University of Crete

School of Medicine

Institute of Vision and Optics

Department of Ophthalmology

"Study of the safety and efficacy of refractive corneal inlay implantation combined with cataract surgery"

"Μελέτη της ασφάλειας και αποτελεσματικότητας του διαθλαστικού ενδοκερατοειδικού ενθέματος σε συνδυασμό με εγχείρηση του καταρράκτη"

DOCTOR OF PHILOSOPHY DISSERTATION

Nela Stojanovic MSc, FEBO

Heraklion, 2017

Advisory committee

Supervisor:

- Ioannis Pallikaris, Professor of Ophthalmology, Medical School, University of Crete

Co-supervisors:

- Charalambos Siganos, Assistant Professor of Ophthalmology, Medical School, University of Crete
- Maria Chatzinikolaidou, Assistant Professor, Department of Materials Science and Technology, University of Crete

Seven-member Examining Committee

- Ioannis Pallikaris, Professor of Ophthalmology, Medical School, University of Crete
- Charalambos Siganos, Assistant Professor of Ophthalmology, Medical School, University of Crete
- Maria Chatzinikolaidou, Assistant Professor, Department of Materials Science and Technology, University of Crete
- Miltiadis Tsilimbaris, Professor of Ophthalmology, Medical School, University of Crete
- Efstathios Detorakis, Assistant Professor of Ophthalmology, Medical School, University of Crete
- Dragana Nikitovic-Tzanakaki, Assistant Professor of Embryology, School of Medicine, University of Crete
- Aristides Tsatsakis, Professor of Toxicology Science, School of Medicine, University of Crete

Dedicated to my father

Acknowledgements

Firstly, I would like to express my deepest appreciation to my Supervisor and my Mentor, Professor Ioannis Pallikaris, for the continuous support through my Ph.D study and related research, for his ideas and immense knowledge, motivation and courageous, innovative spirit. I would like to thank him for believing in me, for letting me become a member of his bright team, and for giving me the opportunity to become under his guidance a better ophthalmologist, a better scientist and a better person. For that I shall be forever grateful.

I would like to thank my Co-Supervisior Assistant Professor Siganos for his support, kindness and encouragement. His guidance helped me in all the time of my PhD research.

I would also like to thank my Advisory committee member, Assistant Professor Maria Chatzinikolaidou, for her suggestions, kind support and supervision.

My sincere thank you goes to Assistant Professor Efstathios Detorakis, who was always encouraging, very generous with sharing his knowledge and experience and whose door was always open for me.

I would like to thank Professor Miltiadis Tsilimbaris for his valuable educational presence and his kind support.

I would also like to thank Professor Aristides Tsatsakis and Assistant Professor Dragana Nikitovic-Tzanakaki for their support and their kind acceptance to be the members of my Examining Committee.

My sincere thanks goes also to Giorgos A. Kounis for his unreserved guidance and help at the critical point of my PhD study.

I am also very grateful to the Management and Staff of the Institute of Vision and Optics and Clinic of Ophthalmology, University Hospital of Heraklion, as well as to my colleagues for their support and assistance.

I would like to thank Sofia Panagopoulou for all her help and valuable advices.

And finally, last but by no means least, I want to thank my father for being on and by my side through the darkest and the brightest moments during my PhD study, for his wholeheartedly encouragement and support.

Thank you!

Abstract

Introduction: Cataract is opacification of the crystalline lens and is the commonest cause of reversible loss of useful vision worldwide. Treatment of cataract consists of surgical removal of opacified crystalline lens. Currently, the procedure of choice for cataract surgery is extracapsular cataract extraction with phacoemulsification followed by intraocular lens implantation. The major drawback of crystalline lens removal is the loss of the accommodative ability of the eye. Traditionally used monofocal intraocular lenses provide exquisite visual acuity at a single, fixed focal length. Thus, correcting the distance vision, patient will require spectacles for near. Increased patients' demands for both distance and near vision and spectacle independence have forced ophthalmologists to search for new solutions.

Intrastromal corneal inlays are a relative new modality for presbyopia correction. Currently, there are three different types of the commercially available inlays, which use different mechanisms to compensate for accommodation loss: increase of the depth of field by fixed small aperture, reshaping inlays that make changes of anterior corneal curvature and refractive inlays that alter the index of refraction using a bifocal optics.

The Presbia Flexivue Microlens® inlay is a transparent, hydrophilic disc with 3.2 mm diameter and an edge thickness of approximately 15 μm, with high refractive index and added optical power. The central 1.6 mm diameter of the disc is near-plano and the peripheral zone has the appropriate addition power. The Presbia Flexivue Microlens® has a bifocal optical system which acts as a modified monovision. The inlay is implanted in the intrastromal corneal tunnel made by femtosecond laser in the non-dominant eye.

Purpose: The purpose of this study is to investigate the clinical outcomes and safety of three different techniques of a combined cataract and refractive corneal inlay implantation surgery for presbyopia compensation over a 12-month follow-up.

Setting: University Hospital of Crete, Department of Ophthalmology and Institute of Vision and Optics, University of Crete, Greece

Study design: This is a comparative pilot study.

Study population: To qualify for enrollment in this study, each candidate was thoroughly evaluated to ensure that they meet all inclusion criteria and that they do not exhibit any of the exclusion criteria specified in the study protocol.

Methods: In this pilot study fifteen patients with bilateral cataract were allocated to one of three groups with different combination of surgical steps (cataract surgery, intrastromal pocket creation and inlay implantation). In Group 1 intracorneal pocket was created in the non-dominant eye and three months later bilateral cataract surgery was performed; three months afterwards, the intracorneal inlay was inserted. In Group 2 three days after pocket creation and the inlay implantation in the non-dominant eye, bilateral cataract surgery was performed. In Group 3 three months after bilateral cataract surgery, the pocket creation and the inlay insertion were performed in the non dominant eye.

Mean Outcome Measurements: Near and distant visual acuity, manifest refraction, contrast sensitivity outcomes were evaluated and compared between three groups. Furthermore, changes in corneal topography, intraocular pressure measurement, endothelial cell density and satisfaction questionnaire were evaluated. The follow-up period was 12 months.

Results: Twelve months after the inlay implantation mean UDVA in Group1 was 0.18 logMAR (20/32), in Group 2 0.16 logMAR (20/32) in Group 3 0.12 logMAR (20/25). Achieved UNVA improved in all groups to 0.08, 0.10 and 0.06 logMAR, respectively. The visual and refractive outcomes obtained no statistically significant difference between the three groups. Contrast sensitivity was similar between groups under mesopic and photopic conditions. Changes in corneal topography, intraocular pressure and endothelial cell density did not show significant difference between groups. Fourteen of 15 patients perceived their distance and near vision as excellent. No intra- or postoperative complications were observed.

Conclusion: Intracorneal refractive inlay, Presbia Flexivue Microlens®, seems to represent an effective and safe method for the presbyopia compensation in pseudophakic patients. Clinical outcomes of three different techniques of combined cataract surgery and the refractive inlay implantation had no significant differences between them. The refractive corneal inlay provided excellent near vision acuity, high patients' satisfaction and high spectacle-independence rate in patients after cataract surgery.

Περίληψη

Εισαγωγή: Ο καταρράκτης χαρακτηρίζεται από τη θόλωση του κρυσταλλοειδούς φακού και τη συνεπακόλουθη μείωση της οπτικής οξύτητας. Η θεραπεία είναι χειρουργική και συνίσταται στην αφαίρεση του φακού και την αντικατάστασή του από έναν τεχνητό ενδοφακό που τοποθετείται στο περιφάκιο. Η σύγχρονη τεχνική εγχείρησης καταρράκτη, η φακοθριψία, χαρακτηρίζεται ιδιαίτερα επιτυχής και ασφαλής καθώς τα ποσοστά σοβαρών επιπλοκών είναι χαμηλά.

Το μειονέκτημα της αφαίρεσης του κρυσταλλοειδούς φακού και της αντικατάστασής του από έναν μονοεστιακό ενδοφακό είναι η απώλεια της ικανότητας προσαρμογής με αποτέλεσμα απώλειας της κοντινής όρασης. Ως πρόσφατα, η μόνη αντιμετώπιση του προβλήματος της κοντινής όρασης μετά την εγχείρηση του καταρράκτη ήταν η χρήση των διορθωτικών φακών (κοντινά γυαλιά, διπλοεστιακά γυαλιά, φακοί επαφής). Αυξημένες απαιτήσεις των ασθενών και η επιθυμία ανεξαρτητοποίησης από διορθωτικά γυαλιά, έστρεψαν την επιστήμη της οφθαλμολογίας προς ανεύρεση μιας πιο ικανοποιητικής λύσης.

Το ενδοκερατοειδικό ένθεμα είναι μια σχετικά καινούργια μέθοδος αποκατάστασης της κοντινής όρασης σε άτομα με πρεσβυωπία. Ο μηχανισμός δράσης είναι διαφορετικός, ανάλογα με το μοντέλο του ενθέματος: διαμόρφωση της καμπυλότητας του κερατοειδούς, pin-hole effect ή διαθλαστική επίδραση.

Το ένθεμα Presbia Flexivue Microlens® είναι ένας διάφανος, υδρόφιλος δίσκος με 3χιλ. διάμετρο και περίπου 15μm πάχος. Η κεντρική ζώνη των 1.6 χιλ. είναι χωρίς διαθλαστική ισχύ (πλάνο) ενώ η περιφερική ζώνη έχει θετική διαθλαστική ισχύ. Το ένθεμα διαθέτει

διπλοεστιακό οπτικό σύστημα το οποίο λειτουργεί ως τροποποιημένη μονοόραση (smart monovision). Το τούνελ στο οποίο τοποθετείται το ένθεμα δημιουργείται στο στρώμα του κερατοειδούς του μη κυρίαρχου οφθαλμού με χρήση του femtosecond laser.

Σκοπός: Τα επιστημονικά ερωτήματα που καλείται να απαντήσει αυτή η μελέτη είναι η ασφάλεια και αποτελεσματικότητα τριών μεθόδων συνδυασμού της ένθεσης του διαθλαστικού ενδοκερατοειδικού μικροφακού Presbia Flexivue Microlens® με εγχείρηση του καταρράκτη, καθώς και οι επιπτώσεις στα χαρακτηριστικά της μακρινής και κοντινής όρασης.

Τοποθεσία: Η μελέτη πραγματοποιήθηκε στο ΒΕΜΜΟ (Βαρδινογιάννειο Εργαστήριο Μεταμοσχεύσεων και Μικροχειρουργικής Οφθαλμού)/Ιατρική Σχολή Πανεπιστημίου Κρήτης και στην Οφθαλμολογική κλινική του Πανεπιστημιακού Νοσοκομείου Ηρακλείου.

Σχεδιασμός: Αυτή είναι μια συγκριτική πιλοτική μελέτη.

Μεθοδολογία: Η μελέτη αυτή περιλαμβάνει την αμφοτερόπλευρη εγχείρηση του καταρράκτη με τοποθέτηση ενδοφακού και μονόπλευρη ένθεση του ενδοκερατοειδικού μικροφακού στο μη κυρίαρχο οφθαλμό. Συμπεριληφθήκαν 15 ασθενείς χωρισμένοι σε 3 ομάδες, οι οποίοι πληρούν όλα τα κριτήρια συμμετοχής.

Στην ομάδα Ι, πρώτα πραγματοποιήθηκε η δημιουργία του κερατοειδικού τούνελ, τρεις μήνες αργότερα η εγχείρηση του καταρράκτη αμφοτερόπλευρα και τρεις μήνες μετά, η ένθεση του ενδοκερατοειδικού ενθέματος. Στην ομάδα ΙΙ τρεις ημέρες κατόπιν της δημιουργίας του τούνελ και ένθεσης του ενδοκερατοειδικού ενθέματος στο μη κυρίαρχο οφθαλμό, πραγματοποιήθηκε η αμφοτερόπλευρη εγχείρηση του καταρράκτη. Στην ομάδα ΙΙΙ τρεις

μήνες μετά την αμφοτερόπλευρη εγχείρηση του καταρράκτη πραγματοποιήθηκε η δημιουργία του τούνελ και ένθεση του ενθέματος.

Κατά τη διάρκεια της δωδεκάμηνης παρακολούθησης μελετήθηκαν οι μεταβολές στη διάθλαση και οπτική οξύτητα τόσο για την κοντινή όσο και για την μακρινή όραση, καθώς και οι μεταβολές στην τοπογραφία του κερατοειδούς, στην ενδοφθάλμια πίεση των χειρουργημένων οφθαλμών, τον αριθμό των ενδοθηλιακών κυττάρων, την παχυμετρία του κερατοειδούς στην ευαισθησία της φωτεινής αντίθεσης, καθώς και τα ερωτηματολόγια ικανοποίησης των ασθενών.

Αποτελέσματα: Δώδεκα μήνες κατόπιν ένθεσης του ενθέματος η μέση μη διορθωμένη οπτική οξύτητα για τη μακρινή όραση στο χειρουργημένο οφθαλμό ήταν στην ομάδα 1 0.18 logMAR (20/32), στην ομάδα 2 0.16 logMAR (20/32) και στην ομάδα 3 0.12 logMAR (20/25). Η μέση μη διορθωμένη οπτική οξύτητα για την κοντινή όραση βελτιώθηκε σε όλες τις ομάδες σε 0.08, 0.10 και 0.06 logMAR, αντίστοιχα. Η ευαισθησία στη φωτεινή αντίθεση ήταν παρόμοια μεταξύ των ομάδων σε σκοτοπικές και μεσοπικές συνθήκες. Η ενδοφθάλμια πίεση, ο αριθμός των ενδοθηλιακών κυττάρων του κερατοειδούς και η κεντρική παχυμετρία του κερατοειδούς των χειρουργημένων οφθαλμών δεν παρουσίασαν σημαντική διαφορά μεταξύ των ομάδων. Ένα χρόνο μετά την εμφύτευση του διαθλαστικού ενδοκερατοειδικού ενθέματος 14 από 15 ασθενείς χαρακτήριζαν την διόφθαλμη μακρινή καθώς και την κοντινή όραση ως άριστη. Δεν προέκυψαν διεγχειρητικές ή μετεγχειρητικές επιπλοκές ένα χρόνο μετά την επέμβαση.

Συμπεράσματα: Το ενδοκερατοειδικό ένθεμα Presbia Flexivue Microlens® σε συνδυασμό με την εγχείρηση του καταρράκτη φαίνεται να συνιστά μία αποτελεσματική και ασφαλή

χειρουργική τεχνική για αποκατάσταση της κοντινής όρασης. Οι παράμετροι που μελετηθήκαν δεν παρουσίασαν ιδιαίτερη διαφορά μεταξύ των 3 μεθόδων. Το ενδοκερατοειδικό ένθεμα προσέφερε ευκρινή κοντινή όραση, υψηλό επίπεδο ικανοποίησης των ασθενών και ψιλό ποσοστό απαλλαγής από τα κοντινά γυαλιά.

Contents

Introduction

Cataract is the commonest cause of reversible loss of useful vision worldwide. Treatment of cataract consists of surgical removal of opacified crystalline lens. Currently, the procedure of choice for cataract surgery is extracapsular cataract extraction with phacoemulsification followed by intraocular lens (IOL) implantation. [1-3] The major drawback of crystalline lens removal is the loss of its accommodative ability. Traditionally used monofocal intraocular lenses provide exquisite visual acuity at a single, fixed focal length. Thus, correcting the distance vision, patient will require spectacles for near. Increased patients' demands for both distance and near vision and spectacle independence have forced ophthalmologists to search for new solutions.

As a response to this challenge, a technique called monovision has been developed. In this technique the dominant eye is corrected by monofocal IOL for distance and the non-dominant eye for near vision. The main disadvantage of the monovision method is loss of binocularity and stereopsis.[4,5]

Multifocal IOLs form another treatment option, resulting in satisfactory vision, for both distant and near, without the use of spectacles. This is accomplished, due to the lens multifocality, which creates a range of optical foci, near, distant and intermediate. Multifocal IOLs provide functional vision for all distances, but at the same time they create quality problems such as reduced contrast sensitivity and photic phenomena such as glare, halo and problematic night vision.[6,7].

Accommodative IOLs were suggested to provide satisfactory vision for all distances by restoring some degree of "pseudoaccommodation". Their function is based upon the movement of the lens in the capsular bag, following accommodative effort. Comparative studies show that accommodative IOLs offer similar distant vision as the monofocal IOLs, improved near vision during the first 6 months after implantation, but loss of this effect in the first year due to capsular opacities.[8-10]

Even though the procedures and techniques mentioned above have undeniable value, contemporary ophthalmology has not completely answered the pseudophakic-presbyopic dilemma. There is still a need for a safe, effective and reversible surgical technique with a short adaptation time for patients.

Intrastromal corneal inlays are a relative new modality for presbyopia correction. Currently, there are three different types of the commercially available inlays, which use different mechanisms to compensate for accommodation loss: increase of the depth of field by fixed small aperture, reshaping inlays that make changes of anterior corneal curvature and refractive inlays that alter the index of refraction using a bifocal optics.

However, the possibility of implanting a corneal inlay where there is monofocal lens cataract surgery offers a surgical solution for patients troubled by pseudophakic presbyopia. It is possible to consider differing combinations of techniques for implantation of the refractive corneal inlay and the cataract surgery. Having the dominant eye with a clear distance focus unaided is a critical step and adding the inlay to the non-dominant eye is the aim to improve near visual acuity in pseudophakic patients.

The purpose of this study is to evaluate safety and efficacy of three different techniques of a combined cataract and refractive corneal inlay implantation surgery over a 12-month follow-up.

Presbyopia and accommodation

Presbyopia is the most common refractive disorder of later life, related to decrease of accommodative amplitude. Scientists have studied the change in the eye's ability to focus (amplitude of accommodation) in relationship to age. They have found that the amplitude of accommodation declines in a linear fashion with age and that this decline occurs universally and predictably.

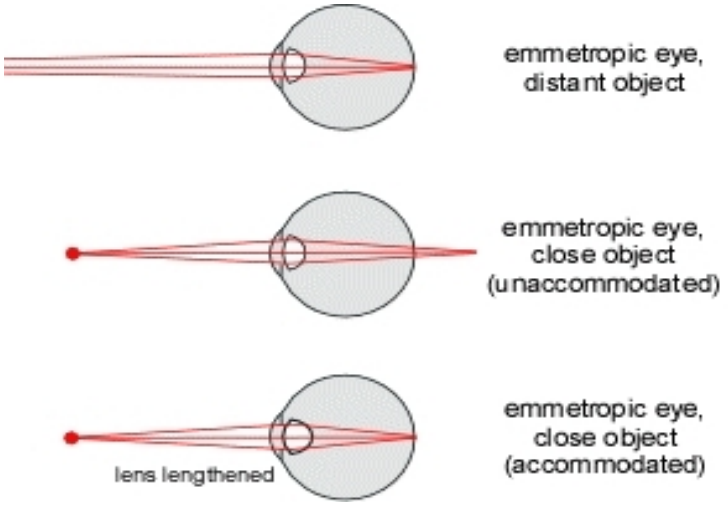

Figure 1. Accommodation in emmetropic eye

Some 4 million new patients emerge as presbyopes in the U.S. population each year [11]. In emmetropes and hyperopes, it is usually manifested at 40 years of age by the need for reading with glasses or contact lenses. Despite its ubiquity and high annual costs, the underlying cause(s) of presbyopia remain unclear.

The Helmholtz accommodation theory is based on the assumption that the ciliary muscle diameter change during accommodation is responsible for the change in shape of the lens.[12] During accommodation, the ciliary muscle contracts and thus the lens diameter is reduced. In this state, the zonula fibers can relax and the lens shape becomes more spherical. The curvature radii of the anterior and the posterior lens surface both decrease, leading to an increase in refractive power. In cycloplegia, the lens is flattened due to the radial tension of the zonula fibers, and hence the refractive power of the lens is diminished.

Coleman and Fish assumed that the lens, together with the zonula fibers, form a diaphragm, which is held in a catenary shape due to the pressure difference between the aqueous and vitreous bodies of the lens.[13] The diameter change of the ciliary body changes the span of this catenary. Thus, the anterior curvature radius is also changed. According to the Coleman theory, a continuous pressure difference acts on the lens, which was measured in primate eyes. The magnitude of this pressure difference is about 2.3 cm of water column, with major changes occurring during the initial seconds of the accommodation phase.

Schachar et al. have recently proposed an alternative accommodative mechanism for the primate eye that is similar to a theory originally proposed by Tscherning. [14,15] Both theories state that the equatorial zonules insert into the anterior ciliary muscle at the root of the iris and the anterior and posterior zonules insert into the posterior ciliary body. Schachar and Anderson alleged that during ciliary muscle contraction, through the action of the radial and longitudinal fibers, the anterior portion of the ciliary muscle curls toward the sclera at the iris root.[16] This movement increases tension on the equatorial zonular fibers while releases tension on the anterior and posterior zonular bundles.

Whereas the term presbyopia refers to the age-related decrease of accommodation, the term pseudophakic presbyopia describes the loss of accommodation caused by removal of crystalline lens and its replacement with an artificial intraocular lens which is the usual practice in cataract surgery.

Cataract

WHO estimates that there are 180 million visually disabled people worldwide, and 40–45 million of these are judged to be without useful vision—ie, they are unable to walk about unaided.[17] An estimated 46% of these cases are the result of cataracts. The worldwide burden of visual impairment is increasing as a result of both growth and ageing of the population. Since cataract is primarily an age-related disorder, the prevalence could double by 2020.[18]

Aetiology and types of cataract

The aetiology of age-related changes in the lens is not fully understood and is likely to be multifactorial.[19,20] There are three main types of age-related cataracts defined by their clinical appearance: nuclear, cortical, and posterior subcapsular. They can present alone or in combination. Typically the changes are bilateral, but they are commonly asymmetrical.

Risk factors and prevention

A growing body of research has addressed risk factors that might contribute to the multifactorial nature of cataract development and preventive factors that might retard their growth [21,22] Personal factors, such as increasing age, have been repeatedly associated with nuclear and cortical opacities. Ethnic variation has been reported, associated with different cataract types and varying prevalence rates. Genetic factors could account for as much as 50% of the severity of nuclear cataract and could be important in the development of cortical cataracts also. Many studies have suggested that women are at slightly greater risk than men of cataract development, and there is conflicting evidence of a possible beneficial effect from hormone replacement therapy in postmenopausal women.

Cataractogenesis is associated with cigarette smoking, exposure to sunlight, alcohol use, nutritional supplements, and lower education. Many of these factors are associated with other health problems, so are of general public-health interest. Common medical problems have also been associated with cataract development, such as obesity, diabetes, hypertension, diarrhoea, dehydration, steroid use, and use of systemic medications. Published epidemiological research on ultraviolet exposure and lens opacities strongly suggests that exposure to ultraviolet B causes cortical cataract changes.[23] Systemic corticosteroid use has been strongly associated with posterior subcapsular cataracts, whereas the data for inhaled corticosteroids are mixed.[24,25]

Management

In general, a cataract is only clinically relevant if the patient's visual function has declined substantially. A patient presenting with a gradual decline in visual function suspected to be due to cataract must have a comprehensive eye examination, including refraction, measurement of intraocular pressure, slit-lamp examination, and a dilated fundus examination. Other causes of reduced vision such as refractive error, glaucoma, diabetic retinopathy, and age-related macular degeneration must be ruled out. Cataract surgery is elective; typically, the indication for surgery is the patient's visual needs. Currently, there is no method to reverse or delay cataract development.

Cataract intervention has always required surgery. Couching is one of the oldest surgical procedures, dating back to 800 BC; it involves use of a needle to dislocate the lens backward and downward into the vitreous cavity.[26] This procedure, with a high complication rate, is now used only in places with limited access to surgical equipment and skilled care. By the

mid-18th century, surgeons had started to use intracapsular cataract extraction, the removal of the entire lens with its capsule through an incision created at the junction of the cornea and sclera. In the second half of the 20th century, when intraocular lenses were developed to replace the extracted natural lens, extracapsular cataract extraction with preservation of the posterior portion of the lens capsule was refined.[27] Intracapsular cataract extraction is still done nowadays, but it is generally indicated for difficult or complicated cases, such as a partly dislocated lens.

Extracapsular cataract extraction without phacoemulsification

The extracapsular procedure involves careful removal of the anterior lens capsule, delivery of the lens nucleus through an incision at the junction of the cornea and sclera, and aspiration of the residual cortical lens material. This procedure leaves the posterior lens capsule intact along with the equatorial zonular attachments—the capsular bag. The preservation of the capsular bag facilitates better anatomical location of an implanted intraocular lens.

Phacoemulsification

Phacoemulsification, first developed by Kelman in 1967, is currently the procedure of choice for the surgical management of cataracts.[28] It can be viewed as a modified form of extracapsular cataract extraction. It also means that much of the capsular bag is left intact. The key difference is that, rather than delivering the whole lens nucleus through a large limbal incision (between the cornea and the sclera) about 11 mm wide, a high-frequency ultrasonic probe is inserted through a smaller corneal incision (about 3 mm) and energy is delivered to emulsify the lens nucleus inside the eye. The fragments are subsequently aspirated through the same probe.

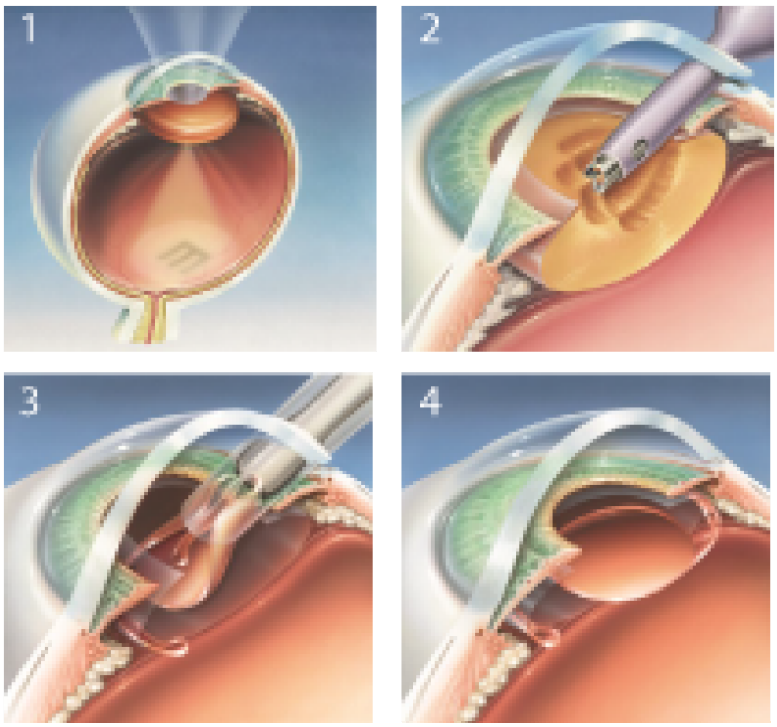

Figure 2. Illustration of surgical steps during cataract surgery with phacoemulsification 1) cloudy lens - cataract, 2) cataract removal-phacoemulsification, 3) IOL implantation, 4) IOL in place

From the points of view of refraction and postoperative wound care, the smaller the incision, the fewer the complications, such as collapse of the contents of the eye during surgery and suture-induced astigmatism. One of the challenges of a smaller incision that was initially encountered was that many replacement intraocular lenses exceeded the size of the incision. This problem was overcome by the development of the foldable intraocular lens; it has a diameter of 6 mm but can be folded and inserted through a 3 mm incision. Most phacoemulsification incisions today are 3 mm or less. The search continues for innovations that allow easier manipulation of intraocular lenses through even smaller incisions. The

smaller incision in phacoemulsification also allows for the maintenance of a near-normal anterior chamber during surgery, decreasing the risk of prolapse of the iris and leakage of vitreous humour into the wound.

Complications are generally classified as intraoperative or postoperative, though the latter are frequently related to the former. The effect of a complication varies widely from delay in visual recovery or protracted ocular discomfort to devastating visual consequences and even loss of the eye.[29,30] Nearly all reported complications occur rarely, under 2% of eyes, except for posterior capsule opacification, which occurs in about 25% of eyes.

Intraocular lenses

Replacement of the cataractous lens with an intraocular lens is the most common form of refractive surgery used today. By choice of an intraocular lens power, the pre-existing refractive error of the eye can be corrected. The development of the modern intraocular lens began in 1949 when Ridley, looking for a lens-replacement substance, noted that fragments of shattered Perspex canopies that had penetrated the eyes of Royal Air Force pilots during World War II had remained inert.[31] Through the years the intraocular lens has undergone many changes in its design and materials (such as acrylic, silicone, and polymethyl methacrylate). The essential decision is selection of the appropriate lens power for the intraocular lens. This selection is achieved through simple preoperative testing involving A-scan ultrasonography, which measures the axial length of the patient's globe, and keratometry, which measures the curvature of the corneal surface. Values from these two tests are inserted in formulae created from regression analyses, which can predict the approximate refractive power of the intraocular lens required, depending on its location inside the eye—posterior chamber (within the capsular bag) or anterior chamber (in front of the iris).

The two basic types of intraocular lens differ in design according to their intended location within the eye. Posterior-chamber lenses are overwhelmingly more frequently used than anterior-chamber lenses in cataract surgery today. A posterior-chamber lens is routinely placed within the intact capsular bag of the posterior lens capsule, in the remnant of the lens capsule purposely left in place in extracapsular cataract extraction done with or without phacoemulsification.

Monovision technique

Monovision is a frequently used technique, and it is used in patients with presbyopia before refractive surgery in preferred practice patterns (PPPs) as recommended by the American Academy of Ophthalmology (AAO).[32] In recent years, monovision design has been adopted in laser corneal refractive surgery and conductive keratoplasty or diode laser thermal keratoplasty to correct presbyopia.[33-36] Pseudophakic monovision is a type of monovision used in lens surgery (most are cataract surgeries) to correct postoperative presbyopia by programmed refractive error from biometry calculations.

In monovision design, one eye is corrected for distance vision and the other eye for near vision. In clinical practice, traditional (or conventional) monovision is where the dominant eye is corrected for distance and the non-dominant eye is corrected for near vision. The reason for this could be that it is easier to suppress blurred vision in the nondominant eye than in the dominant eye. There is another design called cross monovision, in which the dominant eye is corrected for near vision and the non-dominant eye is corrected for distance.

Although frequently used, the monovision technique has its drawbacks. Some visual functions, such as stereopsis, contrast sensitivity and visual fields, can be reduced after monovision correction.

Multifocal Intraocular Lenses

Apart from strategies to provide intraocular lenses with a dynamic optical power or position within the optical system, IOLs can be designed to provide 2 or more fixed optical powers. So-called multifocal IOLs have been designed to result in 2 or more coexisting retinal images in which only the image corresponding to the distance or near focal point is sharp. This concept is known as simultaneous vision, 15 although simultaneous imaging would be a more appropriate term. Multifocal IOLs have 2 or more fixed adapting focal points.

The earliest multifocal IOLs were introduced in the late 1980s.[37,38] Multifocal IOLs using refractive, diffractive, and combinations of both optical principles have been developed. Refraction is based on a change in direction of the light ray due to a change in the optical density of the material transmitting the light ray. Diffraction is based on the observation that light that encounters a discontinuity or edge in the material in which it travels scatters in numerous directions. Light energy arriving at an edge or discontinuity can thus be divided over 2 or more focal points, similar to refractive IOLs. Both effects were described by Fresnel in 1822 when working on lenses for lighthouses and can be used to design IOLs with multiple focal points.[39]

More recently, so-called aspheric multifocal IOLs have been introduced. In these IOLs, optical properties of the IOL have been altered to decrease higher-order aberrations (HOAs) of the total optical system, primarily by compensating for the increased spherical aberration of the cornea in older subjects.[40] Studies comparing aspheric and spherical monofocal IOLs have reported superior visual performance of aspheric IOLs compared with their spherical counterparts, especially with respect to mesopic visual acuity and contrast sensitivity. In the

case of multifocal IOLs, implantation of aspheric IOLs has been found to result in superior or equal visual performance compared with their spherical counterparts.[41]

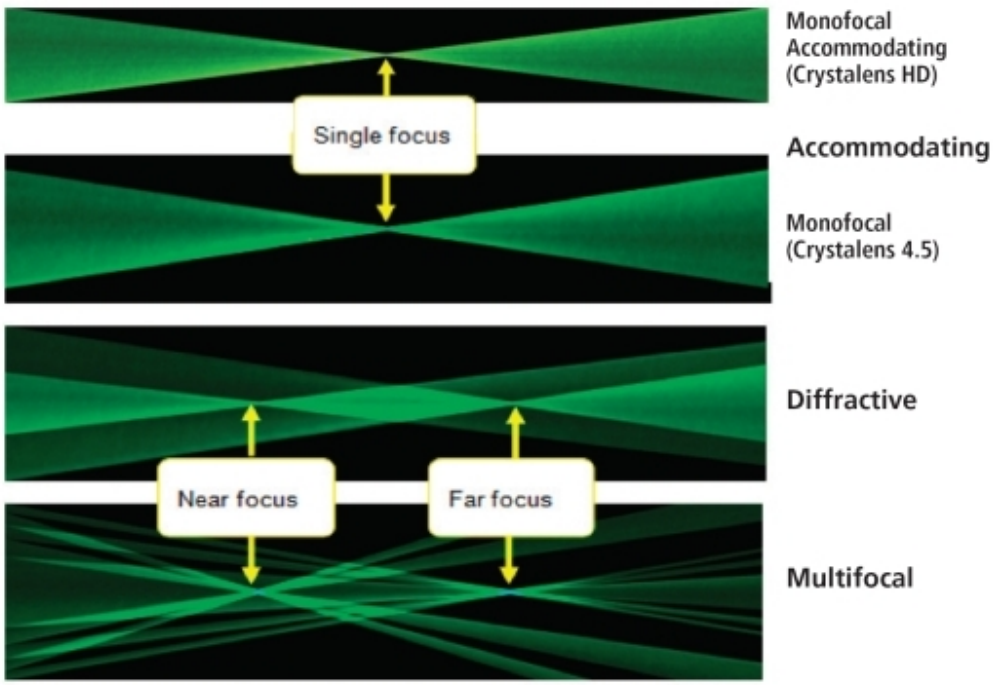

Figure 3. Light paths simulation through accommodating vs. multifocal intraocular lenses

Apart from refractive versus diffractive designs and spherical versus aspheric designs, multifocal IOL designs can be described as pupil dependent or pupil independent. In zonal refractive designs and designs with a central diffractive structure, the division of the light energy is dependent on pupil size. Intraocular lens designs with a similar peripheral and central optical zone are pupil independent.

