the device (lens). However, the design of these contact lenses must be carefully considered as they must be comfortable for the user to wear and able to provide the required change in focal power (usually about +2.00D). Progress towards different lens designs, which includes lens geometry, liquid crystal choices and suitable alignment modes, are reviewed and strongly considered to be the future of presbyopia treatment (James_Morgan_Jones, 2018). At the present time, most of the available approaches cannot match the effectiveness of the youthful accommodation system in providing sharply focused and high-contrast imagery over a wide range of object vergence. As the word presbyopia comes from Greek roots meaning “old eye”, past, current and -especially- future treatments for presbyopia aim to make that old eye young again.

1.1 Small apertures in correcting presbyopia

Contact-lens (CL) methods have figured prominently among the various newer approaches that have been explored for presbyopia correction. Many of the optical concepts pioneered by the CL workers, such as monovision, simultaneous-image lenses and modified monovision, have been transferred to presbyopic refractive surgery techniques and intraocular lens designs. It is, however, surprising to find that, in recent years, variants of the very old technique of using a circular stenopic aperture (‘pinhole’) to increase ocular depth-of-focus (DOF) and hence allow reasonable imagery over a range of object distances in the absence of any active accommodation have re-emerged as serious contenders as aids for presbyopes who have low levels of distance ametropia. This pinhole effect, by which a reduction in

the effective pupil diameter reduces the diameter of the retinal blur circle formed for any error of focus and hence improves the clarity of the associated retinal image, is, of course, widely used in the clinical pinhole test to determine whether reduced acuity is due to refractive error or amblyopia. Theoretically, for an aberration-free eye the DOF would be expected to vary with the inverse square of the pupil diameter but the DOF found in practice is increased by the monochromatic and chromatic aberrations of real eyes, particularly at larger pupil diameters (Charman, 2019).

Early use of pinholes in spectacles.

It is interesting that although the earliest workers recognized that pinholes increased ocular DOF, they felt that stenopaic spectacles and similar devices were of most value for those who suffered from high levels of irregular astigmatism or intraocular scattered light, as a result of such problems as corneal scarring, keratoconus or multiple opacities. Daza de Valdes, in his 1619 'Uso de los Antojos' (The Use of Spectacles) suggested, for example, that his stenopaic spectacles, in which the 'lenses' were opaque disks containing a series of small circular holes across a horizontal diameter, were particularly suitable for albinos.

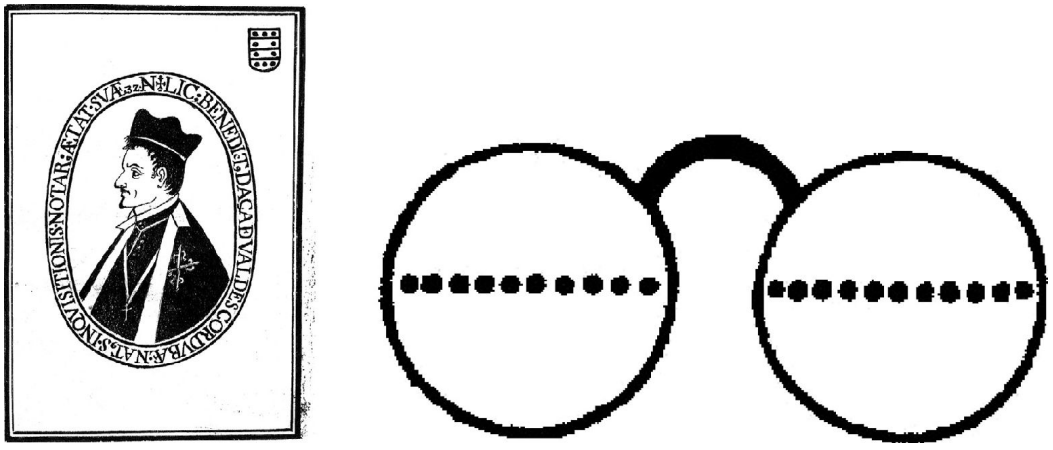


Fig. 1 Daza de Valdes (1591 – ca.1636) and his pinhole spectacles.

Much later, Donders (1884) made similar recommendations, and also advocated pinhole use to improve the acuity of high myopes. He pointed out, however, that pinhole spectacles possessed the disadvantage that they caused a loss of retinal illuminance and visual field, the latter shrinking as the vertex distance increased. Helmholtz summarized the enhancement of DOF associated with viewing through a small aperture by noting that 'A screen with a narrow opening in it may be placed in front of the eye to enable it to get a distinct view of an object for which the eye is not accommodated.

Pinhole contact lenses (CLs) and other developments.

A new approach in the use of pinholes was pioneered by Ziller, working at the Zeiss School, Jena, who in the 1930s designed a glass scleral CL with a pinhole aperture and an opaque periphery, reasoning that DOF would be increased and near vision would be improved. This idea was revived by Freeman, who in 1952 made customized scleral prescription CLs incorporating a colored artificial iris with a small artificial pupil. He suggested that a pupil diameter of 2 mm gave a DOF which was sufficient for most presbyopes while avoiding excessive restriction of the visual field. Field restriction with pinholes is less of a problem with CLs than with spectacle lenses: the artificial pupil is axially much closer to the natural pupil, so that vignetting effects between the artificial and natural pupil are reduced. Pinholes were also among the various other artificial-pupil CLs considered by Wesley (1970). Other opaque shell lenses with small artificial pupils were used by Freeman (1952) in cases of albinism, irregular astigmatism and polycoria. At a later date, following suggestions by Bier (1981) and others, Abadi & Papas (British Contact Lens Assoc. 1987) were able to demonstrate that soft contact lenses of similar basic design could improve contrast sensitivity in tyrosinase-negative albinos, and occasional reports consider cases where opaque soft lenses with pinhole apertures have been helpful in cases of corneal scarring. Quantitative aspects of the vignetting and field restriction that occurs with CLs of this type were investigated theoretically by Carkeet (1998). Curiously, Freeman's work with presbyopes attracted few immediate followers, and it was not acknowledged by Miller and Johnson when they explored pinhole techniques in 1977. Their own valuable study was inspired by the hope that

the method might be applicable to the problems of aphakes, and offer an alternative to the use of high-power positive lenses, with their unwanted bulk, magnification and distortion effects. Miller and Johnson's results, however, had a much wider potential applicability, particularly to the possible role of pinholes in presbyopia correction. Demonstrating that the dioptric range over which acuity was better than 6/12 (20/40, 0.3 logMAR) increased as the pupil diameter was reduced over the range 2.0–0.5 mm, they found that with a 1.5 mm diameter pupil at least 6/12 vision was achieved with up to 3D of refractive blur. They noted that, at best focus, diffractive blur was just noticeable with a 1 mm pupil but not with a 2 mm pupil This agreed with the conclusions of Lebensohn, who found that the pupil diameter which offered the best compromise between maximizing the DOF while minimizing the effects of diffraction was 1.3 mm. Miller and Johnson (Quantification of the pinhole effect 1977) admitted, however, that the use of an artificial pupil which is smaller than the natural pupil has an adverse effect on resolution and other aspects of visual function at low ambient light levels, and that, if the artificial pupil is placed in the spectacle plane, there is a substantial loss in visual field. Like Freeman they found that this field loss was reduced when a 1.5 mm pupil was incorporated in an otherwise opaque soft CL rather than being placed in the spectacle plane, although it was still significant. Importantly, they then confirmed that the visual field was even less affected if a clear soft CL containing only a black annulus (in their study the inner and outer diameters were 1.5 and 4.5 mm) was used instead of a simple pinhole in an otherwise opaque lens. They also suggested that the use of a miotic might yield benefits similar to those of small artificial pupils.

In optics, particularly in relation to film and photography, the depth of field (DOF), also called the focus range or effective focus range, is the distance between the nearest and farthest objects in a scene that appear acceptably sharp. Although a lens can only precisely focus at one distance at a time, the decrease in sharpness is gradual on each side of the focused distance, so that within the DOF, the lack of sharpness is imperceptible under normal viewing conditions. In some cases, it is desirable to have the entire image sharp, so a large DOF is appropriate. In other

cases, a small DOF may be more effective, emphasizing the subject while de-emphasizing the foreground and background.

Precise focus is possible at only one distance; at that distance, a point object will produce a point image. At any other distance, a point object is defocused, and will produce a blur spot shaped like the aperture, which for the purpose of analysis is usually assumed to be circular. When this circular spot is sufficiently small, it is indistinguishable from a point, and appears to be in focus; it is rendered as "acceptably sharp". The diameter of the circle increases with distance from the point of focus; the largest circle that is indistinguishable from a point is known as the “acceptable circle of confusion”, or informally, simply as the “circle of confusion”. The acceptable circle of confusion is influenced by visual acuity, viewing conditions, and the amount by which the image is enlarged. The increase of the circle diameter with defocus is gradual, so the limits of depth of field are not hard boundaries.

For a given subject framing and camera position, the DOF is controlled by the lens aperture diameter, which is usually specified as the f-number, the ratio of lens focal length to aperture diameter. Reducing the aperture diameter (increasing the f-number) increases the DOF because the circle of confusion is shrunk directly and indirectly by reducing the light hitting the outside of the lens which is focused to a different point than light hitting the inside of the lens due to spherical aberration caused by the construction of the lens; however, it also reduces the amount of light transmitted, and increases diffraction, placing a practical limit on the extent to which DOF can be increased by reducing the aperture diameter.

Within the eye, the aperture size is controlled by the pupil which typically changes size based on the lighting conditions but it can be affected by outside influences and drugs.

Pharmacological approaches.

Rather than using some form of artificial pupil, several authors have recently re-explored the idea put forward by Miller & Johnson, of using the small pupils created by topical instillation of suitably-formulated miotic eye drops. Abdelkar

(Improved presbyopic vision with miotics. Eye Contact Lens 2015) demonstrated significant improvements in binocular near acuity when a mixture of carbachol (2.25%) and brimonidine (0.2%) drops was instilled monocularly in the non-dominant eye, the near vision achieved being good enough to allow his emmetropic presbyopes to dispense with their glasses during the working day: no changes in distance acuity occurred. Similar improvements in near vision have been found by later authors, using more complex drug mixtures and binocular drug instillation. Some of these authors postulate that factors other than reduced pupil diameter may contribute to the observed improvement in presbyopic near vision, but as yet no direct evidence for such effects, e.g. in terms of measurable changes in ocular aberrations or partial restoration of objective accommodative changes in ocular power, has been offered. Discomfort following drop instillation was experienced by some patients in some studies and long-term side effects remain to be fully explored. Since the miotic natural pupil provides the aperture stop of the eye, there is no effect on the visual field although, as with artificial pupils, retinal illuminance is reduced.

1.2 Pilocarpine

Currently there is interest in the use of drugs to change the “depth of vision” of the eye to treat progressive loss of accommodation resulting in loss of ability to focus at near distance. It has been proposed that miotic drugs such as pilocarpine (acting to reduce the size of the pupil) may be useful for this application, but to date no definitive studies have been undertaken on their effect on the depth of vision of the eye.

Pilocarpine, a parasympathomimetic, is known to induce miosis and to decrease the intraocular pressure (Krill and Newell, 1964). Pilocarpine belongs to the miotics family of medication. It works by activating cholinergic receptors of the muscarinic type which cause the trabecular meshwork to open and the aqueous humor to drain from the eye. More specifically pilocarpine acts on a subtype of muscarinic receptor (M3) found on the iris sphincter muscle, causing the muscle to contract - resulting in pupil constriction (miosis). Pilocarpine also acts on the ciliary muscle and causes it to contract. When the ciliary muscle contracts, it opens the trabecular meshwork

through increased tension on the scleral spur. This action facilitates the rate that aqueous humor leaves the eye to decrease intraocular pressure. Paradoxically, when pilocarpine induces this ciliary muscle contraction (known as an accommodative spasm) it causes the eye's lens to thicken and move forward within the eye. This movement causes the iris (which is located immediately in front of the lens) to also move forward, narrowing the Anterior chamber angle. Narrowing of the anterior chamber angle increases the risk of increased intraocular pressure (Davies's, n.d.).

