# EVALUATION OF VISUAL PERFORMANCE AND VISION QUESTIONNAIRES IN INTRAOCULAR LENS IMPLANTATION AND LASER REFRACTIVE SURGERY

**Emmanuel Eric Pazo MSc MD**
**Faculty of Life and Health Sciences**
**Ulster University**

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**I confirm that the word count of this thesis is less than 100,000 words.**

## Table of Contents

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**ABSTRACT**

The anterior refractive segment comprises the tear film (TF), cornea and lens. This composite of structures primarily contributes to the refractive power and the quality of vision (QOV). Postoperative small incision lenticule extraction had significantly better and expedient corneal surface physiology recovery than femtosecond laser-assisted laser in situ keratomileusis patients; thereby enhancing their QOV scores. Postoperative tear lipid measurements correlated with postoperative glare and fluctuating vision. Further research is needed to explore other preoperative TF parameters.

Functional vision is a binocular function; however, clinical assessment of vision is routinely monocular. This dichotomy to some degree confounds the subjective questionnaire assessments. Pupil size (PS) has a direct influence upon light and aberration entering the eye. Moreover, diffraction of light can be induced iatrogenically by refractive surgeries, intra- and extraocular implants and ageing. The major factor found to impact the QOV in an asymmetric multifocal intraocular lens (IOL) was preoperative PS and visual axis eccentricity (angle kappa). Since PS generally decreases with age, a larger preoperative pupil ensures that postoperatively there is adequate exposure of the IOL.

Corneal cross-linking (CXL) is a well-accepted treatment for keratoconus. Transepithelial phototherapeutic keratectomy (trans-PTK) can remove the epithelium and smoothen the anterior cornea. Nine-month follow-up of trans-PTK and CXL procedures showed benefits of improved visual acuity and stabilisation of KC at nine-months follow-up.

Since the 1980's vision-related quality of life (VR-QOL) questionnaires have been explored to capture and measure this concept. The results demonstrate that VR-QOL questionnaire performs better than VF-14 questionnaire with less variability in the mean range scores. This suggests that the customisable items of VR-QOL questionnaire is better at assessing the individuals VR-QOL.

This body of work demonstrates the impact of these pathologies and anatomical variations upon VA, QOV and VR-QOL. These findings should help guide clinicians preoperatively stratify and postoperatively manage patients.

**Abbreviations**:

AL: Axial length

CXL: Corneal collagen crosslinking

CDVA: Corrected distance visual acuity

CIVA: Corrected intermediate visual acuity

CNVA: Corrected near visual acuity

DE: Dry eye

ELP: Effective lens position

ETDRS: Early Treatment of Diabetic Retinopathy Study Chart

Fs-LASIK: Femtosecond laser-assisted laser in situ keratomileusis

IOL: Intraocular lens

KC: Keratoconus

MGD: Meibomian gland dysfunction

QOV: Quality of vision

QOL: Quality of life

SMILE: Small incision lenticule extraction

UDVA: Unaided distance visual acuity

OCT: Optical coherence tomography

TBUT: Tear break up time

TF: Tear Film

Trans-PTK: Trans-epithelial phototherapeutic keratectomy

UCVA: Uncorrected distance visual acuity

UNVA: Unaided near visual acuity

UIVA: Unaided intermediate visual acuity

VA: Visual acuity

OSDI: Ocular Surface Disease Index

IDEEL: The Impact of Dry Eye on Everyday Life questionnaire

SRI: Surface regularity index

SAI: Surface asymmetry index

LASEK: Laser subepithelial keratectomy

LIPCOF: Lid parallel conjunctival folds

PCO: Posterior capsule opacification

D: Dioptres

CTR: Capsular tension ring

NIBUT: Non-invasive tear break-up time

CXL: Corneal collagen cross-linking

PMD: Pellucid marginal degeneration

KC: Keratoconus

UV-A: Ultraviolet-A

PRK: Photorefractive keratectomy

ISV: Index of Surface Variance

IVA: Index of vertical asymmetry

KI: Keratoconus Index

CKI: Central keratoconus index

IHA: Index of height asymmetry

IHD: Index of height decentration

Rmin: Minimum radius of Curvature

BCVA: Best-corrected distance visual acuity

VR-QOL: vision-related quality of life

VF-14: Visual function-14 questionnaire

## CHAPTER 1: INTRODUCTION

Refractive surgery traditionally has been designed with the aim to enable patients to see clearly in both the distance and near. In pre-presbyopic patients, that is achieved by trying to correct any distance refractive error. If this is successfully achieved, the natural focusing mechanisms within the eye enable intermediate and distance vision (Miranda and Krueger, 2004). However, presbyopic patients, poses more significant problems as correction of distance vision in both eyes does not naturally enable near or intermediate vision; especially when the focusing mechanisms have been compromised through the ageing process (Salvi, 2006). Currently there is no interventional system that can perfectly simulate and substitute the natural focusing mechanism within the eye. However, various imperfect solutions that use either laser or lens-based techniques have been developed to overcome this intrinsic problem (Alió *et al.*, 2009; Reinstein, Archer and Gobbe, 2011; Alió and Pikkel, 2014; McNeely *et al.*, 2017). Traditional surgical approaches used by ophthalmologists for the treatment of presbyopia (both laser and lens-based) has been through the use of monovision techniques (Miranda and Krueger, 2004; Finkelman, Ng and Barrett, 2009). This consists of making one eye clear for distance and the fellow eye for near vision. In the early '90s, multifocal IOLs were developed which enabled the simultaneous viewing of both distance and near vision through the use of one IOL. These multifocal IOLs used more than one focal point within the IOL (Duffey, Zabel and Lindstrom, 1990; Kohnen, 2008).

Meanwhile, laser refractive surgery was developed at a similar period and the first human eye treated in 1989 by Marguerite B. MacDonald MD (McDonald *et al.*, 1989). This advancement enabled surgeons to treat ametropia by changing the shape of the cornea. It was achieved by either flattening or steepening the cornea to treat myopia or hyperopia respectively. The early stages of laser development produced remarkable success in correcting myopia through flattening of the central cornea. Myopic laser treatments were initially planned through the use of the Munnerlyn formula to define the amount of corneal flattening required (Chang *et al.*, 2003). This represented a very successful commencement to laser refractive surgery. However, it was noted that some patients suffered from significant dysphotopic symptoms of glare and haloes postoperatively (O'Brart *et al.*, 1994; Pop and Payette, 2004). The lesson

learnt from this problem was that the peripheral corneal shape also needed to be modified along with the flattening of central cornea. This understanding prevented the induction of large amounts of spherical aberrations which occurred due to a change in corneal shape (from a prolate to an oblate shape) (Chang *et al.*, 2003). The advancements in assessment tools *in vivo* corneal and whole eye allowed the measurement of aberrations induced by laser surgery. This allowed iterative modification of laser profiles to enhance the corneal shape and measure improvements achieved using berrometers (Oshika *et al.*, 1999). These aberrometers and topographers allowed clinicians and researchers to study topographic alterations and induction of higher-order aberrations in keratoconic eyes. These tools have demonstrated that corneal cross-linking (CXL) treatment not only stops the progression of disease but also improves visual acuity (VA), spherical equivalent (SE), astigmatism and keratometric parameters of the diseased cornea. These findings have prompted researchers to investigate outcomes by combining CXL with other refractive procedures in- order to improve visual and topographic outcomes. These findings have prompted researchers to investigate outcomes by combining CXL with other refractive procedures in order to improve visual and topographic outcomes.

In addition to the development of these further objective measurements of optical quality within the cornea and eye, the importance of assessing patients' subjective perception of their vision through the use of questionnaires was also recognised by clinicians and researchers. Various questionnaires have since been developed and validated in an attempt to objectively document the subjective quality of vision (QOV) (Wolffsohn and Cochrane, 2000; McAlinden, Pesudovs and Moore, 2010). Psychometric methods were also used to document these subjective aspects of vision. This was done so that questionnaires could be deemed valid, reproducible and objective as possible in recording subjective symptoms. The importance of subjective symptom documentation gained importance while trying to document subjective issues regarding multifocal IOLs. Additionally, various researchers and clinicians have come to the conclusion that VA alone cannot capture the entire aspects of vision function (Massof and Rubin, 2001; Stelmack, 2001).

As surgical techniques have advanced, so have patients' expectations. This has prompted constant research in an attempt to enhance patients visual and quality of

life (QOL) outcomes. This thesis attempts to investigate the impact of various anterior segment and ocular surface factors upon the quality of outcomes.

The median age of the UK population according to statistical data has increased steadily from 38.7 years in 2005 to 40.0 years in 2015. Increased prevalence of presbyopia among the population is due to the increase in the middle-age population. As the middle-aged and elderly population continues to increase in UK and Europe, it is estimated that visual impairment and cataract will increasingly become the leading causes of disability (Holden *et al.*, 2015). Therefore, this will potentially have a negative impact on QOL and productivity in these patients (Desai *et al.*, 1996; Alan L. Robin,Thulasiraj Ravilla, Rengaraj Venkatesh, 2016). Dry eye (DE) is one of the most common ocular complaints among patients visiting eye clinics (Hyman *et al.*, 2009) and the prevalence of DE increases with age (Schaumberg, 2009).

Laser refractive surgery has now become one of the most common elective ophthalmic surgical procedures. This is due its excellent postoperative uncorrected VA, and minimal and accelerated corneal wound healing. This is a result of improved technique, laser technology and ablation nomograms (Denoyer, 2015). Change in lifestyle of patients has also prompted current multifocal IOL design to accommodate extended spectacle-free use of computers and mobile devices. As there is a growing trend of patients who desire to be spectacle-free following cataract surgery, these also include patients who previously had laser refractive surgery for myopia (Khor and Afshari, 2013; Chang *et al.*, 2017). The ever-increasing number of post-refractive surgery patients and contact lens wearers who consequently develop DE is an issue that needs to be addressed imperatively by clinicians.

A better understanding of pre-- and postoperative factors and their influence upon the postoperative QOV and VR-QOL can help guide treatments as per individual needs. The purpose of this body of work is to build upon the knowledge of screening, monitoring and management of these ophthalmic anomalies and their effects upon QOV and VR-QOL.

This introductory chapter presents details of the ophthalmic anomalies and a review of the current literature.

## 1.1 The tear film

The tear film (TF) envelops the anterior surface of the eye. The TF represents a dynamic conglomerate of lipids, proteins, and mucins in an aqueous saline solution suspended over the hydrophobic surface of the epithelium (Foulks, 2007). The TF has been classically described as a three-layer system, each with a specific composition and function (Rolando and Zierhut, 2001). Apart from providing a moist physical shield to the corneal epithelium, the TF also has a surface power of 43.08 diopters (D) which contributes to the retinal image quality and visual function (Montés-Micó, 2007). There are various methodologies for measuring the TF thickness. Optical coherence tomography (OCT) is one such tool that is a non-invasive, *in vivo* imaging modality that generates images of biological tissues with high axial and transverse resolutions. Non-invasive measurement of tear film thickness has yielded values of approximately 3.4 ± 2.6 μm. These measurements have been found to be reliable with an intra-class correlation coefficient of 0.97. (Prydal *et al.*, 1992; Kaya *et al.*, 2015).

The TF is found to vary in volume, composition and stability in various ocular surface pathologies. Of these, tear film evaporation leading to DE is the most researched and published topic (Nichols *et al.*, 2011). In a healthy ocular surface, meibomian glands secrete the outer lipid layer which acts to prevent rapid evaporation of the aqueous and mucin layer (McCulley and Shine, 1997). The blinking action of the eyelids reassembles the tri-layered structure of the TF, which is immediately exposed to the environment and subject to evaporation and disorganisation. This process of tear film layer disorganisation, termed as tear break up time (TBUT). Lower TBUT is indicative of underlying ocular pathology such as meibomian gland dysfunction (MGD) or another systemic physiological irregularity. It has been documented that alterations to the TF brought about by DE unveils underlying corneal irregularities leading to poor QOV due to glare and decrease in contrast sensitivity (Huang *et al.*, 2002; Miljanović *et al.*, 2007).

## 1.2 Definition of dry eye

The Dry Eye Workshop (DEWS) defines DE as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and TF instability, with potential damage to the ocular surface. It is accompanied by increased tear osmolarity and inflammation of the ocular surface' (Lemp, Baudouin and Baum, 2007a). Evidence by research conducted on tissue culture, animal models and DE patients demonstrates that hyperosmolarity is the core mechanism and plays a major role in the pathogenesis of DE. This initiates a vicious cascade of inflammatory processes that leads to mucin deficiency, dryness of the corneal surface and damage to the overlying corneal epithelium (Lemp, Baudouin and Baum, 2007a). DE can be categorised into either aqueous deficient or evaporative type. Additionally, these two conditions are not mutually exclusive and can occur concurrently as mixed type. It is reported that MGD-dependent evaporative DE is the most common form of DE overall (Pult, Riede-Pult and Nichols, 2012) This is primarily due to decreased or obstructed secretion of meibum to the lid margin or negative alterations to the composition of meibum which leads to inflammation (Millar and Schuett, 2015).

## 1.3 Risk factors for dry eye

Cohort studies such as the Beaver Dam Eye Study have explored the relationship between various risk factors for DE. They have revealed that demographics and clinical factors such as age, gender, and androgen levels have been found to predispose towards the development and progression of DE (Moss and Klein, 2000; Paulsen *et al.*, 2014). Additionally, lifestyle and environmental factors such as computer use and seasonal allergies are also associated with abnormal tear function and DE symptoms (Tsubota and Nakamori, 1993; Nakamura *et al.*, 2010; Paulsen *et al.*, 2014). Surveys have also reported that more than 50% of contact lens wearers experience ocular dryness and decreased corneal sensitivity (Pritchard, Fonn and Brazeau, 1999; Stahl *et al.*, 2009). Various systemic diseases can also have manifestations of DE symptoms, particularly those of autoimmune or immune-mediated nature. Several studies have examined transient and chronic DE after laser

refractive surgery as DE has been documented to be frequently observed in patients immediately after surgery (De Paiva *et al.*, 2006; Denoyer, Landman, Trinh, J.-F. Faure, *et al.*, 2015). The incidence of DE in the nasal and superior hinge group in LASIK procedure was found to be different, 47.06% and 52.94% respectively at week 1, with consequent improvement over the following weeks and months (Savini, Barboni and Zanini, 2006). In comparison, the incidence of DE after cataract surgery is documented to be significantly less, in the region of 10% (Kasetsuwan *et al.*, 2013) This is due to the fact that corneal nerve damage is much more severe with laser ablation in comparison to that produced by a corneal incision in cataract surgery.

### 1.4 Clinical evaluation of dry eye

Currently there are a wide array of tests that have been developed to screen, test and diagnose the onset and progression of DE (Bron *et al.*, 2014; McGinnigle, Eperjesi and Naroo, 2014). However, due to the lack of a gold standard diagnostic test, complex aetiology and pathophysiology diagnosis of DE is difficult (Benjamin D Sullivan *et al.*, 2014). Clinical tests for DE include Schirmer test, TBUT, fluorescein staining of the cornea and conjunctiva, meibomian gland assessment, interferometry examination of the TF and meibomian gland assessment (Bron *et al.*, 2014). These DE tests to a large extent can diagnose moderate to severe forms of DE. However, mild forms of DE, usually remain an undiagnosed disorder (Agarwal *et al.*, 2016).

#### 1.4.1 Subjective assessment of dry eye

Invariably the examination and assessment of DE starts with history talking and symptoms of the patient by the clinician. The most frequent symptom among DE patient includes the sensation of burning ocular discomfort and dryness (Begley, Chalmers and Abetz, 2003; Williamson *et al.*, 2014). Although, symptom assessment in DE patients has been considered one of the components of DE assessment, literature reports that symptom questionnaires and ocular signs in DE don't typically correlate with each other (Johnson, 2009; Benjamin D. Sullivan *et al.*, 2014; Bartlett,

Keith and Sudharshan, 2015). The poor association between signs and symptoms could also be explained by the fact that symptom measures may assess properties of the disease (e.g. grittiness or fatigue) but may not be related to measurable signs. Several researchers also have suggested that sensory changes on the ocular surface may be an important factor. One theory postulates that in early/mild DE, corneal hyperalgesia may cause ocular discomfort before any clinical signs are evident and tear osmolarity is potentially the best approach as they both demonstrated close agreement (Schiffman, 2000; Suzuki *et al.*, 2010). However, other studies have shown increasing variability in DE subjects (Sullivan *et al*., 2014). Ocular dryness followed by discomfort and tired eyes are the most reported symptom in DE patients (Begley, Chalmers and Abetz, 2003). Validated DE questionnaires are still the most effective screening tool to assess individuals in research or clinic settings (Oden *et al.*, 1998). DE symptomology and QOL questionnaires consists of a series of questions that have numeric values attributed to their corresponding answers, thereby allowing the symptoms to be scored and the severity numerically quantified and compared. The most widely used DE questionnaires are Ocular Surface Disease Index (OSDI), the Impact of Dry Eye on Everyday Life questionnaire (IDEEL) and McMonnies Dry Eye Index (Grubbs *et al.*, 2014; Bartlett, Keith and Sudharshan, 2015). Other researches such as Chalmers have tried to streamline the subjective assessment by asking only five questions to distinguish between patients with and without DE (Nichols, Nichols and Mitchell, 2004; Chalmers, Begley and Caffery, 2010).

### 1.4.2 Objective evaluation of dry eye

A consensus among DE researchers has ranked the following diagnostics tests as follows, per their use: TBUT (93%), corneal staining (85%), TF assessment (76%), conjunctival staining (74%), and the Schirmer test (54%) (Lin and Yiu, 2014). These are widely administered diagnostic tests for initial assessment of DE (Serin *et al.*, 2007). An ideal diagnostic method should preferably be non-invasive in assessment, objective, specific, reproducible, cost effective and non-time consuming. Currently none of the DE diagnostic tools meet these standards. Aside from the standard clinical tests, recently accepted clinical tests such as tear hyperosmolarity and TF interferometry will also be reviewed.

## Tear breakup time

Measuring the TF stability can provide valuable information about the DE condition of the patient (Sweeney, Millar and Raju, 2013). There are a variety of methodologies that ascertain different aspects of the TF and provide insights into the stability of the TF. TBUT was first introduced by Norn in 1969 and to date is the most frequently used diagnostic test used to assess TF stability (Norm, 1969). TBUT can be observed with and without instilling fluorescein dye. Cho, *et al.*, found that the instillation of fluorescein did not cause any significant change in the non-invasive TBUT in a Hong Kong, Chinese sample population (Cho *et al.*, 2004). Conversely, Mengher *et al.*, using non-invasive methodology (using grid lines projected onto the corneal surface and distortion or discontinuity of the image was regarded as tear break-up), found that instillation of fluorescein significantly decreases the stability of the tear (Mengher *et al.*, 1985). Non-invasive TBUT can be assessed using aberrometry, confocal microscopy, corneal topography and interferometry and the first discontinuity or break of the anterior tear surface is recorded in seconds from the last blink as the TBUT.

## Topographical analysis systems

In comparison to eyes with normal TF, DE patients have TF irregularities on the corneal surface. The corneal topography can be used to monitor optical changes associated with irregular TF surface and generate indices such as, surface regularity index (SRI), surface asymmetry index (SAI) and topographic pattern. These findings can be used to assess the corneal surface regularity and TF stability. These indices enable the objective quantification of the quality of the TF, its breakdown and its consequent effects upon the QOV (Montés-Micó, Cáliz and Alió, 2004).

## Interferometry

Interference between light reflected from the surface of the lipid layer and the interface between the lipid layer and aqueous layer of the TF generates observable patterns. These interference patterns can be observed using the interferometry and captured using photograph or video and can be used to infer the thickness and stability of the TF (Lin and Yiu, 2014). Since interference patterns have been correlated with the thickness of tear lipid layer, quantitative values from interference patterns of lipid layer thickness can be derived (Yokoi, Takehisa and Kinoshita, 1996). Tear lipid thickness has been used in research to assess changes in MGD (Lin and Yiu, 2014).

**Optical coherence tomography**

Apart from measuring the anterior segment of the cornea, OCT can also measure the TF thickness (Wang *et al.*, 2003), tear meniscus (Shen *et al.*, 2009), grading lid parallel conjunctival folds (LIPCOF) (Bandlitz *et al.*, 2016), corneal epithelial thickness (Bayhan, Aslan Bayhan and Can, 2014) and meibomian gland structures (Liang *et al.*, 2015). The advantages of using optical coherence tomography is that it achieves in producing non-invasiveness scans of high resolution, good accuracy, and repeatability. Studies by Nguyen *et al*. suggests that lower tear meniscus measurement by the OCT correlates well with symptoms of DE and Schirmer test (Nguyen *et al.*, 2012).

**Confocal microscopy**

Corneal *in vivo* confocal microscopy is a non-invasive, high-resolution tool that allows imaging of the cornea at the cellular level and produces images comparable to histochemical methods. These images enable the microscopic visualisation of corneal epithelium, corneal stroma and keratocytes, endothelial cells, corneal nerves, corneal immune and inflammatory cells, conjunctiva and meibomian glands in various ocular and systemic pathologies. It can also be used for diagnostic purposes and measure therapeutic efficacy in patients with DE. *In vivo* confocal microscopy in DE patients can capture conjunctival epithelial cyst formation, decreased density of conjunctival epithelial cells, goblet cells and increased inflammatory cell density. As therapeutic trauma caused by laser can trigger a cascade of responses and potentially affect the

optical properties of corneal tissue (Spadea, Giammaria and Trabucco, 2016). *In vivo* confocal microscopy has provided researchers with a better understanding of the conjunctival wound healing process, and corneal changes induced by medications and their preservatives (Villani *et al.*, 2014).

**Corneal and conjunctival staining**

This a minimally invasive procedure as it requires the instillation of dye such as sodium fluorescein, rose bengal, or lissamine green and examining the cornea and conjunctiva staining under a slit lamp biomicroscope. The evaluation and scoring of the staining is subjective, however the Oxford, Van Bijsterveld, and CLEK grading schemes can facilitate consistent recording of staining severity (Bron, Evans and Smith, 2003). The repeatability of staining tests in some studies has been found to be poor and lacks the ability to discriminate between mild and moderate cases of DE (Sullivan *et al.*, 2010). The SS International Registry modified the Oxford grading scheme to allow simultaneous grading of the cornea and bulbar conjunctiva using a combination of 0.5% fluorescein (1 drop) for corneal staining and 1% lissamine green (1 drop) for conjunctival staining. Grades between 0 and 3 are assigned for staining the cornea, the nasal and the temporal conjunctiva. The maximum possible total score is 9 points. Three additional points are then allotted for fluorescein only if there is confluent staining (t1), staining in the pupillary area (t1), or if one or more filaments are present (t1), granting a maximum possible score of 12 (Whitcher *et al.*, 2010).

**Conjunctival impression cytology or brush cytology**

Impression cytology requires harvesting conjunctival epithelial, goblet, and inflammatory cells from the bulbar mucosa (Reddy, Reddy and Reddy, 1991). It is a rapid and minimally invasive, and relatively painless. Studies have demonstrated that cytokines IL-1a, mature IL-1b, and IL-1Ra are found in a significantly greater percentage of conjunctival cytology specimens from eyes with DE due to Sjögren's syndrome (Solomon *et al.*, 2001; Barabino *et al.*, 2010). Along with flow cytometry, the DE group was found to have a significant difference in the CD4/CD8 ratio, CD14

positive cells (monocytes/macrophages), HLA-DR expression in CK19 positive conjunctival epithelial cells and elevated matrix metalloproteinases levels (Solomon *et al*. 2001). These studies exhibit the role and nature of immune cells on the superficial layer of the conjunctiva in DE pathology.

Conjunctival brush cytology is another variation in which a soft brush is used to harvest superficial cells (as in impression cytology) and basal cells. These sample are then examined for squamous metaplasia, inflammatory cells, and the expression of surface markers on the ocular surface epithelium (Tsubota *et al.*, 1990; Wakamatsu *et al.*, 2009). In combination with flow cytology, it is highly sensitive and specific analysis of epithelial cell markers, goblet cells and inflammatory cells (Wakamatsu et al. 2009)

### 1.4.3 Treatment for dry eye

Three steps towards treating DE were identified in a European Ocular Surface Workshop held in Italy in 2009 (Rolando *et al.*, 2010):
1. 'Patient education, monitoring the eyelid environment, use of artificial tear substitute and eyelid therapy'.
2. 'Addition of temporary anti-inflammatory agents, temporary punctual occlusion, secretagogue administration'.
3. 'Autologous serum and amniotic membrane.'

There are a variety of treatments available for DE and these are used according to the severity of the problem (Lemp *et al*. 2007). Combinations of artificial tears, oral omega-3 essential fatty acid supplements, mucin secretagogues, short-term steroids, and daily cyclosporine A (CsA) are a few methods used to alleviate underlying inflammation. These treatments can help revive normal TF and ocular function in patients suffering with mild-to-moderate forms of DE. The next level of treatment for more severe forms of DE consists of autologous serum, oral tetracyclines, and prosthetic lens. The use of systemic immune-suppressants is restricted to patients with higher levels of DE severity (Behrens *et al.*, 2006). DE due to systemic origin such

as Sjogren's syndrome, Stevens–Johnson syndrome are treated surgically by tarsorrhaphy and amniotic membrane transplant.

Since the primary aim of DE treatment is symptomatic relief, the use of tear substitutes can provide transient symptomatic relief. Ideally, the tear substitute should be analogous in composition to natural tears. Eye drops containing glucans, such as sodium hyaluronate (0.1–0.4 %) and carboxymethylcellulose (0.5 %) compounds have been tested in various clinical trials and concluded to be effective and better in comparison to saline solution eye drops (Aragona, 2002; Brignole *et al.*, 2005; Rolando *et al.*, 2009; Lee *et al.*, 2011). These drops are usually recommended to be administered at least four times a day. Although gel formulations have a longer lasting effect, they are usually recommended for night-time use, but frequency can be increased with severity of DE symptoms. Topical steroids such as fluorometholone, clobetasone, loteprednolol, and methylprednisolone have also proven to be beneficial in terms of initial therapy and symptomatic relief of DE. However, these formulations cannot be used continuously as they pose they increase the risk of developing subcapsular cataracts (Aragona, 2002; Lee *et al.*, 2014). Since fatty acids such as omega-3 have be attributed anti-inflammatory action, studies have shown that dietary supplementation of fatty acids has proven beneficial to symptomatic relief in DE patients. Additionally, improved ocular tests, decreased ocular discomfort, and decreased tear osmolarity are some of the documented benefits(Bhargavaa *et al.*, 2015; Deinema *et al.*, 2017).

### 1.5 The cornea

The average horizontal diameter of an adult human cornea is between 11.5 to 12.0 mm, and about 1.0 mm larger than the vertical diameter. It is also approximately 0.5 mm thick in the centre and the thickness increases towards the periphery (Rüfer, Schröder and Erb, 2005). Common pathologies associated with the structural changes to the cornea are Keratoconus (KC) (collagen disorders) and Fuchs' endothelial dystrophy (endothelial-based corneal dystrophies), which alter the corneal central thicknesses beyond the normal variance (Ehlers and Hjortdal, 2004). The dome shape

of the cornea which is flatter at the periphery and steeper centrally constructs an aspheric optical structure. The cornea consists of 6 recognised layers:

- 3 cellular layers: epithelium, stroma and endothelium
- 2 interface layers: Bowman membrane and Descemet membrane
- Dua's layer (pre-Descemet's layer) has also been accepted since its discovery in 2013 (Dua *et al.*, 2013).

The epithelium covering the cornea surface constitutes the initial cellular barrier to the external environment. It is an essential component of the TF cornea interface that is significant to the refractive power of the eye. It comprises of stratified, non-keratinizing squamous layer characterized by extreme uniformity which is 4 to 6 cell layers thick (50 to 52μm). The TF covering the epithelium smoothens out micro-irregularities of the anterior epithelial surface. This air–TF interface, along with the underlying cornea, accounts for two thirds of the total refractive power of the eye. The TF also provides a protective barrier to the corneal surface from microorganisms, toxins and small foreign particles. It also provides immunological and growth factors that nurture epithelial growth and repair (Derek W. DelMonte, 2011). The mucinous layer of the TF is in direct contact with the corneal epithelium, which is produced by the conjunctival goblet cells. This allows the hydrophilic spread of the TF over the corneal epithelial cell glycocalyx. The superficial epithelia also utilises mechanisms of scaffolding with the help of microvilli and microplicae to bind to mucin (Nichols, Dawson and Togni, 1983). A compromised glycocalyx due to injury or disease can results in loss of TF stability and subsequent breakdown of the ocular surface homeostasis. The epithelial basement membrane is approximately 0.05μm thick and comprises of type IV collagen and laminin secreted by basal cells. During injury, fibronectin levels rises and the healing process can last for up to 6 weeks. Throughout this process, the epithelium bonds to the underlying, newly laid basement membrane tend to be unstable and weak (Dua, Gomes and Singh, 1994). The Bowman layer lies between the epithelial basement membrane and anterior stroma. It is not a true membrane but rather the acellular condensate of the most anterior part of the stroma which is approximately 15μm thick and aids the cornea uphold its shape. When injured, it does not have the regenerative capacity and can form a scar.

Light and electron microscope scans have shown that in KC, the basement layer undergoes disintegration that results in irregular thinning, fragmentation and consequent breaks (Chi, Katzin and Teng, 1956; McPherson and Kiffney, 1968; Sawaguchi and Fukuchi, 1995; Sawaguchi *et al.*, 1998; Sykakis *et al.*, 2012). These structural changes are observed when the stroma is minimally affected, suggesting that basement membrane assessment can serve as a diagnostic method to possibly predict KC progression (Tuori *et al.*, 1997). Ophthalmic pathologists have long used these signs for *in vitro* diagnosis of KC using light microscopy. However, advancements and the use of high-speed ultra-high resolution spectral domain optical coherence tomography has enable clinicians to visualise this layer *in vivo* (Xu *et al.*, 2015).

The corneal stroma constitutes approximately 80% to 85% of the total thickness of the cornea. The stroma differs from other collagenous structures in its transparency, due to its precise organization of the stromal fibres and extracellular matrix (Wilson, 1970; Boote *et al.*, 2003).

Keratocytes are the major cell type of the stroma and maintain the extracellular environment by synthesising the collagen molecules, glycoaminoglycans and matrix metalloproteases important in maintaining stromal homeostasis. Most keratocytes reside in the anterior stroma and contain 25% to 30% corneal crystallins; a soluble protein in the cells which is responsible maintaining corneal transparency and reducing backscatter of light from the keratocytes (Jester *et al.*, 1999).

The endothelial layer of the cornea preserves corneal clarity by ensuring it remains in a relatively dehydrated state. Endothelial cell density and topography continue to change throughout life, declining from 4000 to 3000 cells/mm$^2$ from the second decade of life to about 2600 cells/mm$^2$ at the eighth decade with a total reduction of 60% to 75% in hexagonal cells (Yee *et al.*, 1985). It has been observed endothelial cell counts below 500 cells/mm$^2$ can be a risk factor for the development of corneal oedema. The density of endothelial cells varies with location, being approximately 10% higher in the periphery of cornea (Amann *et al.*, 2003). Studies have observed that the peripheral endothelial cells are resilient and can remodel and radiate to cover damaged sections

(Edelhauser, 2000). Since the human cornea is avascular in nature it therefore must rely on components of the blood supplied by the end branches of the facial and ophthalmic arteries via the aqueous humour and TF (Langham *et al.*, 2009).

The cornea is considered as one of the most densely innervated tissue and therefore is one of the most sensitive tissue of the body. Corneal nerves are derived from the nasociliary branch of the first (ophthalmic) division of the trigeminal nerve. In the superficial cornea, the nerves enter the stroma radially in thick trunks forming plexiform arrangements. These nerves eventually perforate Bowman membrane to provide a rich plexus beneath the basal epithelial layer while the internal cornea can also receive innervations from the maxillary branch (Müller *et al.*, 1997).

### 1.5.1 The cornea and surgery

Injury can occur to the cornea after intraocular and corneal refractive surgery. The injury or detachment of the Descemet's membrane is rare but considered to be one of the most serious complications in an anterior segment surgery. This can lead to significant loss and decompensation of endothelial cells (Al-Mezaine, 2010). Inappropriate surgical technique, substandard equipment (Yi and Dana, 2002) and phacoemulsification of a dense nuclear cataract (Luo *et al.*, 2014) can all lead to injury or detachment of the Descemet's membrane. Since the deposition of a new basement membrane requires endothelium cell migration, the use of an air bubble tamponade to hold in place the loose membrane tags against the posterior cornea has been found to facilitate the healing process (Ti *et al.*, 2013). Direct mechanical injury, high ultrasound energy and effects of irrigation solution can also lead corneal oedema (Polack and Sugar, 1977). Endothelial cell health can be maintained by carefully managing the temperature, pH, osmolarity, irrigation solution preservation method and ocular medication (Edelhauser *et al.*, 1976; Edelhauser, 2000). Corneal wound healing after laser refractive surgery procedures is an important factor that can determine the success of the treatment. Therapeutic trauma caused by laser can trigger a cascade of physiological responses and potentially affect the optical properties of corneal tissue (Spadea, Giammaria and Trabucco, 2016). Overcorrection, undercorrection, regression, haze and refractive instability is to a large extent related to corneal wound

healing response (Netto *et al.*, 2005). Since laser ablation of the cornea has the ability to stimulate a fibrotic response that leads to opacity, contraction and alteration to the corneal curvature, controlling fibroblast activation is key for optimal recovery (Fini and Stramer, 2005). The healing response of the cornea varies from surface area and depth of stromal ablation procedures. In surface ablation procedures, the fibrotic response is more aggressive, the possible reason for which may be disruption of the basement membrane (Fini and Stramer, 2005; Nishida, 2012). Conversely, non-disruption of the basement membrane leads to cellular repair without fibrosis (Netto *et al.*, 2005). It has also been documented, in LASIK surgery, that protecting the integrity of the central corneal epithelium leads to less keratocyte apoptosis and necrosis due to reduced epithelial stromal cell interaction (Wilson, Mohan and Ambrosio, 2003). Less haze and regression has also been found to correlated with less keratocyte proliferation and myofibroblastic differentiation (Siganos, Katsanevaki and Pallikaris, 1999). Regression after LASIK has been mostly attributed to epithelial hyperplasia and stromal remodelling (Lohmann and Guell, 1998; Reinstein *et al.*, 1999) whereas in SMILE, the observed epithelial changes do not appear to affect the refractive outcome (Sekundo *et al.*, 2014). Haze occurrence can be in the stromal tissue at the flap junction where there is direct contact between the normal and activated keratocytes (Vesaluoma *et al.*, 2000) or a diffuse lamellar keratitis which can lead to central haze (Linebarger, Hardten and Lindstrom, 2000). Doughnut shaped flaps and retention of epithelial debris in the interface can also occur (Wilson, 1998). Hyperopic SMILE has less postoperative corneal wound healing response and stromal interface reaction than hyperopic LASIK treatment. However, compared to myopic SMILE, hyperopic SMILE treatment results in greater central derangement of collagen fibrils (Liu *et al.*, 2016). Laser subepithelial keratectomy (LASEK), which uses ethanol to create an epithelial flap, has reduced pain, promotes faster visual recovery and less haze as the flap serves as a mechanical barrier to protect the stroma from the TF that contains growth factors (Lee *et al.*, 2002; Vinciguerra, Camesasca and Randazzo, 2003). However, these conclusions have been contested on the viability of the removed epithelial cell layer in relation to re-adhesion when the basement membrane is not present on the stroma (Litwak *et al.*, 2002; Espana *et al.*, 2003).

## 1.6 Cataract classification

There are several clinical classifications systems that can be used to evaluate cataract, such as the Age-Related Eye Disease Study (AREDS, 2001) system of classification, Laser slit-lamp evaluation (Hall *et al.*, 1999) and LOCS III (Chylack *et al.*, 1993) which is the most establish method of assessment. However, LOCS III and other clinical measurements methods employ a subjective assessment of grading the cataract, therefore the assessment is dependent on the examiner (Brown, Bron and Sparrow, 1988) and their level of training and experience (Kashima *et al.*, 1993). The possible drawback to this method is that it could lead to inconsistencies when results are compared between different assessors. To minimise this discrepancy studies have resorted to Scheimpflug imaging of cataracts (Kim, Chung and Joo, 2009; Nixon, 2010). Scheimpflug images can present sections of the lens which are evenly focused from the anterior to posterior capsule. These images are continuous measurements as compared with the LOCS III, which has stepwise grading system. This allows the Scheimpflug imaging to detect minimal cataract progression (Grewal, 2009). However, the limitations of using Scheimpflug imaging for assessing cataracts is that the internal crystalline lens is observed through the anterior refractive surfaces, which is the cornea and the anterior lens surface, and the refraction at these two surfaces has the tendency to distort the internal structure image of the crystalline lens. Another drawback is that inadequate dilatation of the pupil can interfere with the Scheimpflug camera's image acquisition. Similarly, eyes with abnormalities such as pseudoexfoliation, intraoperative floppy iris syndrome, or white cataracts cannot be assessed accurately using a Scheimpflug camera (Grewal, Brar and Grewal, 2009).

### 1.6.1 Cataract surgery

The goal of cataract surgery is to rehabilitate the blind or visually impaired patients by restoring normal or close to normal sight as possible. This goal can generally be achieved by extracapsular cataract extraction (ECCE) that utilises phacoemulsification or nuclear expression and the lens capsule is reserved for the implantation of an

intraocular lens. However, during an intracapsular cataract extraction (ICCE), the entire capsule holding the lens and the lens are removed.

ECCE extraction by phacoemulsification involves the opening and removal of the central section of the anterior capsule following the emulsification of the nucleus with an ultrasonic probe. The emulsified nucleus is then removed by a suction device. The posterior lens capsule is left intact to facilitate the placement of a posterior chamber IOL in the capsular bag (Minassian *et al.*, 2001). This extraction and implantation of the IOL is performed through incisions less than 2mm which allows fast healing and recovery of the cornea and improved visual outcomes (Minassian *et al.*, 2001).

### 1.7 Modern multifocal intraocular lens design

There has been considerable evolution and improvement in the field of cataract surgery techniques over the last few decades. Cataract surgery by phacoemulsification of the crystalline lens and replacing it with an artificial IOL is now considered a safe, effective and predictable treatment for cataract (Powe *et al.*, 1994). It is also considered to be the most common surgery performed globally (WHO, 2002; Richard Lindstrom, 2015). Modern techniques such as the micro-incisional cataract surgery has minimal impact upon postoperative astigmatism (Kohnen and Kasper, 2005). Advancements in IOL designs and materials have also significantly reduced the risk of complications such as posterior capsule opacification (Kohnen *et al.*, 2008). Monofocal IOL can provide good visual acuity at a fixed focal length. They are usually targeted for distance viewing and therefore for near and intermediate vision, spectacle correction is required. Spherical IOLs were found to induce spherical aberrations and thereby compounding the positive spherical aberrations of the cornea. This led to the development of aspheric IOLs, which improved contrast sensitivity and VA. However since aspheric IOLs are pupil dependent and therefore perform less optimally on small pupil size than spherical IOLs (Kohnen, Klaproth and Bühren, 2009).

Independence from glasses is an important concern in presbyopia patients and was highlighted by Luo et al. (2008), who found 10% of presbyopic patients would trade 5%

of their life expectancy for good all round unaided vision. This is one of the reasons that has led to the development of multifocal IOLs. Multifocal IOLs can provide high levels of spectacle independence, independent of ciliary body function. Even though monofocal IOLs can also provide near vision with the addition of monovision or blended vision methods. This technique compromises on binocularity and effectiveness within a difference of 1.50 dioptres. There are a variety of multifocal IOLs with varying optical properties. Refractive multifocal IOLs are either concentric or sectorial and diffractive lenses are partially of entirely diffractive. Presbyopia is considered one of the most challenging and final frontiers in cataract and refractive surgery. Surgical removal and replacement of the crystalline lens with either monofocal or multifocal IOL has advantages and disadvantages and no available treatment option has so far proven to be problem free.

### 1.7.1 Zonal multifocal intraocular lenses

Zonal multifocal IOLs consists of multiple concentric refractive zones. These zones have different curvature thereby creates two or more refractive powers. The first multifocal IOL that was approved in the USA was AMO array (Abbot Medical Optics Inc. CA, USA) which had a spherical posterior surface optic with a central zone for distance surrounded by four alternating zones for distance and near (Steinert *et al.*, 1999). A prospective, fellow eye, non-randomised study on this IOL revealed that the mean uncorrected and corrected VA for distance and near at one-year after implantation improved by two lines on the VA LogMAR chart. However, the side-effects were glare, haloes and reduced contrast sensitivity (Steinert *et al.*, 1999). This design was further refined in the Rezoom (Abbot Medical Optics Inc. CA, USA) IOL which incorporated aspherical surface. MFlex (Rayner Intraocular Lens Ltd, Hove, UK), further added the option of two additions of either four or five refractive zones relative to the power of the IOL. The addition of multiple refractive zones was to reduce the IOLs dependency to pupil size and IOL decentration. However, the downside of combining small pupil and concentric ring multifocal IOL was that the majority of the light energy was being directed towards the distance zone (Lane *et al.*, 2006). It has been documented that in ReZoom (Advanced Medical Optics, Santa Clara, California,

USA) refractive multifocal IOL with its five concentric refractive zones, that the distribution of light is dependent on the pupil size. In a 2 mm pupil, approximately 83% of the light entering the pupil is projected towards the distance zone an 17% towards the intermediate zone, while in a 5 mm pupil, approximately 60%, 10% and 30% of light is directed towards distance, intermediate and near zones of the IOL respectively (Lan *et al.*, 2017).

### 1.7.2 Sectorial multifocal intraocular lenses

Refractive asymmetric IOL with sectorial design has been in clinical use for over 5 years and is currently been widely accepted by surgeons globally. The sectorial design brought a new concept to multifocal IOL technology. Although the physical IOL design resembles a bifocal spectacle lens. However, it provides simultaneous vision similar to other multifocal IOLs. The difference in its design is that sectorial multifocal IOLs have two sectors: a larger sector for distance vision and a smaller sector for near vision. Theoretically, it has been argued that fewer transition zones from one power to the next results in less dispersion of light, hence improved contrast sensitivity (Venter *et al.*, 2014). McAlinden & Moore (2011) found that Lentis MPlus (Oculentis GmbH, Berlin, Germany) resulted in good VA with high-level contrast sensitivity thereby resulting in significant improvement in QOL.

Venter et al. (2014) while assessing the assess efficacy, safety, predictability, and patient satisfaction on SBL-3 (Lenstec, Inc., Christ Church, Barbados) concluded that SBL-3 multifocal IOL implantation resulted in good range of vision for near, intermediate, and distance. However, these IOLs are also dependent on pupil size and pupil centroid shift as documented by Pazo et al. (2016).

### 1.7.3 Diffractive multifocal intraocular lenses

Diffractive multifocal IOLs creates two or more focal points by using the principle of diffraction. The concentric ring boundary creates an interference of light and the

separation between the edges of the rings determines the power. However, the major drawback to this design is that the light energy is lost to higher order and results in aberrations (Hütz *et al.*, 2006).

Total diffractive multifocal IOLs such as the Tecnis ZM900 (Abbott Medical Optics Inc., Santa Ana, CA, USA) are pupil independent as it can split light between distance and near (Hwang, Kim and Kim, 2014). Clinical studies carried out by Kretz et al. (2015) that Tecnis ZKB00 IOL with a lower near addition (+2.75 D.) increased intermediate VA and had satisfactory near vision. These IOLs are found to have less photopic phenomena in comparison to Rezoom (Abbot Medical Optics Inc., Santa Ana, CA, USA) (Cillino *et al.*, 2008).

Partially diffractive multifocal IOLs have a combination of diffractive and refection surfaces. ReSTOR (Alcon, Fort Worth, Texas, US), has a single refractive surface dedicated for distance and is surrounding the diffractive section. The anterior of this IOL is apodized and therefore there is a step height of the concentric rings. To counter the positive corneal spherical aberration. The posterior side of the IOL is convex aspheric. Since this IOL is pupil dependent, larger pupils tend to allow more light to the distance section. Vingolo *et al*. (2007) found that 10% of the patients implanted with ReSTOR (Alcon, Fort Worth, Texas, US) had severe haloes, glare and the intermediate vision was also not satisfactory (De Vries *et al.*, 2010). By increasing the near power to +4 dioptres Rasp *et al*. (2012) found that good reading performance was achievable which was significantly better than that obtained with a refractive multifocal or monofocal IOL.

### 1.8 Management of patients with multifocal intraocular lenses

Various studies have evaluated the aetiology of patient dissatisfaction after multifocal IOL implantation. The primary factors that lead to dissatisfaction are reduced distance, intermediate and near vision, along with reduced contrast sensitivity and photopic phenomena. Kamiya *et al*. (2014) conducted a retrospective study and evaluated 50 eyes of 37 patients who underwent multifocal IOL explantation. The most common

complaints for IOL explantation were waxy vision, glare and halos, blurred vision at distance viewing, dysphotopsia, blurred vision at near, and blurred vision at intermediate respectively. The most common reasons for undergoing IOL explantation were decreased contrast sensitivity, followed by photic phenomenon, unknown origin, failure to neuroadapt, error in IOL power calculation, excessive preoperative expectation, IOL dislocation/decentration, and anisometropia. Similar findings from other studies highlights these key issues with multifocal IOL implantation (Woodward, Randleman and Stulting, 2009). Therefore, appropriate patient selection and preoperative stratification of patients can improve postoperative patient satisfaction. The initial step is the proper education of patients about the procedure and clearly communicating the cost and benefits of the multifocal IOL implantation treatment to the potential patient (Pepose, 2008; Lichtinger and Rootman, 2012; De Vries and Nuijts, 2013). Since multifocal IOL are sensitive to factors such as pupil size and minor ocular aberrations (De Vries and Nuijts, 2013), it is therefore imperative that careful screening and selection is mandatory for postoperative patient satisfaction.

# CHAPTER 2: THE IMPACT OF PUPIL SIZE AND VISUAL AXES UPON QUALITY OF VISION FOLLOWING CATARACT SURGERY

## 2.1 Introduction

The experimental chapters of this thesis aim to investigate what pre or postoperative factors may influence or impact upon the QOV after laser or lens based refractive surgery. A comprehensive series of both objective and subjective tests incorporating a variety of diagnostic instruments and techniques were used within this study. Visual acuity (VA) assessment has been traditionally the primary method of quantifying visual outcomes in both clinical setting and clinical studies. However, it is well recognised that VA measurements alone cannot not adequately define the complex concept of vision (de Boer *et al.*, 2004). Patients with the same objectively measured VA may have totally different subjective perspective as to how good or bad they feel that their QOV and therefore VA may not capture all important aspects of visual function from the patient's perspective (Massof and Rubin, 2001; Stelmack, 2001).

Refractive surgery traditionally has been designed with the aim to enable patients to see clearly for distance and near. In the prepresbyopic patient, VA can be improved by correcting distance refractive error. If this is successfully achieved the natural focusing mechanisms within the eye enables intermediate and distance vision (Miranda and Krueger, 2004). However, presbyopic patients pose more significant problems as correction of distance vision in both eyes does not naturally enable near or intermediate vision. Since the focusing mechanisms is compromised by the ageing process (Salvi, 2006). Currently there is no interventional system which perfectly simulates the natural focusing mechanism within the eye. Although various imperfect solutions utilising either laser or lens-based techniques have been developed to overcome this intrinsic problem (Reinstein, Archer and Gobbe, 2011; McNeely *et al.*, 2017). In the early 90s multifocal IOLs were developed which enabled the simultaneous viewing of both distance and near vision through the one IOL. This technology used more than one focal point within the one IOL (McNeely *et al.*, 2017).

Recent studies on multifocal IOLs report good VA for both near and distance vision in terms of spectacle independence (McNeely *et al.*, 2017).