Currently there are three multifocal IOLs (ReZoom; AMO, Santa Clara, California, USA; and ReSTOR and aspheric ReSTOR; Alcon Laboratories; Fort Worth, Texas, USA) in the United States approved for the correction of aphakia and presbyopia. ReZoom is a distance-dominant zonal-progressive refractive lens with a variation in distribution of light energy between near and far that is pupil dependent. The ReSTOR and aspheric ReSTOR feature hybrid refractive-diffractive lens designs with a central 3.6-mm apodized optic region harboring 12 concentric diffractive zones on the anterior surface, thereby creating a light energy continuum directed at two primary foci.

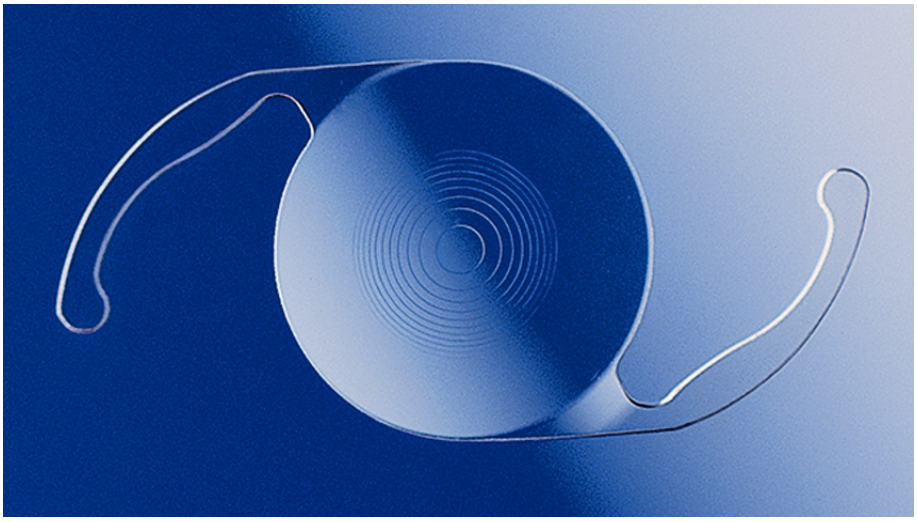

Figure 4. Diffractive multifocal IOL - ReSTOR

Accommodative Intraocular Lenses

Ideally, an IOL would allow the presbyopic patient to regain his or her ability to accommodate. Although refilling the capsular bag with a clear but elastic substance would theoretically lead to the desirable result, experiments in this area have been unsuccessful. Similarly, a change in position of the IOL or parts of it within the optical system would change the optical power of the optical system as a whole, thus providing the patient with the ability to accommodate. Ultrasound studies have shown changes in the position of accommodating IOLs within the optical system in response to physiological or pharmaceutical stimuli, although other studies have not found significant movement of these IOLs.[42]

Several different IOL designs have been developed with the hope of restoring accommodation when implanted in eyes that have undergone lens removal. They can be grouped into three different categories on the basis of their design: 1. single optic plate-style hinged lenses; 2. thin optic lens systems; 3. capsule-filling devices.

There are currently two plate-style single optic hinged lenses that are in development. The AT-45 IOL, also known as the Crystalens IOL (EyeOnics; Aliso Viejo, California), is a silicone lens with a modified three-piece haptic. The Crystalens is an accommodating lens that may function through a combination of accommodative and pseudoaccommodative mechanisms, including accommodative lens arching that creates a central refractive power gradient. It is designed to allow axial movement of the lens in an anterior-posterior direction, with the intent of providing vision at near and intermediate-in addition to distance-based on the relative location of the lens in the eye.

Figure 5. Crystalens HD accommodative intraocular lens

The other hinge plate style lens currently under development is the Human Optics AG Akkommodative 1CU Accommodative IOL design (Erlangen, Germany). The 1CU posterior chamber IOL is a foldable single-piece lens, made of a hydrophilic acrylic material, with an ultraviolet filter and a 1.46 refractive index. It has a spherical optic that is 5.5 mm in diameter and an overall diameter of 9.9 mm. Like the AT-45 IOL, the 1CU lens has a hinge-like design, which allows for the forward movement of the optic when the ciliary body contracts.

The Synchrony lens, developed by Visiogen Inc. (Irvine, California) consists of a +30 D lens that moves anteriorly and a fixed minus lens that is located posteriorly. The two optics are connected to each other by spring-loaded haptics. The lens is made in one piece out of silicone and has the following dimensions: 2.2 mm thick, 9.5 mm in length, 9.8 mm in width, and an optic size of 5.5 mm. This lens is expected to be able to produce 2.0 D to 2.25 D of accommodation.

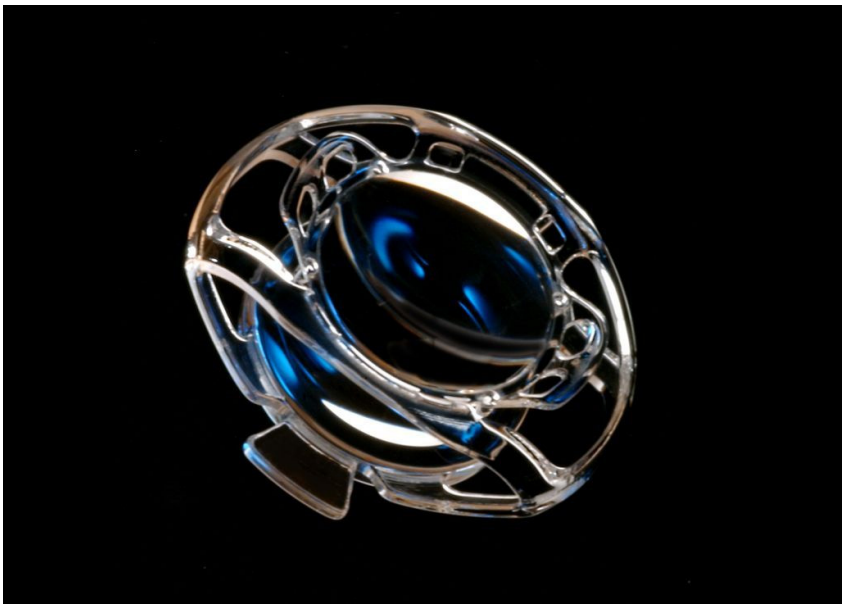

Figure 6. Synchrony - dual optic accommodative IOL

As opposed to psychophysical evaluation techniques, laser interferometry measures what shift lenses are designed to provide: axial shift on accommodative effort. While under pilocarpine some movement was recorded, no movement at all was found under near-point stimulation with any of the lenses currently marketed. The near vision findings with these lenses could be explained by pseudoaccommodation. The phenomenon of pseudoaccommodation is thought to originate from extralenticular sources. These factors may include slightly myopic end points post-IOL implantation, corneal myopic astigmatism, or an increase in depth of focus, resulting from small pupil sizes.

Dual optic implants significantly increase the impact of axial optic shift. The main potential problem, however, is delayed formation of interlenticular regenerates. Lens refilling procedures offer the potential of fully restoring accommodation due to the great impact of

increase in surface curvature on refractive lens power. However, various problems remain to be solved before clinical use can be envisaged, above all, again, after-cataract prevention. The concept of passive single-optic shift lenses has failed. Concomitant poor capsular bag performance makes these lenses an unacceptable trade-off. Magnet-assisted systems potentially combine clinically useful accommodation with satisfactory after-cataract performance. Dual optic lenses theoretically offer substantial accommodative potential but may allow for interlenticular after-cataract formation. Lens refilling procedures have the greatest potential for fully restoring natural accommodation, but will again require years of extensive laboratory and animal investigations before they may function in the human eye.

Intracorneal inlays

One of the great achievements in the history of refractive surgery was the development and adoption of corneal inlays to treat presbyopia. One of the early approaches for presbyopia correction was additive refractive keratoplasty, in which human donor material was added to corneal tissue to change the refraction.[43] Furthermore, Barraquer introduced the idea of corneal inlays in the late 1940s, initially as a treatment for aphakia and high myopia. These early inlays were made of flint glass or polymethyl methacrylate (PMMA) and succeeded in treating the refractive error, but to the cost of corneal necrosis and implant extrusion.[43,44]

Dohlman et al. introduced the use of hydrogel polymers as corneal inlays to improve nutrient and metabolic gradients in animals.[45] Materials improved over the years, and finally Steinert introduced a well-biocompatible lens for aphakia: the Kerato-Gel lens (Allergan, Inc., Irvine, CA, USA), one of the precursors of modern corneal inlays.[46]

At the moment, there are three different types of corneal inlays commercially available. There is the group of refractive inlays that alters the index of refraction by the means of a bifocal optic (the Presbia Flexivue Microlens™ (Presbia Coöperatief U.A., Irvine, CA, USA) and the Icolens™ (Neoptics AG, Hünenberg, Switzerland)), the group of reshaping inlays that makes changes in corneal curvature (the Raindrop® Near Vision Inlay (ReVision Optics, Lake Forest, CA, USA), and finally the third group of inlays that relies upon the principle of small-aperture optics to increase depth of focus (the KAMRA™ inlay (AcuFocus Inc., Irvine, CA, USA).

The Raindrop inlay

The Raindrop corneal inlay is a clear, permeable, positive meniscus-shaped hydrogel implant. It has a diameter of 2 mm, a center thickness of 32 µm, and approximately the same refractive index as the cornea. Therefore, the inlay has no intrinsic refractive power itself, but it alters the eye's refractive power by increasing the central radius of curvature of the cornea overlaying the implant. Because the inlay is thinner at the edge than in the center, the increase in anterior corneal height transitions from the region anterior to the inlay diameter through an intermediate region and back to the unaltered cornea. It thus creates a hyperprolate corneal shape, resulting in a multifocal cornea. The hydrogel material used for the implant is highly permeable and allows for the free passage of oxygen and nutrients, therefore ensuring stable corneal conditions. As it is the case for the other inlays, the Raindrop is implanted in the nondominant eye, but relatively shallowly in the cornea (130–150 µm). At the moment, there are two peer-reviewed articles on the Raindrop inlay that have reported on the use and results following implantation of the Raindrop.

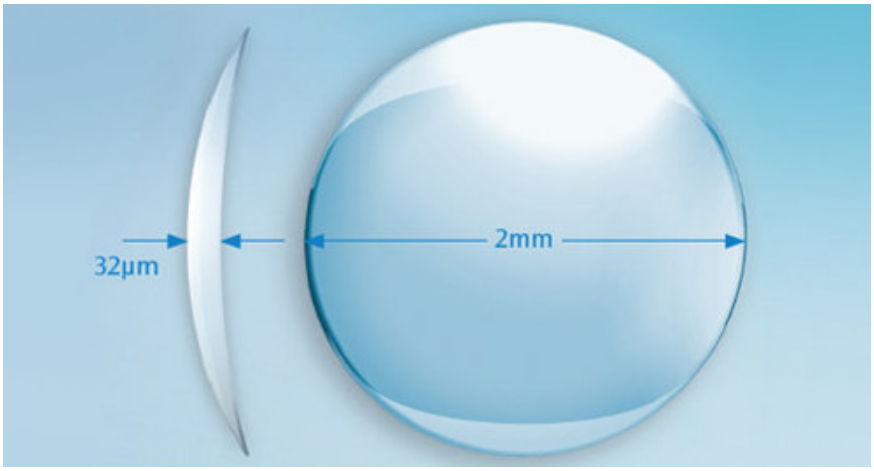

Figure 7. Raindrop intracorneal inlay

Garza et al. and Chayet et al. used keratotomy according to their standard clinical procedures and created a flap with a diameter greater than 8 mm and a depth of 130–150 μm using a femtosecond laser.[47,48] The Raindrop inlay was placed in the stromal bed by the inserter provided by the manufacturer and correctly positioned over the center of the pupil. Finally, the flap was replaced over the inlay on the corneal bed.

Garza et al. reported their results 12 months after implanting the device in 19 presbyopic emmetropes. One hundred percent of patients achieved UNVA of 0.2 logMAR or better in the operated eye. The mean UNVA was better than 0.1 logMAR at all visits, including the final follow-up after 12 months. One hundred percent of patients achieved a binocular UNVA of 0.18 logMAR or better. By 1 month postoperatively, mean binocular UDVA was 0.01 logMAR and remained at this level or better until the last postoperative visit.[47]

Chayet et al. presented the results of 16 hyperopic presbyopic patients implanted with the Raindrop inlay immediately after the laser corneal correction of the hyperopia. The mean UNVA in the implanted eye was 20/21 (Snellen) ±0.04 (logMAR) after 12 months. The mean uncorrected intermediate visual acuity (UIVA) was 20/26±0.07 and the UDVA was 20/31±0.14 after 12 months. The mean binocular UNVA was 20/21±0.03 after 12 months. The mean binocular UIVA was 20/26±0.08, and the mean UDVA was 20/19±0.11 after 12 months.[48]

The KAMRA inlay

The KAMRA inlay is the one inlay that has been studied the most among its class. The current generation of the inlay (model ACI7000PDT) is a 5 μm thin microperforated artificial aperture, with a total diameter of 3.8 mm and a central aperture of 1.6 mm made of polyvinylidene fluoride with incorporated nanoparticles of carbon. The opaque permeable material has a light transmission of 6.7%; it further features a pseudorandom microperforation pattern consisting of 8,400 holes ranging in size from 5–11 μm in diameter to allow water and nutrition flow in order to prevent corneal thinning and epithelial decompensation.

Based on the pinhole effect, the inlay increases depth of focus and consequently improves near and intermediate visual acuity. The KAMRA does not split light between near, intermediate, and distance focal points. The patient, therefore, maintains his binocular summation despite the monocular implantation in the nondominant eye. The inlay is implanted in the non-dominant eye to improve near and intermediate visual acuity with minimal compromise to distance vision.

Inlay implantation is now usually performed in a lamellar pocket that is 220 μm or deeper, created with a full-spectrum laser using a 6×6 spot/line separation or the equivalent. It used to be inserted under a shallower flap (170–180 μm). If the procedure is combined with LASIK, a dual interface technique is used. First, the excimer laser correction is performed under a thin flap; secondly, the inlay is implanted at least 100 μm below in a pocket interface. The inlay is always inserted directly in the line of sight.

Tomita et al. have published the two largest reported series with any presbyopia correcting inlay to date. In one study, 223 eyes were implanted with the current version of the KAMRA inlay (all eyes had received LASIK treatment before).[49] In an earlier study comprising 360 eyes (180 patients), simultaneous corneal inlay implantation and LASIK were performed for presbyopia in patients with hyperopia, myopia, or emmetropia.[50]

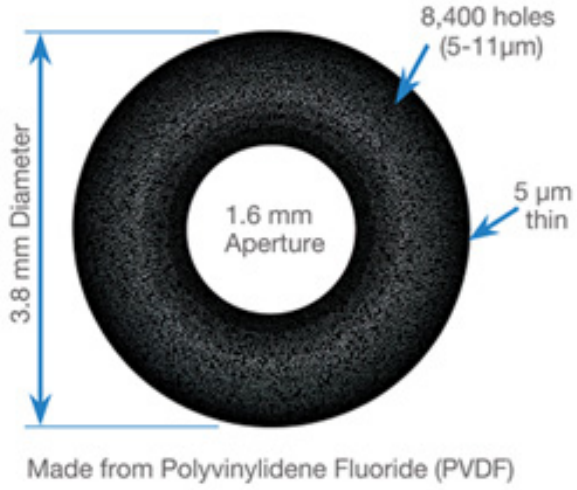

Figure 8. KAMRA intracorneal inlay

The first study enrolled 223 eyes (223 patients) with a mean age of 53.6 years (range: 44–65 years) and a mean manifest spherical equivalent of −0.18 D (range: −1.00 to +0.50 D). The mean UDVA in the operated eye decreased one line from 20/16 preoperatively to 20/20 6 months postoperatively (P<0.001). The mean UNVA improved four lines from Jaeger (J) 8–J2 (P<0.001). At 6 months, significant improvements were observed in patient dependence on reading glasses and patient satisfaction with vision without reading glasses.[49]

In regard to long-term results, Yilmaz et al. published data on a 4-year follow-up on 39 patients, Seyeddain et al. published 3-year follow-up data in 32 patients, and Dexl et al. published 5-year follow-up results in 32 patients.[51-53] All three studies showed safe and good results for the prior generation of the KAMRA inlay. Mean UNVA in the 3-year and 4-year follow-up studies was J1 with 96%–97% of treated eyes seeing J3 or better. Preoperative and postoperative binocular UDVA did not change significantly. Intermediate visual acuity was found to be satisfactory with this device, with 91% of patients being able to see at least 20/32.

The Icolens inlay

The Icolens™ (Neoptics AG, Hünenberg, Switzerland) is a hydrogel microlens with a central zone for distance vision and a peripheral zone for near vision correction. The 3.0 mm inlay has a bifocal design with a central zone for distance and a peripheral positive refractive zone for near. The central zone has a diameter of 1.8 mm, an edge thickness of 15 µm, and a 150 µm central hole to facilitate nutrient flow. It is manufactured using a copolymer of 2-hydroxyethyl methacrylate and methyl methacrylate, both of which have hydrogel properties.

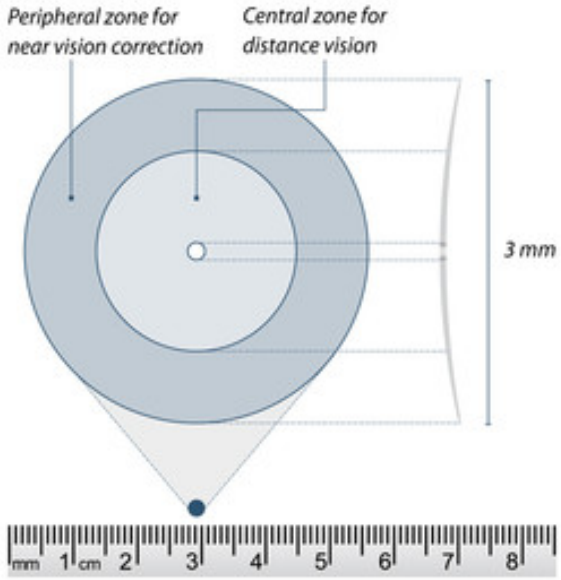

Figure 9. Icolens intracorneal inlay

Standard pocket-creation software settings of the Femto LDV femtosecond laser were used for pocket creation. Different suction ring sizes were used to account for patient-specific variations in physiognomy (eg, white-to-white distance). The pocket incision was always temporal, starting approximately 0.8 mm from the limbus and ending 1.7 mm beyond the

centration point. Pocket tunnel entry and the pocket bed had a diameter of 3.6 mm, and pockets were created at a depth of 290 μm. After pocket creation, the preloaded device was inserted into the corneal pocket until the hole located on the leaves was centric to the mark on the cornea.

Baily et al published recently one-year results of the Icolens inlay implanted in 52 patients.[54] The mean uncorrected near visual acuity (UNVA) in the surgical eye improved from N18/N24 preoperatively to N8 postoperatively; all patients had a UNVA of N16 or better and 9 (17%), of N5 or better. The uncorrected distance visual acuity (UDVA) in the surgical eye increased from 0.05 logMAR ± 0.12 (SD) preoperatively to 0.22 ± 0.15 logMAR postoperatively. There was a mean loss of 1.67 ± 1.77 lines of UDVA. Binocularly, there was a mean gain of 0.48 ± 1.16 lines of UDVA postoperatively, with 22 patients (42%) gaining more than 1 line. The mean loss of corrected distance visual acuity postoperatively was 1.78 ± 1.04 lines.

Materials and Methods

Importance of the study

During the past decades there has been an increased demand for spectacle independence in patients after cataract surgery. Several methods on corneal, lenticular and scleral level have been proposed for compensation of the accommodation loss after cataract surgery.

Recently, an intracorneal inlay was introduced as a method for improving near vision in patients with presbyopia. The intracorneal inlay is placed under a corneal stromal flap or inside a stromal pocket made by femtosecond lasers.

The Presbia Flexivue Microlens® inlay (Presbia Coöperatief U.A., Irvine, Amsterdam, Netherland) is a refractive intracorneal inlay. The lens has a bifocal optical system which acts as modified monovision and is inserted into an intrastromal corneal pocket made by a femtosecond laser in the non-dominant eye. Recent studies support the efficacy and safety of the Presbia Microlens® corneal inlay for the treatment of presbyopia in patients with clear crystalline lens.[55,56]

This is the first study to describe and compare three techniques of cataract surgery and refractive corneal inlay combination, as a new method for near vision improvement in pseudophakic patients after cataract surgery.

Study questions and objectives

The questions regarding combined refractive inlay implantation and cataract surgery to which this study is to give answers are:

1. Could this method compensate presbyopia in pseudophakic patients?

2. Is this method of presbyopia compensation safe?

3. Are the results stable?

4. Are the patients satisfied with their vision?

5. Which one of three studied techniques provides the best results?

Objectives of this study are:

- to implant the refractive Microlens inlay and perform cataract surgery in patients using three different combination technique
- to follow up patients for at least 12 months
- to analyze safety and efficacy of the techniques during this period

Clinical Hypothesis

The working clinical hypothesis for this study is that implantation of the refractive inlay of the appropriate power in the non-dominant eye provides functional near vision in pseudophakic patients. The lens is placed in the center of the cornea corresponding to the visual axes in a corneal pocket created by femtosecond laser.

Purpose of the study

The purpose of this pilot study is to evaluate and compare safety and efficacy of three different techniques of combined cataract and refractive corneal inlay implantation surgery over a 12-month follow-up. Near and distant visual acuity, manifest refraction, contrast sensitivity and patients' satisfaction outcomes were evaluated and compared. Furthermore, astigmatic changes, changes in corneal topography, intraocular pressure measurement and endothelial cell density were evaluated.

The Presbia Flexivue™ Microlens

The Presbia Flexivue™ Microlens is a transparent, hydrophilic disc with 3 mm diameter and approximately 15 μm edge thickness. The central 1.6 mm diameter of the disc is plano and the peripheral zone has an add power. The base power available range from +1.50 D to 3.50 D in 0.25 D increments. (Figure 10). The lens is implanted inside a pocket of the corneal stroma at the line of sight of the non dominant eye.

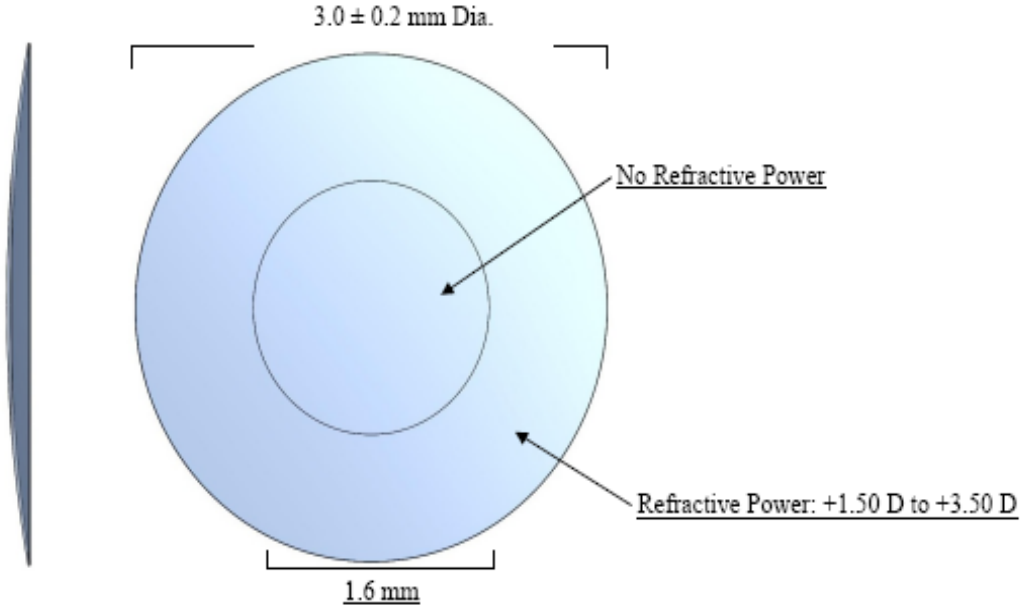

Figure 10. The Flexivue™ Micro-Lens is a transparent, hydrophilic disc with 3 mm diameter and approximately 15 μm edge thickness depending on the add power. The central 1.6 mm diameter of the disc is plano and the peripheral zone has an add power. The base power available range from +1.50 D to +3.50 D in 0.25 D increments.

The lens has a bifocal optical system which acts as a modified monovision (smart monovision). During far vision the rays pass through the central zone of the inlay without refractive effect and will be sharply focused on the retina, whereas the rays which pass through the refractive peripheral zone will be out of focus in front of the retina (Figure 11a). During near vision, the rays which pass through the central zone will be out of focus behind the retina and the rays which pass through the lens peripheral refractive zone will be focused on the retina (Figure 11b). As a result, only the peripheral zone of the lens provides the near vision correction, and affects far vision, whereas the central zone of the lens and the peripheral unaltered part of the cornea do not affect the far vision.

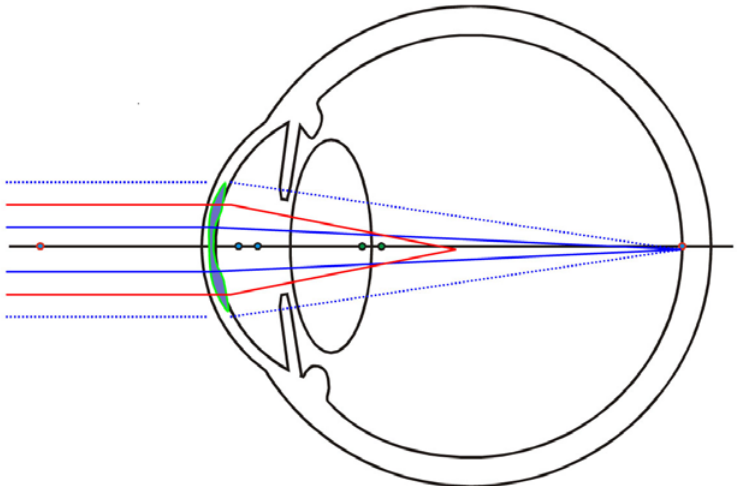

Figure 11a: During far vision the rays pass through the central zone of the implant (blue line) and through the free peripheral corneal tissue (interrupted blue line) without the lens added refractive effect and will be sharply focused on the retina, whereas the rays which pass through the refractive peripheral zone (red line) will be focused in front of the retina

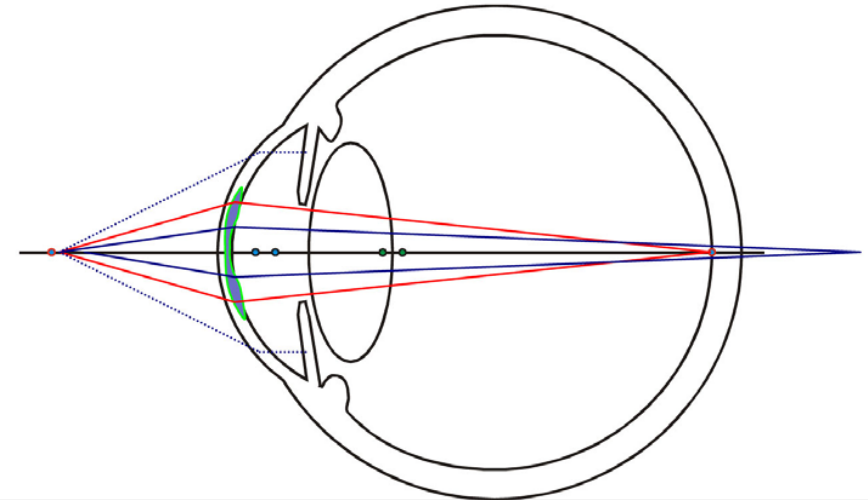

Figure 11b: During near vision the rays passing through the central zone of the implant (blue line) will be out of focus behind the retina and the rays passing through the peripheral clear cornea will be blocked by the pupil (interrupted blue lines) .The rays passing through the peripheral refractive zone (red lines) will be focused on the retina

Study design

This comparative pilot study was conducted at the Institute of Vision and Optics, University Hospital of Crete, Greece. Patients who met the selection criteria were randomly divided into three groups of five patients.

In Group 1 a “three-step” technique was performed: step one, an intra-corneal femtosecond laser pocket was created in the non-dominant eye and the stroma was separated using a spatula; step two, three months later bilateral cataract surgery was performed; step three, three months afterwards, the pocket was re-opened and the intracorneal inlay was inserted.

In Group 2 patients had a “short two-step” technique performed: three days after pocket creation and the inlay implantation in the non-dominant eye, bilateral cataract surgery was performed.

In Group 3 a “two-step” technique was carried out: three months after bilateral cataract surgery, the pocket creation and the inlay insertion were performed in the non-dominant eye.

Study population

Fifteen patients scheduled for bilateral cataract surgery and the inlay implantation were randomly allocated to one of three study groups. To qualify for enrollment in this study, each candidate was thoroughly evaluated to ensure that they meet all inclusion criteria and that they do not exhibit any of the exclusion criteria specified in the study protocol.

Inclusion criteria

Patients must:

- be male or female 50-80 years of age who have nuclear sclerosis of crystalline lens in both eyes;
- have uncorrected distance vision of 20/32 or worse in the study eye;
- have best spectacle corrected distance visual acuity 20/25 or worse in the study eye;
- have less than 1.50 D of corneal astigmatism;
- have at least 1500 endothelial cells on specular microscopy;
- have cornea with a minimum thickness of 500 μm;
- have normal and clear cornea, anterior segment, and vitreous media;
- have normal macula and post pole retina;
- be capable of understanding the scope and the purpose of the surgical procedure, its potential risks and benefits, and is willing to sign an informed consent form;
- have a non-dominant eye that can be determined;
- have a bilateral vision;
- be able to tolerate monovision;
- be able to tolerate topical anesthesia;

Exclusion criteria

Patients may not:

- have mature or hypermature cataract that makes fundoscopy difficult;
- have congenital, traumatic or complicated cataract;
- have iris neovascularization;
- have optic nerve atrophy;
- have intraoperative complications during cataract surgery (posterior capsular tear, haemorrghage, etc.)
- have a history of serious, acute or any chronic ocular disease including but are not limited to corneal irregularities, pterygium, glaucoma, diabetic retinopathy, macular degeneration or peripheral retinal disease;
- have amblyopia in the study or the contra-lateral eye;
- have strabismus;
- have a history of congenital or acquired corneal disease;
- have a history of previous ocular surgery;
- have history or predisposition of retinal detachment or diabetic retinopathy;
- have active inflammation of anterior or posterior ophthalmic segment of unknown aetiology, iridocyclitis, uveitis;

- have implant(s) or previous corneal incision(s) that may interfere with pocket creation;
- have distorted, non-reactive or decentered pupils; or have photopic diameter <3.0 mm; or dilate poorly after mydriatic drops instillation;
- have acute or chronic systemic diseases that could increase operative risks or interfere with ordinary healing process (immuno-compromised, connective tissue disease, uncontrolled diabetes, any neoplastic disease);
- be taking systemic medication that may interfere with corneal health or with corneal healing (steroids, antimetabolites, chemotherapy, amiodarone, etc.);
- in the opinion of the investigator have emotional problems that may interfere with their ability to undergo the procedure or to comply with the postoperative regimen of treatment and follow-up;
- have severe dry eye;
- if female and of childbearing potential, be pregnant or nursing;
- be using telescopes or microscopes for professional reasons, or be having a high professional near vision expectations like surgeons, architectures, accountants, professional athletes or pilots.

Consenting of prospective patients

Institutional review board approval was obtained and all patients were appropriately informed before their participation in the study about the possible outcomes and the current clinical experience, and provided written informed consent in accordance with the institutional guidelines, according to the Declaration of Helsinki (Appendix 1). All patients were informed about the potential risks and benefits of the cataract surgery. They were informed about the inlay implantation procedure and potential complications. They were also informed about alternative surgical and non-surgical procedures to correct near vision after cataract surgery. Patients were assured that the corneal inlay is removable and that if they decide to have the implant removed for any reason, it would have been done at no charge to them.

Clinical examination

Careful evaluation of the patient's optical and medical record was performed. Patients who may have had objective or subjective difficulties complying with protocol schedules and procedures were not enrolled. Prospective candidates who seemed to be suitable for the study proceeded to the preoperative evaluation.