It was isolated in 1874 by Hardy and Gerrard and has been used to treat glaucoma for more than 100 years. Pilocarpine is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. It is used to reduce pressure inside the eye and treat dry mouth. As eye drops it is used to manage angle closure glaucoma until surgery can be performed, ocular hypertension, primary open angle glaucoma, and to bring about constriction of the pupil following its dilation. Onset of effects with the drops is typically within an hour and lasts for up to a day. Common side effects of the eye drops may include irritation of the eye, tearing, headache, and blurry vision when used in high dosage (Davies's, n.d.) (Zimmerman T.J, n.d.).

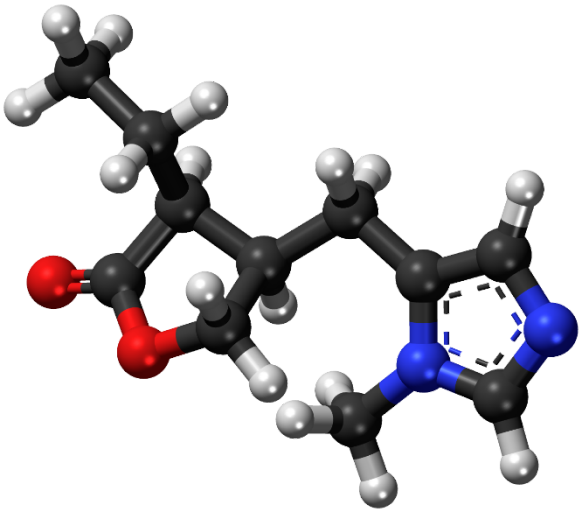


Fig. 2 Pilocarpine chemical structure.

Pilocarpine eye drops are commercially available in concentrations of 1%, 2% and 4%. The advantage of using the low dosage is to minimize any adverse effect such as headache, as it is well known from glaucoma patient experience that pilocarpine causes a dull headache on instillation of the drop (Bartlett and Jaanus, 2007).

Clinical uses of Pilocarpine.

Since pilocarpine stimulates ciliary muscle contraction, it has been therapeutically used for more than a century in the treatment of open-angle glaucoma, reducing intraocular pressure through the enhancement of aqueous outflow (Kanski, 1994). Pilocarpine drops have also been advocated clinically to induce miosis and control glare symptoms in patients who have undergone implantation of phakic intraocular lenses (IOLs) (Ellis, 2001; Maldonado et al., 2006) following cataract extraction. More recently, pilocarpine has been used in trials investigating the efficacy of pseudo-accommodating IOLs in reversing presbyopia (Langenbucher et al., 2003; Findl et al., 2004; Koeppl et al., 2005; Kriechbaum et al., 2005; Findl and Leydolt, 2007; Menapace et al., 2007). Accommodating IOLs are supposed to partially restore accommodation of the human eye, through forward movement of the IOL optics mediated by a contraction of the ciliary muscle (Kuchle et al., 2002; Doane, 2004; Dick, 2005; Findl and Leydolt, 2007). It is now well established that the increase in axial thickness of the natural crystalline lens, as a result of ciliary muscle contraction when a young eye accommodates, is also accompanied by a forward movement of the lens surfaces, which results in a more powerful form (Koeppl et al., 2005; Charman, 2008). Moreover, it has been shown that the ability of the muscle to contract remains almost intact throughout the lifespan (Glasser and Campbell, 1999; Pardue and Sivak, 2000). Pilocarpine is therefore used in pseudophakic eyes to pharmacologically stimulate muscle contraction, in order to objectively evaluate accommodative response. The use of objective methods in assessing the effectiveness of accommodative restoration procedures is essential, since the common subjective clinical measurement of the amplitude of accommodation often overestimates true accommodation, due to the increased depth-of-focus provided by small pupil size (Tucker and Rabie, 1980), or by corneal multifocality (Fukuyama et

al., 1999), residual astigmatism (Huber, 1981) and higher-order ocular aberrations with larger pupils (Rocha et al., 2007). Objective methods have the further advantage that they do not necessitate active co-operation from the patient, which is a pre-requisite in voluntary blur-driven accommodation measurements.

1.3 Surgical approaches

For many years, traditional courses of action to help people with presbyopia have been spectacles and contact lenses, either suggesting monovision or multifocal based solutions. Meanwhile, numerous accommodative and pseudoaccommodative approaches to treat presbyopia surgically have taken action. Each has its own benefits and limitations, and may involve some degree of compromise between the distance and near visual acuities (VA). Accommodative approaches attempt to restore the true, dynamic and continuous range of the defocusing ability of the eye. Pseudoaccommodative approaches provide functional near vision from a variety of non-accommodative factors (Gil-Cazorla R, 2016). Presbyopia's therapeutic options have been employed through corneal, lenticular, and scleral surgical approaches in an effort to either enhance depth of focus or attempt to restore accommodation.

The history of surgical presbyopia treatment has oscillated with numerous promising ideas that have fallen short of success. An early effort included addition of human donor corneal tissue to a patient's host cornea to change the refraction, a procedure called additive refractive keratoplasty. Then, in 1949, we were introduced to Jose Barraquer's first corneal inlay prototype. Created for the treatment of high myopia or aphakia, it was designed from polymethylmethacrylate or flint glass. These early inlays showed initial signs of success in treating the targeted refractive error. However, the abhorrent rates of implant extrusion and corneal necrosis from reactions to the material quickly resulted in these inlays becoming out of favor (Barraquer JI., 1966). Two decades after Barraquer experimented with his initial prototype, the concept was revived with the discovery of more biocompatible materials, like hydrogel. These new materials showed promise in that they were transparent and permeable to fluids and nutrients, which provided some assurance

the corneal tissue would tolerate them. Unfortunately, the majority of these devices were explanted because of the aggressive rates of stromal thinning, melting, haze, inlay decentration and corneal opacification (DP., 1968). Thus, there is a need for a minimally invasive and reversible surgical technique with an easy learning curve for patients aged between 45 and 60 years. This has led to the development of new approaches, based on the use of corneal inlays, which can easily be removed in cases where they do not satisfy the demands of the patient. In the past, the implantation of inlays for presbyopia or hyperopia has been described using flaps or pockets created by mechanical microkeratomes. Recently, the femtosecond laser has been used for the creation of pockets or flaps, thus increasing the precision and allowing the implantation depth and position of the inlay to be customized to the individual patient. (Moarefi, 2017)

1.3.1 Treating the lens

The ultimate goal of cataract extraction and clear lens extraction is to replace the crystalline lens with an intraocular lens (IOL) that simulates the original function of the crystalline lens and provides the patients with a full range of functional vision for all distances. Currently, the available IOLs can be grouped into accommodating (AIOLs) or pseudoaccommodating IOLs (although the mechanism of action of some ‘accommodative lenses’ may be pseudoaccommodative in nature). With pseudoaccommodative multifocal IOLs (MIOLs), the patient has two or three points in focus but primarily perceives only the focused image of interest. Precise biometry, accurate IOL power calculation, good surgical technique as well as patient selection are crucial in achieving the best visual outcome and patient satisfaction (Cazorla_Sunil_Naroo, 2016).

PSEUDOACCOMMODATIVE APPROACHES

- Pseudophakic multifocal intraocular lens.

Multifocal intraocular lenses are used following patients with cataract or in clear lens extraction and excellent clinical out-comes have been reported. However, patient dissatisfaction and secondary procedures, including IOL exchange, can also be significant. Some of the MIOLs are based on multifocal CL designs, however the visual results may defer between them. First, CLs and IOLs are placed in different locations in the eye which results in different plane corrections, and second, the CL moves during the blink versus the stability of the IOL. These differences could lead to different visual outcomes. Complications of theses MIOLs include reduction in quality of vision, especially loss of CS, dysphotopsia, and reduced inter-mediate vision and near vision (Murphy, 2010).

- Refractive MIOLs

Refractive MIOLs have the incorporation of two different powers integrated into two or more typically circular refractive zones. Due to each lens zone having a different effective aperture, the image quality can depend on the pupillary response to light and the accommodation reflex.

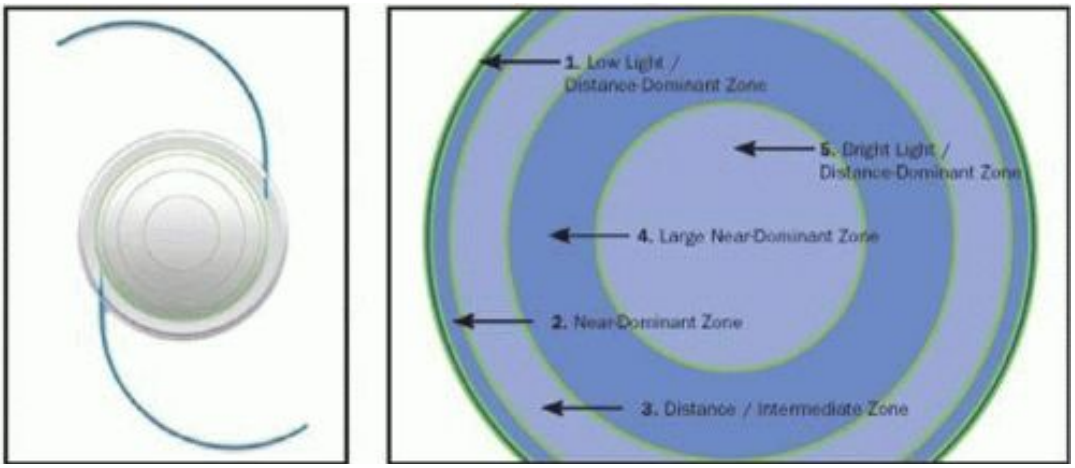


Fig. 3 ReZoom MIOL and its 5 optical zones

The ReZoom (Abbot Medical Optics (AMO), Irvine, California, USA) is a refractive MIOL (the original model being called the ARRAY) and the Food and Drug Administration (FDA) approved it in 2005. It is a three-piece MIOL and has five refractive optical zones; zones 1, 3 and 5 are adjusted for far vision, while zones 2

and 4 are adjusted for near vision. This design gives good distance vision and good intermediate-range vision although the reading performance is variable. Disadvantages of this lens, like many MIOLs, include dysphotopsia.

The M-fl ex, another MIOL, (Rayner IOLs Limited, Hove, UK) is based on a multizoned refractive aspherical optical technology, with either 4 or 5 annular zones (depending on IOL base power) providing +3.00 D or +4.00 D of additional refractive power at the IOL plane (equivalent to +2.25 D or +3.00 D at the spectacle plane). Cezon et al, reported good visual performance and high rate of spectacle independence at 1 year.

Refractive MIOLs appear to be associated with more photic phenomena compared with diffractive MIOLs. Photic phenomena are among the most frequent reasons for patient dissatisfaction following implantation of MIOLs (Murphy, 2010) (Cazorla_Sunil_Naroo, 2016).

- Diffractive MIOLs

These are based on the principle of diffraction, whereby light slows down and changes direction when it encounters an obstacle. These lenses use microscopic steps (diffractive zones) across the lens surface. As light encounters these steps, it is directed towards the distant and near focal points (the amount of light is directly related to the step height as a proportion of wavelength). Diffractive MIOLs can be subdivided into apodised (gradual reduction in diffractive step heights from center to periphery) or non-apodised (uniform height): both categories are designed to reduce the severity of night haloes compared with refractive MIOLs. Examples include the ReSTOR (Alcon Lab, Fort Worth, Texas, USA) (apodised) and Tecnis Multifocal (Abbott Medical Optics, Santa Ana, California, USA) and AT LISA 809 IOL (Carl Zeiss Meditec, Hennigsdorf, Germany) (both non-apodised). Most studies report good and stable distance vision and near vision, leading to low spectacle dependence and high patient satisfaction. Although these designs have good visual

outcomes, their weakest points can be their inability to provide good levels of vision at an intermediate distance and loss of CS.