Laser refractive surgery was developed to enable the surgeon to treat either myopia or hyperopia by changing the shape in the cornea. The cornea is flattened in myopia eyes and steepen for hyperopia eyes. The early stages of laser development produced remarkable success in correcting myopia through flattening of the central cornea. Good VA was achieved by using the Munnerlyn formula to predict the amount of corneal flattening required for myopic treatments. It was later made apparent that patients often suffered postoperative glare and haloes (Chang *et al.*, 2003). The lesson learnt early laser treatment for myopes was that the peripheral corneal shape also needed to be modified during the flattening of the central cornea. This prevented the induction of large amounts of spherical aberrations which occurred due to a change in corneal shape from a prolate to an oblate shape. As advancements were made in measurement tools that measured corneal and whole eye aberrations. It made possible for clinicians and researchers to measure the induced aberrations that occurred through laser surgery. This allowed iteratively modification of laser profiles to enhance corneal shape and measure the improvements achieved via these modifications (Cervio *et al.*, 2007). In addition to the development of aberrometers and topographers that measures the objective optical quality, the importance of recording patient's subjective appreciation of the vision was also was recognized (Aaronson, 1988). In an attempt to objectively document the subjective appreciation of vision, various questionnaires were developed to record visual symptoms and its impact upon the QOL. Psychometric methods were also used to validate questionnaires so that it could be deemed as valid, reproducible and objective as possible in recording subjective symptoms (de Boer *et al.*, 2004). The importance of subjective documentation was recognized to be very useful when studying subjective issues which occurred secondary to multifocal IOL implantation. This allowed for an objective assessment of dysphotopic side effects of various multifocal IOLs (McNeely *et al.*, 2017).

It has been long understood that though the eye is often graphically depicted as a sphere. It is in fact not spherical but rather asymmetric with the light sensitive macula temporally displaced. Angle kappa, is defined as the difference between the primary

line of sight and the pupillary axis (Hage and Grand, 1980). Measuring the distance between the pupillary axis and the visual axis is directly related to angle kappa. The pupillary axis is the line from the centre of the entrance pupil and the visual axis is the line that connects the fixation point and the fovea in the retina (Figure 2.1). In shorter eyes with larger angle kappa the displacement of the corneal reflex is usually inter related and therefore larger (Artal, Benito and Tabernero, 2006).

The importance of the intrinsic angle kappa in an individual eye to subsequent surgical outcomes from either laser or IOLs is being increasingly investigated (Reinstein, Gobbe and Archer, 2013; Karhanová *et al.*, 2015). Reinstein *et al*. documented that in high hyperopic corneal ablations eyes with large angle kappa lead to poor visual outcomes when compared to patients with eyes with negligible angle kappa (Reinstein *et al*., 2013).

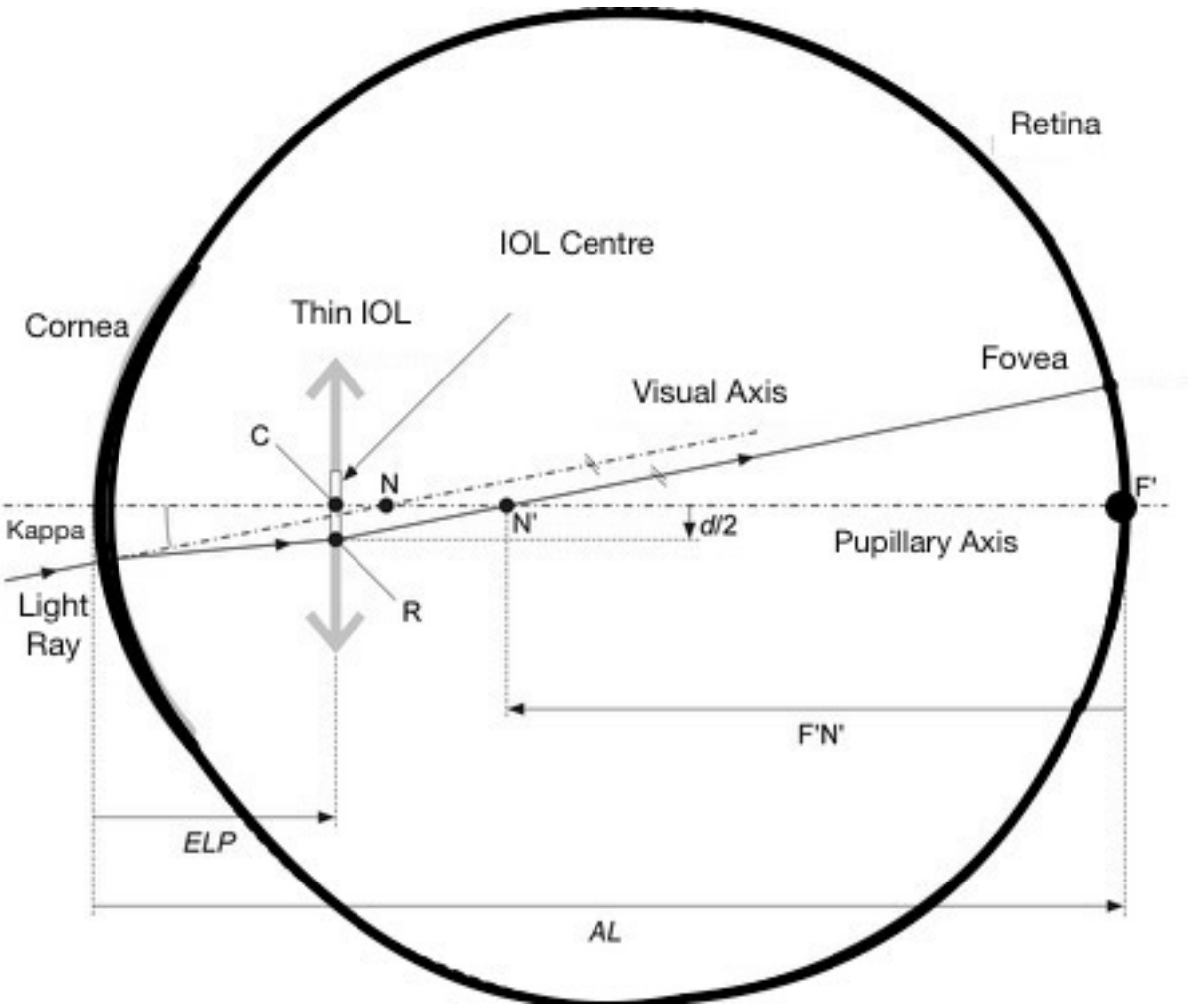
Prakash *et al.* found that on Rezoom multifocal IOLs there was a low correlation between visual acuity and angle kappa (Prakash *et al.*, 2011), it may possibly allude that large angle kappa (negative or positive) might be responsible for night time photopic phenomenon and visual symptoms such as glare and hales due to misalignment of light passing through the IOL and projecting abnormally upon the retina (Moshirfar, Hoggan and Muthappan, 2013). Recent advancement in multifocal IOL technology provides an increasing variety of IOL choices to the ophthalmic surgeon. It is well recognised that patients can experience different subjective responses to these IOLs with a small number of patients being dissatisfied with the QOV postoperatively (Dick *et al.*, 1999; Häring *et al.*, 2001; Pepose, 2008; Woodward, Randleman and Stulting, 2009). There is therefore a need to investigate and ascertain what pre or postoperative factors can impact the postoperative QOV. This will enable the surgeon to stratify patients' preoperatively with regards to those who would be less likely to obtain substandard QOV postoperatively. This would allow either greater levels of preoperative counselling to specific patient groups less likely to be totally satisfied and enable the surgeon to advise against the actual use of a multifocal IOL. Patients undergoing refractive-cataract procedures have high expectations and failing to stratify has been shown to result in less satisfied patients obtaining less than optimal visual performance (Cochener *et al.*, 2011).

The general concept of the asymmetric multifocal IOLs is relatively recent and asymmetrical IOLs are now available in commercial practice. The design of asymmetrical multifocal IOL means that potential IOL deviation from the centre of the pupil. Particularly, in the presence of a small pupil could result in reduced exposure of either the near or distance component of the IOL. As the near component usually utilizes a reduced surface area in Lentis MF20, 40% of IOL surface area compared to 60% for distance refractive component (McAlinden and Moore, 2011; de Wit *et al.*, 2015). Therefore, it can potentially be affected by deviation of IOL from the pupil centre.

## 2.2 Objective measurement of angle kappa

In a ray diagram, angle kappa represents a misalignment of light passing through the cornea and entering the pupil Figure 2.1. The assessment of large angle kappa is relevant because failing to intraoperatively align the multifocal IOL with respect to the angle kappa may lead to misalignment and decentration.

**Figure 2.1**. Schematic ray diagram showing the critical angle kappa with the optical model of the pseudophakic eye with an optical axial length (AL) and an effective position (ELP) of a thin multifocal IOL with the centre (C) of the multifocal IOL on the eye optical axis. 'R' marks the border of the central part of the IOL of the diameter 'd'. The points N and N' represent the first and second nodal points of the pseudophakic optical system, F' is the second focal point of this system




The standard method of measuring angle kappa is by using a non-invasive topography-aberrometry system which utilises two different techniques to calculate the result: a Placido-disk system, assesses anterior corneal topographical representation map, while horizontal moving scanning camera acquires slit-lamp images. The angle kappa calculated automatically with the internal software that

calculates the distance between the pupil centration and the centre of the Placido ring reflection on the cornea. This analysis of the angle kappa has a resolution of 0.01 mm.

Various clinical studies and clinical ophthalmic practice have used topography-aberrometry system for the assessment of angle kappa. The distribution of angle kappa using more than once measuring device has been studies (Basmak, Sahin, Yildirim, Saricicek, *et al.*, 2007; Hashemi *et al.*, 2010) and the prevalence of high angle kappa has been confirmed in conditions such as albinism and strabismus (Brodsky and Fray, 2004; Merrill *et al.*, 2004; Basmak, Sahin, Yildirim, Saricicek, *et al.*, 2007). While others have explored the implication in laser refractive study (Reinstein, Gobbe and Archer, 2013).

### 2.3 Evaluation of angle kappa assessment using NIDEK OPD-Scan II

The NIDEK OPD Scan II aberrometer/corneal topographer workstation which is has a touchscreen user interface which provides autorefractor, keratometry, angle kappa and pupillometry assessments. It plots sixteen different maps which displays information about the patients' corneal shape, wavefront, internal aberrations and visual quality. The software in the workstation can also assist in the management of KC, cataract surgery and refractive laser surgery. The measurement range of the NIDEK OPD Scan II is -20.00 to +22.00 dioptres, 0 to ± 22.00D cylinder and 0 to 180° axis, and a minimum measurable pupil size of 2.6 mm. These assessments can be obtained in one particular session, therefore all of the data gathered can be referenced to each other. It uses the principle of dynamic skiascopy wavefront sensor. As a serial, double-pass aberrometer, an infrared light slit and photodetectors are locate on a revolving wheel that rotates along a fixed axis across the pupil (MacRae and Fujieda, 2000). As the incident beam moves along a specific pupillary perimeter which results in a reflected beam that travels in the same or reverse direction. When the wheel revolves the instrument assesses the time delay for light to peak at each photodiode after passing a beam splitter (Jonathan D Solomon, 2010). The device then calculates the optical pathway difference and derives the wavefront error by comparing the results with the theoretical reference time and creates a refractive map, wavefront

profile and angle kappa coordinates (Buscemi, 2002; Jonathan D Solomon, 2010; Jonathan D. Solomon, 2010).

### 2.4 Angle kappa measurements in the general population

The general prevalence of a minor positive angle kappa in the non-hyperopic demographic was first reported by Srivannaboon *et al*. where 97% of the eyes that underwent myopic refractive surgery had a positive angle kappa of 0.5 mm or less (Srivannaboon and Chotikavanich, 2005).

Various other studies have also confirmed that in a general population the mean angle kappa value is positive. The results of these studies stating this finding is summarised in Table 2.1.

**Table 2.1:** Summary of studies report angle kappa values

| Author | Study type | Sample size | Method of assessment | Angle kappa values | Findings |
|---|---|---|---|---|---|
| Basmak *et al*. (2007) | Prospective group comparison | 108 strabismic subjects and 102 healthy controls | Synoptophore Topographer (Clement Clarke, London, UK) | Esotropic: OD 2.35° ±0.41° OS 2.55° ±0.42°. Exotropic: OD 3.83° ±0.36° OS 4.38° ±0.28° | Exotropes have significantly higher values of angle kappa than esoptropes or controls. Angle kappa was found to be larger in left eye than in right eye. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Positive correlation between angle kappa and positive refractive errors. |
| Basmak *et al*. (2007) | Prospective group comparison | 150 men and 150 women | Synoptophore Topographer and Orbscan II (Bausch and Lomb, USA) | Synoptophore: Myopic: OD 1.74° ±0.13° OS 1.91° ±0.14 Hyperopic: OD 3.44° ±0.14° OS 3.84° ±0.17° Orbscan II: Mypoic : OD 4.51° ±0.11° OS 4.73° ±0.11° Hyperopic: OD 5.65° ±0.10° OS 5.73° ±0.10° | Orbscan II values were on an average of 1.55 mm larger than Synoptophore values |

| | | | | | |
|---|---|---|---|---|---|
| Hashemi *et al*. (2010) | Cross sectional survey | 442 subjects, 800 eyes. | Orbscan Topographer (Bausch and Lomb, USA) | Myopic: 5.13° ±1.50° Emmertropic Group: 5.72° ±1.10° Hyperopic: 5.52° ±1.19° Mild Hyperopic: 5.53° ±1.24° Moderate Hyperopic: 5.45° ±1.26° | Angle kappa is larger in hyperopes than myopes. Angle kappa slightly decreases with age. Angle Kappa did not correlated to gender |
| Zarei-Ghanavati *et al*. (2014) | Prospective controlled study | 48 myopic subjects, 96 eyes | Orbscan Topographer (Bausch and Lomb, USA) | Severe Hyperopic: 5.59° ±2.61°. Preoperative mean angle kappa values: 4.97° ±1.24°. Postoperative mean angle kappa values: 4.99° ±1.10° | No significant change were found in angle kappa pre and post PRK |

According to the current body of research the mean angle kappa value in a normal demographic of emmetropes lies between 2.78 ± 0.12° in right eyes and 3.32 ± 0.13° in left eyes. However, these values have only been assessed by a single instrument, Syntophore corneal topography system (Clement Clarke International Ltd, London, UK) (Basmak, Sahin, Yildirim, Papakostas, *et al.*, 2007). However, studies using the

Orbscan II corneal topographer (Bausch and Lomb, USA) have found the values to be 4.97 ± 1.24°(Zarei-Ghanavati *et al.*, 2014).

Variation in angle kappa values with regards to different machines used for assessment or significant of eye dominance have yet to be completely understood, however, it has been noted gender goes not correlated with angle kappa (Hashemi *et al.*, 2010) and has a tendency show a non-significant decrease with age (Berrio, Tabernero and Artal, 2010).

### 2.5 Multifocal intraocular lenses and angle kappa

Asymmetric and symmetric multifocal IOLs are designed to provide functional vision for distance, intermediate and far. These multifocal IOLs have specifically designed optical surfaces that allows them to provide optimal vision, therefore decentration or misalignment of the lens can adversely affect VA and the QOV (Hayashi *et al.*, 2001; Pazo *et al.*, 2016). Although the effects of decentration and angle kappa on various designs of IOLs have not been completely assessed. However, photopic phenomenon as a result of multifocal IOL decentration has been documented to be one of the main reasons for multifocal exchange (Woodward, Randleman and Stulting, 2009). It has been postulated that an increase in angle kappa values could contribute to functional misalignment on the multifocal optical zones to the pupillary or visual axis and thereby lead to photopic side-effects.

Prakash *et al*. (2011) reported that larger preoperative angle kappa values in symmetrical multifocal intraocular lens (Rezoom IOL, Abbott Medical Optics) correlated with photopic phenomenon such as glare ($R^2$= *0.26, P= 0.033*). Severity of haloes in this study also correlated to angle kappa and postoperative uncorrected distance visual acuity (UCVA) ($R^2$ = *0.26, P = 0.029*) (Prakash *et al.*, 2011). Although there was a correlation between angle kappa and photopic phenomenon but patient dissatisfaction can have multiple aetiologies' (de Vries *et al.*, 2011). Rosales et al. (2010) research used anatomical, Purkinje, and Sheimpflug data to simulate

aberration models of 21 eyes to demonstrate that aspheric intraocular lenses (Tecnis, AMO, and AcrySof IQ, Alcon Research labs) tilt and decentration (mean tilt of 1.54 degrees and mean decentration of 0.21mm) had a small effect on higher order aberrations. However, Hayashi *et al*. (2001) states that in zonal-progressive multifocal lens decentration greater than 0.7mm has the consequence of substantial VA impairment. The premise of large angle kappa negatively affecting the QOV lies in the fact the human eye is not geometrically symmetrical, the fovea and the optical axis do not lie on the same point therefore optical region of a multifocal IOL which fails to accommodate the large angle kappa can miss centration leading to less optimal vision.

### 2.5.1 Study aim

Since the human eye is not geometrically symmetrical, the fovea and the optical axis do not lie on the same point (Prakash *et al.*, 2011). Therefore, the angular distance between the visual axis and the pupillary axis measured by the Nidek OPD Scan is calculated as angle kappa (Basmak, *et al*. 2007; Okamoto *et al*. 2011). The aim of the study assesses the impact of preoperative angle kappa upon QOV of patients implanted with asymmetrical multifocal IOL. Since high angle kappa could potentially impair/reduce light transmission through either the distance or near component of these IOLs without actual physiological IOL decentration within the pupil.

### 2.5.2 Sample size

The power calculation was conducted using G*Power 3.1 (Faul *et al.*, 2007) (ANOVA repeated measures within factor) to show a medium effect size with 90% power and an alpha level of 0.05. Two hundred eyes of 100 cataract patients (41 men, 59 women; mean age: 64.3 years ± 4.9) who had undergone phacoemulsification and implantation of an asymmetrical IOL (Lentis-Mplus MF20) were assessed. The maximum number of subjects required was 100 and therefore 100 subjects were retrospectively assessed to ensure adequate statistical power. Sample size was determined using power calculation (90% power at the 5% level of statistical significance, $\alpha$=0.05) to

detect a change of 1 unit change in QOV Score with 90% power (β=0.2) at the 5% level of statistical significance (α=0.05), 100 subjects were required based upon published data (standard deviation in patients =± 1.08) (McNeely *et al.*, 2017)

### 2.5.3 Subjects

This retrospective, case series is from a population of patients seeking IOL implantation surgery due to cataracts at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective study, only informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent (ref: Appendix D). A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery. Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery.

### 2.5.3 Experimental procedure

Preoperatively, all patients had a full ophthalmic examination including unaided distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) (4m logMAR, Early Treatment of Diabetic Retinopathy Study Chart 1 [ETDRS]), unaided near visual acuity (UNVA) and corrected near visual acuity (CNVA) at 40cm with Radner reading charts under a standard mesopic lighting condition, (Radner charts allow direct conversion i.e. 0.2 logMAR distance acuity is comparable to 0.2 logRAD reading acuity with high correlation at 40 cm to a logMAR equivalent for size of letters) and unaided intermediate visual acuity (UIVA) and corrected intermediate visual acuity

(CIVA) at 70cm. Further examinations included keratometry, topography and auto refraction (OPD-Scan aberrometer (NIDEK Co. Ltd., Gamagori, Japan), subjective refraction, uncorrected and corrected distance visual acuity (UDVA+CDVA), uncorrected near visual acuity (UNVA), contrast sensitivity (Pelli-Robson Contrast Sensitivity Chart), slit-lamp examination, Goldmann tonometry, dilated funduscopy and biometry (IOL Master, version 4.3, Carl Zeiss Meditec AG). and angle kappa (mm) with Nidek OPD Scan II (NIDEK Co. Ltd. Gamagori, Japan).

The IOL Master was used to measure corneal curvature, anterior chamber depth, axial length and subsequent IOL calculation using the Hoffer Q formula for eyes with AL <22 mm and SKR/T formula for AL 22-25 mm and Haigis for AL >25 mm (A- constant of 118.2 for SRKT and a0 constant of 0.83, a1, a2 for Haigis). Emmetropia was the target in all cases. QOV scores were obtained using a validated QOV questionnaire (McAlinden, Pesudovs and Moore, 2010) assessing the outcome measures of symptom frequency, severity, and bothersome nature. The safety and efficacy of Lentis-Mplus MF20 IOL implantation were calculated by the mean change in preoperative CDVA at six months and mean change in preoperative UDVA at six months respectively. Postoperatively, patients were evaluated at one month, three months and six months and further in addition to the above-mentioned examinations, unaided vision, CDVA and near vision were assessed looking for evidence of differences in their mean or in their level of variation through assessment of outlier differences. Posterior capsule opacification was graded as follows: 1=none, 2=mild (early development of PCO), 3 = moderate (increased PCO with early visual acuity changes not requiring secondary capsulotomy) and 4 = severe (PCO affecting vision and requiring neodymium: YAG laser capsulotomy).

### 2.5.4 Surgical technique

One experienced surgeon (JEM) performed all surgeries. The steep axis was marked in all patients preoperatively at the slit-lamp. Subtenons or topical anaesthesia was carried out on all patients. A standard sutureless on-steep axis corneal phaco surgery (2.75mm incision) was performed through a 5.0 mm anterior capsulorrhexis in all

patients without complication. After irrigation/aspiration of cortex the MIOL mentioned above were implanted in all cases with recommended injector cartridge. All residual viscoelastic was removed prior to intracameral antibiotic injection (cefuroxime). Where on-axis surgery was not possible, a 2.75mm supero-temporal corneal position was used to minimise induced astigmatism. Postoperative topical therapy included 1 drop of ofloxacin 0.3% (Exocin) four times daily for two weeks, one drop of ketorolac trometamol 0.5% (Acular) four times daily for one month and one drop of dexamethasone 0.1% (Maxidex) four times daily for three weeks.

### 2.5.5 Questionnaire

For this study a validated QOV Questionnaire (McAlinden, Pesudovs and Moore, 2010) was used (ref: Appendix A). The questionnaire was administered preoperatively and postoperatively at one month, three months and six months follow-up to assess for possible neural adaption. The patients were asked to rate their overall QOV separately for day and night from (0) very poor, to (10) excellent. Photopic phenomenon was scored from of (0) normal, (1) mild, (2) moderate and (3) severe.

### 2.5.6 Statistical analysis

Subjective and objective results were entered into Microsoft Excel spreadsheet. Descriptive statistics were created using SPSS (Statistical Package for the Social Sciences, Version 11.5, Chicago, Illinois, USA) and Excel (Microsoft; Redmond, Washington, USA). The Kolmogorov-Smirnov test was used to assess normality. The Student t test for paired parametric data was applied to assess the significance of differences between preoperative and postoperative data; the Wilcoxon rank-sum test was used when non-parametric data prevailed. Linear regression analysis was conducted to evaluate predictors and response. Ordinal median data was assessed using the non-parametric test; Mann Whitney U. P values less than 0.05 were considered statistically significant.

## 2.6 Results

Due to the retrospective nature of this study all 100 patients in this study reported no intraoperative complications during the six months postoperative follow-up. The mean preoperative angle kappa was 5.69 ± 0.97 and postoperative at one month and six months was 5.64 ± 0.92 and 5.67 ± 0.94 respectively. There was no significant difference between pre and postoperative angle kappa measurements.

### Quality of Vision

A regression analysis was performed between the preoperative angle kappa and the postoperative QOV following cataract surgery to assess for evidence of correlation. The results show that one-month postoperative QOV at day and night correlated with the preoperative angle kappa with a coefficient of determination: ($r^2$=0. 677; p<0.05 and $r^2$=0. 726; p<0.05 respectively) (Figure 2.1 and 2.2). However, the correlation between angle kappa and QOV day and night diminished at three months after operation assessment ($r^2$=0.281; p<0.05 and $r^2$=0.319; p<0.05 respectively) (Figure 2.3 and 2.4). At six months QOV at day and night correlated with the preoperative angle kappa with a coefficient of determination: ($r^2$=0. 255; p<0.05 and $r^2$=0. 268; p<0.05 respectively) (Figure 2.5 and 2.6).

Analysis of the relationship between pupil diameter and QOV during day at one month and three months after operation revealed that it was statistically significant $r^2$=0.652; p<0.05 and $r^2$=0.461; p<0.05 (Table 2.2). The correlation of QOV and pupil diameter at night was also significant ($r^2$=0.622; p<0.05 and $r^2$=0.527; p<0.05). (Table 2.2). The mean combined QOV day and night score preoperative saw a significant improvement postoperatively (Table 2.3).

**Figure 2.1.** Scatterplot of the association between the angle kappa vs. QOV day at one-month after operation.

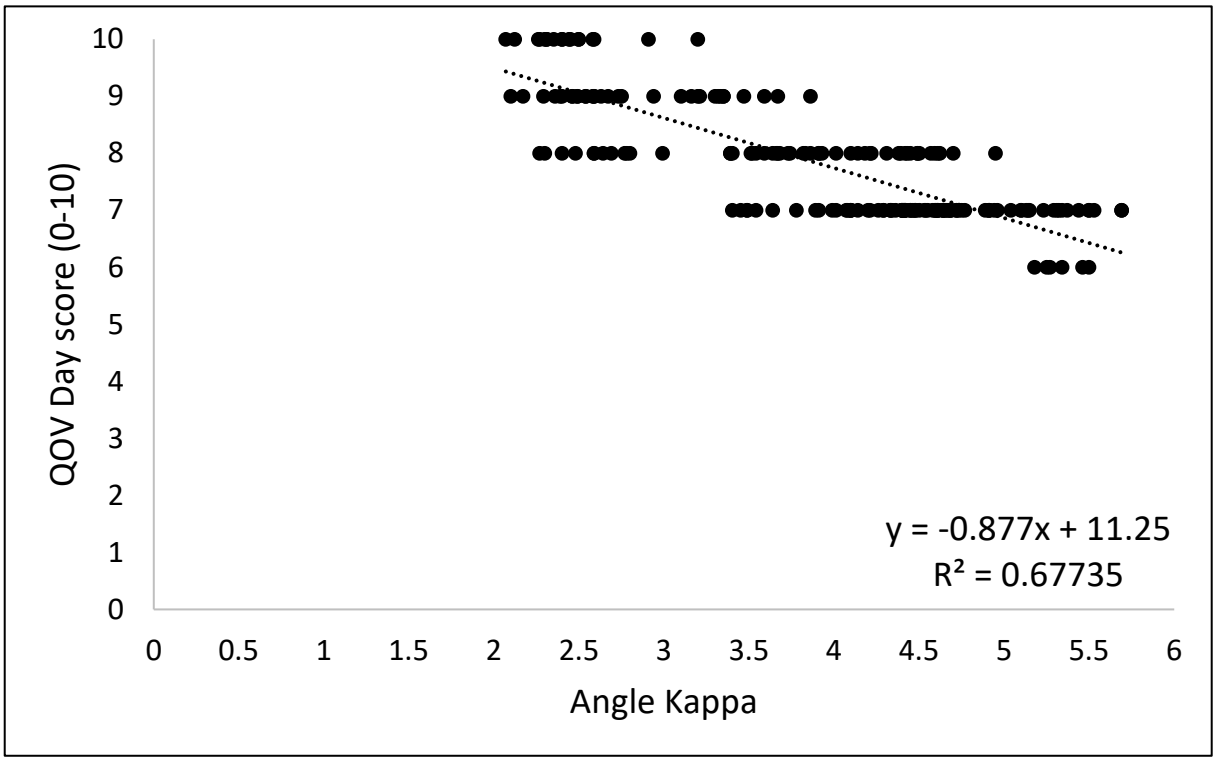


**Figure 2.2.** Scatterplot of the association between the angle kappa vs. QOV night at one-month after operation.

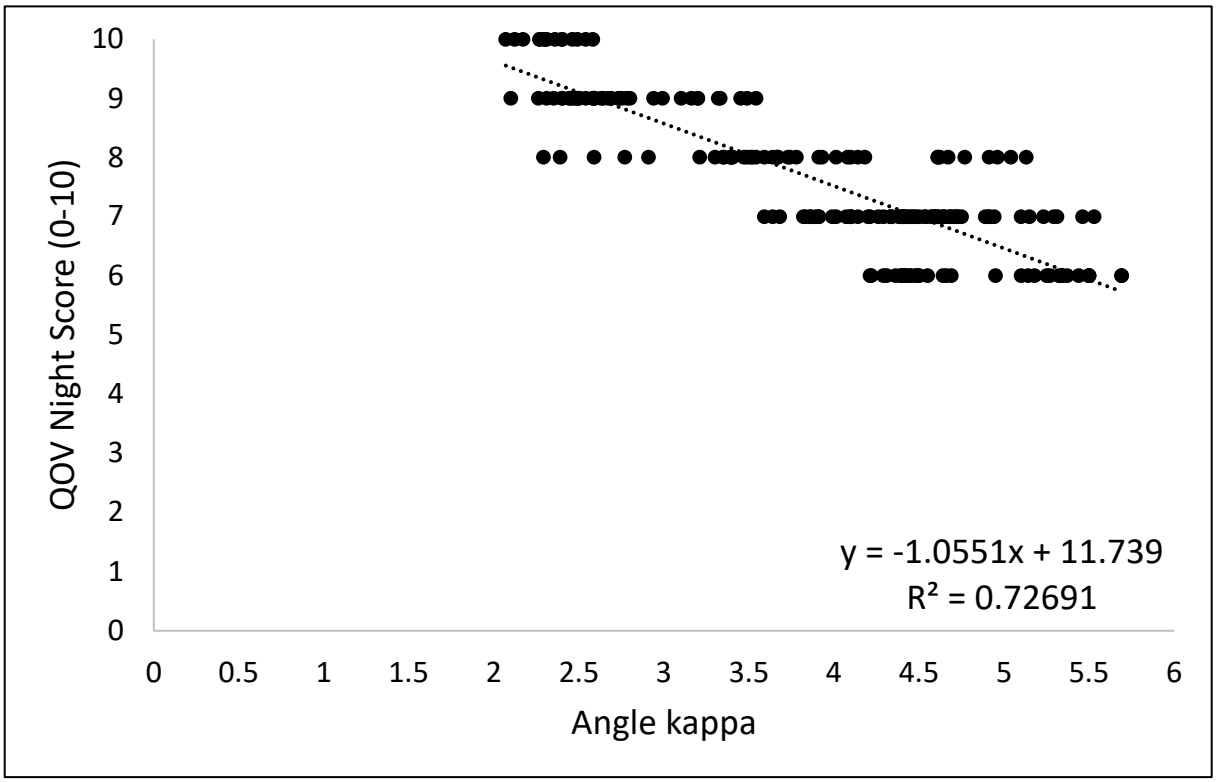


**Figure 2.3.** Scatterplot of the association between the angle kappa vs. QOV day at three months after operation.

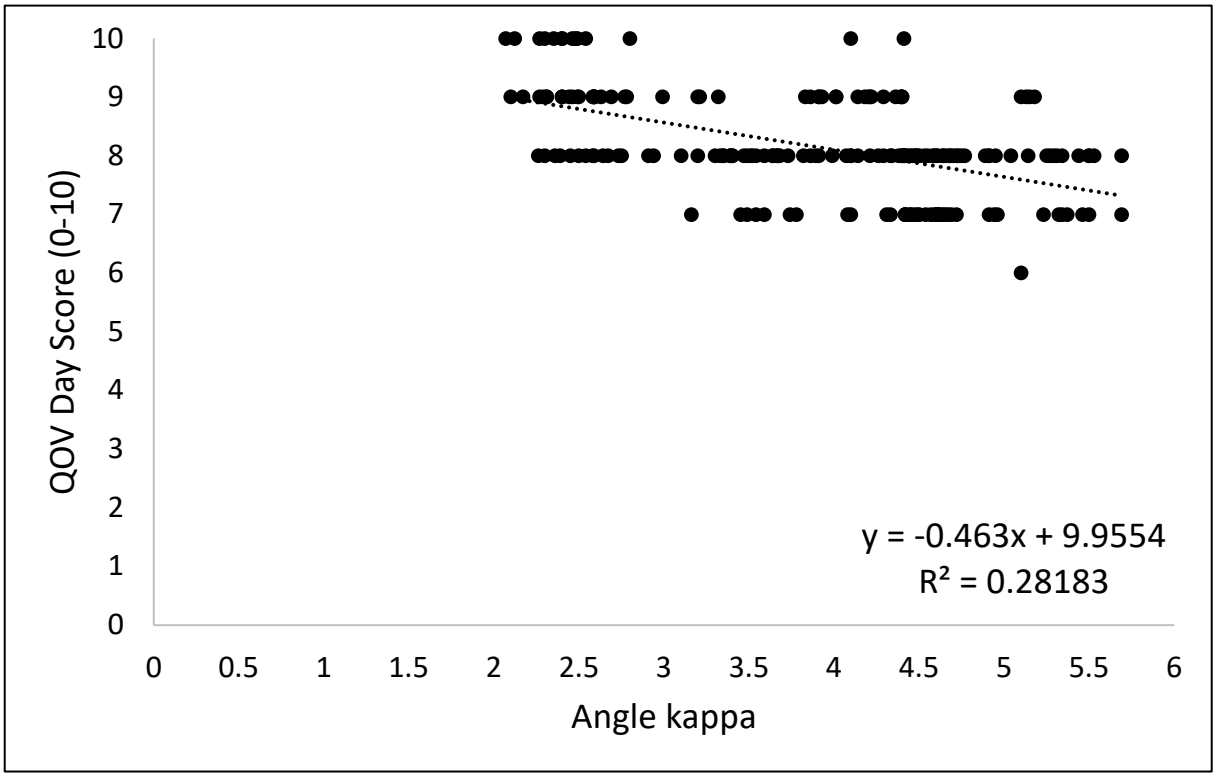


**Figure 2.4.** Scatterplot of the association between the angle kappa vs. QOV night at three months after operation.

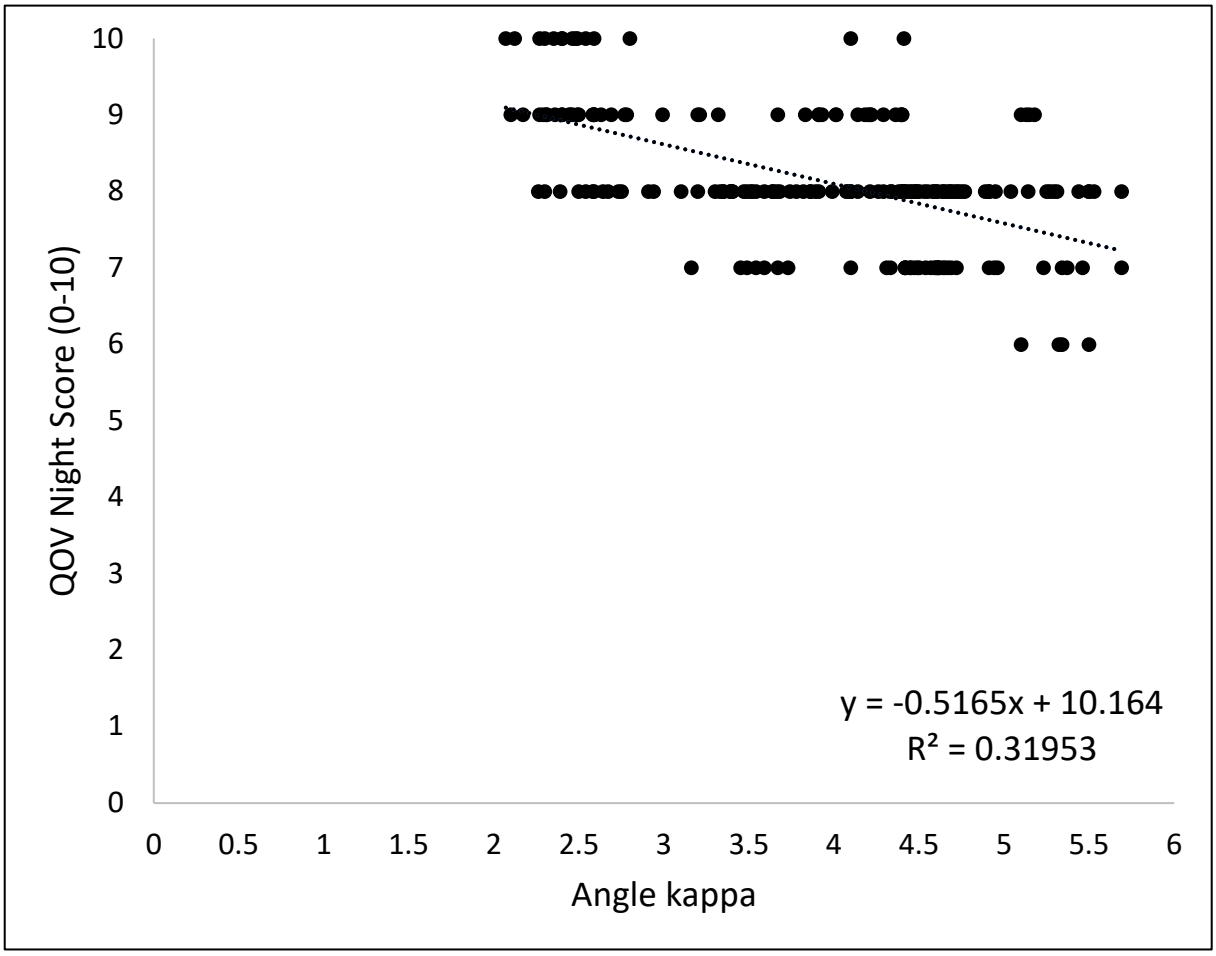


**Figure 2.5.** Scatterplot of the association between the angle kappa vs. QOV day at six months after operation.

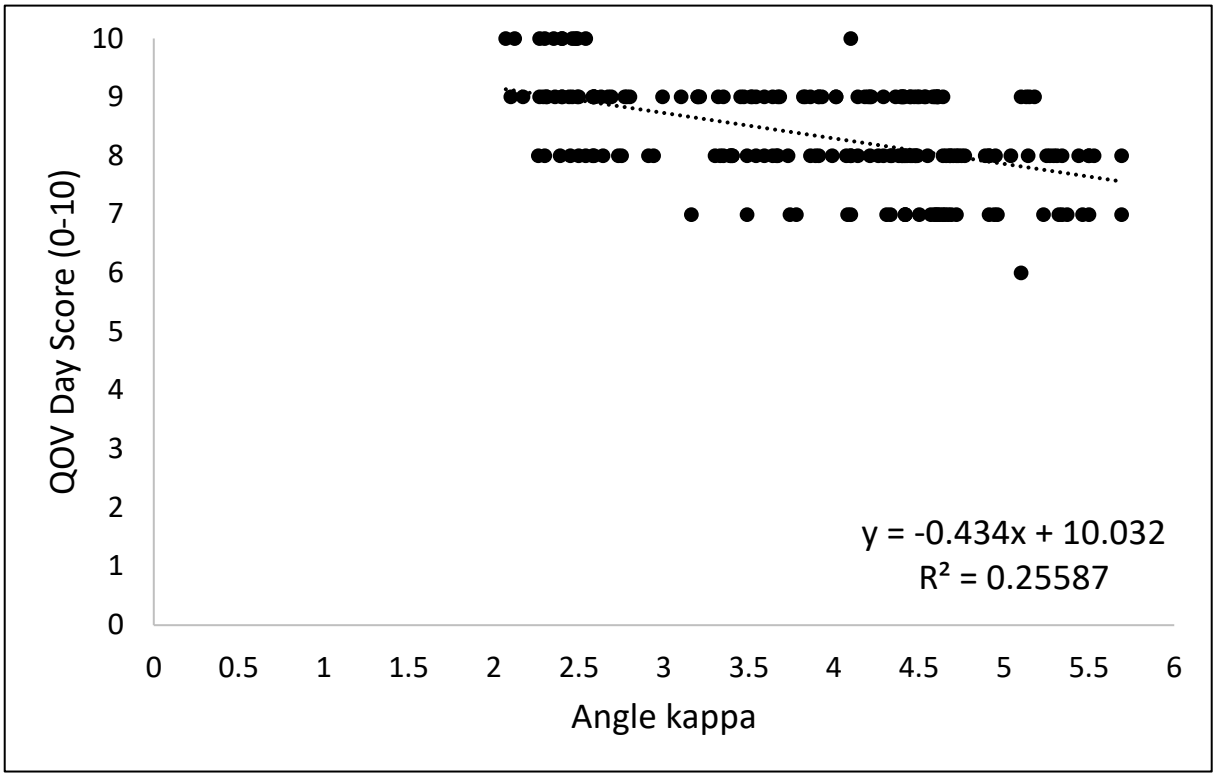


**Figure 2.6.** Scatterplot of the association between the angle kappa vs. QOV night at six months after operation.

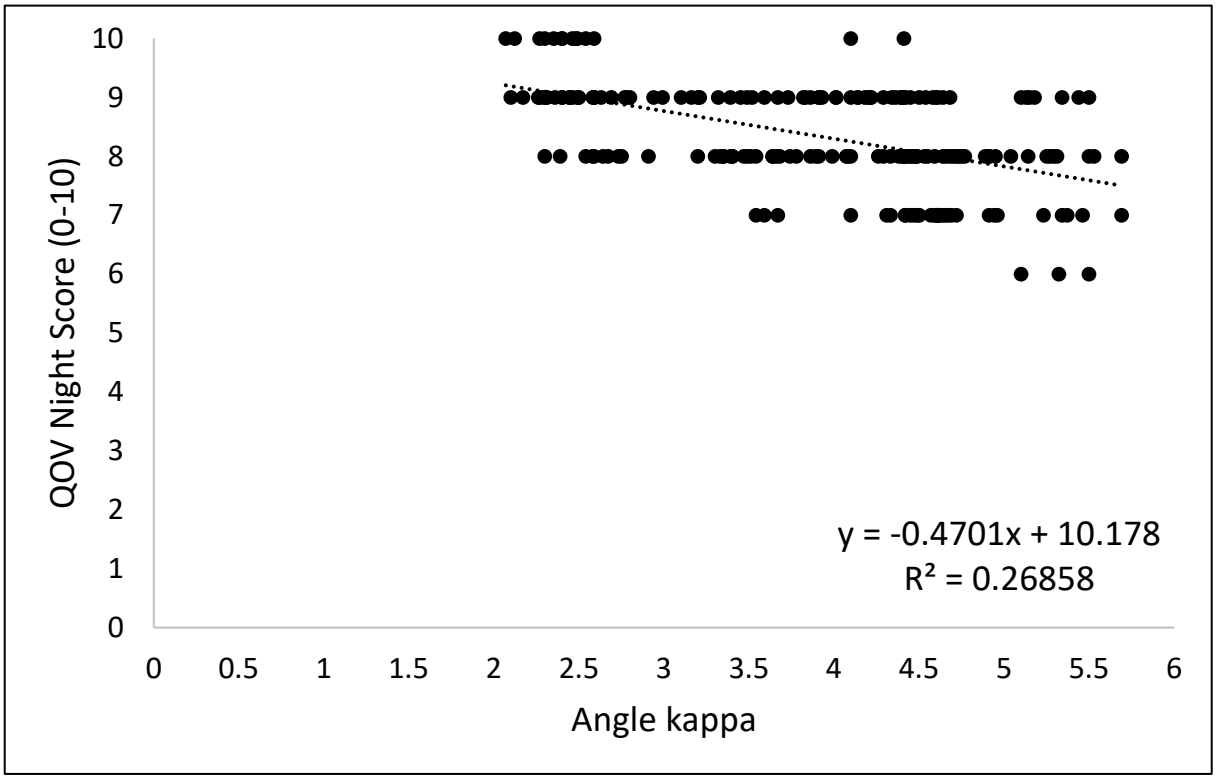


**Table 2.2.** Analysis of the relationship between pupil diameter and QOV.

| | 1-month postop | P-value | 3-months postop | P-value | 6-months postop | P-value |
|---|---|---|---|---|---|---|
| Correlation of QOV and pupil diameter | | | | | | |
| Day | r2=0.652 | 0.016 * | r2=0.622 | 0.029* | r2=0.540 | 0.021* |
| Night | r2=0.461 | 0.022 * | r2=0.527 | 0.034* | r2=0.472 | 0.037* |

*statistically significant

**Table 2.3**. Comparison of preop, 1-month and 3-months and 6-month subjective data after asymmetric multifocal IOL implantation.

| **Parameter** | **Preop** | **1-month postop** | **3-month postop** | **6-month postop** | **P-value** |
|---|---|---|---|---|---|
| **QOV Day** | 5.27 ± 1.95 | 7.83 ± 1.03 | 8.95 ±1.70 | 9.01 ±0.10 | 0.030* |
| **QOV Night** | 4.95 ± 2.10 | 7.10 ± 1.10 | 7.86 ± 1.05 | 8.10 ± 0.22 | 0.023* |
| **Glare** | 0.84 ± 0.72 | 0.45 ± 0.45 | 0.27 ± 0.20 | 0.18 ± 0.15 | 0.041* |
| **Haloes** | 0.86 ± 0.65 | 0.40 ± 0.20 | 0.19 ± 0.22 | 0.15 ± 0.10 | 0.019* |
| *: P-value <0.05<br>QOV scale: 0 (bad) to 10 (Good).<br>Glare and haloes grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very | | | | | |

**Visual Acuity**

Figure 2.7, 2.8 and 2.9 shows the 6-month postoperative cumulative monocular UDVA, UIVA, and UNVA visual outcomes respectively. The safety plots in Figure 2.10 and Figure 2.11 show the accuracy of the attempted spherical equivalent (SE). At six months after operation, 0% of eyes lost two or more lines of CDVA vision compared to preoperative vision.