Preoperative Examination

The pre-operative examination data included patient age, sex, ocular and general health history, manifest refraction, uncorrected distance visual acuity (UDVA), uncorrected near visual acuity (UNVA), corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, cataract grading (LOCS III), computerized corneal topography and central keratometry with iTrace (Tracey Technologies, Houston, USA) and Galilei (Ziemer, Biel, Switzerland), intraocular pressure measurement (Goldmann applanation tonometry), central corneal thickness measurement (50 MHz [Corneo-Gage Plus; Sonogage Inc, Cleveland, USA]), and dilated fundus evaluation. Quantitative analysis of endothelial cell density was performed with Tomey EM-3000 specular microscopy (Tomey Corporation, Nagoya, Japan). Contrast sensitivity was measured using the Functional Acuity Contrast Test (Stereo Optical Co Inc, Chicago, USA) in photopic and mesopic conditions (with and without glare), binocularly, and monocularly.

The IOLMaster® 500 (Carl Zeiss Meditec, Jena, Germany) was used for biometry and SRK-T formula for intraocular lens power calculations. Targeting refraction was emmetropia in both dominant and non-dominant eyes. A one-piece aspheric intraocular lens AcrySof IQ

model SN60WF with 6.0 mm optic diameter and 13.0 mm haptic diameter, using an A-constant of 118.7 was implanted in all eyes.

Visual acuity

Visual acuity was measured for distance and near in LogMar or Snellen equivalent. Scoring and conversion was performed using standardized forms. Manifest refraction (MR) was performed for distance and near vision. Uncorrected visual acuity (UVA) and best spectacle corrected visual acuity (BSCVA) for distance were assessed using an ETDRS chart placed 4 meters from the patient. The chart background luminance was set approximately at 85-120 cd/m2 and cabinet light standardized >120 cd/m2. The information was recorded in LogMar or Snellen Equivalents.

For near visual acuity the University of Crete (UoC) chart and score table was used (Appendix 2). UoC chart were placed at 33 cm from the patient to measure UVA and BCVA for near. A 2000 light source was used at 50 cm from the chart. The information was recorded in LogMar or Snellen Equivalents.

Monovision selection and trial

For the selection of the non-dominant eye a card with a central hole (25 mm diameter) was used. Using manifest refraction (MR) for distance the patient looked through the central hole with the dominant eye. In addition, in order to verify the results, a four dot test was used. After selecting the non-dominant eye, a monovision trial using spectacles or contact lenses was performed with an additional power of +1.50 D to MR for distance in the non-dominant eye. The patient had to try the monovision for at least 30 minutes.

Contrast sensitivity

Contrast sensitivity was measured using the FACT (Functional Acuity Contrast Test, Stereo Optical Co. Inc.USA) in photopic and mesopic conditions. In mesopic conditions contrast sensitivity was measured with and without glare, binocularly and monocularly. The FACT is a chart displaying sinusoidal gratings of five different spatial frequencies with nine contrast levels for each spatial frequency. The corresponding spatial frequencies are 1.5, 3, 6, 12, and 18 cycles per degree. The decrements of the grating contrast are 0.15 log CS units for each spatial frequency change. Gratings are displayed as circular patches with blurred edges either orientated vertically or tilted 15º to the right or left.

Target illumination and glare were manually set by the examiner. The patients observed the test rows in a random sequence. The patient had to decide if the grating is directed vertically or tilted to the right or left. The CS at a certain spatial frequency was the last correct response before two successive wrong responses. If a patient did not recognize the lowest CS value, CS was recorded as zero for the tested spatial frequency.

Satisfaction questionnaire

During the pre-operative evaluation, a detailed discussion with each patient revealed his/her ideal near working distance or range, the amount of dependence on spectacles for near vision, as well as his/her overall satisfaction regarding vision throughout the day. At last follow-up, patients were asked to complete a satisfaction questionnaire (Appendix 3) for the subjective evaluation of binocular UNVA, monocular and binocular UDVA, frequency of eventual use of reading glasses, and for the presence or absence of halos and/or glare. A scale of 1 to 4 was used for UNVA and UDVA evaluation, in which a score of 1 indicates “excellent”, 2 “good”,

3 “fair” and 4 indicates “poor” satisfaction’. The results are presented as a mean score in each group. The presence of glare and halos, as well as the need for reading glasses, was described as “never”, “sometimes” “frequently” and “always”.

Surgical Technique

Pocket creation and inlay implantation

The corneal inlay was implanted into a pocket created by a femtosecond laser in the corneal stroma at the line of sight of the non-dominant eye. The surgical procedure was performed under topical anesthesia using proxymetacaine hydrochloride 0.5% eye drops (Alcon Laboratories Inc, Ft Worth, USA). The intrastromal corneal pocket was created using a femtosecond laser (IntraLase iFS 150; Abbott Medical Optics, Santa Ana, USA). Using the standard pocket-creation software of the IntraLase femtosecond laser, a lamellar cut of a pocket of 9.0 mm chord diameter and temporal pocket access tunnel 4.20 mm chord width were created at a depth of 300 µm with a line separation/spot size of 2/2 µm (Figure 12a). The pocket access tunnel was temporal. Table 1 shows the femtosecond laser parameters of the procedure.

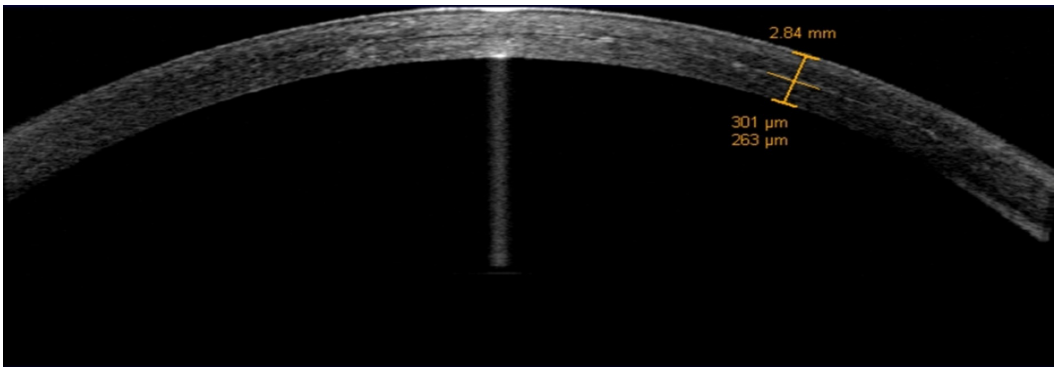

Figure 12a. Anterior segment optical coherence tomography (AS OCT) showing the inlay inside the intrastromal corneal pocket at a depth of 300 µm

Table 1. Femtosecond-assisted Pocket Laser Parameters

Femtosecond laser	iFS 150
Treatment type	inlay
Channel width (mm)	4.20
Channel offset (mm)	0.00
Channel depth (μm)	300
Channel spot separation (μm)	2
Channel line separation (μm)	2
Channel energy (μJ)	0.75
Side cut radius (mm)	4.50
Side cut angle (°)	30
Side cut spot separation (μm)/ Side cut layer separation (μm)	3/3
Side cut energy (μJ)	1.20

The inlay was implanted with a special injector (Presbia Cooperatief U.A.) inside the tunnel at the line of sight (pupil centration) (Figure 12b). To determine the line of sight, the microscope and centration device of the excimer laser (Allegretto Wave 400; WaveLight Technologie AG, Erlangen, Germany) were used.

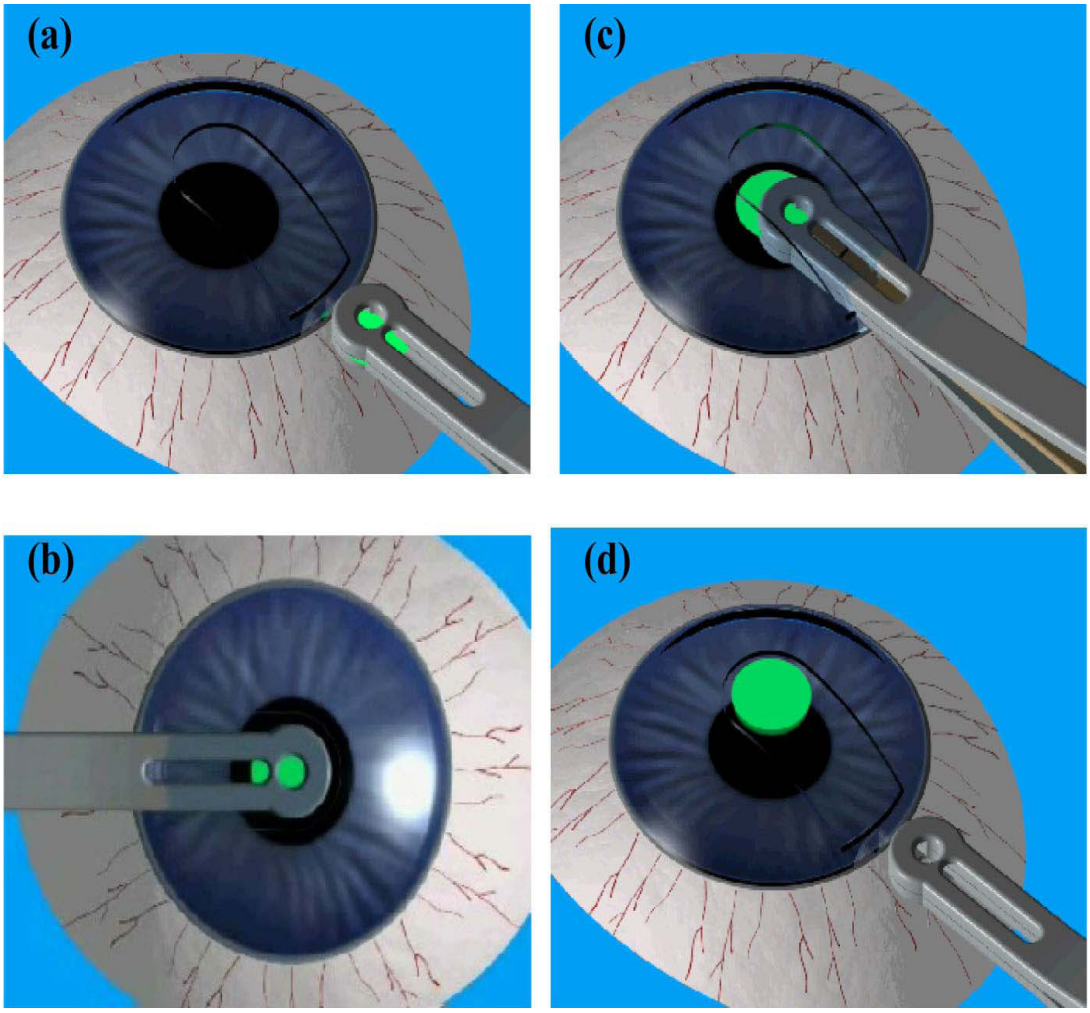

Figure 12b. After the femtosecond assisted creation of an intrastromal pocket (a) using a special injector (b, c) the lens is implanted inside the stroma of the cornea (d).

Post-operatively, after pocket separation and/or inlay implantation, patients were treated with topical antibiotic-steroid drops (tobramycin/dexamethasone, Tobradex; Alcon Laboratories Inc, Ft Worth, USA) for 10 days along with preservative-free artificial tears.

Cataract surgery

All surgical procedures were performed under sterile conditions and topical anesthesia by the same experienced surgeon, using a standard manual phacoemulsification technique. A superior clear corneal incision of 2.8 mm was made and an anterior curvilinear continuous capsulorhexis not larger than 5.5 mm was performed. Phacoemulsification was performed using the Infiniti Vision System (Alcon, Laboratories Inc, Fort Worth, USA), with thorough cortical removing and meticulous cleaning of the posterior capsule and anterior capsular leaflets. After phacoemulsification and lens removal, the IOL (AcrySof IQ SN60WF) was implanted into the capsular bag using the standard injector device.

Post-operative topical therapy included topical antibiotic-steroid drops (tobramycin/dexamethasone, Tobradex; Alcon Laboratories Inc, Ft Worth, USA) four times a day for 4 weeks with a weekly tapering regimen.

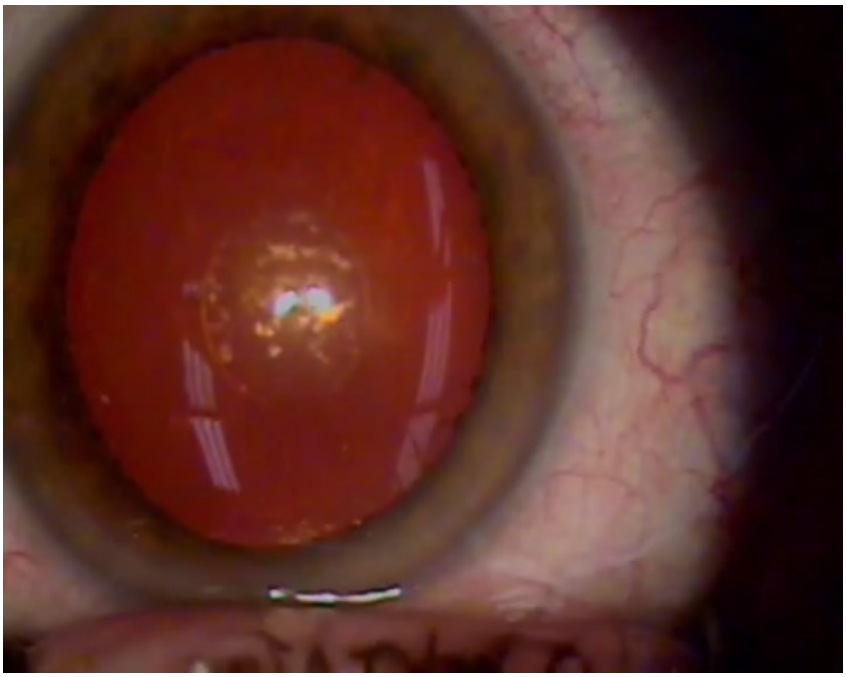

Figure 13. Photo taken through the operating microscope at the beginning of cataract surgery showing transparency of the inlay

Study duration, schedule of visits and post-operative examinations

The study duration was approximately 12 months. Post-operative follow-up was scheduled in 1, 3, 6 and 12 months and followed examinations were performed at each visit: visual acuity and manifest refraction, slit-lamp biomicroscopy, corneal topography, intraocular pressure, central corneal thickness, endothelial cell density and contrast sensitivity.

Statistical analysis

Excel 2007 (Microsoft, USA) and a customized Ophthalmic Data Analysis Software (ODAS) by Georgios A. Kounis PhD (©2014 Ophthalmic Data Analysis Software GNEMS-Greece) were used for data collection and analysis. Calculation of the surgical induced astigmatism (SIA) was performed using Harris' method. Non parametric paired tests (Wilcoxon rank signed sum test) were used to compare preoperative and post-operative data. Comparison between groups was performed using non parametric tests (Wilcoxon / Kruskal-Wallis Tests (Rank Sums). All distributions were examined for normality with Kolmogorov-Smirnov tests. Statistical analysis was performed by SAS JMP 10.0 (http://www.jmp.com/ 2012). A P value less than 0.05 was considered statistically significant.

Results

In total forty-six patients were examined, of which 15 met all the inclusion criteria and were enrolled in the study. Patient demographics, the implanted inlay and IOL power and pre-operative clinical data of non-dominant eyes are depicted in Table 2. There was no statistically significant difference in any parameter between three groups. All patients completed the 12-month follow-up.

Table 2. Patient demographics and clinical information (Abbreviations: CDVA = corrected distance visual acuity; SEQ = spherical equivalent; UDVA = uncorrected distance visual acuity; UNVA = uncorrected near visual acuity)

Parameter	Group 1	Group 2	Group 3	*P* value
No. of patients	5	5	5	-
Males/Females	3/2	1/4	1/4	-
Right/Left	3/2	1/4	2/3	-
Age (year)				
Mean ± SD	63.00±2.00	65.40±4.28	64.40±4.39	0.607
Range	60, 65	58, 68	61, 71	

Axial length (mm)				
Mean ± SD	23.54±0.96	23.39±0.41	24.06±1.46	0.585
Range	22.41, 24.83	23.04, 23.86	22.93. 26.54	
Inlay power (D)				
Mean ± SD	2.65± 0.34	2.30± 0.21	2.25± 0.59	0.393
Range	2.50, 3.25	2.00, 2.50	1.50, 2.75	
UDVA (logMAR)				
Mean ± SD	0.88±0.30	0.76± 0.29	0.82± 0.25	0.069
Range	0.40, 1.20	0.50, 1.20	0.50, 1.00	
UNVA (logMAR)				
Mean ± SD	0.87± 0.37	0.86± 0.40	0.88±0.33	0.948
Range	0.26, 1.18	0.30, 1.20	0.50, 1.20	
CDVA (logMAR)				
Mean ± SD	0.28± 0.21	0.30± 0.07	0.40± 0.16	0.509
Range	0.10, 0.70	0.20, 0.40	0.20, 0.60	
Sphere (D)				

Mean ± SD	0.40± 3.45	-0.80± 4.25	-2.85±5.14	0.546
Range	-5.00, 3.50	-7.25, 2.75	-7.75, 4.00	
Cylinder (D)				
Mean ± SD	-0.35± 0.34	-0.60± 0.42	-0.90± 0.42	0.156
Range	-0.75, 0.00	-1.00, 0.00	-0.50, -1.50	
SEQ refraction (D)				
Mean ± SD	0.23±3.51	-1.10±4.36	-3.30±5.20	0.527
Range	-5.38, 3.25	-7.75, 2.75	-8.50, 3.50	
Corneal thickness (μm)				
Mean ± SD	545±29.80	530±32.84	556±30.71	0.363
Range	507,574	503, 578	514, 589	
Corneal topographic astigmatism (D)				
Mean ± SD	0.48±0.33	0.85±0.66	0.77±0.28	0.532
Range	0.14, 0.87	0.22, 1.55	0.46, 1.10	

Endothelial cell density (cells/mm^2)				
Mean ± SD	2454±244	2418±486	2544±307	0.778
Range	2123, 2760	2027, 3001	2198, 2935	
IOL power (D)				
Mean ± SD	21.20± 2.06	22.00± 0.79	21.70± 2.46	0.716
Range	16.50, 22.50	21.00, 23.00	21.00, 24.00	
IOP (mmHg)				0,722
Mean ± SD	14.60± 1.34	15.00± 2.35	14.60± 1.82	
Range	13.00, 16.00	11.00, 17.00	12.00, 17.00	

Visual acuity and manifest refraction

Table 3 shows post-operative monocular (eyes with the inlay) visual acuity and manifest refraction at 12-month follow-up. Table 4 shows the post-operative binocular visual acuity at 12-month follow-up. No statistically significant differences were found in uncorrected or corrected monocular or binocular visual acuity between the examinations during the follow-up ($P > .05$ for all values in three groups).

Table 3. Monocular visual acuity and refractive results of non-dominant eyes (Abbreviations: CDVA = corrected distance visual acuity; SEQ = spherical equivalent; UDVA = uncorrected distance visual acuity; UNVA = uncorrected near visual acuity)

		P Values	
Parameter	Results	Preop vs Postop	Between Groups
UDVA (logMAR)			0.377
Group 1			
Mean ± SD	0.18±0.04	0.125	
Range	0.10,0.20		
Group 2			
Mean ± SD	0.16±0.05	0.063	
Range	0.10, 0.20		
Group 3			
Mean ± SD	0.12±0.08	0.125	
Range	0.00, 0.20		

UNVA (logMAR)			0.498
Group 1			
Mean ± SD	0.08±0.02	0.125	
Range	0.06, 0.10		
Group 2			
Mean ± SD	0.10±0.02	0.063	
Range	0.08, 0.12		
Group 3			
Mean ± SD	0.06±0.04	0.125	
Range	0.00, 0.10		
CDVA (logMAR)			1.000
Group 1			
Mean ± SD	0.04±0.05	0.125	
Range	0.00, 0.10		
Group 2			
Mean ± SD	0.04±0.05	0.063	
Range	0.00, 0.10		
Group 3			
Mean ± SD	0.04±0.05	1.125	
Range	0.00, 0.10		
Sphere (D)			0.523
Group 1			
Mean ± SD	0.00±0.50	0.125	
Range	-0.75, 0.50		

Group 2			
Mean ± SD	-0.25±0.61	0.063	
Range	-1.00,0.50		
Group 3			
Mean ± SD	0.15±0.42	0.125	
Range	-0.25,0.75		
Cylinder (D)			0.763
Group 1			
Mean ± SD	-0.45±0.27	0.250	
Range	-0.75, 0.00		
Group 2			
Mean ± SD	-0.60±0.38	0.500	
Range	-1.25, -0.25		
Group 3			
Mean ± SD	0.40±0.42	0.125	
Range	-1.00, 0.00		
Spherical equivalent refraction (D)			0.601
Group 1			
Mean ± SD	-0.23±0.56	0.125	
Range	-1.00, 0.25		
Group 2			
Mean ± SD	-0.43±0.46	0.810	
Range	-1.13, 0.00		

Group 3			
Mean ± SD	-0.05±0.48	0.310	
Range	-0.50, 0.75		

Table 4. Binocular visual acuity results (Abbreviations: CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity; UNVA = uncorrected near visual acuity)

		P Values	
Parameter	Results	Preop vs Postop	Between Groups
UDVA (logMAR)			0.262
Group 1			
Mean ± SD	0.04±0.05	0.125	
Range	0.00, 0.10		
Group 2			
Mean ± SD	0.11±0.07	0.125	
Range	0.00, 0.20		
Group 3			
Mean ± SD	0.09±0.07	0.125	
Range	0.00, 0.20		
UNVA (logMAR)			0.864
Group 1			
Mean ± SD	0.06±0.03	0.125	
Range	0.02, 0.10		
Group 2			

Mean ± SD	0.06±0.03	0.063	
Range	0.02, 0.10		
Group 3			
Mean ± SD	0.05±0.04	0.125	
Range	0.00, 0.10		
CDVA (logMAR)			1.000
Group 1			
Mean ± SD	0.02±0.04	0.125	
Range	0.00,0.10		
Group 2			
Mean ± SD	0.02±0.04	0.063	
Range	0.00, 0.10		
Group 3			
Mean ± SD	0.02±0.04	0.125	
Range	0.00, 0.10		

Between-steps results and surgically induced astigmatism

In Group 1, three months after pocket creation no statistically significant changes occurred in the examined parameters. Corneal astigmatism changed from 0.48±0.33 to 0.65±0.11 D. The surgically induced astigmatism after pocket creation was 0.72±0.50 D at mean axis 56±32°. Three months after cataract surgery UDVA improved to 0.13±0.12 logMAR and CDVA to 0.04±0.05 logMAR. Other parameters had values similar to pre-cataract surgery values, UNVA was 0.77±0.09 logMAR, SEQ refraction 0.25±0.28 D and corneal astigmatism 0.53±0.40 D. The SIA after phacoemulsification with superior clear corneal incision was 0.84±0.40 D at mean axis 45±67°. Binocular UDVA was 0.06±0.09 logMAR, UNVA 0.68±0.17 logMAR, CDVA 0.02±0.04 logMAR. After inlay implantation the SIA was 0.43±0.23 D at mean axis 86±42°.

In Group 3, three months after cataract surgery UDVA improved to 0.08±0.03 logMAR and CDVA 0.04±0.06 logMAR. The rest of the results were similar to preoperative, UNVA was 0.71±0.09 logMAR, SEQ refraction -0.05±0.42 D and corneal astigmatism 0.79±0.21 D. Achieved binocular UDVA was 0.02±0.02 logMAR, UNVA 0.63±0.13 logMAR, CDVA 0.02±0.04 logMAR. The SIA after cataract surgery was 0.82±0.85 D at mean axis 63±59°, and after the inlay implantation 0.69±0.56 D at 62±46°.

Total surgically induced astigmatism in eyes with the inlay (preoperative vs. 12 months after inlay implantation) in Group 1 was 0.52±0.42 D at 86±42°, in Group 2 was 0.88±0.33 D at 87±43° and in Group 3 was 0.92±0.41 D at 96±19°.

Efficacy

Figure 14 shows the percentage of eyes with the inlay in each group with a cumulative uncorrected near visual acuity after the surgery. The monocular UNVA was 20/25 or better in all eyes with the inlay in all groups.

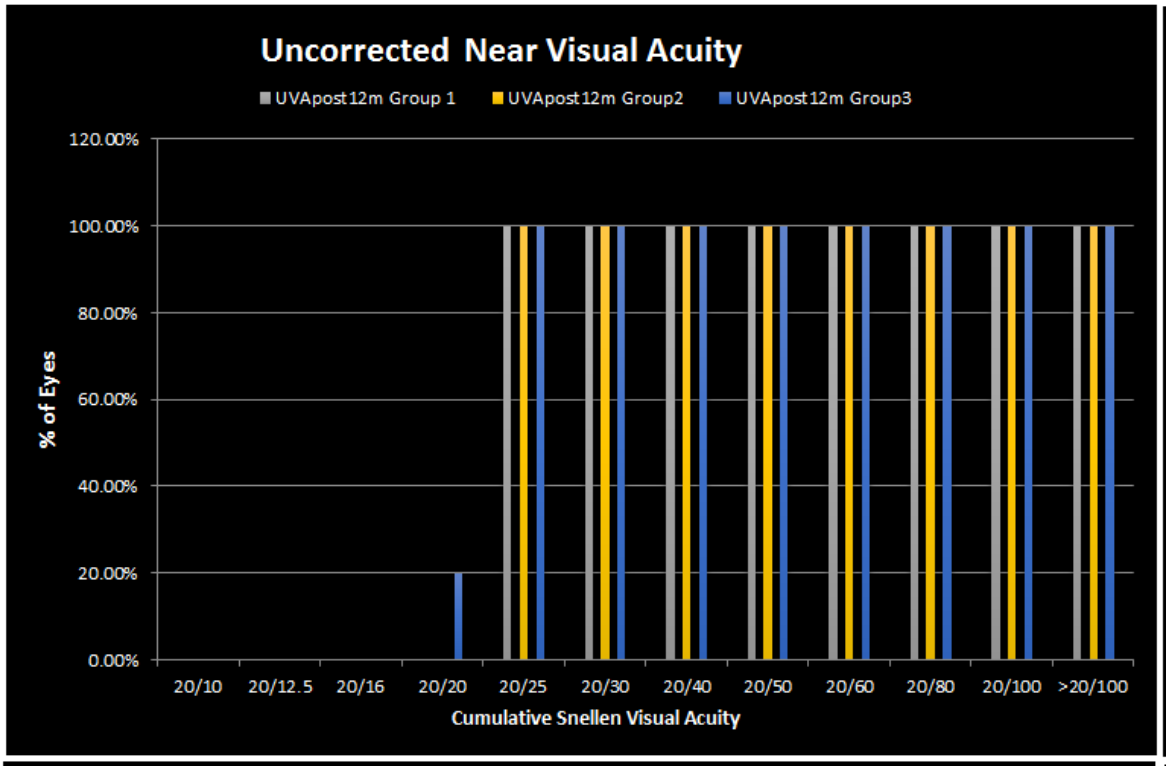

Figure 14. Cumulative uncorrected near vision acuity

Accuracy

At the 12-month follow-up, the spherical refraction was within ±0.50 D of the attempted spherical correction in 3 eyes with the inlay in Group 1, 3 eyes in Group 2, and 5 eyes in Group 3. (Figure 15) All eyes in groups 2 and 3 were within ±1.00 D. One eye in Group 1 was within ±1.50 D.

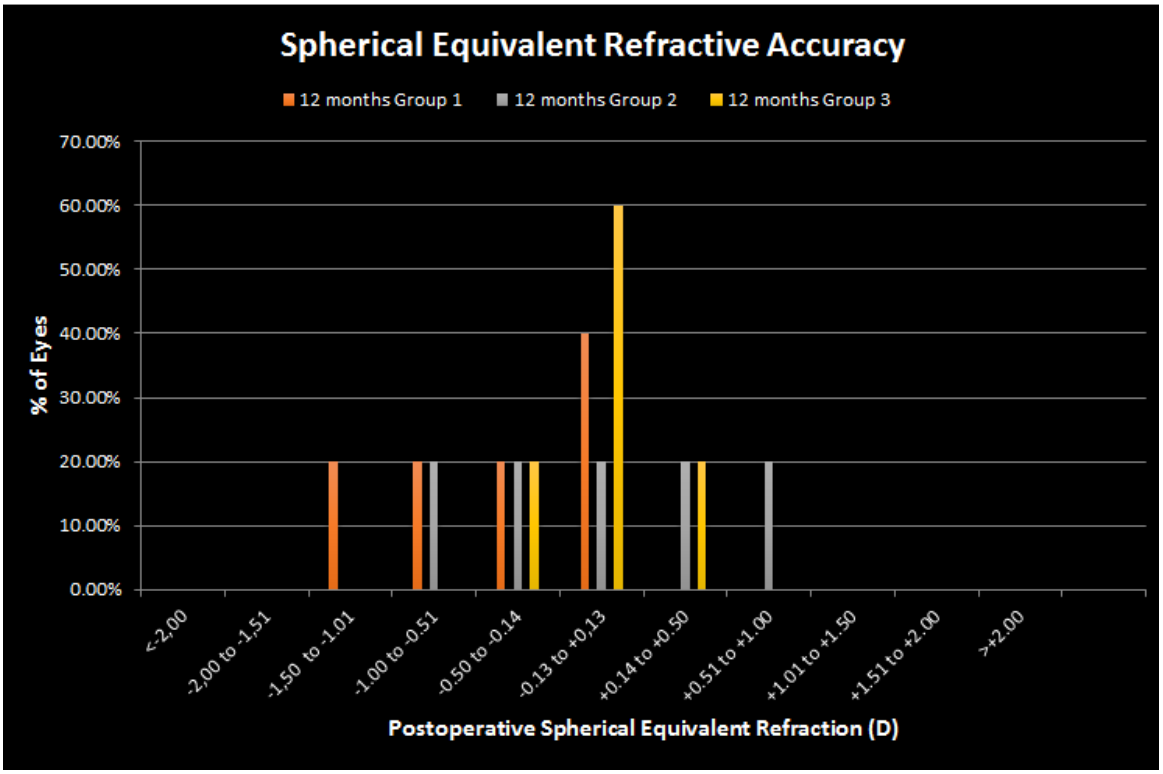

Figure 15. Spherical equivalent refractive accuracy

Safety and Complications

Figure 16 shows the change in Snellen lines of CDVA. All eyes with the inlay in three groups gained lines of CDVA. During the one-year follow-up none of the operated eyes had loss of line of CDVA.

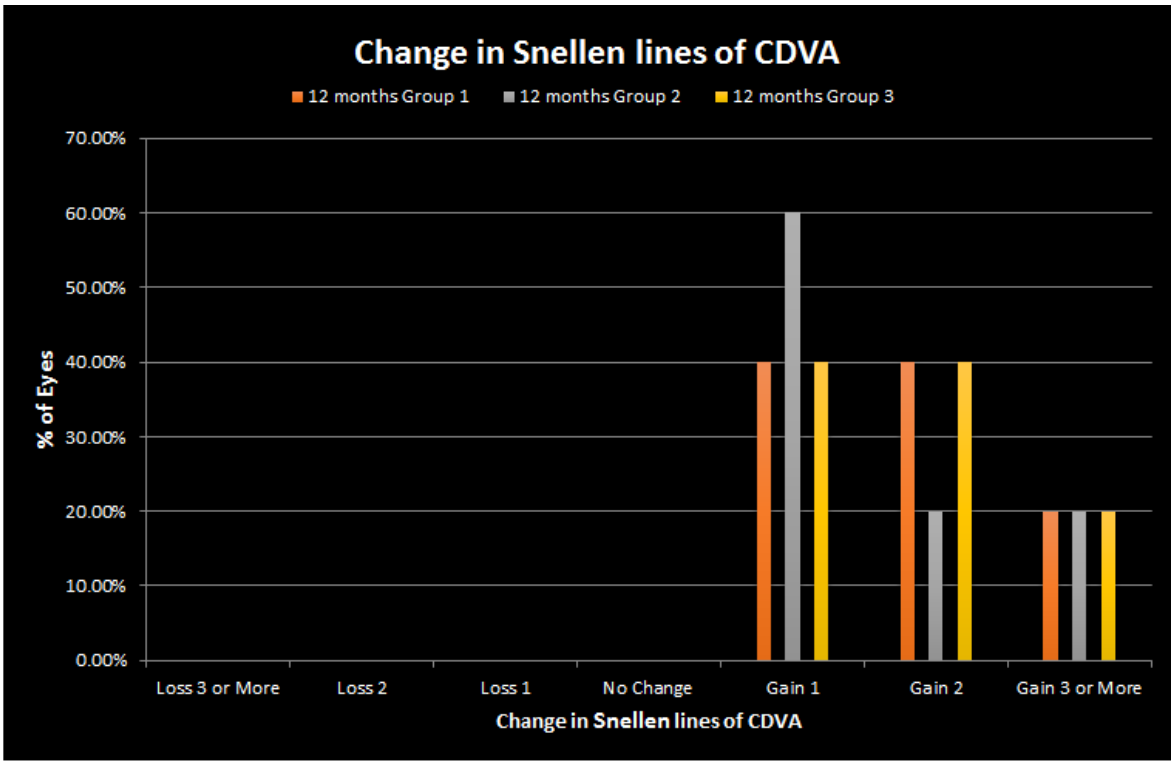

Figure 16. Change in Snellen lines of CDVA

During the 12-month follow-up, no intra-operative or post-operative complications occurred. No inlay was explanted or recentered during the reported follow-up. No epithelial ingrowth was observed.