Aiming to improve intermediate vision, trifocal MIOL designs were introduced in the market: AT Lisa tri 839MP novel design (Carl Zeiss Meditec, Hennigsdorf, Germany), FineVision (PhysIOL SA, Liège, Belgium) and MIOL-Record trifocal IOL (Reper NN, Nizhny Novgorod, Russia). Results reported so far of theses lenses show a significant improvement in uncorrected VA at all distances. The trifocal designs may be the emerging technology in the field of the diffractive IOLs. The prevalence of complications still needs to be assessed with larger clinical studies (Cazorla_Sunil_Naroo, 2016).

- Rotationally asymmetrical MIOLs

All traditional MIOLs are based on the concept of rotational symmetry. Recently, MIOLs with rotational asymmetry were introduced. One such lens, the Lentis MPlus LS-312 (Oculentis GmbH, Berlin, Germany), consists of a single-piece, aspherical surface that is independent of pupil size. Different near additions are available allowing customizations for each individual and can be used with a mix and match philosophy.

Results indicate good distance, intermediate and near VAs with a high level of CS. 59–61 The authors recently conducted a study with the latest version: Lentis Mplus X LS-313 in 34 eyes showing excellent visual performance.

The SBL-3 MIOL (Lenstec, St Petersburg, Florida, USA) is another asymmetrical segmented MIOL that is also designed to improve CS, minimize dysphotopsia and provide good far vision, intermediate vision and near vision. The SBL-3 has a three-dimensional sector-shaped near vision addition with a seamless transition zone between the distance and near segments. Venter et al, recently published a study conducted in 106 eyes showing excellent outcomes.

Rotationally asymmetrical MIOLs seem to provide a good visual outcome at distance vision and near vision with minimal dysphotopsia and retain intermediate vision. The design mini-mises loss of light from splitting of the incoming light. Patients also were

satisfied with their uncorrected near vision. Further studies with larger cohorts and longer follow-up period are necessary.

- Phakic MIOL

Staar (Staar Surgical Company, Monrovia, California) is known to be developing a new multifocal phakic implantable contact lens that would potentially correct ametropia and presbyopia. Ametropia and presbyopia can also be corrected using an anterior chamber phakic MIOL. George Baikoff designed one of the first models and this anterior chamber multifocal design has been marketed under the trade names of Newlife (IOLTECH, SA, La Rochelle, France) and Vivarte Presbyopic (CibaVision, Duluth, Georgia, USA) and provides a single addition of +2.5 D for near vision.

Baikoff et al, also performed the first clinical trial with this type of multifocal IOL in 55 eyes showing that this IOL was effective and gave good predictability. Alio and Mulet, in another pilot study with a multifocal phakic IOL prototype (AMO, Irvine, California, USA), also showed good results. However, the complications reported by these anterior phakic IOLs include endophthalmitis, surgically induced astigmatism, corneal endothelial cell loss, pupil distortion, chronic uveitis, pupillary block glaucoma, pigment dispersion syndrome and cataracts. (Cazorla_Sunil_Naroo, 2016)

ACCOMMODATIVE APPROACHES

There are many different concepts and designs for Accommodative IOL (AIOLs) including mouldable gels, fluid displacement and flexible haptics. These IOLs are designed to use ciliary muscle contraction, capsular bag elasticity and changes in vitreous cavity pressure to induce change or movement in the shape of the IOL to produce an optical change in the eye based on the optic-shift concept, that is, on the axial movement of the optic resulting from action of the ciliary muscle. A hinge between the optic and haptics allows the lens to move forward as the eye focuses on

near objects and backward as the eye focuses on distant objects, thereby increasing the dioptrical power of the pseudophakic eye.

- Synchrony IOL

Though not yet approved in the United States, the Synchrony Dual Optic Accommodating IOL (Abbott Medical Optics) is a single-piece, foldable, accommodating lens with two separate optics that are connected by a spring system. It's designed to mimic the accommodating ability of the natural lens. Two-year follow-up data in patients who had bilateral implantation found that both distance vision and reading speed actually increased at two years compared to one-year post-op. Specifically, best-corrected distance vision was 20/28 at one year and 20/23 at two years post-operatively. Reading speed was statistically significantly improved at two years, as was mean reading acuity (0.07 logMAR vs. 0.15 logMAR) and critical print size (0.28 logMAR vs. 0.48 logMAR).

Fig. 4 The Synchrony IOL accommodates by means of two separate optics.

- PresbyLASIK (*Multifocal Surgery)*

This technique employs an excimer laser to create a multifocal ablation pattern on the cornea to correct the patient's distance or near vision, depending on the approach. In the center-distance approach (also called peripheral PresbyLASIK), the

ablation pattern creates an aspheric cornea that is flatter in the center for good distance vision and steeper away from the center for good intermediate and near vision. Using this peripheral approach in 44 eyes (22 patients) with presbyopia and low to moderate hyperopia, investigators reported that the mean uncorrected distance vision was about 20/20 and the mean uncorrected near vision was about 20/25 at six months postop. In the center-near approach (also called central PresbyLASIK), the ablation steepens the central cornea for good near vision and flattens the mid-peripheral cornea for clear intermediate and distance vision. Six-month post-op data from an early study found that 64% of patients achieved uncorrected distance vision of 20/20 or better and 72% of patients achieved uncorrected near vision of 20/40 or better. However, more than one-fourth of patients lost a maximum of two lines of best spectacle-corrected visual acuity. According to the reported results, both central and peripheral PresbyLASIK achieve adequate spectacle independence for both far and near. However, peripheral PresbyLASIK requires a neuroadaptation process, which may last as long as a year. Patient selection is also extremely important for either approach.

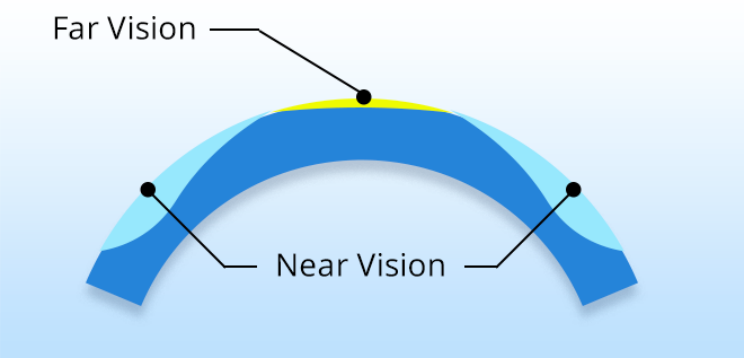


Fig. 5 The center-distance approach (also called peripheral PresbyLASIK).

- Femtosecond lentotomy (*Softening the Lens)*

A corollary to the Helmholtz theory of accommodation is that presbyopia occurs due to the hardening of the lens. So, if the presbyopic lens could be softened or its

flexibility improved, then accommodation would be restored. This is the concept behind the use of femtosecond laser to make micro cuts inside the crystalline lens (lentotomy) to increase or even re-establish the flexibility of the lens, and eliminate presbyopia. (This assumes that the ciliary body and lens capsule stay functional in old age). A German laser company, Laser Zentrum Hannover, has developed a “steering wheel” cutting pattern to restore elasticity of the lens. Using a femtosecond laser, this pattern creates “gliding planes” in all directions, but leaves the lens capsule intact and the central field of view unaffected. So far, tests on enucleated pig eyes and human donor lenses have shown that femtosecond lentotomy did increase the flexibility of the crystalline lens.

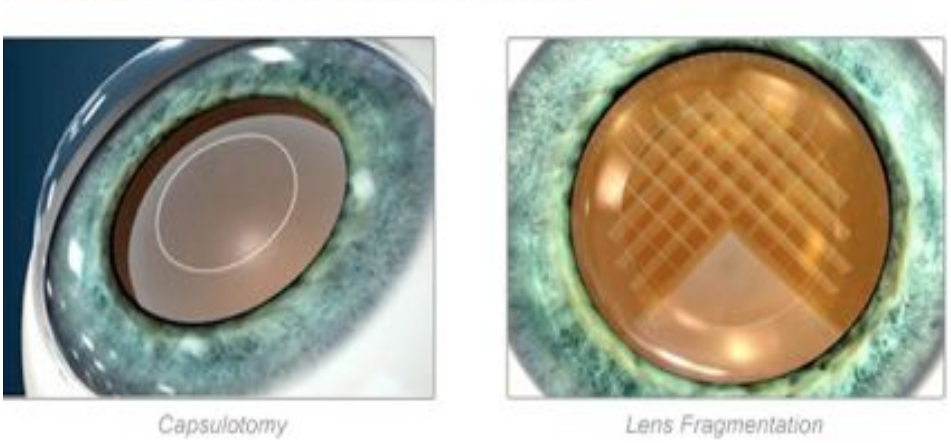


Fig. 6 The capsulotomy and next the lens fragmentation (lentotomy) softening pattern.

- Lens refilling.

The lens filling techniques have been under investigation for years. It consists of replacing the lens with a soft gel that would allow modifying the shape for accommodation. The Medennium SmartLens IOL (Medennium, Irvine, California, USA) is a ‘smart’ hydrophobic acrylic material with unique thermodynamic property. When implanted into the capsular bag, the body’s temperature causes the material to transform into a gel-like polymer and take the shape of the natural lens. To the general knowledge no data has been published yet. It should be noted that objective

measurement of the accommodative capability of AIOLs is extremely difficult to obtain.

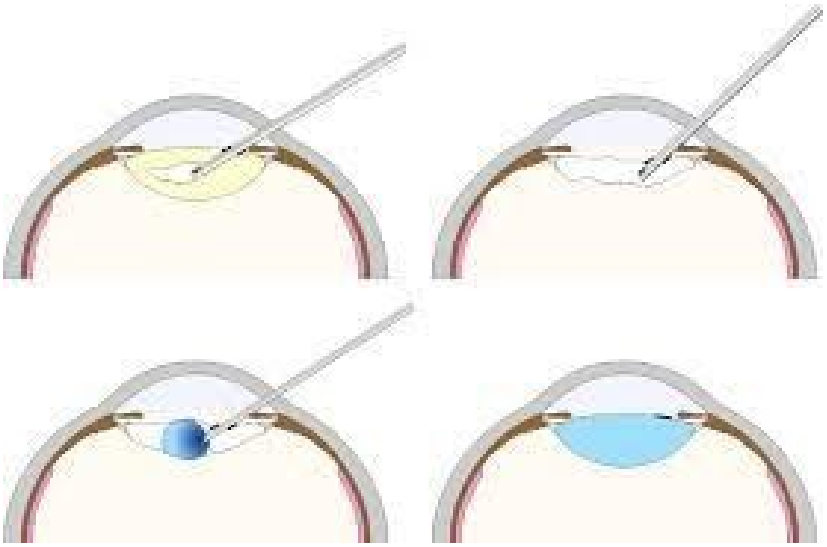


Fig.6 Illustration of the lens refilling principle

On the other hand, replacement of the lens with an IOL is the standard treatment for cataract surgery. But, even an accommodating IOL is made of a harder material than the natural lens cortex. So, it only makes sense to replace the sclerotic lens with a malleable or even liquid material, such as a soft polymer, to restore accommodation. That's the focus of several investigations. But a number of hurdles have to be overcome before this procedure can be called a success. For example, in a study (Murphy, 2010) of nine rhesus monkeys whose lenses were refilled with silicone polymer, the maximum accommodative amplitude of the surgically treated eyes was only about 40% (6.30D). After 37 weeks of follow-up, the accommodative amplitude decreased to almost zero in three monkeys. Yet, in two other monkeys, the accommodative amplitude remained stable at about 4.00D during the follow-up period. (An accommodative amplitude of approximately 3.00D to 4.00D in presbyopic human eyes would be sufficient for reading purposes, the investigators wrote.) Additional hurdles to overcome include defining the exact type of polymer to be used, the correct amount to be used, and halting rapidly developing posterior capsule opacification.