**Figure 2.7.** Cumulative monocular UDVA at 6 months postoperative assessment.

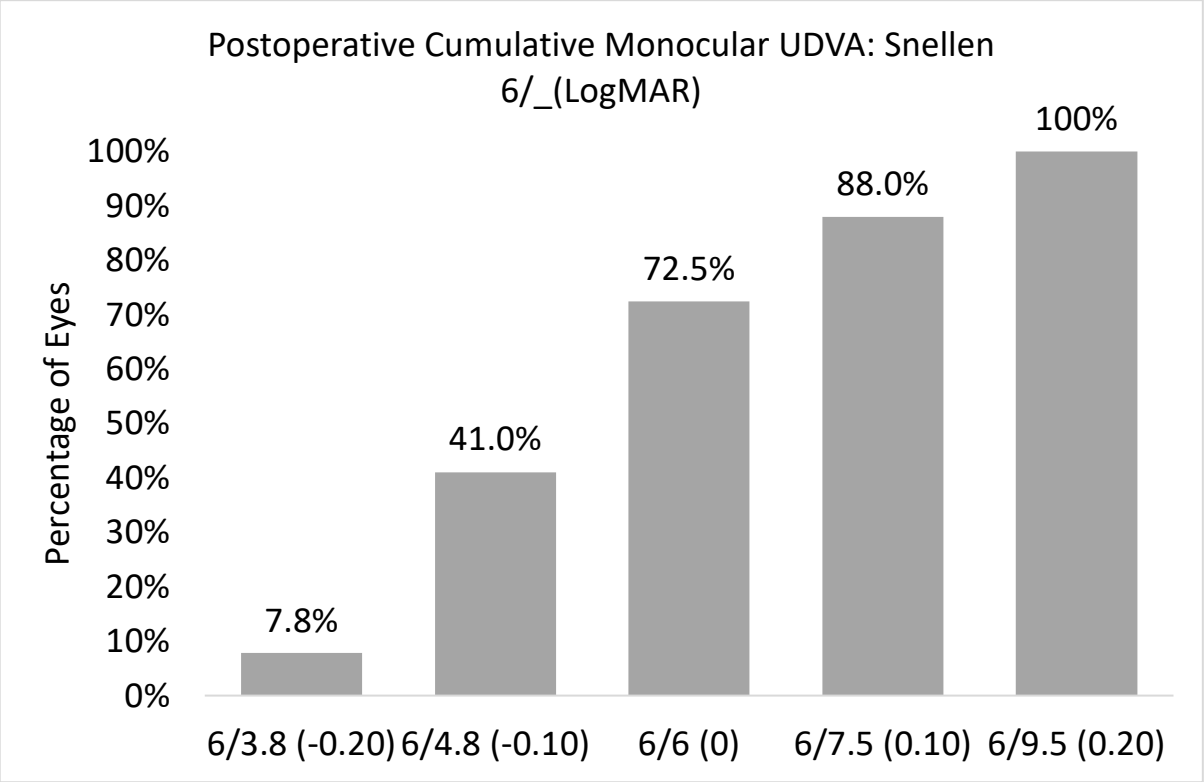


**Figure 2.8.** Cumulative monocular UIVA at 6 months postoperative assessment.

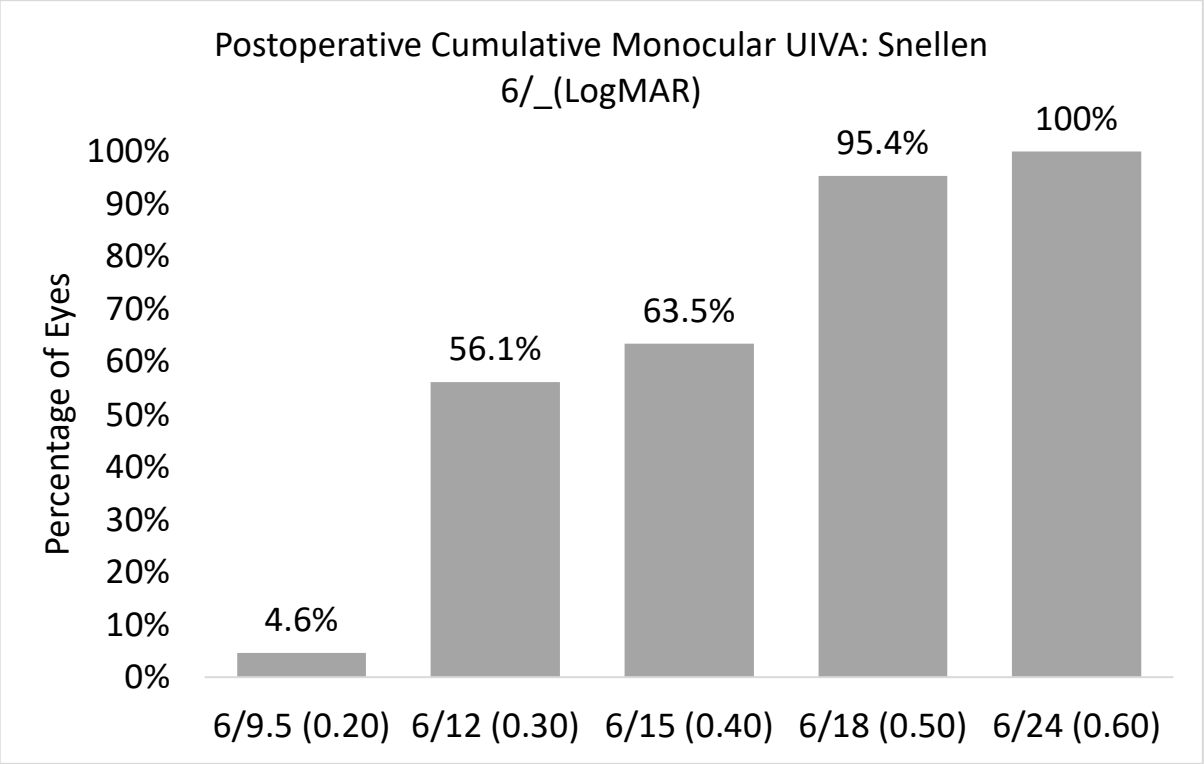


**Figure 2.9.** Cumulative monocular UNVA at 6 months postoperative assessment.

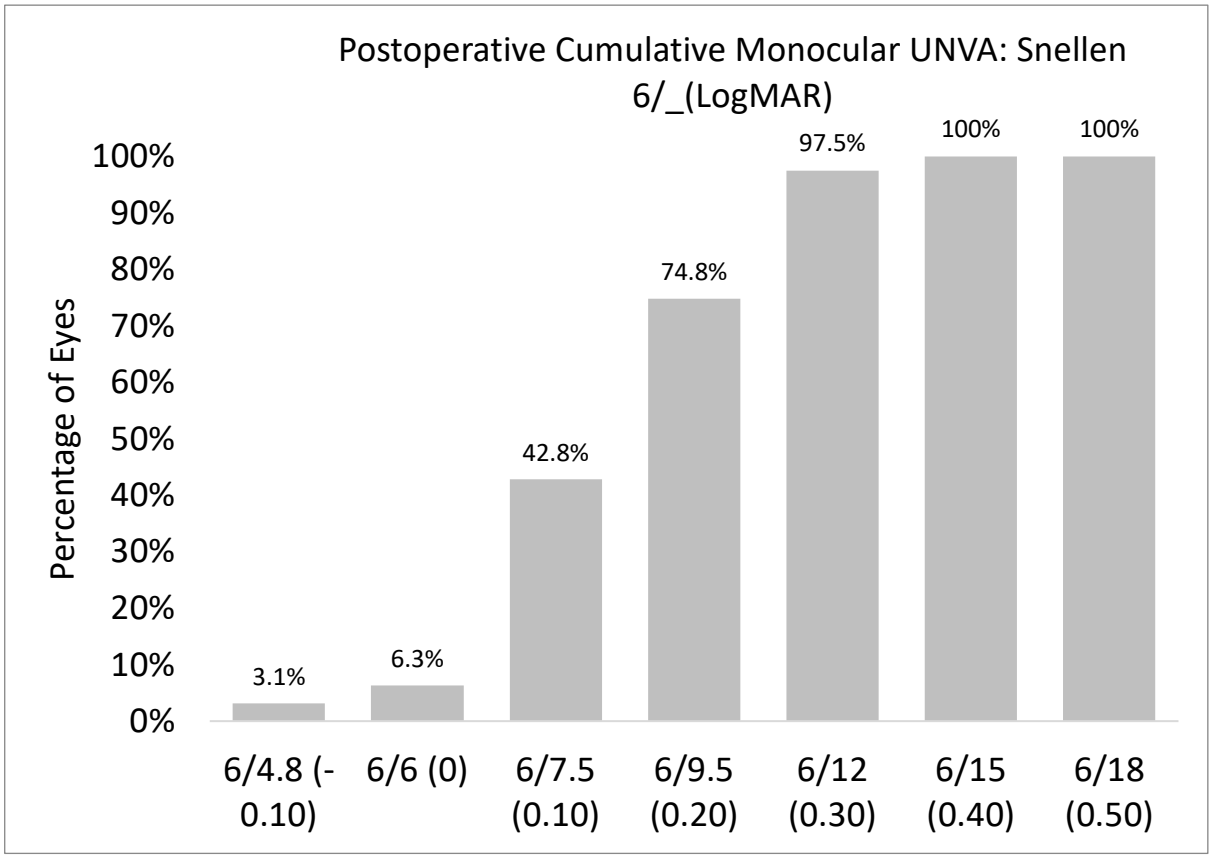
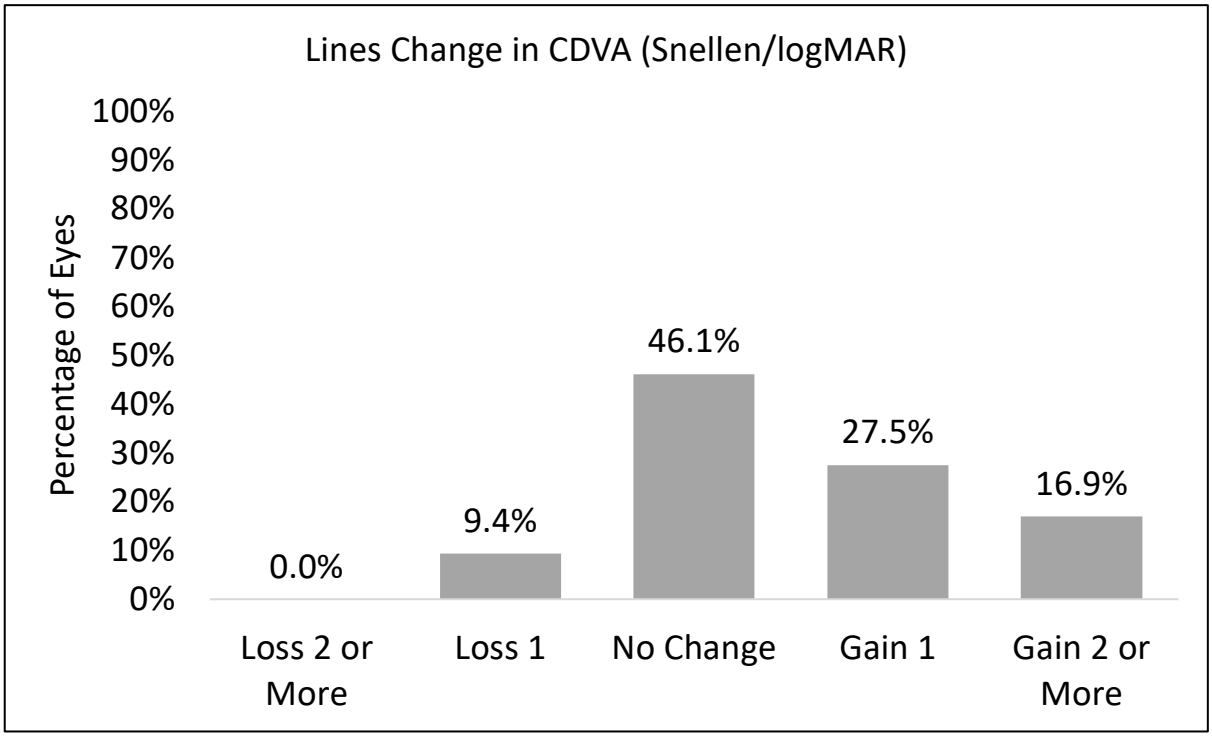
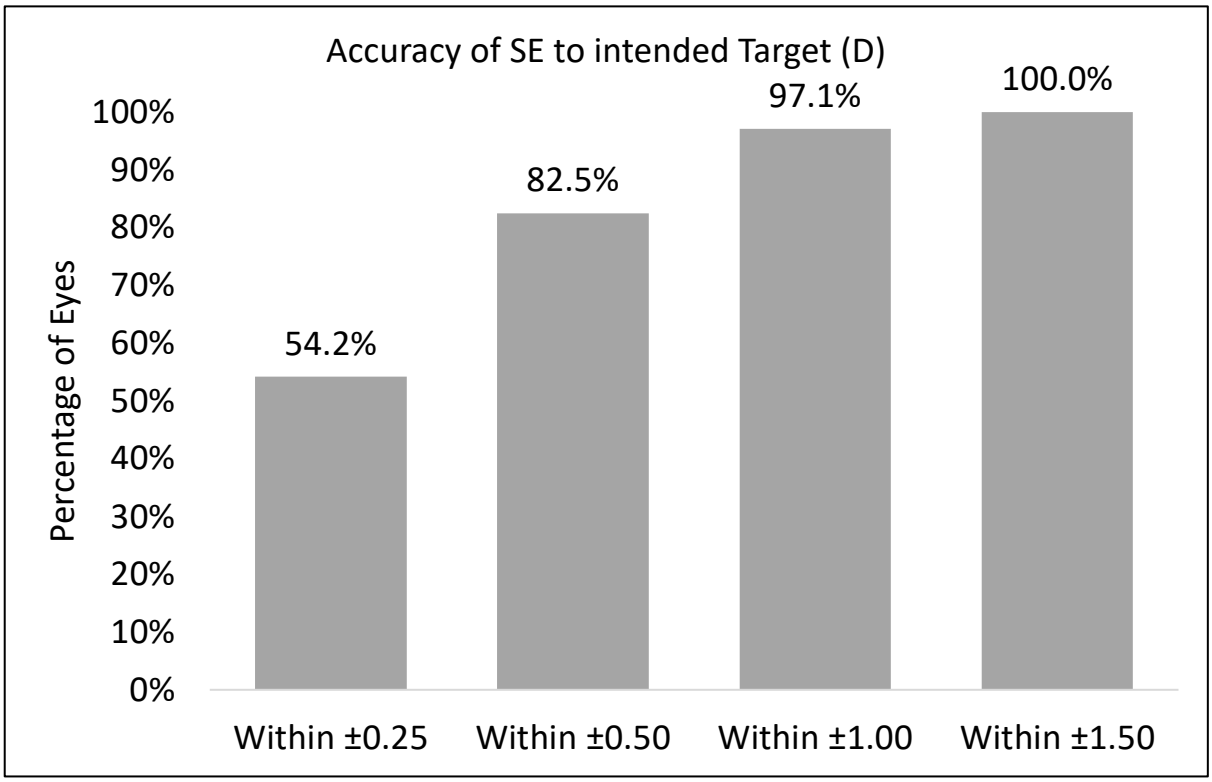


**Figure 2.10.** Monocular CDVA at 6 months postoperative assessment.




CDVA: corrected distance visual acuity.

**Figure 2.11.** Accuracy to the intended SE refraction at 6 months postoperative assessment.




SE: spherical equivalent.

**Efficacy**

The mean preoperative CDVA was −0.06 ± 0.10 logMAR, at one month it was −0.08 ± 0.06 logMAR and at six months it was −0.08 ± 0.09 logMAR. The mean UDVA also saw improvements, postoperatively at one month and six months it was stable at −0.02 ± 0.17 logMAR and −0.01 ± 0.25 logMAR respectively. The mean UIVA at one month postoperatively was 0.35 ± 0.15 logMAR and 0.32 ± 21 logMAR after six months. The mean UNVA improved from 0.14 ± 0.12 logMAR at one month and 0.15 ± 0.12 logMAR at six months after operation (Table 2.4).

**Refractive Error**

The postoperative sphere at one month and six months was 0.13 ± 0.35 D and 0.21 ± 0.37 D respectively and mean cylinder was −0.25 ± 0.30 D and −0.32 ± 0.25 D at one and six months postoperatively (Table 2.4).

**Table 2.4.** One month and three months objective postoperative data after bilateral asymmetric multifocal IOL implantation. D: dioptres; CDVA: corrected distance visual acuity; logMAR: logarithm of minimum angle of resolution; UDVA: uncorrected distance visual acuity; UIVA: uncorrected intermediate visual acuity; UNVA: uncorrected near visual acuity

| **Parameters** | **Preoperative** | **Postop 1-month** | **Postop 3-month** | **Postop 6-month** |
|---|---|---|---|---|
| Sphere (D) | 1.23 ± 2.85 | 0.13 ± 0.35 | 0.20 ± 0.40 | 0.21 ± 0.37 |
| Cylinder (D) | −0.53 ± 0.50 | −0.25 ± 0.30 | −0.35 ± 0.35 | −0.32 ± 0.25 |
| CDVA (LogMAR) | −0.06 ± 0.10 | −0.08 ± 0.06 | −0.09 ± 0.04 | −0.08 ± 0.09 |
| UDVA (LogMAR) | -- | −0.02 ± 0.17 | −0.01 ± 0.15 | −0.01 ± 0.25 |
| UIVA (LogMAR) | -- | 0.35 ± 0.15 | 0.30 ± 20 | 0.32 ± 21 |
| UNVA (LogMAR) | -- | 0.14 ± 0.12 | 0.13 ± 0.10 | 0.15 ± 0.12 |

**Complications**

No serious complications (posterior capsule rupture, endophthalmitis, macular edema or persistent raised intra-ocular pressure) occurred during the study. None of the eyes lost any lines of BCVA at the latest follow-up (six months).

## 2.7 Discussion

There was an overall high level of patient satisfaction (Figure 4 and 5) despite obvious improvements and good objective overall VA, glare and haloes were perceived by some patients (3.3%) with a range of severity (Table 2.3) resulting in an overall reduced QOV in a small percentage at one-month review period. Dysphotoptic symptoms are well-recognised problems perceived from various types of multifocal IOLs (Cochener *et al.*, 2011; Gil *et al.*, 2012; Schmickler *et al.*, 2013). However, in this study there was a rapid diminution in their severity resulted in increased QOV by the three month and six-month review. This improvement in QOV night scores can be attributed to postoperative neuroadaptation (Voskresenskaya *et al.*, 2010; Prakash *et al.*, 2011) which is congruent with the findings of other studies (Voskresenskaya *et al.*, 2010) where postoperative improvement in the QOV of patients was reported between six to twelve months. Therefore, in our study we also found that the initial severity of photic phenomenon in asymmetrical multifocal improved within three and six months. A comparative study with other lens design to evaluate parameters that affect neural adaptation will be a further extension of this study.

In order to better define potential causes for variation in postoperative QOV, this study sought to analyse a comprehensive set of preoperative factors. The factors assessed included: angle kappa, pupil diameter, UNVA, CNVA, UNVA, CNVA, spherical error, cylindrical power, age and gender. Among these, regression analysis demonstrated substantial association between the postoperative visual experience and angle kappa and pupil diameter.

When comparing the scatter plot of QOV one-month scores and angle kappa, the findings were: QOV night scores ($r^2=0.726$; $p<0.5$) were more correlative to angle kappa as compared to QOV day scores ($r^2=0.677$; $p<0.05$). This suggests that alignment error due to larger angle kappa is a possible cause of dysphotopsia, hence poor QOV during night. However, this influence of angle kappa over the QOV at three months during night gradually diminished. A higher angle kappa leads to a fovea-centric ray passing closer to the edge of the IOL and not through the pupillary area exactly concentric with the centre of the IOL. This raises the question as to whether it is possible to modify the IOL centration with the prior knowledge of a large angle kappa.

IOL currently centre themselves based upon their haptics pushing against the edge of the capsular bag. A capsular tension ring may prevent capsular contraction to some degree but if the actual capsule is not centred either on the pupil or the visual axis there is a potential to result in less than optimal visual outcome (Mester *et al.*, 2007). A different option available to the asymmetric IOL is the ability to rotate the smaller near segment to different regions of the pupil such as in the opposite vectoral position to angle kappa, thus maximising the exposure of the near segment surface area within the pupil.

Multiple variable factors are involved in the position of the multifocal IOL, capsular contraction, memory of the haptics and IOL rotation. Surgeons have performed pupilloplasty to centre the pupil to realigning the visual axis in cases of significant angle kappa to improve the QOV.

It is well recognised from various studies on symmetrical multifocal IOLs that pupil size can affect the performance. The effect of the pupil size upon QOV in this study was analysed (Table 2.3) and it is evident that larger pupil size providing better QOV during the day and night. Asymmetric multifocal IOLs differ from symmetric IOLs since in the prior the near or distance segment can be affected by loss of surface area of IOL exposed during pupil meiosis. This effect would potentially be more heightened by pupil meiosis due to bright lights and reading close-up. An increase in pupil diameter results in greater proportion of light being directed to the distance section and near section of the asymmetrical multifocal IOL, thereby resulting in good QOV for distance and near. The reduction of light available due to a smaller pupil diameter is likely to cause a significantly poorer visual acuity in photopic compared to mesopic conditions due to the loss of IOL surface area exposure to either distance or near section. We found that pupils with greater diameter appear to help in maintaining good night vision and could possibly even be compensating for high angle kappa in some patients (Pazo *et al*, 2018). However, an assessment of a larger sample of significant angle kappa and small pupil size is warranted to make definitive claims on this phenomenon. As for now, it is safe to speculate that potentially the combined effects of ‘small pupils and large angle kappa (visual angle offset)’ can lead to poor QOV in asymmetric multifocal IOL patients.

The validated QOV questionnaire (McAlinden, Pesudovs and Moore, 2010) demonstrated improvement in QOV between one, three and six months. The overall increase in satisfaction can be attributed to the decrease in photopic phenomena as patients in this study experienced less dysphotopsia as time progressed (Table 2.3). Glare demonstrated a statistically significant improvement while halo remained stable and did not worsen. It can be argued that VA plays a more significant role in patient satisfaction rather than dysphotopsia as the sheer time spent in harsh lighting conditions is less. In our VA analysis we found that VA from one month to six months postoperatively did not have significantly improvement. Hence the reduction in dysphotopic phenomenon can be safely accredited for the improvement in QOV scores and over-all visual satisfaction. Therefore, it is vital for lens manufactures to focus on negating dysphotopsia in order improve patient satisfaction. Similarly, it would be of value to study whether a lens could be customized to match the angle kappa and pupil diameter measurements of individual patients'. The overall photic components like glare, haloes and starburst were reported greater in high angle kappa patients but as the percentage of cases with a high angle kappa was only 8.6% of the total study population, these findings are statistically less reliable. A larger sample size of 'large angle kappa' patient group could be used in the future to segregate specific components of dysphotopsia that are potentially affected by angle kappa and other visual axes.

## 2.8 Conclusion

In summary, the QOV of cataract patients in this study improved within two to three months. However, a small subgroup of patients with significant angle kappa and small pupil diameter had unsatisfactory visual performance outcomes during the first month due to photic phenomena but neural adaption during postoperative at two and three months resulted in improved QOV. This study proves that preoperative angle kappa and pupil diameter have an influence on the postoperative QOV in asymmetrical multifocal IOL patients. Further studies will be conducted to demonstrate if these findings are similar in other forms of asymmetric multifocal IOLs. The influence of

angle kappa on QOV coincides with studies such as Prakash *et al*. (2011) study on symmetric multifocal IOLs. Although angle kappa had a strong correlation with QOV especially during night, it cannot be used as an isolated parameter because approximately 20% of the patients in this study that experienced poor QOV have normal to small angle kappa and therefore this solidifies the fact that postoperative QOV experience is an interplay between various factors and angle kappa alone is not sufficient to predict the final visual performance. However, one of the limitations to this study is that the groups were not gender and age matched. Additionally, it can be used along with pupil diameter to counsel and help patient better understand the potential initial postoperative outcomes and the implication of neural adaptation when opting for asymmetric multifocal IOL.

## 2.8 Summary

Visual axes and pupil diameter are some of the parameters that affect QOV in patients with bilateral implantation of asymmetrical IOL. The combined effects of these two parameters, improves a surgeon's ability to predict potential problem cases. Chapter 3 will investigate the effects of pupil size on visual performance in asymmetric multifocal IOLs.

# CHAPTER 3: PUPIL INFLUENCE ON THE QUALITY OF VISION IN ROTATIONALLY ASYMMETRICAL MULTIFOCAL IOLS WITH SURFACE-EMBEDDED NEAR SEGMENT

## 3.1 Introduction

The previous chapter demonstrated a relationship between the magnitude of angle kappa and the postoperative QOV after asymmetric multifocal IOL implantation. It also demonstrated the value of the Nidek OPD-Scan II to accurately and efficiently measure angle kappa. The role of the aberrometer/corneal topographer extends beyond this basic assessment of angle kappa. Pupil size measurements and wavefront sensing over a wide range of photopic and mesopic pupil performance within an eye can also be analysed. The assessment of preoperative pupil diameter and pupil centroid shift has been recognized as an important preoperative screening criteria in both laser refractive and IOL implantation surgeries. Studies have shown that larger scotopic pupil size in refractive surgery can lead symptoms such as glare, halos and monocular diplopia postoperatively (Martnez *et al.*, 1998; Haw and Manche, 2001)

## 3.2 Analysis of pupil size

There are various methodologies that can employed to evaluate pupil size. Colvard Colvard hand-held infrared pupillometer (Oasis Medical, Glendora, Calif) has been considered the standard for pupil measurement in refractive surgery. Additionally, Procyon pupilometer (Procyon, London, United Kingdom) is considered an accurate pupilometer (Schmitz *et al.*, 2003). OPD Scan (NIDEK Co Ltd, Gamagori, Japan), is designed to perform pupillometry. A comparison study by McDonnell *et al*. (2006) found that the OPD Scan measurements of the pupils produce similar results to Procyon pupillometer and Colvard pupilometer readings. Mantry and colleagues also confirmed that the mean pupil diameter with the Colvard pupillometer (4.8 ±1.0 mm) and OPD Scan (4.8 ± 0.9 mm) were comparable in low mesopic light conditions. The

mean photopic pupil diameter with Colvard pupillometer and OPD Scan was 3.3 ± 0.8 mm with the and 3.9 ± 0.8 mm respectively (Mantry *et al.*, 2005).

Table 3.1 shows the studies that have related to pupil assessment using various devices. Since there is plenty of variations among studies, it is important to precisely assess each individual eye before IOL implantation surgery.

**Table 3.1**. Pupil diameter assessment with different devices.

| **Device** | **Illumination (lux)** | **Eyes** | **Pupil diameter (mm)** |
|---|---|---|---|
| Colvard IR pupilometer (Colvard, 1998) | 15, 3 | 200 | 6.2 (3.2–9.0) SC |
| Colvard IR pupilometer (Kohnen *et al.*, 2003) | 0.28 | 100 | 5.78 SC |
| Procyon IR pupilometer (Kohnen *et al.*, 2003) | 0.07, 0.88, 6.61 | 100 | 5.90 SC |
| Procyon IR pupilometer (Rosen *et al.*, 2002) | 0.02, 0.15, 10.6 | 116 | 6.61 SC |
| Colvard IR pupilometer (Schnitzler, Baumeister and Kohnen, 2000) | 0.5–0.6 | 66 | 6.08 LM |
| Colvard IR pupilometer (Mantry *et al.*, 2005) | 0.1 | 46 | 5.6 LM |
| Nidek OPD IR auto-refractor (Mantry *et al.*, 2005) | 0.1 | 46 | 4.9 LM |
| IR, infrared; SC, scotopic; LM, low mesopic. | | | |

### 3.3 Pupil size and multifocal intraocular lens

The aim of multifocal IOL use is to restore distance, intermediate and near visual function after cataract or clear lens extraction surgery (de Wit *et al.*, 2015; Gil-Cazorla *et al.*, 2016). Various methods have been implemented to achieve some degree of pseudo-accommodation, such as: aiming for myopic astigmatism (Huber, 1981) targeting one eye for myopia (monovision) (Boerner and Thrasher, 1984) or multifocal IOL implantation (De Vries and Nuijts, 2013). The impact of pupil size in multifocal IOL implantation plays varying roles in the visual performance and optical quality with respect to design of the IOL. Therefore, individual assessment of each multifocal IOL design across various pupil sizes is necessary (García-Domene *et al.*, 2015; Wang *et al.*, 2016). The new generation of refractive rotationally asymmetrical multifocal IOLs aims to alleviate the occurrence of optical side effects (Venter *et al.*, 2014). Asymmetrical multifocal IOLs such as the SBL-3 (Lenstec. Inc., Christ Church, Barbados) in general provide both far and near vision by splitting light to two or more focal points (Venter *et al.*, 2014). The SBL-3 IOL has a +3.0 dioptre near portion with a seamless transition zone between the distance and near section (Figure 3.1). It is crucial that ophthalmologists help retain the ability of elderly patients to see a range of distances enabling multiple daily life scenarios, including driving (Hessemer *et al.*, 1994). Anecdotal evidence from patients and a case report by Pazo *et al*. (2016) on bilateral implantation of asymmetrical multifocal IOL suggests that due to the asymmetrical design of the IOL, patients can experience a reduced QOV while driving and in bright supermarket lighting conditions (Javitt and Steinert, 2000). The centre of the pupil has a tendency to move slightly nasally when constricting (Yang Y, Thompson K, 2002). Therefore, a small photopic pupil can alter the amount of incident light directed to either the distance or near section. Therefore, the visual performance and subjective experience of asymmetric multifocal IOLs is dependent upon pupil size (Montés-Micó *et al.*, 2004; Kawamorita and Uozato, 2005a; Alfonso *et al.*, 2007). A case report by Pazo *et al*. (2016) and the findings of Montés-Micó *et al*. (2004) highlights the point that variation of pupil size affects the relative exposure of sections of IOLs. However, to our knowledge, there is no report of the influence of pupil diameter on VA and subjective QOV in patients with the SBL-3 IOL. Kawamorita & Uozato's (2005) investigation with zonal progressive multifocal IOLs found that a pupil diameter of 3.4 mm or larger was desirable to enhance near vision. Table 3.2 shows

the studies that have assessed the impact of pupil size in various multifocal IOLs. Since there are variations among studies due to the multifocal IOL designs, it is therefore important to precisely assess each multifocal IOL for their individual optical visual outcome.

**Figure 3.1.** SBL-3 asymmetrical multifocal intraocular lens (Lenstec Barbados, Inc., Christ Church, Barbados) with a superior distance sector and inferior near addition.

**Table 3.2.** Chronological order of studies that have assessed the impact of pupil size with various multifocal IOL designs.

| Study | IOL Type | Findings |
|---|---|---|
| Effect of pupil size and astigmatism on contrast acuity with monofocal and bifocal intraocular lenses | True Vista™ bifocal IOL; monofocal IOL | BCCA decreased slightly with increasing pupil size in each group, and differences between 2.0 mm and 6.0 mm pupils were significant at each contrast level. In all |

| | | |
|---|---|---|
| (Knorz *et al.*, 1994). | | bifocal groups, BCCA decreased significantly with increasing pupil size and decreased with increasing corneal astigmatism; differences were significant at most pupil sizes and contrasts tested. |
| Correlation between Pupillary Size and Intraocular Lens Decentration and Visual Acuity of a Zonal-progressive Multifocal Lens and a Monofocal Lens (Hayashi *et al.*, 2001). | Array multifocal IOL (PA154N; Allergan) Monofocal IOL (MA60BM; Alcon Surgical, Fort Worth, TX). | Smaller pupil size correlated significantly with worse near VA. Pupil diameter of less than 4.5 mm could not provide useful near VA, and decentration of 0.9 mm is the maximum allowable limit for adequate distance VA. Pupil size and IOL decentration did not influence VA in eyes with monofocal IOLs. |
| Visual performance with multifocal intraocular lenses: Mesopic contrast sensitivity under distance and near conditions (Montés-Micó *et al.*, 2004). | Zonal-progressive multifocal IOL implantation (Allergan Medical Optics Array SA-40N); Monofocal IOL implantation (Allergan Medical Optics SI-40NB). | Zonal-progressive multifocal IOL distance CS was within normal limits under bright photopic conditions. Deficits at higher spatial frequencies (more than approximately 12 cpd) under dim mesopic conditions. Near CS obtained with the multifocal IOL is below that which can be achieved by monofocal near correction, for all spatial |

| | | |
|---|---|---|
| | | frequencies and illumination conditions. |
| Modulation transfer function and pupil size in multifocal and monofocal intraocular lenses in vitro (Kawamorita & Uozato 2005). | Refractive multifocal IOL Array SA-40N (Allergan); Monofocal IOL PhacoFlex SI-40NB (AMO) | Zonal progressive multifocal IOL, the pupil size was a trade-off between the far and near MTFs: The near MTF increased at the expense of the far MTF at large pupil sizes (effective pupil diameter >3.4 mm). For near vision with a multifocal IOL, the desirable effective pupil diameter should be 3.4 mm or larger. |
| Correlation of pupil size with visual acuity and contrast sensitivity after implantation of an apodized diffractive intraocular lens (Alfonso *et al.*, 2007). | AcrySof ReSTOR IOL (SN60D3, Alcon). | A larger pupil was correlated significantly with better distance visual acuity and with worse near visual acuity. For all pupil diameters, intermediate visual acuity worsened significantly as the distance of the test increased. Distance contrast sensitivity was better with larger pupils at all spatial |

| | | |
|---|---|---|
| | | frequencies in bright-light and dim-light conditions. |
| Functional outcomes after implantation of Tecnis ZM900 and Array SA40 multifocal intraocular lenses (Mester *et al.*, 2007). | Tecnis ZM900 and the Array SA40 multifocal IOLs | Diffractive Tecnis multifocal IOL is independent of the pupil size, a 3.0 mm pupil should not theoretically have an impact on visual performance. |
| Optical performance of two new trifocal intraocular lenses: through-focus modulation transfer function and influence of pupil size (Ruiz-Alcocer *et al.*, 2014). | AT LISA tri 839MP with a trifocal diffractive design; FineVision apodized bifocal diffractive IOL. | For larger pupil sizes, the FineVision provided better results at far Vision while the AT LISA tri 839MP provides better vision at intermediate and near distance and is less pupil size-dependent. |

| | | |
|---|---|---|
| Pupil influence on the quality of vision in rotationally asymmetrical multifocal IOLs with surface-embedded near segment. (Pazo *et al*, 2017 Under Press) | SBL-3 (Lenstec. Inc., Christ Church, Barbados) asymmetrical multifocal IOL. | The preoperative photopic pupil is an important parameter for consideration in this type of IOL as smaller pupil sizes demonstrate a significant negative subjective impact upon the QoV. |

### 3.3.1 Study aim

The objective of our study was to assess whether varying pupil sizes has an impact upon the QOV in eyes implanted with asymmetrical multifocal IOLs.

### 3.3.2 Sample size

The maximum sample size was calculated using G*Power 3.1 (Faul *et al.*, 2007) using two way paired t-test to show a medium effect size with 85% power and an alpha level of 0.05. The maximum number of subjects required was 180 eyes of 90 subjects and therefore 90 subjects were recruited to ensure adequate statistical power. Sample size was determined using power calculation (85% power at the 5% level of statistical significance, $\alpha=0.05$) to detect a change of 1 unit change in QOV Score 90 subjects were required based upon published data (standard deviation in patients =± 1.08) (McNeely *et al.*, 2017).

### 3.3.3 Subjects

This retrospective, case series is from a population of patients seeking IOL implantation surgery at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective study, only informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent (ref: Appendix D). A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery. Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery.

### 3.3.4 Experimental procedure

The preoperative characteristics of patients are shown in Table 3.3. This retrospective study included cataract patients that had undergone bilateral phacoemulsification followed by SBL-3 Lenstec, IOL implantation. The near section of the SBL-3 IOL was placed in an inferonasal position within a dilated pupil. In all patients, photopic pupil diameters were assessed using NIDEK OPD-Scan (NIDEK Co Ltd, Gamagori, Japan). To determine the effect of pupil size on the QOV during the day, patients were divided into groups based on photopic pupil diameter: 2.50 to 2.99 mm (group A), 3.00 to 3.50mm (group B), 3.51 to 4.00 mm (group C), and 4.00 to 4.50 mm (group D). All patients received thorough informed consent detailing individual benefits, risks and alternatives to surgery. In addition, each signed a consent form indicating their permission to publish their anonymized results. The study adhered to the tenants of the Helsinki Declaration and was approved by the local ethics committee. Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery.

**Table 3.3.** Patient demographics

| | Group A | Group B | Group C | Group D | P-value |
|---|---|---|---|---|---|
| Age (years) | 59.80±8.30 | 60.12±7.42 | 59.63±7.90 | 61.37±7.65 | 0.004 |
| Sex M/F (patients) | 8/14 | 10/12 | 11/10 | 10/15 | -- |
| Follow-up time (months) | 19.33±5.24 | 19.25±5.62 | 19.80±5.83 | 20.12±6.21 | 0.281 |
| Mean Astigmatism (D) | 0.79±0.10 | 0.76±0.24 | 0.77±0.45 | 0.82±0.10 | 0.342 |
| Mean CDVA LogMAR | 0.2±0.12 | 0.18±0.17 | 0.2±0.15 | 0.19±0.13 | 0.097 |
| Mean QOV Score (0-10) | 6.5±1.2 | 6.7±1.1 | 6.5±1.5 | 6.7±1.4 | 0.265 |
| M: Male; F: Female; D: Dioptres; CDVA: Corrected Distance Visual Acuity; QOV: Quality of Vision | | | | | |

### 3.3.5 Preoperative and Postoperative Examinations

Preoperatively, all patients had a full ophthalmic examination including uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) (4m logMAR, Early Treatment of Diabetic Retinopathy Study Chart 1 [ETDRS]), uncorrected near visual acuity (UNVA) and corrected near visual acuity (CNVA) at 40cm with Radner reading charts under a standard mesopic lighting condition, (Radner charts allow direct conversion i.e. 0.2 logMAR distance acuity is comparable to 0.2 logRAD reading acuity with high correlation at 40 cm to a logMAR equivalent for size of letters) and uncorrected intermediate visual acuity (UIVA) and corrected intermediate visual acuity (CIVA) at 70cm. Further examinations included keratometry, topography and auto refraction (OPD-Scan aberrometer (NIDEK Co. Ltd., Gamagori, Japan), subjective refraction, slit-lamp examination, Goldmann tonometry, dilated funduscopy and biometry (IOL Master, version 4.3, Carl Zeiss Meditec AG), and pupil diameter, angle kappa/p-dist with the Nidek OPD Scan II (NIDEK Co. Ltd. Gamagori, Japan).

The IOL Master was used to measure corneal curvature, anterior chamber depth, axial length and subsequent IOL calculation using the Hoffer Q formula for eyes with AL <22 mm and SKR/T formula for AL 22-25 mm and Haigis for AL >25 mm (A- constant of 118.2 for SRKT and a0 constant of 0.83, a1, a2 for Haigis). Emmetropia was the target in all cases. Postoperatively, patients were evaluated at 1 day, 1-month, 3 months, 6-months, 1-year, and 18-months. In addition to the above-mentioned examinations, UIVA, UNVA, distance corrected intermediate visual acuity (DCIVA) and distance corrected near visual acuity (DCNVA) were assessed looking for evidence of differences in their mean or in their level of variation through assessment of outlier differences. Posterior capsule opacification (PCO) was graded by an ophthalmologist as follows: 1=none, 2=mild (early development of PCO), 3 = moderate (increased PCO with early visual acuity changes not requiring secondary capsulotomy) and 4 = severe (PCO affecting vision and requiring neodymium: YAG laser capsulotomy).

### 3.3.6 Surgical technique

One experienced surgeon (J.E.M.) performed all surgeries. The steep axis was marked in all patients preoperatively at the slit-lamp. Sub-tenons or topical anaesthesia was carried out on all patients. A standard sutureless on-steep axis corneal phaco surgery (2.75 mm incision) was performed through a 5.0 mm anterior capsulorhexis in all patients without complication. After irrigation/aspiration of cortex the multifocal IOL mentioned above were implanted in all cases with recommended injector cartridge. All residual viscoelastic was removed prior to intracameral antibiotic injection (cefuroxime). Where on-axis surgery was not possible, a 2.75 mm supero-temporal corneal position was used to minimise induced astigmatism. Capsular tension ring (CTR) was used in all 180 eyes to benefit tilt and decentration. Postoperative topical therapy included 1 drop of ofloxacin 0.3% (Exocin) 4 times daily for two weeks, 1 drop of ketorolac trometamol 0.5% (Acular) 2 times daily for 1 month and 1 drop of dexamethasone 0.1% (Maxidex) 4 times daily for three weeks.

### 3.3.7 Pupil assessment

All pupil assessments using the NIDEK OPD-Scan (NIDEK Co Ltd, Gamagori, Japan) were performed in a single test room that had a constant ambient illumination of 0.63 lux. To standardise the postoperative pupil assessments, the ambient lighting was continuously monitored using a handheld Illuminometer light meter (Sekonic, Japan). Concurrently, before measuring the pupil size, the patient's orbital region illumination was recorded and maintained at 0.63 lux to have minimum discrepancy among patient groups. The minimum luminance the photometer could record was 0.63 lux.

### 3.3.8 Intraocular lens tilt and centration assessment

As the designs of multifocal IOLs have improved and become more sophisticated the need to understand and improve lens misalignment on optical performance has increased. Scheimpflug image processing techniques can assess the pupillary axis, IOL centre and pupil centre from the three-dimensional anterior segment image capture system. Validation of this techniques by de Castro *et al*. on a physical eye demonstrates that IOL decentration and tilt can be approximated within an accuracy of 0.228 mm for decentration and 0.243 degree for tilt, in comparison to 0.094 mm and 0.279 degree respectively using the Purkinje imaging apparatus (Rosales *et al.*, 2010). The Scheimpflug imaging system (Pentacam; Oculus, Wetzlar, Germany) was used to assess IOL decentration and tilt. Postoperative IOL decentration and tilt were carefully measured according to methodology applied by de Castro *et al*., which is as follows: The pupil centre was calculated by locating as the midpoint between the two visible pupil segments and the IOL centre was determined as the midpoint intersection of the two diameter lines from the anterior and posterior edges of the IOL. The reference axis was calculated as the line passing through the centre of the pupil, known as the pupillary axis. The IOL axis (L) is calculated as the line joining the centres of curvature of the anterior and posterior lens edges. These axes are referred to a vertical axis in each image. IOL decentration and tilt was calculated from the distance between the IOL centre and the pupillary axis. A scale of 0.02 mm in the lateral plane was used. Since there were no optical surfaces in the object, optical

distortion did not have any influence on the scale. The angles between these two axes are obtained to determine the IOL decentration. A CTR was used in all eyes. Eyes were examined at 6-months, 1-year and 18-months after IOL implantation to confirm both IOL clarity and tilt.

### 3.3.9 Questionnaire

For this study a validated QOV Questionnaire (McAlinden, Pesudovs and Moore, 2010) was used. The questionnaire was administered after six months, one year and eighteen months follow-up to assess for possible neural adaption. The patients were asked to rate their overall QOV separately for day and night from very poor (0), to excellent (10).

### 3.3.10 Statistical analysis

Data analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences, Version 22, Chicago, Illinois, USA.). The relationship between the pupil size and QOV was modelled using a linear regression model and the differences in QOV between pupil size groups were evaluated by analysis of variance (ANOVA). Normality was checked by the Shapiro-Wilk test and Q-Q plot test. To assess the contribution of pupil size to the QOV, a correlation analysis was performed. Differences were considered statistically significant when the P value was less than 0.05.

## 3.4 Results

All 90 patients had no intra-operative or postoperative complications at eighteen months follow-up.

### Quality of vision and pupil size

Statistically significant differences in postoperative QOV questionnaire score for six months, one year and eighteen months were found between the groups (P<0.001). A regression analysis was performed between the pupil diameter (photopic and mesopic) and the QOV (day and night) score to find out whether pupil size was a predictor for the QOV. At the six months postoperative assessment, QOV score correlated with the postoperative photopic pupil area with a $r^2$ =0.517; p<0.001 (Figure 3.2). The relationship between postoperative photopic pupil diameter with QOV score decreased slightly at one-year after operation assessment but was still significant at $r^2$ =0.480; p<0.001 (Figure 3.3) and the relation for QOV score at eighteen months was also significant at $r^2$ =0.472; p<0.001 (Figure 3.4). The regression analysis between mesopic pupil size and QOV night scores were: $r^2$ =.397; p<0.001 (six months postoperative) (Figure 3.5), $r^2$ =379; p<0.001 (1-year postoperative) (Figure 3.6) and $r^2$ =.360; p>0.001 (eighteen months postoperative) (Figure 3.7). The mean preoperative photopic and mesopic pupil size was 4.3±0.3mm and 5.6±1.4mm respectively, eighteen months postoperative both the photopic and mesopic pupil diameter decreased by 0.5mm and 0.7mm respectively (Table 3.4). There were statistically significant differences between the mean preoperative pupil size (photopic and mesopic) and eighteen months postoperative pupil size (photopic and mesopic) (P<0.001). The comparison between the mean QOV scores between groups showed a statistical difference at six months, one year and eighteen months postoperatively (Table 3.4). Group B, C and D with pupil size >2.99mm reported better mean QOV scores for day and night in comparison to group A.

**Figure 3.2.** A correlation analysis was performed between photopic pupil diameter and the QOV day score at six months after operation.

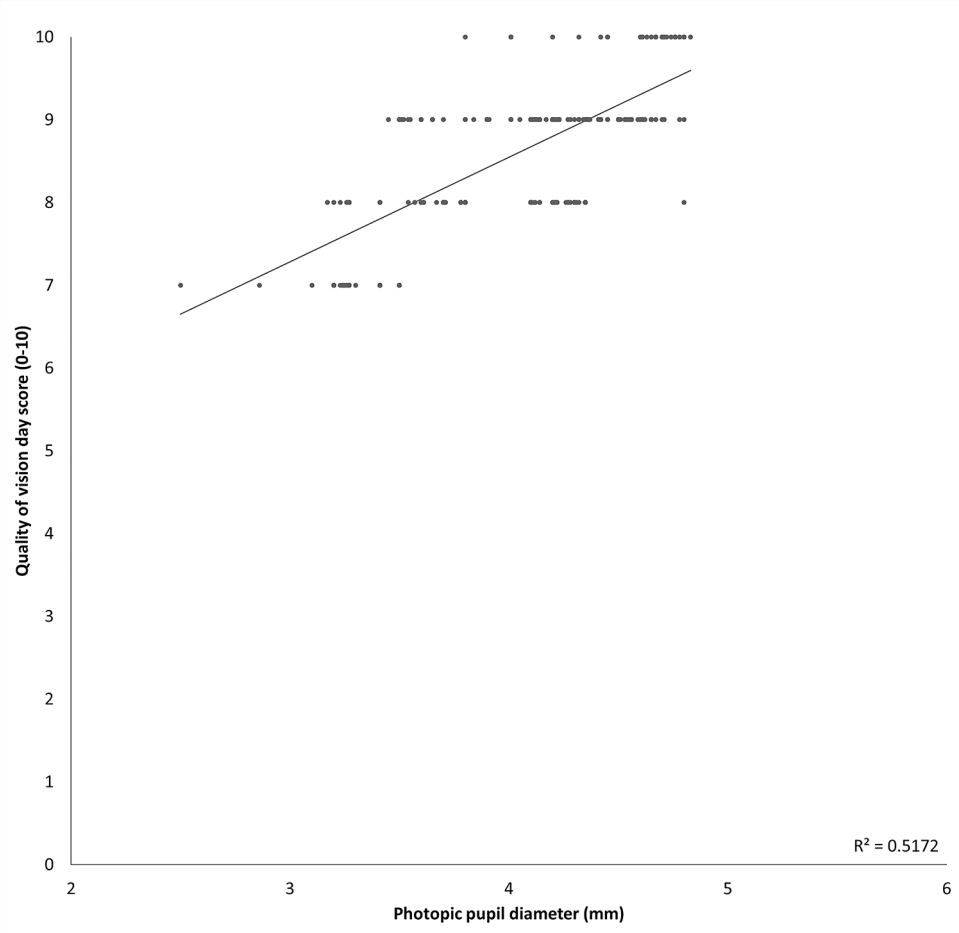


**Figure 3.3.** A correlation analysis was performed between photopic pupil diameter and the QOV day score at twelve months after operation.

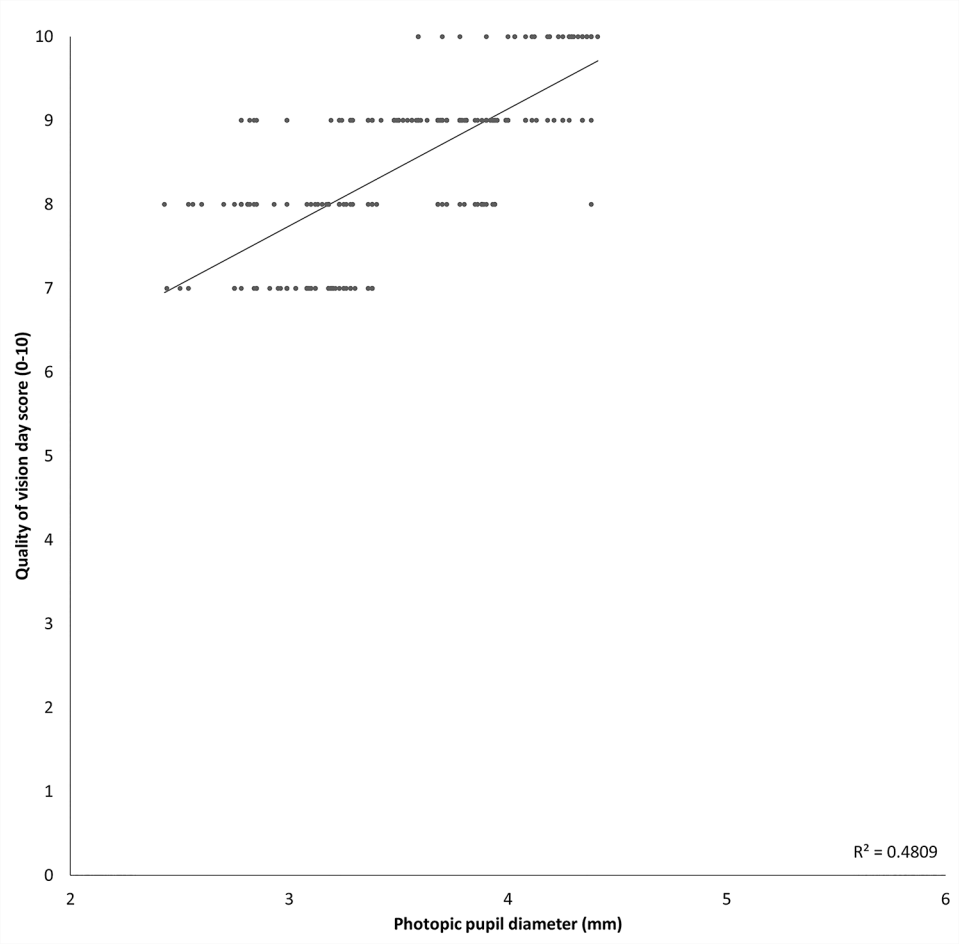


**Figure 3.4**. A correlation analysis was performed between photopic pupil diameter and the QOV day score at eighteen months after operation.