Mean central corneal thickness in the eyes with the inlay did not change significantly at 12 months in any of groups (P=0.063, P=0.125, P=0.063, respectively). Post-operative intraocular pressure was similar to pre-operative and between groups post-operatively in all groups (P>.05).

The mean endothelial cells loss, one year after the cataract surgery, was similar between groups 1, 2, and 3 and was 8.92 %, 8.05%, and 8.39%, respectively, (P=0.42).

In the retroillumination examination 12 months after surgery, there was no significant posterior capsule opacification influencing the visual or refractive outcome.

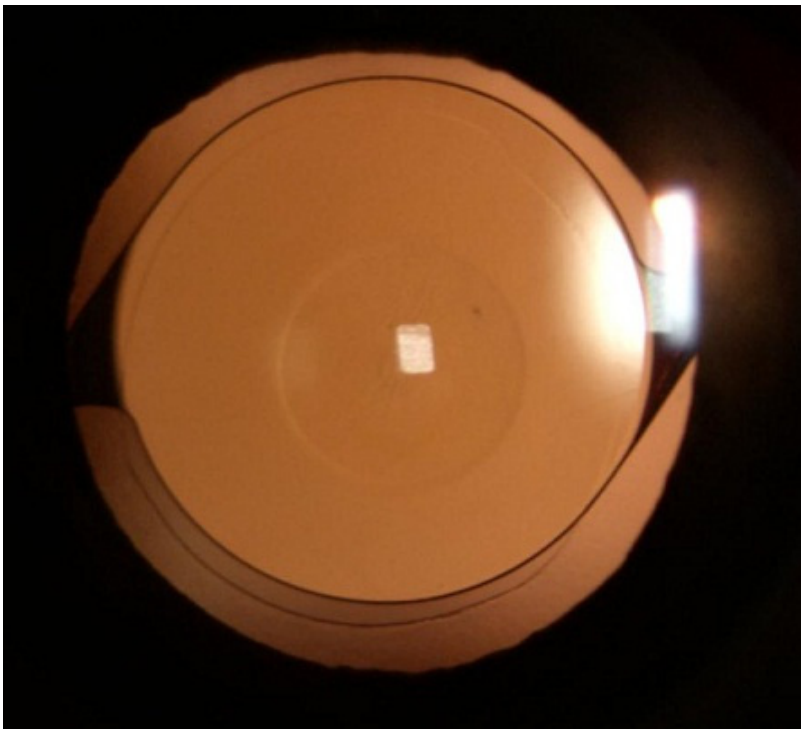

Figure 17. Retroillumination photo of the eye with the Microlens inlay and intraocular lens

Stability

Figure 18 shows the stability of SEQ refraction in non-dominant eyes over time. Apart from the minor changes (increase of 0.25 D in Group 1 and decrease of 0.50 D in Group 2) between the 1-month and 3-month follow-up, SEQ refraction remained stable over a one-year follow-up in all groups.

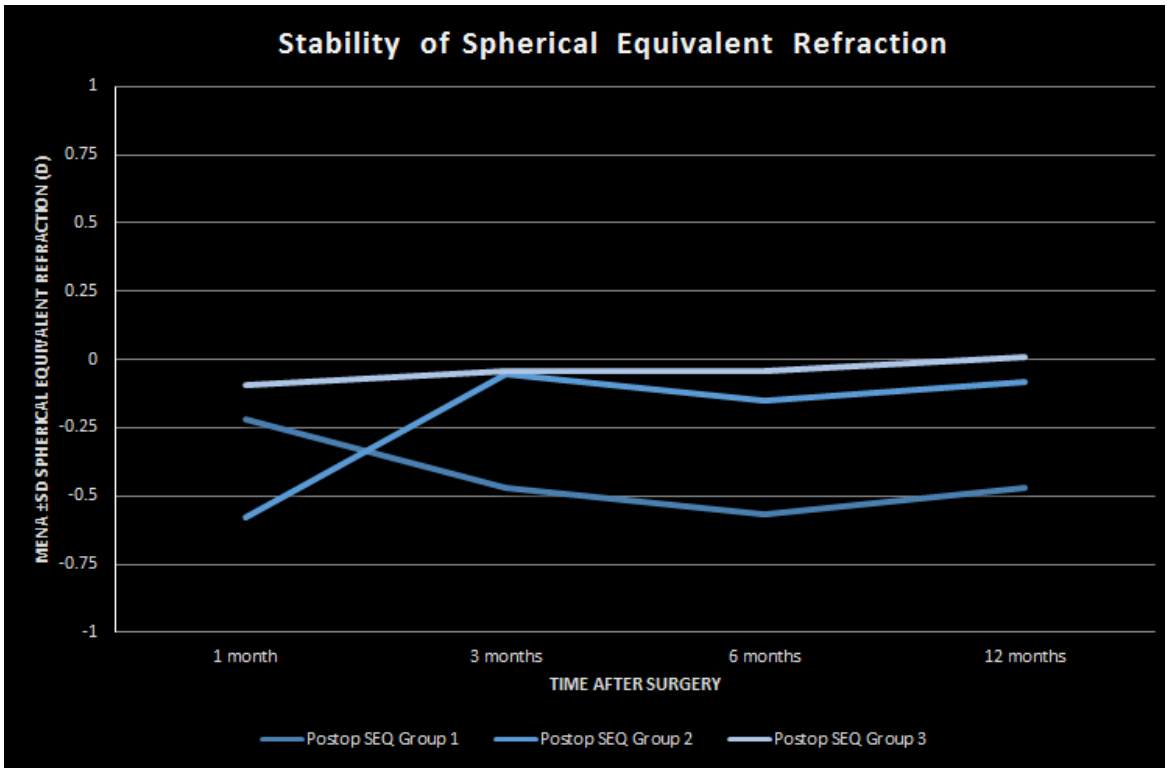

Figure 18. Stability of spherical equivalent refraction

Figure 19 shows the stability of monocular UDVA and CDVA refraction over time in eyes with the inlay. UDVA in groups 2 and 3 showed minor tendency of improvement over 12-month follow-up, whereas in Group 1 after initial improvement UDVA remained stable. CDVA in Group 2 showed slight improvement over the first 6 months, whereas groups 1 and 3 remained stable over a one-year follow-up.

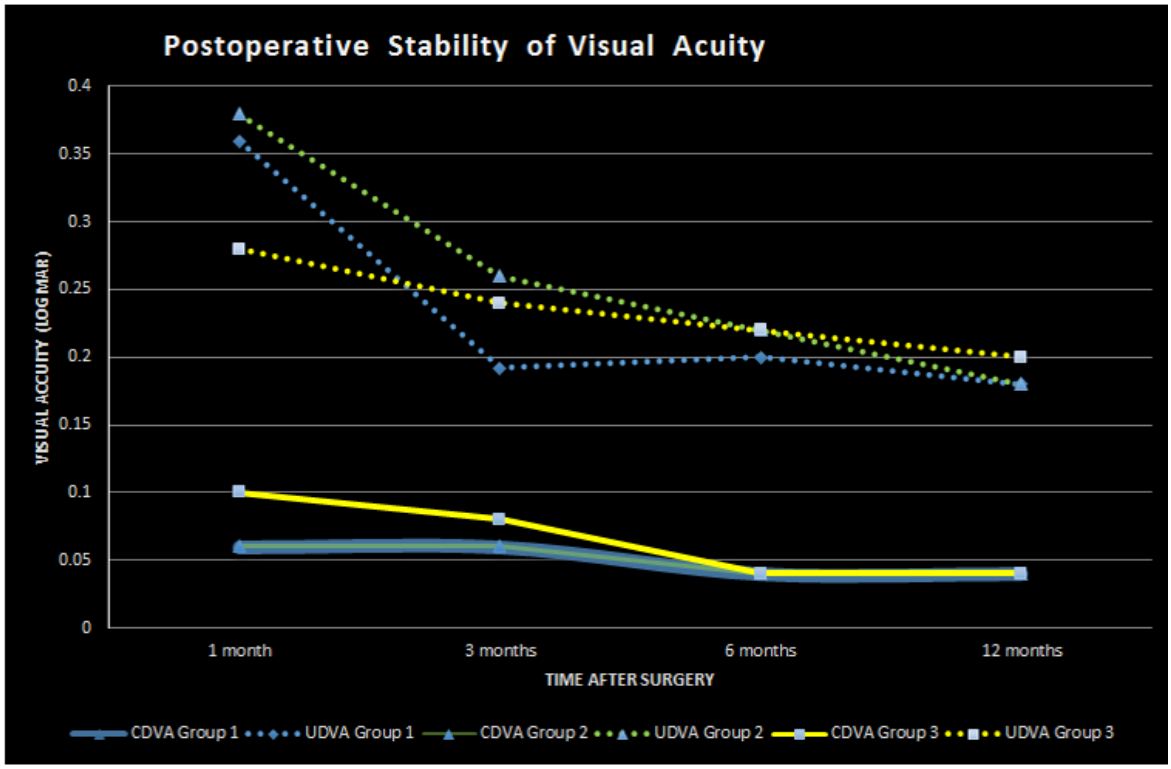

Figure 19. Postoperative stability of uncorrected and corrected distance visual acuity

Predictability

Figures 20, 21 and 22 show the attempted versus achieved spherical equivalent (SEQ) refraction for three groups.

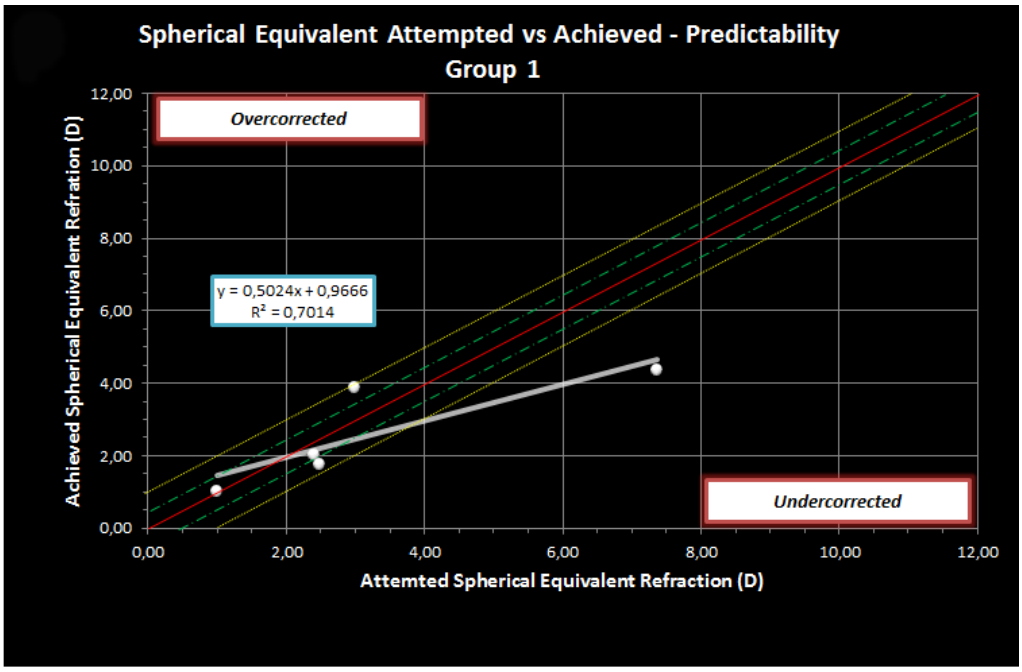

Figure 20. Predictability presented as spherical equivalent attempted vs achieved in group 1

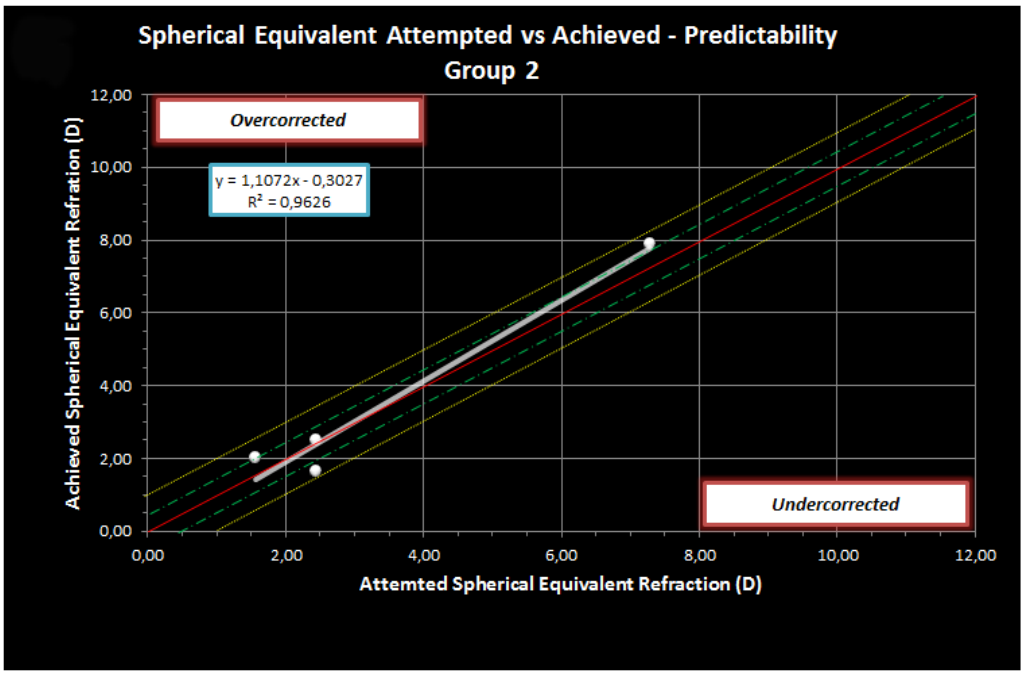

Figure 21. Predictability presented as spherical equivalent attempted vs achieved in group 2

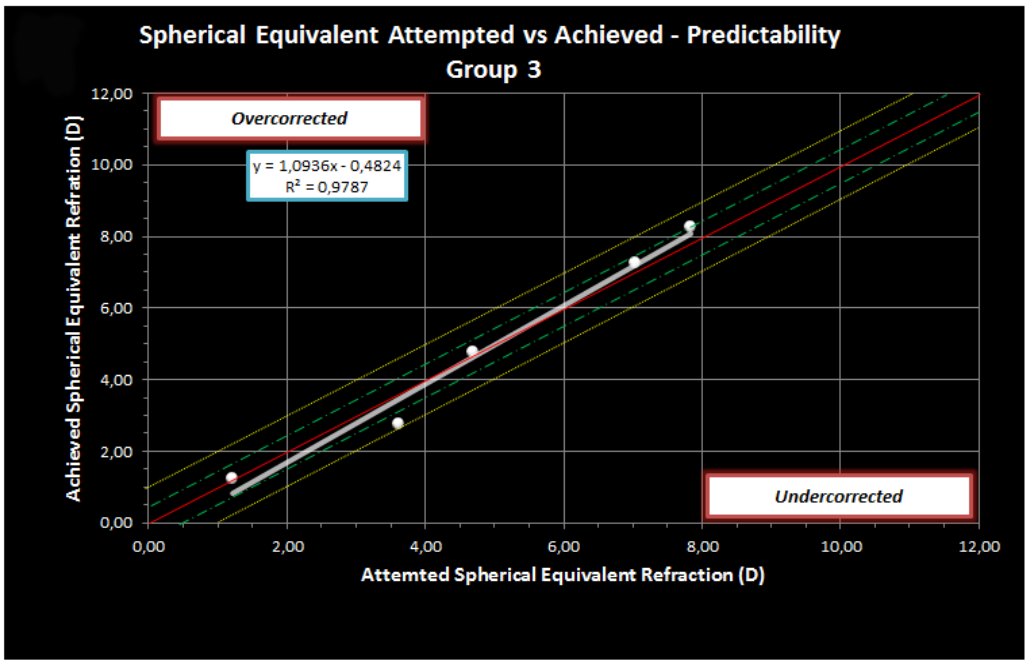

Figure 22. Predictability presented as spherical equivalent attempted vs achieved in group 3

Contrast Sensitivity

There was no difference between groups in pre-operative contrast sensitivity under photopic and mesopic conditions. At 12-month follow-up, at all the spatial frequencies tested, the monocular and binocular contrast sensitivity score, under mesopic and photopic conditions, were similar between the three groups ($P > .05$).

Monocular contrast sensitivity, in eyes with the inlay, at frequencies 12 and 18 cpd was lower in all groups, under both mesopic and photopic conditions, compared to contrast sensitivity of contralateral eyes (Figures 23).

Figure 24 shows binocular contrast sensitivity at 12-month follow-up, under photopic and mesopic in each group. Under mesopic conditions (with and without glare) Group 3 had slightly lower score than other two groups, at frequencies 12 and 18 cpd, but without statistically significance (at 12 cpd $P=0.963$ $P=1.000$, at 18 cpd $P=1.000$, $P=0.855$, respectively).

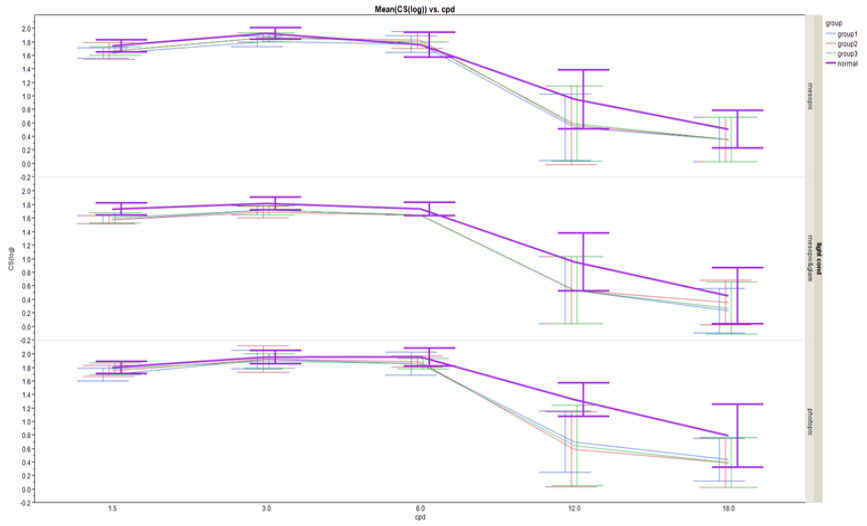

Figure 23. Monocular contrast sensitivity 12 months post-operatively in eyes with the inlay

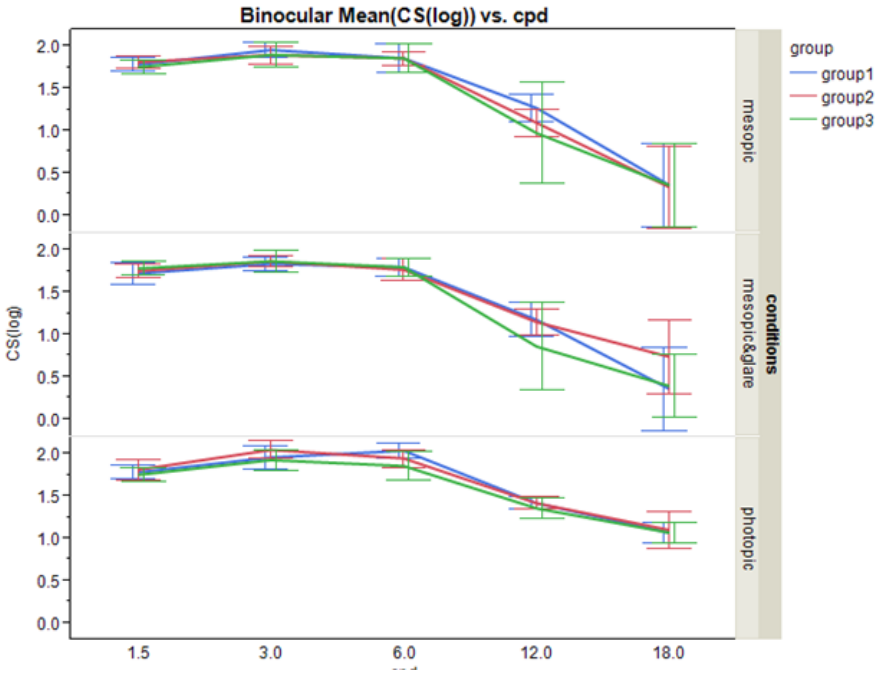

Figure 24. Binocular contrast sensitivity 12 months post-operatively

Corneal topography

Corneal astigmatism of non-dominant eyes changed from 0.48±0.33 D in Group 1, 0.85±0.66 D in Group 2 and 0.77±0.28 D in Group 3 pre-operatively to 0.50±0.37, 0.89±0.26, and 0.73±0.45, respectively. The change was not statistically different between groups (P=0.284).

Patient Satisfaction Questionnaire

During the pre-operative evaluation, patients answered questions about their profession, everyday needs, frequency of using a computer, and preferable working distance. These questions assisted the surgeon in deciding on the ideal inlay power for each patient. A general complaint about their inability to function without spectacles for near vision, annoyance for constantly having to put them on and off, and satisfactory UDVA were noted.

At last follow-up, all the patients, except one in Group 2, perceived their binocular UDVA as excellent (mean score 1.00 in Group 1, 1.20 Group 2, 1.00 in Group 3). Twelve months after inlay implantation, monocular UDVA, in eyes with the inlay, was perceived as good, with the best mean score in Group 3 (1.80 in Group 1, 2.00 in Group 2 and 1.40 in Group 3). No patient used spectacles for distance vision.

During the last follow-up, all but one patient perceived their binocular UNVA as excellent (mean score Group 1 1.00, Group 2 1.20, Group 3 1.00). One of fifteen patients reported use of near vision spectacles occasionally, only at evening for reading books.

One year after inlay implantation, two patients in Group 2, and one in Group 1 and 3 experienced sometimes glare and halos. The overall satisfaction score in Group 1 was 8.2, Group 2 was 9.2, and Group 3 was 7.8.

Discussion

Presbyopia, phakic or pseudophakic, is the most common refractive error, currently affecting approximately 2 billion people worldwide, with a steep predicted rise to 2.1 billion in 2020.[57,58] Presbyopia itself is defined as a loss of accommodation. This condition can amount to a considerable decrease in the quality of life for many of those affected.[59,49] Therefore, the general demand for spectacle independence has been growing strongly in recent times, and has made the correction of presbyopia one of the most important last frontiers of refractive surgery.

One of the established strategies for presbyopia compensation after cataract surgery is implantation of multifocal intraocular lenses. The results of bilateral implantation of multifocal IOLs in cataract surgery demonstrate that implantation of both refractive and diffractive multifocal IOLs result in high levels of uncorrected distance and near visual acuity and therefore to increased levels of spectacle independence compared with monofocal IOLs.[60-63]

Despite their benefits of uncorrected visual acuity at multiple distances, multifocal IOLs are associated with certain drawbacks. First, halos and glare are more often reported by patients with a multifocal IOL than with a monofocal IOL.[64,65] Refractive multifocal IOLs appear to be associated with more photic phenomena than diffractive multifocal IOLs.[61] Photic phenomena are among the most frequent reasons for dissatisfaction after multifocal IOL implantation.[66,67] Second, multifocal IOLs are associated with lower contrast sensitivity than monofocal IOLs.[68,69]

Monovision technique is also far from perfect. Studies of monovision have shown that on average, 24% of patients cannot adapt to this condition.[70,71] As the effect of monovision is increased to more than 1.5 diopters (D) in the nondominant eye, there is a more significant loss of stereopsis, binocular contrast sensitivity and binocular summation.[72,73] One recent study postulated that uncorrected monovision may play a role in an increase in the rate of falling and injury in elderly people.[74] The decrease in stereopsis and binocular contrast sensitivity in patients with 0.75 D of monovision is lower, but their ability to perform near tasks without correction also is compromised.

Ideally, an IOL would allow the presbyopic patient to regain his or her ability to accommodate. Although refilling the capsular bag with a clear but elastic substance would theoretically lead to the desirable result, experiments in this area have been unsuccessful.[75] In clinical practice, movement of accommodating IOLs has been shown to be insufficient to result in large changes in the power of the optical system.[76] At the moment, there is no perfect presbyopia-correcting IOL currently available to meet the needs of all patients.

Intrastromal corneal inlays have a long history, but they are a relative new modality for presbyopia correction. Currently, there are three different commercially available types of inlay, which use different mechanisms to compensate for accommodation loss. There is an inlay that increases depth of focus by using fixed small aperture (KAMRA™, AcuFocus Inc., Irvine, CA, USA), a corneal change in curvature inlay that makes a change to the anterior corneal curvature (Raindrop®, ReVision Optics, Lake Forest, CA, USA) and refractive inlays that alter the index of refraction using a bifocal optic (the Presbia Flexivue Microlens®, Presbia Coöperatief U.A., Amsterdam, Netherlands and the Icolens (Neoptics AG, Hunenburg, Switzerland).

Implantation of a refractive corneal inlay in a femtosecond laser created intrastromal pocket is a relatively simple and effective surgical treatment for presbyopes aged between 45 and 60 years with a clear crystalline lens. In their study, Limnopoulou et al. showed the refractive outcome of 47 patients implanted with the Flexivue Microlens with a follow-up term of 12 months. One year postoperatively, the mean uncorrected near visual acuity (UNVA) significantly improved from 0.68±0.03 logarithm of the minimum angle of resolution (logMAR) to 0.14±0.9 logMAR in the operated eyes and from 0.53±0.13 logMAR preoperatively to 0.13±0.13 logMAR binocularly ($P<0.001$). UNVA of the operated eyes was 20/32 or better in 75% of patients 12 months after inlay implantation. The mean uncorrected distance visual acuity (UDVA) in operated eyes significantly decreased from 0.06±0.09 logMAR preoperatively to 0.38±0.15 logMAR, whereas it did not change significantly binocularly. In this study, no intraoperative or postoperative complications were encountered, and no removal or replacement of the inlay was performed.[56]

Bouzoukis et al. reported the results of insertion of the Invue Lens (Biovision AG), a precursor lens to the Flexivue Microlens, in 45 eyes. They created an intrastromal pocket using a mechanical keratome (Visitome 20-10 microkeratome, Biovision AG). In their study, the UNVA was 20/30 or better in 98% of operated eyes and the UDVA was 20/40 or better in 93% of operated eyes at the 12-month follow-up. Only 3 patients lost 1 line of CDVA in the operated eye.[55]

Three years after Flexivue inlay implantation, one patient presented at our Institute with bilateral cataract and blurred vision complain. After all possible options were thoroughly discussed, the patient opted for bilateral cataract surgery without removal of the corneal inlay in order to improve far and preserve near vision and spectacle independence. Biometry and

intraocular lens (IOL) power calculation were performed without removing the inlay. Phacoemulsification and IOL insertion were carried out in both eyes in a usual manner. On day one postoperatively, the patient achieved binocular uncorrected distance visual acuity 20/20 and uncorrected near visual acuity J1. The vision remained stable during the one-year follow-up period.[77] No complications occurred intra-operatively or post-operatively. This case gave the idea of a possible combination of two procedures, cataract surgery and inlay implantation, in order to improve near vision in pseudophakic patients.

Before this study was designed and performed, in order to assess the feasibility of the method, a single patient, after bilateral cataract surgery, underwent refractive corneal inlay implantation in the non-dominant eye for near vision improvement.[78] One month after the inlay implantation the patient achieved UDVA of 20/32 and UNVA of J1 in the operated eye and UDVA of 20/20 and UNVA of J1 binocularly. The BCVA in the nondominant eye was 20/25 with manifest refraction of -2.00-0.50x150º. The patient was happy and reported no need for reading glasses.

Two years after cataract surgery, the patient started to complain about blurred vision in her nondominant eye. The patient's UDVA upon examination was 20/50 and UNVA was J1; however, she was reading with some difficulty. Under the slit-lamp examination we determined she had posterior capsule opacification. The patient was scheduled for Nd:YAG capsulotomy, which was performed in the standard manner and no complications occurred during or after capsulotomy. On the last follow-up examination, six months later, her UDVA was 20/20 in the dominant and 20/32 in the nondominant eye. The UNVA was J3 (dominant eye) and J1 (nondominant eye), and binocular UDVA was 20/20 and UNVA was J1. The patient's CDVA was 20/20 in the dominant and 20/25 in the nondominant eye with refraction

of +0.25-0.50x70° and -2.00sph, respectively. The patient remained spectacle-independent and very happy. This case showed that a combination of cataract surgery with an intraocular lens implantation and refractive Microlens inlay for presbyopia correction is not only feasible, but a promising option which deserves further studies.

This Dissertation represents the first study to evaluate the Microlens refractive inlay implantation in combination with cataract surgery as a new method for near vision improvement in pseudophakic patients. Furthermore, three techniques for implantation of the refractive corneal inlay and the cataract surgery were studied. Visual, refractive and contrast sensitivity outcomes were evaluated and compared. The purpose was to assess safety and efficacy, as well as to evaluate which technique provides the best clinical outcomes and the highest patients' satisfaction.

In the present study, twelve months after the inlay implantation mean monocular UDVA was 20/32 (0.18 logMAR) in Group 1, 20/32 (0.16 logMAR) in Group 2 and 20/25 (0.12 logMAR) in Group 3. Mean monocular UNVA improved in all groups from 20/125 pre-operatively, albeit in the presence of a cataract, to 20/25 and better with pseudophakia and the inlay. The two-step technique in Group 3 appeared to have slightly better results (0.08 logMAR, 0.10 logMAR, 0.06 logMAR, respectively). Refractive results were slightly better in Group 3, with post-operative spherical equivalent refraction within ±0.50 D of the attempted correction in non-dominant eyes.

Binocular UDVA was slightly better with the three-step procedure 20/20 (0.04 logMAR), than in other two groups 20/25 (0.11 logMAR) and 20/25 (0.09 logMAR) but this may be variation due to the small numbers of eyes. Binocular UNVA outcomes, however, were

similar between groups 20/25 (0.06 logMAR), 20/25 (0.06 logMAR) and 20/25 (0.05 logMAR), respectively.

Cochener et al. compared the clinical outcome of different multifocal intraocular lenses based on information reported in the international literature.[79] Average UNVA with monofocal IOLs was 0.47 logMAR and with multifocal IOLs 0.15 logMAR. Furthermore, average UNVA in refractive IOLs group was 0.232 logMAR, in diffractive IOLs group 0.091 logMAR and more specifically to ReSTOR IOL 0.08 logMAR. The present study's results of UNVA were better than average UNVA in refractive IOLs group, but similar to diffractive IOLs group and more specifically to ReSTOR IOL.

Recently, two studies have reported results of intracorneal inlay implantation for near vision improvement in pseudophakic patients, although the follow-up period was only 3 months in both studies. In a prospective non-randomised multicenter study Chu et al. assessed the feasibility of implanting a hydrogel corneal inlay (Raindrop® ReVision Optics, Lake Forest, USA) in 13 patients that previously underwent cataract surgery with monofocal IOL implantation.[80] At 3 months, 83% of patients had 20/20 or better uncorrected near visual acuity. Measurement of the uncorrected binocular vision showed that 83% of the pseudophakic group achieved 20/20 or better at distance and near.

Another study evaluated the improvement in near visual acuity after KAMRA corneal inlay (AcuFocus, Inc., Irvine, CA) implantation in patients with pseudophakia.[81] Mean uncorrected near visual acuity improved five lines (from J10 to J4) postoperatively. Mean uncorrected distance visual acuity, corrected distance visual acuity, and corrected near visual acuity remained stable and were 20/20, 20/16, and J1, respectively, before and after KAMRA

implantation. Four patients underwent LASIK for improved distance acuity at the time of inlay implantation.

In the present study, mean total surgically induced astigmatism was the lowest in Group 1, 0.52 D with 40° change of axis. In other two groups the SIA was higher and with higher change in axis (0.88 D at 87° and 0.92 D at 96°, respectively). However, the total SIA in all groups was lower than the SIA after sutureless phacoemulsification with superior corneal incision, 1.44±0.33 D, reported by Simşek et al.[82] The temporal pocket access with femtosecond laser and superior corneal incision during cataract surgery were created in every patient in all groups. The study was designed in this manner so that the results would be comparable between groups. However, individual adjustment of axis of pocket creation as well as corneal incision based on preoperative astigmatism is a possibility worth further research.

Achieved monocular or binocular CDVA showed no significant difference between groups. During the one-year follow-up none of the operated eyes had loss of line of CDVA, suggesting the safety of procedures. Furthermore, in groups 1 and 3 where the inlay was implanted three months after cataract surgery, CDVA remained same after inlay implantation. Previous studies with intracorneal inlays in presbyopic patients report that loss of CDVA after inlay implantation may occur. Limnopoulou et al. reported that 17 of 47 patients lost 1 line of CDVA and no patient lost 2 lines of CDVA in the operated eye, while Bouzoukis et al. reported that only 3 of 45 patients lost 1 line of CDVA in the operated eye.[55,56] Huseynova et al. reported that two eyes lost two lines and 1 eye lost 1 line of corrected distance visual acuity after implantation of Kamra inlay in 13 pseudophakic patients.[81] Although not proved,

it is believed that loss change in CDVA is caused by difficulty in obtaining an accurate manifest refraction due to the multifocality of refractive inlays.