1.3.2 Treating the cornea

Intracorneal Inlays

Refractive surgery reached a milestone in innovation with the development and introduction of the new generation of corneal inlays for the treatment of presbyopia. Using newer materials with enhanced biocompatibility alongside advances in technology (i.e., the Femtosecond Laser) has raised the ceiling of successful outcomes for our patients. Additional features of the inlays that have amplified their success include their thin design, small diameters, high nutrient and fluid permeability, and the capacity to be implanted relatively deep within the stromal tissue. Previous large and impermeable inlays disrupted the cornea's natural state by hindering natural metabolic functions. Depth of placement varies for each inlay design, given the different mate-rials and mechanisms each provides. Inlays designed to utilize a small aperture or a different index of refraction are usually implanted deeper to avoid unintended changes in surface curvature, whereas inlays designed to deliberately modify the surface curvature are placed more superficially. It should be noted that there are inherent risks with surgical approaches, and one should consider balancing the positives and negatives between comfort and safety when discussing the surgical treatment of presbyopia with corneal inlays (Amir M, 2017).

Another advantage of these corneal inlays is that they are additive and do not actually remove any tissue, which preserves the capacity for reversal/removal or future options of any other type of presbyopia correction. This is true only when there are no complications of corneal scarring, opacification, stromal thinning, or melting, which may occur in the aftermath of corneal surgery. After designated implantation in the non-dominant eye, inlay procedures can be combined with other refractive procedures. There tend to be fewer risks associated with the corneal inlay surgery com-pared to intraocular surgery, as these procedures are all limited to the cornea. With monovision, there is a one-to-one loss in distance vision for every line gained in

near vision. However, with corneal inlays, the majority of patients lose only 1 or no lines of distance vision for about a line improvement in near vision.

The femtosecond laser offers consistency in terms of creating a more dependable flap or stromal pocket, which in turn provides improved accuracy of implantation depth and inlay centration. A major advantage of the pocket technique, compared to the flap technique, is the salvation of more peripheral corneal nerves. This defends against the diminished corneal sensation associated with flap creation, which in turn allows for a reduced incidence of dry eyes and a potential faster visual recovery. Due to less tissue alteration, a pocket procedure is theoretically more biomechanically stable versus a lamellar procedure. Pockets are also less likely cause striae, which can be seen with lamellar flaps. However, lamellar flaps do have scenarios where they are more appealing than a pocket creation such as when an inlay is placed in combination with an excimer laser procedure to attain ametropia. The flap procedure is preferred as it allows for easy access in case the inlay is decentered or requires explanation. Another option includes the creation of a stromal pocket roughly 100–120 microns deeper to a previous or sequential LASIK flap if refractive surgery is combined with the inlay at that time.

Three different types of inlays with 3 different principles of action are currently available for the corneal compensation of presbyopia. The Flexivue Microlens (Presbia, Los Angeles, CA) is a small, transparent, hydrophilic lens that acts by changing the refractive index of the central cornea. The KAMRA (formerly ACI-7000; AcuFocus, Inc, Irvine, CA) is a small-diameter diaphragm with a central hole that increases the DOF. The Vue+ (formerly PresbyLens; Revision Optics, Lake Forest, CA) is a small, hydrogel inlay that changes the anterior curvature of the central cornea. All of these inlays are usually implanted monocularly in the non-dominant eye of natural or postoperative emmetropic, presbyopes (Pallikaris I. Plainis S & Charman WN, 2012).

Flexivue Microlens	KAMRA	Raindrop (formerly Vue+)

Procedure	Modified monovision	Modified monovision	Modified monovision
Principle of action	Changes of Rx index	Increase central DOF	Changes anterior corneal curvature
Surgery	Pocket	Flap or Pocket	Flap
Stromal depth (µm)	280 to 300	>200	120
Biocompatible	Yes	Yes	Yes
Inlay thickness (µm)	15 to 20	10	20 to 40
Diameter	3.2 mm	3.8 mm	2 mm
Nutrient flow	Yes (hydrogel based + central hole)	Yes (central hole + micropores)	Yes (hydrogel permeable material)
Transparency	Yes	No	Yes
FDA Approved	No (in clinical trials)	No (in clinical trials)	No (in clinical trials)
CE Mark	Yes	Yes	Yes

Table 1. Summary table of current corneal inlays for presbyopia.

- Flexivue Microlens

The Flexivue Microlens is an intracorneal bifocal lens implant that is about 3mm in diameter, less than 20µm thick, and made of a hydrophilic polymer. It is implanted in the nondominant eye, inserted into a pocket within the stroma created by a femtosecond laser. The central zone of the lens has no refractive power, while the periphery has a positive add for near vision. It is designed to correct between 2.50D and 3.50D of presbyopia, but can be removed if the patient's prescription changes.

Investigators reported one-year results at the American Academy of Ophthalmology's annual meeting in October (Murphy, 2010). In 15 eyes, mean baseline near-vision acuity was 20/50. By the third month post-op—and for the remainder of the full year of follow-up—it improved to 20/25. In the implanted eye, mean uncorrected distance-vision acuity dropped from 20/20 at baseline to 20/40 during the first month, and then recovered to 20/30 at six months. All of the patients reported that their uncorrected near vision after the procedure was good or excellent, and 92% had stopped all use of reading glasses. "Intracorneal lenses for the correction of presbyopia using a femtosecond laser seems to be a safe and effective method to correct presbyopia in patients aged between 45 to 55 years old—a target group that is considered too old for refractive laser surgery and too young for clear lens extraction," investigators wrote. The Flexivue Microlens obtained the CE Mark in Europe, but is not approved in the U.S.

- KAMRA inlay

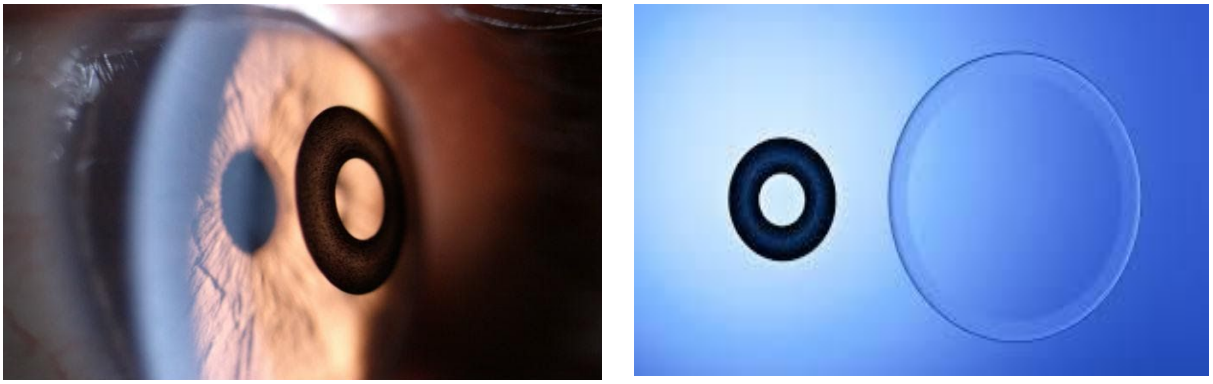


Fig. 7 KAMRA inlay on the eye (left), KAMRA compared to the size of a soft contact lens (right)

Another inlay method which has been studied in great detail is the use of small-aperture optics to increase the depth of focus based on the pinhole effect. This commercially available inlay is known as the KAMRA™ inlay (AcuFocus Inc., Irvine, CA, USA).

The KAMRA design (ACI7000PDT) consists of a 3.8 mm diameter microperforated (8,400 holes 5–11 μm in diameter) tinted disc with 1.6 mm central aperture at 6 μm thick and is made of polyvinylidene fluoride and carbon nanoparticles. Figure 1 shows the size of the KAMRA inlay compared to a 14 mm soft contact lens. The inlay is designed to be inserted in the line if sight of the nondominant eye and implanted in a femto-laser created corneal lamellar pocket at least 220 μm deep. Figure 8 shows a schematic of the inlay design.

The inlay is designed to allow light to enter through the central aperture, thus reducing retinal image blur and increasing depth of focus to allow increased near and intermediate visual acuity. As the inlay does not split light between different focal points, this allows the patient to maintain binocular summation. Figure 7 (left) shows the inlay in situ in a patient's cornea.

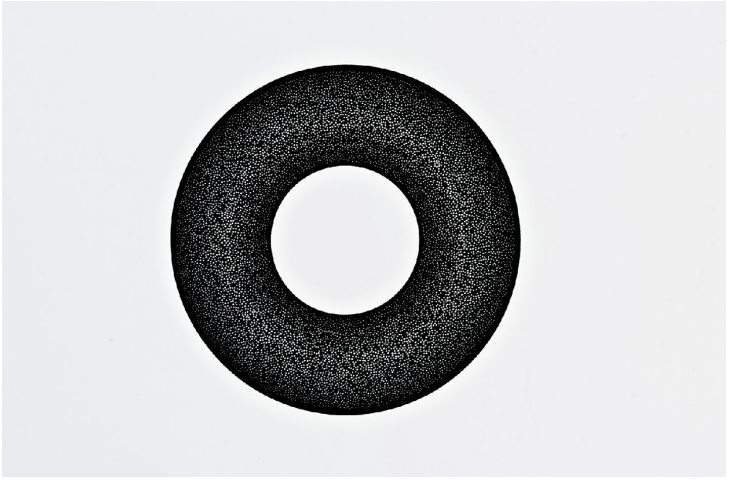


Fig. 8 A schematic of the KAMRA inlay design.

Given that this is an additive procedure (i.e., no corneal tissue is removed), it can be combined with refractive laser vision correction procedures where the eyes are made emmetropic – here the inlay is situated in a lamellar pocket at least 100 μm beneath the initial laser in situ keratomileusis (LASIK) flap. Further, it can be implanted in previously pseudophakic eyes, which has been shown, albeit in a few cases, to produce a significant improvement in near acuity without affecting distance acuity. Based on an eye model, it has been suggested that the best depth of focus is

achieved where the dominant eye is made plano and the nondominant eye is made myopic (-0.75 to -1.00 D) (*Tabernero J, Artal P. 2012)*.

Clinical performance

The efficacy of the KAMRA inlay has been investigated in several studies, albeit in case series where pre- and postoperative measures were compared rather than case-control clinical studies. Nonetheless, all have reported significant improvements in near visual acuity following implantation. However, it should be borne in mind by the reader that all currently published studies are company sponsored (AcuFocus). (Naroo, 2016)

The KAMRA inlay appears to be a safe and effective clinical procedure for the treatment of presbyopia, where significant improvement in near and intermediate visual acuity and function has been reported in several large and long-term follow-up studies. Although distance visual acuity has been compromised in some patients, the reductions were not clinically significant. Iron deposits within the corneal epithelium have been observed, but these are not considered to affect vision, and the incidence has reduced with improvements in surgical methods and the inlay design itself. Further studies with the latest KAMRA inlay are required to establish the longer-term safety and clinical stability of visual acuity.

- Raindrop (formerly Vue+ inlay).

The Raindrop corneal implant, formerly called Vue+ inlay and PresbyLens (ReVision Optics), recently completed Phase I of its FDA clinical trial. (Its CE approved in Europe). Made of a proprietary hydrogel polymer, the Vue+ implant is 2mm in diameter, extremely thin and designed to fit beneath a corneal flap in the non-dominant eye. The implant is designed to steepen the central cornea. When the pupil constricts during an accommodative response, the inlay creates pseudo-accommodation to improve near and intermediate vision.

Results at six months post-op found that near vision improved to 20/25 or better in all the patients, with 86% percent seeing 20/20 or better, compared with a mean of 20/60 near vision at baseline. Mean uncorrected intermediate acuity was 20/25 at six months. There was a trade-off in distance vision, though, which decreased to 20/40 at worst. However, 72% of patients achieved 20/30 or better at distance. (Murphy, 2010)

Other Corneal approaches

- IntraCor.