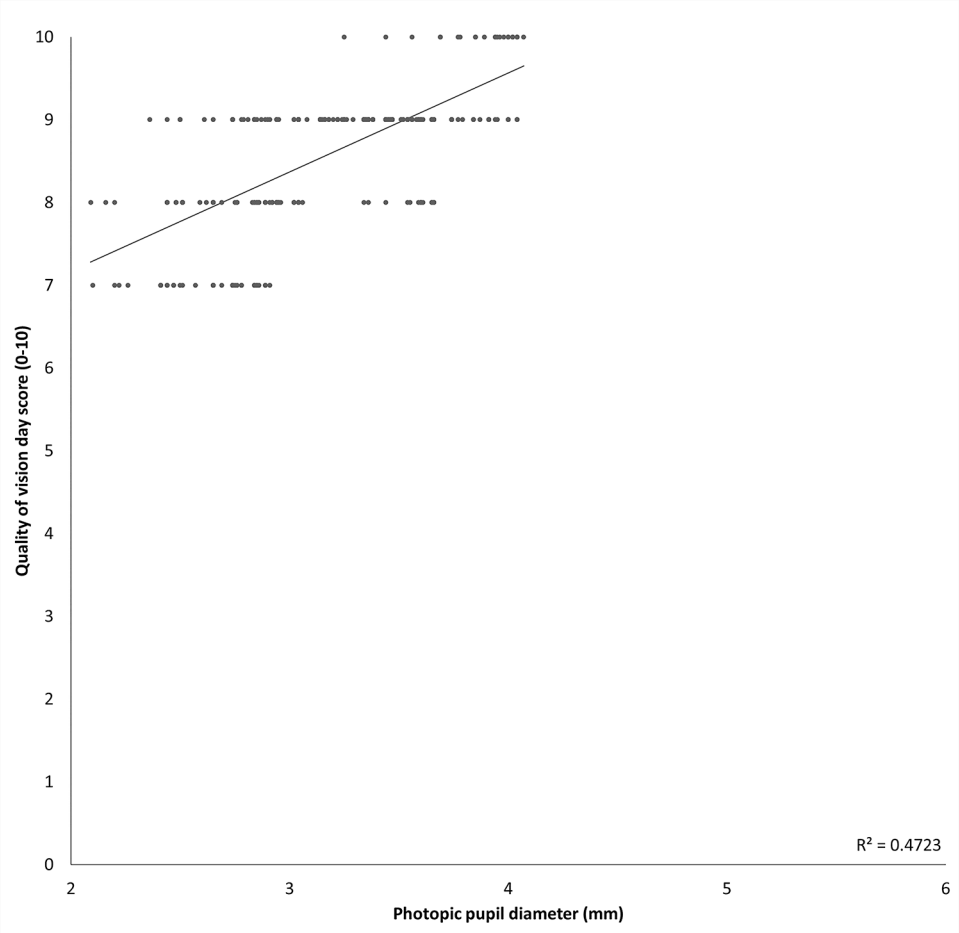


**Figure 3.5.** A correlation analysis was performed between mesopic pupil diameter and the QOV night score at six months after operation.

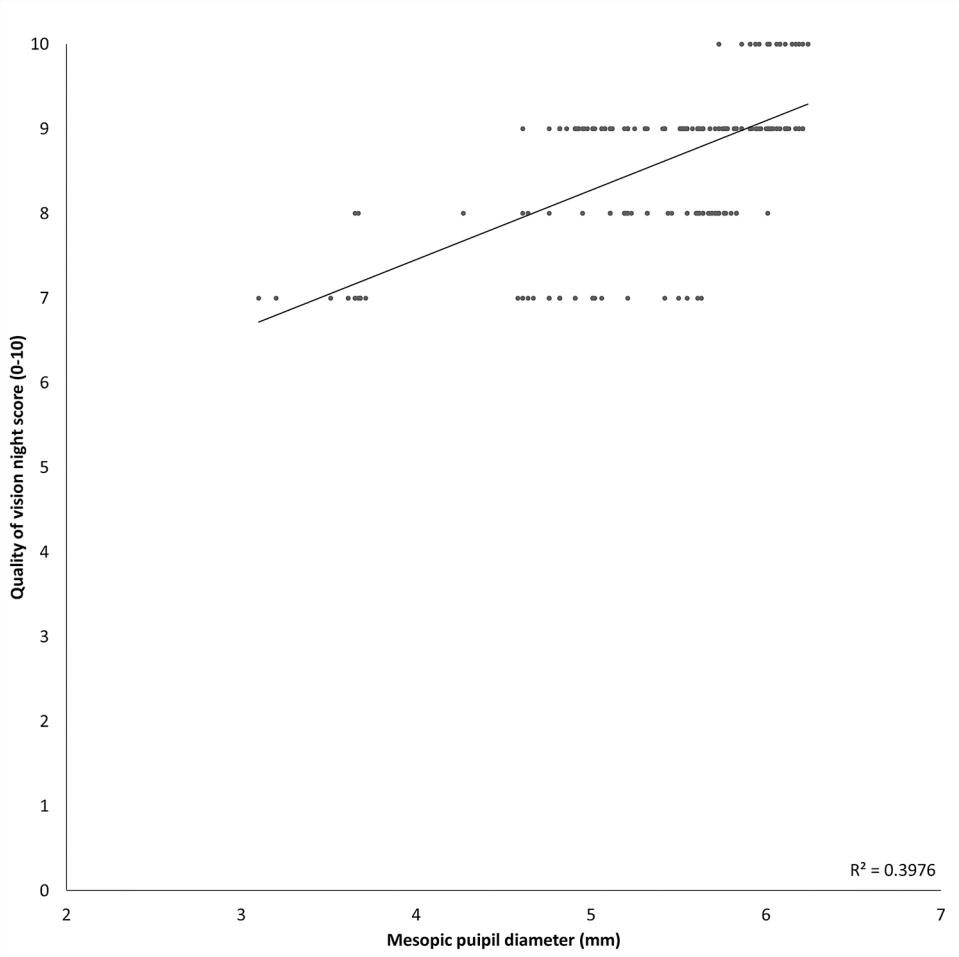


**Figure 3.6.** A correlation analysis was performed between mesopic pupil diameter and the QOV night score at twelve months after operation.

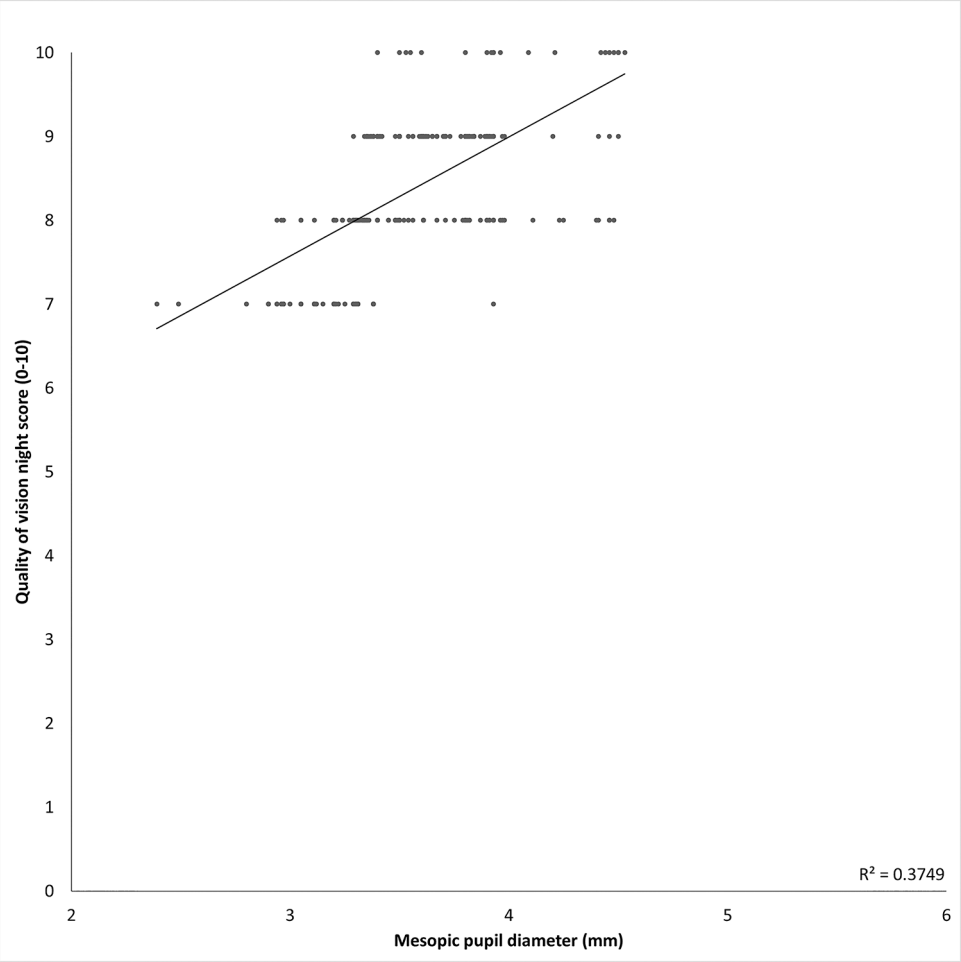


**Figure 3.7.** A correlation analysis was performed between mesopic pupil diameter and the QOV night score at eighteen months after operation.

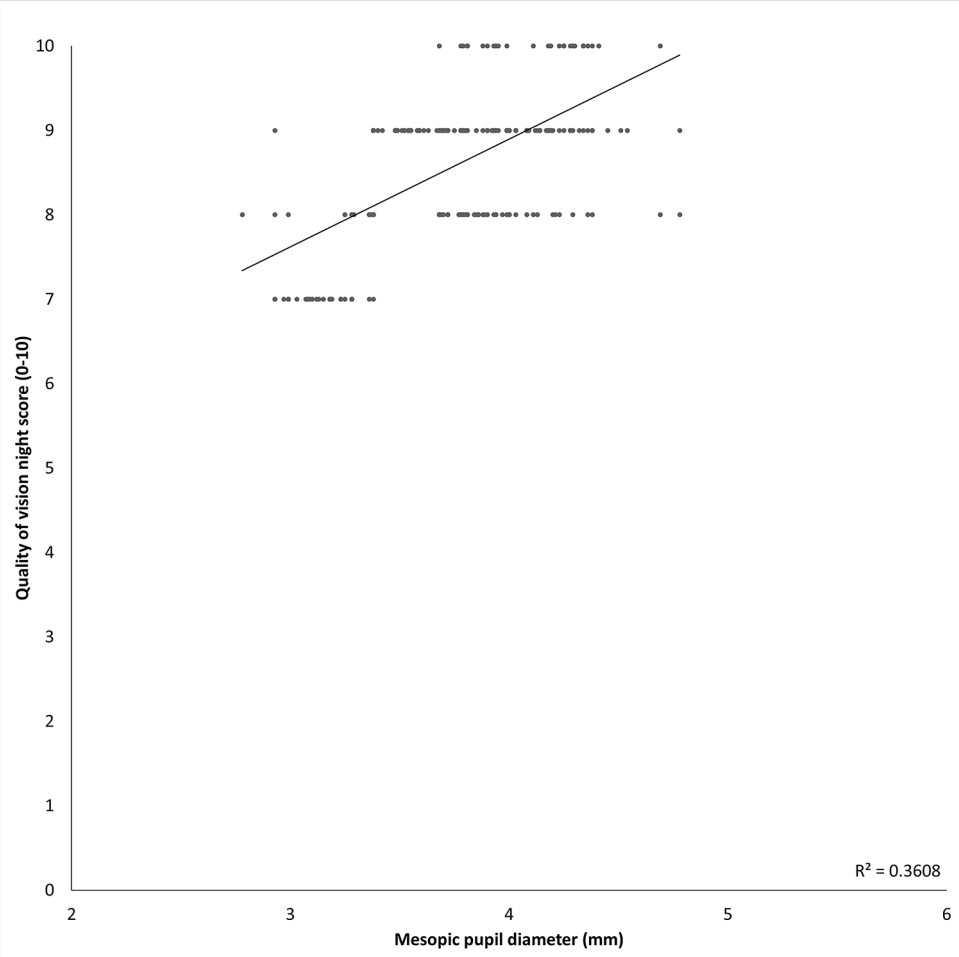



**Table 3.4.** Comparison of pupil diameter

| Photopic Pupil Size (mm) | | | |
|---|---|---|---|
| Preoperative | Postoperative 6 months | Postoperative 12 months | Postoperative 18 months |
| 4.3 ± 0.3§‖ | 4.2 ± 1.21‖ | 4.1 ± 1.05† | 3.8 ± 0.7 †‡§ |
| Mesopic Pupil Size (mm) | | | |
| Preoperative | Postoperative 6 months | Postoperative 12 months | Postoperative 18 months |
| 5.6 ± 1.4§‖ | 5.4 ± 1.63‖ | 4.9 ± 1.73 †‡ | 4.9 ± 1.2 †‡ |
| | | | |

mm: millimetre; n= 180 eyes *Statistically significant across groups †
Statistically significant change compared with preoperative
‡ Statistically significant change compared with 6-months postoperative
§ Statistically significant change compared with 12-months postoperative
|| Statistically significant change compared with 18-months postoperative

**Visual Acuity and Refraction**

Table 3.5 shows the between-group comparison of postoperative data. The mean at six months, one year and eighteen months postoperative ocular parameters, visual and refractive outcomes had no statistically significant differences. The mean UNVA was better in patients with larger pupil group (group B, C and D) postoperative as compared to patients with smaller pupils (group A). Figure 3.8, 3.9 and 3.10 shows 18-month postoperative cumulative monocular UDVA, UIVA, and UNVA visual outcomes comparison respectively. The safety plots in Figure 3.11 and Figure 3.12 show the accuracy of the attempted spherical equivalent (SE).

**Table 3.5.** Between-group comparison.

| Postoperative 6-month data. | | | | | |
|---|---|---|---|---|---|
| Parameter | Group A (2.50-2.99mm) | Group B (3.00-3.50mm) | Group C (3.51-4.00mm) | Group D (4.01-4.50mm) | P Value * |
| Sphere (D) | | | | | |
| Mean ± SD | 0.16±0.36 | 0.09±0.47 | 0.18±0.21 | 0.1±0.44 | 0.081 |
| Cylinder (D) | | | | | |
| Mean ± SD | 0.37±0.40 | 0.4±0.34 | 0.29±0.35 | 0.39±0.33 | 0.174 |
| logMAR UDVA (monocular) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Mean ± SD | -0.04 ±0.21 | -0.03 ± 0.10 | -0.03 ± 0.07 | -0.03± 0.09 | 0.132 |
| logMAR UIVA (monocular) | | | | | |
| Mean ± SD | 0.26 ± 0.2 | 0.25 ± 0.09 | 0.25 ± 0.3 | 0.24 ± 0.15 | 0.077 |
| logMAR UNVA (monocular) | | | | | |
| Mean ± SD | 0.09 ± 0.15 | 0.09 ± 0.11 | 0.08 ± 0.11 | 0.09 ± 0.10 | 0.952 |
| Angle Kappa (degree) | | | | | |
| Mean ± SD | 4.7 ± 0.8 | 4.3 ± 0.4 | 4.2 ± 0.9 | 4.2 ± 0.6 | 0.074 |
| QOV (0-10) | | | | | |
| Day | 7.7±0.4‡§ǁ | 8.5±0.3† | 8.7±0.7† | 8.6±0.5† | 0.029 * |
| Night | 7.0±1.6‡§ǁ | 7.5±1.7† | 7.6±1.5† | 7.6±0.8† | 0.015 * |
| Tilt (degree) | | | | | |
| Mean ± SD | 1.5° ± 0.50 | 1.5° ± 0.50 | 1.5°± 0.50 | 1.7°± 0.70 | 0.59 |
| Centration (mm) | | | | | |
| Mean ± SD | 0.20±0.05 | 0.25±0.05 | 0.25±0.05 | 0.15±0.05 | 0.24 |
| Postoperative 1-year data | | | | | |
| Sphere (D) | | | | | |
| Mean ± SD | 0.15±0.35 | 0.09±0.49 | 0.19±0.33 | 0.11±0.32 | 0.084 |
| Cylinder (D) | | | | | |
| Mean ± SD | 0.35+0.44 | 0.39±0.37 | 0.3±0.38 | 0.39±0.30 | 0.061 |

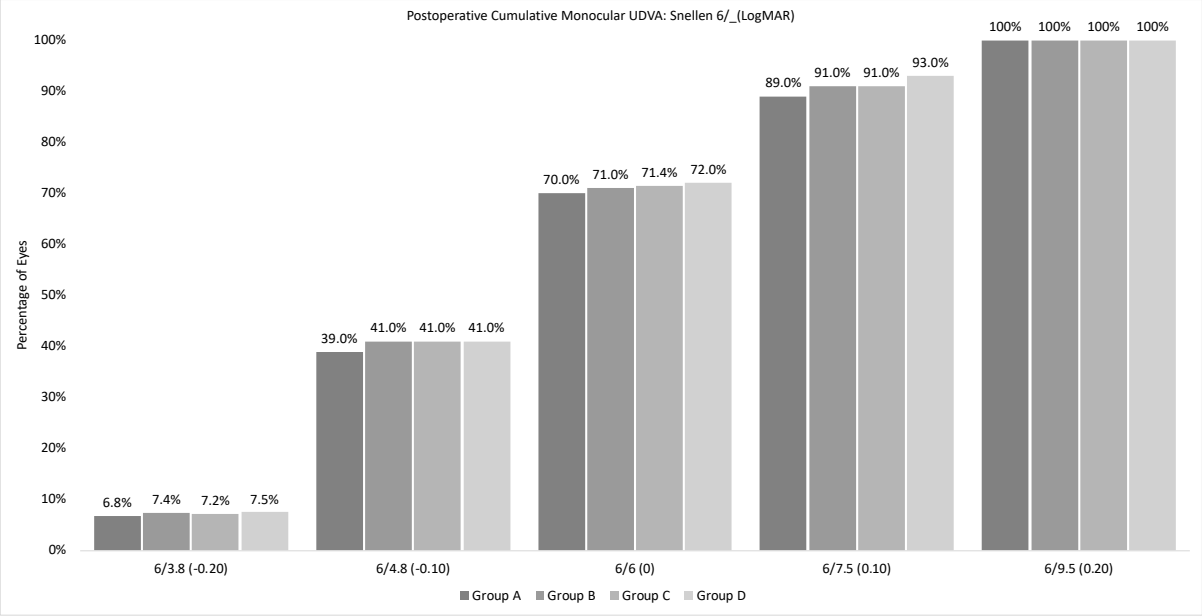
| | | | | | |
|---|---|---|---|---|---|
| logMAR UDVA (monocular) | | | | | |
| Mean ± SD | -0.04±0.03 | -0.03± 0.04 | -0.03 ± 0.15 | -0.03± 0.03 | 0.752 |
| logMAR UIVA (monocular) | | | | | |
| Mean ± SD | 0.27±0.10 | 0.24 ± 0.15 | 0.25 ± 0.10 | 0.24 ± 0.14 | 0.461 |
| logMAR UNVA (monocular) | | | | | |
| Mean ± SD | 0.09±0.12 | 0.08±0.15 | 0.08±0.25 | 0.08±0.12 | 0.952 |
| Angle Kappa | | | | | |
| Mean ± SD | 4.3±0.8 | 4.3±0.9 | 4.1±0.2 | 4.2±0.5 | 0.145 |
| QOV (0-10) | | | | | |
| Day | 7.5±0.7‡§ǁ | 8.6±0.5† | 8.7±0.5† | 8.7±0.4† | 0.041 * |
| Night | 7.2±0.3‡§ǁ | 7.7±1.2† | 7.7±0.5† | 7.9±1.1† | 0.028 * |
| Tilt (degree) | | | | | |
| Mean ± SD | 1.5°±0.50 | 1.5°±0.70 | 1.5°±0.60 | 1.5°±0.60 | 0.675 |
| Centration (mm) | | | | | |
| Mean ± SD | 0.20±0.05 | 0.25±0.05 | 0.35±0.05 | 0.25±0.05 | 0.091 |
| Postoperative 18-months data | | | | | |
| Sphere (D) | | | | | |
| Mean ± SD | 0.16±0.38 | 0.1±0.48 | 0.18±0.35 | 0.1±0.32 | 0.065 |
| Cylinder (D) | | | | | |
| Mean ± SD | 0.34±0.43 | 0.37±0.40 | 0.29±0.31 | 0.38±0.40 | 0.057 |

| | | | | | |
|---|---|---|---|---|---|
| logMAR UDVA (monocular) | | | | | |
| Mean ± SD | -0.04±0.12 | -0.04± 0.10 | -0.03 ± 0.09 | -0.03± 0.13 | 0.065 |
| logMAR UIVA (monocular) | | | | | |
| Mean ± SD | 0.27±0.13 | 0.25 ± 0.10 | 0.26 ± 0.12 | 0.25 ± 0.15 | 0.072 |
| logMAR UNVA (monocular) | | | | | |
| Mean ± SD | 0.10 ± 0.12 | 0.09 ± 0.12 | 0.08 ± 0.15 | 0.08 ± 0.10 | 0.729 |
| Angle Kappa | | | | | |
| Mean ± SD | 4.3 ± 0.9 | 4.4 ± 0.1 | 4.2 ± 0.3 | 4.3±0.7 | 0.29 |
| QOV (0-10) | | | | | |
| Day | 7.8 ± 0.5‡§‖ | 8.7 ±0.4† | 8.8 ± 0.7† | 8.7±0.6† | 0.034 * |
| Night | 7.2±0.10‡§‖ | 7.7±0.9† | 7.8±1.2† | 7.9±0.9† | 0.023 * |
| Tilt (degree) | | | | | |
| Mean ± SD | 1°±0.50 | 1.5°±0.60 | 1.5°±0.50 | 1.5°±0.60 | 0.621 |
| Centration (mm) | | | | | |
| Mean ± SD | 0.20±0.05 | 0.25±0.05 | 0.25±0.05 | 0.24±0.07 | 0.248 |

*Statistically significant across groups, P-value <0.05
† Statistically significant change compared with group A
‡ Statistically significant change compared with group B
§ Statistically significant change compared with group C

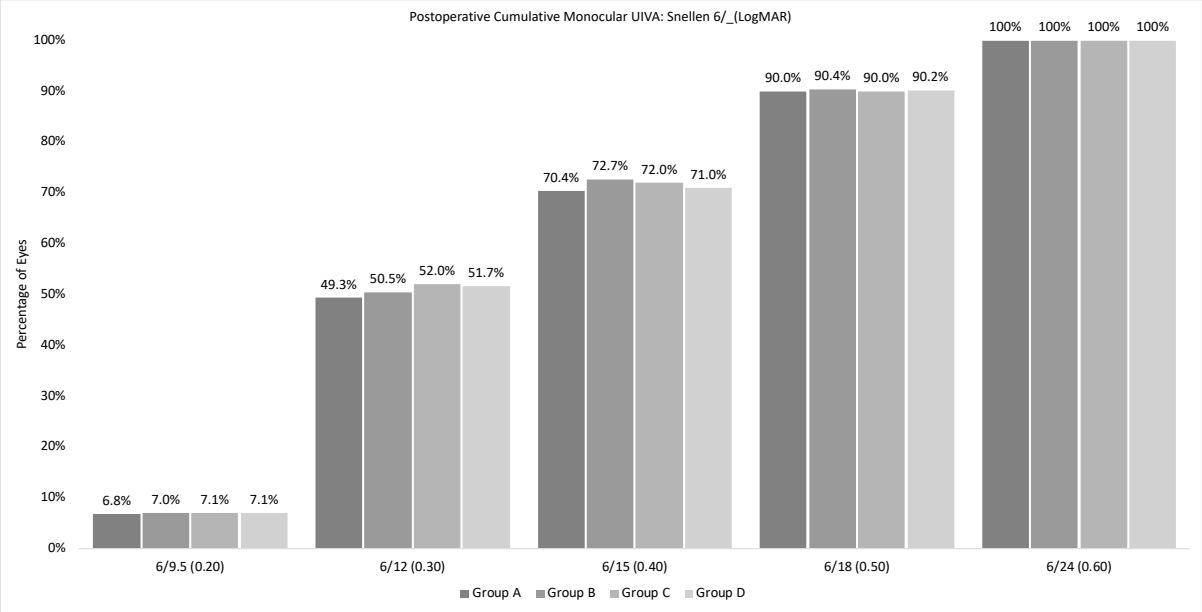
|| Statistically significant change compared with group D
UDVA: Unaided distance visual acuity; UIVA: Unaided intermediate visual acuity; UNVA: Unaided near visual acuity; SD: Standard deviation; mm: millimetre

**Figure 3.8.** Cumulative monocular UDVA comparison between groups at 18-month postoperative assessment.



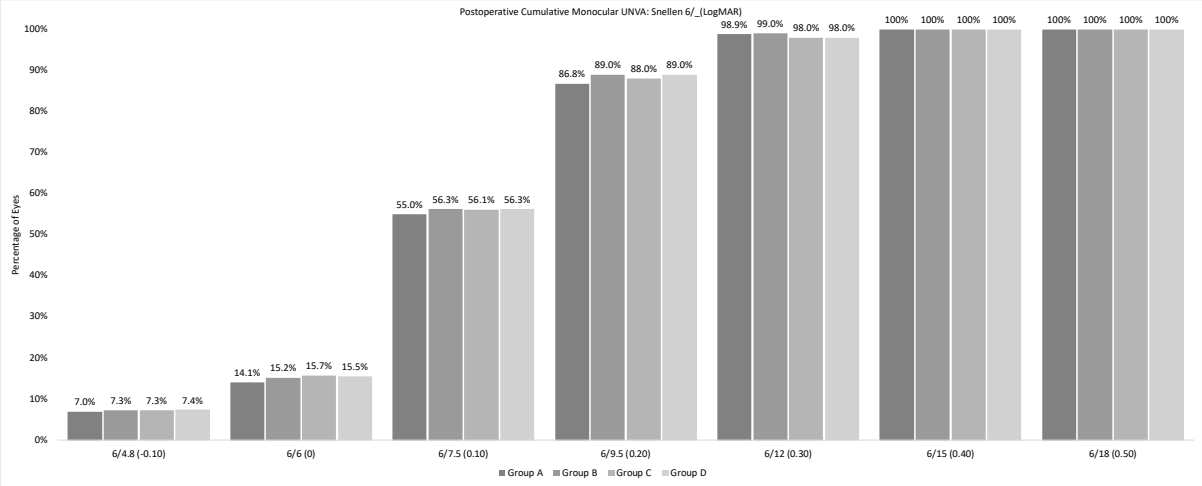

UDVA: uncorrected distance visual acuity.

**Figure 3.9.** Cumulative monocular UIVA comparison between groups at 18-month postoperative assessment.



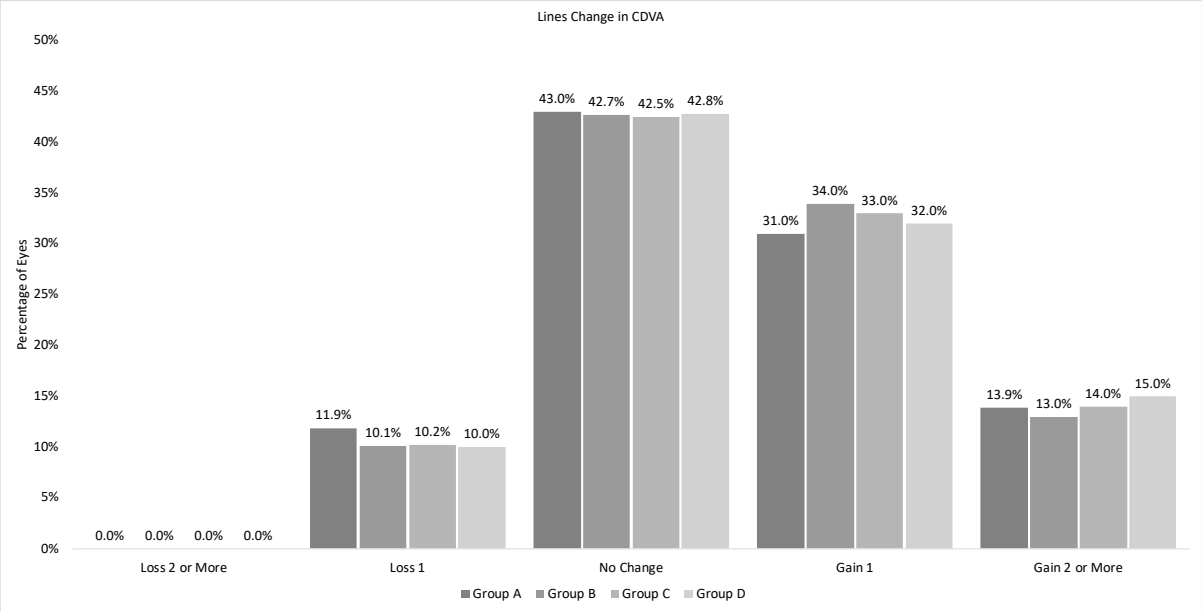

UIVA: uncorrected intermediate visual acuity.

**Figure 3.10.** Cumulative monocular UNVA comparison between groups at 18- month postoperative assessment.



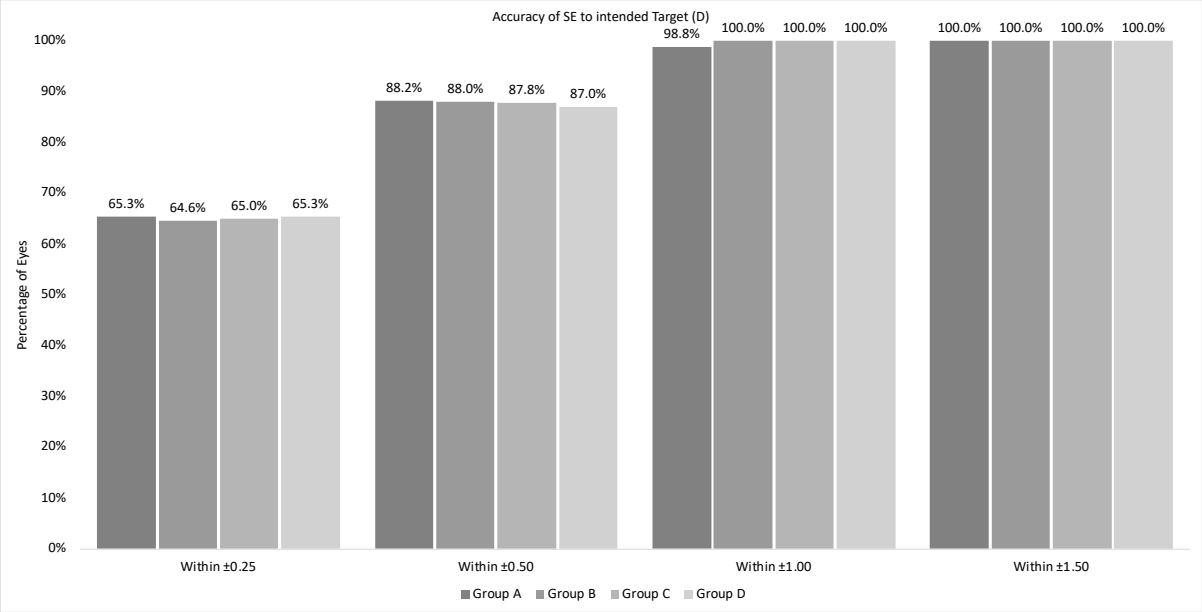

UNVA: uncorrected near visual acuity.

**Figure 2.11.** Monocular CDVA comparison between groups at 18-month postoperative assessment.




CDVA: corrected distance visual acuity.

**Figure 2.12.** Accuracy to the intended SE refraction comparison between groups at 18-month postoperative assessment.




SE: Spherical equivalence; D: dioptre.

## Efficacy

The mean preoperative UDVA was 0.67±0.09 logMAR and following eighteen months postoperatively it improved to -0.02±0.12 logMAR, -0.02±0.10 logMAR, -0.03±0.09 logMAR and -0.03±0.13 logMAR between group A, B, C and D respectively. Preoperatively, UIVA was 0.25 ± 0.01 logMAR and postoperatively at eighteen months it was 0.18±0.11 logMAR, 0.17±0.09 logMAR, 0.17±0.12 logMAR, and 0.16±0.10 logMAR respectively. The mean preoperative UNVA was 0.75 ± 0.25 logMAR and postoperatively it was 0.09±0.08 logMAR, 0.08±0.05 logMAR, 0.08±0.15 logMAR, and 0.07±0.15 logMAR respectively.

## Tilt and Centration

All IOLs retained complete clarity throughout the eighteen months follow-up as demonstrated after pupil dilation and direct slitlamp examination. Mean absolute lens

tilt between the groups was less than 2° ± 0.5 (SD), exceeding the standard for stability (≥90% of eyes with ≤5°). None of the lenses was repositioned during the study. There were also no statistical differences between the lens tilt (Table 3.5). Grossly decentred IOLs cases on dilated slit lamp biomicroscope examination and photographic analysis were excluded.

**Adverse Events and Posterior Capsule Assessments**

No serious complications (posterior capsule rupture, endophthalmitis, macular oedema or persistent raised intra-ocular pressure) occurred during the study. All 180 eyes (90 patients) were retrospectively assessed and categorised into the respective pupil size groups. At six months, one-year and eighteen months, a single experienced ophthalmologist examined all 180 eyes and confirmed no or mild PCO was present. Cases with PCO were excluded from this retrospective analysis.

**Visual Disturbances and Photopic Phenomena**

Table 3.6 shows the individual symptom responses found in each group. 'Glare' and 'Halos' were significantly different across the groups at 6-months postoperatively with group A experiencing the highest mean score for 'Glare' and 'Halos' in comparison to other groups. During one-year assessment only 'Glare' was found to be significantly different among the groups and group A once again had the highest mean 'Glare' score. At eighteen months assessment, none of the visual disturbances was significantly different across the groups, and the mean scores of all groups were all lower than the mean six months postoperative score.

**Table 3.6.** Between-group comparison of subjective responses postoperatively

| Postoperative 6-month |
|---|

| QoV questions for visual symptoms | Group A (2.50-2.99mm) | Group B (3.00-3.50mm) | Group C (3.51-4.00mm) | Group D (4.01-4.50mm) | P Value |
|---|---|---|---|---|---|
| How much does glare bother you? | 0.64 ± 0.73‡§ \|\| | 0.36 ± 0.49 † | 0.38 ± 0.50 † | 0.28 ± 0.46 † | 0.039* |
| How much do the halos bother you? | 0.55 ± 0.67‡§ \|\| | 0.32 ± 0.60† | 0.38 ± 0.50 † | 0.36 ± 0.49 † | 0.023* |
| How much do the starbursts bother you? | 0.50 ± 0.60 | 0.45 ± 0.60 | 0.33 ± 0.48 | 0.32 ± 0.48 † | 0.835 |
| How much does hazy vision bother you? | 0.27 ± 0.55 | 0.25 ± 0.51 | 0.33 ± 0.58 | 0.28 ± 0.54 | 0.286 |
| How much does blurred vision bother you? | 0.32 ± 0.57 | 0.32 ± 0.57 | 0.29 ± 0.56 | 0.24 ± 0.52 | 0.557 |
| How much does distortion bother you? | 0.15 ± 0.22 | 0.05 ± 0.21 | 0.14 ± 0.36 | 0.12 ± 0.33 | 0.253 |
| How much do double images bother you? | 0.18 ± 0.39 | 0.18 ± 0.39 | 0.10 ± 0.30 | 0.08 ± 0.28† | 0.211 |
| Postoperative 1-year | | | | | |
| How much does glare bother you? | 0.47± 0.50\|\|‡§ | 0.22 ± 0.48† | 0.23 ± 0.48† | 0.20 ± 0.41† | 0.042* |

| | | | | | |
|---|---|---|---|---|---|
| How much do the halos bother you? | 0.36 ± 0.58 | 0.30 ± 0.50 | 0.29 ± 0.46 | 0.20 ±0.41 | 0.521 |
| How much do the starbursts bother you? | 0.45 ± 0.57 | 0.32 ± 0.48 | 0.33 ± 0.48 | 0.28 ± 0.46 | 0.311 |
| How much does hazy vision bother you? | 0.23 ± 0.53 | 0.23 ± 0.53 | 0.29 ± 0.56 | 0.24 ± 0.52 | 0.152 |
| How much does blurred vision bother you? | 0.27 ± 0.50 | 0.25 ± 0.55 | 0.22 ± 0.54 | 0.24 ± 0.52 | 0.647 |
| How much does distortion bother you? | 0.18 ± 0.08 | 0.00 ± 0.20 | 0.05 ± 0.22 | 0.00 ± 0.00 | 0.402 |
| How much do double images bother you? | 0.09 ± 0.29 | 0.14 ± 0.35 | 0.10 ±0.30 | 0.28 ± 0.08 | 0.233 |
| Postoperative 18-months | | | | | |
| How much does glare bother you? | 0.27± 0.46 | 0.23 ± 0.43 | 0.24 ± 0.44 | 0.16 ± 0.37 | 0.138 |
| How much do the halos bother you? | 0.27± 0.55 | 0.24 ±0.39 | 0.19 ± 0.40 | 0.16 ± 0.37 | 0.291 |
| How much do the starbursts bother you? | 0.35±0.47‖ | 0.32 ± 0.48 | 0.14 ± 0.36 | 0.16± 0.37† | 0.623 |

| | | | | | |
|---|---|---|---|---|---|
| How much does hazy vision bother you? | 0.26±0.55‖ | 0.22 ± 0.43 | 0.24 ± 0.44 | 0.12± 0.33† | 0.541 |
| How much does blurred vision bother you? | 0.23 ±0.53 | 0.18 ± 0.39 | 0.19 ± 0.40 | 0.24± 0.52 | 0.642 |
| How much does distortion bother you? | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.05 ± 0.25 | 0.04 ±0.20 | 0.376 |
| How much do double images bother you? | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.10 ± 0.30 | 0.08 ±0.28 | 0.753 |
| *Statistically significant across groups, P-value <0.05 | | | | | |
| † Statistically significant change compared with group A | | | | | |
| ‡ Statistically significant change compared with group B | | | | | |
| § Statistically significant change compared with group C | | | | | |
| ‖ Statistically significant change compared with group D | | | | | |
| Grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very | | | | | |

**Patient Satisfaction**

Table 3.7 shows the key questions related to the visual performance from a computer-based questionnaire 18-months postoperatively. The number of patients participating was 90. The results show high patient satisfaction with 0 (0%) being dissatisfied or very dissatisfied. Of the 90 patients, 81 (90%) reported they were very satisfied and 9 (10%) satisfied with the outcome of the procedure. Ninety-six percent of patients stated that they would choose the procedure again and 98% said that they would recommend the procedure.

**Table 3.7.** Postoperative SBL-3 IOL patient survey at 18-months

| | Group A | Group B | Group C | Group D | Total | Percentage |
|---|---|---|---|---|---|---|
| How is your vision after the procedure? | | | | | | |
| Very satisfied | 15 | 20 | 21 | 25 | 81 | 90 |
| Satisfied | 7 | 2 | 0 | 0 | 9 | 10 |
| Dissatisfied | 0 | 0 | 0 | 0 | 0 | 0 |
| Very Dissatisfied | 0 | 0 | 0 | 0 | 0 | 0 |
| Would you choose this procedure again? | | | | | | |
| Yes | 21 | 20 | 21 | 24 | 86 | 96 |
| Maybe | 1 | 2 | 0 | 1 | 4 | 4 |
| No | 0 | 0 | 0 | 0 | 0 | 0 |
| Would recommend the procedure | | | | | | |
| Yes | 21 | 22 | 21 | 24 | 88 | 98 |
| Maybe | 1 | 0 | 0 | 1 | 2 | 2 |
| No | 0 | 0 | | 0 | 0 | 0 |
| n=90 patients | | | | | | |

### 3.5 Discussion

The use of rotationally asymmetric multifocal IOLs to achieve pseudo-accommodation is a popular surgical option to improve postoperative visual performance and spectacle independence. Although several studies (Venter *et al.*, 2014; de Wit *et al.*, 2015; Pazo *et al.*, 2016) have reported clinical outcomes following rotationally asymmetric

multifocal IOL implantation there is a paucity of literature comparing the subjective optical performance of these IOLs in daily routines, such as driving and shopping in brightly lit rooms.

In addition to postoperative unaided VA, the aim of multifocal IOL implantation has been to improve quality of life, through better contrast sensitivity and night vision (de Wit *et al.*, 2015). The SBL-3 multifocal IOL is a relatively new asymmetric IOL and a case series of bilateral implantation on 53 eyes published by Venter et al. (2014) reported a good range of visual acuity retaining intermediate vision with minimal dysphotopsias.

Lens tilt and decentration play an essential role in multifocal IOLs QOV postoperatively and has been found to significantly decrease retinal image quality when more than 5 degrees (Gil-Cazorla *et al.*, 2016). In our study, tilt in all groups was found to be within 2 degrees, and the difference among the groups was not significant (>0.05). This relatively low level of tilt and decentration can also be attributed to the better haptic design of the IOL and the use of CTR and in all study eyes. Therefore, we can safely state that the QOV among groups was not affected by postoperative IOL tilt and decentration.

Assessment of pupil (photopic and mesopic) diameter and pupil shift (Porter *et al.*, 2006) has become an integral part of preoperative patient suitability evaluation criteria for refractive surgery (Koch *et al.*, 1996; Kamiya, 2014). The varying designs of multifocal IOL along with pupil size has proven to have a considerable effect on the objective and subjective vision of the patient (Hayashi *et al.*, 2001; De Vries and Nuijts, 2013). Ageing, in general, has been documented to have an impact on pupil size (Birren, Casperson and Botwinick, 1950; Hayashi *et al.*, 2001). The data from this study showed a decrease in the mean photopic and mesopic pupil size as time progressed. Although, the pupil size data were limited to Caucasian eyes there is no conclusive evidence regarding differences between races. However, Koch *et al*. (1996) did find that brown iris had larger pupil size in comparison to other iris colours. The mean preoperative photopic and mesopic pupil diameter in our study decreased at eighteen months by 0.5mm and 0.7mm respectively. Studies have suggested that the decrease in pupil size after cataract surgery could be due to the release of

neuropeptides (Miyake *et al.*, 1978; Kamiya, 2014). However, in our study, we did not observe a significant early postoperative reduction in pupil size. The change in pupil size overtime is crucial in understanding postoperative visual outcome (Van Der Linden *et al.*, 2013; McNeely *et al.*, 2016; Pazo *et al.*, 2016) in a long-term prospective, as significant changes in pupil size after IOL implantation has a tendency to impact the subjective and objective QOV.

In this study a curious but consistent finding was that among all the groups, group A (2.5 to 2.99mm) experienced reduced subjective QOV scores but overall had similar unaided distance VA after surgery as measured in clinic lighting conditions (Table 3). Conventional wisdom would suggest that patients with good visual acuity after surgery would also likely experience better subjective visual outcomes and report a higher level of visual satisfaction and QOV scores. However, in the findings from this study it was found that group A had a lower mean QOV when compared to other groups (Table 3.5). Even though all the groups provided equivocal and excellent distance, intermediate and near vision, however their subjective scores were significantly different. These findings are congruent with earlier reports that variations in normal pupil size have little to no effect upon the VA in patients with asymmetrical multifocal IOLs (Venter *et al.*, 2014). The overall objectively measured UDVA, UIVA and UNVA in this study demonstrated significant improvements between pre and postoperative periods and this improvement was found across the groups (Table 3). The reason for either groups performing similarly well during VA tests may possibly be that under controlled 'office room' lighting conditions (Watson and Yellott, 2012) the design of the IOL allows both the principal refractive foci to lie on the central axis and not on diffractive concentric constructive interference for a clear image at a given focal length (Choi and Schwiegerling, 2008). However, the subjective QOV may have been affected by pupil miosis that prevents sufficient incident light to expose the central axis of the IOL, thereby only partial exposure of the distance or near section of these asymmetrical multifocal IOL. Therefore, the energy light distribution to distance focus and near focus seems to have an impact upon the QOV experienced by the patients. Additionally, we also found that the correlation ($r^2$ value) between pupil size and QOV decreases over time, this may be due to possible neuroadaptation after IOL implantation. While comparing the $r^2$ (correlation) value of photopic pupil and mesopic pupil, mesopic pupil size had a weaker relation with the QOV as compared to photopic

pupil size. This may be due to increased dysphotopsias at night increased by the effect of larger pupils (Table 3.6 and Table 3.7).

A case report in press by Pazo *et al*. (2016) reported that by increasing the distance section of an asymmetric multifocal IOL within a photopic pupil resulted in improved subjective and objective visual outcome. This highlights the importance of SBL-3 IOL centration and pupil area (Montés-Micó *et al.*, 2004; Kawamorita and Uozato, 2005a; Alfonso *et al.*, 2007; Sheppard *et al.*, 2013) in attaining good QOV. Pre-operative prediction of the centration of any multifocal IOL with respect to the physiological pupil centre can be difficult to determine exactly. As this is generally dictated by the position of capsular bag periphery (Alfonso *et al.*, 2007) and during surgery the only reference a surgeon has is the pharmacologically dilated pupil, whose centre can be quite different to the photopic pupil centre (Pazo *et al.*, 2016).

A recent literature search shows no published data on the impact of near or distance segment exposed within a photopic/small pupil in a rotationally asymmetric multifocal IOL. Studies on the near segment of Mplus (Lentis) asymmetric IOLs by de Wit *et al*. (2015) and Song *et al*. (2016) have only focused on the placement of the IOL and its resulting VA. The specific assessment of percentage or area of near and distance segment in a rotationally asymmetrical multifocal IOL especially within a small or photopic pupil has yet to be explored. Anecdotal evidence for patients experiencing mild to moderate blurred, glare and hazy vision while driving at night and in brightly lit rooms coincide with the fact that pupil constriction can occur while driving at night with incoming headlights or while shopping in brightly lit supermarkets. Although this study has not completely addressed the relationship between the pupil size and the surface area of near and distance segments exposed to incident light. However, our initial findings suggest: smaller photopic pupils (Group A; 2.50-2.99 mm) have a tendency to affect the postoperative QOV in asymmetric multifocal IOLs during miosis with no alterations in VA (Table 3.5). Our study will be extended to further assess the relationship between pupil and the area of asymmetrical multifocal IOL segment exposed by the incident light entering through the mesopic and photopic pupil.

All groups reported a low incidence of visual symptoms. However, Group A was the most affected by each of the questioned symptoms, except for ‘double image’ at six

months postoperative assessment. However, these symptoms in all groups subsided at one year and eighteen months postoperative assessment, suggesting a neuroadaptive effect. However, group A had a greater mean score in comparison to other groups and especially with group D suggestion that pupil size has an impact upon visual symptoms in asymmetric multifocal IOL.

It is well documented that decentration of multifocal IOL can lead to decreased VA and decreased QOV for the patient (Pazo *et al.*, 2016). The findings of IOL centration and tilt in our study show all eyes had well centred IOL, with <0.5 mm of mean decentration and the mean tilt was of less that 3 degrees, a CTR was also used in all eyes and no significant capsular contraction was found between one and eighteen months; nor was there any evidence of IOL rotation or movement indicating that small photopic pupil size is the most probable reason for the reduced postoperative QOV scores. Kawamorita & Uozato (2005) reported that in AMO Array multifocal refractive IOL, pupil size <4.5 mm was not able to achieve useful near VA. However, in asymmetric multifocal IOLs, VA with a small photopic pupil (Group A) was at par with large photopic pupil (Group B, C and D) but the subjective QOV was lower in group A. One benefit of this study is the follow-up of eighteen months which demonstrates a possible neuroadaptive effect with a general improvement in QOV overall groups with time. However, despite this, the deleterious impact of smaller pupil size is still retained even at eighteen months. Future investigations of the visual performance of multifocal IOL patients will include contrast sensitivity and optical aberrations to verify and validate the neuroadaptation phenomenon. However, one of the limitations to this study is that the groups were not gender matched.