Mean central corneal thickness was not statistically significantly different after implantation of the inlay to pre-operative mean central thickness in any of the groups. This fact could be related to the thinness of the inlay (15 μm), which is even thinner than the standard deviation of the measurements. The loss of endothelial cells and intraocular pressure were similar in all groups and consistent with cataract surgery using phacoemulsification.[83] During the one-year follow-up, no complications were observed in any of operated eyes. These results suggest that intracorneal inlay implantation in combination with cataract surgery did not lead to any complications within the first 12 post-operative months.

The present study's results showed lower monocular contrast sensitivity at spatial frequencies 12 and 18 cpd in all groups, under mesopic and photopic conditions, compared to reference values of contralateral eyes. Reduced contrast sensitivity was reported also after Flexivue inlay implantation in presbyopic patients.[56] Change in contrast sensitivity of the operated eye one year postoperatively in mesopic conditions was statistically significant at 1.5 cycles per degree (cpd), 6 cpd, and 12 cpd, whereas in photopic conditions it was statistically significant at 6 cpd, 12 cpd, and 18 cpd.

Possible explanation for contrast sensitivity changes may be an increase or change in dynamics of corneal and internal higher order aberrations.[84] However, wavefront analysis was not performed in the present study.

Multifocal IOLs are also associated with lower contrast sensitivity particularly in mesopic circumstances.[60,61,85] The lower contrast sensitivity was attributed to multifocality. Refractive

corneal inlays similar to multifocal IOLs result in coexisting images, 1 sharp and 1 out of focus, with the light from the latter reducing the detectability of the former image. Furthermore, effect of age on contrast sensitivity becomes evident in subjects aged 60 years or older, as a result of reduced retinal sensitivity and neural capacity in visual processing.

The objective visual acuity test results were in accordance with the subjective patient questionnaire results, indicating that patients had significantly fewer problems performing near distance tasks without correction than before surgery. The patient satisfaction rate was high, 5 of 5 of patients in Groups 1 and 3 perceived both binocular UDVA and binocular UNVA as excellent, while in the second group 4 of 5 patients perceived it as excellent. Overall satisfaction was slightly higher in patients who had the inlay implanted three months after cataract surgery.

One year after surgery, four of our 15 patients experienced sometimes glare and/or halos, but they were not being bothered by these. Intracorneal inlays, as well as intraocular lenses, are known to cause photic phenomena, such as glare and halos.[54,56,86,87] Homogeneity of the ocular structures affects retinal image quality. Light scattered from the edge of the inlay spreads at larger angles over the retina and possibly contributes to the observed increase in glare and halos. This would probably be more evident in cases where the inlay is slightly tilted. It is not expected to be remarkable when using a femtosecond laser to create the pocket, as was the case in this study.

The femtosecond laser technology has brought new levels of safety, accuracy and predictability to corneal refractive surgery. Femtosecond lasers are known to provide more predictable flap thickness, lower incidence of dry eye, quicker visual recovery, and better

visual acuity results than mechanical mikrokeratomes.[88-90] In this study, the depth of the implantation was selected to be 300 μm, as the posterior stroma of the cornea has reduced concentrations of keratocytes, which may improve tolerability of the inlay. The creation of femtosecond laser–assisted pockets improves the surgical procedure and increase the precision of the inlay position. Furthermore, making a pocket interface by femtosecond laser minimizes the impact on the corneal nerves when compared to creating a flap, in which more nerve-fiber bundles are cut; as a result of the cut, the risk of dry eye disease is higher and this might affect outcomes.

Conclusions

Answers to the study questions

All the study questions were provided with an answer:

1. The pseudophakic presbyopia was satisfactory compensated in all patients enrolled in the study.

2. No intra-operative or post-operative complications occurred during the one year follow-up.

3. Clinical results showed stability during the 12-month follow-up.

4. Both patients' satisfaction and spectacle independence were high.

5. No significant difference was found between three studied techniques of cataract surgery and the refractive inlay combination.

Combined inlay implantation with cataract surgery seems not only to be safe and efficient method for compensation of pseudophakic presbyopia, but also to provide high patients' satisfaction and spectacle independence. It would seem that refractive intracorneal inlays could in the future represent a valuable option for presbyopia compensation in pseudophakic patients. One of the benefits of the corneal inlay procedure is that the inlay can be removed and, hence, the potential reversibility. This would offer a significant advantage over procedures that involve corneal ablation or premium intraocular lenses.

Study limitations and future studies

Even though this pilot study, by its very definition, has critical limitations, it provides useful clinical information and indications for future studies. Our statistical analysis did not show statistical significance ($P<0.05$), even when there was clearly significant clinical improvement. Possible reason for this is a small sample size in this study. A larger number of patients with a longer observation period is needed to confirm the stability and safety these new methods of the combined cataract-inlay surgery for presbyopia correction.

During this study emerged some observations and questions, which deserve to be further researched and answered in future studies. In this study wavefront aberration were not evaluated, but it would be interesting to evaluate changes induced by the pocket creation alone, by inlay implantation, as well as total aberrations induced by intraocular lens implantation.

Although transparency of the Microlens inlay allows slit-lamp examination of anterior segment and fundoscopy, further studies are necessary to determine its influence in managing potential cataract surgery complications, like posterior capsule opacification and Nd:YAG capsulotomy. Furthermore, potential influence of the refractive inlay on visual field examination and optical coherence tomography should be investigated. Quality of vision should be further evaluated, including stereopsis of vision and reading speed.

Comparing the outcomes between pseudophakic eyes with and without the inlay was not the purpose of this study. It is necessary though to perform a study of combined inlay implantation and cataract surgery which includes a control group with cataract surgery alone.

Effect that an individual adjustment of the femtosecond laser corneal pocket axis and the clear corneal incision placement during cataract surgery may have on the surgical induced astigmatism, should be investigated in future studies.

Final conclusion

In summary, the refractive corneal inlay seems to be safe and efficient method of presbyopia compensation in pseudophakic patients. The three studied techniques of combined refractive corneal inlay-cataract surgery for presbyopia correction provided excellent binocular distance and near visual outcomes. The overall patient satisfaction rate and post-operative spectacle independence was high. Differences in outcomes between three groups were minimal. Having that in mind, it would seem that the most logical of the techniques is to perform cataract surgery first and then, if the dominant eye has good unaided distance vision, can inlay implantation be considered.

References

1. Olson R.J, Mamalis N., Werner L., Apple D.J. Cataract treatment in the beginning of the 21st century Original Research Article American Journal of Ophthalmology, Volume 136, Issue 1, July 2003, Pages 146-154
2. Kohnen T, Baumeister M, Kook D, Klaproth OK, Ohrloff C. Cataract Surgery With Implantation of an Artificial Lens Dtsch Arztebl Int. 2009 Oct;106(43):695-702. Epub 2009 Oct 23. Review
3. Apple DJ, Kincaid MC, Mamalis N and Olson RJ, Intraocular Lenses. Evolution, Designs, Complications, and Pathology, Williams & Wilkins, Baltimore (1989).
4. Olson R.J., Werner L., Mamalis N., Cionni R.. New intraocular lens technology, Am J Opthalmol 2005; 140; 709-16.
5. Jain S, Arora I, Azar DT. Success of monovision in presbyopes: review of the literature and potential applications to refractive surgery. Surv Ophthalmol. 1996 May-Jun; 40(6):491-9.
6. Versteeg FF. Multifocal IOLs for presbyopia. J Cataract Refract Surg. 2005 Jul;31(7):1266
7. Bellucci R. Multifocal intraocular lenses. Curr Opin Ophthalmol. 2005 Feb;16(1):33-7.
8. Cumming JS, Kammann J Experience with an accommodating IOL. Cataract Refract Surg. 1996 Oct;22(8):1001.
9. Dick HB. Accommodative intraocular lenses: current status. Curr Opin Ophthalmol.2005Feb;16(1):8-26.

10. Marchini G, Mora P, Pedrotti E, Manzotti F, Aldigeri R, Gandolfi SA. Functional assessment of two different accommodative intraocular lenses compared with a monofocal intraocular lens. Ophthalmology. 2007 Nov;114(11):2038-43. Epub 2007 Jun 6
11. Milder B, Rubin ML. Progressive power lenses. Surv Ophthalmol 1987;32:189-98.
12. Von Helmholtz H. Physiological Optics. New York: Dover, 1962; vol.I, 143-172,375-415.
13. Coleman DJ, Fish SK. Presbyopia, accommodation and the mature catenary. Ophthalmology 2001; 108 (9):1544-51.
14. Schachar RA, Cudmore DP, Black TD. Experimental support for Schachar's hypothesis of accommodation. Ann Ophthalmol 1993;25:404-9.
15. Tscherning M. Physiologic Optics: Dioptrics of the Eye, Functions of the Retina, Ocular Movements, and Binocular Vision, 2nd ed. Philadelphia: Keystone, 1904;160-89.
16. Schachar RA, Anderson DA. The mechanism of ciliary muscle function. Ann Ophthalmol 1995;27:126-32
17. WHO Global initiative for the elimination of avoidable blindness Fact sheet number 213, Geneva (2000) Available http://www.who.int/mediacentre/factsheets/fs213/en/
18. WHO Blindness and visual disability: major causes worldwide Fact sheet number 143, WHO, Geneva (1997) Available http://www.who.int/mediacentre/factsheets/fs413/en/
19. Streeten BW Pathology of the lens DM Albert, FA Jakobiec (Eds.), Principles and practice of ophthalmology (2nd edn.), WB Saunders, Philadelphia (2000), pp. 3685–3749

20. Van Newkirk M, Alfonso CE, Chuang EL (Eds.), et al., International ophthalmology: chapter XIV, cataract, section 13, basic and clinical science course, American Academy of Ophthalmology, San Francisco (2002), pp. 157–166
21. West SK, Valmadrid CT Epidemiology of risk factors for age-related cataracts Surv Ophthalmol, 39 (1995), pp. 323–334
22. Masket S, Fine HI, Kidwell TP, et al. Cataract in the adult eye, American Academy of Ophthalmology, San Francisco (2001)
23. McCarty CA, Taylor HR A review of the epidemiologic evidence linking ultraviolet radiation and cataracts
24. Urban RC Jr, Cotlier ECorticosteroid-induced cataracts Surv Ophthalmol, 31 (1986), pp. 102–110
25. Carnahan MC, Goldstein DA Ocular complications of topical, peri ocular, and systemic corticosteroids Curr Opin Ophthalmol, 11 (2000), pp. 478–483
26. Floyd RP History of cataract surgery DM Albert, FA Jakobiec (Eds.), Principles and practice of ophthalmology (2nd edn.), WB Saunders, Philadelphia (2000), pp. 1463–1476
27. Linebarger EJ, Hardten DR, Shah GK, Lindstrom RL Phacoemulsification and modern cataract surgery Surv Ophthalmol, 44 (1999), pp. 123–147
28. Kelman CD Phaco-emulsification and aspiration: a new technique of cataract removal Am J Ophthalmol, 64 (1967), pp. 23–35
29. Jaffe NS, Jaffe MS, Jaffe GF Cataract surgery and its complications (6th edn.), Mosby, St Louis (1997)

30. Ng DT, Rowe NA, Francis IC, et al. Intraoperative complications of 1000 phacoemulsification procedures: a prospective study J Cataract Refract Surg, 24 (1998), pp. 1390–1395
31. Ridley H Intraocular acrylic lenses Trans Ophthalmol Soc UK, 71 (1951), pp. 617–621
32. Evans BJ. Monovision: A review. Ophthalmic Physiol Opt. 2007;27:417–39.
33. Reinstein DZ, Couch DG, Archer TJ. LASIK for hyperopic astigmatism and presbyopia using micro-monovision with the Carl Zeiss Meditec MEL80 platform. J Refract Surg. 2009;25:37–58.
34. Gatinel D. Presbyopia surgery. Rev Prat. 2008;58:1049–54.
35. Ayoubi MG, Leccisotti A, Goodall EA, McGilligan VE, Moore TC. Femtosecond laser in situ keratomileusis versus conductive keratoplasty to obtain monovision in patients with emmetropic presbyopia. J Cataract Refract Surg. 2010;36:997–1002.
36. Du TT, Fan VC, Asbell PA. Conductive keratoplasty. Curr Opin Ophthalmol.2007;18:334–7.
37. Keates RH, Pearce JL, Schneider RT. Clinical results of the multifocal lens. J Cataract Refract Surg 1987; 13:557–560
38. Hansen TE, Corydon L, Krag S, Thim K. New multifocal intraocular lens design. J Cataract Refract Surg 1990; 16:38–41
39. Fresnel A. Memoire Sur un Nouveau Syst eme d' Eclairage des Phares; lu a l'Acad emie des Sciences le 29 juillet 1822. Paris, France, Imprimerie Royale, 1822; 7.

40. Holladay JT, Piers PA, Koranyi G, van der Mooren M, Norrby NES. A new intraocular lens design to reduce spherical aberration of pseudophakic eyes. J Refract Surg 2002; 18:683–691
41. Tzelikis PF, Akaishi L, Trindade FC, Boteon JE. Spherical aberration and contrast sensitivity in eyes implanted with aspheric and spherical intraocular lenses: a comparative study. Am J Ophthalmol 2008; 145:827–833
42. Findl O, Leydolt C. Meta-analysis of accommodating intraocular lenses. J Cataract Refract Surg 2007; 33:522–527Barraquer JI. Modification of refraction by means of intracorneal inclusions. Int Ophthalmol Clin. 1966;6(1):53–78.
43. Choyce DP. The correction of refractive errors with polysulfone corneal inlays. A new frontier to be explored? Trans Ophthalmol Soc U K. 1985; 104(Pt 3):332–342.
44. Dohlman CH, Refojo MF, Rose J. Synthetic polymers in corneal surgery. I. Glyceryl methacrylate. Arch Ophthalmol. 1967;77(2):252–257.
45. Steinert RF, Storie B, Smith P, et al. Hydrogel intracorneal lenses in aphakic eyes. Arch Ophthalmol. 1996;114(2):135–141.
46. Garza EB, Gomez S, Chayet A, Dishler J. One-year safety and efficacy results of a hydrogel inlay to improve near vision in patients with emmetropic presbyopia. J Refract Surg. 2013;29(3):166–172.
47. Chayet A, Barragan Garza E. Combined hydrogel inlay and laser in situ keratomileusis to compensate for presbyopia in hyperopic patients: one-year safety and efficacy. J Cataract Refract Surg. 2013;39(11):1713–1721.

48. Tomita M, Kanamori T, Waring GO, Nakamura T, Yukawa S. Small-aperture corneal inlay implantation to treat presbyopia after laser in situ keratomileusis. J Cataract Refract Surg. 2013;39(6):898–905.
49. Tomita M, Kanamori T, Waring GO, et al. Simultaneous corneal inlay implantation and laser in situ keratomileusis for presbyopia in patients with hyperopia, myopia, or emmetropia: six-month results. J Cataract Refract Surg. 2012;38(3):495–506.
50. Yilmaz OF, Alagöz N, Pekel G, et al. Intracorneal inlay to correct presbyopia: Long-term results. J Cataract Refract Surg. 2011;37(7):1275–1281.
51. Seyeddain O, Hohensinn M, Riha W, et al. Small-aperture corneal inlay for the correction of presbyopia: 3-year follow-up. J Cataract Refract Surg. 2012;38(1):35–45.
52. Dexl AK, Jell G, Strohmaier C, et al. Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. J Cataract Refract Surg. In press 2014.
53. Baily C, Kohnen T, O'Keefe M. Preloaded refractive-addition corneal inlay to compensate for presbyopia implanted using a femtosecond laser: one-year visual outcomes and safety. J Cataract Refract Surg. 2014;40(8):1341–8
54. Bouzoukis DI, Kymionis GD, Panagopoulou SI, Diakonis VF, Pallikaris AI, Limnopoulou AN, Portaliou DM, Pallikaris IG Visual outcomes and safety of a small diameter intrastromal refractive inlay for the corneal compensation of presbyopia J Refract Surg, 28 (2012), pp. 168–173
55. Limnopoulou AN , Bouzoukis DI, Kymionis GD, Panagopoulou SI, Plainis S, Pallikaris AI, Feingold V, Pallikaris IG Visual outcomes and safety of a refractive

corneal inlay for presbyopia using femtosecond laser J Refract Surg, 29 (2013), pp. 12–18

56. Lindstrom RL, Macrae SM, Pepose JS, Hoopes PC. Corneal inlays for presbyopia correction. Curr Opin Ophthalmol. 2013;24(4):281–287.
57. Seyeddain O, Bachernegg A, Riha W, et al. Femtosecond laser-assisted small-aperture corneal inlay implantation for corneal compensation of presbyopia: two-year follow-up. J Cataract Refract Surg. 2013; 39(2):234–241.
58. McDonnell PJ, Lee P, Spritzer K, Lindblad AS, Hays RD. Associations of presbyopia with vision-targeted health-related quality of life. Arch Ophthalmol. 2003;121(11):1577–1581.
59. Alfonso JF, Fernandez-Vega L, Puchades C, Mont es-Mic o R. Intermediate visual function with different multifocal intraocular lens models. J Cataract Refract Surg 2010; 36:733–739
60. Cillino S, Casuccio A, Di Pace F, Morreale R, Pillitteri F, Cillino G, Lodato G. One-year outcomes with new-generation multifocal intraocular lenses. Ophthalmology 2008; 115:1508–1516
61. Chang DF. Prospective functional and clinical comparison of bilateral ReZoom and ReSTOR intraocular lenses in patients 70 years or younger. J Cataract Refract Surg 2008; 34:934–941
62. de Vries NE, Webers CAB, Montes-Mico R, Ferrer-Blasco T, Nuijts RMMA. Visual outcomes after cataract surgery with implantation of a C3.00 D or C4.00 D aspheric diffractive multifocal intraocular lens: comparative study. J Cataract Refract Surg 2010; 36:1316–1322

63. Chiam PJT, Chan JH, Aggarwal RK, Kasaby S. ReSTOR intraocular lens implantation in cataract surgery: quality of vision. J Cataract Refract Surg 2006; 32:1459–1463; errata, 1987

64. Haring G, Dick HB, Krummenauer F, Weissmantel U, € Kroncke W. Subjective photic phenomena with refractive multifocal and monofocal intraocular lenses; results of a multicenter questionnaire. J Cataract Refract Surg 2001; 27:245–249

65. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. J Cataract Refract Surg 2009; 35:992–997

66. de Vries NE, Webers CAB, Touwslager WRH, Bauer NJC, de Brabander J, Berendschot TT, Nuijts RMMA. Dissatisfaction after implantation of multifocal intraocular lenses. J Cataract Refract Surg 2011; 37:859–865

67. Alfonso JF, Fernandez-Vega L, Merayo C, Montes-Mico R. Contrast sensitivity comparison between AcrySof ReSTOR and Acri.LISA aspheric intraocular lenses. J Refract Surg 2010; 26:471–477

68. Mesci C, Erbil HH, Olgun A, Aydin N, Candemir B, Akcakaya AA. Differences in contrast sensitivity between monofocal, multifocal and accommodating intraocular lenses: long-term results. Clin Exp Ophthalmol 2010; 38:768–777

69. Jain S, Arora I, Azar DT Success of monovision in presbyopes: review of the literature and potential applications to refractive surgery Surv Ophthalmol, 40 (1996), pp. 491–499

70. Greenbaum S Monovision pseudophakia J Cataract Refract Surg, 28 (2002), pp. 1439–1443

71. Durrie DS The effect of different monovision contact lens powers on the visual function of emmetropic presbyopic patients (an American Ophthalmological Society thesis) Trans Am Ophthalmol Soc, 104 (2006), pp. 366–401
72. Handa T, Shimizu K, Mukuno K, Kawamorita T, Uozato H Effects of ocular dominance on binocular summation after monocular reading adds J Cataract Refract Surg, 31 (2005), pp. 1588–1592
73. Vale A, Scally A, Buckley JG, Elliott DB The effects of monocular refractive blur on gait parameters when negotiating a raised surface Ophthal Physiol Opt (2008), pp. 135–142
74. Nishi Y, Mireskandari K, Khaw P, Findl O. Lens refilling to restore accommodation. J Cataract Refract Surg 2009; 35:374–382
75. Menapace R, Findl O, Kriechbaum K, Leydolt-Koeppl C. Accommodating intraocular lenses: a critical review of present and future concepts. Graefes Arch Clin Exp Ophthalmol 2007; 245:473–489
76. Stojanovic NR, Panagopoulou SI, Pallikaris IG. Cataract Surgery with a Refractive Corneal Inlay in Place. Case Rep Ophthalmol Med. 2015;2015:230801
77. Stojanovic NR, Panagopoulou SI, Pallikaris IG. Refractive corneal inlay for near vision improvement after cataract surgery. J Cataract Refract Surg. 2014 Jul;40(7):1232-5
78. Cochener B, Lafuma A, Khoshnood B, Courouve L, Berdeaux G. Comparison of outcomes with multifocal intraocular lenses: a meta-analysis. Clinical Ophthalmology (Auckland, NZ). 2011;5:45-56.

79. Chu RY, Hovanesian JA, Whitman J, Tran DB, Parkhurst GD. Nonrefractive Corneal Inlay Implantation After Cataract Surgery: U.S. Clinical Study Experience. Presented at the American Society of Cataract and Refractive Surgery Meeting, April 2015, San Diego, CA, USA

80. Huseynova T, Kanamori T, Waring GO 4th, Tomita M. Outcomes of small aperture corneal inlay implantation in patients with pseudophakia. J Refract Surg. 2014 Feb;30(2):110-6.

81. Simşek S, Yaşar T, Demirok A, Cinal A, Yilmaz OF. Effect of superior and temporal clear corneal incisions on astigmatism after sutureless phacoemulsification. J Cataract Refract Surg. 1998 Apr;24(4):515-8.

82. Diaz-Valle D, Benitez del Castillo Sanchez JM, Castillo A, et al. Endothelial damage with cataract surgery techniques. J Cataract Refract Surg 1998; 24: 951–955

83. Oshika T, Okamoto C, Samejima T, Tokunaga T, Miyata K. Contrast sensitivity function and ocular higher-order wavefront aberrations in normal human eyes. Ophthalmology. 2006;113(10):1807-1812

84. Hayashi K, Manabe S-I, Hayashi H. Visual acuity from far to near and contrast sensitivity in eyes with a diffractive multifocal intraocular lens with a low addition power. J Cataract Refract Surg 2009; 35:2070–2076

85. Häring G, Dick HB, Krummenauer F, Weissmantel U, Kröncke W. Subjective photic phenomena with refractive multifocal and monofocal intraocular lenses. results of a multicenter questionnaire. J Cataract Refract Surg. 2001 Feb;27(2):245-9.

86. Alió JL, Abbouda A, Huseynli S, Knorz MC, Homs ME, Durrie DS. Removability of a small aperture intracorneal inlay for presbyopia correction. J Refract Surg. 2013; 29:550-6.

87. Kezirian GM, Stonecipher KG. Comparison of the IntraLase femtosecond laser and mechanical keratomes for laser in situ keratomileusis. J Cataract Refract Surg. 2004;30(4):804–811.

88. Salomão MQ, Ambrósio R Jr, Wilson SE. Dry eye associated with laser in situ keratomileusis: Mechanical microkeratome versus femtosecond laser. J Cataract Refract Surg. 2009;35(10):1756–1760.

89. Tanna M, Schallhorn SC, Hettinger KA. Femtosecond laser versus mechanical microkeratome: a retrospective comparison of visual outcomes at 3 months. J Refract Surg. 2009;25(7 Suppl):S668–S671.

Appendices

Appendix 1

Consent form for Group 1

Μελέτη της ασφάλειας και αποτελεσματικότητας του ενδοκερατοειδικού διαθλαστικού ενθέματος "Flexivue T.M." μετά την εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού

Έντυπο συγκατάθεσης
και ενημέρωσης του ασθενούς

ΠΛΗΡΟΦΟΡΙΕΣ ΑΣΘΕΝΟΥΣ

Αριθμός αναγνώρισης: _____

Όνομα/Επώνυμο Ασθενούς: _____

Όνομα ερευνητή: _____

Τοποθεσία: _____

Ημερ/νία: _____

Διαδικασία Μελέτης

Αυτή η μελέτη είναι σχεδιασμένη για άτομα τα οποία έχουν σκλήρυνση του κρυσταλλοειδούς φακού και είναι υποψήφιοι για εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού. Λόγω της απώλειας της κοντινής όρασης μετά την αφαίρεση του φυσικού φακού και αυξημένης ανάγκης για ανεξαρτητοποίηση από διαθλαστικά γυαλιά, προτάθηκε ως λύση η ένθεση ενός ενδοκερατοειδικού μικροφακού Flexivue™. Αυτός ο μικροφακός είναι σχεδιασμένος έτσι ώστε να προσφέρει μια ικανοποιητική κοντινή όραση.

Κατά τη διάρκεια του ενός έτους θα υπάρχουν προγραμματισμένες επισκέψεις για κάθε συμμετέχοντα στην μελέτη . Η πρώτη επίσκεψη είναι μια επίσκεψη ελέγχου κριτηρίων. Κατά την διάρκεια αυτής της επίσκεψης ο γιατρός σας θα κάνει οφθαλμολογική εξέταση και διάφορα οπτικά τεστ για να επαληθεύσει ότι διαθέτετε τα κριτήρια επιλογής που υπάρχουν στην λίστα του πρωτοκόλλου. Αν ο γιατρός σας αποφασίσει ότι ίσως είστε ένας κατάλληλος υποψήφιος για την μελέτη, θα σας εξηγήσει τις λεπτομέρειες αυτής της μελέτης, τα πιθανά πλεονεκτήματα για σας και τους πιθανούς κινδύνους που μπορεί να συναντήσετε εάν συμμετάσχετε. Στο τέλος της εξήγησης θα σας δοθεί η ευκαιρία να κάνετε ερωτήσεις σχετικά με αυτήν την μελέτη.

Αν συμφωνήσετε να συμμετάσχετε σε αυτήν την μελέτη και αφού διαβάσετε αυτήν την φόρμα συγκατάθεσης και συμφωνήσετε να την υπογράψετε, ο ερευνητής σας θα προγραμματίσει να υποβληθείτε στη διαδικασία επεμβάσεως. Οι επεμβάσεις θα προγραμματιστούν να γίνει μία κοινώς αποδεκτή ημερομηνία για εσάς και το ιατρό σας και θα εκτελεστεί στο χειρουργείο που χρησιμοποιεί ο οφθαλμίατρος σας. Στην ομάδα Ι πρώτα πραγματοποιείται η δημιουργία του κερατοειδικού τούνελ, τρεις μήνες αργότερα η εγχείρηση του καταρράκτη αμφοτερόπλευρα και τρεις μήνες μετά, η ένθεση του ενδοκερατοειδικού ενθέματος.

Πριν γίνει η δημιουργία του τούνελ, το μάτι θα αναισθητοποιηθεί με οφθαλμικές σταγόνες που περιέχουν τοπικό αναισθητικό. Θα γίνει αποστείρωση και προετοιμασία σύμφωνα με τις διαδικασίες που ακολουθούνται πάντα στις επεμβάσεις στα μάτια. Ο γιατρός σας θα

χρησιμοποιήσει το femtosecond laser για να δημιουργήσει ένα στενό τούνελ στον κερατοειδή σας, το οποίο θα έχει περίπου 3χιλ στο πλάτος και 6-8χιλ στο μάκρος. Μέσα σε αυτό το τούνελ, ο γιατρός σας θα τοποθετήσει τον φακό Flexivue™ σε ένα σημείο στον κερατοειδή που είναι μπροστά από το κέντρο της κόρης. Ο γιατρός σας κατόπιν θα σας γράψει μια συνταγή για οφθαλμικές σταγόνες που θα ενσταλάζονται στο χειρουργημένο μάτι πολλές φορές την ημέρα και επίσης θα σας προγραμματίσει μια επίσκεψη για παρακολούθηση την επόμενη μέρα.

Κατά την επίσκεψή την πρώτη μέρα μετά την διαδικασία, ο οφθαλμίατρός σας θα κάνει διάφορα οφθαλμολογικά τεστ και μετρήσεις για να εκτιμήσει τη επιτυχία της διαδικασίας. Ο γιατρός σας επίσης θα σας ζητήσει να συμπληρώσετε ένα ερωτηματολόγιο το οποίο θα σας ζητά την γνώμη σας για την εγχείρηση και της αλλαγές στην όραση που βιώνετε.

Μετά, θα σας δοθούν οδηγίες για το πώς θα συνεχίσετε τα φάρμακα και θα προγραμματιστούν οι επισκέψεις για παρακολούθηση.

Σε κάθε μία από αυτές τις επισκέψεις, θα πραγματοποιούνται μετρήσεις όρασης και πολλά καθιερωμένα ιατρικά τεστ και θα σας ζητηθεί να συμπληρώσετε επιπρόσθετα ερωτηματολόγια.

Βασικά Κριτήρια Συμμετοχής:

Για να επιλεγείτε για αυτήν την έρευνα, θα πρέπει οπωσδήποτε:

- Να είστε 50-80 ετών και να έχετε σκλήρυνση του κρυσταλλοειδούς φακού και στα δύο μάτια.
- Να μην έχετε άλλα οφθαλμολογικά προβλήματα.
- Να μπορείτε να τηρήσετε το πρόγραμμα των μετεγχειρητικών επισκέψεων για παρακολούθηση.
- Να είστε πρόθυμοι να υπογράψετε μια ενημερωτική φόρμα συγκατάθεσης.

- Να μην έχετε οξείες ή χρόνιες συστηματικές παθήσεις που θα μπορούσαν να αυξήσουν τους κινδύνους της εγχείρησης ή να εμποδίσουν την φυσιολογική διαδικασία επούλωσης (πάθηση του συνδετικού ιστού, διαβήτης, οποιαδήποτε νεοπλασματική νόσος).

Ενδεχόμενες παρενέργειες ή ενοχλήσεις

Κάποιες ενοχλήσεις κατά την διάρκεια κάθε οφθαλμικής εγχείρησης είναι αναμενόμενες. Ο γιατρός σας θα χρησιμοποιήσει αναισθητικό κολλύριο κατά την διάρκεια της εγχείρησης για να μειώσει την ενόχληση στο ελάχιστο.

Όταν πραγματοποιείται μια τομή σε έναν οφθαλμό, ίσως υπάρξουν κίνδυνοι που προέρχονται από κακή διαχείριση, κακή λειτουργία ή κάθε είδους λάθος. Για να ελαχιστοποιήσουμε αυτούς τους κινδύνους στην περίπτωσή σας, έχουμε εκτελέσει όλα τα τεστ στο φακό Flexivue™.

Η ενόχληση, μετά την εγχείρηση, μπορεί να υπάρχει στο χειρουργημένο μάτι αλλά αυτή αναμένεται να είναι ήπια και μικρής διάρκειας.

Επίσης, μολύνσεις μπορεί να υπάρξουν μετά από οποιαδήποτε οφθαλμολογική επέμβαση. Για να ελαχιστοποιηθούν οι πιθανότητες, μετεγχειρητικά θα ακολουθήσετε ειδικές τοπικές φαρμακευτικές οδηγίες. Έχουν τηρηθεί επίσης αυστηρές μέθοδοι αποστείρωσης κατά την διάρκεια αυτής της διαδικασίας.

Ο φακός του κερατοειδή που θα τοποθετηθεί είναι στο στάδιο κλινικής μελέτης. Ίσως υπάρξουν παρενέργειες και ενοχλήσεις από τον φακό, οι οποίες δεν είναι ακόμα πλήρως γνωστές. Ίσως, επίσης, παρατηρήσετε αλλαγές στην όραση μετά την διαδικασία, στις οποίες ίσως χρειαστεί χρόνος για να προσαρμοστείτε. Αυτές μπορεί να είναι θολή όραση, δυσκολία στην εστίαση σε μακρινά ή κοντινά αντικείμενα. Ίσως επίσης νιώσετε σαν να βλέπετε διπλά στο χειρουργημένο μάτι. Αν οποιοδήποτε από αυτά τα συμπτώματα εμφανιστούν μετά την

διαδικασία, πιστεύουμε ότι θα είναι ήπια και ότι θα εξαφανιστούν μετά από μία περίοδο λίγων ημερών.

Σε περίπτωση που δυσκολεύεστε να ανεχτείτε αυτά τα συμπτώματα, ο γιατρός σας μπορεί να αντιστρέψει την εγχείρηση, αφαιρώντας τον φακό Flexivue™ που έχει εμφυτευτεί. Αναμένεται ότι τα συμπτώματά σας θα εξαφανιστούν σταδιακά με την πάροδο κάποιων ημερών μετά την αφαίρεση του εμφυτεύματος.

Δεν αναμένεται να προκληθεί μόνιμη βλάβη στον κερατοειδή σας ακόμα και αν ο φακός χρειαστεί να μετακινηθεί, αλλά δεν υπάρχει τρόπος να αποκλείσουμε εντελώς την πιθανότητα ότι μπορεί να προκληθεί μία μόνιμη βλάβη στον κερατοειδή σας και/ή στην όρασή σας .

Οφέλη που θα προκύψουν από την μελέτη

Το προσωπικό πλεονέκτημα που θα έχετε από την συμμέτοχή σας σε αυτή την μελέτη είναι η ευκαιρία να έχετε καλή μακρινή και κοντινή όραση μετά την εγχείρηση του καταρράκτη, χωρίς να εξαρτάστε από γυαλιά οράσεως. Αυτό μπορεί να βελτιώσει την ποιότητα ζωής σας και την ικανότητά σας να λειτουργείτε στο σπίτι και στην δουλειά.