The IntraCor procedure is similar to PresbyLASIK, but employs a femtosecond laser to remove tissue only in the stroma, leaving the corneal epithelium and Bowman's membrane intact. Because no corneal incision is required, the IntraCor procedure maintains the structural integrity of the cornea, which promotes wound healing and greatly minimizes the risk of infection. For this procedure, the femtosecond laser creates an intrastromal ablation, forming consecutive rings. These intrastromal ring cuts reshape the cornea and redistribute the biomechanical forces, which results in a change in corneal refraction. Recent results of 25 patients (mean age of 56) showed improvement in near-vision acuity from about 20/100 at baseline to about 20/30 at two years post-op. Most patients had gained five to six lines of uncorrected near acuity on a standard chart relative to baseline, allowing them to read newspapers held at a normal distance without reading glasses. Intermediate vision was unchanged. However, the procedure does induce a degree of myopia for distance vision. (Murphy, 2010)

1.3.3 Treating the sclera

Extraocular approaches have been developed based on Schachar's theory. This model states that accommodation results of an increase of zonular traction at the lens equator to increase the lens diameter, therefore, presbyopia occurs as a result

of increased lens growth causing a reduction in the space between the lens and the ciliary body (circumlenticular space), such that upon contraction the zonules can no longer exert their effect on the lens due to a loss of tension. MRI studies have shown that the circumlenticular space decreases with age as a result of the inward movement of the ciliary muscle ring that occurs with advancing age and an increase of the lens thickness. However, goniovideography, infrared photography and MRI studies have shown that the lens decreases in diameter and surface area with accommodation. Despite the controversy of this theory, Schachar postulated that expanding the dimensions of the overlying scleral wall by pulling the ciliary muscle away from the equatorial edge of the lens, would reverse the process of presbyopia and increase accommodative amplitude. LaserACE (Ace Vision Group, Silver Lake, Ohio, USA) and VisAbility Implant System surgery Scleral Implants (Refocus Group, Dallas, Texas, USA) were originally developed on the basis of this theory but the actual mechanism of action is still under investigation (Cazorla_Sunil_Naroo, 2016).

- Laser-assisted presbyopia reversal

Laser assisted presbyopia reversal aims to restore dynamic accommodation increasing pliability in the sclera and net forces of the ciliary muscles on the lens facilitating accommodation. The postulated mechanism of action of laser assisted presbyopia reversal is to decrease ocular rigidity. The procedure is per-formed using a handheld fibre-optic handpiece that delivers pulses of an erbium-YAG laser ablating a diamond matrix pattern of nine laser spots into each oblique quadrant of the sclera. These are presumed to decrease the distance between the ora serrata and the scleral spur, restore the anatomical relation-ships of the system and free the ciliary muscle to contract normally. The spots delivered in a diamond matrix pattern of nine laser spots into each oblique quadrant. The results so far (in 134 eyes of 67 patients after 18 months follow-up) are promising. Hipsley reported restoration of 1.25–1.75 D of objective accommodation, which remained stable through 18 months in initial results (2011 ASCRS meeting).

- Scleral expansion bands

Scleral expansion band surgery for the treatment for presbyopia is based on the model of accommodation theorized by Schachar. Scleral expansion bands have therefore been used for this purpose, but previous studies have demonstrated mixed results and have demonstrated limited success with temporary improvement in amplitude of accommodation.83–85 Most recently, Refocus group has developed The VisAbility Implant System surgery scleral implants. The technique consists of implanting four prostheses (size of a grain of rice) within elongated pockets in the sclera. The prostheses are thought to exert traction on the sclera in the region overlying the ciliary body which expands the sclera and the underlying ciliary body: thus, restoring the effective working distance of the ciliary muscle and increasing the amplitude of accommodation. The actual surgical technique has evolved markedly from the initial use of manual diamond blade to the current use of disposable scleratome improving consider-ably the accuracy of tunnel creation. Furthermore, the original implant was a one-piece device, which was pushed into place and was difficult to thread through the tunnel. This one-single piece had a tendency to slip out of the tunnel over the long term resulting in a return or regression of patients' preoperative near vision. Nowadays, the implant is a two-piece locking implant that pre-vents the implanted device from slipping out. Currently, Refocus group is conducting an FDA clinical trial. (Cazorla_Sunil_Naroo, 2016)

Chapter 2

An Investigation of Change in Depth of Vision with Constriction of the Pupil.

2. Methods and Results

Aim

Aim of this study is to address the effect of pilocarpine drops regarding changes in depth of focus, pupil size, visual acuity and reading performance metrics.

2.1 Subjects and methods

Ten participants, 5 males and 5 females, were recruited during a period of 3 months. Subjects' age ranged from 41 to 67 years (mean 52 ± 9). They were all English native speakers. Refractive error ranged between +4.00 to -3.00 (see table 2).

Subjects	Gender	Age (yrs.)	Spherical Equivalent R/L (D)
No1	M	50	+0.25/plano
No3	F	45	-1.00/-1.00
No4	M	51	+4.00/plano
No5	M	52	-1.50/-3.25
No6	M	51	+0.50/+0.50
No7	F	41	-3.00/-3.00
No8	F	67	+1.00/+1.00
No9	M	58	+3.00/+3.50
No10	F	66	+0.50/+1.00
No11	F	41	+0.25/+0.25

Table 2 Demographics of the participants.

Exclusion criteria included those with ocular diseases or underwent intraocular surgery, use of medication that may influence the cognitive ability and presence of binocular vision anomalies and reading disorder (e.g. dyslexia). Also, exclusion criteria included subjects with iritis or pupillary block glaucoma, diabetic or hypertensive with clinical evidence of retinal pathology, those with macular degenerative pathology.

Ethical approval was obtained from Aston University Ethical Committee and all the subjects gave their consent to participate in the study. General health history and ocular history were recorded. Ocular surface slit lamp examinations were performed to all participants to ensure the absence of any inflammation before participation in the study.

Procedure

Drops of 1% pilocarpine were instilled in participants' non-dominant eyes to evaluate its effect on the pupil and the depth of focus after 1 hour of instillation. Dominant eye was determined by the eye used for sighting when subjects looked at a distant target through a ring hole held in both hands and with both eyes open. There were 6 subjects with right eye dominance and 4 with left eye dominance.

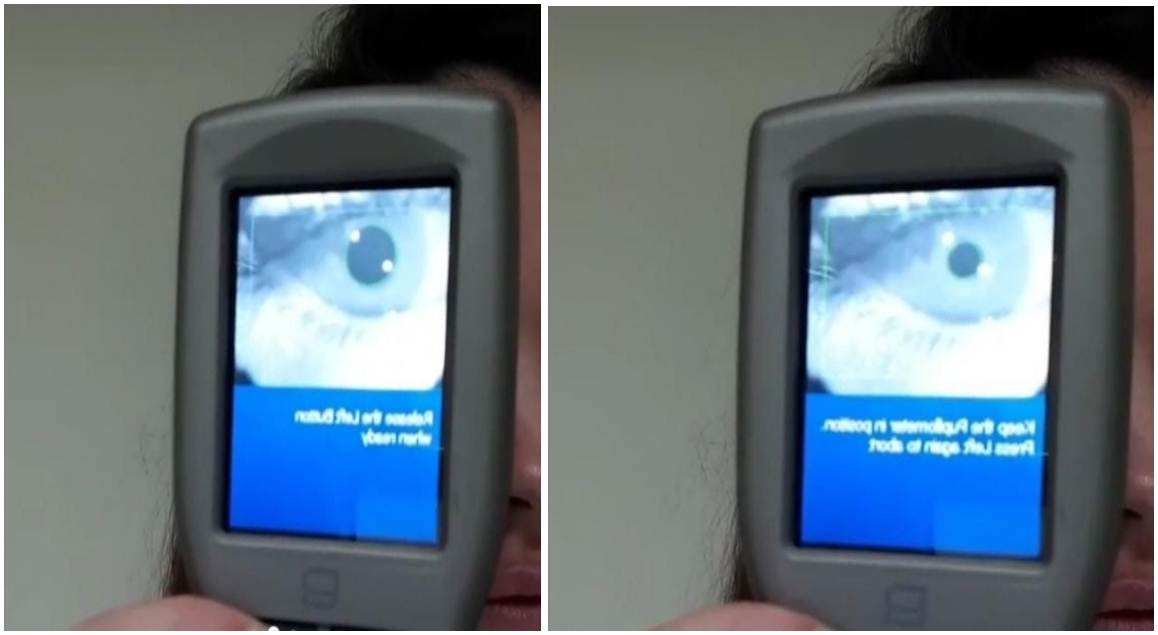
Intraocular pressure (IOP)

Intraocular pressure (IOP) was recorded for each eye before and after installation of pilocarpine using a non-contact tonometer (Reichert® 7CR Auto Tonometer, airpuff). Three measurements were taken for each eye, giving more reliable average IOP values. It has been found that the non-contact tonometer provides results comparable to those of the gold standard (Goldman Applanation Tonometer) (Yilmaz et al., 2014).

Pupil size

A NeurOptics VIP-300 pupilometer (NeurOptics, Inc.) was used to measure the pupil size before and after instillation of pilocarpine drop according to the company instructions. This pupilometer, hand-held infrared, uses a monocular occlusion and

objectively measures the maximum pupil diameter before constriction and minimum pupil diameter at peak constriction at different background illumination. Mean and standard deviation of the maximum and minimum pupil diameters were calculated for both, before and after pilocarpine installation.



(a) (b)

Fig. 9 (a) maximum pupil diameter measurement, (b) minimum pupil diameter measurement

Visual acuity

Distance visual acuity was measured monocularly and binocularly with best correction (BCVA) and without (UCVA) the distance correction using standardized an Early Treatment Diabetic Retinopathy Study (ETDRS) chart displayed by software CSO vision chart v2.6.0 on an LCD screen at a distance of 4m. Near visual acuity was measured monocularly for each eye and binocularly with best correction and without near correction using ETDRS near vision chart (Precision Vision) at 40cm.

Reading performance

Reading performance was evaluated using test charts in English language: the Radner reading chart was used in this study. To ensure fluency in the English language, which may affect reading performance measurements results, all the

participants were native English speakers. The Radner reading chart consists of 14 sentences with 14 words per sentence presented in three lines with controlled position of the words and equal number of characters (Fig.10). The print sizes in the Radner chart range from +1.1 to -0.2 logMAR and was arranged in logarithmic progression. To avoid repetitions during the test, Radner reading test has three different charts. The reading test charts were presented on a reading stand at a distance of 40cm determined by using a centimeter ruler. The luminance from all the reading test charts was 120 cd/m².

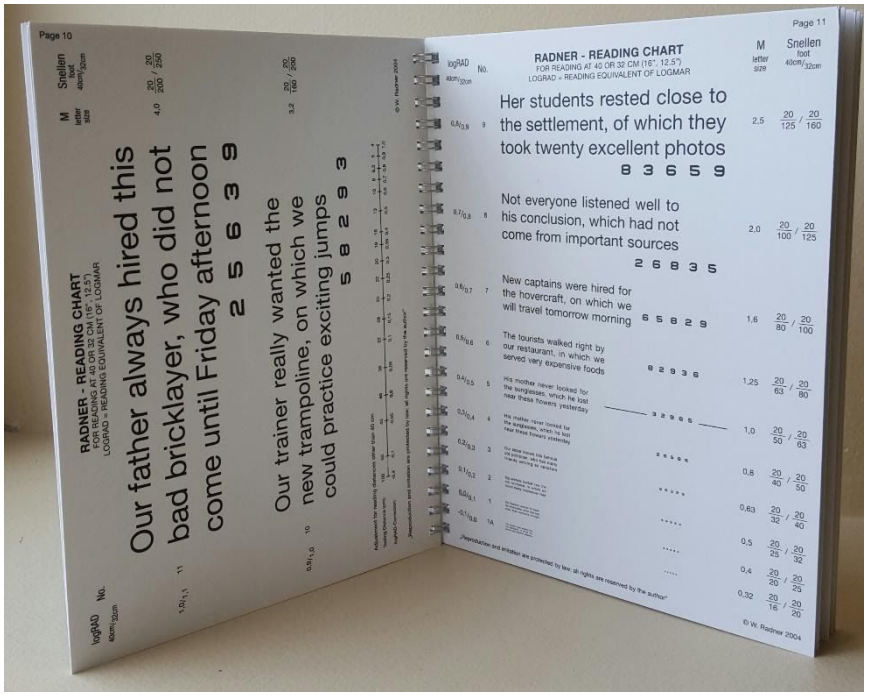


Fig. 10 Radner reading test

Each reading chart was covered by a piece of paper and the participants were asked to read the sentences as soon as the examiner removed the cover. Participants were instructed to read the sentences one after the other, loudly and accurately, as quickly as possible without correcting themselves when they made errors and without repeating the words or stopping in-between. Reading performance metrics were measured monocularly and binocularly with and without near correction.