### 3.6 Conclusion

Postoperative pupil diameter in rotationally asymmetric multifocal IOLs demonstrates significant subjective effects upon the QOV under miosis. Pupil size was shown to significantly decrease in size from its preoperative level at eighteen months after surgery. It is key to ensure that both the near and distance sections of asymmetric multifocal IOL are proportionally exposed under photopic pupil conditions. Since

asymmetric multifocal IOLs are not circular and nor is the capsular bag. The most effective method of ensuring proportionate exposure of near and distance sections is to ensure that the postoperative photopic pupil size of >2.99 mm for SBL-3 asymmetric multifocal IOL implantation.

### 3.7 Summary

This chapter showed that in rotationally asymmetric multifocal IOL is subjectively affected by decreasing photopic pupil size. The asymmetrical design makes this multifocal IOL more suitable for postoperative patients with a photopic pupil diameter greater than 2.99 mm. Chapter 4 will investigate the effect of pupil centroid shift upon the QOV in asymmetric multifocal IOLs.

# CHAPTER 4: THE IMPACT OF PUPIL CENTROID SHIFT UPON THE QUALITY OF VISION IN PATIENTS IMPLANTED ASYMMETRICAL MULTIFOCAL INTRAOCULAR LENS

## 4.1 Introduction

Locating the centre of the pupil is important for laser refractive treatment (Camellin, Gambino and Casaro, 2005) and multifocal IOL implantation (Pazo *et al.*, 2016). However, pupil dilatation is not concentric and therefore its geometric centre alters under various lighting conditions (Camellin, Gambino and Casaro, 2005). Pupil assessment tools such as the Aladdin (Topcon, Tokyo, Japan) (Mandal *et al.*, 2014) and OPD-Scan II (NIDEK Co Ltd, Gamagori, Japan) allows the dynamic assessment and graphical representation of pupil centroid shift. An off centred laser optical zone can lead to patient dissatisfaction due to induced aberrations and glare while a decentred multifocal IOLs (Fay, Trokel and Myers, 1992; Pazo *et al.*, 2016) can result in reduced QOV. Additionally, it is important to accurately define the pupil diameter during preoperative assessment to enable the surgeon to predetermine the optical effects of a multifocal IOL (Sobaci *et al*. 2007; Pazo *et al*. 2017).

## 4.2 Pupil centroid shift

Several studies have examined the shift of centration of a pupil when subjected to varying lighting conditions. Walsh *et al*. used photographic methodology to assess the change in pupil centration between light-adapted, dark-adapted, and pharmacologically dilated pupil conditions (Walsh, 1988). In this study 39 (78 eyes) participants were found to have an average change of 0.19 mm and the direction of the pupil centroid shift was superior nasal during pupil constriction. Wilson *et al*. using video recording methodology with eight participants found a larger centroid shift of up to 0.59 mm and the direction of the shift varied in all participants (Wilson and Campbell 1992). This contrast in the direction of pupil shift between studies may have been due to the fact that Wilson and Campbell (1992) used achromatic axis of the eye for

reference as compared to limbus centre reference by Walsh (1988). Therefore, an accurate comparison of direction of pupil shit cannot be ascertained by these two studies. Wyatt (1995) used a modified slit lamp biomicroscope to determine the change in pupil centration in natural dilated pupil in 23 participants and documented that the pupil had a tendency to move superior and nasally during constriction, these findings were similar to Walsh *et al*. with an average movement of approximately 0.1 mm. However, these studies did not investigate factors such as refractive status or age.

### 4.3 Evaluation of pupil centroid shift using OPD-Scan II

The OPD Scan II (NIDEK Co Ltd, Gamagori, Japan) aberrometer/corneal topographer workstation which is has a touch screen user interface which provides autorefractometry, keratometry, angle kappa and pupillometry assessments. It plots sixteen different maps which displays information about the patient's corneal shape, wavefront, internal aberrations and visual quality. The software in the workstation can also assist in the management of KC, cataract surgery and refractive laser surgery. The measurement range of the OPD Scan II (NIDEK Co Ltd, Gamagori, Japan) is -20.00 to +22.00 dioptres, 0 to ± 22.00 cylinder and 0 to 180° axis, and a minimum measurable pupil size of 2.6 mm. All of these assessments can be obtained in one particular session, therefore all of the data gathered can be referenced to each other. It uses the principle of dynamic skiascopy wavefront sensor. As a serial, double-pass aberrometer, an infrared light slit and photodetectors are located on a revolving wheel that rotates along a fixed axis across the pupil (MacRae and Fujieda, 2000). As the incident beam moves along a specific pupillary perimeter, it results in a reflected beam that travels in the same or reverse direction. When the wheel revolves, the instrument assesses the time delay for light to peak at each photodiode after passing a beam splitter (Jonathan D Solomon, 2010). The device then calculates the optical pathway difference and derives the wavefront error by comparing the results with the theoretical reference time and creates a refractive map, wavefront profile and angle kappa coordinates (Buscemi, 2002; Cervio *et al.*, 2007). Pupil centroid shift refers to a shift in pupil centre between photopic and low mesopic pupil states. The OPD Scan II

(NIDEK Co Ltd, Gamagori, Japan) can measure pupil shift under low light mesopic (0.06 lux) and photopic (60 lux) illumination condition. The pupil size and shift are automatically calculated with OPD Scan software. The OPD Scan II has automated check of measurement quality, and alignment procedures that can be verified manually (Rozema, Van Dyck and Tassignon, 2005).

### 4.4 Evaluation of intraocular lens centration and pupil shift using digital overlay technique

Optimal visual outcome after multifocal IOL implantation requires precise IOL alignment and centration within the photopic pupil (Pazo *et al.*, 2016). In addition to VA, refraction and keratometry, various studies generally assess IOL rotation and positioning subjectively (Viestenz, Seitz and Langenbucher, 2005) with the aid of slitlamp biomicroscope eyepiece graticule (Ruhswurm *et al.*, 2000) or eyepiece protractor (De Silva, Ramkissoon and Bloom, 2006). These methodologies of assessing the IOL with the capsular bag rely on the participant maintaining a steady head posture during the assessment and the assumption that in all intervals of assessment the participant has the same head posture as before. This technique has an estimation approximation of 1- 5 degrees. Digital image analysis can assess the location of the IOL. This methodology has been used by several studies along with generic (Nguyen and Miller, 2000; Goto *et al.*, 2002; Becker, Auffarth and Volcker, 2004) or custom image analysis software (Bender *et al.*, 2004). A six month postoperative photographic analysis of rotational stability of toric IOL performed by Viestenz *et al*.(2005) revealed that there was an average of 2.5 degrees of rotation between visits; patients with greater rotation also had worse VA. The limitations to this study and methodology were head rotation, position of fixation light and error induced due to mounting of camera. These limitations can be alleviated by using an integrated slitlamp bio-microscope camera that allows visualisation of the iris, bulbar conjunctiva and retro-illumination with its external light source and slit beam. Since accurate overlay of two or more digital images is essential in assess the movement of the IOL and/or pupil; Viestenz *et al*. (2005) recommended the land-marking the image with the use of conjunctival vessels, Axenfeld loops, or iris structure as references to

account for the intrinsic rotation of the IOL. While using this methodology Weinand *et al*. (2007) found that only 17 out of the 40 eyes could be analysed due to insufficient dilatation of the pupil that resulted in poor visualisation of the IOL. Patel *et al*. (1999) used preoperative corneal ink-marking at 6 o' clock position to compensate for head and eye rotation and found that the intra-observer variability was from 2.3 to 3.1 degrees. Shah *et al*. (2009) estimated the IOLs centration with a rectangle overlay on the visualised IOL and was documented to have a precision of 0.1 degrees. This study also used a single prominent episcleral vessel line joining the centre of the IOL to compensate for the possible movement of the eye and head of the participant. Intraocular lens positioning and centration has been assessed by image analysis in which the boundary for IOL is marked along with the limbus and the centres of the IOL optical disc and limbus centres are compared (Becker, Auffarth and Volcker, 2004; Bender *et al.*, 2004; Tassignon, 2007) and the repeatability of the analysis of these objective retro-illuminated images at different postoperative periods of the IOL was found to be a sensitive assessment of IOL stability, rotation and centration (Wolffsohn and Buckhurst, 2010).

### 4.5 Pupil centroid shift and multifocal intraocular lens

The previous chapter demonstrated that pupil size influences the QOV in asymmetric multifocal IOLs (Pazo *et al*, 2017. in press). As the pupil dilates and constricts in an asymmetric manner the geometric centre of the pupil shifts (Moller, Buchholz and Huebscher, 2000; Wang *et al.*, 2016). Although there have been significant improvements in multifocal design and material, pupillary influence is still an important preoperative factor to consider. Sobachi *et al*. examined 55 patients with unilateral pseudophakic (study group) age and gender matched patients with bilateral cataracts (control group) using the OPD Scan (Sobaci *et al.*, 2007). The study reported that the differences in pupil shift between pseudophakic (0.11± 0.08 mm) and phakic (0.12 ± 0.10 mm) eyes were not statistically significant in the study group. In the control group, differences in pupil size were not statistically significant. Sobaci *et al*. (2007) concluded that uncomplicated in-the-bag AcrySof MA30BA IOL (Alcon Laboratories Inc.) implantation has no influence on pupil size and shift as the pupil centroid shift was not

significantly large. Sobaci *et al*. (2007) also found a mean 0.11-mm pupil centroid shift in the infero-temporal direction. Asymmetric multifocal IOL implanted eyes can be more prone to centroid shift side-effects because changes in the pupil centre can lead to a relatively large change in the refractive state of the eye can occur (Pazo *et al.*, 2016) because the pupil can only expose a certain section, either for distance or near of the asymmetric multifocal IOL. Majority of studies assessing the performance multifocal IOLs assume the pupil is centred on the model axis whereas in the human eye the pupil is typically shifted approximately 0.3 mm nasal to the optical axis. This results in the decentration of the multifocal IOL which can induce photopic phenomena, thereby resulting in less optimal QOV.

### 4.5.1 Study aim (Part-A)

The aim of the study is to analyse the impact of pupil centroid shift upon QOV of patients implanted with asymmetrical multifocal IOL and a solution to compensate for larger pupil shift that could potentially impair / reduce light transmission through either the distance or near component of these IOLs without actual IOL decentration.

### 4.5.2 Sample size

The power calculation was conducted using G*Power 3.1 (Faul *et al.*, 2007) (ANOVA repeated measures within factor) to show a medium effect size with 80% power and an alpha level of 0.05. One hundred eyes of 50 patients (22 men, 28 women; mean age: 64.5 years ± 4.6) who had undergone phacoemulsification and bilateral implantation of an asymmetrical IOL (SBL-3, Lenstec Inc.) were assessed. Sample size was determined using power calculation (80% power at the 5% level of statistical significance, $\alpha=0.05$) to detect a change of 1 unit change in QOV Score with 80% power ($\beta=0.2$) at the 5% level of statistical significance ($\alpha=0.05$), 50 subjects were required based upon published data (standard deviation in patients =± 1.08) (McNeely *et al.*, 2017).

### 4.5.3 Subjects

This retrospective, case series is from a population of patients seeking IOL implantation surgery due to cataracts at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective study, only informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent (ref: Appendix D). A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery. Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery.

### 4.5.4 Experimental procedure

The preoperative characteristics of patients are shown in Table 4.1. This retrospective study included cataract patients that had undergone phacoemulsification followed by bilateral implantation of SBL-3 asymmetric multifocal IOL. The near section of the SBL-3 IOL was placed in an inferonasal position within a dilated pupil. In all patients. Pupil diameters and pupil centroid shift were assessed using OPD Scan (NIDEK Co. Ltd. Gamagori, Japan) and Aladdin scan (Topcon medical systems, Inc.). To determine the effect of pupil centroid shit on the QOV, patients were divided into two groups based on pupil centroid shift: 0.00 to 0.30 mm (group A), 0.31 to 0.59 (group B). The categorization of these groups were based on previous studies on multifocal IOLs that suggest that 0.30 mm of pupil shift had nonsignificant impact upon the quality of vison (Sobaci *et al.*, 2007). Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery.

**Table 4.1** Patient demographics

| | Group A (0.00 to 0.30mm) | Group B (0.31 to 0.59mm) | P-value |
|---|---|---|---|
| Age (years) | 59.80±8.30 | 60.12±7.42 | 0.524 |
| Number of eyes | 86 | 14 | -- |
| Follow-up time (months) | 8.2±1.24 | 8.5±1.32 | 0.37 |
| Mean Astigmatism (D) | 0.78±0.12 | 0.77±0.22 | 0.21 |
| Mean CDVA logMAR | 0.14±0.15 | 0.1±0.20 | 0.083 |
| Pupil centroid shift (mm) | 0.20±0.06 | 0.42±0.05 | 0.017* |
| Mean QOV Score (0-10) | 6.6±1.4 | 6.7±1.2 | 0.143 |
| *P-value <0.05, Statistically significant across groups D: Dioptres; CDVA: Corrected Distance Visual Acuity; mm: millimetres; QOV: Quality of Vision; *P<0.05 | | | |

### 4.5.5 Preoperative and postoperative examinations

Preoperatively, all patients had a full ophthalmic examination including uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) (4m logMAR, Early Treatment of Diabetic Retinopathy Study Chart 1 [ETDRS]), uncorrected near visual acuity (UNVA) and corrected near visual acuity (CNVA) at 40cm with Radner reading charts under a standard mesopic lighting condition, (Radner charts allow direct conversion i.e. 0.2 logMAR distance acuity is comparable to 0.2 logRAD reading acuity with high correlation at 40 cm to a logMAR equivalent for size of letters) and uncorrected intermediate visual acuity (UIVA) and corrected intermediate visual acuity (CIVA) at 70cm. Further examinations included keratometry, topography and auto refraction OPD-Scan II aberrometer, subjective refraction, slit-lamp examination, Goldmann tonometry, dilated funduscopy and biometry (IOL Master, version 4.3, Carl Zeiss Meditec AG), and pupil diameter with the OPD Scan II and Aladdin scan. The IOL Master was used to measure corneal curvature, anterior chamber depth, axial length and subsequent IOL calculation using the Hoffer Q formula for eyes with AL <22mm and SKR/T formula for AL 22-25mm and Haigis for AL >25mm (A- constant of 118.2 for SRKT and a0 constant of 0.83, a1, a2 for Haigis).

Emmetropia was the target in all cases. Postoperatively, patients were evaluated at 6-months. In addition to the above-mentioned examinations, UIVA, UNVA, distance corrected intermediate visual acuity (DCIVA) and distance corrected near visual acuity (DCNVA) were assessed looking for evidence of differences in their mean or in their level of variation through assessment of outlier differences. Posterior capsule opacification (PCO) was graded by an ophthalmologist as follows: 1=none, 2=mild (early development of PCO), 3 = moderate (increased PCO with early visual acuity changes not requiring secondary capsulotomy) and 4 = severe (PCO affecting vision and requiring neodymium: YAG laser capsulotomy).

### 4.5.6 Surgical technique

One experienced surgeon (J.E.M.) performed all surgeries. The steep axis was marked in all patients preoperatively at the slit-lamp. Sub-tenons or topical anaesthesia was carried out on all patients. A standard sutureless on-steep axis corneal phaco surgery (2.75 mm incision) was performed through a 5.0 mm anterior capsulorhexis in all patients without complication. After irrigation/aspiration of cortex the multifocal IOL mentioned above were implanted in all cases with recommended injector cartridge. All residual viscoelastic was removed prior to intracameral antibiotic injection (cefuroxime). Where on-axis surgery was not possible, a 2.75mm supero-temporal corneal position was used to minimise induced astigmatism. Capsular tension ring (CTR) was used in all 100 eyes to benefit tilt and decentration. Postoperative topical therapy included 1 drop of ofloxacin 0.3% (Exocin) 4 times daily for two weeks, 1 drop of ketorolac trometamol 0.5% (Acular) 2 times daily for 1 month and 1 drop of dexamethasone 0.1% (Maxidex) 4 times daily for three weeks.

### 4.5.7 Pupil centroid shift assessment

All pupil assessments using the Aladdin scan were performed in a single test room that had a constant ambient illumination of 0.63 lux. To standardize the postoperative pupil assessments, the ambient lighting was continuously monitored using a handheld

Illuminometer light meter (Sekonic, Japan). Concurrently, before measuring the pupil size, the patient's orbital region illumination was recorded and maintained at 0.63 lux to have minimum discrepancy among patient groups. The minimum luminance the photometer could record was 0.63 lux.

### 4.5.8 Intraocular lens centration within the photopic pupil and IOL tilt assessment

The pupil centroid shift in respect to the IOL centration in all eyes was assessed by using a validated methodology developed by Wolffsohn & Buckhurst (2010) was applied. All pupils of the eyes prior to dilated with tropicamide 1.0% were photographed to capture the normal pupil location under photopic condition. After dilatation the IOL was imaged with 5 times magnification in retroillumination using a SL 120 digital slit biomicroscope (Carl Zeiss Meditec). This was conducted six months after IOL implantation. The centration of the IOL was determined by encircling the circular optical disc and intersecting this circle with two perpendicular lines (Figure 4.1). The location and centre of the photopic pupil centre was also determined circular photic pupil boundary and intersecting this circle with two perpendicular lines (Figure 4.2). This was normalized for rotation of the eye and head in front of the slitlamp between photographs and visits by comparing the axis of a line joining 3 consistent conjunctival vessels (Figure 4.3). All landmark features were visible on the images captured at every assessment. The photograph of the IOL centration and photopic pupil centration and three consistent conjunctival vessels were overlaid to determine the location of the IOL within the photopic pupil (Figure 4.3) using Adobe PS suite (Adobe Systems, Inc., San Jose, CA). Images from three random patients were analysed six times to assess the repeatability of the analysis. CTR was used in all eyes. At six months after IOL implantation IOL clarity was also assessed along with IOL tilt using the Pentacam-Scheimpflug camera.

**Figure 4.1.** Determining the centre of the IOL within a pharmacologically dilated pupil by encircling the circular boundary of the IOL and intersecting the circle with two perpendicular lines at a right angle.

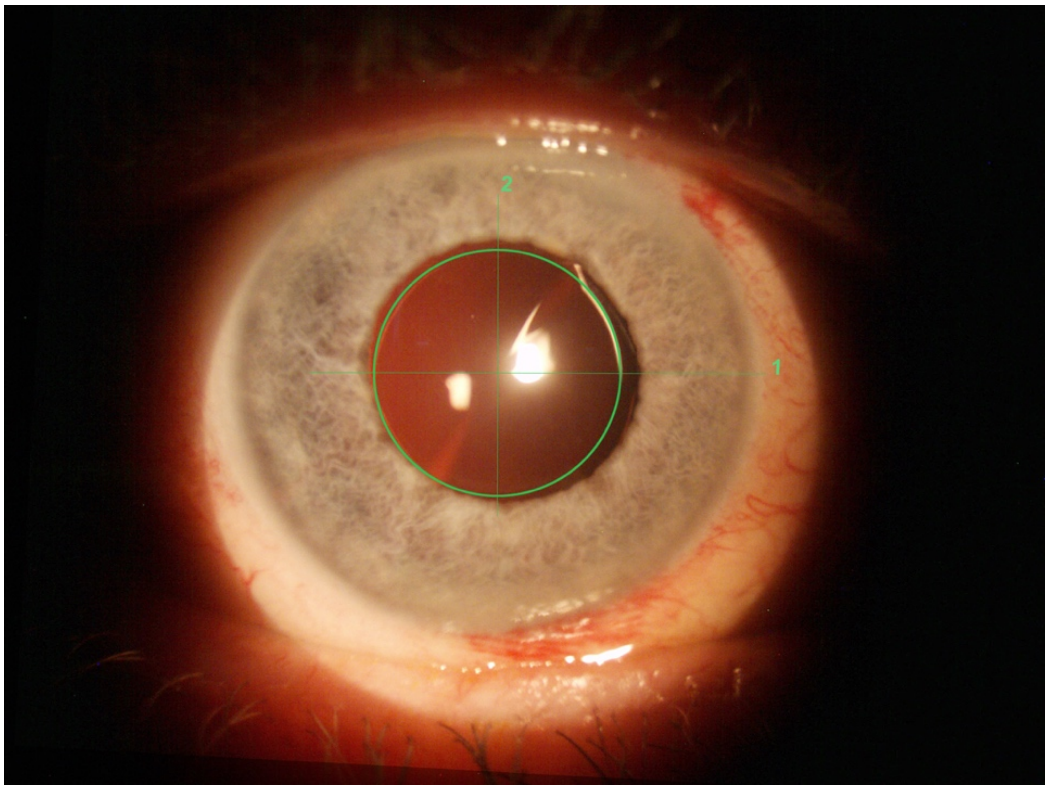


**Figure 4.2**. Determining the centre of a photopic pupil by encircling the circular boundary of the photopic pupil and intersecting the circle with two perpendicular lines at a right angle.

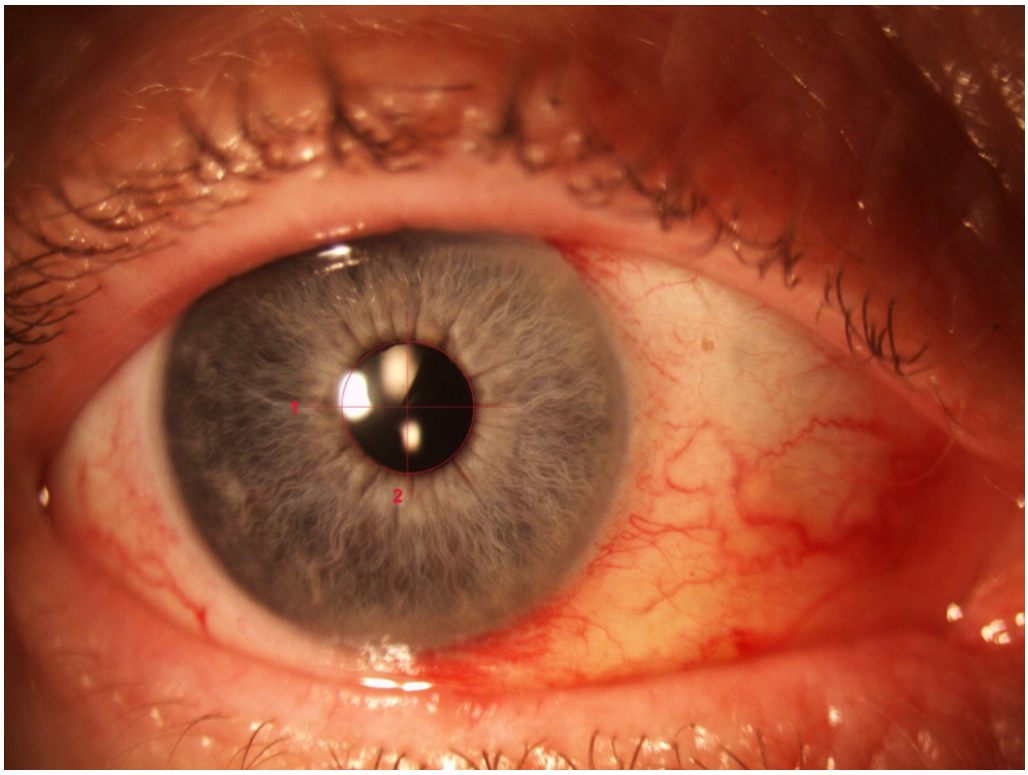


**Figure 4.3.** Overlaying the centre of the IOL and the photopic pupil over 3 consistent conjunctival vessels landmarks.

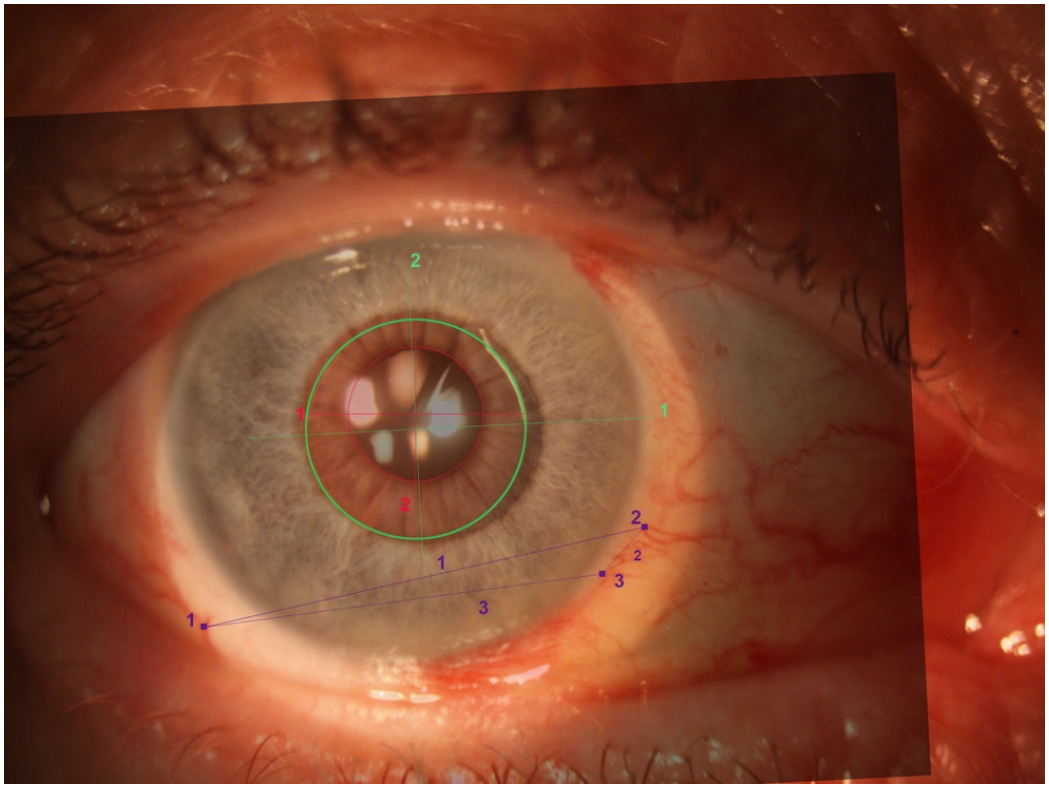


**Figure 4.4.** Scheimpflug image of the horizontal cross-section of the anterior segment after SBL-3 IOL implantation. The central anterior chamber depth was measured from the central corneal posterior endothelium to the IOL anterior surface.

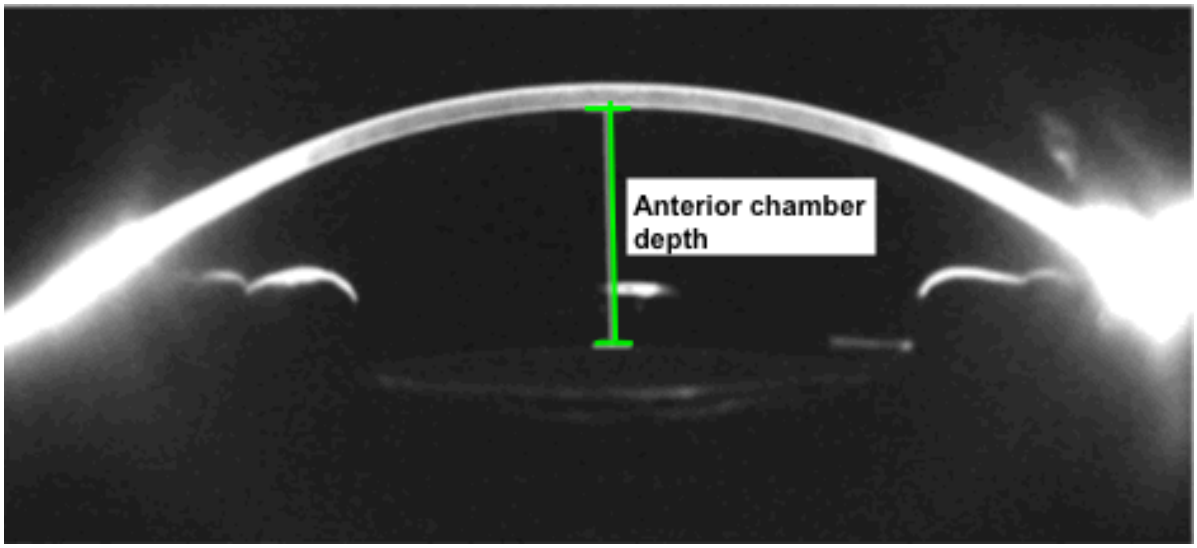
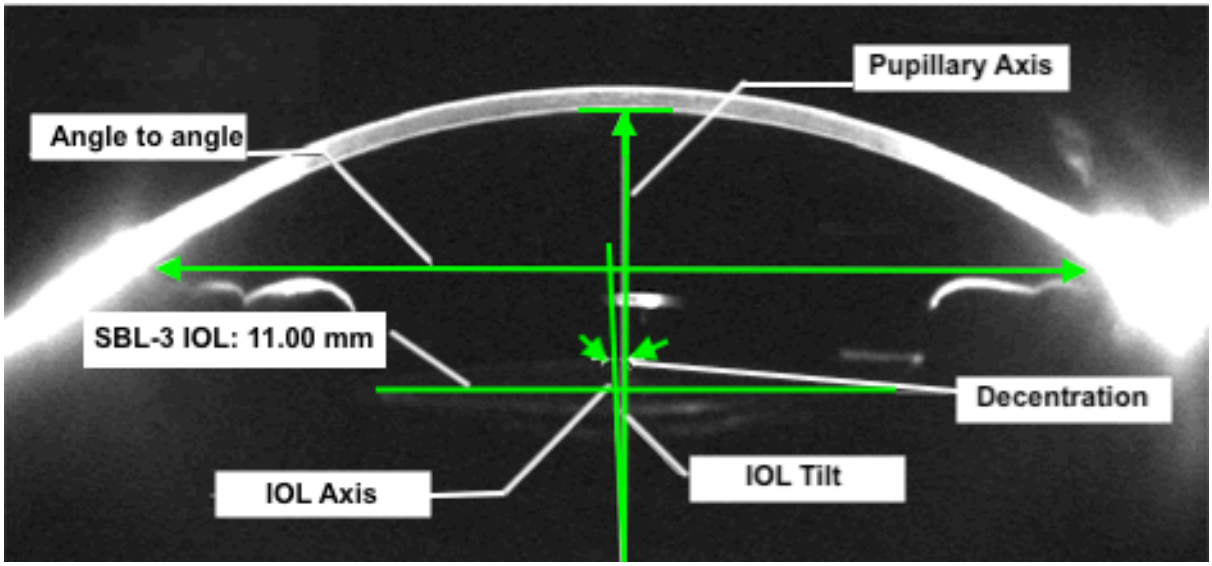



**Figure 4.5.** Schematic drawing of the decentration and tilt measurement over the above depicted image (figure 4.4). Decentration was measured from the centre of the SBL-3 IOL anterior surface to the pupillary axis. Tilt was measured between the IOL axis and the pupillary axis.



### 4.5.9 Questionnaire

For this study a validated QOV Questionnaire (McAlinden, Pesudovs and Moore, 2010) was used. The questionnaire was administered at six months follow-up to assess for possible neural adaption. The patients were asked to rate their overall QOV separately for day and night from very poor (0), to excellent (10).

### 4.5.10 Statistical analysis

Data analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences, Version 22, Chicago, Illinois, USA.). The relationship between the pupil size and QOV was modelled using a linear regression model and the differences in QOV between pupil size groups were evaluated by analysis of variance (ANOVA). Normality was checked by the Shapiro-Wilk test and Q-Q plot test. To assess the impact of pupil size to the QOV, a linear regression analysis was performed. Differences were considered statistically significant when the P value was less than 0.05.

## 4.6 Results

All 50 patients (100 eyes) had no intra-operative or postoperative complications at six months follow-up.

### Quality of Vision and Pupil Shift

The mean postoperative pupil shift was 0.14±0.13mm for group A and 0.41±0.15mm for group B at six months (Table 4.2). There were no significant differences between the mean preoperative and postoperative pupil shift in group A and group B at six months assessment. There were statistically significant differences in postoperative QOV questionnaire score at six months in both groups ($P<0.05$) (Table 4.3). A

regression analysis was performed between pupil centroid shift and the QOV (day and night) score to find out whether pupil shift had an impact upon the QOV. At six month postoperative assessment, QOV day score correlated with the postoperative pupil shift with a $r^2$ =0.506; p<0.05 (Figure 4.4) and QOV night score correlated with the postoperative pupil shift with a $r^2$ =0.418; p<0.05 (Figure 4.5). Postoperatively group A with pupil shift $\leq$ 0.30 mm reported better mean QOV scores for day and night in comparison to group B.

**Table 4.2.** Patient demographic.

| | Group A (0.00 to 0.30mm) | Group B (0.31 to 0.59mm) | P-value |
|---|---|---|---|
| Age (years) | 59.80±8.30 | 60.12±7.42 | 0.414 |
| Number of eyes | 86 | 14 | -- |
| Follow-up time (months) | 8.2±1.24 | 8.5±1.32 | 0.37 |
| Mean Astigmatism (D) | 0.78±0.12 | 0.77±0.22 | 0.21 |
| Mean CDVA logMAR | 0.14±0.15 | 0.1±0.20 | 0.083 |
| Pupil centroid shift (mm) | 0.14±0.13 | 0.41±0.15 | 0.017* |
| Mean QOV Day Score (0-10) | 6.6±1.4 | 6.7±1.2 | 0.143 |
| Mean QOV Night Score (0-10) | 5.9±0.51 | 6.1±0.2 | 0.526 |
| *P-value <0.05, Statistically significant across groups<br>D: Dioptres; CDVA: Corrected Distance Visual Acuity; mm: millimetres; QOV: Quality of Vision; *P<0.05 | | | |

**Table 4.3.** Pre and postoperative comparison.

| | Group A (0.00 to 0.30mm) | | Group B (0.31 to 0.59mm) | |
|---|---|---|---|---|

| | Preoperative | Postoperative | P-value | Preoperative | Postoperative | P-value |
|---|---|---|---|---|---|---|
| Pupil centroid shift (mm) | 0.20±0.06 | 0.21±0.04 | 0.411 | 0.42±0.05 | 0.42±0.09 | 0.42 |
| Mean QOV Day Score (0-10) | 6.6±1.4 | 8.66±0.69 | 0.05* | 6.7±1.2 | 7.21±0.57 | 0.03* |
| Mean QOV Night Score (0-10) | 5.9±1.5 | 8.15±0.52 | <0.05* | 6.1±1.1 | 7.01±0.39 | 0.02* |
| *P-value <0.05, Statistically significant across groups<br>mm: millimetres; QOV: Quality of Vision. | | | | | | |

**Figure 4.4.** A correlation analysis was performed between pupil centroid shift and the QOV day score at six months after operation.

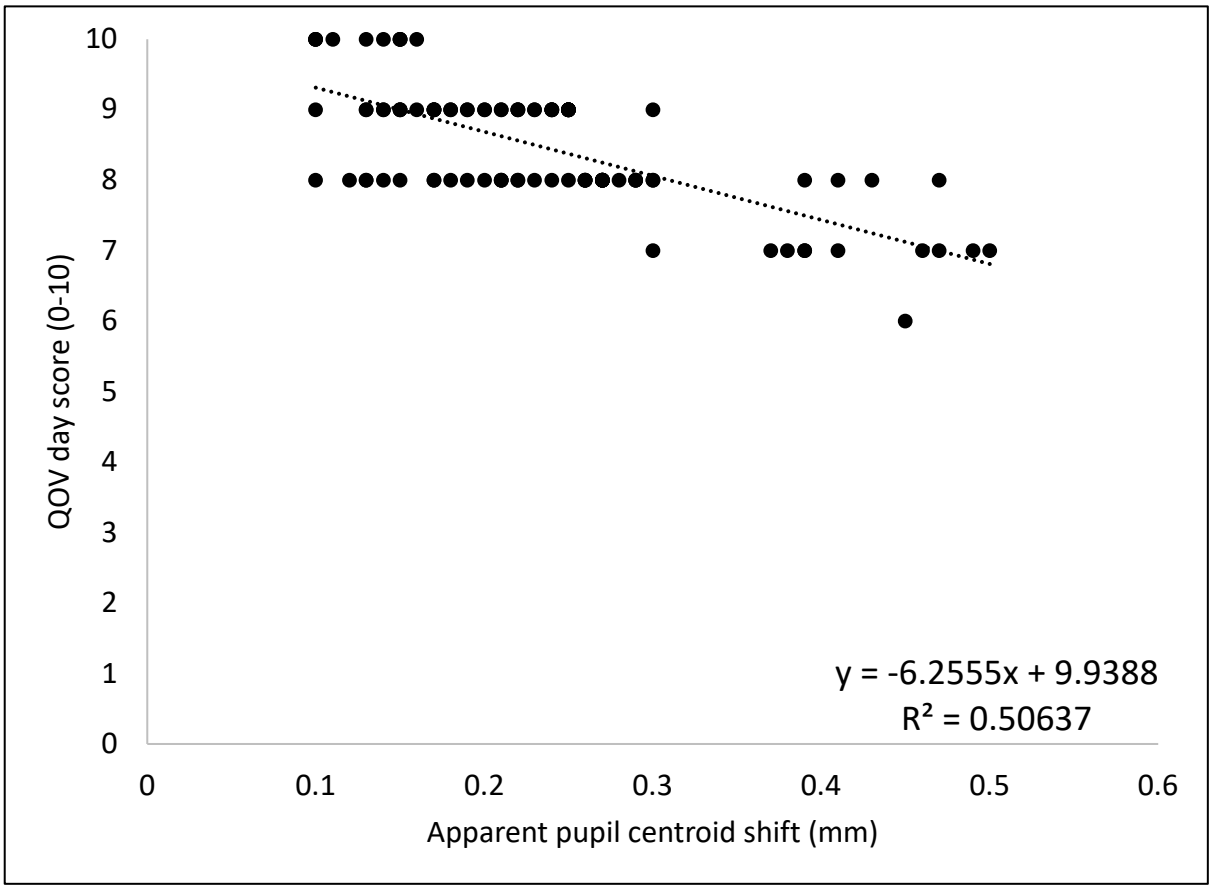
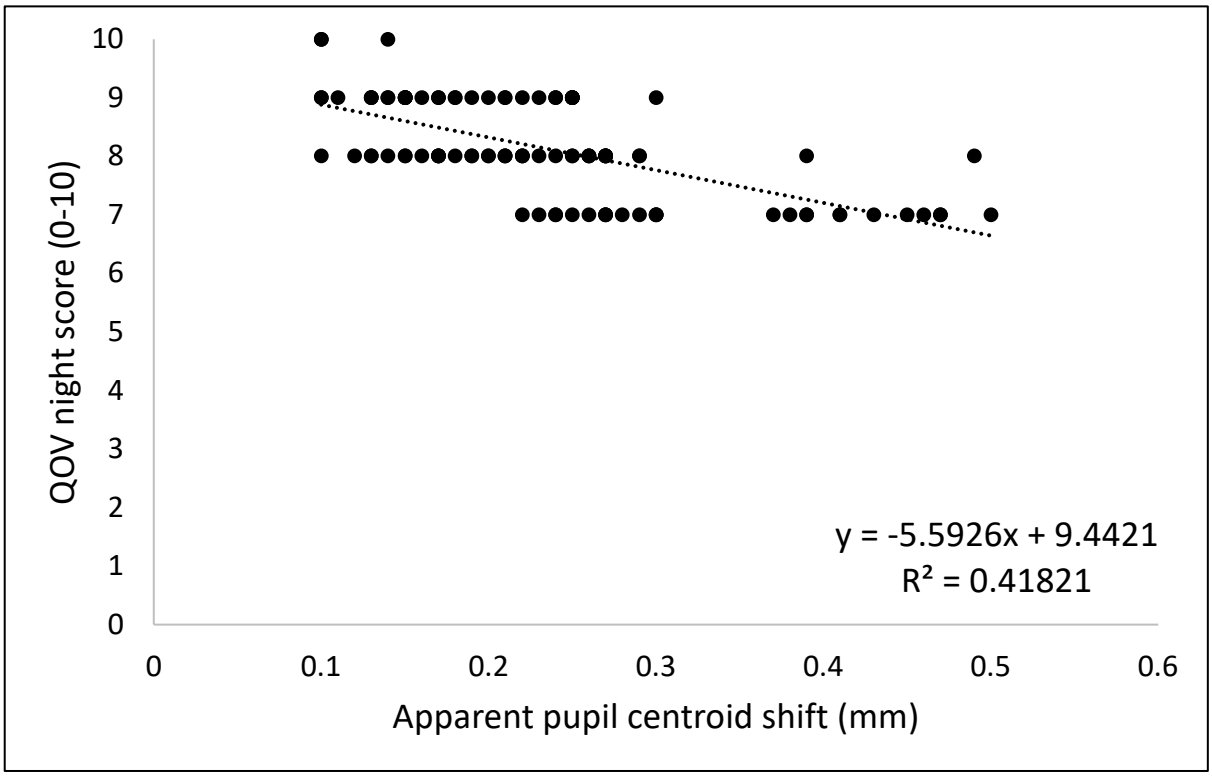


**Figure 4.5.** A correlation analysis was performed between pupil centroid shift and the QOV night score at six months after operation.




**Visual Acuity and Refraction**

Table 4.4 shows the between-group comparison of postoperative data. The mean at six months postoperative ocular parameters, visual and refractive outcomes had no statistically significant differences. The mean VA was better in patients with smaller pupil shift group (group A) postoperative in comparison to patients with larger pupil shift (group B).

**Table 4.4.** Postoperative 6-month data.

| Postoperative 6-month data. |
|---|

| Parameter | Group A (0.00 to 0.30mm) | Group B (0.31 to 0.59mm) | P Value* |
|---|---|---|---|
| Sphere (D) | | | |
| Mean ± SD | 0.12±0.42 | 0.14±0.34 | 0.087 |
| Cylinder (D) | | | |
| Mean ± SD | 0.38±0.27 | 0.37±0.30 | 0.129 |
| logMAR UDVA (monocular) | | | |
| Mean ± SD | -0.03± 0.09 | -0.04 ±0.15 | 0.274 |
| logMAR UIVA (monocular) | | | |
| Mean ± SD | 0.17 ± 0.13 | 0.20 ± 0.10 | 0.084 |
| logMAR UNVA (monocular) | | | |
| Mean ± SD | 0.19 ± 0.11 | 0.23 ± 0.20 | 0.490 |
| QOV (0-10) | | | |
| Day | 8.66±0.69 | 7.21±0.57 | 0.014* |
| Night | 8.15±0.52 | 7.01±0.39 | 0.030* |
| Pupil centroid shift (mm) | | | |
| Mean ± SD | 0.21±0.04 | 0.42±0.09 | 0.029* |
| Tilt (degree) | | | |
| Mean ± SD | 1.5°± 0.20 | 1.6° ± 0.10 | 0.73 |

*P-value <0.05, Statistically significant across groups
UDVA: Unaided distance visual acuity; UIVA: Unaided intermediate visual acuity; UNVA: Unaided near visual acuity; SD: Standard deviation; mm: millimetre

**Efficacy**

Six months after operation, UDVA improved to -0.03 ± 0.09 logMAR and -0.04 ± 0.15 logMAR, in group A, and B respectively. At six months postoperative UIVA for group A and group B was 0.17 ± 0.13 logMAR and 0.20 ± 0.10 logMAR, respectively. UNVA at six months postoperatively was 0.19 ± 0.11 logMAR and 0.23 ± 0.10 logMAR respectively.

**Adverse Events and Posterior Capsule Assessments**

No serious complications (posterior capsule rupture, endophthalmitis, macular oedema or persistent raised intra-ocular pressure) occurred during the study. All 100 eyes (50 patients) were retrospectively assessed and categorised into the respective pupil size groups. At 6-months a single experienced ophthalmologist examined all 100 eyes and confirmed no or mild PCO was present. Cases with PCO were excluded from this retrospective analysis.

**Visual disturbances and photopic phenomena**

Table 4.5 shows the individual symptom responses found in each group. Group B experienced significantly higher mean score for ‘Glare’, ‘Halos’ and ‘Hazy vision’ in comparison to group A.

**Table 4.5.** Postoperative comparison at 6-month

| QOV questions for visual symptoms | Group A (0.00 to 0.30mm) | Group B (0.31 to 0.59mm) | P Value |
|---|---|---|---|
| How much does glare bother you? | 0.25 ± 0.10 | 2.05 ± 0.20 | 0.018* |

| | | | |
|---|---|---|---|
| How much do the halos bother you? | 0.28 ± 0.15 | 2.20 ± 0.18 | *0.031 |
| How much do the starbursts bother you? | 0.23 ± 0.13 | 0.25 ± 0.09 | 0.081 |
| How much does hazy vision bother you? | 0.16 ± 0.10 | 0.49 ± 0.12 | 0.020* |
| How much does blurred vision bother you? | 0.18 ± 0.09 | 0.57 ± 0.24 | 0.385 |
| How much does distortion bother you? | 0.14 ± 0.05 | 0.16 ± 0.11 | 0.527 |
| How much do double images bother you? | 0.10 ± 0.05 | 0.18 ± 0.10 | 0.092 |
| *P-value <0.05, Statistically significant across groups<br>Grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very | | | |

### 4.7 Study aim (Part-B)

The aim of part B of this study was to optimise the QOV and reduce visual symptoms of glare and haloes by repositioning the IOL with a second surgical procedure on group B patients by rotating the IOL and centering it to the photopic pupil rather than the pharmacologically dilated pupil centre. The rational for rotating the IOL was based on the findings of the case study by Pazo *et al*. (2016), where rotating the previously implanted asymmetric multifocal IOL to compensate for the pupil shift resulted in improved QOV and significant reduction of photopic symptoms.

#### 4.7.1 Surgical technique

One experienced surgeon (J.E.M.) performed all IOL rotation surgeries. On assessing the pupil of the affected eye under photopic conditions using a slit lamp biomicroscope, it was observed that the near-add surface had high exposure. Of the 100 eyes implanted with SBL-3 IOLs, fourteen of which had a pupil centroid shift of >0.3 mm nasally and experienced significant photopic phenomena such as glare, haloes and

hazy vision as shown in Table 4.6. These fourteen patients were explained about the risk and benefits of this second surgical intervention, the inferonasally placed (near-add) asymmetric multifocal IOL was rotated clockwise according to the individuals' pupil centroid shift and pupil size in order to enhance the exposure of both the distance and near component of the asymmetric multifocal IOL.

### 4.7.2 Marking for intraocular lens rotation

Preoperative marking when using asymmetric multifocal IOLs before pupil centroid shift correction is important because deviations of the IOL centre in the horizontal and vertical meridians within the photopic pupil may result in a relevant reduction in visual quality. Patients were asked to put their chin in the chinrest. The examiner first centred the slitlamp on the centre of the cornea and the slit of the slitlamp was turned on. The pupil was allowed to contract to a photopic state. The directional axis of pupil centroid shift was verified with the previous photographic overlay analysis performed. Next, the photopic centre of the pupil was marked on the cornea by initially indenting the epithelium with the sharp end of LASIK spatula. This was then turned into a microabrasion and subsequently stained with a sterile blue marker. The microabrasion provided the surgeon the reference to understand the centre of the photopic pupil when the pupil was pharmacologically dilated for IOL rotation. The degree of IOL rotation required to compensate for the photopic pupil centroid shift could not be precisely determined preoperatively as the IOL position is also dictated by the capsular periphery. Therefore, the degree of IOL rotation required for centration was done intraoperatively using the visual aid of the micro-abrasion as reference.