Η συμμετοχή σας στη μελέτη και οι πληροφορίες οι οποίες θα μας δώσει αυτή, ίσως μελλοντικά να ωφελήσει άλλους ανθρώπους με παρόμοιες παθήσεις.

Εναλλακτικές θεραπείες

Εναλλακτικές μέθοδοι για να διορθωθεί το πρόβλημα της όρασης σας, η απώλεια της κοντινής όρασης μετά την εγχείρηση του καταρράκτη, είναι διαθέσιμες εδώ και χρόνια. Αυτές συμπεριλαμβάνουν τα γυαλιά οράσεως, τους φακούς επαφής και άλλων μορφών επεμβάσεις. Όλες αυτές είναι καλές επιλογές και μπορείτε να διαλέξετε οποιαδήποτε από αυτές αντί του να συμμετάσχετε στην μελέτη.

Εμπιστευτικότητα

Οι πληροφορίες από αυτήν την μελέτη ίσως δοθούν στον χορηγό Βιο-όρασης AG, και στην Διοίκηση Φαγητού και Φαρμάκων (FDA). Πληροφορίες μπορεί επίσης να δοθούν σε regulatory agencies σε άλλες χώρες. Τα αποτελέσματα από αυτή την μελέτη ίσως δημοσιευτούν αλλά η ταυτότητά σας θα είναι απόρρητη.

<u>Υπεύθυνη Δήλωση ασθενούς</u>

Δηλώνω υπεύθυνα:

- *Ότι ενημερώθηκα αναλυτικά από τον ιατρό του ΒΕΜΜΟ (Βαρδινογιάννειο Εργαστήριο Χειρουργικής και Μεταμοσχεύσεων Οφθαλμού) για τα πιθανά οφέλη και τους ενδεχόμενους κινδύνους της χειρουργικής επέμβασης διόρθωσης της κοντινής όρασης μετά την εγχείρηση του καταρράκτη με το ενδοκερατοειδικό ένθεμα «Flexivue T.M.».*
- *Ότι ο ιατρός απάντησε ικανοποιητικά σε όλα μου τα ερωτήματα.*
- *Ότι γνωρίζω ότι η χειρουργική αυτή επέμβαση αποτελεί μέρος κλινικής μελέτης για την ασφάλεια και την αποτελεσματικότητα του ενδοκερατοειδικού ενθέματος « Flexivue T.M.».*
- *Ότι έχω διαβάσει και έχω κατανοήσει πλήρως το ενημερωτικό έντυπο συγκατάθεσης.*
- *Ότι ενημερώθηκα για τις υπάρχουσες εναλλακτικές μεθόδους αντιμετώπισης της απώλειας της κοντινής όρασης μετά την εγχείρηση του καταρράκτη.*
- *Ότι γνωρίζω ότι η επέμβαση της δημιουργίας του τούνελ και όλες οι μετεγχειρητικές εξετάσεις θα πραγματοποιηθούν στο ΒΕΜΜΟ.*
- *Ότι γνωρίζω ότι η εγχείρηση του καταρράκτη και η ένθεση ενδοκερατοειδικού ενθέματος « Flexivue T.M.» θα πραγματοποιηθούν στο Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλίου.*
- *Ότι επιθυμώ με τη θέληση μου να συμμετέχω σε αυτήν τη μελέτη.*

(Ασθενής) (Ημερομηνία)

(Χειρουργός) (Ημερομηνία)

Consent form for Group 2

Μελέτη της ασφάλειας και αποτελεσματικότητας του ενδοκερατοειδικού διαθλαστικού ενθέματος "Flexivue T.M." μετά την εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού

Έντυπο συγκατάθεσης
και ενημέρωσης του ασθενούς

ΠΛΗΡΟΦΟΡΙΕΣ ΑΣΘΕΝΟΥΣ

Αριθμός αναγνώρισης: _____

Όνομα/Επώνυμο Ασθενούς: _____

Όνομα ερευνητή: _____

Τοποθεσία: _____

Ημερ/νία: _____

Διαδικασία Μελέτης

Αυτή η μελέτη είναι σχεδιασμένη για άτομα τα οποία έχουν σκλήρυνση του κρυσταλλοειδούς φακού και είναι υποψήφιοι για εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού. Λόγω της απώλειας της κοντινής όρασης μετά την αφαίρεση του φυσικού φακού και αυξημένης ανάγκης για ανεξαρτητοποίηση από διαθλαστικά γυαλιά, προτάθηκε ως λύση η ένθεση ενός ενδοκερατοειδικού μικροφακού Flexivue™. Αυτός ο μικροφακός είναι σχεδιασμένος έτσι ώστε να προσφέρει μια ικανοποιητική κοντινή όραση.

Κατά τη διάρκεια του ενός έτους θα υπάρχουν προγραμματισμένες επισκέψεις για κάθε συμμετέχοντα στην μελέτη . Η πρώτη επίσκεψη είναι μια επίσκεψη ελέγχου κριτηρίων. Κατά την διάρκεια αυτής της επίσκεψης ο γιατρός σας θα κάνει οφθαλμολογική εξέταση και διάφορα οπτικά τεστ για να επαληθεύσει ότι διαθέτετε τα κριτήρια επιλογής που υπάρχουν στην λίστα του πρωτοκόλλου. Αν ο γιατρός σας αποφασίσει ότι ίσως είστε ένας κατάλληλος υποψήφιος για την μελέτη, θα σας εξηγήσει τις λεπτομέρειες αυτής της μελέτης, τα πιθανά πλεονεκτήματα για σας και τους πιθανούς κινδύνους που μπορεί να συναντήσετε εάν συμμετάσχετε. Στο τέλος της εξήγησης θα σας δοθεί η ευκαιρία να κάνετε ερωτήσεις σχετικά με αυτήν την μελέτη.

Αν συμφωνήσετε να συμμετάσχετε σε αυτήν την μελέτη και αφού διαβάσετε αυτήν την φόρμα συγκατάθεσης και συμφωνήσετε να την υπογράψετε, ο ερευνητής σας θα προγραμματίσει να υποβληθείτε στη διαδικασία επέμβασης. Η επέμβαση θα προγραμματιστεί να γίνει μία κοινώς αποδεκτή ημερομηνία για εσάς και το ιατρό σας και θα εκτελεστεί στο χειρουργείο που χρησιμοποιεί ο οφθαλμίατρος σας. Στην ομάδα ΙΙ τρεις ημέρες κατόπιν της δημιουργίας του τούνελ και ένθεσης του ενδοκερατοειδικού ενθέματος στο μη κυρίαρχο οφθαλμό, θα πραγματοποιηθεί η εγχείρηση του καταρράκτη αμφοτερόπλευρα.

Πριν γίνει η δημιουργία του τούνελ, το μάτι θα αναισθητοποιηθεί με οφθαλμικές σταγόνες που περιέχουν τοπικό αναισθητικό. Θα γίνει αποστείρωση και προετοιμασία σύμφωνα με τις διαδικασίες που ακολουθούνται πάντα στις επεμβάσεις στα μάτια. Ο γιατρός σας θα χρησιμοποιήσει το femtosecond laser για να δημιουργήσει ένα στενό τούνελ στον κερατοειδή

σας, το οποίο θα έχει περίπου 3χιλ στο πλάτος και 6-8χιλ στο μάκρος. Μέσα σε αυτό το τούνελ, ο γιατρός σας θα τοποθετήσει τον φακό Flexivue™ σε ένα σημείο στον κερατοειδή που είναι μπροστά από το κέντρο της κόρης. Ο γιατρός σας κατόπιν θα σας γράψει μια συνταγή για οφθαλμικές σταγόνες που θα ενσταλάζονται στο χειρουργημένο μάτι πολλές φορές την ημέρα και επίσης θα σας προγραμματίσει μια επίσκεψη για παρακολούθηση την επόμενη μέρα.

Κατά την επίσκεψή την πρώτη μέρα μετά την διαδικασία, ο οφθαλμίατρός σας θα κάνει διάφορα οφθαλμολογικά τεστ και μετρήσεις για να εκτιμήσει τη επιτυχία της διαδικασίας. Ο γιατρός σας επίσης θα σας ζητήσει να συμπληρώσετε ένα ερωτηματολόγιο το οποίο θα σας ζητά την γνώμη σας για την εγχείρηση και της αλλαγές στην όραση που βιώνετε.

Μετά, θα σας δοθούν οδηγίες για το πώς θα συνεχίσετε τα φάρμακα και θα προγραμματιστούν οι επισκέψεις για παρακολούθηση.

Σε κάθε μία από αυτές τις επισκέψεις, θα πραγματοποιούνται μετρήσεις όρασης και πολλά καθιερωμένα ιατρικά τεστ και θα σας ζητηθεί να συμπληρώσετε επιπρόσθετα ερωτηματολόγια.

Βασικά Κριτήρια Συμμετοχής:

Για να επιλεγείτε για αυτήν την έρευνα, θα πρέπει οπωσδήποτε:

- Να είστε 50-80 ετών και να έχετε σκλήρυνση του κρυσταλλοειδούς φακού και στα δύο μάτια.
- Να μην έχετε άλλα οφθαλμολογικά προβλήματα.
- Να μπορείτε να τηρήσετε το πρόγραμμα των μετεγχειρητικών επισκέψεων για παρακολούθηση.
- Να είστε πρόθυμοι να υπογράψετε μια ενημερωτική φόρμα συγκατάθεσης.

- Να μην έχετε οξείες ή χρόνιες συστηματικές παθήσεις που θα μπορούσαν να αυξήσουν τους κινδύνους της εγχείρησης ή να εμποδίσουν την φυσιολογική διαδικασία επούλωσης (πάθηση του συνδετικού ιστού, διαβήτης, οποιαδήποτε νεοπλασματική νόσος).

Ενδεχόμενες παρενέργειες ή ενοχλήσεις

Κάποιες ενοχλήσεις κατά την διάρκεια κάθε οφθαλμικής εγχείρησης είναι αναμενόμενες. Ο γιατρός σας θα χρησιμοποιήσει αναισθητικό κολλύριο κατά την διάρκεια της εγχείρησης για να μειώσει την ενόχληση στο ελάχιστο.

Όταν πραγματοποιείται μια τομή σε έναν οφθαλμό, ίσως υπάρξουν κίνδυνοι που προέρχονται από κακή διαχείριση, κακή λειτουργία ή κάθε είδους λάθος. Για να ελαχιστοποιήσουμε αυτούς τους κινδύνους στην περίπτωσή σας, έχουμε εκτελέσει όλα τα τεστ στο φακό Flexivue™.

Η ενόχληση, μετά την εγχείρηση, μπορεί να υπάρχει στο χειρουργημένο μάτι αλλά αυτή αναμένεται να είναι ήπια και μικρής διάρκειας.

Επίσης, μολύνσεις μπορεί να υπάρξουν μετά από οποιαδήποτε οφθαλμολογική επέμβαση. Για να ελαχιστοποιηθούν οι πιθανότητες, μετεγχειρητικά θα ακολουθήσετε ειδικές τοπικές φαρμακευτικές οδηγίες. Έχουν τηρηθεί επίσης αυστηρές μέθοδοι αποστείρωσης κατά την διάρκεια αυτής της διαδικασίας.

Ο φακός του κερατοειδή που θα τοποθετηθεί είναι στο στάδιο κλινικής μελέτης. Ίσως υπάρξουν παρενέργειες και ενοχλήσεις από τον φακό, οι οποίες δεν είναι ακόμα πλήρως γνωστές. Ίσως, επίσης, παρατηρήσετε αλλαγές στην όραση μετά την διαδικασία, στις οποίες ίσως χρειαστεί χρόνος για να προσαρμοστείτε. Αυτές μπορεί να είναι θολή όραση, δυσκολία στην εστίαση σε μακρινά ή κοντινά αντικείμενα. Ίσως επίσης νιώσετε σαν να βλέπετε διπλά στο χειρουργημένο μάτι. Αν οποιοδήποτε από αυτά τα συμπτώματα εμφανιστούν μετά την

διαδικασία, πιστεύουμε ότι θα είναι ήπια και ότι θα εξαφανιστούν μετά από μία περίοδο λίγων ημερών.

Σε περίπτωση που δυσκολεύεστε να ανεχτείτε αυτά τα συμπτώματα, ο γιατρός σας μπορεί να αντιστρέψει την εγχείρηση, αφαιρώντας τον φακό Flexivue™ που έχει εμφυτευτεί. Αναμένεται ότι τα συμπτώματά σας θα εξαφανιστούν σταδιακά με την πάροδο κάποιων ημερών μετά την αφαίρεση του εμφυτεύματος.

Δεν αναμένεται να προκληθεί μόνιμη βλάβη στον κερατοειδή σας ακόμα και αν ο φακός χρειαστεί να μετακινηθεί, αλλά δεν υπάρχει τρόπος να αποκλείσουμε εντελώς την πιθανότητα ότι μπορεί να προκληθεί μία μόνιμη βλάβη στον κερατοειδή σας και/ή στην όρασή σας .

Οφέλη που θα προκύψουν από την μελέτη

Το προσωπικό πλεονέκτημα που θα έχετε από την συμμέτοχή σας σε αυτή την μελέτη είναι η ευκαιρία να έχετε καλή μακρινή και κοντινή όραση μετά την εγχείρηση του καταρράκτη, χωρίς να εξαρτάστε από γυαλιά οράσεως. Αυτό μπορεί να βελτιώσει την ποιότητα ζωής σας και την ικανότητά σας να λειτουργείτε στο σπίτι και στην δουλειά.

Η συμμετοχή σας στη μελέτη και οι πληροφορίες οι οποίες θα μας δώσει αυτή, ίσως μελλοντικά να ωφελήσει άλλους ανθρώπους με παρόμοιες παθήσεις.

Εναλλακτικές θεραπείες

Εναλλακτικές μέθοδοι για να διορθωθεί το πρόβλημα της όρασης σας, η απώλεια της κοντινής όρασης μετά την εγχείρηση του καταρράκτη, είναι διαθέσιμες εδώ και χρόνια. Αυτές συμπεριλαμβάνουν τα γυαλιά οράσεως, τους φακούς επαφής και άλλων μορφών επεμβάσεις. Όλες αυτές είναι καλές επιλογές και μπορείτε να διαλέξετε οποιαδήποτε από αυτές αντί του να συμμετάσχετε στην μελέτη.

Εμπιστευτικότητα

Οι πληροφορίες από αυτήν την μελέτη ίσως δοθούν στον χορηγό Βιο-όρασης AG, και στην Διοίκηση Φαγητού και Φαρμάκων (FDA). Πληροφορίες μπορεί επίσης να δοθούν σε regulatory agencies σε άλλες χώρες. Τα αποτελέσματα από αυτή την μελέτη ίσως δημοσιευτούν αλλά η ταυτότητά σας θα είναι απόρρητη.

<u>Υπεύθυνη Δήλωση ασθενούς</u>

Δηλώνω υπεύθυνα:

- Ότι ενημερώθηκα αναλυτικά από τον ιατρό του ΒΕΜΜΟ (Βαρδινογιάννειο Εργαστήριο Χειρουργικής και Μεταμοσχεύσεων Οφθαλμού) για τα πιθανά οφέλη και τους ενδεχόμενους κινδύνους της χειρουργικής επέμβασης διόρθωσης της κοντινής όρασης μετά την εγχείρηση του καταρράκτη με το ενδοκερατοειδικό ένθεμα «Flexivue T.M.».
- Ότι ο ιατρός απάντησε ικανοποιητικά σε όλα μου τα ερωτήματα.
- Ότι γνωρίζω ότι η χειρουργική αυτή επέμβαση αποτελεί μέρος κλινικής μελέτης για την ασφάλεια και την αποτελεσματικότητα του ενδοκερατοειδικού ενθέματος « Flexivue T.M.».
- Ότι έχω διαβάσει και έχω κατανοήσει πλήρως το ενημερωτικό έντυπο συγκατάθεσης.
- Ότι ενημερώθηκα για τις υπάρχουσες εναλλακτικές μεθόδους αντιμετώπισης της απώλειας της κοντινής όρασης μετά την εγχείρηση του καταρράκτη.
- Ότι γνωρίζω ότι η ένθεση ενδοκερατοειδικού ενθέματος « Flexivue T.M.» και όλες οι μετεγχειρητικές εξετάσεις θα πραγματοποιηθούν στο ΒΕΜΜΟ.
- Ότι γνωρίζω ότι η εγχείρηση του καταρράκτη θα πραγματοποιηθεί στο Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλίου.
- Ότι επιθυμώ με τη θέληση μου να συμμετέχω σε αυτήν τη μελέτη.

(Ασθενής) (Ημερομηνία)

(Χειρουργός) (Ημερομηνία)

Consent form for Group 3

Μελέτη της ασφάλειας και αποτελεσματικότητας του ενδοκερατοειδικού διαθλαστικού ενθέματος "Flexivue T.M." μετά την εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού

Έντυπο συγκατάθεσης
και ενημέρωσης του ασθενούς

ΠΛΗΡΟΦΟΡΙΕΣ ΑΣΘΕΝΟΥΣ

Αριθμός αναγνώρισης: _____

Όνομα/Επώνυμο Ασθενούς: _____

Όνομα ερευνητή: _____

Τοποθεσία: _____

Ημερ/νία: _____

Διαδικασία Μελέτης

Αυτή η μελέτη είναι σχεδιασμένη για άτομα τα οποία έχουν σκλήρυνση του κρυσταλλοειδούς φακού και είναι υποψήφιοι για εγχείρηση του καταρράκτη και ένθεση ενδοφθάλμιου φακού. Λόγω της απώλειας της κοντινής όρασης μετά την αφαίρεση του φυσικού φακού και αυξημένης ανάγκης για ανεξαρτητοποίηση από διαθλαστικά γυαλιά, προτάθηκε ως λύση η ένθεση ενός ενδοκερατοειδικού μικροφακού Flexivue™. Αυτός ο μικροφακός είναι σχεδιασμένος έτσι ώστε να προσφέρει μια ικανοποιητική κοντινή όραση.

Κατά τη διάρκεια του ενός έτους θα υπάρχουν προγραμματισμένες επισκέψεις για κάθε συμμετέχοντα στην μελέτη . Η πρώτη επίσκεψη είναι μια επίσκεψη ελέγχου κριτηρίων. Κατά την διάρκεια αυτής της επίσκεψης ο γιατρός σας θα κάνει οφθαλμολογική εξέταση και διάφορα οπτικά τεστ για να επαληθεύσει ότι διαθέτετε τα κριτήρια επιλογής που υπάρχουν στην λίστα του πρωτοκόλλου. Αν ο γιατρός σας αποφασίσει ότι ίσως είστε ένας κατάλληλος υποψήφιος για την μελέτη, θα σας εξηγήσει τις λεπτομέρειες αυτής της μελέτης, τα πιθανά πλεονεκτήματα για σας και τους πιθανούς κινδύνους που μπορεί να συναντήσετε εάν συμμετάσχετε. Στο τέλος της εξήγησης θα σας δοθεί η ευκαιρία να κάνετε ερωτήσεις σχετικά με αυτήν την μελέτη.

Αν συμφωνήσετε να συμμετάσχετε σε αυτήν την μελέτη και αφού διαβάσετε αυτήν την φόρμα συγκατάθεσης και συμφωνήσετε να την υπογράψετε, ο ερευνητής σας θα προγραμματίσει να υποβληθείτε στη διαδικασία επεμβάσεως. Οι επεμβάσεις θα προγραμματιστούν να γίνει μία κοινώς αποδεκτή ημερομηνία για εσάς και το ιατρό σας και θα εκτελεστεί στο χειρουργείο που χρησιμοποιεί ο οφθαλμίατρος σας. Στην ομάδα ΙΙΙ τρεις μήνες μετά την εγχείρηση του καταρράκτη αμφοτερόπλευρα θα πραγματοποιηθεί η δημιουργία του τούνελ και ένθεση του ενθέματος.

Πριν γίνει η δημιουργία του τούνελ, το μάτι θα αναισθητοποιηθεί με οφθαλμικές σταγόνες που περιέχουν τοπικό αναισθητικό. Θα γίνει αποστείρωση και προετοιμασία σύμφωνα με τις διαδικασίες που ακολουθούνται πάντα στις επεμβάσεις στα μάτια. Ο γιατρός σας θα χρησιμοποιήσει το femtosecond laser για να δημιουργήσει ένα στενό τούνελ στον κερατοειδή

σας, το οποίο θα έχει περίπου 3χιλ στο πλάτος και 6-8χιλ στο μάκρος. Μέσα σε αυτό το τούνελ, ο γιατρός σας θα τοποθετήσει τον φακό Flexivue™ σε ένα σημείο στον κερατοειδή που είναι μπροστά από το κέντρο της κόρης. Ο γιατρός σας κατόπιν θα σας γράψει μια συνταγή για οφθαλμικές σταγόνες που θα ενσταλάζονται στο χειρουργημένο μάτι πολλές φορές την ημέρα και επίσης θα σας προγραμματίσει μια επίσκεψη για παρακολούθηση την επόμενη μέρα.

Κατά την επίσκεψή την πρώτη μέρα μετά την διαδικασία, ο οφθαλμίατρός σας θα κάνει διάφορα οφθαλμολογικά τεστ και μετρήσεις για να εκτιμήσει τη επιτυχία της διαδικασίας. Ο γιατρός σας επίσης θα σας ζητήσει να συμπληρώσετε ένα ερωτηματολόγιο το οποίο θα σας ζητά την γνώμη σας για την εγχείρηση και της αλλαγές στην όραση που βιώνετε.

Μετά, θα σας δοθούν οδηγίες για το πώς θα συνεχίσετε τα φάρμακα και θα προγραμματιστούν οι επισκέψεις για παρακολούθηση.

Σε κάθε μία από αυτές τις επισκέψεις, θα πραγματοποιούνται μετρήσεις όρασης και πολλά καθιερωμένα ιατρικά τεστ και θα σας ζητηθεί να συμπληρώσετε επιπρόσθετα ερωτηματολόγια.

Βασικά Κριτήρια Συμμετοχής:

Για να επιλεγείτε για αυτήν την έρευνα, θα πρέπει οπωσδήποτε:

- Να είστε 50-80 ετών και να έχετε σκλήρυνση του κρυσταλλοειδούς φακού και στα δύο μάτια.
- Να μην έχετε άλλα οφθαλμολογικά προβλήματα.
- Να μπορείτε να τηρήσετε το πρόγραμμα των μετεγχειρητικών επισκέψεων για παρακολούθηση.
- Να είστε πρόθυμοι να υπογράψετε μια ενημερωτική φόρμα συγκατάθεσης.

- Να μην έχετε οξείες ή χρόνιες συστηματικές παθήσεις που θα μπορούσαν να αυξήσουν τους κινδύνους της εγχείρησης ή να εμποδίσουν την φυσιολογική διαδικασία επούλωσης (πάθηση του συνδετικού ιστού, διαβήτης, οποιαδήποτε νεοπλασματική νόσος).

Ενδεχόμενες παρενέργειες ή ενοχλήσεις

Κάποιες ενοχλήσεις κατά την διάρκεια κάθε οφθαλμικής εγχείρησης είναι αναμενόμενες. Ο γιατρός σας θα χρησιμοποιήσει αναισθητικό κολλύριο κατά την διάρκεια της εγχείρησης για να μειώσει την ενόχληση στο ελάχιστο.

Όταν πραγματοποιείται μια τομή σε έναν οφθαλμό, ίσως υπάρξουν κίνδυνοι που προέρχονται από κακή διαχείριση, κακή λειτουργία ή κάθε είδους λάθος. Για να ελαχιστοποιήσουμε αυτούς τους κινδύνους στην περίπτωσή σας, έχουμε εκτελέσει όλα τα τεστ στο φακό Flexivue™.

Η ενόχληση, μετά την εγχείρηση, μπορεί να υπάρχει στο χειρουργημένο μάτι αλλά αυτή αναμένεται να είναι ήπια και μικρής διάρκειας.

Επίσης, μολύνσεις μπορεί να υπάρξουν μετά από οποιαδήποτε οφθαλμολογική επέμβαση. Για να ελαχιστοποιηθούν οι πιθανότητες, μετεγχειρητικά θα ακολουθήσετε ειδικές τοπικές φαρμακευτικές οδηγίες. Έχουν τηρηθεί επίσης αυστηρές μέθοδοι αποστείρωσης κατά την διάρκεια αυτής της διαδικασίας.

Ο φακός του κερατοειδή που θα τοποθετηθεί είναι στο στάδιο κλινικής μελέτης. Ίσως υπάρξουν παρενέργειες και ενοχλήσεις από τον φακό, οι οποίες δεν είναι ακόμα πλήρως γνωστές. Ίσως, επίσης, παρατηρήσετε αλλαγές στην όραση μετά την διαδικασία, στις οποίες ίσως χρειαστεί χρόνος για να προσαρμοστείτε. Αυτές μπορεί να είναι θολή όραση, δυσκολία στην εστίαση σε μακρινά ή κοντινά αντικείμενα. Ίσως επίσης νιώσετε σαν να βλέπετε διπλά

στο χειρουργημένο μάτι. Αν οποιοδήποτε από αυτά τα συμπτώματα εμφανιστούν μετά την διαδικασία, πιστεύουμε ότι θα είναι ήπια και ότι θα εξαφανιστούν μετά από μία περίοδο λίγων ημερών.

Σε περίπτωση που δυσκολεύεστε να ανεχτείτε αυτά τα συμπτώματα, ο γιατρός σας μπορεί να αντιστρέψει την εγχείρηση, αφαιρώντας τον φακό Flexivue™ που έχει εμφυτευτεί. Αναμένεται ότι τα συμπτώματά σας θα εξαφανιστούν σταδιακά με την πάροδο κάποιων ημερών μετά την αφαίρεση του εμφυτεύματος.

Δεν αναμένεται να προκληθεί μόνιμη βλάβη στον κερατοειδή σας ακόμα και αν ο φακός χρειαστεί να μετακινηθεί, αλλά δεν υπάρχει τρόπος να αποκλείσουμε εντελώς την πιθανότητα ότι μπορεί να προκληθεί μία μόνιμη βλάβη στον κερατοειδή σας και/ή στην όρασή σας .

Οφέλη που θα προκύψουν από την μελέτη

Το προσωπικό πλεονέκτημα που θα έχετε από την συμμέτοχή σας σε αυτή την μελέτη είναι η ευκαιρία να έχετε καλή μακρινή και κοντινή όραση μετά την εγχείρηση του καταρράκτη, χωρίς να εξαρτάστε από γυαλιά οράσεως. Αυτό μπορεί να βελτιώσει την ποιότητα ζωής σας και την ικανότητά σας να λειτουργείτε στο σπίτι και στην δουλειά.

Η συμμετοχή σας στη μελέτη και οι πληροφορίες οι οποίες θα μας δώσει αυτή, ίσως μελλοντικά να ωφελήσει άλλους ανθρώπους με παρόμοιες παθήσεις.

Εναλλακτικές θεραπείες

Εναλλακτικές μέθοδοι για να διορθωθεί το πρόβλημα της όρασης σας, η απώλεια της κοντινής όρασης μετά την εγχείρηση του καταρράκτη, είναι διαθέσιμες εδώ και χρόνια. Αυτές συμπεριλαμβάνουν τα γυαλιά οράσεως, τους φακούς επαφής και άλλων μορφών επεμβάσεις. Όλες αυτές είναι καλές επιλογές και μπορείτε να διαλέξετε οποιαδήποτε από αυτές αντί του να συμμετάσχετε στην μελέτη.

Εμπιστευτικότητα

Οι πληροφορίες από αυτήν την μελέτη ίσως δοθούν στον χορηγό Βιο-όρασης AG, και στην Διοίκηση Φαγητού και Φαρμάκων (FDA). Πληροφορίες μπορεί επίσης να δοθούν σε regulatory agencies σε άλλες χώρες. Τα αποτελέσματα από αυτή την μελέτη ίσως δημοσιευτούν αλλά η ταυτότητά σας θα είναι απόρρητη.

<u>Υπεύθυνη Δήλωση ασθενούς</u>

Δηλώνω υπεύθυνα:

- Ότι ενημερώθηκα αναλυτικά από τον ιατρό του ΒΕΜΜΟ (Βαρδινογιάννειο Εργαστήριο Χειρουργικής και Μεταμοσχεύσεων Οφθαλμού) για τα πιθανά οφέλη και τους ενδεχόμενους κινδύνους της χειρουργικής επέμβασης διόρθωσης της κοντινής όρασης μετά την εγχείρηση του καταρράκτη με το ενδοκερατοειδικό ένθεμα «Flexivue T.M.».
- Ότι ο ιατρός απάντησε ικανοποιητικά σε όλα μου τα ερωτήματα.
- Ότι γνωρίζω ότι η χειρουργική αυτή επέμβαση αποτελεί μέρος κλινικής μελέτης για την ασφάλεια και την αποτελεσματικότητα του ενδοκερατοειδικού ενθέματος « Flexivue T.M.».
- Ότι έχω διαβάσει και έχω κατανοήσει πλήρως το ενημερωτικό έντυπο συγκατάθεσης.
- Ότι ενημερώθηκα για τις υπάρχουσες εναλλακτικές μεθόδους αντιμετώπισης της απώλειας της κοντινής όρασης μετά την εγχείρηση του καταρράκτη.
- Ότι γνωρίζω ότι η ένθεση ενδοκερατοειδικού ενθέματος « Flexivue T.M.» και όλες οι μετεγχειρητικές εξετάσεις θα πραγματοποιηθούν στο ΒΕΜΜΟ.
- Ότι γνωρίζω ότι η εγχείρηση του καταρράκτη θα πραγματοποιηθεί στο Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλίου.
- Ότι επιθυμώ με τη θέληση μου να συμμετέχω σε αυτήν τη μελέτη.

(Ασθενής) (Ημερομηνία)

(Χειρουργός) (Ημερομηνία)

Appendix 2

Near vision score table

A.A.: ΦΑΣΗ:

33 CM	ΔΕΞΙΟ					ΑΡΙΣΤΕΡΟ					ΔΙΟΦΘΑΛΜΑ				
1.4	M	B	X	P	O	E	A	P	B	M	M	B	X	P	O
1.3	E	A	H	K	T	T	H	B	A	E	E	A	H	K	T
1.2	O	B	A	E	K	P	H	O	K	M	O	B	A	E	K
1.1	E	O	H	A	N	A	M	K	P	E	E	O	H	A	N
1.0	T	A	X	P	E	P	X	E	H	M	T	A	X	P	E
0.9	N	K	E	X	B	E	P	H	X	B	N	K	E	X	B
0.8	K	E	B	H	X	B	M	A	O	T	K	E	B	H	X
0.7	A	B	P	M	E	O	T	P	M	A	A	B	P	M	E
0.6	H	M	O	B	K	X	O	A	E	P	H	M	O	B	K
0.5	B	H	T	O	X	B	P	X	T	K	B	H	T	O	X
0.4	K	T	M	B	H	O	K	T	M	A	K	T	M	B	H
0.3	H	X	K	E	P	K	T	X	H	O	H	X	K	E	P
0.2	N	P	M	K	O	H	O	M	T	X	N	P	M	K	O
0.1	P	H	O	T	A	M	E	T	A	H	P	H	O	T	A
0.0	M	B	X	P	O	E	A	P	B	M	M	B	X	P	O
	Score:					Score:					Score:				

ARM LENTGH~66 CM:_____

1.1	M	B	X	P	O	E	A	P	B	M	M	B	X	P	O
1.0	E	A	H	K	T	T	H	B	A	E	E	A	H	K	T
0.9	O	B	A	E	K	P	H	O	K	M	O	B	A	E	K
0.8	E	O	H	A	N	A	M	K	P	E	E	O	H	A	N
0.7	T	A	X	P	E	P	X	E	H	M	T	A	X	P	E
0.6	N	K	E	X	B	E	P	H	X	B	N	K	E	X	B
0.5	K	E	B	H	X	B	M	A	O	T	K	E	B	H	X
0.4	A	B	P	M	E	O	T	P	M	A	A	B	P	M	E
0.3	H	M	O	B	K	X	O	A	E	P	H	M	O	B	K
0.2	B	H	T	O	X	B	P	X	T	K	B	H	T	O	X
0.1	K	T	M	B	H	O	K	T	M	A	K	T	M	B	H
0.0	H	X	K	E	P	K	T	X	H	O	H	X	K	E	P
-0.1	N	P	M	K	O	H	O	M	T	X	N	P	M	K	O
-0.2	P	H	O	T	A	M	E	T	A	H	P	H	O	T	A
-0.3	M	B	X	P	O	E	A	P	B	M	M	B	X	P	O
	Score:					Score:					Score:				

Appendix 3

Patient Satisfaction Questionnaire

1. How does the patient perceive his/her binocular uncorrected distance vision?	Excellent	Good	Fair	Poor
2. How does the patient perceive his/her uncorrected distance vision in the study eye?	Excellent	Good	Fair	Poor
3. How does the patient perceive how his/her uncorrected near vision?	Excellent	Good	Fair	Poor
4. How frequently does the patient use glasses for near?	No use of glasses	Use of glasses less than 50%	Use of glasses more than 50%	Use of glasses almost always
5. How frequently does the patient use glasses for far?	No use of glasses	Use of glasses less than 50%	Use of glasses more than 50%	Use of glasses almost always
6. Does the patient experience halos?	No	Sometimes	Very frequently	Always
7. Does the patient experience glare?	No	Sometimes	Very frequently	Always

Publications

Cataract surgery with a refractive corneal inlay in place

Stojanovic NR 1*, Panagopoulou SI 1 and Pallikaris IG 1

1 Institute of Vision and Optics (IVO), Medical School, University of Crete, Heraklion, Crete, Greece

Corresponding author: Stojanovic NR, Institute of Vision and Optics (IVO), University of Crete, Medical School, 71003 Heraklion, Crete, Greece, E-mail: zenskic@yahoo.com

Dr. Pallikaris is the Medical Advisory Board Chair of Presbia Cooperatief U.A. The remaining authors have no financial or proprietary interest in any material or method presented herein.