All testing procedures were monitored with audio recording to measure the reading time for each sentence and reading errors. Reading performance metrics measurements were carried out after the testing session, from the participants' audio

recording. GoldWave Inc (St. John's, Newfoundland, Canada) software was used for playing the audio recordings. In this program the users can reduce the recording speed as well as displaying the time in seconds, digitally, with sound waves. This program allows the examiner to calculate the exact time when the participants start and end reading, which leads to increase the reliability of the measurements.

Following the visit, reading performance metrics outcomes were described as follows: Reading acuity, logRAD score, average reading speed (ARS), maximum reading speed (MRS) and critical print size (CPS).

Reading acuity was determined as the smallest print size that could be read.

LogRAD score was the reading acuity taking the reading errors into account. For Radner test, the number of errors was calculated as the number of syllables of incorrectly read words as recommended by the company. Each syllable in a Radner chart has a value of 0.005.

logRAD score= logRAD + nr. of incorrectly read words in syllables x 0.005

Reading speed was measured in words per minutes (wpm) and calculated, for each sentence, as the number of words read correctly divided by the exposure time taken to read that sentence.

$$\text{RS (wpm)} = \frac{\textit{Number of the words read correctly in a sentence}}{\textit{time in second need to read the sentence}} \text{ X } 60$$

Average reading speed (ARS) was measured as the mean reading speed of all the sentences from 1.1 to 0.1 logMAR print size, taking into consideration the smallest print size all participants could read. For those who could not read the sentences above 0.1 logMAR, time was calculated as 0 sec from the print size they stopped reading until 0.1 logMAR.

Maximum reading speed (MRS) was the average reading speed of the sentences corresponding from 1.1 to 0.8 logMAR print size. Critical print size was determined as the smallest print size that could be read with a speed corresponding to 90% of maximum reading speed (10% decrease).

Defocus curves

Distance Visual acuity, using Landolt C optotypes, for a range of defocus levels was also evaluated binocularly and for the non-dominant eye and the resulting defocus curves were calculated. A range of +1.50D to -5.00D (in steps of 0.5D defocus) were used. The procedure was randomized in in defocus and letter sequences to decrease the effect of memory (Gupta et al., 2007). Only one optotype was used for determining acuity for each logMAR line.

Near Activity Visual Questionnaire (NAVQ)

All participants completed the Near Activity Visual Questionnaire (NAVQ) before pilocarpine installation to assess the near vision ability with their current near correction, and after 2 hours of pilocarpine installation to assess their near vision ability with the effect of pilocarpine drop only and without their habitual near correction. Also, all participants were asked to report any physiological or ocular reactions that they experienced after pilocarpine drop installation.

Post-pilocarpine recordings

After one hour of pilocarpine drop installation participants returned. Their near and distance visual acuities, reading performance metrics, pupil size, IOP, defocus curve and NAVQ questionnaire were evaluate again, with pilocarpine effect this time, at the same room illumination.

2.2 Statistical analysis and results.

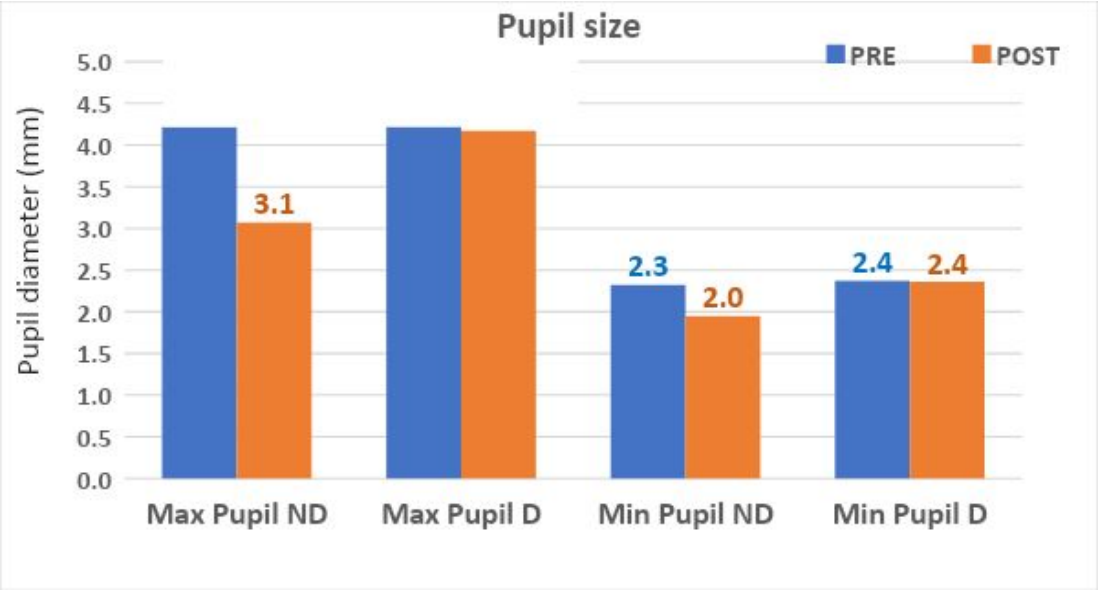
All collected data were normally distributed as assessed by Shapiro-Wilk's test ($p \geq 0.05$). Paired samples t-tests were used to determine whether there were statistically significant mean differences in measurements before and after pilocarpine installation. The cut-off level for statistical significance was $p < 0.05$. Data are shown before (pre) and after (post) 1h of pilocarpine instillation in non-dominant eye:

Pupil size

An average decrease of 1.2 ± 1.0 mm was found in maximal pupil diameter after pilocarpine drops in non-dominant eye, which was statistically significant (p=0.006). Specifically, maximal pupil diameter was reduced, on average, from 4.2 ± 0.8 mm to 3.1 ±1.2 mm. Note, that one patient (No1) did not show a reduced pupil size in the non-dominant eye following pilocarpine instillation.

Minimal pupil diameter for non-dominant eye was also found to decrease, on average, by 0.4 ± 0.4 mm (from 2.3 to 2.0 mm on average) and was also statistically significant (p=0.02). Similarly, patient No1 did not show a difference between the two sessions.

No difference was found, as expected, in both maximum and minimum pupil size for the other eye between the two recordings (p=0.35 and p=0.89 respectively).

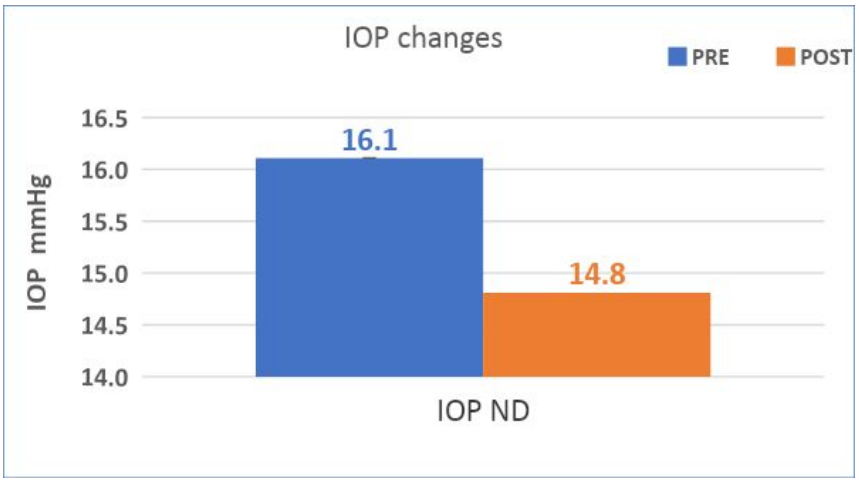


Graph 1. Pupil size before and following 1 hour of pilocarpine instillation.

Pupil returned to normal size after about 8 hours of installation and no statistical differences were found.

IOP

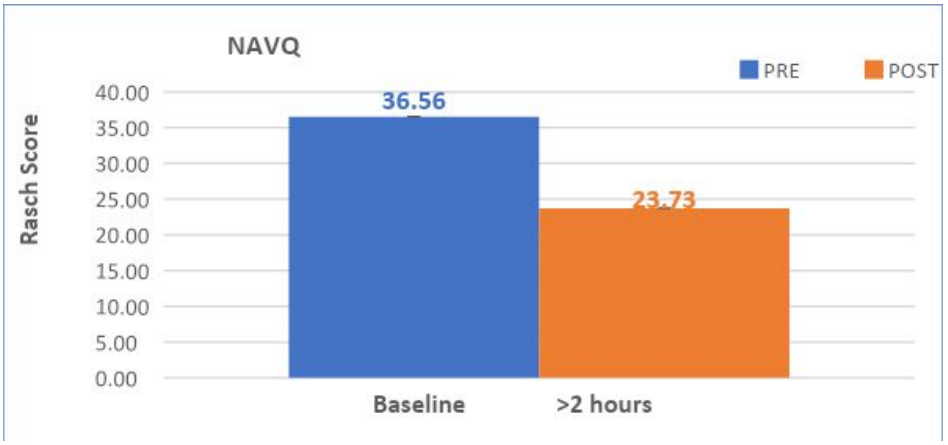
After 1 hour of instillation IOP was found to be decreased on average by 1.3 ± 1.9 mmHg in the non-dominant eye (ND) which was marginally statistically insignificant (p=0.061). This is probably due to the absence of changes in IOP measurements on 2 out of 10 participants. No statistically significant differences were found on the other eye (dominant eye, D) after 1hr of pilocarpine installation (p =0.526).



Graph 2. IOP changes for ND eye pre and post pilocarpine instillation.

NAVQ

Subjective evaluation showed a statistically significant improvement of Rasch score by 12.8 ± 16.1 (p=0.032), on average, from 36.6±15.2 to 23.7±17.2 after pilocarpine, comparing their near vision ability with the effect of pilocarpine drop only and without their habitual near correction. Particularly 6 out of 10 felt better and more comfortable with their vision 1h after pilo drops, 2 of them showed the same results in their Rasch score before and after pilocarpine and the other 2 showed a minor deterioration.

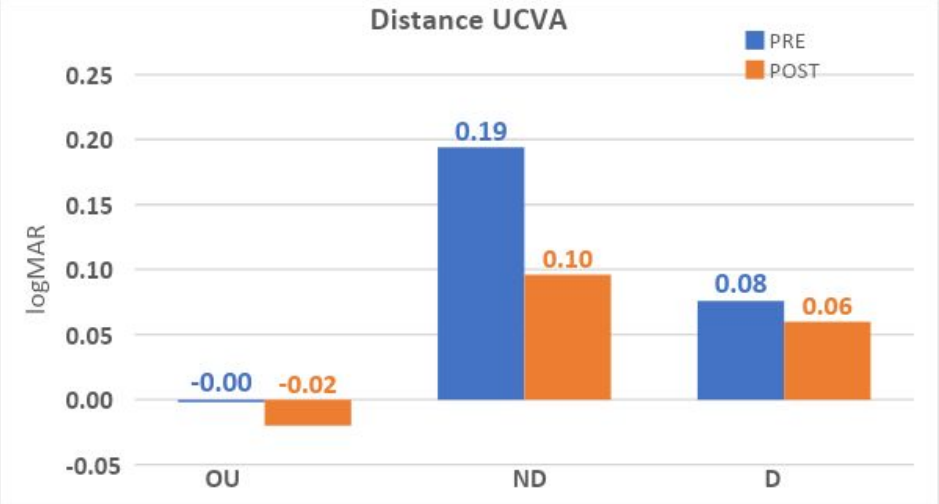


Graph 3. NAVQ score changes pre and post treatment (>2 hours)

Visual Acuity

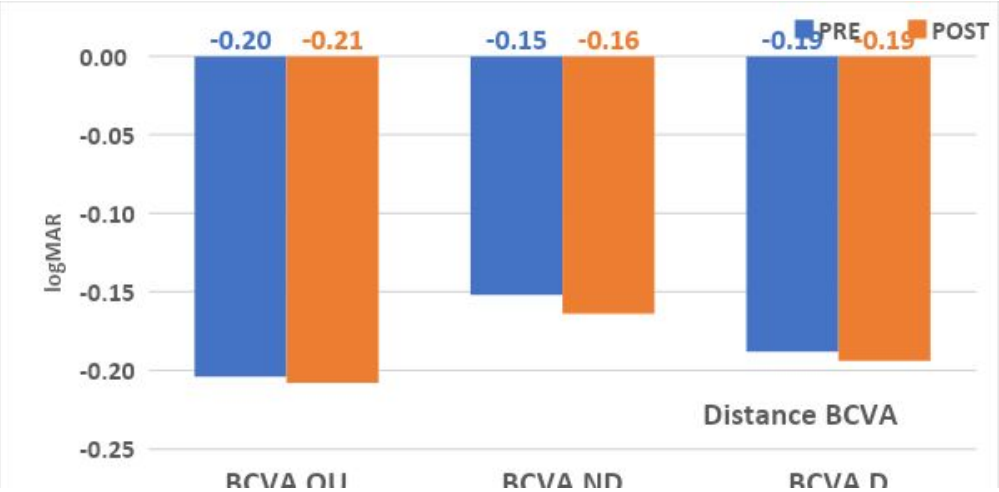
Mean change for Distance UCVA and BCVA at 4m, Near UCVA and BCVA at 40 cm were compared to determine whether there was any statistically significant mean difference before and after 1hr of pilocarpine installation.