**Table 4.6.** IOL rotation patients.

| Patient | Pupil centroid shift (mm) | Eye | Pupil shift axis | Rotation |
|---|---|---|---|---|
| 1 | 0.37 | Right eye | Nasal | 60° clockwise |

| | | | | |
|---|---|---|---|---|
| 2 | 0.38 | Right eye | Nasal | 60° clockwise |
| 3 | 0.39 | Left eye | Nasal | 60° clockwise |
| 4 | 0.39 | Right eye | Nasal | 60° clockwise |
| 5 | 0.39 | Left eye | Nasal | 60° clockwise |
| 6 | 0.41 | Right eye | Nasal | 80° clockwise |
| 7 | 0.41 | Right eye | Nasal | 80° clockwise |
| 8 | 0.43 | Right eye | Nasal | 80° clockwise |
| 9 | 0.45 | Left eye | Nasal | 90° clockwise |
| 10 | 0.46 | Right eye | Nasal | 90° clockwise |
| 11 | 0.47 | Left eye | Nasal | 120° clockwise |
| 12 | 0.47 | Left eye | Nasal | 120° clockwise |
| 13 | 0.49 | Right eye | Nasal | 120° clockwise |
| 14 | 0.5 | Right eye | Nasal | 120° clockwise |

### 4.8 Results: After rotation of IOL (group B)

All fourteen patients (fourteen eyes) had no intra-operative or postoperative complications at six months follow-up.

#### Quality of Vision

There were statistically significant differences between the mean pre-rotation and after rotation assessment at 6-months (Table 4.7).

#### Visual Acuity and Refraction

Table 4.6 shows the comparison of pre-rotation and after rotation data. The mean at after rotation six months visual and refractive outcomes was had no statistically significant differences but was better than pre-rotation.

**Efficacy**

The mean pre-rotation UDVA was -0.04 ± 0.15 logMAR and after rotation at six months it improved to -0.03 ± 0.10 logMAR. Pre-rotation, UIVA was 0.20 ± 0.10 logMAR and after rotation it was 0.20 ± 0.05. The mean pre-rotation UNVA was 0.23 ± 0.20 logMAR and after rotation it was 0.20 ± 0.12 logMAR.

**Table 4.7.** Pre-and after rotation comparison at 6-month.

| Parameter | Pre-rotation Group B 0.31 to 0.59mm) | After rotation Group B (0.31 to 0.59mm) | P Value* |
|---|---|---|---|
| Sphere (D) | | | |
| Mean ± SD | 0.14±0.34 | 0.15±0.47 | 0.40 |
| Cylinder (D) | | | |
| Mean ± SD | 0.37±0.30 | 0.36±0.40 | 0.347 |
| logMAR UDVA (monocular) | | | |
| Mean ± SD | -0.04 ±0.15 | -0.03 ±0.10 | 0.390 |
| logMAR UIVA (monocular) | | | |
| Mean ± SD | 0.20 ± 0.10 | 0.18 ± 0.05 | 0.259 |
| logMAR UNVA (monocular) | | | |
| Mean ± SD | 0.23 ± 0.20 | 0.20 ± 0.12 | 0.273 |
| QOV (0-10) | | | |
| Day | 7.21±0.57 | 8.49±0.42 | 0.021* |
| Night | 7.01±0.39 | 8.14±0.10 | 0.036* |
| Pupil centroid shift (mm) | | | |
| Mean ± SD | 0.42±0.09 | 0.41±0.10 | 0.540 |

| | | | |
|---|---|---|---|
| Tilt (degree) | | | |
| Mean ± SD | 1.6° ± 0.10 | 1.6° ± 0.21 | 0.419 |
| *Statistically significant across groups<br>UDVA: Unaided distance visual acuity; UIVA: Unaided intermediate visual acuity; UNVA: Unaided near visual acuity; SD: Standard deviation; mm: millimetre | | | |

**Adverse events and posterior capsule assessments**

No serious complications (posterior capsule rupture, endophthalmitis, macular oedema or persistent raised intra-ocular pressure) occurred during the study. All fourteen eyes (fourteen patients) were retrospectively assessed and categorised into the respective pupil size groups. At six months a single experienced ophthalmologist examined all fourteen eyes and confirmed no or mild PCO was present.

**Visual disturbances and photopic phenomena**

Table 4.8 shows the individual symptom responses found in each group. 'Glare', 'Halos' and 'Hazy vision' were significantly decreased at 6-months after rotation in group B.

**Table 4.8.** Pre-and after rotation comparison at 6-month.

| QoV questions for visual symptoms | Pre-rotation Group B 0.31 to 0.59mm) | After rotation Group B (0.31 to 0.59mm) | P Value* |
|---|---|---|---|

| | | | |
|---|---|---|---|
| How much does glare bother you? | 2.05 ± 0.20 | 1.09 ± 0.10 | 0.019* |
| How much do the halos bother you? | 2.20 ± 0.18 | 1.12 ± 0.05 | 0.027* |
| How much do the starbursts bother you? | 0.25 ± 0.09 | 0.23 ± 0.04 | 0.328 |
| How much does hazy vision bother you? | 0.49 ± 0.12 | 0.21 ± 0.04 | 0.030* |
| How much does blurred vision bother you? | 0.57 ± 0.24 | 0.49 ± 0.21 | 0.475 |
| How much does distortion bother you? | 0.16 ± 0.11 | 0.16 ± 0.23 | 0.079 |
| How much do double images bother you? | 0.18 ± 0.10 | 0.19 ± 0.03 | 0.146 |
| *P-value <0.05, Statistically significant across groups<br>Grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very | | | |

**4.8 Discussion**

The aim of multifocal IOL use is to restore distance, intermediate, and near visual function following cataract surgery. Photic phenomena are commonly associated with multifocal IOLs but have also been known to occur with monofocal IOLs as well. (Schmitz *et al.*, 2000). The new generation of refractive radially asymmetrical multifocal IOLs aim to alleviate the occurrence of optical side effects. The SBL-3 IOL is a bi-aspheric asymmetrical refractive multifocal IOL with a +3.00 D add in the inferior anterior optic. A transition zone separates the distance and the near-add sections of the lens and the near segment occupies 42% of the total lens optic. The case series of bilateral implantation on 53 eyes published by Venter *et al*. (2014) and McNeely *et al*. (2016) reported a good range of distance, intermediate, and near VA in patients. The rotation of asymmetrical multifocal IOL on its axis was compared before by de Wit *et al*. (2015) who found that the placement of the near-add in the superior or inferior position in the Mplus IOL (Lentis Barbados, Inc.) had no significant overall difference in the mean subjective or objective outcomes. In AMO Array SA40N (Allergan) multifocal IOLs halos correlated with corneal irregularities and astigmatism greater than 1.00 D and glare correlated with monofocal IOL patients over the age of 70 years (Nijkamp *et al.*, 2004). In our patients moderate or severe photopic phenomena was observed in patients with nasal pupil centroid shift of >0.3 mm, however they were still satisfied with good VA. This may be explained by their good postoperative UDVA and reduced dependence on reading spectacles. Nijkamp *et al*. (2004) found that distance vision without glasses correlated significantly with patient satisfaction after cataract surgery. Walkow *et al*. (2001) found that the most influential factor that predicted after cataract surgery satisfaction was UDVA. In our study it was found that although the group B patients experienced good distance and near vision but their overall QOV was severely compromised by photopic phenomena such as glare, haloes and hazy vision. However, after IOL rotation in group B, the IOL was better centred within the photopic pupil which resulted in statistically significant reduction in glare, haloes and hazy vision, including an overall improvement in the QOV for day and night without any significant loss of distance VA. Decentration of any multifocal IOL can lead to decreased VA and photopic phenomenon, which can deleteriously impact the QOV (Pazo *et al.*, 2016). The effect of decentration of a multifocal IOL on visual quality can be further compounded by a large angle kappa, resulting in central optical rays potentially passing through the periphery of the multifocal IOL rather than its centre (Prakash *et al.*, 2011). To ensure the centration of a multifocal IOL with respect to the physiological

pupil centre can be difficult, principally because this is dictated through the IOL haptics by the position of capsular bag periphery. The SBL-3 IOL is radially asymmetric and centration appears to play a crucial role for good QOV. As documented in this chapter that the nasal displacement of the pupil of > 0.3 mm from the centre resulted in poor QOV. Possible factors that can influence this decentration with respect to the physiological pupil include capsular contraction, haptic movement, IOL rotation, or pupil shift (Patel *et al.*, 1999; Crnej *et al.*, 2011; Van Der Linden *et al.*, 2013). However, haptic movement, and IOL rotation was not observed in this study. Pupil shift refers to a slight change in reference to the pupil's central location between mesopic, photopic, and pharmacologically dilated conditions (Yang Y, *et al*. 2002) and this tendency of the pupil to shift makes it more difficult to achieve a precise positioning of the asymmetric multifocal IOL. In this study we observed that pupil shift of less than 0.30 mm (group A) did not have significant impact upon the objective and subjective vison. However, in group B which had pupil shift greater than 0.30 mm suffered from significant photopic phenomenon such as glare, haloes and hazy vision. Closer examination of the photopic pupil of group B patients eye revealed that a photopic pupil shift occurred toward the nasal region and thereby maximized the light exposure to the inferiorly placed near-add of the IOL, making distance vision during bright lighting conditions difficult for the patient. Postoperative rotation of an asymmetric multifocal IOL can be beneficial for some patients experiencing dysphotopsia and poor QOV. It is key to ensure that the dominant eye is optimized for distance viewing by maximizing the area of distance optic within the mesopic and photopic pupil. Determining where the physiological pupil centre lies during surgery in an attempt to centre the IOL within a pharmacologically dilated pupil is difficult. However, rotation of the IOL can result in different final positions for the centre of the IOL. This is due to the asymmetric nature of the capsular bag and the differences between the centre of the bag and the centre of the pupil. Asymmetric multifocal IOLs are not circular and neither is the capsular bag (Strenn, Menapace and Vass, 1997); therefore, one can actively alter the resultant centration of the IOL by rotating it into different positions. Taking these factors into consideration, the near-add positioning should be assessed individually for optimal positioning of a multifocal IOL and potentially different positions used for the dominant and non-dominant eyes.

## 4.9 Conclusion

Preoperative pupil shift assessment in rotationally asymmetric multifocal IOLs is essential. As it allows the surgeon to correctly position the IOL inside the capsular bag. Pupil shift of greater than 0.30 mm was shown to significantly decrease the QOV in asymmetric multifocal IOLs. It is key to ensure that both the near and distance sections of asymmetric multifocal IOL are proportionally exposed under various pupil conditions. Since asymmetric multifocal IOLs are not circular and nor is the capsular bag the most effective method of ensuring proportionate exposure of near and distance sections is by centering the IOL with respect to the photopic pupil centre, taking into consideration the pre-existing individual pupil centroid shit and its direction.

The extension of this study will be to compare the microabrasion methodology of IOL centration with the new intraoperative imaging technology Verion / ORA system (Alcon, UK) to improve surgical centration of these asymmetric IOLs to the visual axis and also to take into account the pupil size and position.

## 4.10 Summary

This chapter showed that preoperative pupil centroid shift is an essential assessment for all patients opting for asymmetric multifocal IOL implantation. In general, the QOV in rotationally asymmetric multifocal IOL is not affected by pupil centroid less than 0.30 mm. However, in pupil that have a centroid shift of greater than 0.30 mm, the implantation of asymmetric multifocal IOL must be personalised accordingly or a non-pupil dependent IOL can be used as an alternative.

# CHAPTER 5: EVALUATION OF DRY EYE AND TEAR FILM TEAR LIPID INTERFERENCE PATTERNS AFTER LASER REFRACTIVE SURGERY

## 5.1 Introduction

Corneal refractive surgery has the tendency to adversely affect the ocular surface, and a reduction of functional meibomian glands can lead to the disturbance and instability of the preocular TF (Lemp *et al*. 2007). The thickness of the preocular TF is approximately 3µm (King-Smith, Fink and Fogt, 2000) which provides nutrients to the corneal epithelium (Mishima, 1965; Bron *et al.*, 2004). It also serves as a shield to the external environment (Govindarajan and Gipson, 2010). Since the precorneal TF is the first refractive interface for light rays entering the eye, it also pays a major role in ensuring optimal QOV (Tutt *et al.*, 2000). The tear lipid layer is located at the outer most layer of the precorneal TF measuring from 20–180 nm (Eom *et al.*, 2013). The tear lipid layer has been said to contribute to the stability of the TF as it provides a protective envelope to the underlying aqueous layer from evaporation (Guillon and Guillon, 1989; Isreb *et al.*, 2003). Since corneal refractive surgery has been reported to alter the distribution of TF layer and the relationship of the ocular surface to the inner lids (Ambrósio, Tervo and Wilson, 2008). These factors have been associated to contribute to the development or aggravation of DE. Studies have reported that underlying DE in patients who undergo laser refractive surgery develop DE due to the combination of neurotrophic and inflammatory response (Toda *et al.*, 2001a; Denoyer, Landman, Trinh, J. F. Faure, *et al.*, 2015). LASIK associated DE is considered to be a major cause of patient dissatisfaction (Bailey *et al.*, 2004). Symptoms of ocular dryness along with fluctuations in vision develop within the first weeks after surgery (Battat et al. 2001; Toda *et al*. 2001; Shen *et al*. 2016). Flattening of the central cornea and steepening after myopic and hyperopic LASIK respectively has been associated to alter the ocular surface TF dynamics (Melki and Azar, 2001). Progressive decrease in tear fluorescein clearance has been observed in LASIK patients (Macri, Rolando and Pflugfelder, 2000). Since clearance of fluorescein dye on the preocular TF depends on aqueous tear volume production, tear spreading over the ocular surface after blinking and the pump mechanism which drains tears into the lacrimal drainage

system (Macri, Rolando and Pflugfelder, 2000). The possible factors leading to decreased tear clearance, include decreased blink rate caused by corneal denervation and resultant increased evaporation of TF. Identifying the factors that influence laser refractive surgery is critical in ensuring proper counselling and optimisation of the ocular surface in-order to achieve the best visual outcome. Understanding the implication of DE is laser refractive surgery is useful in preventing and addressing postoperative conditions.

### 5.2 Analysis of tear film lipid layer

The interaction of the ocular surface epithelium and the TF plays an important role in the maintenance of homeostasis of the ocular surface and the disruption of this homeostasis can lead to DE. Several diagnostic tools and techniques have been developed to examine the TF and DE, however majority of these traditional tests and techniques are invasive procedures and therefore they modify the parameter which they are designed to assess. Non-invasive and minimally invasive tests are the most appropriate test for TF assessment as they do not modify the parameter and hence produce a more accurate assessment of the TF condition.

TF interferometry is a non-invasive screening and evaluating tool for assessing DE severity. TF interferometry in combination with other traditional DE assessment methods can also help determine the pathophysiology of tear lipid layer dysfunction. TF interferometry has been used to obtain to assess the thickness and state of meibomian gland function by observing the interference patterns created by the interferometer light reflecting from the lipid layer of the precorneal TF. The standard variations of the patterns provide useful objective information about the thickness and condition of the lipid layer. The pioneering studies on TF layer assessment was carried out by Mcdonald (1969) along with Hamano (1979), Norn (1979). and Guillon (1982) and the instrumentation for assessment was refined by Doane *et al* (Doane, 1989). Based on these foundations Yokoi *et al*. developed a commercial interferometer DR-1w, Kowa Co. Ltd, Japan and a grading score from 1 to 5. DR-1 classification system

(on a scale of 1-5). A score of 3 or more is suggestive of DE, with higher score indicative of more severe DE (Yokoi, Takehisa and Kinoshita, 1996).

### 5.2.1 Tearscope

The Keeler Tearscope instrument (Keeler, Windsor, UK) can be mounted on a slit-lamp biomicroscope that allows hands-free non-invasive assessment of the TF lipid layer interference patterns. The instrument consists of a tapered conical translucent tube that is illuminated by a cold cathode white light. The light produces a diffuse specular reflection against which the TF lipid layer. The interference pattern image is produced by reflection from the TF lipid layer located in front of the cornea. This device can be mounted on a photographic slit lamp biomicroscope to capture the interferometry patterns. When the eye is blinking normally the observed sees interference patterns and colours. These images can be used to examine grade and scored on a five-point scale using a recognised DR-1 classification system (on a scale of 1-5) (Yokoi, Takehisa and Kinoshita, 1996).

## 5.3 Tear film interferometry and dry eye

It has been proposed that the formation of the tear lipid layer is the result of repeated expansion and compression of the upper and lower lid margins that expresses meibum from the meibomian glands (Holly, 1980; Bron and Tiffany, 1998). This lipid layer of the TF prevents aqueous layer evaporation and maintaining the stability of aqueous TF layer (Mishima and Maurice, 1961). Yokoi *et al*. using the DR-1w system and 2 mm diameter observation area developed the DR-1 interference pattern classification system (Yokoi, Takehisa and Kinoshita, 1996). Grade 1 shows a greyish colour of uniform distribution, grade 2 shows a greyish colour and a non-uniform distribution, grade 3 shows a few colours with a non-uniform distribution, grade 4 shows various colours and a non-uniform distribution, and grade 5 shows that the corneal surface is partially exposed, with no lipid layer interference pattern (Yokoi, Takehisa and Kinoshita, 1996). This study found that these categories of interference patterns

significantly correlated with the severity of DE. The normal control eyes in this study aligned to Grade 1 and 2, while DE patients were classified from 2 to 5 depending upon the severity of the DE. However, there was an overlap in Grade 2 between control and DE, suggesting that the grading scale is not sensitive enough to assess borderline patients. Therefore, the DR-1 grading cannot be used as a standalone system to assess DE but can be used as an adjuvant tool alone with other traditional methods of DE assessment. The merits of the DR-1 grading scale are that it is convenient to use and interpret the dynamic tear lipid layer. As the grade in the DR-1 scale increases from 2 to 4, the colour of the tear lipid layer also increases, the possible explanation to this phenomenon Yokoi el al. was that the increased severity of DE leads to reduced aqueous tear volume which consequently leads to the forward displacement of the lid oil as the TF is compressed during the process of blinking. Therefore, leading to a greater accumulation and distribution of meibum on the precorneal TF (Yokoi, Takehisa and Kinoshita, 1996). Shimazaki *et al*. using the DR-1 grading scale found that when the upper lid was squeezed by the examiner's thumb to actively express some meibomian lipid. The DR-1 grades improved and a positive change in NIBUT was documented. This study showed greater TF stability was seen with thicker tear lipid layer (J, 1995). Hosaka *et al*. using the DR-1 DE severity grading found that TF thickness showed good correlation with other DE examinations. After punctal occlusion, TF thickness increased from 1.7 ± 1.5μm to 4.9 ± 2.8μm ($P$ = .001) with the improvement in tear meniscus height, fluorescein and rose bengal staining scores, TBUT, and Schirmer test. Interferometric TF thickness measurement found that impairment of precorneal TF formation in aqueous tear deficiency DE and was useful for showing the reconstruction of TF after punctal occlusion surgery. This study concluded that interferometry of precorneal TF is a useful tool that can evaluate DE in conjunction with other DE examinations (Hosaka *et al.*, 2011)

### 5.2.1 Study aim

To compare the effects of SMILE and femtosecond laser-assisted in situ keratomileusis (fs-LASIK) on the ocular surface and precorneal lipid layer interference patterns.

### 5.2.2 Sample size

The Power calculation was conducted using G*Power 3.1 (Faul *et al*., 2007) (ANOVA repeated measures within factor). A total of 100 patients (200 eyes) consisting of 50 SMILE and 50 LASIK patients were assessed. Sample size was determined using power calculation (80% power at the 5% level of statistical significance, $\alpha=0.05$) to detect a change of 1 unit change in interferometry DR-1 Score with 80% power ($\beta=0.2$) at the 5% level of statistical significance ($\alpha=0.05$), 100 subjects were required based upon published data (standard deviation in normal patients =±0.7) (Hosaka *et al.*, 2011).

### 5.2.3 Subjects

This retrospective, case series is from a population of patients seeking refractive surgery at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective audit study. Informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent. A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery. Exclusion criteria were previous ocular surgery, disease such as corneal opacity, corneal irregularity, meibomian gland dysfunction, glaucoma or retinal disease, and complications during surgery.

### 5.2.4 Experimental procedure

This retrospective, comparative, case series study was conducted in the Cathedral Eye Clinic, Belfast, Northern-Ireland, UK in accordance with the Declaration of Helsinki. All patients had provided informed consent for use of their anonymised pre and postoperative data for either audit, teaching or research purposes. Prior to the treatment, all patients were advised of the possible risks associated with the operation.

All SMILE and fs-LASIK was performed bilaterally by one experienced surgeon (J.E.M).

### 5.2.5 Patients

Fifty patients (100 eyes) had bilateral SMILE and fifty (100 eyes) spherical equivalent matched subjects with bilateral fs-LASIK were assessed. Myopic SMILE or fs-LASIK (spherical correction range, -1 to -7 dioptres; cylinder range, 0 to -1.5 dioptres), no contraindications to laser refractive surgery, and no previous history of DE were included in this retrospective analysis. Inclusion criteria were age 25 to 45 years, stable myopia for at least 1 year. Patients discontinued contact lenses 2-weeks before pre-operative baseline assessments were taken. Exclusion criteria were any active ocular pathology, previous ocular/eyelid medical or surgical treatment, systemic disorder, and pregnancy. Patients were assessed preoperatively and followed up at day-one, one-week, one-month, three-month and six-month postoperatively (Table 5.1).

A small (S) curved interface cone was used in all eyes. The femtosecond incisions were performed as follows:

- posterior surface of the lenticule (spiral in pattern)
- anterior surface of the lenticule (spiral out pattern)
- followed by a side cut of cap

The femtosecond laser parameters were as follows: 135μm cap thickness, 7.6 mm cap diameter, 6.5 mm lenticule diameter, 149 nJ power for lenticule making a 2.41 mm side cut for access to the lenticule, with angles of 90°.

**Table 5.1.** Demographic data.

| | Mean ± standard deviation |
|---|---|

| | SMILE patients (n=100 eyes) | fs-LASIK patients (n=100 eyes) |
|---|---|---|
| Age (years) | 32.8 ± 6.7 | 31.5 ± 8.4 |
| Range | 25, 42 | 24, 43 |
| Gender (F/M) | 28/22 | 34/16 |
| Preoperative spherical equivalent | –5.50±1.45 (range −1.00 to −7.00 D) | –5.45±1.35 (range −1.00 to −7.00 D) |
| Manifest cylinder (D) | −0.51±0.65 D (range 0.00 to −2.25 D) | −0.52±0.75 D (range 0.00 to -2.25 D) |
| Mean keratometric reading (D) | 43.3±1.33 D (range 40.5–47.0 D) | 44.1±1.41 D (range 40.4–46.0 D) |
| Endothelial cell density (cells/mm2) | 2804±267 (range 2265–3363 cells/mm2) | 2810±252 (range 2195–3422 cells/mm2) |
| Central corneal thickness (µm) | 546.1±32.9 (range 471–614 µm) | 551.2±41.7 (range 475–623 µm) |

### 5.2.6 Clinical exam and questionnaire

Slit-lamp examination of the ocular surface was conducted in a defined sequence including TBUT. QOV questionnaire, and OSDI questionnaires were also administered by a trained interviewer preoperatively and then at day-one, one week, one months and three months postoperatively. QOV visual symptoms questionnaire was also administered preoperatively and postoperatively at three-months. The QOV symptom questionnaire consists of seven questions related to common visual symptoms graded

on a scale from 0 to 3, depending upon the severity of the visual symptom (grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very). Patient satisfaction questionnaire survey was administered to evaluate patient satisfaction survey after SMILE or fs-LASIK treatment at one-month, three-month and six-month follow-up. It consisted of a single question “How were your expectations fulfilled?” and had four distinct scales as responses. This questionnaire was self-administered by the patient and the scale scores increased with satisfaction, ranging from 1 (not fulfilled at all) to 4 (more than fulfilled).

Preoperatively and postoperatively at day-one, one-week, one-month and three-month follow-up, all patients had a full ophthalmic examination on each eye, including manifest refraction (sphere, cylinder, and spherical equivalent), uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), uncorrected near visual acuity (UNVA) and corrected near visual acuity (CNVA) at 40cm with Radner reading charts under a standard mesopic lighting condition, (Radner charts allow direct conversion i.e. 0.2 logMAR distance acuity is comparable to 0.2 logRAD reading acuity with high correlation at 40 cm to a logMAR equivalent for size of letters) and uncorrected intermediate visual acuity (UIVA) and corrected intermediate visual acuity (CIVA) at 70cm. Further examinations included keratometry, corneal topography (Pentacam; Oculus, Germany), and OPD-scan auto refraction (NIDEK Co. Ltd., Japan), subjective refraction, slit-lamp examination, Goldmann tonometry, dilated funduscopy, pupil diameter, and angle kappa/p-dist with the Nidek OPD Scan II (NIDEK Co. Ltd., Japan).

### 5.2.7 Tear osmolarity and lipid layer distribution quality

Tear osmolarity was measured using the TearLab osmolarity system (TearLab Corp, San Diego, CA). An overall classification of the severity of DE was determined according to the modified scheme of the DEW Report (Lemp *et al*., 2007). The tear samples for osmolarity measurements were collected by placing the TearLab probe (TearLab Corp., San Diego, CA) (Albert, 2010) gently at the inferior lateral tear meniscus, taking care not to induce reflex tearing by touch the corneal surface. The

tear lipid layer quality was evaluated by using the Tearscope (Keeler, UK) along with DR-1 grading system (Yokoi, Takehisa and Kinoshita, 1996), based on a 2mm diameter observation area, by observing interference patterns of the lipid layer distribution layer on the corneal surface. Observed patterns were classified into five grades: grade 1, somewhat grey colour, uniform distribution; grade 2, somewhat grey colour, non-uniform distribution; grade 3, a few colours, non-uniform distribution; grade 4, many colours, non-uniform distribution; and grade 5, corneal surface partially exposed (Yokoi, Takehisa and Kinoshita, 1996). Assessments were conducted preoperatively, at day-1, 1-week, 1-month and 3-months postoperatively.

### 5.2.8 Corneal esthesiometry

Corneal sensitivity was measured using the contact nylon thread Luneau 12/100mm Cochet-Bonnet esthesiometer (Luneau, France). Starting from 6.0 cm, the filament length was progressively reduced in 5-mm steps until the first response occurred. The mean of 3 measurements taken at the centre of the cornea was measured preoperatively, at day-one, one-week, one-month, three-month and six-months postoperatively.

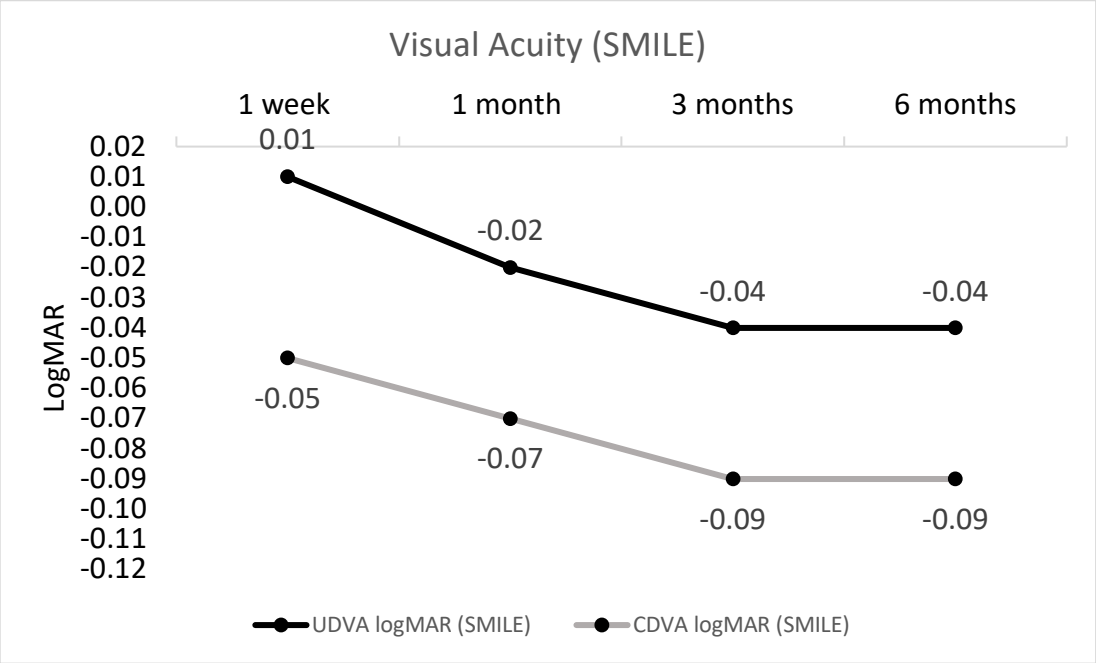
### 5.2.9 Statistical analysis

Descriptive statistics were created using SPSS (Statistical Package for the Social Sciences, Version 22, Chicago, Illinois, USA) and Excel (Microsoft; Redmond, Washington, USA). The Kolmogorov-Smirnov test was used to assess normality. The Student t test for paired parametric data was applied to assess the significance of differences between preoperative and postoperative data. The Wilcoxon rank-sum test was used when non-parametric data prevailed. Windows (Statistical Package for the Social Sciences, Version 22, Chicago, Illinois, USA.). The correlation between the DE tests and visual symptoms was performed using correlation coefficients. Differences were considered statistically significant when the P-value was less than 0.05.

### 5.3 Results

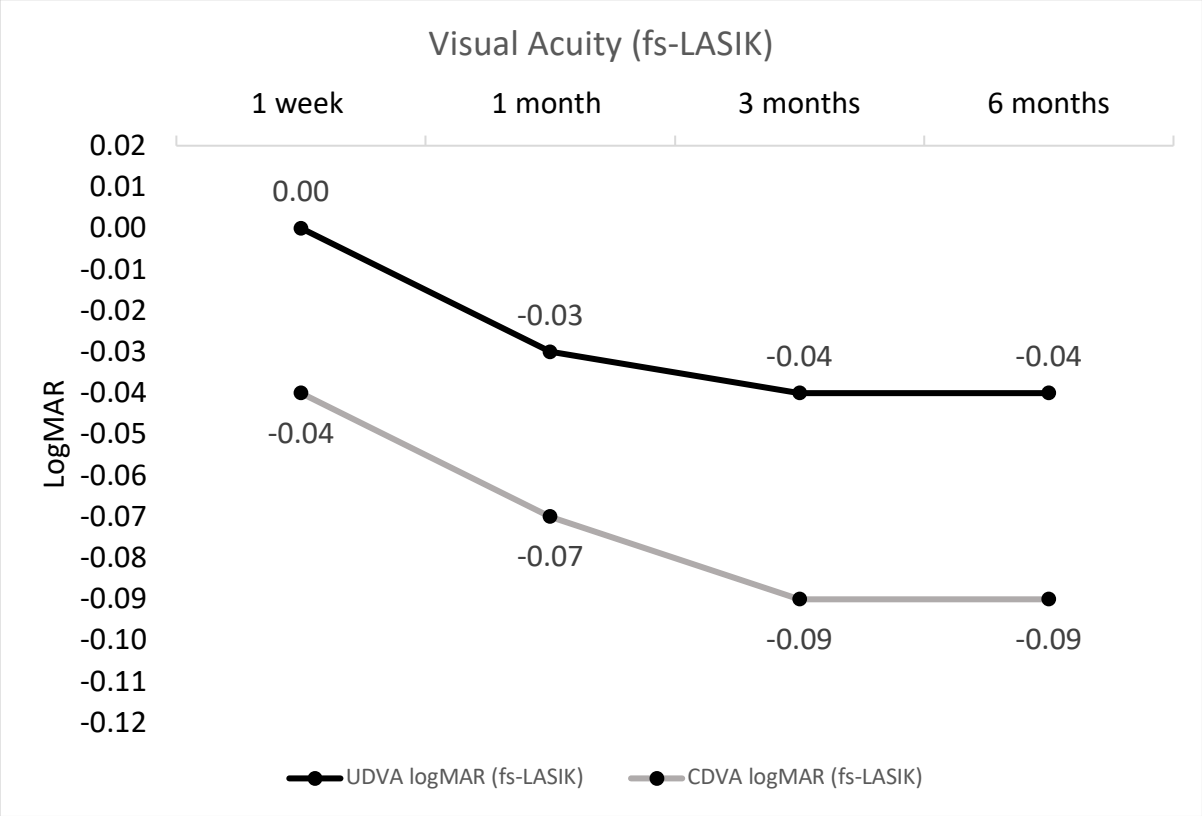
No adverse effects occurred in any of the 200 procedures. Figure 5.1 A and 5.1.B shows the visual outcomes of the 2 groups postoperatively.

**Figure 5.1 A.** Uncorrected distance visual acuity and corrected distance visual acuity postoperative of SMILE patients.



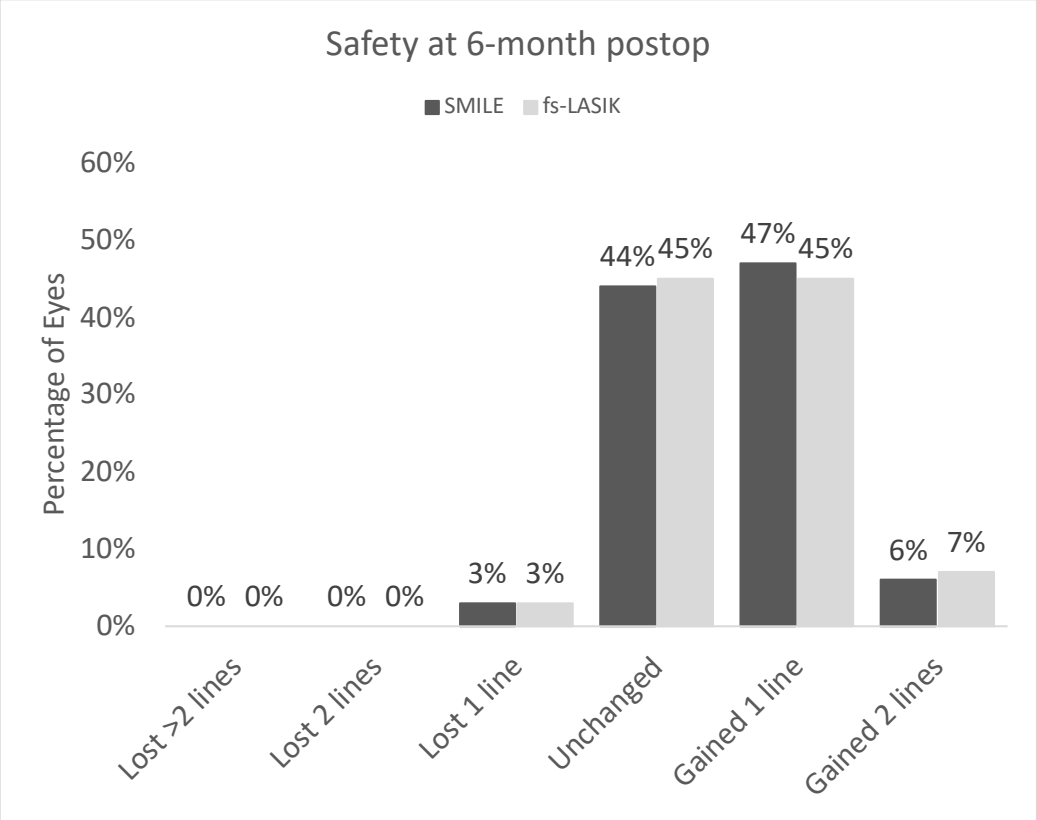

UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity.

**Figure 5.1.B.** Uncorrected distance visual acuity and corrected distance visual acuity postoperative of fs-LASIK patients.




UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity.

**Figure 5.2.** Changes in corrected distance visual acuity (Snellen/ logMAR lines) at 6 months postoperative.




At day-one and one-week postoperatively there was a high rate of signs and symptoms (OSDI questionnaire) of dryness experienced by all patients in both groups (Table 5.2) with no significant differences between the two groups. However, at one-month and six-months after surgery the SMILE patients experienced significantly lower symptoms of dryness as shown in Table 5.2. Tear osmolarity was higher in the fs-LASIK group at one-week, one-month, three-month and six-month postoperatively. At one, and three months after surgery corneal sensitivity, TBUT and tear lipid layer quality were significantly impaired in the fs-LASIK group compared to the SMILE group. When QOV questionnaire scores were analysed, a gradual improvement was found in the SMILE and fs-LASIK patients' subjective appreciation of vision. However, there was no statistically significant difference between SMILE and fs-LASIK groups. The percentage of patients using artificial tears six-months postoperatively in the SIMLE group was 10% and 30% in the fs-LASIK group (Table 5.2).

**Table 5.2.** Comparison of parameters

| | Pre treatment SMILE | Pre treatment F-LASIK | p-value |
|---|---|---|---|
| Tear osmolarity (mOsm/L) | 295.6±11.7 | 292.6±15.2 | 0.032 |
| Esthesiometry scale | 60.1±3.7 | 62.8±5.8 | 0.4 |
| DR-1 grading (1-5) | 2.1±1.2 | 2.3± 1.3 | 0.08 |
| TBUT (s) | 6.9±1.4 | 7.3 ± 1.7 | 0.063 |
| OSDI score (0-100) | 6.3±3.7 | 7.1±2.5 | 0.042 |
| QOV score (1-10) | 8.5±2.1 | 8.2±1.5 | 0.61 |
| Artificial tear use | - | - | - |
| | After treatment SMILE 1-day | After treatment fs-LASIK 1-day | p-value |
| Tear osmolarity (mOsm/L) | 318.7±9.7 | 320.1±12.7 | 0.059 |
| Esthesiometry scale | 37.2±3.4 | 26.2±4.8 | 0.06 |
| DR-1 grading (1-5) | 3.5±1.5 | 3.5±1.5 | 0.51 |

| | | | |
|---|---|---|---|
| TBUT (s) | 4.7±1.1 | 3.9±1.5 | 0.064 |
| OSDI score (0-100) | 22.7±10.7 | 23.9±12.3 | 0.073 |
| QOV score (1-10) | 7.1±1.5 | 6.2±2.8 | 0.06 |
| Artificial tear use | - | - | - |
| | After treatment SMILE 1-week | After treatment fs-LASIK 1-week | p-value |
| Tear osmolarity (mOsm/L) | 309.4±5.2 | 322.3±15.4 | 0.017* |
| Esthesiometry scale | 42.6±2.9 | 30.5±2.4 | 0.032* |
| DR-1 grading (1-5) | 2.7 ± 1.0 | 3.5±1.5 | 0.011* |
| TBUT (s) | 6.2±2.7 | 4.3±2.3 | 0.024* |
| OSDI score (0-100) | 20.4 ± 9.7 | 22.3±11.2 | 0.020* |
| QOV score (1-10) | 9.3±0.5 | 8.1±1.1 | 0.065* |
| Artificial tear use | - | - | - |
| | After treatment SMILE 1-month | After treatment fs- LASIK 1-month | p-value |
| Tear osmolarity (mOsm/L) | 302.9±10.8 | 319.2±9.4 | 0.027* |
| Esthesiometry scale | 55.9±8.1 | 31.7±3.9 | 0.041* |

| | | | |
|---|---|---|---|
| DR-1 grading (1-5) | 2.3±1.1 | 3.5±1.5 | 0.023* |
| TBUT (s) | 6.5±1.8 | 5.1±1.5 | 0.029* |
| OSDI score (0-100) | 15.1±9.4 | 20.3±8.2 | 0.015* |
| QOV score (1-10) | 9.5±0.4 | 8.7±1.2 | 0.32 |
| Artificial tear use | 26% (13 patients) | 44%(22 patients) | - |
| | After treatment SMILE 3-month | After treatment fs-LASIK 3-month | p-value |
| Tear osmolarity (mOsm/L) | 297.1±11.2 | 317.8±9.7 | 0.031* |
| Esthesiometry scale | 56.3±9.1 | 32.9±9.7 | 0.026* |
| DR-1 grading (1-5) | 2.3±1.2 | 3.0±1.5 | 0.015* |
| TBUT (s) | 6.7±1.5 | 5.01±1.3 | 0.034* |
| OSDI score (0-100) | 9.7±5.7 | 19.3±6.5 | 0.009* |
| QOV score (1-10) | 9.3±1.1 | 9.0±0.7 | 0.31 |
| Artificial tear use | 12% (6 patients) | 32% (16 patients) | - |
| | After treatment SMILE 6-month | After treatment fs-LASIK 6-month | p-value |
| Tear osmolarity (mOsm/L) | 297.1±11.2 | 317.8±9.7 | 0.035* |

| | | | |
|---|---|---|---|
| Esthesiometry scale | 56.3±9.1 | 32.9±9.7 | 0.010* |
| DR-1 grading (1-5) | 2.3±1.2 | 3.0±1.5 | 0.041* |
| TBUT (s) | 6.7±1.1 | 5.5±1.2 | 0.027* |
| OSDI score (0-100) | 9.6±3.1 | 15.6±5.2 | 0.011* |
| QOV score (1-10) | 9.2±1.0 | 9.1±1.2 | 0.4 |
| Artificial tear use | 10% (5 patients) | 30% (15 patients) | - |

Comparison between preoperative and postoperative (three-month) QOV visual symptoms (scale of 0-3) revealed that SMILE group had significant increase in 'glare' from 0.10±0.04 to 0.19±0.05. While in fs-LASIK group, 'glare' and 'fluctuation in vision' increased significantly from 0.12±0.05 to 0.25±0.15 and 0.05±0.04 to 0.17±0.10 respectively (Table 5.3).

**Table 5.3. Comparison of visual symptom**

| QOV questions for visual symptoms | Pre-treatment SMILE | After treatment SMILE 3-month | P-value |
|---|---|---|---|
| How much does glare bother you? | 0.10±0.04 | 0.19±0.05 | 0.04* |
| How much do the halos bother you? | 0.15±0.05 | 0.17±0.06 | 0.41 |
| How much do the starbursts bother you? | 0.12±0.10 | 0.13±0.05 | 0.7 |
| How much does hazy vision bother you? | 0.09±0.06 | 0.05±0.09 | 0.92 |
| How much does blurred vision bother you? | 0.18±0.05 | 0.15±0.10 | 0.3 |

| | | | |
|---|---|---|---|
| How much does fluctuating vision bother you? | 0.04±0.05 | 0.06±0.09 | 0.43 |
| How much do double images bother you? | 0 | 0 | - |
| | Pre-treatment fs-LASIK | After treatment fs-LASIK 3-month | P-value |
| How much does glare bother you? | 0.12±0.05 | 0.25±0.15 | 0.02* |
| How much do the halos bother you? | 0.10±0.02 | 0.13±0.05 | 0.08 |
| How much do the starbursts bother you? | 0.10±0.05 | 0.11±0.05 | 0.52 |
| How much does hazy vision bother you? | 0.05±0.05 | 0.03±0.10 | 0.73 |
| How much does blurred vision bother you? | 0.12±0.08 | 0.09±0.05 | 0.28 |
| How much does fluctuating vision bother you? | 0.05±0.04 | 0.17±0.10 | 0.02* |
| How much do double images bother you? | 0 | 0 | - |
| *Statistically significant.<br>Grading scale: 0 = not at all; 1 =a little; 2 = quite; 3 = very | | | |

Correlation between these increased visual symptoms (glare and fluctuating vision) with DE test revealed that tear lipid layer (DR-1 score) and TBUT had a strong correlation with these visual symptoms (Table 5.4).

**Table 5.4.** Correlations between dry eye test and visual symptoms

| | Post treatment SMILE 3-month | | Post treatment fs-LASIK 3-month | | | |
|---|---|---|---|---|---|---|
| | How much does glare bother you? | | How much does glare bother you? | | How much does fluctuating vision bother you? | |
| | R2 | P-value | R2 | P-value | R2 | P-value |
| Tear osmolarity (mOsm/L) | 0.21 | 0.010* | 0.18 | 0.025* | 0.17 | 0.4 |
| Esthesiometry scale | 0.13 | 0.45 | 0.2 | 0.32 | 0.29 | 0.037* |
| DR-1 grading (1-5) | 0.51 | 0.029* | 0.57 | 0.013* | 0.46 | 0.028* |
| TBUT (s) | -0.43 | 0.027* | 0.59 | 0.030* | -0.54 | 0.033* |
| *Statistically significant | | | | | | |

Postoperatively, at one-month 96% and 86% and at three months 98% and 90% of patients undergoing SMILE and fs-LASIK treatments respectively were ‘fulfilled’ and ‘more than fulfilled’ with their treatment (Table 5.5).

**Table 5.5.** Patient satisfaction

| | SMILE: 1 month postop | | fs-LASIK: 1 month postop | |
|---|---|---|---|---|
| How were your expectations fulfilled? | No. of patients | Percentage | No. of patients | Percentage |
| Not fulfilled at all | 0 | 0% | 0 | 0% |
| Sufficiently fulfilled | 2 | 4% | 7 | 14% |
| Fulfilled | 36 | 72% | 30 | 60% |
| More than fulfilled | 12 | 24% | 13 | 26% |
| | SMILE: 6-month postop | | fs-LASIK: 6-month postop | |

| How were your expectations fulfilled? | No. of patients | Percentage | No. of patients | Percentage |
|---|---|---|---|---|
| Not fulfilled at all | 0 | 0% | 0 | 0% |
| | | | | |
| Sufficiently fulfilled | 1 | 2% | 5 | 10% |
| Fulfilled | 28 | 56% | 31 | 62% |
| More than fulfilled | 21 | 42% | 14 | 28% |

### 5.4 Discussion

Since most of the standard DE assessment tools and methods such as Schirmer test, corneal staining and tear osmolarity test are invasive or minimally invasive (Sweeney, Millar and Raju, 2013). These tests therefore involve clinicians or researchers disturbing the natural TF of the patient. Tearscope, on the other hand, allows non-invasive assessment of the TF layer. Along with a digital slitlamp, Tearscope enables the assessor to capture images and videos of interference patterns and non-invasive TBUT of patients non-invasively.

Tearscope is a self-contained unit with a very small footprint. It only requires a USB electric power source. Once plugged into the power source, it can be held in hand or mounted on a slit lamp biomicroscope to make observations of the TF (Elliott *et al.*, 1998). Despite these advantages, there are other considerations before such instruments are likely to be adopted in general clinics. Currently, there is a lack of DE tear interferometry literature on tests, retest and diurnal variations of tear assessment by Tearscope and other similar instruments. Tearscope is a subjective instrument. Therefore, it is important to assess examiner variability, as this can influence the accuracy of results obtained by the Tearscope. In our study to overcome subjective bias; all patients first had their TF photographed and stored digitally. Later these photographs were anonymised, randomised and then scored. The scores were based on the validated DR-1 tear lipid layer grading system by a single experienced DE researcher.