The authors declare that there is no conflict of interests regarding the publication of this paper..

Abstract

Purpose: To present a case of cataract surgery performed in a patient with a refractive corneal inlay in place.

Methods: A 48-year-old female patient presented to our institute with bilateral cataract. The patient had undergone refractive corneal inlay implantation three years ago in her right, nondominant eye for presbyopia correction. Biometry and intraocular lens (IOL) power calculation were performed without removing the inlay. Phacoemulsification and IOL insertion were carried out in both eyes in a usual manner.

Results: On day one postoperatively, the patient achieved binocular uncorrected distance visual acuity 20/20 and uncorrected near visual acuity J1. The vision remained stable during the one year follow-up period.

Conclusion: Cataract surgery was performed in a standard manner in a patient with Presbia Microlens™ corneal inlay in place. Visual outcomes for both near and distance vision were satisfactory.

Keywords: presbyopia; cataract surgery; corneal inlay

Introduction

In recent years, several corneal procedures have been proposed for presbyopia treatment including monovision laser in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), conductive keratoplasty (CK), presbyopic LASIK (presbyLASIK), and more recently, the IntraCor technique and the corneal inlay [1]. The biggest advantage of corneal inlays is the fact that they are additive and do not remove tissue, and they therefore preserve future options for any kind of presbyopia correction as discussed by Lindstrom et al. [2]. Corneal inlays are placed under stromal flaps or inside stromal pockets made by microkeratomes or femtosecond lasers. Different inlay models are reported to use different mechanisms to compensate for accommodation loss, such as positive refractive power, change of anterior corneal curvature, or increase of the depth of field by fixed small aperture [3].

The satisfactory outcomes regarding efficacy and patients' satisfaction after the inlay implantation for presbyopia could be changed by cataract development, due to the normal aging process, resulting in vision deterioration. Given that the number of presbyopic patients with the corneal inlays is increasing, it is important to address some issues regarding cataract surgery in these patients.

We describe our experience of cataract surgery in a patient with the Presbia Microlens^{TM} corneal inlay in place.

Case Presentation

A 48-year-old female patient presented to our institute with a history of blurred vision for the last six months. The patient had undergone refractive corneal inlay implantation three years ago in her right, nondominant eye for presbyopia correction. At presentation, the patient had uncorrected distance visual acuity (UDVA) 20/40 in the right eye, 20/32 in the left eye and binocularly 20/32. Uncorrected near visual acuity (UNVA) was J1 in the right, J3 in the left and binocularly J1. The patient achieved corrected distance visual acuity (CDVA) 20/32 with refraction +1.00-1.25x180 in the nondominant and 20/25 with +0.75-0.25x165 in the dominant eye. Slit lamp examination revealed nuclear sclerosis and posterior subcapsular cataract (NC3 and P3 according to the Lens Opacities Classification System III (LOCS III)) in both eyes [4]. The remaining anterior and posterior segment findings were unremarkable.

After we discussed all options, the patient opted for bilateral cataract surgery without removal of the corneal inlay, in order to improve her far and preserve near vision and spectacle independence. The written informed consent was obtained from the patient.

Routine preoperative evaluation for cataract surgery was performed. Biometry was performed with IOL Master (Carl Zeiss Meditec, Jena, Germany) in a usual manner. The surgeon opted for intraocular lens (IOL) power calculated with SRK-T formula for a one-piece monofocal intraocular lens (AcrySof IQ SN60WF, Alcon), targeting emmetropia.

The bilateral cataract extraction with phacoemulsification and posterior chamber IOL implantation was carried out first in the nondominant and two days later in the dominant eye, which is the surgeon's usual approach. The surgeries were performed under sterile conditions with topical anaesthesia. A clear corneal incision of 2.8 mm was made, and an anterior curvilinear capsulorhexis of 5.5 mm was performed. Phacoemulsification was performed using the Infiniti Vision System (Alcon, Laboratories Inc, Fort Worth, TX), with thorough cortical removing and meticulous cleaning of the posterior capsule and anterior capsular leaflets. After phacoemulsification and lens removal, the IOLs (AcrySof IQ SN60WF OD +21.5D and OS +21.5D) were implanted into the capsular bag using the standard injector device. The surgery was uneventful in both eyes. (Figure 1.)

Postoperative topical therapy included topical antibiotic-steroid drops (tobramycin/dexamethasone, Tobradex; Alcon Laboratories Inc, Ft Worth, Texas) four times a day for 4 weeks with a weekly tapering regimen.

On postoperative day one, the patient had UDVA 20/40 in her right (OD) and 20/20 in her left eye (OS), 20/20 binocularly and UNVA OD J1 and OS J3, binocularly J1. One year postoperatively, the patient yielded UDVA of 20/32 in the nondominant and 20/20 in the dominant eye, CDVA of 20/20 bilaterally with manifest refraction +0.25-1.25x170 and +0.50, respectively. The patient had binocular UDVA 20/20 and UNVA J1. Topography findings did not show significant change before and after cataract surgery. (Figure 2.)

No complications were recorded on any of the follow-up visits. The patient was happy with the final visual outcome and remained spectacle-free.

Discussion

Intrastromal corneal inlays are a new modality for presbyopia correction. The Presbia Microlens^{TM} (Presbia, Amsterdam, Netherlands) is a transparent, hydrophilic disc with 3 mm diameter and

approximately 15 μm edge thickness. The central 1.6 mm diameter of the disc is plano in power and the peripheral zone has the additional positive power. The lens has a bifocal optical system which acts as modified monovision and is inserted into the intrastromal corneal pocket made by femtosecond laser in the nondominant eye. Our previous study showed that refractive corneal inlay is safe and effective method for presbyopia correction [5]. However, some patients may eventually develop cataract and require cataract surgery. At present, there are several available options, including cataract surgery with the inlay in place, inlay removal followed by cataract surgery and subsequent inlay re-implantation and inlay removal followed by cataract surgery with implantation of an accommodative or multifocal intraocular lens. However, if a patient is does not wish to remove the refractive inlay, then monofocal intraocular lens should be used. When choosing the IOL power, emmetropia should be targeted, given that the Presbia Microlens^{TM} is a refractive lens (with positive refractive power).

The major concerns regarding cataract surgery with a corneal inlay in place are the accuracy of preoperative evaluation and biometry readings, technical aspects of the surgery and visual outcomes. In our case, the preoperative evaluation was performed in a standard manner. The slit-lamp evaluation of anterior and posterior segment was not affected by the inlay, due to its transparency. Fundus and iridocorneal angle examination with Goldmann three-mirror contact lens have been performed without any difficulty.

The results of manifest refraction one year after surgery in both eyes suggest that biometry readings and IOL power calculations were reasonably accurate. Biometry findings taken from IOL Master and calculated refraction are presented in Table 1. Regarding the formulas, it would seem that both SRK/T and HofferQ provided satisfying results, but one case is not sufficient to establish validity of either formula in patients with Presbia Microlens^{TM}.

Technical aspects of the surgical procedure were not in the least affected by Microlens^{TM}. The transparent inlay provides excellent visibility through the operating microscope and allows all the usual surgical manipulations.

In conclusion, in our case phacoemulsification and intraocular lens implantation were performed in a patient with Presbia Microlens^{TM} corneal inlay without any modification or additional surgical manoeuvre. Visual outcomes for both near and distance vision were satisfactory. The inlay does not appear to have had significant effect on biometry or IOL power calculation. However, larger studies are needed for drawing definite conclusions regarding safety and visual outcome of cataract surgery with the refractive corneal inlay in place, as well as to establish the appropriate formula for calculation of intraocular lens power.

References

1. Torricelli AA, Junior JB, Santhiago MR, Bechara SJ Surgical management of presbyopia. Clin Ophthalmol. 2012;6:1459-66.

2. Lindstrom RL, Macrae SM, Pepose JS, Hoopes PC Sr. Corneal inlays for presbyopia correction Curr Opin Ophthalmol.2013 Jul;24(4):281-7.

3. Arlt EM, Krall EM, Moussa S, Grabner G, and Dexl AK Implantable inlay devices for presbyopia: the evidence to date Clin Ophthalmol. 2015; 9: 129–137.

4. Chylack LT, Jr, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol. 1993;111(6):831–836.

5. Limnopoulou AN, Bouzoukis DI, Kymionis GD, Panagopoulou SI, Plainis S, Pallikaris AI, Feingold V, Pallikaris IG. Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. J Refract Surg. 2013 Jan;29(1):12-8.

Figure 1. A slit-lamp retroillumination photograph of the Presbia Microlens^{TM} and intraocular lens

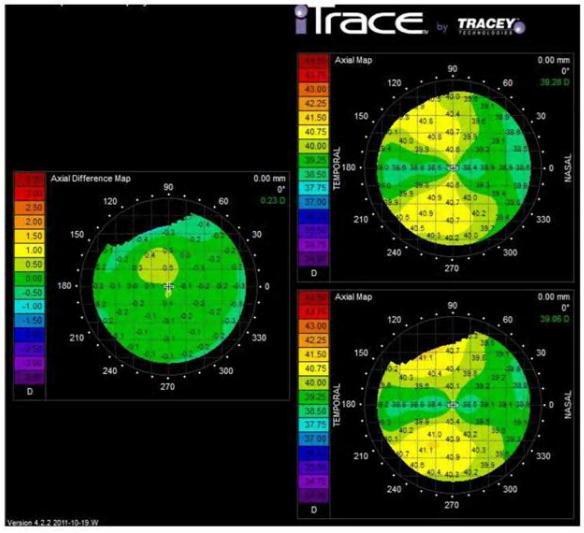

Figure 2. Corneal Topography maps preoperatively and one year after the cataract surgery (the map on the upper right is preoperative and the lower right is one year postoperative axial map, the map on the left is the pre- and postoperative axial differential map)

	AL(mm)	K1(D)	K2(D)	ACD(mm)	SRK/T Ref(D)	HofferQ Ref(D)	Haigis Ref(D)	Manifest Refraction after cataract surgery (D)
OD	24.67	39.79	41.31	3.48	-0.06	0.5	0.76	+0.25-1.25x170
OS	24.54	39.99	40.71	3.40	-0.03	0.5	0.70	+0.50

Table 1. Biometry readings, target refractions for +21.5D intraocular lens calculated with three different formulas and manifest refraction one year after surgery (Abbreviations: AL, axial length; K1,K2, Keratometry readings; ACD, anterior chamber depth; Ref (D), calculated refraction)

CASE REPORT

Refractive corneal inlay for near vision improvement after cataract surgery

Nela R. Stojanovic, MD, MSc, FEBO, Sophia I. Panagopoulou, PhD, Ioannis G. Pallikaris, MD, PhD

We present the case of a patient who had refractive corneal inlay implantation for near vision improvement after bilateral cataract surgery. The patient had a history of bilateral cataract, and a 2-step procedure was suggested to improve her near and distance visual acuities. The first step was bilateral cataract extraction with a power target of plano intraocular lens implantation. Six months later, a refractive corneal inlay, Presbia Microlens, was implanted in the nondominant eye in the intracorneal pocket made with the femtosecond laser. No intraoperative or postoperative complications occurred. The bilateral uncorrected near visual acuity improved from less than Jaeger (J)6 to J1 and remained stable during the 2-year follow-up. The refractive corneal inlay is a safe, simple, and efficient method for improving near visual acuity in patients after cataract surgery.

Financial Disclosure: Dr. Pallikaris is the chair of the medical advisory board of Presbia Coöperatief U.A. No other author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2014; 40:1232–1235 © 2014 ASCRS and ESCRS

Cataract surgery is one of the most common surgical procedures in ophthalmology. The number of cataract patients is growing due to the increasing aging population. The current standard surgical procedure involves removal of the opaque crystalline lens fibers with phacoemulsification, followed by implantation of an intraocular lens (IOL) in the capsular bag. Because patients' demand for spectacle independence has increased, several methods to compensate for the accommodation loss after cataract surgery have been proposed.[1] Accommodating IOLs use ciliary muscle contraction to change the dioptric power of the eye by focus shift.[2] Multifocal IOLs use diffractive or refractive technology to provide near, intermediate, and distance vision.[3] The monovision technique corrects 1 eye for near vision and the other eye for distance vision.[4] Although these techniques are good options for improving near visual acuity after cataract surgery, the single perfect solution has not been found.

Recently, a cornea-based approach to improve near vision in patients with presbyopia was introduced. Corneal inlays are placed under stromal flaps or inside stromal pockets made by special microkeratomes or femtosecond lasers. Different models use different mechanisms to compensate for accommodation loss, such as positive refractive power, change of anterior corneal curvature, or an increase in the depth of field by fixed aperture (pinhole).[5,6] The Presbia Microlens (Presbia Coöperatief U.A.) is a transparent hydrophilic acrylic disk with a 3.0 mm diameter and an edge thickness of 15 μm. The peripheral zone contains the near vision power, and the central 1.6 mm of the disk has no refractive effect (plano). The inlay comes in a range of refractive powers from +1.50 diopters (D) to +3.50 D. At the center of the disk is a 0.51 mm diameter hole. The inlay is inserted in an intrastromal corneal pocket created in the nondominant eye.

Our previous study of this inlay showed it is safe and effective for the improvement of uncorrected near visual acuity in presbyopic patients.[7] We present a case in which the patient had bilateral cataract surgery followed by corneal inlay implantation in the nondominant eye 6 months later for improvement of near visual acuity.

Submitted: January 24, 2014.
Final revision submitted: February 20, 2014.
Accepted: February 20, 2014.

From the Institute of Vision and Optics, Medical School, University of Crete, Heraklion, Crete, Greece.

Corresponding author: Nela R. Stojanovic, MD, MSc, FEBO, Institute of Vision and Optics, University of Crete, Medical School, 71003 Heraklion, Crete, Greece. E-mail: zenskic@yahoo.com.

0886-3350/$ - see front matter
http://dx.doi.org/10.1016/j.jcrs.2014.05.016

CASE REPORT

A 61-year-old woman presented to our clinic with a history of blurred vision for the previous 2 years. The uncorrected distance visual acuity (UDVA) was 20/200 in the right eye and 20/400 in the left eye. The uncorrected near visual acuity (UNVA) was less than Jaeger (J)6. The corrected distance visual acuity (CDVA) was 20/20 in the right eye and 20/50 in the left, with a manifest refraction of −6.25 −1.00 × 85 and −7.75 −1.75 × 90, respectively. Slitlamp examination revealed a nuclear cataract in both eyes, with a more advanced cataract in the left eye. Additional ophthalmic examination findings were unremarkable.

After thorough discussion with the patient of the options and considering her desire for spectacle independence, a 2-step procedure consisting of bilateral cataract surgery followed by refractive corneal inlay implantation in the nondominant eye was chosen. A complete preoperative evaluation was performed, including biometry (IOLMaster, Carl Zeiss Meditec AG) and IOL power calculation, eye dominancy test, and monovision contact lens trial. Informed written consent was obtained for the procedures.

All surgical procedures were performed by the same experienced surgeon (I.G.P.). The cataract surgery was performed first in the nondominant eye (left eye) and 2 days later in the dominant eye (right eye), which is the usual practice in our clinic. The IOL powers selected for implantation targeted plano in both eyes. The cataract extraction was done in a standard manner by phacoemulsification in sterile conditions and under topical anesthesia. After the nucleus and cortical fibers were removed, monofocal IOLs (right eye +16.5 D and left eye +15.0 D, Acrysof IQ SN60WF, Alcon Laboratories, Inc.) were implanted in the capsular bag using the standard injector device. The surgeries were uneventful in both eyes, and the IOLs were well-centered. Postoperative therapy included topical antibiotic and steroid drops (tobramycin and dexamethasone [Tobradex]) 4 times a day for 4 weeks with a weekly tapering regimen.

Six months after cataract surgery, the patient returned for the corneal inlay implantation. The pre-implantation UDVA was 20/20 in the dominant eye, 20/25 in the nondominant eye, and 20/20 binocularly; the UNVA was Jaeger (J)3 in both eyes and binocularly J3 at 30 cm. After implantation, the CDVA was 20/20 in the right eye and 20/20 in the left eye with a refraction of +0.50 −0.75 × 70 and plano −0.75 × 70, respectively. The UDVA, UNVA, and CDVA in the dominant eye remained stable through the last follow-up examination. The refractive corneal inlay power (+1.50 D) was selected based on the patient's near vision correction with spectacles and considering her near vision needs at approximately 45 cm.

An intrastromal corneal pocket was created in the nondominant eye using a femtosecond laser (iFS, Intralase, Abbott Medical Optics, Inc.) under topical anesthesia. The femtosecond laser parameters used to create the pocket are shown in Table 1. A 300 µm deep channel measuring 4.2 mm in width was created temporally and then extended to the center of the cornea corresponding to the visual axis. A special injector (Presbia Coöperatief U.A.) was used to insert the inlay in the pocket. The inlay was centered at the line of sight using the microscope and centration green light of the excimer laser (Allegretto Wave 400, Wavelight Technologie AG). After inlay implantation, an evaluation with anterior segment optical coherence tomography (Visante 3.0, Carl Zeiss Meditec AG) was performed and the position of the inlay and the depth of the corneal intrastromal pocket were confirmed (Figure 1). Postoperatively, the patient was treated with topical antibiotic and steroid drops (tobramycin and dexamethasone) 4 times a day for 10 days.

Table 1. The femtosecond laser parameters used for creation of the pocket.

Channel width	4.2 mm
Channel depth	300 µm
Channel spot separations	3 µm
Channel line separations	3 µm
Energy	0.75 µJ
Side-cut energy	1.20 µJ
Side-cut radius	4.5 mm
Side-cut angle	30 degrees
Side-cut spot separation	6 µm
Side-cut layer separation	6 µm

One month after inlay implantation, the UDVA was 20/32 and the UNVA was J1 in the operated eye; the UDVA was 20/20 and the UNVA J1 binocularly. The CDVA in the nondominant eye was 20/25 with a manifest refraction of −2.00 −0.50 × 150. The patient was happy and reported no need for reading glasses (Figure 2).

Two years after cataract surgery, the patient began to complain of blurred vision in the nondominant eye. On examination, the UDVA was 20/50 and the UNVA was J1; however, the patient was reading with some difficulty. The slitlamp examination showed posterior capsule opacification (PCO). The patient was scheduled for neodymium:YAG (Nd:YAG) capsulotomy, which was performed in the standard manner, and no complications occurred during or after capsulotomy. At the last follow-up examination 6 months later, the UDVA was 20/20 in the dominant eye and 20/32 in the nondominant eye. The UNVA was J3 and J1, respectively, and binocular UDVA was 20/20 and UNVA was J1. The CDVA was 20/20 in the dominant eye and 20/25 in the nondominant eye with a refraction of +0.25 −0.50 × 70 and −2.00 sph, respectively. The patient remained spectacle independent and very happy.

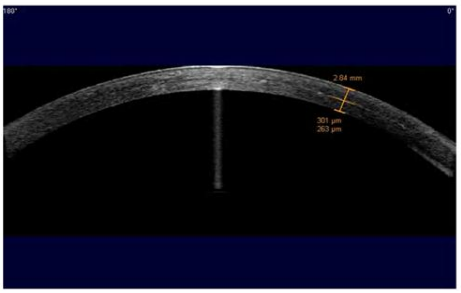

Figure 1. Anterior segment optical coherence tomography showing the inlay inside the corneal intrastromal pocket.

Figure 2. Slitlamp retroillumination photograph of the corneal inlay and IOL.

DISCUSSION

Improving near visual acuity in presbyopic patients or after cataract surgery is one of the most challenging tasks in refractive surgery today. Options currently available to refractive surgeons include accommodating IOLs, multifocal IOLs, and monovision techniques. Although accommodating IOLs appear to provide better near vision than monofocal IOLs, there are reports of inconsistent results and lens tilt causing reduced visual quality.[8,9] The major drawback of monovision techniques is that the patient may have difficulties in binocularity and stereopsis.[10] Multifocal IOLs create a range of optical foci: near, distant, and intermediate. Because of the multifocality, the defocused image causes blurring of the focused image and reduces modulation. Multifocal IOLs provide functional vision for all distances but, at the same time, create quality issues such as reduced contrast sensitivity and visual symptoms such as glare, halo, and problematic night vision.[11,12]

Recently, several intrastromal corneal inlays to improve near vision in presbyopia patients have been introduced. Our positive experience with the Presbia Microlens in our previous study led us to use the same technique in this patient.[7] The refractive corneal inlay is a bifocal optical system that provides patients with modified monovision. During far vision, the rays pass through the central zone of the inlay without refractive effect and are sharply focused on the retina, whereas the rays that pass through the refractive peripheral zone are out of focus in front of the retina. During near vision, the rays that pass through the central zone are out of focus behind the retina and the rays that pass through the lens peripheral refractive zone are focused on the retina.

In the case presented, the patient's binocular UNVA improved after inlay implantation from J3 to J1 using a refractive power of +1.50 D, which was customized to the patient's reading needs. Since the inlay is available in a range of refractive powers, the surgeon is able to provide the patient with improvement in near vision at the distance the patient is comfortable with, which is based on specific patient needs and preferred working or reading distance. Based on these considerations, the surgeon can select the appropriate power for the inlay in exactly the same manner as for near-vision glasses.[7] Preoperative evaluation and patient selection is important when considering use of this technology. First, based on our previous experience with this inlay, patients selected for implantation should have strong ocular dominance and a positive experience with a monovision trial. Patients who cannot tolerate monovision are not good candidates for this procedure. Second, patient motivation is important. Patients who wish to be spectacle independent are, in our experience, the best candidates. The reason seems to be that although less than in standard monovision techniques, there is a difference in vision between the dominant eye and the nondominant eye. Motivated patients and those with a positive monovision trial may more easily adapt to their new vision.

One advantage of the refractive intracorneal inlay over monovision is that with the same power correction, the uncorrected visual acuity is dramatically decreased in monovision, whereas this is not the case with the refractive intracorneal inlay. In our case, the patient achieved visual acuity of 20/32 without correction but had a manifest refraction spherical equivalent of −2.25 D. The explanation for this lies in the bifocal design of the inlay.

In our previous study of the inlay in presbyopic patients,[7] we reported that some patients had glare and halos that tended to become less intense over time and did not interfere with their activities, such as night driving. In our case, the patient did not experience glare, halos, or night-vision issues. However, the decrease in CDVA after inlay implantation in the nondominant eye may be attributed to the difficulty in performing manifest refraction over the inlay because of its 2 separate focal points. No topographic changes occurred to account for the decrease in CDVA.

In our experience, it is advisable to wait a minimum of 3 months after cataract surgery before creating the pocket and implanting the inlay. This ensures that the eye that had cataract surgery and implantation of the IOL is stable prior to performing the inlay procedure. A major advantage of this technology is that

the inlay can be easily removed if necessary, leaving the eye essentially unchanged after the procedure. This is important in cases in which the patient requires additional refractive power (in which case the lens can be exchanged) or if the patient is dissatisfied with the outcome.

Considering the mean age of patients having cataract surgery, it is expected that some changes will appear in the fundus, such as macular degeneration. The transparency of the Presbia Microlens provides excellent visibility of the entire fundus. Furthermore, if PCO occurs, the transparency of the inlay permits excellent visualization for Nd:YAG capsulotomy, as demonstrated in this case report. In conclusion, our case report suggests that this refractive corneal inlay is a safe and effective technology for improving near visual acuity following cataract surgery.

REFERENCES

1. Olson RJ, Werner L, Mamalis N, Cionni R. New intraocular lens technology. Am J Ophthalmol 2005; 140:709–716
2. Dick HB. Accommodative intraocular lenses: current status. Curr Opin Ophthalmol 2005; 16:8–26
3. Versteeg FFH. Multifocal IOLs for presbyopia [letter]. J Cataract Refract Surg 2005; 31:1266; reply by G Baïkoff, 1266
4. Jain S, Arora I, Azar DT. Success of monovision in presbyopes: review of the literature and potential applications to refractive surgery. Surv Ophthalmol 1996; 40:491–499
5. Yilmaz ÖF, Bayraktar S, Agca A, Yilmaz B, McDonald MB, van de Pol C. Intracorneal inlay for the surgical correction of presbyopia. Cataract Refract Surg 2008; 34:1921–1927
6. Waring GO IV. Correction of presbyopia with a small aperture corneal inlay. J Refract Surg 2011; 27:842–845
7. Limnopoulou AN, Bouzoukis DI, Kymionis GD, Panagopoulou SI, Plainis S, Pallikaris AI, Feingold V, Pallikaris IG. Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. J Refract Surg 2013; 29:12–18
8. Cumming JS, Kammann J. Experience with an accommodating IOL [letter]. J Cataract Refract Surg 1996; 22:1001
9. Findl O, Leydolt C. Meta-analysis of accommodating intraocular lenses. J Cataract Refract Surg 2007; 33:522–527
10. Durrie DS. The effect of different monovision contact lens powers on the visual function of emmetropic presbyopic patients (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2006; 104:366–401. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809906/pdf/1545-6110_v104_p366.pdf. Accessed March 29, 2014
11. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. J Cataract Refract Surg 2009; 35:992–997
12. Leyland M, Zinicola E. Multifocal versus monofocal intraocular lenses in cataract surgery; a systematic review. Ophthalmology 2003; 110:1789–1798

First author:
Nela R. Stojanovic, MD, MSc, FEBO

Institute of Vision and Optics, University of Crete, Medical School, Heraklion, Crete, Greece

ORIGINAL ARTICLE

Combined Cataract and Refractive Corneal Inlay Implantation Surgery: Comparison of Three Techniques

Nela R. Stojanovic, MSc, FEBO; Vladimir Feingold; Ioannis G. Pallikaris, MD, PhD

ABSTRACT

PURPOSE: To compare clinical outcomes of three different techniques of combined cataract and Presbia Flexivue Microlens refractive corneal inlay (Presbia Coöperatief U.A., Amsterdam, Netherlands) implantation surgery for presbyopia compensation over a 12-month follow-up.

METHODS: In this comparative pilot study, 15 patients with bilateral cataract were allocated to one of three groups with a different combination of surgical steps (cataract surgery, intrastromal pocket creation, and inlay implantation). In the three-step group, the intracorneal pocket was created in the non-dominant eye, bilateral cataract surgery was performed 3 months later, and the intracorneal inlay was inserted 3 months after that. In the two-step at 3 days group, bilateral cataract surgery was performed 3 days after pocket creation and inlay implantation in the non-dominant eye. In the two-step at 3 months group, the pocket creation and the inlay implantation were performed in the non-dominant eye 3 months after bilateral cataract surgery. Visual, refractive, and contrast sensitivity outcomes were evaluated and compared between the three groups.

RESULTS: Twelve months after the inlay implantation, mean monocular uncorrected distance visual acuity was 20/32 in the three-step group, 20/32 in the two-step at 3 days group, and 20/25 in the two-step at 3 months group. Achieved mean monocular uncorrected near visual acuity was similar in the three groups (20/25). The visual and refractive outcomes did not show significant differences between groups. Contrast sensitivity was similar between groups under mesopic and photopic conditions. No intraoperative or postoperative complications were observed.

CONCLUSIONS: Clinical outcomes of three different techniques of combined cataract surgery and refractive corneal inlay implantation had no apparent differences between them. The corneal inlay provided excellent near vision acuity, with high patient satisfaction and a high spectacle independence rate after cataract surgery.

[*J Refract Surg.* 201X;X(X):XX-XX.]

In 1949 Barraquer proposed corneal implantation to alter the corneal refractive power.[1] From the 1960s on, corneal inlays have been researched with the aim of developing more biocompatible materials and reliable placement within the cornea. Modern materials science and decades of research together with corneal femtosecond lasers have made this 65-year-old idea a clinical reality. An intracorneal inlay was recently introduced as a method for improving near vision in patients with presbyopia.[2] The intracorneal inlay is placed under a corneal stromal flap or inside a stromal pocket made by special microkeratomes or femtosecond lasers.

The Presbia Flexivue Microlens inlay (Presbia Coöperatief U.A., Amsterdam, Netherlands) is a refractive intracorneal inlay. The lens has a bifocal optical system that acts as modified monovision and is inserted into an intrastromal corneal pocket made by a femtosecond laser in the non-dominant eye. Recent studies support the efficacy and safety of the Presbia Flexivue Microlens corneal inlay for the treatment of presbyopia in patients with a clear crystalline lens.[3,4] However, the possibility of implanting a corneal inlay where there is monofocal lens cataract surgery offers a surgical solution for patients troubled by pseudophakic presbyopia. It is possible to consider differing combinations of techniques for implantation of the refractive corneal inlay and the cataract surgery.

The purpose of this pilot study was to compare the clinical outcomes of three different techniques for combined cataract and refractive corneal inlay implantation surgery over a 12-month follow-up period.

From the Institute of Vision and Optics, Medical School, University of Crete, Crete, Greece (NRS, IGP); and Presbia Cooperatief U.A., Amsterdam, Netherlands (VF).

Submitted: August 16, 2015; Accepted: January 15, 2016

Dr. Pallikaris is the Medical Advisory Board Chair and Mr. Feingold is Executive Vice President of Presbia Cooperatief U.A. Ms. Stojanovic has no financial or proprietary interest in the materials presented herein.

Correspondence: Nela R. Stojanovic, MSc, FEBO, Institute of Vision and Optics, Medical School, University of Crete, 71003 Heraklion, Crete, Greece. E-mail: zenskic@yahoo.com

doi:10.3928/1081597X-20160225-02

PATIENTS AND METHODS

This comparative pilot study was conducted at the Institute of Vision and Optics, University Hospital of Crete, Crete, Greece. Institutional review board approval was obtained and all patients were appropriately informed before their participation in the study about the possible outcomes and the current clinical experience, and provided written informed consent in accordance with the institutional guidelines, following the tenets of the Declaration of Helsinki.

Inclusion criteria were patient age between 50 and 80 years, monovision trial tolerance, and bilateral cataract grade 2 or greater according to the Lens Opacities Classification System (LOCS) III. A minimum central corneal thickness of 500 µm and minimum endothelial cell density of 2,000 cells/mm^2 on specular microscopy were necessary. Exclusion criteria included more than 1.50 diopters (D) of corneal astigmatism, corneal dystrophy, anterior segment or retinal pathologic features, glaucoma, congenital or polar cataracts, intraoperative complications with the cataract surgery, a photopic pupil size of less than 3 mm, acute or chronic systemic disease, or any immunosuppressive disorder.

Patients scheduled for bilateral cataract surgery and inlay implantation and who met the selection criteria were randomly allocated to one of three study groups (each containing 5 patients). In the first group, a three-step technique was performed: (1) an intracorneal femtosecond laser pocket was created in the non-dominant eye and the stroma was separated using a spatula; (2) 3 months later bilateral cataract surgery was performed; (3) 3 months after that, the pocket was reopened and the intracorneal inlay was inserted. In the second group, a two-step technique performed: (1) 3 days after pocket creation and inlay implantation in the non-dominant eye, bilateral cataract surgery was performed. In the third group, a two-step technique was performed: 3 months after bilateral cataract surgery, the pocket creation and the inlay insertion were performed in the non-dominant eye.

CLINICAL EVALUATION

The preoperative examination data included patient age, sex, ocular and general health history, manifest refraction, uncorrected distance visual acuity (UDVA), uncorrected near visual acuity (UNVA), corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, cataract grading (LOCS III), computerized corneal topography and central keratometry with iTrace (Tracey Technologies, Houston, TX) and GALILEI (Ziemer, Biel, Switzerland), intraocular pressure measurement (Goldmann applanation tonometry), central corneal thickness measurement (50-MHz Corneo-Gage Plus; Sonogage Inc., Cleveland, OH), and dilated fundus evaluation. Quantitative analysis of endothelial cell density was performed with Tomey EM-3000 specular microscopy (Tomey Corporation, Nagoya, Japan). Contrast sensitivity was measured using the Functional Acuity Contrast Test (Stereo Optical Co. Inc., Chicago, IL) in photopic and mesopic conditions (with and without glare), binocularly, and monocularly. The IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany) was used for biometry and SRK-T formula for IOL power calculations. Targeting refraction was emmetropia in both dominant and non-dominant eyes. A one-piece aspheric IOL (AcrySof IQ model SN60WF; Alcon Laboratories, Inc., Fort Worth, TX) with 6-mm optic diameter and 13-mm haptic diameter using an A-constant of 118.7 was implanted in all eyes.

Distance visual acuity was tested using Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR charts (Precision Vision, La Salle, IL) at 4 m distance. Near visual acuity was tested at 33 cm under a light source of 100 cd/m^2 using the modified ETDRS chart for European wide use (Precision Vision). All tests were performed monocularly and binocularly. The dominant eye was determined using a card with a central 1-inch hole test and confirmed with a 4-dot test, and a monovision trial was performed for at least 60 minutes, adding half of the add power for near in the non-dominant eye.