UCVA for distance in treated (ND) eye showed a non-statistically significant improvement of 0.10 ± 0.22 logMAR (p=0.202). This improvement was expected due to the decrease in pupil size which has induced a pinhole-like effect that helped participants' visual performance under blur conditions. Binocular UCVA for distance also improved by 0.02 ± 0.05 logMAR, yet no statistically differences were found after treatment (*p*=0.302). No differences were found in the dominant eye.



Graph 4. Mean changes for Distance UCVA pre and post pilo drops.

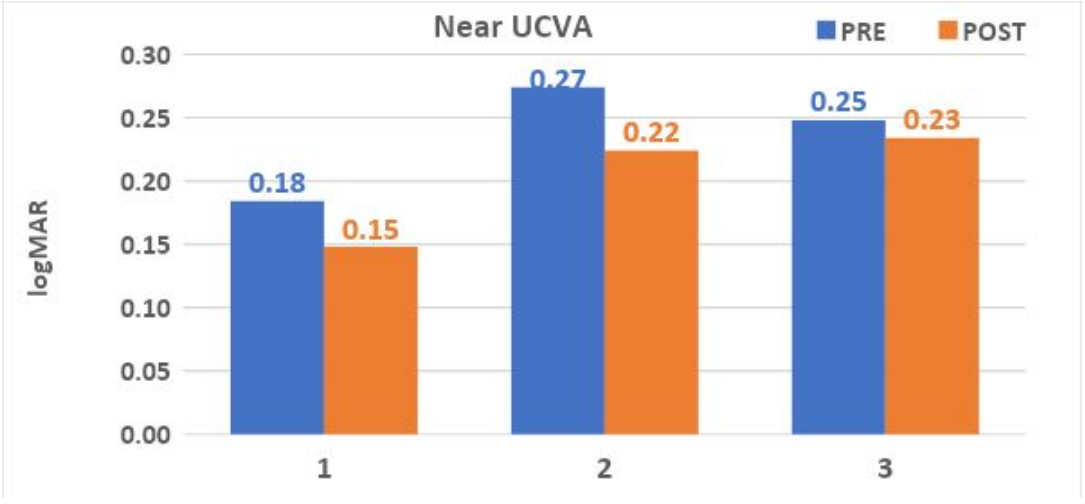
No difference was found, as expected, in BCVA before and after pilocarpine instillation.



Graph 5. Mean changes for Distance BCVA pre and post pilo drops.

Near UCVA in ND eye, pre and post pilocarpine instillation, was found to be the same in 4 participants, 4 of them slightly improved and the other 2 showed a mean decrease of 0.06 logMAR. As a result, mean UCVA for near in ND eye improved only by 0.05 ± 0.12 logMAR (p=0.218), which was not statistically significant.

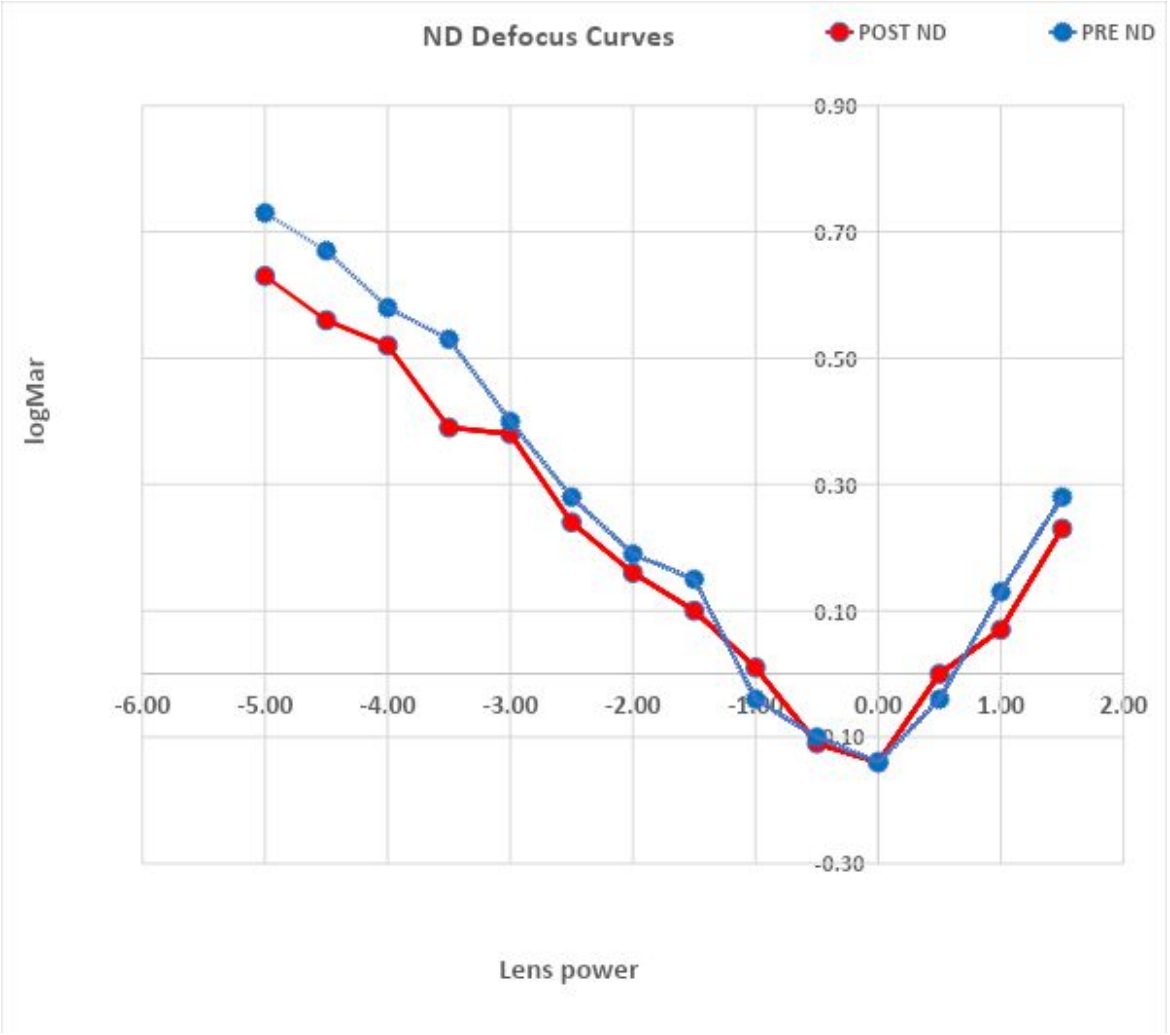
A moderate increase, but yet not significant, was also found for near UCVA respectively for OU and dominant eye.



Graph 6. Mean changes for near UCVA pre and post pilo drops.

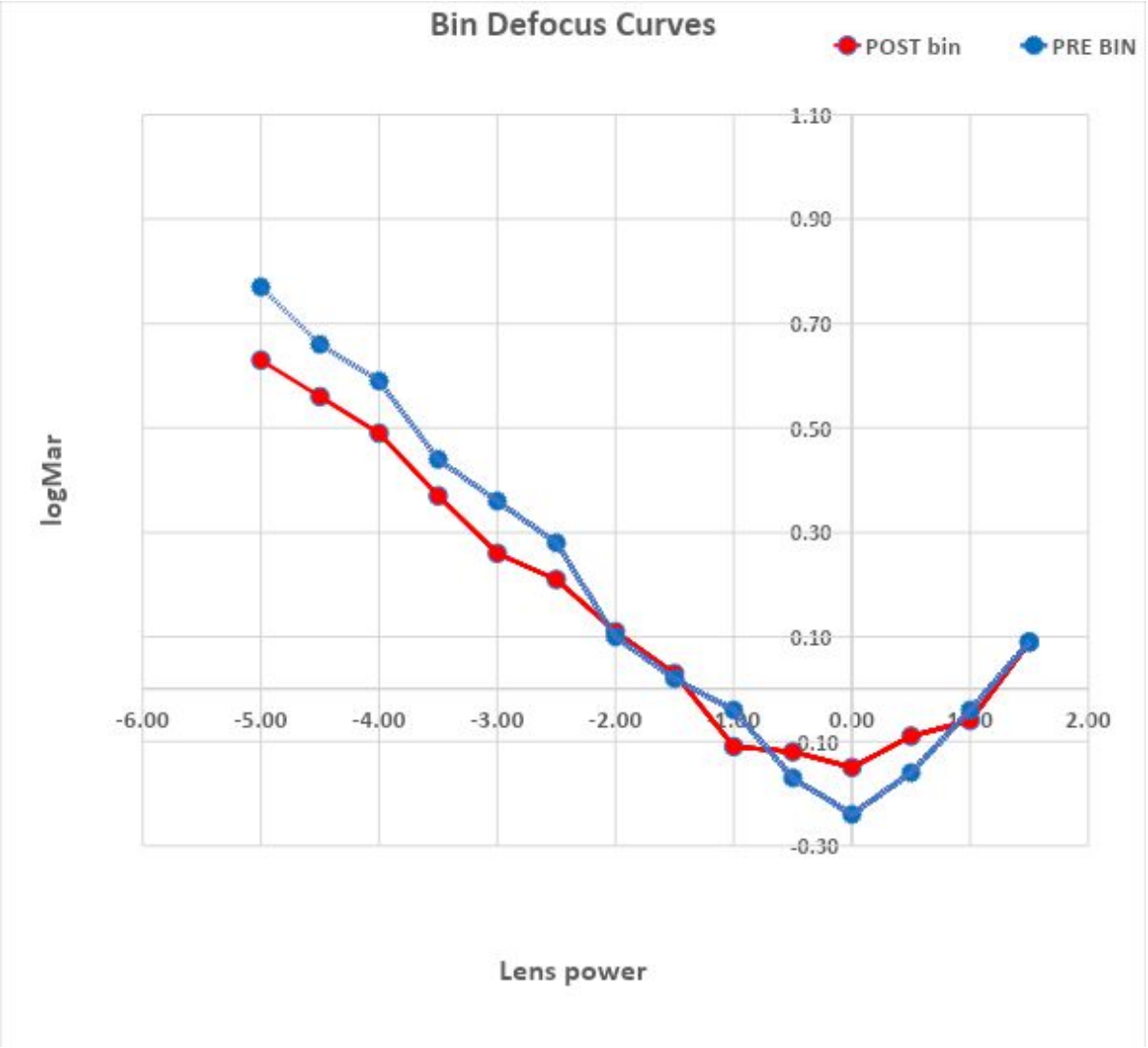
Defocus Curves

Mean monocular defocus curve difference before and after pilocarpine instillation showed an improvement, yet not statistically significant (p>0.05), in visual acuities which corresponded to lens power -3.50D (28cm), -4.50D (22cm) and -5.00D (20cm). No statistically significant differences were found for lens power from 0.00D to -3.00D to +1.50D (distance, intermediate and near vision; p>0.05).