Pathological changes in the TF physiology such as DE can frequently lead to decreased visual performance in patients during work and leisure activities. It has been well documented that a stable TF is essential in maintaining ocular health, visual quality and QOL (Jabbur *et al*. 2004; Lemp *et al.* 2007; De Paiva *et al*. 2006). Patients who have a myopic refraction are also frequently contact lens wearers and can be more prone to DE. Therefore, these patients frequently opt for laser refractive surgery (Solomon *et al.*, 2009). fs-LASIK for the past two decades has predominantly been the most popular corneal refractive surgery used to correct myopia (Solomon *et al.*, 2009). Studies have shown that although the refractive outcomes of fs-LASIK are excellent, ocular surface complaints such as DE are highly prevalent in postoperative patients (Toda, 2007; Solomon *et al.*, 2009). Post fs-LASIK DE symptoms can be sufficiently alleviated with artificial tear use, however artificial tears lack the complex mixture found in the healthy TF and only provide temporary relief. The current understanding of ocular surface physiology suggests that the disruption of corneal nerves during flap creation and excimer photoablation are the probable cause of DE post fs-LASIK (Toda *et al*. 2001; Albietz & Lenton 2004; Ang *et al*. 2001). As a result, there can be a decrease in TF quality, quantity and impairment in the epithelial wound healing process (Battat *et al.*, 2001). Although femtosecond laser in fs-LASIK improves patients' VA it is relatively common to suffer some degree of post-operative DE (Albietz and Lenton, 2004). SMILE is a procedure that involves femtosecond laser to create an intrastromal lenticule, which is then removed through a small corneal incision. In comparison to fs-LASIK, SMILE does not require excimer laser photoablation or complete flap creation. It is a minimally invasive approach as it requires only a key hole/ small incision which can potentially reduce the impact of corneal refractive surgery upon the corneal nerves and the general ocular surface, thereby protecting patients against DE (Reinstein, Archer and Gobbe, 2014). The Dry Eye Workshop defines DE to be multifactorial in origin at the ocular surface, which includes TF changes with or without corneal damage, ocular symptoms, visual degradation, and increased tear osmolarity resulting in a degradation of QOL (Lemp *et al*. 2007). Therefore, an objective and subjective assessment were included in this study. DE has been recorded to be the most frequent complication following laser refractive surgery (Ang *et al*. 2001; Solomon *et al*. 2009; Denoyer *et al*. 2015). Although DE is usually benign and transient, it has the potential to impair visual performance and QOV. The injury to corneal nerves results in a decrease in corneal sensitivity which leads to

altered tear production both in quality and quantity (Battat *et al.*, 2001; Benitez-del-Castillo *et al.*, 2001; Barequet, Hirsh and Levinger, 2008). Inflammation can also decrease tear lipid layer quality and toxicity from medication can further compound DE problems (Peng *et al.*, 2014). In our study an alteration to TF physiology and corneal sensitivity was observed immediately after surgery in both the SMILE and fs-LASIK groups and was more prominent and prolonged in the fs-LASIK group. The findings at day-one post laser refractive surgery in both groups may not be conclusive, as they might have been influenced by post-operative medication and drops. However, at one-week, one-month, three-months and six-months significant differences in post-operative findings were observed. We know that laser refractive surgery has an influence upon TF physiology and thereby also affects the tear lipid layer quality. Tear lipid layer quality and quantity has been documented to play an important role in DE (Versura, Profazio and Campos, 2010; Peng *et al.*, 2014). Meibum from meibomian glands contribute to the outermost lipid layer of the TF and a stable lipid layer is important for a healthy corneal surface (Peng *et al.*, 2014). Since the meibum secretion is modulated by the blink rate (Korb and Greiner, 1994) and it has been observed that meibomian gland dysfunction can be exacerbated by fs-LASIK as it disrupts the blink rate (Pflugfelder *et al.*, 1998; Benitez-del-Castillo *et al.*, 2001; Chao, Golebiowski and Stapleton, 2014). In creation of the LASIK flap, the femtosecond laser energy level is higher and the position and extent of treatment impacts to greater degree than SMILE upon the corneal nerves. The resultant nerve injury and inflammatory response may lead to disruption of the neuroanatomic reflex controlling blink rate, aqueous tear production and in turn affect lipid expression from meibomian glands. In our study the increase in visual symptoms of ‘glare’ and ‘fluctuating vision’ correlated significantly with the tear lipid layer and TBUT suggesting the importance percorneal in QOV and the disruption in the tear lipid layer leads to increased DE symptoms following laser refractive surgery. This in turn, had an influence in the visual performance in patients (Table 5.4). Corneal sensitivity, tear lipid layer, and osmolarity along with VA improved in both groups at six-months but corneal sensitivity, tear lipid layer, osmolarity and OSDI scores were significantly better in the SMILE group. It is there for plausible to state that reduced surgical impact upon the corneal and principally the corneal nerves is the reason for reduced post-refractive DE present in the SMILE cohort (Li *et al.*, 2013)(Table 5.2).

The corneal sensitivity findings in our study are consistent with other studies that have documented a delay in the normalisation of corneal sensitivity in fs-LASIK patients compared to SMILE patients at six-months post-surgery (Versura, Profazio and Campos, 2010; Sekundo, Kunert and Blum, 2011; Vestergaard *et al.*, 2013). However, these published studies have indicated that it took up to twelve-months for corneal sensitivity to reach preoperative levels. This study to date has been assessed only up to six months postoperatively, it is yet to be seen if and at what postoperative period both corneal sensitivity along with TF osmolarity, tear breakup time and tear lipid quality will fully normalise. The difference in QOV scores between the two groups was not significant postoperatively, suggesting that the optical performance of both the procedures were at par with each other. This study also observed that the mean QOV gradually improved in both the groups. This gradual improvement was also observed with other objective parameters such as corneal sensitivity, TBUT and tear lipid layer. This gradual change therefore can be attributed to the healing process of the ocular surface post operation.

The boundary between the TF and the outer environment accounts for the largest refractive index differential and therefore is crucial for good vision. DE due to unstable TF and tear lipid layer can therefore lead to glare and fluctuations in vision and affect the overall QOV in patients. The gradual improvement in the QOV questionnaire scores up the three months period may be partly explained by the demonstrable improvement in TF and general ocular surface function also demonstrated by a gradual reduction in OSDI scores.

This study indicates a possible advantage of the SMILE procedure over LASIK, with regards to postoperative recovery time of the ocular surface health. This could indicate a value in stratifying patients preoperatively into either SMILE or fs-LASIK, depending upon the risk of postoperative DE problems. A limitation in our study however, was that patients the two groups were not matched by gender.

## 5.5 Conclusion

SMILE procedure demonstrated improved TF characteristics and subjective DE symptoms over fs-LASIK up to six months post laser refractive surgery for myopic patients. Reduction in lipid layer was demonstrated to be greater in the fs-LASIK group and correlated with the subjective symptoms of glare and fluctuation of vision postoperatively. Non-invasive interferometry assessment of precorneal TF may be helpful for evaluating DE along with other DE examinations. It can be a usefully tool assess and monitor recovery from laser procedures.

### 5.6 Summary

This chapter showed that the severity and TF dysfunction can vary between different refractive surgeries; these differences should be considered in patient management. TF lipid layer contributes to the overall QOV and can be used for pre and postoperative assessment of DE along with other DE examinations.

# Chapter 6: THE IMPACT OF CROSSLINKING AND TRANSEPITHLIAL PHOTOTHERAPEUTIC KERATECTOMY UPON THE QUALITY OF VISION AND QUALITY OF LIFE IN KERATOCONIC EYES

## 6.1 Introduction

The concept of corneal collagen cross-linking (CXL) was described over a decade ago and now it is considered as one of the most important findings in modern ophthalmology. In biological science, the term 'cross-linking' refers to the formation of chemical links following a chemical reaction between proteins or other molecules. Cross-links are usually formed by chemical reactions facilitated by heat, pressure, or radiation. Enzymatic and non-enzymatic cross-linking can be observed in the ageing process of the human body where various tissues such as the skin and arteries undergo stiffening and hardening. An important observation that led to the therapeutic use of CXL for kerataconic eyes was the finding that diabetic patients often did not express the progression of corneal ectatic disorders as nonenzymatic cross-linking was occurring on the cornea due to the pathophysiology of diabetes (Seiler *et al.*, 2000). Prior to CXL, there were no available treatments to address the underlying pathology. Management simply consisted of, observation and using hard contact lenses to optimise the VA. If the use of contact lens resulted in scarring or corneal ectasia due to the loss of corneal weakness, corneal transplantation was preformed to regain vision. CXL is able to arrest the progression of corneal ectasia by strengthening the biomechanical structure of the corneal and increasing the resistance of the treated collagen to collagenases (Spoerl, Wollensak and Seiler, 2004). Long term safety and efficacy of CXL has now been established and documented in several studies. CXL has not only shown to stop the progression of disease but also significantly improve VA, spherical equivalent, astigmatism and keratometric parameters of the diseased cornea. These positive findings of CXL treatment have prompted researchers to investigate outcomes from combining CXL with other refractive procedures (termed CXL plus) in-order to optimise visual and topographic outcomes. Overall, CXL and CXL plus has demonstrated significant promise and represents a clear example of recent advances in ocular therapy.

### 6.2 Scheimpflug imaging for keratoconus and ectatic disease

Scheiumpflug cross sectioning anterior segment imaging systems have several advantages in comparison to the traditional placido curvature analysis and ultrasound pachymetry. A three-dimensional reconstruction of the anterior segment is achieved by measuring the anterior and posterior corneal surface along with the anterior and posterior surface of the lens. Since changes on both posterior cornea and corneal thickness are early indicators of ectatic change, Scheimpflug imaging improves identification of these pathological changes. Additionally, a larger surface of the cornea is assessed in comparison to placido devices. This added coverage allows for the diagnosis of peripheral diseases such as pellucid marginal degeneration (PMD).

The advent of corneal refractive surgery and CXL has revealed that better and more accurate imaging systems are required for the diagnosis and treatment of KC and therefore cannot be solely based on central corneal thickness and anterior curvature analysis of the cornea (Ciolino, Khachikian and Belin, 2008; Li *et al.*, 2008; Greenstein, Fry and Hersh, 2011). The removal of the corneal tissue in refractive surgery places a physical demand on the cornea. Therefore it is imperative to identify and locate potential corneal ectatic changes (Holland and Reinstein *et al*. 2000). Additionally, in CXL, in-order to stabilise early progression and prevent visual loss the ectatic changes must be identified prior to significant changes to the corneal structure. Ultrasonic central pachymetry has been proven to be a useful corneal assessment tool in very early KC where epithelial compensation can be masked by the presence of an underlying cone as seen on front surface topography (Reinstein, Archer and Gobbe, 2009).

There have been numerous advancements in imaging techniques such as optical cross-sectioning, and OCT that enables the assessor to measure the anterior and posterior cornea, corneal thickness maps and greater corneal assessment coverage using videokeratoscopes (Belin and Khachikian, 2007; Kim *et al.*, 2009; Yazici *et al.*, 2010). The advantages of using Scheimpflug photography system is its ability to construct a full corneal thickness map that can be used to locate and identify the location and magnitude of the thinnest part on the cornea (Belin and Ambrósio, 2013).

The Pentacam (OCULUS GmbH, Wetzlar, Germany) currently provides a comprehensive refractive screening display (Belin/Ambrosio Enhanced Ectasia Display III– (BAD III)) that combines nine different tomographic parameters as a screening tool. The parameters are also displayed as a regression analysis plot to enable the assessor to identify potential risk for ectatic change (Belin and Ambrósio, 2013):

- Anterior elevation at the thinnest point
- Posterior elevation at the thinnest point
- Anterior elevation change
- Posterior elevation change
- Corneal thickness at thinnest point
- Thinnest point on cornea (x/y postion)
- Pachymetric progression
- Ambrósio relational thickness
- Kmax

### 6.3 Corneal cross-linking in keratoconus

CXL has been documented to be a minimally invasive surgical treatment for managing ectatic corneal disorders, such as KC, PMD and post-LASIK corneal ectasia (Wollensak, Spoerl and Seiler, 2003; Wollensak, 2006; Hafezi *et al.*, 2007; Spadea, 2010). It has been documented in previous studies that in KC there is a significant reduction in diagonal linking collagen fibrils (Sherwin and Brookes, 2004). Since these fibrils contribute to the mechanical stability of the cornea. The reduction of these fibrils contributes to the weakening of the corneal structure and thinning of the central and para-central areas. Consequently, leading to irregular astigmatism, myopia and reduction in VA. CXL therapy leads to the formation of cross-links which are chemical bonds among stromal collagen fibrils which results in strengthening and stabilisation of the weak cornea. CXL uses riboflavin (vitamin B2) in conjunction with UV-A irradiation upon the cornea that allows the formation of crosslinks between collagen fibrils in the corneal stroma. This results in stiffening and arrests the progression of

corneal ectasia (Wollensak, Spoerl and Seiler, 2003; Wollensak, 2006). Prior to therapeutic CXL the treatment options for ectatic corneal disorders were spectacle correction, contact lenses, intrastromal and corneal ring segment (Siganos *et al.*, 2003). In advanced cases of KC, lamellar or penetrating keratoplasty (Frost *et al.*, 2006). These interventions only provided symptomatic solution and did not address the pathology of ectatic disorder. In comparison, CXL has been documented to halt the progress by intervening at the pathophysiology level rather than purely symptom alleviation.

Dresden protocol is the original surgical CXL technique which was first described by Wollemsak *et al*. (Wollensak, Spoerl and Seiler, 2003). The Dresden treatment protocol constitutes the benchmark for all other CXL procedures to be evaluated against for safety and efficacy. The CXL procedure is conducted under a sterile operating room after the application of topical anaesthesia. The central 8 to 9 mm of the epithelium is removed with the aid of mechanical removers such as a blade or rotating brush. It can also be removed with the use of alcohol or laser. Riboflavin (B2) solution (0.1%) is applied at an interval of 2 to 5 mins for approximately 30 minutes to promote the complete penetration of the riboflavin into the corneal stroma. A yellow flare in the anterior chamber signifies complete stroma penetration of riboflavin. The riboflavin in CXL treatments functions as a photo sensitizer for the induction of cross-links and selectively filters, which protects the underlying tissues from the harmful influence of UV-A. Wollensak *et al* demonstrated the cytotoxic irradiance levels is at 0.5 mW/cm2 for keratocytes after UV-A irradiation combined with the photosensitizer riboflavin, which is 10-times lower than the cytotoxic irradiance of 5 mW/cm2 after UV-A-irradiation alone (Wollensak *et al*. 2003). Wollensak *et al.* also demonstrated that the minimum preoperative corneal thickness required to safely prevent posterior corneal tissue injury during CXL was 400 um (Wollensak, 2006). These findings were also verified by Spoerl *et al*. who reported that the safety threshold of 400 um was necessary to limit UV-A irradiance to less than 1 J/cm2 at the level of the corneal endothelium, anterior chamber, lens and retina (Spoerl *et al.*, 2007). The riboflavin saturated cornea is exposed to UV-A energy for a total of 30 minutes. During the CXL treatment, riboflavin is applied every 2 to 5 minutes to ensure adequate absorption. After the completion of the procedure, a bandage contact lens is applied until the

epithelium is completely healed along with the application of topical corticosteroids, non-steroidal anti-inflammatory agents and antibiotic.

The factors related to successful CXL treatment in-terms of postoperative VA, improved keratometry and absence of adverse events have been investigated and have concluded that preoperative VA, eccentricity of the cone, pretreatment maximum keratometry (Kmax), age above 35 years, and sex are all predictors of CXL efficacy and safety (Koller *et al*. 2009; Koller *et al*. 2011). In addition, the negative association between smoking and KC has also been reported (Spoerl, 2008). While Hafezi (2009) suggests that smoking could possibly alter the biomechanical structure of the cornea and precorneal TF lipid layer (Altinors *et al.*, 2006).

### 6.4 Corneal cross-linking plus

The term 'CXL Plus' was first introduced by Kymionis in 2011, which generally refers to the addition of laser refractive procedures to optimise the outcome of CXL therapy (Kymionis, 2011). It has documented that CXL therapy on its own cannot significantly improve vision. Therefore, the addition of other complimentary procedures such as laser refractive surgery, intracorneal ring segments, phakic intraocular lens implantation along with CXL has shown to significantly improve VA. Currently, controlled clinical studies on CXL plus procedures are:

- Transepithlial phototherapeutic keratectomy (trans-PTK).
- Topography -guided and other forms of photorefractive keratectomy (PRK).
- Corneal implants, also known as intracorneal ring segments.

Kymionis *et al*. (2012) found that modifying Cretan protocol by removal of epithelium using trans-PTK resulted in better visual and refractive outcome in comparison to mechanical epithelial debridement. Labiris *et al*. (2012) investigated the effect of CXL and CXL combined with trans-PTK upon the QOL by means of the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25). The study concluded that CXL, and especially CXL combined with trans-PRK, had a greater positive impact on

self-reported QOL (Labiris *et al.*, 2012). While Kanellopoulos & Binder (2011) were successful with topography-guided PRK–CXL in post-LASIK ectasias, using the Athens protocol, results from Coskunseven *et al*. and Awady *et al*. have shown the benefits of combining intracorneal ring segments along with CXL in keratoconic eyes (Coskunseven *et al.*, 2009; El Awady, Shawky and Ghanem, 2012). Historically, trans-PTK using an excimer laser has been used to effectively smooth the anterior, irregular cornea as well as to remove the epithelium (Ambrósio & Wilson 2003; Holzer *et al*. 2005; Greenstein *et al.* 2011). In all the published studies it is apparent that there is significant variation in the postoperative responses to either the CXL treatment or the combined CXL plus treatments. It is likely that here are many factors which may be involved in the effectiveness and consequences of trans-PTK CXL treatment. In this chapter a comprehensive set of pre and postoperative factors are analysed in an attempt to determine the influence of preoperative factors that might impact subsequent postoperative VA outcomes in kertoconic eyes undergoing trans-PTK treatment. The aim of this study is to determine preoperative factors that can predictive positive outcomes from CXL plus trans-PTK treatment. Table 6.1 summarises various CXL studies performed in eyes with progressive KC.

**Table 6.1.** Outcomes with CXL and combined trans-PTK and CXL procedures

| Author | Number of Eyes | Follow-up (months) | Procedure | Outcomes |
|---|---|---|---|---|
| G Wollensak *et al*. (2003) | 23 | 3 to 48 | CXL | ↓2.01 D Ksteep*; ↑1.26 lines in 65 per cent |
| Raiskup-Wolf *et al*. (2008) | 480 | 6 to 72 | CXL | ↓Ksteep 2.68D at 1year; ↓4.84D at 3-years*; ≥1 line in 53 per cent at 1-year and 58 per cent at 3-years* |

| | | | | |
|---|---|---|---|---|
| Coskunseven, Jankov & Hafezi (2009) | 38 | 5 to 12 | CXL | ↓Kmax 1.57 D*; ↑UCV 0.06 logMAR; ↑ VA 0.1* |
| Caporossi *et al*. (2010) | 44 | 48 to 60 | CXL | ↓Kave 2.26 at 4-years; ↑UCV 2.85 Snellen lines. |
| Koller *et al*. (2011) | 151 | 12 | CXL | ↓Kmax >1.00 D in 37.7 per cent, ↓ Kmax >2.00 D in 13 per cent, 60.3 per cent stable |
| Wittig-Silva *et al*. (2008)** | 66 | 12 | CXL | ↓Ksteep 1.45, 50 per cent > 1.00 D |
| Hassan Hashemi (2013) | 40 | 60 | CXL | ↓Kmax 0.16 D |
| Kymionis *et al*. (2012) | 38 | 12 | trans-PTK+CXL (group 1) and<br>CXL (group 2) | ↑ VA*, ↓Ksteep* in group 1 |
| Kapasi *et al*. (2012) | 34 | 1 | trans-PTK+CXL (group 1) and<br>CXL (group 2) | ↓SE* in group 1 |
| *Statistically significant result. **Randomised controlled trial. UCVA: uncorrected vision, VA: best visual acuity, Ksteep: maximum keratometry value on the steepest | | | | |

axis, Kmax: maximum keratometry, Kave: average keratometry reading, PTK: photorefractive keratectomy, CXL: corneal collagen cross-linking

### 6.4.1 Study aim

This was an interventional case series of 41 patients (48 eyes). The primary purpose of this study was to evaluate the outcomes of a series of patients who were treated with either simultaneous trans-PTK or mechanical epithelial removal prior to CXL for progressive KC and to determine the possible preoperative factors that promote improved VA after trans-PTK treatment.

### 6.4.2 Sample size

Kapasi *et al*. (2012) had compared visual outcomes of patients with KC treated with either trans-PTK or mechanical epithelial removal prior to CXL based on this data, a sample size calculation using G*Power 3.1 (Faul *et al.*, 2007) using two-way paired t-test to achieve 80% power at an alpha level of 0.05, indicating a total of 48 eyes).

### 6.4.3 Subjects

This retrospective, case series is from a population of patients seeking treatment for KC at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective study, only informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent. A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery. Exclusion criteria were previous ocular surgery, ocular disease such as corneal opacity, corneal irregularity, DE, and any degree of amblyopia, glaucoma or retinal disease, and complications during surgery. In this retrospective nonrandomized comparative case series study, 41 patients (44

eyes; in a consecutive series), 29 men and 12 women, with progressive KC were included. The clinical diagnosis of KC was based on corneal topography data (Pentacam; Oculus, Germany). Inclusion criteria were progressive KC (KC was described as progressive when there was an increase in the cone apex keratometry of 0.75 diopters (D) or an alteration of 0.75 D in the spherical equivalent refraction in the last six months) (Gore, Shortt and Allan, 2013). Once the diagnosis of KC was confirmed, the patients were informed of their options, including CXL and CXL with trans-PTK. All the patients were advised of the possible risks associated with the operation. Surgery was performed in the following manner: same-day simultaneous trans-PTK and CXL in group-1 eyes and CXL on group-2 eyes. Expected corneal thickness at the apex of the cone after phototherapeutic keratectomy (trans-PTK) was more than 400μm, and no other corneal pathologic sign was observed.

### 6.4.4 Experimental procedure

Clinical Assessment

The preoperative and postoperative (at one, three, six, and nine months) evaluations consisted of general and ocular health history assessment; corneal topography (Oculus Pentacam), assessment of uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and manifest refraction, Aladdin pupillometry (Topcon), and slit-lamp examination of the anterior and posterior segments were performed on all eyes. Patient reported outcome measures for the QOV and DE were captured using the QOV, QOV-L (McAlinden, Pesudovs and Moore, 2010) and OSDI questionnaires respectively at (preoperative and postoperative at one, three, six, and nine months). The QOV questionnaire is a validated questionnaire that assesses visual satisfaction of a patient on a linear 0 to 10 scale, to define each patient's comprehensive subjective view of total QOV. The QOV-L questionnaire is a six-question instrument for the evaluation of the impact of vision impairment upon the QOL of the patient. It is a vision-specific instrument that assesses 3 vision-depended domains that include patient specific distance activities, intermediate activities and near activities rated on a scale of 1 to 5, depending according to level of visual

impairment (1=clear; 2=slight impairment; 3=moderate impairment; 4=severe impairment; 5=intolerable).

Table 6.2 describes abnormal and pathological values for the topography indices (from topography device user's manual).

Index of Surface Variance (ISV) was assessed in all treatment eyes. ISV is a measure of the standard deviation of individual corneal sagittal radii from the mean curvature of the same eye. It expresses the corneal surface irregularity. It is elevated when the corneal surface is irregular. An index of surface variance equal to or greater than 37μm is considered abnormal and larger than 41μm is considered pathological (Kanellopoulos and Asimellis, 2013).

Index of vertical asymmetry (IVA) which is expressed in mm was assessed in all treatment eyes. IVA is the mean difference between the superior and inferior corneal curvature. Therefore, IVA denotes the value of curvature symmetry with respect to the horizontal meridian as the axis of reflection. An IVA value of larger than 0.28 is abnormal and larger than 0.32 is considered pathological (Kanellopoulos and Asimellis, 2013).

Keratoconus Index (KI) was also assessed. KI is the ratio between mean radius values in the upper and lower segment (r sagittal superior to r sagittal inferior). A value equal to or larger than 1.07μm is considered abnormal/pathological (Kanellopoulos and Asimellis, 2013).

Central keratoconus index (CKI) is the ratio between the mean radius values in a periphery ring divided by the central. CKI is found to be elevated in central pachymetric and increases with central KC severity. A value of greater than 1.03 is considered as abnormal and pathological (Kanellopoulos and Asimellis, 2013).

Index of height asymmetry (IHA) is the mean difference between the height values superior minus the height values inferior with the horizontal meridian as minor axis and is expressed in um. It denotes the degree of symmetry of the height measurements with respect to the horizontal meridian as the axis of reflection. IHA

and IVA are similar, however since IHA is based on corneal elevation, it is considered to be more sensitive. An IHA value of greater than 19 is considered abnormal while greater than 21 is considered pathological (Kanellopoulos and Asimellis, 2013).

Index of height decentration (IHD) is the value of decentration of elevation data in the vertical direction and is expressed in um. It is calculated on a ring of radius of 3mm and provides the degree of decentration in the vertical direction. An IHD value of greater than 0.014 is abnormal while a value of larger than 0.016 is considered pathological (Kanellopoulos and Asimellis, 2013).

Additionally, minimum radius of Curvature (Rmin) of all treated eyes was measured. This is a measurement of the smallest/minimum radius of sagittal corneal curvature (i.e. the maximum steepness of the cone). Values less than 6.71mm are considered abnormal and/or pathological (Kanellopoulos and Asimellis, 2013).

**Table 6.2.** Description of topography indices

| Index | Abnormal | Pathological |
|---|---|---|
| ISV | ≥37 | ≥41 |
| IVA | ≥0.28 | ≥0.32 |
| KI | ≥1.07 | ≥1.07 |
| CKI | ≥1.03 | ≥1.03 |
| Rmin | <6.71 | <6.71 |
| IHA | ≥19 | >21 |
| IHD | >0.014 | ≥0.016 |
| ISV: index of surface variance; IVA: index of vertical asymmetry; KI: keratoconus index; CKI: central keratoconus index; Rmin: minimum radius of curvature; IHA: index of height asymmetry; IHD: index of height decentration. | | |

### 6.4.5 Surgical Technique (Dresden protocol and modified Dresden protocol)

All procedures were performed at Cathedral Eye Clinic, Northern-Ireland, Belfast by the same surgeon (J.E.M.) under sterile conditions. All patients received CXL, according to the Dresden protocol (Wollensak, 2006). Additionally, group 1 patients underwent a modification of the Dresden protocol with trans-PTK ablation using a 5.5mm optical zone and a depth of 55μm with Amaris excimer laser (Schwind, GmbH) prior to their CXL treatment. The epithelial defect was then manually enlarged using an epithelial scraper.

### 6.4.6 Numerical Evaluation

Corneal flattening at 6-months post-CXL was defined by a decrease in the maximum K reading compared with the preoperative value. Thus, the main variable was:

$$\Delta Kmax = Kmax\ (preop) - Kmax\ (9\ month)$$

where ΔKmax is the change in the maximum K value, Kmax (preop) is the maximum preoperative K value, and Kmax (9month), is the maximum K value at 9 months postoperatively.

The magnitude of change of outcomes in parameters such as ΔKmin, ΔUDVA, ΔCDVA, Δindex of surface variance, Δkeratoconus index, ΔRmin, ΔQOV score, ΔQOV-L score ΔOSDI questionnaire, and Δendothelial cell count was also calculated.

### 6.4.7 Statistical Analysis

Statistical analysis was performed using SPSS for Windows software (version 22, SPSS, Inc.) and Excel software (Microsoft Corp.). The Kolmogorov-Smirnov test was used to assess normality. For assessing continuous normal data, 1-way analysis of variance (ANOVA) with Tukey post hoc comparison was used. For assessing nonparametric data, the Kruskal-Wallis and Mann-Whitney U tests were applied. Linear regression analysis was performed to seek possible correlations. For all statistical analysis, the level of significance was a P value less than 0.05.

## 6.5 Results

Follow-up time was 9 months for all patients included in the study. Table 6.3 shows the demographic data. Figures 6.1 and 6.2 show preoperative and postoperative topographies of sample patients' A and B who had undergone simultaneous trans-PTK prior to CXL (group 1) and manual debridement CXL (group 2), respectively.

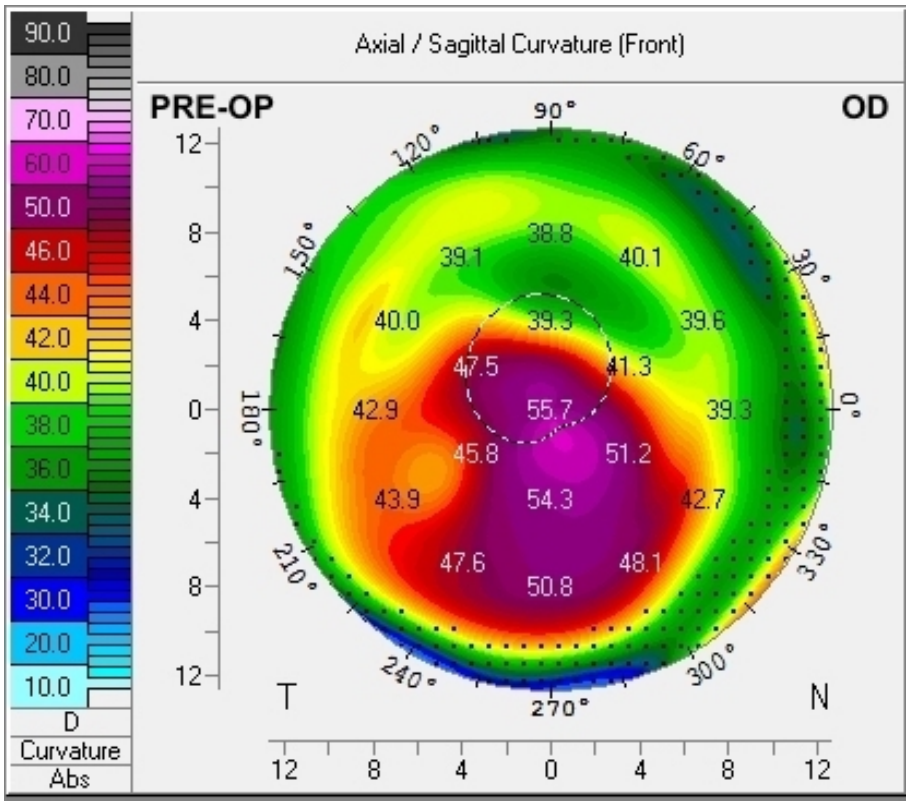
**Table 6.3.** Patient demographics

| | | |
|---|---|---|
| Patients | | |
| Trans-PTK (group 1) | 20 | |
| Manual debridement (group 2) | 21 | |
| Total | 41 | |
| Eyes | | |
| Trans-PTK (group 1) | 24 | |
| Manual debridement (group 2) | 24 | |
| Total | 48 | |
| Age (years) | | |
| Trans-PTK (group 1) | 28±3.5 | |
| Manual debridement (group 2) | 27±4.7 | |
| | | |
| Sex | | |
| Trans-PTK (group 1) | 14 males | 6 females |
| Manual debridement (group 2) | 15 males | 6 females |
| | | |
| Parameters | Preop | |
| SE (D) | | |
| Trans-PTK (group 1) | -4.2±3.5 | |
| Manual debridement (group 2) | -3.7±3.1 | |
| P-value | 0.12 | |
| | | |
| Corneal Pachymetery (µm) | | |

| | |
|---|---|
| Trans-PTK (group 1) | 442±45 |
| Manual debridement (group 2) | 467±42 |
| P-value | 0.09 |

D: Dioptre; SE: Spherical equivalent; trans-PTK: transepithelial phototherapeutic keratectomy; µm: micrometre.

**Figure 6.1.** Topographies obtained from patient A. Remodelling process following CXL: topographical changes. Scheimpflug analysis of the anterior corneal surface at nine-months after CXL with trans-PTK.



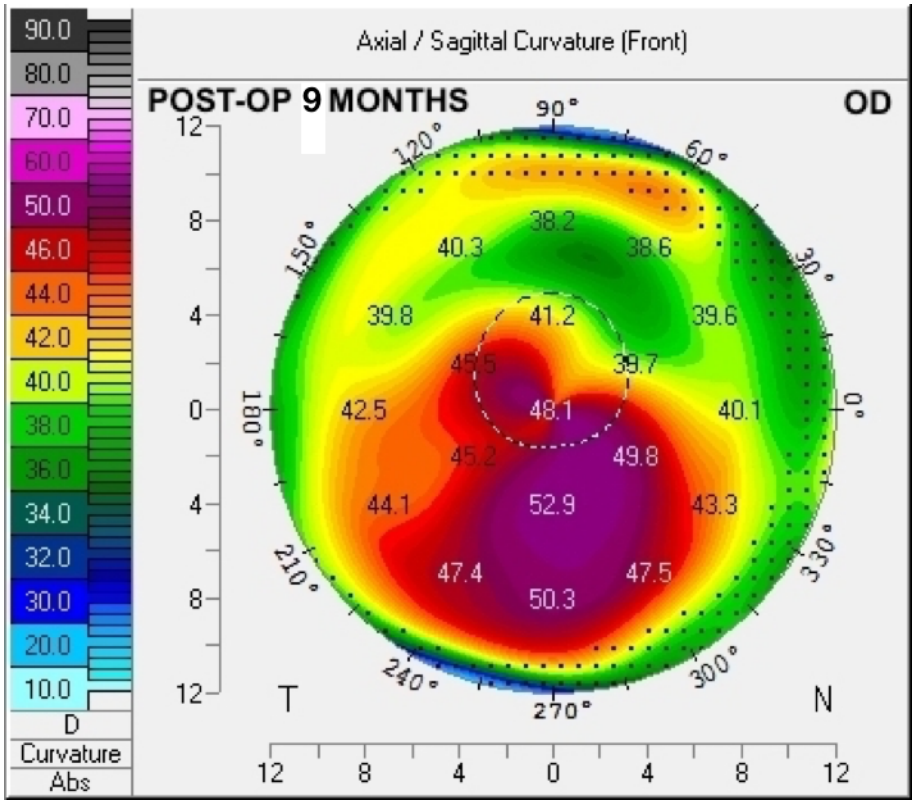
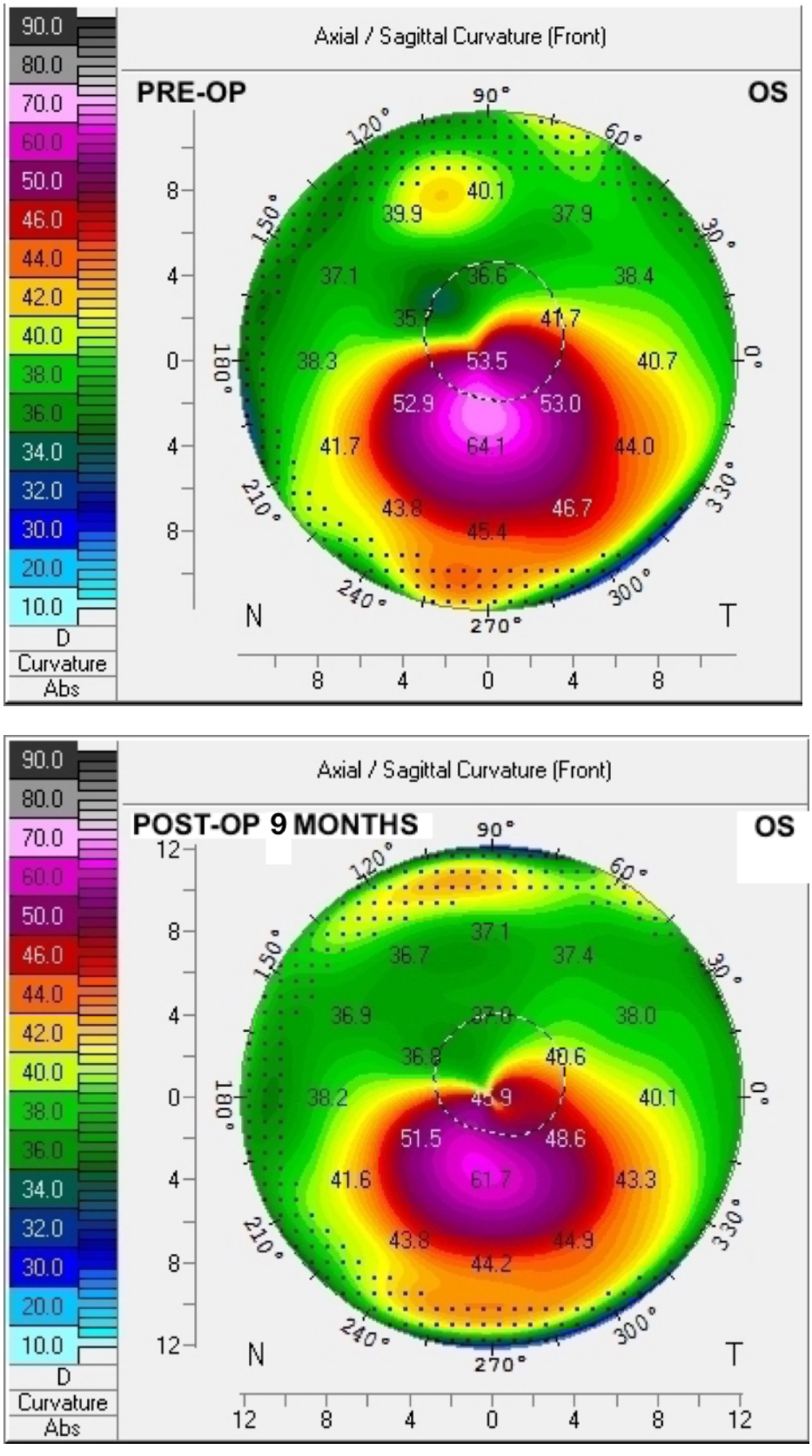

Axial / Sagittal Curvature (Front)
POST-OP 9 MONTHS
OD
90.0
80.0
70.0
60.0
50.0
46.0
44.0
42.0
40.0
38.0
36.0
34.0
32.0
30.0
20.0
10.0
D
Curvature
Abs
90°
120°
60°
150°
30°
180°
0°
210°
330°
240°
300°
270°
T
N
38.2
40.3
38.6
39.8
41.2
39.6
39.7
42.5
48.1
40.1
49.8
44.1
52.9
43.3
47.4
47.5
50.3
12
8
4
0
4
8
12

**Figure 6.2.** Topographies obtained from patient B. Remodelling process following CXL: topographical changes. Scheimpflug analysis of the anterior corneal surface at nine-months after CXL.



**Visual Acuity**

Table 6.4 shows UDVA and CDVA over nine-months follow-up. The inter-group statistical analysis between group 1 and 2 at baseline found no significant differences between them. The mean UDVA in group 1 at baseline was 0.84±0.43 logMAR and improved to 0.55±0.24 logMAR at nine-months ($P<0.05$). In group 2, mean baseline UDVA was 0.81±0.24 logMAR and at nine-months postoperative assessment it improved to 0.62±0.23 logMAR ($P<0.05$). The mean UDVA of group 1 was better than group 2 at three, six and nine months ($P<0.05$). The mean CDVA in group 1 at baseline was 0.31±0.23 and improved to 0.19±0.10 logMAR at 9-months ($P<0.05$). In group 2, mean baseline was 0.27±0.20 and at 9-months postoperative it improved to 0.22±0.16 logMAR ($P<0.05$). The improvement in mean CDVA in group 1 and group 2 reached significance difference at nine months ($P<0.05$).

**Tomography**

Table 6.4 shows the inter-group statistical analysis between group 1 and 2 Kmax at baseline found no significant differences between them ($P=0.062$). Group 1 and group 2, showed significant improvements in Kmax at nine-months after treatment to 47.39±4.20 ($P<0.05$) and 46.45±4.61 ($P<0.05$) respectively. However, group 1 had a greater magnitude of change (ΔKmax) compared to group 2 at nine-months postoperative assessment. Kmax in group 1 was significantly better than group 2 at three, six and nine months ($P<0.05$). Kmin preoperatively for group 1 and 2 was 46.40±4.30 and 45.20±5.10 ($P=0.093$) respectively. At six-months mean Kmin in group 1 (42.57±4.60) had a significantly better improvement in comparison to group 2 (43.10±3.39) ($P<0.05$). ΔKmin for group 1 was 3.83 and 2.1 for group 2.

Table 6.4 summarises the QOV and OSDI data. Mean baseline QOV for group 1 and group 2 was 7.3 ± 2.5 and 7.0±1.9 respectively. At nine-month post treatment, mean QOV improved in both groups to 8.5±1.25 ($P<0.05$) and 8.05±2.13 ($P<0.05$) respectively.

QOV Lifestyle score for distance and near improved significantly in both groups at

nine-months postoperative assessment. The mean Δ QOV-L score for distance, intermediate and near was larger in group 1 in comparison to group 2. The baseline OSDI score for group 1 and 2 was 37.51±7.15 and 35.34 ±6.35 respectively, and at nine-months it was relatively the same at 36.76±4.92 (P=0.173) and 35.14±3.14 (P=0.089) respectively. As shown in Table 6.4, the mean OSDI scores for the keratoconic group 1 and 2 are higher than the average of healthy patients, signifying the severity of these symptoms in keratoconic eyes.

**Endothelial cell count**

Mean baseline endothelial cell count (ECC) for group 1 and 2 was 2429±213.5 cell/mm2 and 2361±206.70 cell/mm2 respectively. Nine months after the procedure, it was 2420±239.1 cell/mm2 and 2363±204.0 cell/mm2 respectively (Table 6.4).

**Table 6.4.** Preoperative and postoperative comparison.

| | Preoperative | Postoperative | | | | |
|---|---|---|---|---|---|---|
| Parameter | Baseline | 1 Month | 3 Months | 6 Months | 9 Months | P-value (within group) |
| UDVA (LogMAR) | | | | | | |
| Trans-PTK (group 1) | 0.84±0.43 | 0.75±0.35 | 0.57±0.21 | 0.56±0.20 | 0.55±0.24 | 0.01* |
| Manual debridement (group 2) | 0.81±0.24 | 0.78±0.21 | 0.62±0.20 | 0.63±0.19 | 0.62±0.23 | 0.03* |
| P-value (inter group) | 0.07 | 0.13 | 0.02* | 0.02* | 0.04* | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Δ UDVA (group 1) | 0.29 | | | | | |
| Δ UDVA (group 2) | 0.19 | | | | | |
| | | | | | | |
| CDVA (LogMAR) | | | | | | |
| Trans-PTK (group 1) | 0.31±0.23 | 0.27±0.19 | 0.22±0.21 | 0.20±0.16 | 0.19±0.10 | 0.04* |
| Manual debridement (group 2) | 0.27±0.20 | 0.38 ± 0.19 | 0.23±0.20 | 0.22±0.18 | 0.22±0.16 | 0.03* |
| P-value | 0.15 | 0.06 | 0.07 | 0.01 | 0.02* | |
| Δ CDVA (group 1) | 0.12 | | | | | |
| Δ CDVA (group 2) | 0.05 | | | | | |
| | | | | | | |
| Kmax (D) | | | | | | |
| Trans-PTK (group 1) | 49.72±5.00 | 49.51±4.20 | 48.43±4.30 | 47.37±4.50 | 47.39±4.20 | <0.05* |
| Manual debridement (group 2) | 47.36±4.60 | 48.12±5.00 | 47.23±4.90 | 46.49±4.70 | 46.45±4.61 | <0.05* |
| P-value | 0.062 | 0.059 | 0.04* | 0.02* | 0.03* | |
| Δ Kmax (group 1) | 2.33 | | | | | |
| Δ Kmax (group 2) | 0.91 | | | | | |
| | | | | | | |
| Kmin (D) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Trans-PTK (group 1) | 46.40±4.30 | 45.32±3.70 | 44.27±4.10 | 43.25±3.70 | 42.57±4.60 | 0.04* |
| Manual debridement (group 2) | 45.20±5.10 | 46.41±4.20 | 44.12 ± 4.30 | 44.13±3.80 | 43.10±3.39 | 0.018 |
| P-value | 0.09 | 0.02* | 0.07 | 0.03* | 0.03* | |
| Δ Kmin (group 1) | 3.83 | | | | | |
| Δ Kmin (group 2) | 2.1 | | | | | |
| | | | | | | |
| QOV Day score | | | | | | |
| Trans-PTK (group 1) | 7.3±2.50 | 8.1±1.20 | 8.5±1.50 | 8.7±1.10 | 8.8±1.25 | 0.01* |
| Manual debridement (group 2) | 7.0 ±1.90 | 7.9±2.30 | 8.3±2.20 | 8.0±2.50 | 8.0±2.13 | 0.04* |
| P-value | 0.08 | 0.03* | 0.06 | 0.02* | 0.02* | |
| Δ QOV (group 1) | 1.2 | | | | | |
| Δ QOV (group 2) | 1.05 | | | | | |
| | | | | | | |
| QOV Night score | | | | | | |
| Trans-PTK (group 1) | 6.5±2.70 | 7.10±1.40 | 7.60±1.40 | 7.95±1.20 | 8.05±1.15 | 0.03* |
| Manual debridement (group 2) | 6.7 ±2.50 | 7.05±1.20 | 7.15±1.05 | 7.10±1.10 | 7.22±1.11 | 0.04* |
| P-value | 0.120 | 0.080 | 0.240 | 0.04* | 0.04* | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Δ QOV (group 1) | 1.55 | | | | | |
| Δ QOV (group 2) | 0.52 | | | | | |
| | | | | | | |
| QOV Lifestyle score (1-5) | | | | | | |
| QOV-Distance vision score | | | | | | |
| Trans-PTK (group 1) | 3.50±0.2 | 2.97±0.4 | 3.00±0.75 | 2.98±0.59 | 2.45±0.45 | 0.02* |
| Manual debridement (group 2) | 3.20±0.4 | 3.10±0.1 | 3.10±0.20 | 3.03±0.22 | 3.00±0.13 | 0.04* |
| P-value | 0.120 | 0.03* | 0.04* | 0.04* | 0.04* | |
| Δ QOV-D (group 1) | 1.05 | | | | | |
| Δ QOV-D (group 2) | 0.20 | | | | | |
| | | | | | | |
| QOV-Intermediate vision score | | | | | | |
| Trans-PTK (group 1) | 3.30±0.5 | 3.16±0.5 | 3.12±0.75 | 2.98±0.59 | 2.45±0.45 | 0.03* |
| Manual debridement (group 2) | 3.22±0.3 | 3.13±0.4 | 3.15±0.5 | 3.14±0.4 | 3.12±0.5 | 0.07 |
| P-value | 0.08 | 0.02* | 0.16 | 0.04* | 0.04* | |
| Δ QOV-I (group 1) | 0.85 | | | | | |
| Δ QOV-I (group 2) | 0.10 | | | | | |
| | | | | | | |
| QOV-Near vision score | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Trans-PTK (group 1) | 4.20±0.50 | 3.50±1.10 | 3.50±0.70 | 3.00±1.10 | 3.00±0.75 | 0.04* |
| Manual debridement (group 2) | 4.10±0.40 | 3.80±1.28 | 3.70±1.20 | 3.50±1.50 | 3.46±1.00 | 0.03* |
| P-value | 0.12 | 0.21 | 0.07 | 0.03* | 0.02* | |
| Δ QOV-N (group 1) | 1.20 | | | | | |
| Δ QOV-N (group 2) | 0.64 | | | | | |
| | | | | | | |
| OSDI Score | | | | | | |
| Trans-PTK (group 1) | 37.51±7.15 | 40.16±6.65 | 35.32±5.28 | 36.52±5.42 | 36.76±4.92 | 0.17 |
| Manual debridement (group 2) | 35.34±6.35 | 39.47±7.26 | 36.67±6.74 | 35.28±4.39 | 35.14±3.14 | 0.08 |
| P-value | 0.83 | 0.21 | 0.29 | 0.3 | 0.62 | |
| Δ OSDI (group 1) | 0.75 | | | | | |
| Δ OSDI (group 2) | 0.2 | | | | | |
| | | | | | | |
| ECC (cells/mm2) | | | | | | |
| Trans-PTK (group 1) | 2429±213.5 | 2313±240.3 | 2417±220.6 | 2418±231.4 | 2420±329.1 | 0.24 |
| Manual debridement (group 2) | 2361±206.7 | 2309±190.9 | 2357±231.5 | 2363±224.0 | 2363±204.0 | 0.19 |
| P-value | 0.92 | 0.31 | 0.06 | 0.075 | 0.093 | |

| | | |
|---|---|---|
| Δ ECC (group 1) | 9 | |
| Δ ECC (group 2) | 2 | |

* Statistically significant
Kmax: Maximum keratometry
Kmin: Minimum keratometry
CDVA: Corrected distance visual acuity
UDVA: Uncorrected distance visual acuity QOV: Quality of vision questionnaire
OSDI: Ocular surface disease index questionnaire
ECC: Endothelial cell count
ΔKmax = Kmax pre-op - Kmax 9-months
ΔKmin = Kmin pre-op - Kmin 9-months
ΔUDVA = UDVA pre-op - UDVA 9-months
ΔCDVA = CDVA pre-op - CDVA 9-months
ΔQOV = QOV pre-op - QOV 9-months
ΔOSDI Score = OSDI pre-op - OSDI 9-months
ΔECC = ECC pre-op - ECC 9-months
QOV Lifestyle score: 1=Clear; 2=Slight; 3=Moderate; 4= Severe; 5=Intolerable.

**Index of Surface Variance**

The baseline measurements in group 1 (100.80±56.6) and group 2 (99.50±18.20). In group 1, at nine-months the ISV decreased from baseline (mean change 10.06μm; $P<0.05$). In group 2, there was an overall mean decrease of 4.26μm at nine-months assessment (Table 6.5).