Contrast sensitivity was measured using the Functional Acuity Contrast Test in photopic and mesopic conditions (with and without glare), binocularly, and monocularly at spatial frequencies 1.5, 3, 6, 12, and 18 cycles per degree (cpd). Contrast sensitivity of the contralateral eye without inlay was used as the reference range. Photopic and mesopic conditions were standardized by the machine at 200 lux for the photopic conditions and at 1 lux for the mesopic conditions.

During the preoperative evaluation, a detailed discussion with each patient revealed his or her ideal near working distance or range, the amount of dependence on spectacles for near vision, and his or her overall satisfaction regarding vision throughout the day. At last follow-up, patients were asked to complete a satisfaction questionnaire for the subjective evaluation of binocular UNVA, monocular and binocular UDVA, frequency of eventual use of reading glasses, and the presence or absence of halos and/or glare. A scale of 1 to 4 was used for UNVA and UDVA evaluation, in which a score of 1 indicated "excellent," 2 indicated "good," 3 indicated "fair," and 4 indicated "poor" satisfaction. The results are presented as a mean score in each group. The presence of glare and halos and the need for reading glasses were described as "never," "sometimes," "frequently," and "always."

TABLE 1
Femtosecond Laser-Assisted Pocket Laser Parameters

Parameter	Value
Femtosecond laser	iFS 150
Treatment type	Inlay
Channel width (mm)	4.20
Channel offset (mm)	0.00
Channel depth (μm)	300
Channel spot separation (μm)	2
Channel line separation (μm)	2
Channel energy (μJ)	0.75
Side cut radius (mm)	4.50
Side cut angle (°)	30
Side cut spot separation (μm)/ side cut layer separation (μm)	3/3
Side cut energy (μJ)	1.20

Postoperative follow-up was scheduled in 1, 3, 6, and 12 months.

Refractive Corneal Inlay

The Presbia Flexivue Microlens inlay is a transparent, hydrophilic disc of 3.2 mm diameter and an edge thickness of approximately 15 μm, with high refractive index and added optical power. The central 1.6-mm diameter of the disc is near-plano and the peripheral zone has the appropriate addition power. At the center of the disc there is a 0.5-mm diameter hole. The available inlay refractive power ranges from +1.25 to +5.00 D in 0.25-D increments.

The refractive corneal inlay has a bifocal optical system that acts as a modified monovision. In distance vision, the rays passing through the central zone of the inlay and the free peripheral corneal tissue outside of the inlay will be sharply focused on the retina, whereas rays that pass through the refractive peripheral zone of the inlay will be focused in front of the retina. During near vision, rays passing through the central zone of the implant will be out of focus behind the retina and rays passing through the peripheral clear cornea will be blocked by the miosed pupil. The rays passing through the peripheral refractive zone of the inlay will be focused on the retina.

Surgical Technique

Pocket Creation and Inlay Implantation. The corneal inlay was implanted into a pocket created by a femtosecond laser in the corneal stroma in the center of the visual axis of the non-dominant eye. The surgical procedure was performed under topical anesthesia using proxymetacaine hydrochloride 0.5% eye drops (Alcon Laboratories Inc.). The intrastromal corneal pocket was created using a femtosecond laser (IntraLase iFS 150; Abbott Medical Optics, Santa Ana, CA). Using the standard pocket creation software of the IntraLase femtosecond laser, a lamellar cut of a pocket of 9-mm chord diameter and temporal pocket access tunnel 4.2-mm chord width were created at a depth of 300 μm with a line separation/spot size of 2/2 μm. The pocket access tunnel was temporal. **Table 1** shows the femtosecond laser parameters of the procedure.

The inlay was implanted with a special injector (Presbia Cooperatief U.A.) inside the tunnel at the line of sight (pupil centration). To determine the line of sight, the microscope and centration device of the excimer laser (Allegretto Wave 400; WaveLight Technologie AG, Erlangen, Germany) were used.

Postoperatively, after pocket separation and/or inlay implantation, patients were treated with topical tobramycin/dexamethasone antibiotic-steroid drops (Tobradex; Alcon Laboratories, Inc.) for 10 days along with preservative-free artificial tears.

Cataract Surgery. All surgical procedures were performed under sterile conditions and topical anesthesia by the same experienced surgeon (IGP), using a standard manual phacoemulsification technique. A superior clear corneal incision of 2.8 mm was made and an anterior curvilinear continuous capsulorhexis not larger than 5.5 mm was performed. Phacoemulsification was performed using the Infiniti Vision System (Alcon Laboratories, Inc.), with thorough cortical removing and meticulous cleaning of the posterior capsule and anterior capsular leaflets. After phacoemulsification and lens removal, the IOL (AcrySof IQ SN60WF) was implanted into the capsular bag using the standard injector device.

Postoperative topical therapy included Tobradex topical antibiotic-steroid drops four times a day for 4 weeks with a weekly tapering regimen.

Statistical Analysis

Excel 2007 (Microsoft Corporation, Redmond, WA) and a customized Ophthalmic Data Analysis Software by Georgios A. Kounis, PhD (©2014 Ophthalmic Data Analysis Software GNEMS-Greece) were used for data collection and analysis. Calculation of the surgically induced astigmatism (SIA) was performed using Kaye and Harris' method.[5] Non-parametric paired tests (Wilcoxon rank signed sum test) were used to compare preoperative and postoperative data. Comparison between groups was performed using non-parametric tests (Wilcoxon rank signed sum/Kruskal–Wallis tests.

TABLE 2
Binocular Visual Acuity Results

Parameter	Results (logMAR)	Preop vs Postop (*P*)	Between Groups (*P*)
UDVA (logMAR)	–	–	.262
Three-step group, mean ± SD (range)	0.04 ± 0.05 (0.00 to 0.10)	.125	
Two-step at 3 days group, mean ± SD (range)	0.11 ± 0.07 (0.00 to 0.20)	.125	
Two-step at 3 months group, mean ± SD (range)	0.09 ± 0.07 (0.00 to 0.20)	.125	
UNVA (logMAR)	–	–	.864
Three-step group, mean ± SD (range)	0.06 ± 0.03 (0.02 to 0.10)	.125	
Two-step at 3 days group, mean ± SD (range)	0.06 ± 0.03 (0.02 to 0.10)	.063	
Two-step at 3 months group, mean ± SD (range)	0.05 ± 0.04 (0.00 to 0.10)	.125	
CDVA (logMAR)	–	–	1.000
Three-step group, mean ± SD (range)	0.02 ± 0.04 (0.00 to 0.10)	.125	
Two-step at 3 days group, mean ± SD (range)	0.02 ± 0.04 (0.00 to 0.10)	.063	
Two-step at 3 months group, mean ± SD (range)	0.02 ± 0.04 (0.00 to 0.10)	.125	

UDVA = uncorrected distance visual acuity; SD = standard deviation; UNVA = uncorrected near visual acuity; CDVA = corrected distance visual acuity

All distributions were examined for normality with Kolmogorov–Smirnov tests. Statistical analysis was performed by SAS JMP 10.0 (http://www.jmp.com/2012). A *P* value less than .05 was considered statistically significant.

RESULTS

Patient demographics, the implanted inlay and IOL power, and preoperative clinical data of non-dominant eyes are depicted in **Table A** (available in the online version of this article). There was no statistically significant difference in any parameter between the three groups. All patients completed the 12-month follow-up.

Visual Acuity and Refraction

Table B (available in the online version of this article) shows postoperative monocular (eyes with the inlay) visual acuity and refraction at 12 months of follow-up. **Table 2** shows the postoperative binocular visual acuity at 12 months of follow-up. No statistically significant differences were found in uncorrected or corrected monocular or binocular visual acuity between the examinations during the follow-up ($P > .05$ for all values in all three groups).

Total SIA in eyes with the inlay (preoperative vs 12 months after inlay implantation) was 0.52 ± 0.42 D at 86° ± 42° in the three-step group, 0.88 ± 0.33 D at 87° ± 43° in the two-step at 3 days group, and 0.92 ± 0.41 D at 96° ± 19° in the two-step at 3 months group.

Figure 1 presents the monocular results of non-dominant eyes in the three groups. **Figure 1A** shows the percentage of eyes with the inlay in each group with a cumulative UNVA after the surgery. The monocular UNVA was 20/25 or better in all eyes with the inlay in all groups. At the 12-month follow-up, the spherical refraction was within ±0.50 D of the attempted spherical correction in 3 eyes with the inlay in the three-step group, 3 eyes in the two-step at 3 days group, and 5 eyes in the two-step at 3 months group (**Figure 1B**). All eyes were within ±1.00 D in both two-step groups. One eye in the three-step group was within ±1.50 D.

Figure 1C shows the change in Snellen lines of CDVA. All eyes with the inlay in the three groups gained lines of CDVA. **Figure 1D** shows the stability of spherical equivalent refraction over time. Apart from the minor changes (increase of 0.25 D in the three-step group and decrease of 0.50 D in the two-step at 3 days group) between the 1- and 3-month follow-up, spherical equivalent refraction remained stable over a 1-year follow-up in all groups. **Figure 1E** shows the stability of monocular UDVA and CDVA refraction over time. UDVA in both two-step groups showed a minor tendency of improvement over the 12-month follow-up, whereas after initial improvement UDVA remained stable in the three-step group. CDVA in the two-step at 3 days group showed slight improvement over the first 6 months, whereas the three-step and two-step group at 3 months group remained stable over a 1-year follow-up. **Figures 1F-1H** show the attempted versus achieved spherical equivalent refraction for the three groups.

Corneal Topography

Corneal astigmatism changed from 0.48 ± 0.33 D in the three-step group, 0.85 ± 0.66 D in the two-

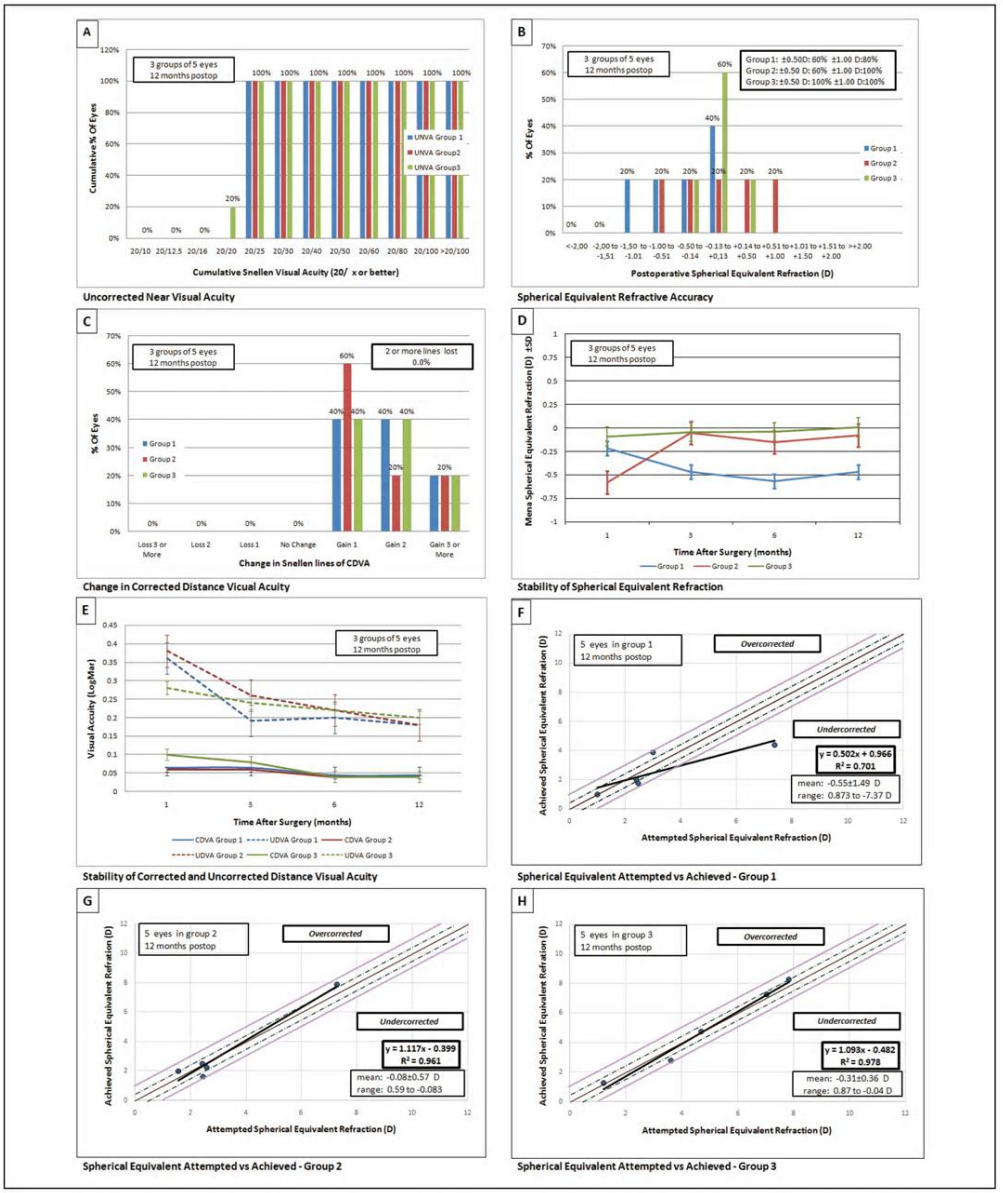

Figure 1. Visual acuity and refractive results of non-dominant eyes. CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity; UNVA = uncorrected near visual acuity; group 1 = three-step group; group 2 = two-step at 3 days group; group 3 = two=step at 3 months group

step at 3 days group, and 0.77 ± 0.28 D in the two-step at 3 months group preoperatively to 0.50 ± 0.37, 0.89 ± 0.26, and 0.73 ± 0.45 postoperatively, respectively. The change was not statistically different between groups ($P = .284$).

COMPLICATIONS

During the 12-month follow-up, no intraoperative or postoperative complications occurred. No inlay was explanted or recentered during the reported follow-up. No epithelial ingrowth was observed.

Mean central corneal thickness in the eyes with the inlay did not change significantly at 12 months in any of the groups ($P = .063$, .125, and .063, respectively). Postoperative intraocular pressure was similar to preoperative values and between groups postoperatively in all groups ($P > .05$).

The mean endothelial cell loss 1 year after the cataract surgery was similar between the three-step, two-step at 3 days, and two-step at 3 months groups at 8.92%, 8.05%, and 8.39%, respectively ($P = .42$).

On the retroillumination examination 12 months after surgery, there was no significant posterior capsule opacification influencing the visual or refractive outcome visible.

CONTRAST SENSITIVITY

There was no difference between groups in preoperative contrast sensitivity under photopic and mesopic conditions. At the 12-month follow-up, the monocular and binocular contrast sensitivity scores at all spatial frequencies tested under mesopic and photopic conditions were similar between the three groups ($P > .05$).

Monocular contrast sensitivity in eyes with the inlay at frequencies of 12 and 18 cpd was lower in all groups under both mesopic and photopic conditions compared to contrast sensitivity of contralateral eyes (**Figure A**, available in the online version of this article).

Figure B (available in the online version of this article) shows binocular contrast sensitivity at the 12-month follow-up under photopic and mesopic conditions in each group. Under mesopic conditions (with and without glare), the two-step at 3 months group had a slightly lower score than the other two groups at frequencies of 12 and 18 cpd, but without statistical significance (mesopic without glare: $P = .963$ at 12 cpd; $P = 1.000$ at 18 cpd; mesopic with glare: $P = 1.000$, $P = .855$, respectively).

PATIENT SATISFACTION QUESTIONNAIRE

During the preoperative evaluation, patients answered questions about their profession, everyday needs, frequency of using a computer, and preferable working distance. These questions assisted the surgeon in deciding on the ideal inlay power for each patient. A general complaint about their inability to function without spectacles for near vision, annoyance for constantly having to put them on and off, and satisfactory UDVA were noted.

At last follow-up, all patients except one in the two-step at 3 days group perceived their binocular UDVA as excellent (mean score was 1.00 in the three-step group, 1.20 in the two-step at 3 days group, and 1.00 in the two-step at 3 months group). Twelve months after inlay implantation, monocular UDVA in eyes with the inlay was perceived as good, with the best mean score in the two-step at 3 months group (1.80 in the three-step group, 2.00 in the two-step at 3 days group, and 1.40 in the two-step at 3 months group). No patient used spectacles for distance vision.

During the last follow-up, all but one patient perceived their binocular UNVA as excellent (mean score was 1.00 in the three-step group, 1.20 in the two-step at 3 days group, and 1.00 in the two-step at 3 months group). One of 15 patients reported use of near vision spectacles occasionally, only in the evening for reading books.

One year after inlay implantation, two patients in the two-step at 3 days group and one patient in the three-step group sometimes experienced glare and halos. The overall satisfaction score was 8.2 in the three-step group, 9.2 in the two-step at 3 days group, and 7.8 in the two-step at 3 months group.

DISCUSSION

To our knowledge, this is the first study to describe and compare three techniques of cataract surgery and refractive corneal inlay combination as a new method for near vision improvement after cataract surgery. In the current study, mean monocular UDVA 1 year after the inlay implantation was 20/32 (0.18 logMAR) in the three-step group, 20/32 (0.16 logMAR) in the two-step at 3 days group, and 20/25 (0.12 logMAR) in the two-step at 3 months group. Mean monocular UNVA improved in all groups from 20/125 preoperatively, albeit in the presence of a cataract, to 20/25 or better with pseudophakia and the inlay. The two-step technique in the two-step at 3 months group appeared to have slightly better results (0.08, 0.10, and 0.06 logMAR, respectively). Refractive results were slightly better in the two-step at 3 months group, with postoperative spherical equivalent refraction within ±0.50 D of the attempted correction in non-dominant eyes.

Cochener et al. compared the clinical outcome of different multifocal IOLs based on information reported in the international literature.[6] Our UNVA was bet-

ter than average UNVA with monofocal (0.47 logMAR) or multifocal (0.15 logMAR) IOLs. Furthermore, our UNVA was better than average UNVA in the refractive IOL group (0.232 logMAR), but similar to the diffractive IOL group (0.091 logMAR) and more specifically to ReSTOR IOL (0.08 logMAR).

In our study, binocular UDVA was slightly better with the three-step procedure (20/20; 0.04 logMAR) than in the other two groups (20/25; 0.11 logMAR and 20/25; 0.09 logMAR, respectively), but this variation may be due to the small numbers of eyes. However, binocular UNVA outcomes were similar between groups at 20/25 (0.06 logMAR), 20/25 (0.06 logMAR), and 20/25 (0.05 logMAR), respectively.

Mean total SIA was the lowest in the three-step group (0.52 D with 40° change of axis). In the other two groups, the SIA was higher and with higher change in axis (0.88 D at 87° and 0.92 D at 96°, respectively). However, the total SIA in all of our groups was lower than the SIA after sutureless phacoemulsification with superior corneal incision (1.44 ± 0.33 D) reported by Simsek et al.[7] The effect that an individual adjustment of the femtosecond laser-created corneal pocket axis and the clear corneal incision location may have on the SIA should be investigated in future studies.

We found no difference in monocular or binocular CDVA achieved in the three groups. During the 1-year follow-up, none of the operated eyes had loss of line of CDVA.

Recently, two studies have reported results of intracorneal inlay implantation for near vision improvement in pseudophakic patients, although the follow-up period was only 3 months in both studies. In a prospective non-randomized multicenter study, Chu et al. assessed the feasibility of implanting a hydrogel corneal inlay (Raindrop ReVision Optics) in 13 patients who previously underwent cataract surgery with monofocal IOL implantation.[8] At 3 months, 83% of patients had 20/20 or better UNVA. Measurement of the uncorrected binocular vision showed that 83% of the pseudophakic group achieved 20/20 or better at distance and near. Eight percent of the patients with pseudophakia reported ocular dryness and none reported either glare or halos postoperatively.

Another study evaluated the improvement in near visual acuity after KAMRA corneal inlay implantation in 13 patients with pseudophakia.[9] Mean UNVA improved five lines (from J10 to J4) postoperatively. Mean UDVA, CDVA, and CNVA remained stable and were 20/20, 20/16, and J1, respectively, before and after KAMRA inlay implantation. Four patients underwent LASIK for improved distance acuity at the time of inlay implantation. Three eyes lost two lines and 1 eye lost one line of UDVA. Two eyes lost two lines and 1 eye lost one line of CDVA.

In the current study, mean central corneal thickness was not statistically significantly different after implantation of the inlay to preoperative mean central thickness in any of the groups. This fact could be related to the thinness of the inlay (15 µm), which is even thinner than the standard deviation of the measurements. The loss of endothelial cells and intraocular pressure were similar in all groups and consistent with cataract surgery using phacoemulsification.[10] During the 1-year follow-up, no complications were observed in any of the operated eyes. These results suggest that intracorneal inlay implantation in combination with cataract surgery did not lead to any complications within the first 12 postoperative months.

Our results showed lower monocular contrast sensitivity at spatial frequencies of 12 and 18 cpd in all groups, under mesopic and photopic conditions, compared to reference values of contralateral eyes. A possible explanation for this outcome may be an increase or change in the dynamics of corneal and internal higher order aberrations.[11] However, we did not perform wavefront analysis in the current study. Furthermore, the effect of age on contrast sensitivity becomes evident in patients aged 60 years or older as a result of reduced retinal sensitivity and neural capacity in visual processing.

Intracorneal inlays and IOLs are known to cause photic phenomena, such as glare and halos.[1,12,13] One year after surgery, 4 of our 15 patients sometimes experienced glare and/or halos, but they were not bothered by these.

The objective visual acuity test results were in accordance with the subjective patient questionnaire results, indicating that patients had significantly fewer problems performing near distance tasks without correction than before surgery. The patient satisfaction rate was high; 5 of 5 of patients in the three-step group and two-step at 3 months group perceived both binocular UDVA and binocular UNVA as excellent, whereas 4 of 5 patients in the two-step at 3 days group perceived it as excellent. Overall satisfaction was slightly higher in patients who had the inlay implanted 3 months after cataract surgery.

Although our pilot study has critical limitations, we believe it provides useful information and indications for future studies. Our statistical analysis did not show statistical significance ($P < .05$), even when there was clearly significant clinical improvement. A possible reason for this is the small sample size in our study. A larger number of patients with a longer observation period is needed to evaluate the stability and safety

of these new methods in the combined cataract inlay surgery for presbyopia correction.

The three techniques of combined refractive corneal inlay cataract surgery for presbyopia correction provided excellent binocular distance and near visual outcomes. The overall patient satisfaction rate and postoperative spectacle independence was high. Differences in outcomes between the three groups were minimal. Therefore, it would seem that the most logical of the techniques is to perform cataract surgery first and then to reassess ocular dominance without a cataract being present. The dominant eye has to have good unaided distance vision and then inlay implantation can be considered.

AUTHOR CONTRIBUTIONS

Study concept and design (NRS, VF, IGP); data collection (NRS); analysis and interpretation of data (NRS); writing the manuscript (NRS); critical revision of the manuscript (VF, IGP); administrative, technical, or material support (VF); supervision (IGP)

REFERENCES

1. Barraquer JI. Modification of refraction by means of intracorneal inclusions. *Int Ophthalmol Clin*. 1966;6:53-78.
2. Arlt EM, Krall EM, Moussa S, Grabner G, Dexl AK. Implantable inlay devices for presbyopia: the evidence to date. *Clin Ophthalmol*. 2015;9:129-137.
3. Limnopoulou AN, Bouzoukis DI, Kymionis GD et al. Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. *J Refract Surg*. 2013;29:12-18.
4. Bouzoukis DI, Kymionis GD, Panagopoulou SI, et al. Visual outcomes and safety of a small diameter intrastromal refractive inlay for the corneal compensation of presbyopia. *J Refract Surg*. 2012;28:168-173.
5. Kaye SB, Harris WF. Analyzing refractive data. *J Cataract Refract Surg*. 2002;28:2109-2116.
6. Cochener B, Lafuma A, Khoshnood B, Courouve L, Berdeaux G. Comparison of outcomes with multifocal intraocular lenses: a meta-analysis. *Clin Ophthalmol*. 2011;5:45-56.
7. Simsek S, Yasar T, Demirok A, Cinal A, Yilmaz OF. Effect of superior and temporal clear corneal incisions on astigmatism after sutureless phacoemulsification. *J Cataract Refract Surg*. 1998;24:515-518.
8. Chu RY, Hovanesian JA, Whitman J, Tran DB, Parkhurst GD. Nonrefractive corneal inlay implantation after cataract surgery: U.S. Clinical Study Experience. Presented at the American Society of Cataract and Refractive Surgery Meeting; April 17-21, 2015; San Diego, CA.
9. Huseynova T, Kanamori T, Waring GO 4th, Tomita M. Outcomes of small aperture corneal inlay implantation in patients with pseudophakia. *J Refract Surg*. 2014;30:110-116.
10. Díaz-Valle D, Benítez del Castillo Sánchez JM, Castillo A, Sayagués O, Moriche M. Endothelial damage with cataract surgery techniques. *J Cataract Refract Surg*. 1998;24:951-955.
11. Oshika T, Okamoto C, Samejima T, Tokunaga T, Miyata K. Contrast sensitivity function and ocular higher-order wavefront aberrations in normal human eyes. *Ophthalmology*. 2006;113:1807-1812.
12. Häring G, Dick HB, Krummenauer F, Weissmantel U, Kröncke W. Subjective photic phenomena with refractive multifocal and monofocal intraocular lenses. results of a multicenter questionnaire. *J Cataract Refract Surg*. 2001;27:245-249.
13. Alió JL, Abbouda A, Huseynli S, Knorz MC, Homs ME, Durrie DS. Removability of a small aperture intracorneal inlay for presbyopia correction. *J Refract Surg*. 2013;29:550-556.

TABLE A

Patient Demographics and Clinical Information

Parameter	Three-Step Group	Two-Step at 3 Days Group	Two-Step at 3 Months Group	*P*
No. of patients	5	5	5	–
Males/females	3/2	1/4	1/4	–
Right/left eye	3/2	1/4	2/3	–
Age (y), mean ± SD (range)	63.00 ± 2.00 (60 to 65)	65.40 ± 4.28 (58 to 68)	64.40 ± 4.39 (61 to 71)	.607
Axial length (mm), mean ± SD (range)	23.54 ± 0.96 (22.41 to 24.83)	23.39 ± 0.41 (23.04 to 23.86)	24.06 ± 1.46 (22.93 to 26.54)	.585
Inlay power (D), mean ± SD (range)	2.65 ± 0.34 (2.50 to 3.25)	2.30 ± 0.21 (2.00 to 2.50)	2.25 ± 0.59 (1.50 to 2.75)	.393
UDVA (logMAR), mean ± SD (range)	0.88 ± 0.30 (0.40 to 1.20)	0.76 ± 0.29 (0.50 to 1.20)	0.82 ± 0.25 (0.50 to 1.00)	.069
UNVA (logMAR), mean ± SD (range)	0.87 ± 0.37 (0.26 to 1.18)	0.86 ± 0.40 (0.30 to 1.20)	0.88 ± 0.33 (0.50 to 1.20)	.948
CDVA (logMAR), mean ± SD (range)	0.28 ± 0.21 (0.10 to 0.70)	0.30 ± 0.07 (0.20 to 0.40)	0.40 ± 0.16 (0.20 to 0.60)	.509
Sphere (D), mean ± SD (range)	0.40 ± 3.45 (-5.00 to 3.50)	-0.80 ± 4.25 (-7.25 to 2.75)	-2.85 ± 5.14 (-7.75 to 4.00)	.546
Cylinder (D), mean ± SD (range)	-0.35 ± 0.34 (-0.75 to 0.00)	-0.60 ± 0.42 (-1.00 to 0.00)	-0.90 ± 0.42 (-0.50 to -1.50)	.156
SEQ refraction (D), mean ± SD (range)	0.23 ± 3.51 (-5.38 to 3.25)	-1.10 ± 4.36 (-7.75 to 2.75)	-3.30 ± 5.20 (-8.50 to 3.50)	.527
Corneal thickness (μm), mean ± SD (range)	545 ± 29.80 (507 to 574)	530 ± 32.84 (503 to 578)	556 ± 30.71 (514 to 589)	.363
Corneal topographic astigmatism (D), mean ± SD (range)	0.48 ± 0.33 (0.14 to 0.87)	0.85 ± 0.66 (0.22 to 1.55)	0.77 ± 0.28 (0.46 to 1.10)	.532
Endothelial cell density (cells/mm^2), mean ± SD (range)	2,454 ± 244 (2,123 to 2,760)	2,418 ± 486 (2,027 to 3,001)	2,544 ± 307 (2,198 to 2,935)	.778
IOL power (D), mean ± SD (range)	21.20 ± 2.06 (16.50 to 22.50)	22.00 ± 0.79 (21.00 to 23.00)	21.70 ± 2.46 (21.00 to 24.00)	.716

SD = standard deviation; D = diopters; UDVA = uncorrected distance visual acuity; UNVA = uncorrected near visual acuity; CDVA = corrected distance visual acuity; SEQ = spherical equivalent; IOL = intraocular lens

TABLE B

Monocular Visual Acuity and Refractive Results of Non-dominant Eyes

Parameter	Results	Preop vs Postop (*P*)	Between Groups (*P*)
UDVA (logMAR)	–	–	.377
Three-step group, mean ± SD (range)	0.18 ± 0.04 (0.10 to 0.20)	.125	
Two-step at 3 days group, mean ± SD (range)	0.16 ± 0.05 (0.10 to 0.20)	.063	
Two-step at 3 months group, mean ± SD (range)	0.12 ± 0.08 (0.00 to 0.20)	.125	
UNVA (logMAR)	–	–	.498
Three-step group, mean ± SD (range)	0.08 ± 0.02 (0.06 to 0.10)	.125	
Two-step at 3 days group, mean ± SD (range)	0.10 ± 0.02 (0.08 to 0.12)	.063	
Two-step at 3 months group, mean ± SD (range)	0.06 ± 0.04 (0.00 to 0.10)	.125	
CDVA (logMAR)	–	–	1.000
Three-step group, mean ± SD (range)	0.04 ± 0.05 (0.00 to 0.10)	.125	
Two-step at 3 days group, mean ± SD (range)	0.04 ± 0.05 (0.00 to 0.10)	.063	
Two-step at 3 months group, mean ± SD (range)	0.04 ± 0.05 (0.00 to 0.10)	1.125	
Sphere (D)	–	–	.523
Three-step group, mean ± SD (range)	0.00 ± 0.50 (-0.75 to 0.50)	.125	
Two-step at 3 days group, mean ± SD (range)	-0.25 ± 0.61 (-1.00 to 0.50)	.063	
Two-step at 3 months group, mean ± SD (range)	0.15 ± 0.42 (-0.25 to 0.75)	.125	
Cylinder (D)	–	–	.763
Three-step group, mean ± SD (range)	-0.45 ± 0.27 (-0.75 to 0.00)	.250	
Two-step at 3 days group, mean ± SD (range)	-0.60 ± 0.38 (-1.25 to -0.25)	.500	
Two-step at 3 months group, mean ± SD (range)	0.40 ± 0.42 (-1.00 to 0.00)	.125	
SEQ refraction (D)	–	–	.601
Three-step group, mean ± SD (range)	-0.23 ± 0.56 (-1.00 to 0.25)	.125	
Two-step at 3 days group, mean ± SD (range)	-0.43 ± 0.46 (-1.13 to 0.00)	.810	
Two-step at 3 months group, mean ± SD (range)	-0.05 ± 0.48 (-0.50 to 0.75)	.310	

UDVA = uncorrected distance visual acuity; SD = standard deviation; UNVA = uncorrected near visual acuity; CDVA = corrected distance visual acuity; D = diopters; SEQ = spherical equivalent

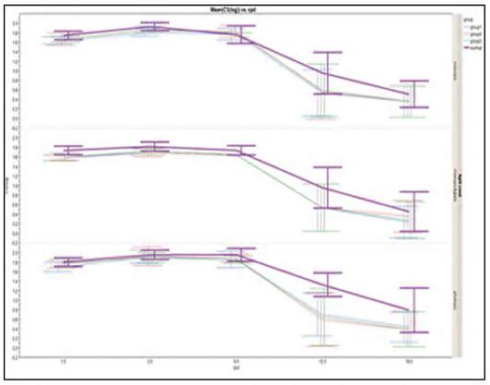

Figure A. Monocular contrast sensitivity under photopic and mesopic (with and without glare) conditions. Cslog = contrast sensitivity in $\log_{10}$; cpd = frequency in cycles per degree; group 1 = three-step group; group 2 = two-step at 3 days group; group 3 = two=step at 3 months group

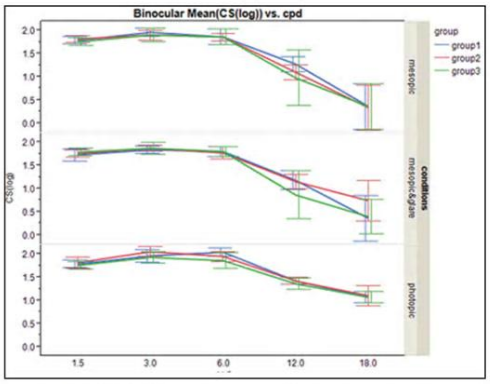

Figure B. Binocular contrast sensitivity under photopic and mesopic conditions. Cslog = contrast sensitivity in $\log_{10}$; cpd = frequency in cycles per degree; group 1 = three-step group; group 2 = two-step at 3 days group; group 3 = two=step at 3 months group