Graph 7. Mean monocular (ND) defocus curve pre and post pilocarpine installation.

On the other hand, binocular defocus curve before and after pilocarpine instillation showed a greater improvement in total compared to monocular defocus curve. Specifically, for the vergences of -1.00D (1m), -3.00D (33cm) and -4.00D (25cm) this improvement was statistically significant (p<0.05).



Graph 8. Mean Binocular defocus curve pre and post pilocarpine installation.

Reading Performance

A statistically significant difference was found only in logRAD score in the ND eye, which is mostly a reading acuity metric. Specifically, logRAD score for ND eye, measured without near correction statistically improved from 0.40±0.41 logRAD to 0.37 ± 0.35 logRAD at 1 hour following pilocarpine instillation (p = 0.02). A slight improvement of 22 wpm was observed in MRS but this was marginally statistically insignificant (p=0.08). No statistically significant differences were found in other reading performance metrics (ARS and CPS) measured without near correction before and after pilocarpine instillation for ND eye.

Binocularly, a statistically significant difference was found only for ARS, which improved on average by 11 wpm, after instillation (*p*=0.02). Although the binocular measurements without near correction significantly improved after 1 hour, this improvement was at a mean of 10 wpm, which may be not clinically insignificant.

A slight improvement was also observed in MRS (10 wpm) but this was again marginally statistically insignificant (p=0.06).

Table 3. summarizes the mean change in the reading performance metrics measurements monocularly and binocularly.

Reading performance metrics	Mean before pilocarpine installation	Mean after 1hr of pilocarpine installation	t-test (p- value)
ND eye			
logRAD score	**0.40 ± 0.41**	**0.32 ± 0.36**	**p=0.01**
ARS (wpm)	119 ± 66	128 ± 62	p=0.15
MRS (wpm)	158 ± 63	180 ± 45	p=0.08
CPS (logRAD)	0.7 ± 0.3	0.7 ± 0.2	p=0.70
Binocularly			
logRAD sore	0.24 ± 0.31	0.22 ± 0.23	p=0.59
ARS (wpm)	**140 ± 49**	**151 ± 42**	**p=0.02**
MRS (wpm)	183 ± 28	193 ± 24	p=0.06
CPS (logRAD)	0.6 ± 0.2	0.6 ± 0.2	P=0.71

Table 3. Mean change in reading performance before and after 1 hour of pilocarpine installation.

Chapter 3

3.1 Discussion

This study assessed the efficacy of low concentration (1%) pilocarpine drops to increase DOF and improve near vision in presbyopia by comparing a range of reading performance metrics in addition to the standard visual acuity before and after 1 hour of instillation. The treatment of only one eye, using a low dosage of pilocarpine, had several advantages; no symptoms of headache were reported and no ocular complications were observed whatsoever, during or after the examination and it did not cause any blur concerning distance vision.

Regarding the effect of pilocarpine on pupil size, 1% pilocarpine reduced significantly maximal pupil diameter by 1.2 ±1.0 mm (from 4.2 ± 0.8 mm to 3.1 ±1.2 mm). At the same time, minimal pupil diameter for non-dominant eye was also reduced by 0.4 ± 0.4 mm (from 2.3 to 2.0 in average). As expected, no difference was found in both maximal and minimal pupil size for the other eye, which was like a control eye, between the two recordings. Pupil returned to normal size after about 8 hours of installation.

Comparing to other methods of presbyopia correction that used the same principle of small pupil size such as intracorneal inlays and pinhole contact lens which aim to reduce pupil size to 1.6mm, 1% pilocarpine reduced the pupil size to a lesser but still statistically significant extent regarding the dosage, but this was only evident at photopic light levels, which are usually employed when reading or doing near tasks. At lower light levels pupil size would increase, and any effects would be lessened. Note, that one patient (No1) did not show a reduced pupil size in the non-dominant eye following pilocarpine instillation, while a significant variability between subjects was observed. This means that some subjects might be better candidates for pilocarpine use, compared to others.

In the present study, monocular and binocular uncorrected near visual acuity, after pilocarpine instillation, measured with ETDRS chats, showed an improvement of about 0.05 and 0.04 logMAR, respectively. This increase was moderate and

non-significant (p=0.218), possibly due to the fact that 4 out of 10 subjects showed no changes at all, 4 of them slightly improved, while the other 2 showed a decrease in visual acuity. This inter-subject variability shows that with a number of 10 participants, it is difficult to arise statistically significant differences.

Monocular uncorrected VA for distance showed a minor improvement of about on line of logMAR acuity. This improvement was probably the result of the pinhole effect in the ND eye, yet no statistical significance was obtained.

Defocus curve test forms an effective way to assess the clear range of vision (Gupta et al., 2009a). In the non-dominant eye, the mean visual acuity measurement as a function of defocus curve showed improvement in visual acuity after pilocarpine instillation for very near distances between 28cm to 20cm. No improvement was found in the near and intermediate distances. On the other hand, binocular defocus curve after pilocarpine instillation showed a greater improvement in total regarding monocular defocus curve. Specifically, for the vergences which correspond to distances 33cm (-3.00D) and 25cm (-4.00D) improvement of 1 line was found respectively ($p<0.05$). This may be a sufficient improvement regarding statistics, although 33cm or less is quite a short distance for near work, yet it provides further support in pilocarpine usage to correct presbyopia. Therefore, pilocarpine, even though does not seem to improve the functional intermediate vision measured monocularly, it seems to increase VA mostly for very near distances under binocular observation.

Despite the moderate increase of the near VA, some reading performance metrics (logRAD score, ARS, MRS) showed significant or marginally insignificant statistical differences after pilocarpine drops administration. More specifically, statistically significant differences were evident for binocular ARS (improvement of 10wpm) and monocular logRAD score (p=0.02). These results might not represent clinically significant differences, but they show that there was an increase in DOF after pilocarpine instillation which, with further study, could lead to great results.

The importance of these differences found before and after 1 hour of pilocarpine can be further explained by the NAVQ results as subjects' satisfaction about reading

different material was better, as only 20% of them reported slightly worse reading experience and 60% of them were really satisfied, despite the minor improvement in the near VA.

During this study, numerous limitations appeared, including the small sample size, probably small pilocarpine dosage and a quite large age range (40 yo to 68 yo) which indicate that the study would be better performed over a longer follow-up to properly address the effect and with participants of a younger range (e.g. early presbyopes). Taking into account these limitations, statistical analysis for a smaller age range was performed, excluding the 3 oldest participants, decreasing mean age to 47 ± 5 years old. Data analysis showed no differences neither in VA nor in reading performance. Decreasing the sample size to only 7 participants creates specific boundaries and cannot lead to reliable results.

3.2 Conclusions

Improving depth-of-focus by reducing pupil diameter, using 1% pilocarpine in the non-dominant eye, showed a minor improvement in near vision acuity measured with ETDRS chart (isolated letters) in presbyopic subjects while keeping good distance visual acuity. Defocus curves showed great enhancement of DOF for specific distances. Furthermore, a significant improvement of the reading performance metrics was found after pilocarpine instillation, especially for binocular ARS.

To summarize, the anisocoric monovision approach that this study evaluated, gives a green light in the use of pilocarpine to offer useful improvements in vision to the emmetropic presbyopes who wish to be spectacle-free and to be able to perform distance and near visual tasks which are reasonably well-lit and are not too taxing.

While pupil diameter impacts on many aspects of visual performance at all ages, the immediate challenge is the presbyopic pupil, since the through-focus retinal image quality given by many methods of correction is critically linked to the presbyopes pupil diameter. More data are needed and further research is necessary.

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Appendices

Appendix 1: Ethical approval

Aston University
Aston Triangle
Birmingham B4
7ET 0121 204
3000

Date: 21 May 2019

Dr Shehzad Naroo School of Life
and Health Sciences

Study title: An investigation of change in depth of vision with constriction of the pupil REC REF: #744

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favorable opinion for the amendment to this research as described in your Notice of Amendment form dated 29th April 2019. This approval is conditional on Ms. Jenny Spaho replacing the stated personal email address with an Aston University email address as a contact point on the information sheet when she is registered at the University.

Documents approved

Document Version Date Participant Information Sheet 3 30/04/2019

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Richard Booth Acting Chair of the University

Research Ethics Committee

Appendix 2: Consent form

An Investigation of Change in Depth of Vision

with Constriction of the Pupil

CONSENT FORM

Participant Identification Number:

Please initial box

1. I confirm that I have read and understand the information sheet dated 13th June 2019 (version 4.0) for the above study. I have had the opportunity to consider the information provided, ask questions and have had these answered to my satisfaction. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and my legal rights being affected. ☐
3. I understand that my data may be reviewed by authorised individuals from Aston University responsible for ensuring the quality of the research. ☐
4. I agree to my General Practitioner (GP) being informed of my participation in the study. ☐
5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of Researcher	Date	Signature

1 copy for the participant, 1 for researcher site file

Appendix 3: Near Activity Visual Questionnaire (NAVQ)

THE NEAR ACTIVITY VISUAL QUESTIONNAIRE (NAVQ)

Demographic Information

Name: _____ DOB: ___ / ___ / 19___ Gender: Male/Female Date: ___ / ___ / 20___

Type of Correction: (Please Tick ONE Option ONLY)

Spectacles:	❑ Single Vision	❑ Bifocals	❑ Varifocals
Contact Lenses:	❑ Distance CL + Reading Specs	❑ Monovision	❑ Multifocals
IOL:	❑ Single Vision	❑ Multifocal	❑ Accommodating

INSTRUCTIONS – Please read carefully

THIS QUESTIONNAIRE ASKS YOU TO RATE HOW MUCH **DIFFICULTY** YOU EXPERIENCE IN DOING VARIOUS NEAR-VISION RELATED ACTIVITIES.

Please answer ALL questions for **IF/WHEN YOU DO THE DESCRIBED ACTIVITY WITHOUT EXTRA READING OR MAGNIFYING AIDS** (therefore ONLY with your normal correction). Simply CIRCLE THE NUMBER THAT CORRESPONDS TO THE LABEL OF YOUR RESPONSE, as shown in the example:

EXAMPLE:	N/A *or* Stopped for Non-visual Reasons	A Little Difficulty	Moderate Difficulty	Stopped for Visual Reasons
How much difficulty do you have reading road signs when driving?	0	(1)	2	3

If you do not do the described activity or you have stopped for reasons that are not related to your vision, then please circle the *'N/A'* option.

How much difficulty do you have:	**Not Applicable *Or* Stopped for Non-visual Reasons *Or* No Difficulty**	**A Little Difficulty**	**Moderate Difficulty**	**Extreme Difficulty *Or* Stopped for Visual Reasons**
1. Reading small print, e.g. newspaper articles, books, magazine articles, menus at a restaurant, telephone directories, etc.?	0	1	2	3
2. Reading labels / instructions / ingredients / prices on, e.g. medicine bottles, food packaging, etc.?	0	1	2	3
3. Reading your post / mail, e.g. electric bills, greetings cards, bank statements, letters from friends and family, etc.?	0	1	2	3
4. Seeing the screen & keyboard when using a computer?	0	1	2	3
5. Seeing the display & keypad on a mobile or fixed telephone, or calculator?	0	1	2	3
6. Seeing objects close to you to engage in your hobbies, e.g. playing games such as cards, bingo and dominoes, gardening, seeing photographs and pictures, etc.?	0	1	2	3
7. Doing fine handwork, e.g. threading a needle, sewing, knitting, crochet, etc.?	0	1	2	3
8. Seeing objects near to you in poor or dim light?	0	1	2	3
9. Seeing objects near to you if there is glare from lights and shiny surfaces?	0	1	2	3
10. Maintaining focus for prolonged near work?	0	1	2	3

FINALLY	**Completely Satisfied**	**Very Satisfied**	**Very to Moderately Satisfied**	**Moderately to A Little Satisfied**	**A Little Satisfied**	**Completely Unsatisfied**
Overall how satisfied are you with the near visual ability that you have?	0	1	2	3	4	5

THIS IS THE END OF THE QUESTIONNAIRE. THANK YOU FOR YOUR TIME.