**Index of vertical asymmetry**

In group 1, at nine-months, the IVA decreased from baseline (mean change 0.08; P>0.05). In group 2, at nine months the IVA also decreased but this improvement was not significant (mean change 0.04; P>0.05) (Table 6.5).

**Keratoconus Index**

In group 1, at nine months, the KI decreased from baseline (mean change 0.12; P<0.05). In group 2, at nine months the KI also decreased but this improvement was not significant (mean change 0.05; P=0.179) (Table 6.5).

**Central keratoconus index**

In group 1 and 2, at nine months, the CKI decreased from baseline. The mean change was 0.03 and 0.01 respectively. The decreased IN CKI was not significant (Table 6.5).

**Minimum radius of curvature**

Baseline measurements between group 1 (5.54±0.48) and 2 (5.77±0.19). In group 1, at 9-months, the Rmin increased significantly (the cornea was flattened) from baseline (mean change 0.48; P<0.05). In group 2, there was a significant improvement in the Rmin between baseline and 9 months (mean change 0.19; P<0.05) (Table 6.5). Rmin at nine months was better in group 1 (6.02±0.41mm) than group 2 (5.96±0.30mm).

**Index of height asymmetry**

In group 1, at nine months, the IHA decreased from baseline (mean change 6.32; P<0.05). In group 2, at nine months the IHA also decreased (mean change 4.25; P<0.05) (Table 6.5).

**Index of height decentration**

The baseline measurements in group 1 and 2 was 0.091±0.057 and 0.089±0.068 respectively. In group 1, at nine months the IHD decreased from baseline (mean change 0.049; P<0.05). In group 2, there was an overall mean decrease of 0.029 at nine months assessment (Table 6.5).

**Table 6.5.** Comparison of corneal topography indices

| | Preoperative | Postoperative | Postoperative | P-value (within group) |
|---|---|---|---|---|
| Parameter | Baseline | 6 Months | 9 Months | |
| ISV (µm) | | | | |
| Trans-PTK (group 1) | 100.80±56.6 | 93.60±43.40 | 90.74±44.52 | 0.02* |
| Manual debridement (group 2) | 99.50±18.20 | 96.00±13.70 | 95.24±15.63 | 0.25 |
| Δ ISV (group 1) | 10.06 | | | |
| Δ ISV (group 2) | 4.26 | | | |
| | | | | |
| IVA (mm) | | | | |
| Trans-PTK (group 1) | 1.10±0.52 | 1.02±0.55 | 1.02±0.54 | 0.46 |
| Manual debridement (group 2) | 1.08±0.40 | 1.05±0.43 | 1.04±0.49 | 0.72 |
| Δ IVA (group 1) | 0.08 | | | |
| Δ IVA (group 2) | 0.04 | | | |
| | | | | |
| KI (µm) | | | | |
| Trans-PTK (group 1) | 1.33±0.24 | 1.22±0.26 | 1.21±0.30 | 0.04* |

| | | | | |
|---|---|---|---|---|
| Manual debridement (group 2) | 1.30±0.21 | 1.27±0.11 | 1.25±0.28 | 0.27 |
| Δ KI (group 1) | 0.12 | | | |
| Δ KI (group 2) | 0.05 | | | |
| | | | | |
| CKI | | | | |
| Trans-PTK (group 1) | 1.10±0.10 | 1.08±0.06 | 1.07±0.09 | 0.25 |
| Manual debridement (group 2) | 1.07±0.03 | 1.06±0.05 | 1.06±0.03 | 0.49 |
| Δ CKI (group 1) | 0.03 | | | |
| Δ CKI (group 2) | 0.01 | | | |
| | | | | |
| Rmin (mm) | | | | |
| Trans-PTK (group 1) | 5.54±0.48 | 5.89±0.38 | 6.02±0.41 | 0.04* |
| Manual debridement (group 2) | 5.77±0.19 | 5.90±0.21 | 5.96±0.30 | 0.04* |
| Δ Rmin (group 1) | 0.48 | | | |
| Δ Rmin (group 2) | 0.19 | | | |
| IHA | | | | |
| Trans-PTK (group 1) | 27.13±15.24 | 21.20±14.10 | 20.81±12.48 | 0.03* |
| Manual debridement (group 2) | 26.51±16.01 | 23.30±17.25 | 22.26±18.63 | 0.04* |
| Δ IHA (group 1) | 6.32 | | | |

| | | | | |
|---|---|---|---|---|
| Δ IHA (group 2) | 4.25 | | | |
| | | | | |
| IHD | | | | |
| Trans-PTK (group 1) | 0.091±0.057 | 0.049±0.055 | 0.042±0.050 | 0.02* |
| Manual debridement (group 2) | 0.089±0.068 | 0.062±0.040 | 0.060±0.047 | 0.03* |
| Δ IHD (group 1) | 0.049 | | | |
| Δ IHD (group 2) | 0.029 | | | |
| ΔISV= ISV preop - ISV 9 months<br>ΔIVA=IVA preop - IVA 9 months<br>ΔKI= KI preop - KI 9-months;<br>ΔCKI= CKI preop - CKI 9-months<br>ΔRmin= Rmin preop - Rmin 9-months<br>ΔIHA= IHA preop - IHA 9 months<br>ΔIHD= IHD preop - IHD 9 months<br>* Statistically significant | | | | |

Table 6.6 compares the outcomes between the subgroups in group 1, i.e group 1A (higher ΔCDVA change) and 1B (lower ΔCDVA change). This comparison was performed to statistically compare and differentiate the Group 1A and Group 1B with regards to factors that may be related to the higher or lower change in CDVA. The only statistically significant differences between the two groups were in the postoperative maximum K value, ISV and IHA indices. To investigate whether these significant postoperative differences in the maximum K value, ISV and IHA indices were also present preoperative, preoperative statistically comparison of maximum K value, ISV and IHA indices between Group 1A and Group 1B was also performed. The only statistically significant differences between the two groups were in the preoperative maximum K value. To verify the impression that preoperative maximum K might have upon the postoperative improvement of CDVA, Odds Ratio (OR) and

Confidence Interval (CI) algorithm must be used, however due to the small sample size, this simplified statistical comparison was carried out providing a pilot for further investigation.

**Table 6.6.** Comparison within Group 1.

| | Group 1A | Group 1B | |
|---|---|---|---|
| | ΔCDVA ≥0.30 (n=9 eyes) | ΔCDVA ≤0.10 (n=6 eyes) | p-value |
| | | | |
| Kmax[b] (D) | 45.24±3.12 | 46.51±4.17 | 0.03* |
| | | | |
| Kmin[b] (D) | 40.79±4.18 | 41.32±3.29 | 0.49 |
| | | | |
| ISV[b] | 88.45±31.25 | 91.17±25.10 | 0.02* |
| | | | |
| IVA[b] | 0.99±0.35 | 1.05±0.26 | 0.102 |
| | | | |
| KI[b] | 1.15±0.04 | 1.23±0.08 | 0.72 |
| | | | |
| CKI[b] | 1.04±0.11 | 1.10±0.15 | 0.29 |
| | | | |
| Rmin[b] | 6.27±0.52 | 5.13±0.32 | 0.5 |
| | | | |
| IHA[b] | 19.35±7.15 | 21.24±5.23 | 0.02* |
| | | | |
| IHD[b] | 0.040±0.020 | 0.054±0.010 | 0.23 |
| | | | |
| Comparison of pre-operative parameters between groups | | | |
| | ΔCDVA ≥0.30 (n=10 eyes) | ΔCDVA ≤0.10 (n=7 eyes) | p-value |
| | | | |
| Kmax[a] (D) | 51.10±3.20 | 45.05±2.60 | <0.05* |
| | | | |

| | | | |
|---|---|---|---|
| ISV[a] | 102.40±25.10 | 105±19±20 | 0.08 |
| | | | |
| $Rmin_a$ | 5.67±0.70 | 5.80±0.50 | 0.4 |

Kmax: Maximum keratometry
Kmin: Minimum keratometry
CDVA: Corrected distance visual acuity
ISV: index of surface variance
IVA: index of vertical asymmetry
KI: keratoconus index
CKI: central keratoconus index
Rmin: minimum radius of curvature
IHA: index of height asymmetry
IHD: index of height decentration
a: preoperative
b: postoperative 9 months

### 6.6 Discussion

Table 1 summarises various CXL studies performed in eyes with progressive KC. There is a variability in the definition of 'progression' between studies and preoperative groups. This poses significant difficulty when trying to compare between studies particularly to define the effect of different CXL treatment protocols upon progression of the disease. Nevertheless, clinical studies provide evidence that suggests CXL and modified CXL treatments halt progression of KC with a failure rate of only approximately 3% and a complication rate of 1% or less (Coskunseven, Ii and Hafezi, 2008; Caporossi *et al.*, 2010). However, here is a paucity of clinical study literature identifying which preoperative parameters are likely to be associated with enhanced corneal flattening post CXL. In this study, group 1 and group 2 had comparable preoperative findings in topography and VA and endothelial cell counts to previous studies.

Koller *et al*. (2011) investigated various factors such as age, CDVA, minimum corneal

thickness, ISV, KI, and asphericity of the anterior corneal shape, to determine their influence upon corneal flattening post-CXL. In their cohort of 151 eyes (151 patients), preoperative maximum curvature (Kmax) was the only factor that showed a statistically significant correlation with the flattening of corneal post-CXL. Curvature between the range of 54D and 58D of Kmax had a flattening rate greater than 50% and a failure rate of less than 1%. Kmax of ≤54D had subsequent less flattening but stabilisation of KC was achieved outside the 54D to 58D (>99% success rate) range as well. Additionally, Koller *et al*. (2011) stated that a Kmax value greater than 58 D predicts more flattening but increased rates of failures. In our study, the mean preoperative Kmax for group 1 and group 2 was 49.72±5.00 D and 47.36±4.60 D respectively and a greater magnitude of improvement was observed in group 1 (Δ 2.33) in comparison to group 2 (Δ 0.91). These changes could possibly be due to the higher curvature as suggested by Koller *et al*. (2011). Furthermore, greater improvements in group 1 can be attributed due to the combination of larger preop Kmax values.

As progression or improvement of KC is generally recorded by maximum and minimum keratometric value. Raiskup *et al*. (2015) found that mean Kmax values decreased by 2.57 D at six years and at six months was close to 1 D, these findings are similar to group 2 (CXL group; mean Kmax: 47.36±4.60 D) of our study. However, studies such as Coskunseven *et al*. (2009) reported greater than 1 D of improvement within six to nine months post-CXL treatment, again the groups had relatively high mean preoperative Kmax of 54.02±4.15 D and 53.02±8.42 D respectively. These studies that indicate improvements of greater than 2D in the mean Kmax could possibly have been due to their higher pre-operative Kmax in comparison to our study, thereby resulting in a greater flattening change. Kymionis *et al*. (2012) reported that Ksteep value decreased by 1.11D in the group that was treated with PTK and CXL at SIX months postop. In our study, patients in group 1 (CXL with PTK) at 9 months postoperatively had a mean Kmax improvement of 2.33 D. The magnitude of change in topography are similar, however in comparison, our study had a lower preoperative mean Kmax in comparison to Kymionis *et al* (2012). In our study, the mean improvement in CDVA and UDVA at nine months in group 1 was 0.12 and 0.05 respectively. At nine months postop our study found that 38.5% of eyes gained ≥1 lines, 57.3% of eyes neither gained nor lost any line and 4.2% lost 1 line of CDVA. While Kymionis *et al*. (2012) in their twelve month comparative, prospective report

found that CDVA improved by 0.08 at six months post-op in the CXL with PTK group; it further improved by 0.11 at twelve months postop. At twelve months 42.1% of eyes gained ≥1 lines of CDVA, 52.6% of eyes neither gained nor lost any line and only 5.3% lost 1 line of CDVA.

On the other hand, CXL group in Kymionis *et al*. (2012) at twelve months follow-up reported 33.3% of eyes gained ≥1 lines of CDVA, 55.6% of eyes neither gained nor lost any line and 11.1% lost 1 line of CDVA. At nine-month follow-up of our CXL group, 26.7% of eyes gained ≥1 lines and 65.2% of eyes neither gained nor lost any line of CDVA, while 8.1% lost 1 line of CDVA. The percentage lines gained of CDVA either groups were greater in Kymionis *et al*. (2012). This could be attributed to the longer post-CXL recovery in the Kymionis paper, as visual and topography improvements are known to gradual improve over twelve months postop. Therefore, it is possible that our CDVA will also improve over twelve months. However, lost lines of CDVA were similar to our study.

Regarding UDVA, Kymionis *et al*. (2012) at twelve month reported 53% of trans-PTK-CXL treated eyes presented 0.6 LogMAR or better and 28% of CXL eyes presented 0.6 LogMAR or better. While in our study at nine months, group 2 improved by 0.19. In group 1, 51% had 0.6 LogMAR or better at nine months and 36% of group 2 eyes presented 0.6 LogMAR or better.

The mean ECCs remained stable in both groups during the entire follow-up, as reported in most series. In our group 1, trans-PTK was used to help flatten the apex of the cone before CXL. To prevent the progression of the KC, corneal damage and endothelial cell toxicity from UV-A irradiation, trans-PTK ablation was performed to an intended depth of only 55μm which avoided removing significant amounts of corneal stromal tissue which could further compromise the biomechanical integrity of the keratoconic cornea. In most cases the 55μm PTK treatment although obviously smoothing the steep parts of the cornea had not fully removed all the epithelium within the 5.5mm region. This would provide the potential to treat further PTK amounts to utilize the full effects of epithelial masking. This was deliberately not not done to reduce the thinning effect upon steeper ectatic stromal regions.

The mean OSDI score 35 or greater was observed in both groups. However, OSDI scores were already elevated and at similar levels prior to treatment and may have had some negative impact upon the QOV and QOV-L scores pre and postoperatively. Postoperatively, both treatment groups had a significant improvement in their QOV and QOV-L scores. The negative impact of KC on the QOL has been indicated by various former studies and our findings indicate that CXL with and without trans-PTK improved the QOL significantly (Tatematsu-Ogawa *et al.*, 2008; Cingu *et al.*, 2015). This might be attributed to the improvement in subtle visual disturbances because of irregular astigmatism, coma, and light scatter postoperatively. Significant differences in the QOV-L scores detected, suggests that keratoconic patients experience significant visual impairment that affects the majority of their distance vision and near vision activities.

The degree of stromal ablation in these cases is directly related to the degree of thinning of the epithelium overlying the area of conic protrusion. At one-week after procedure full re-epithelialisation was observed in all patients. Similar to Carracedo *et al*. (2014) our study also found that the OSDI scores were high in both keratoconic groups at baseline and postoperatively (Dienes *et al.*, 2015).

Our findings suggest that group 1 had a significantly greater improvement in various parameters of both corneal shape and visual outcomes (Table 6.4 and 6.5). The trans-PTK prior to CXL procedure, makes use of epithelial masking to guide the laser stromal treatment to produce a subsequent smoother corneal surface with very limited stromal treatment confined to only those regions where there has been compensatory epithelial thinning over irregular areas of stromal protrusion. This enables a relative treatment of the irregular astigmatism present to allow quicker visual recovery post CXL. Reinstein *et al*. (2009) found that an epithelial doughnut pattern with epithelial thinning over the cone surrounded by a region of thickened epithelial. This pattern was consistent with an underlying stromal cone. Due to this phenomenon, removal of epithelial at a constant depth removes some stromal and epithelial tissue at the top cone, resulting in a smoothening effect.

Enhancement in postoperative visual acuity was observed in both groups along with improved contour of the cornea. Since group 1 had a greater magnitude of anterior

corneal changes (denoted by Δ). Significantly greater improvement in visual acuity was observed in group 1 at nine months postoperative assessment in comparison to group 2. Group 1 also demonstrated incremental improvement in topography indices postoperatively. While in group 2, these improvements were documented mostly at nine months post treatment. This improvement with group 1 is expected to result from improved topography regularity by the PTK smoothening (flattening) procedure. Therefore, this study documents significant improvement in topography and VA changes in trans-PTK combined with CXL treatment group (Group 1) for KC, as early as 1-month post treatment. At 9-months significant inter-group improvements were observed in Rmin, IHA and IHD indices for both groups suggesting that the cone had decreased in curvature and flattened thereby becoming more optically regular and symmetric. However, long-term follow-up is needed to determine the differences in outcome of the two groups. Additionally, postoperative astigmatism smoothing of the 5.5mm corneal visual axis zone in group 1 (Figure 6.1) appears to have resulted in improved visual outcomes in comparison with group 2 (Figure 6.2). Visual rehabilitation between these groups are evident by their respective ΔCDVA (Table 6.4). These initial results require larger sample sizes and longer follow-up to determine long-term effectiveness of this combination treatment methodology.

Currently the information about factors affecting the visual outcome trans-PTK are limited. Toprak *et al*. (2014) reported in patients with progressive KC: age, baseline VA and baseline thinnest pachymetry had a determining impact upon the visual outcome. In comparison, our study did not have a large enough sample size to assess this. De Angelis *et al*. (2015) reported that low preoperative best-corrected distance visual acuity (BCVA), high refractive astigmatism, and advanced KC as factors predictive of BCVA improvement. Kirgiz *et al*. (2016) found correlation between preoperative and postoperative visual acuity. In this study, we sought to determine what factors in the PTK-CXL group were associated with a higher improvement of CDVA between pre and postoperatively.

To assess this, we first determined the magnitude of improvement in corrected VA: ΔCDVA. Then arranged the cases into those with greatest improvement (higher ΔCDVA change: Group 1A) and those with the least improvement (lower ΔCDVA change) (Group 1B). An analysis of postoperative factors was then carried out to

statistically compare and differentiate what factors differed between the two groups: Group 1A and Group 1B with the higher or lower change in CDVA postoperatively. The only statistically significant differences between the two groups were in the postoperative maximum K value, ISV and IHA indices. Preoperative statistically comparison of maximum K value, ISV and IHA indices between Group 1A and Group 1B was then also performed to determine whether these factors were different preoperatively between the Group 1A who demonstrated the postoperative enhanced change CDVA compared to the less significantly improving Group 1B. The only preoperative statistically significant differences between the two groups were in the maximum K value. None of the other indices were significantly different preoperatively among group 1A and 1B.

These findings might suggest that the impact of trans-PTK CXL upon the postoperative visual performance is not clearly predictable by changes in corneal indices. The limitations of these findings are that a larger sample size, longer follow-up and possibly other pre and postoperative testing measures are required to attempt to determine predictive factors indicative of better or worse visual outcomes post PTK CXL treatments. Additionally, the flattening effect of this PTK treatment could potentially have been enhanced through deeper ablations which used the full epithelial masking effect. Longer follow-up and other studies demonstrating the safety of this type of procedure in ectatic corneas will potentially enable surgeons to be more aggressive in attempting to utilise either PTK or topography guided laser treatments to improve corneal shape and hence VA in addition to stabilising the ectatic condition.

## 6.7 Conclusion

This study appears to indicate that the combination of trans-PTK with CXL is a safe treatment which can potentially provide earlier functional improvement in vision and QOL, while still producing stabilization of the ectatic disorder. Further follow-up and additional cases will be required to draw final conclusions about the benefit of this combined technique in keratoconic patients.

## 6.8 Summary

This chapter showed that combine trans-PTK with CXL may enhance visual quality along with improved corneal topography. This preliminary study serves to lay the foundation for a more robust, prospective study but also highlighted the potential factors that benefit visual acuity post trans-PTK CXL treatment.

# CHAPTER 7: COMPARISON OF TWO VISION-RELATED QUALITY OF LIFE QUESTIONNAIRES

## 7.1 Introduction

VA tests on patients in a routine postoperative assessment have been used to determine a successful outcome in visual rehabilitation; these measures include distance acuity, intermediate acuity, near acuity, and contrast sensitivity. 'Success' in visual rehabilitation is often defined based on the improvement in these measurements. After 1980s, clinicians and researchers started to explore visual function from a patients' perspective using questionnaires because VA test alone was not able to capture all aspects of the patient's QOV and its impact upon their QOL; henceforth emphasis upon visual function and vision related quality of life (VR-QOL) was established (Massof and Rubin, 2001; Stelmack, 2001). The multidimensional structure of QOL includes physical, functional, social and psychological dimensions (Aaronson, 1988). Generic VR-QOL questionnaires generally contain all these four domains, while disease specific QOL instruments are more specific and may not have all these domains included in them.

The improved understanding of the concept of VR-QOL has led to the development of instruments that aim to capture and measure this concept. Majority of VR-QOL assessment instruments are sets of questionnaires. Although the growing trend to patient-based questionnaires is commendable; however currently there is an overabundance of overlapping questionnaires with regards to functionality. This plethora of questionnaires can sometimes pose problems for a clinician or researcher. As it can be unclear which of these questionnaires are of sufficient psychometric quality. However, a systematic review of existing questionnaires could serve as a guide for selecting the appropriate instrument.

There have also been developments in the methodology of re-evaluating questionnaires with the use of Rasch analysis (Velozo, Lai and Mallinson, 2000; Massof and Fletcher, 2001; Pesudovs *et al.*, 2003). Various VR-QOL questionnaires have been validated for refractive surgery patients; these include Activities of Daily

Vision Scale (ADVS) (Mangione *et al.*, 1992), the Visual Disability Assessment (VDA) (Pesudovs, Wright and Gothwal, 2010), Visual Functioning 25 (VF-25) (Nordmann *et al.*, 2004) and the Visual Functioning 14 (VF-14) (Steinberg *et al.*, 1994). These questionnaires have been shown to be sensitive to clinically meaningful change after surgery (Mangione *et al.*, 1992; Schein *et al.*, 1995). However, further validation using item response theory, Rasch analysis, and variability of responses has shown limitations in questionnaire development and validation that were previously not highlighted (Pesudovs *et al.*, 2003; Mallinson, Stelmack and Velozo, 2004). Table 7.1 highlights collect all the subjective questionnaires previously designed to address QOL; such as activities of daily living, social and emotional factors. However, all of these questionnaires have pre-determined items based on Rasch or Classic test theory analysis, excluding VR-QoL questionnaire; in which the items are user defined.

**Table 7.1** List of subjective questionnaires designed for assessing quality of life.

| Questionnaire Authors | Condition | Items | Grading Scales |
|---|---|---|---|
| Ross and colleagues (1984) | Glaucoma | Pre-determined | Ordinal 1–5 |
| Mills and Drance (1986) | Glaucoma | Pre-determined | Yes, uncertain, no |
| Nilsson and Nilsson (1986) | ARMD | Pre-determined | Yes, no |
| Lowe and Drasdo (1992) | Retinitis pigmentosa | Pre-determined | Yes, no; 2 to 4 categories; open ended |
| Mangione and colleagues (1992) | Cataract (ADVS) | Pre-determined | Five categories |

| | | | |
|---|---|---|---|
| Leat and colleagues (1994) | Low vision | Pre-determined | Yes, no; 3 to 5 categories; open ended |
| Rubin and colleagues (1994) | Old age visual impairment | Pre-determined | Three categories |
| Steinberg and colleagues (1994a,b) | Cataract (VF-14) | Pre-determined | Yes (4 categories), no/not applicable |
| Ellwein and colleagues (1995) | Blindness | Pre-determined | Four categories/does someone help you |
| Parrish (1996) | Glaucoma | Pre-determined | Three to 5 categories; ordinal 0–10 |
| Abrahamsson and colleagues (1996) | Cataracts | Pre-determined | Yes, no |
| Wu and colleagues (1996) | Cytomegalovirus | Pre-determined | Yes, no |
| Cleary and colleagues (1997) | Optic neuritis | Pre-determined | Five categories/not applicable |
| Javitt and colleagues (1997) | Cataract | Pre-determined | Ordinal 0–4 or 0–10; 5 categories; open ended |
| Lundstrom andcolleaguess (1997) | Cataract (Catquest) | Pre-determined | Yes, no; yes (3 categories), no; 2 to 5 categories/cannot say |

| | | | |
|---|---|---|---|
| Carta and colleagues (1998) | ARMD, branch retinal vein occlusion, cataract, primary open-angle glaucoma | Pre-determined | Ordinal 1–3 with descriptors |
| Moore and colleagues (Current study) | Cataract and laser refractive surgery (QoL) | User defined | Yes, 3 categories |
| ARMD = age-related macular degeneration. ADVS = Activities of Daily Vision Scale. | | | |

### 7.2. Dimensions of QOL

To specify and categorise the items of the questionnaires, these items are assigned to one of the four dimensions of QOL: physical dimensions, functional dimensions, social dimensions and psychological dimensions (Aaronson, 1988).

### 7.3. Response categories

Response categories of the questionnaire reflect the number of ordered responses that an item in the questionnaire contains. Not applicable (NA) response is not counted as a response category. In any given questionnaire, the number of response categories to an item may vary (Frost *et al.*, 2001).

### 7.4. Psychometric aspects

The psychometric aspects impart information about the psychometric quality of the questionnaires. This information helps researcher and clinician in their choice between potentially applicable instruments. Generally psychometric properties of VR-QOL are

based on classic test theory (CTT) or on Rasch rating scale analysis (Sébille *et al.*, 2010) .

### 7.5. Mode of administration and languages

Modes of administration of questionnaires can be: self-administered, interviewer administered, telephone administered, electronically administered (website or App based) and possibly proxy versions. The psychometric properties of an instrument have been found to differ with modes of administration, languages or cultures (Frost *et al.*, 2001).

### 7.6. VF-14 questionnaire

The Visual Function-14 (VF-14) questionnaire (Ref: Appendix B), contains 14 fixed (pre-defined) vision-dependent activities questions, which was first developed for use in patients with cataract. Since then, it has been used with several other chronic eye diseases. Each question is scored on a scale of 0 (unable to perform an activity at all) to four (able to engage in activity fully). The average score is multiplied by 25 to give an overall score ranging from 0 to 100. For VF-14 the scores are given in points. Zero implies inability to do any of the activities, whereas a score of 100 denotes ability to perform all activities without any difficulty (Steinberg *et al.*, 1994).
In-order for VR-QOL questionnaires to be useful for research and clinical applications, a VR-QOL questionnaires needs to be reliable and valid. Reliability refers to the extent to which the measure yields the same number or score each time it is administered, all other things being equal (i.e., no true change in the attribute being measured has occurred). Validity is the degree to which the measure reflects what it is supposed to measure rather than something else. The distinction between reliability and validity is important because a measure may be reliable (i.e., always yield the same score for the same patient), but it may be consistently measuring the wrong thing (i.e., not what it is supposed to measure).

Due to the 14 pre-defined nature of questions in the VF-14 questionnaire, frequently clinicians encounter missing information (as these fixed questions at times are not applicable or relevant to every individual patient). There is a strong possibility that a compilation of these missing data error can lead to bias in measurement as it causes the score to be consistently too high or too low relative to the true score.

The well accepted traditional questionnaires such as VF-14 assess the ability of the patient with pre-defined items, such as the visual ability to perform tasks like 'cooking' and 'filling checks or forms' before and after vision rehabilitation on the assumption that these questions are meaningful and relevant to the individual's VR-QOL. Although, these pre-defined items have the benefit of expediency, at times these items may not represent the visual function needs of the patient. The alternative to this methodology would be to have a detailed questionnaire that encompasses all the possible items that might be relevant to an individual; however, such a questionnaire would be time consuming and expensive to administer. The next best approach would be to administer a short questionnaire that is individually tailored to the patients' visual function needs.

This chapter hypothesises that by asking the patient two specific items that are relevant and meaningful to their VR-QoL questionnaire for distance, intermediate and near vision (total 6 items) will generate a more accurate status and representation of their visual function in comparison to generic items on a questionnaire.

### 7.6.1 Study aim

To compare VF-14 and VR-QoL questionnaire for measuring preoperative cataract patient reported outcomes.

### 7.6.2 Sample size

The power calculation was conducted using G*Power 3.1 (Faul *et al.*, 2007) (ANOVA repeated measures within factor). Sample size was determined using power

calculation (80% power at the 5% level of statistical significance, α=0.05) to detect a change of ±1.99 unit change in VF-14 score based on the Gothwal *et al*. (2010).

### 7.6.3 Subjects

This retrospective, case series is from a population of patients seeking IOL implantation surgery due to cataracts at Cathedral Eye Clinic, Belfast, Norther-Ireland, UK. Because this was a retrospective study, only informed consent and permission to use their data for analysis and publication was obtained from each patient as part of our routine preoperative protocol. The nature of the study was explained verbally and on paper to the participants by trained clinicians before obtaining a written informed consent. A complete ocular examination was performed to screen for ocular abnormalities and determine patient candidacy for surgery.

This study retrospectively assessed 51 patients who were administered VF-14, VR-QoL and QOV questionnaires consecutively on the same day prior to cataract surgery. The mean age was 74, and the age range was 50 to 85 (Table 7.2). In this study, along with the VF-14 questionnaire and VR-QOL questionnaire and previously developed QOV questionnaire (McAlinden *et al*., 2010) was completed.

**Table 7.2** Patient demographics

| | |
|---|---|
| Number of patients | 51 |
| Age (years) | 74 ± 17 |
| Gender (% males) | 37 |
| Visions status | Cataract |

### 7.6.4 Experimental procedure

Fifty-one pre-operative patients were asked to complete three questionnaires, namely: VF-14, VR-QoL and QOV questionnaires. The results were used to evaluate their VR-QOL status.

The VF-14 questionnaire (Ref: Appendix B), contains 14 vision-dependent activities questions. Each question is scored on a scale of 0 (unable to perform an activity at all) to 4 (able to engage in activity fully). The average score is multiplied by 25 to give an overall score ranging from 0 to 100. The VF-14 the scores are given in points. Zero implies inability to do any of the activities, whereas a score of 100 denotes ability to perform all activities without any difficulty (Steinberg *et al.*, 1994).

The VR-QoL questionnaire (Ref: Appendix C) comprises of six questions which are categorised into 3 subgroups, namely; distance vision related activity, intermediated vision related activity and near vision related activity. The subject is asked to mention two relevant activities regarding distance vision, intermediate vision and near vision to the assessor and rate them on a scale of 1 to 5 (1=clear; 2=slight difficulty; 3=moderate difficulty; 4=severe difficulty; 5=intolerable). The total score and mean score are not derived as each item is treated individually based on the rational that averaging the score will misrepresent the individual's appreciation of vision. However, due to the comparative nature of this study between VF-14 and VR-QoL questionnaire scores mean range was derived for both.

Since this study was the comparison of VR-QoL questionnaires, only two components of the QOV questionnaire was used for this study, namely: Overall QOV for day and overall QOV for night. This was measured on a Likert scale of 0-10, zero represented worst visual appreciation while ten represented best visual appreciation.

First, the original scores obtained from the 2 questionnaires were categorised into three groups: distance vision, intermediate vision and near vision related activities. In VF-14, higher scores represent better visual functioning (less difficulty) and, therefore, greater ability in performing the activity while in VR-QoL questionnaire, higher scores represent poor visual functioning (more difficulty). Since the two questionnaires had two different methods of measuring visual function (although both used ordinal/Likert 5-point scale where numerical values in an increasing order are assigned to categories

of increasing or decreasing difficulty) variable transformation was performed before comparative analysis, namely the conversion of VF-14 scores into VR-QoL equivalent and the rescaling of the 0-10 QOV score into a score in the range 1-5. This transformation was necessary in-order to carry out a meaningful comparison between the scores from the two questionnaires (VF-14 and VR-QoL questionnaire) and the QOV score.

The VF-14 scores were converted into VR-QoL equivalent by subtracting each VF-14 item score from 5. This variable transformation resulted in a both VF-14 and QoL score becoming equivalent. The overall QOV score for day and night (0-10) was also rescaled to 1 to 5 by subtracting the half of the QOV 0-10 score from 5.

The purpose of the rescaling VF-14 and QOV scores was to standardise the 5-point Likert scale where numerical values in an increasing order represented increasing difficulty of visual function for a meaningful comparison.

Paired samples t-test was conducted to compare the mean of the ranges of scores. Rasch analysis of the median scores for both questionnaires, where the items were: distance vision, intermediate vision, near vision, QOV Day and QOV Night was also performed. Rasch analysis was also used to determine how visual function tasks were affected the QOV during day and night.

### 7.6.5 Statistical analysis

Statistical analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences, Version 22, Chicago, Illinois, USA) and Excel (Microsoft; Redmond, Washington, USA). The Kolmogorov-Smirnov test was used to assess normality. One-way ANOVA with Tukey post hoc comparison procedures were used when assessing continuous normal data. For ordinal and non-normally distributed data, the non-parametric Mann-Whitney *U* test was applied. For all statistical analysis, the level of significance was $P<0.05$.

## 7.7 Results

Figure 1 shows the relative distribution of the VF-14 and VR-QoL scores preoperatively and in the overall group. As hypothesized, all paired t-test conducted to compare the mean of the ranges of scores for:

- VF-14 questionnaire and VR- QoL for distance vision (Pair A) (Figure 7.1)
- VF-14 questionnaire and VR- QoL for intermediate vision (Pair B) (Figure 7.2)
- VF-14 questionnaire and VR-QoL for near vision (Pair C) (Figure 7.3)

The above-mentioned analysis revealed significantly less variability in VR-QoL questionnaire in discriminating visual function of preoperative patients (Table 7.3). There was a statistically significant difference ($P<0.05$) in the mean range score obtained with the VF-14 questionnaire compared to mean range score obtained with VR-QoL questionnaire for pair A, B and C (Table 7.3).

In ***Pair A***: There was a statistically significant difference, at level 0.05 ($p=6.85e^{-15}$) in the mean range score obtained with the VF-14 questionnaire compared to mean range score obtained with VR-QoL questionnaire. ***In Pair B:*** There was a statistically significant difference, at level 0.05 ($p=1.40e^{-15}$) in the mean range score obtained with the VF-14 questionnaire compared to mean range score obtained with VR-QoL questionnaire. ***In Pair C:*** There was a statistically significant difference, at level 0.05 ($p=2.979e^{-9}$), in the mean range score obtained with the VF-14 questionnaire compared to mean range score obtained with VR-QoL questionnaire.

**Figure 7.1.** Comparision of score range of VF-14 and VR-QoL questionnaires for distance vision related visual function.

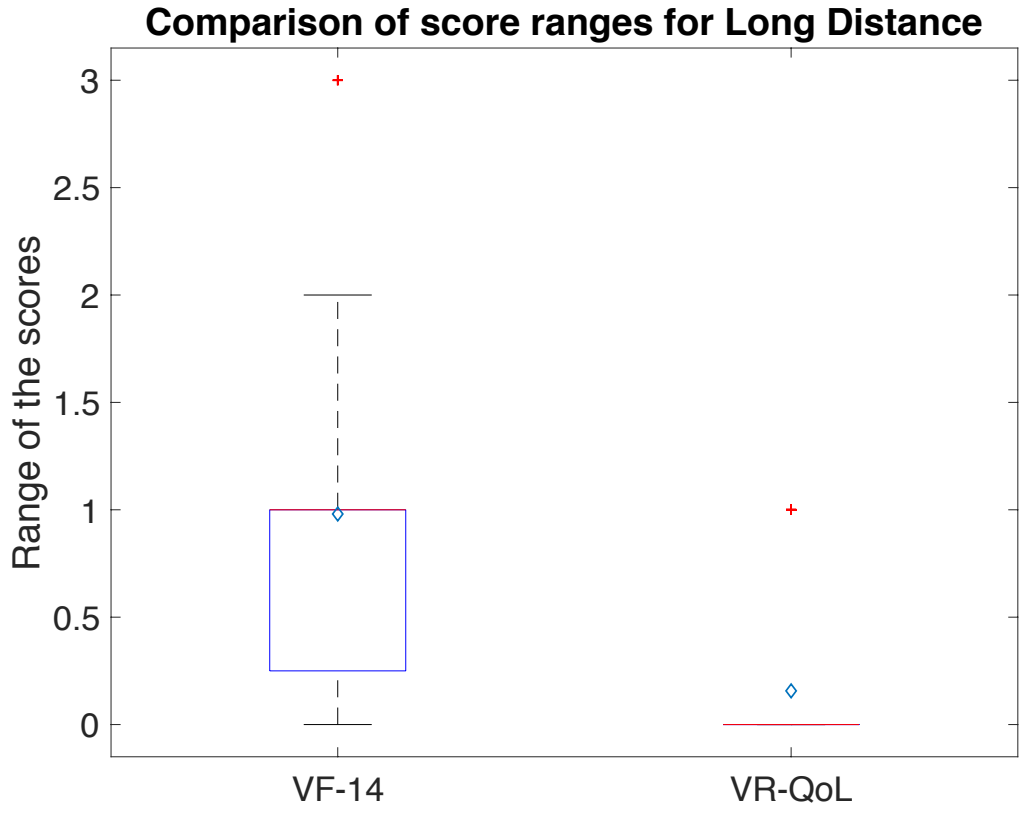


**Figure 7.2.** Comparision of score range of VF-14 and VR-QoL questionnaires for Intermediate vision related visual function.

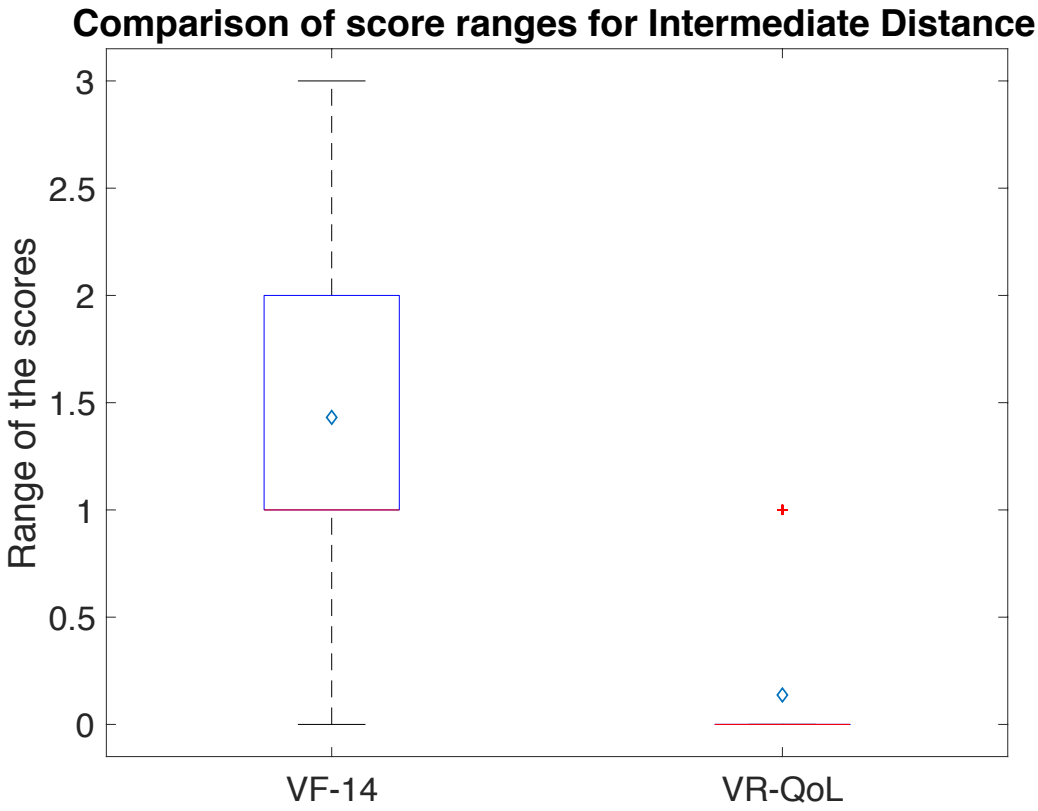


**Figure 7.3.** Comparision of score range of VF-14 and VR-QoL questionnaires for Intermediate vision related visual function.

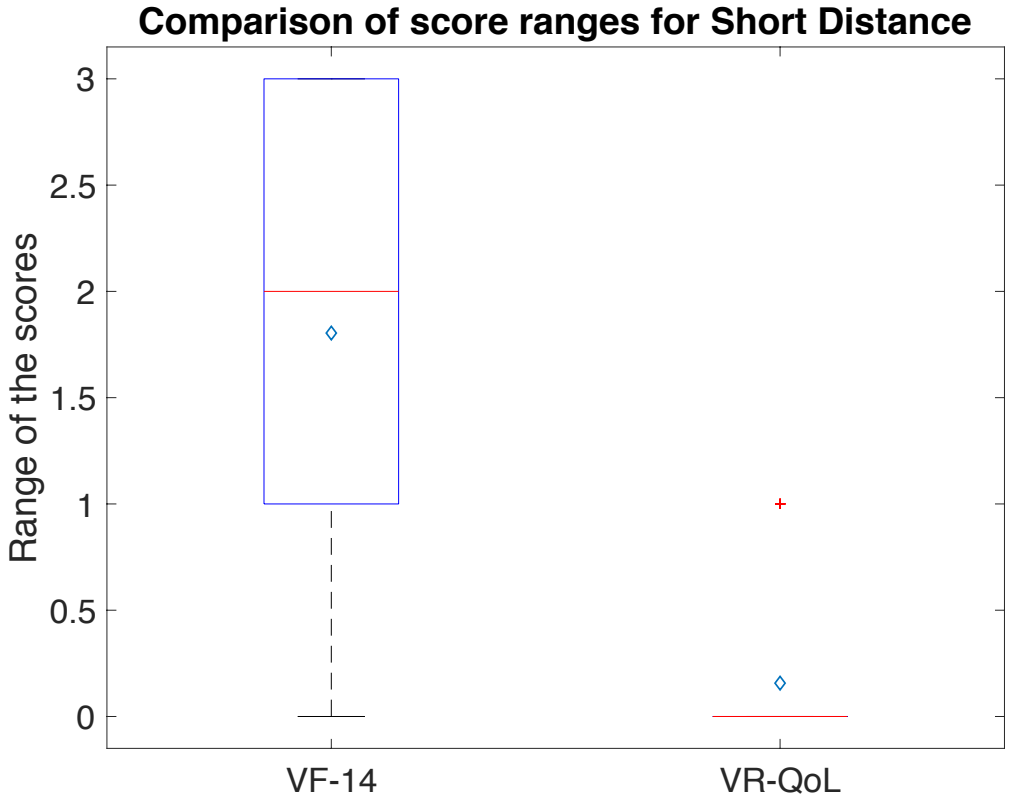



**Table 7.3** Paired t-test for the mean ranges of the scores

| Paired Samples t-test Statistics | | | | | |
|---|---|---|---|---|---|
| | p-value | Confidence Interval (CI) at 95% | Value of t-test statistic (t) | Degree of freedom (df) | Std. Deviation of the pair difference |
| Pair A | $6.85e^{-15}$ | [1.345; 1.949] | 10.954 | 50 | 1.074 |
| Pair B | $1.40e^{-15}$ | [1.067; 1.521] | 11.448 | 50 | 0.807 |

| | | | | | |
|---|---|---|---|---|---|
| Pair C | 2.979e-9 | [0.593; 1.053] | 7.194 | 50 | 0.817 |

Similar in all Rasch analysis revealed that VF-14 questionnaire underestimates the item difficulty parameter, and this can be attributed to the variability caused by irrelevant questions from the item categories (distance, intermediate vision and near vision) in the VF-14 questionnaire (Table 7.4). Table 7.5 displays the number of patients that found the items on the VF-14 questionnaire was not relevant to their daily visual function.

**Table 7.4** Rasch analysis of the median scores for both questionnaires, where items related to near, intermediate and distance vision, QOV for day and QOV for night.

| VR-QoL | | | | |
|---|---|---|---|---|
| Items | Items difficulty | Standard Error | Outfit MNSQ | Infit MNSQ |
| Near vision | -5.41 | 0.35 | 1.84 | 0.96 |
| Distance vision | -1.9 | 0.33 | 0.73 | 0.76 |
| Intermediate vision | -1.63 | 0.33 | 1.04 | 1.14 |
| QOV-Night | 3.07 | 0.37 | 1 | 0.97 |
| QOV-Day | 5.88 | 0.39 | 1.02 | 1.03 |
| VF-14 | | | | |
| Items | Items difficulty | Standard Error | Outfit MNSQ* | Infit MNSQ* |
| Near vision | -3.97 | 0.34 | 0.84 | 0.87 |
| Distance vision | -1.6 | 0.31 | 1.29 | 1.19 |
| Intermediate vision | -1.11 | 0.31 | 1.2 | 1.14 |

| | | | | |
|---|---|---|---|---|
| QOV-Night | 2.04 | 0.35 | 0.98 | 0.91 |
| QOV-Day | 4.63 | 0.39 | 0.81 | 0.9 |

*MNSQ = Mean Squared

**Table 7.5** Patients perspective on VF-14 questionnaire

| Items on VF-14 | Not relevant to patients | Not relevant to patients (%) |
|---|---|---|
| playing sports | 30 | 58 |
| watching television | 5 | 9 |
| difficulty driving during the day | -- | -- |
| difficulty driving at night | 10 | 19 |
| reading signs | 5 | 9 |
| recognizing people | -- | -- |
| seeing steps or curbs or stairs | -- | -- |
| writing checks or filling out forms | 12 | 23 |
| playing board games | 20 | 39 |
| cooking | 15 | 29 |
| reading small print | 14 | 27 |
| reading a newspaper or book | -- | -- |
| reading a large print publication | -- | -- |
| doing handwork | 25 | 49 |
| n=51 patients | | |

## 7.8 Discussion

Although several questionnaires are available to measure VR-QOL. A brief, valid, relevant and easily comprehensible questionnaire that allows for a precise monitoring of severity is essential. The VF-14 questionnaire is a validated questionnaire developed by Steinberg *et al*. It has gained increasing acceptance in clinical and

research settings. In contrast, the VR-QoL questionnaire is short and personalised questionnaire that measures distance, intermediate and near visual function relevant to the patient. These unique characteristics of the VR-QoL questionnaire has demonstrated to be more precise with less variability in assessing patient's VR-QOL (Table 7.3).

The results from the Rasch analysis demonstrates that this cohort of patients are more affected by near vision task. Since the items for "Near vision" had the lowest item difficulty for both questionnaires, suggesting that both questionnaires were in agreement with near vision tasks being difficult. However, the item difficulty score for VR-QoL questionnaire was greater than VF-14. This finding implies that pre-defined items/questions on the VF-14 questionnaire did not clearly define and capture near vision related tasks of the patient. The item difficulty in VR-QoL questionnaire is greater than VF-14 questionnaire for distance and intermediate vision. This highlights the fact that pre-determined visual function questions on a questionnaire cannot correctly assess the true visual function of an individual (Table 7.4). Additionally, the item difficulty for QOV questionnaire at night was lower than the item difficulty parameter for the QOV questionnaire at day. This indicates that the patients are more affected by near vision tasks particularly during the night.

Gothwal *et al*. (2010) also demonstrated that out of the fourteen items in VF-14 questionnaire, two items measured a construct different than the remaining twelve items (not visual functioning). Principal component analysis conducted by Gothwal *et al*. (2010) further confirmed the lack of unidimensionality by revealing the presence of a secondary dimension. Conversely, VR-QoL questionnaire items are defined by the patient and highly relevant to the patients QOL. The VR-QoL questionnaire demonstrated to be better at capturing with less variations. Although the sample size was small, significant differences was found. The analysis of VF-14 questionnaire responses revealed that 58% of the patients did not find the item 'playing sports' relevant. This low level of relevance of this item can explained by the patient demographics (mean age: 74 ± 17; morbidity: cataract). 'Playing board games' 'cooking' and 'doing handy work' also had high percentage of not being relevant to the patients (39%, 29% and 49% respectively). These findings of high irrelevancy of items in the VF-14 questionnaire to patients suffering from age related cataract suggest the

weakness of the questionnaire to capture the QOL status of the individual. Finally, with only 6 relevant items on the VR-QoL questionnaire, the respondent burden and administration time are minimal.

The proposed VR-QoL questionnaire and this study is not without limitations. This current study is pilot study for the validation of VR-QoL questionnaire. For this purpose, a larger sample size visual function score would have to correlate with VA. This will be tested using the VA data and Pearson correlation coefficients.

## 7.9 Conclusion

In conclusion, our results show that VR-QoL questionnaire performs better than VF-14 questionnaire in-terms of less variability in the mean range scores. The tailored items of VR-QoL questionnaire was better able to assess the patients VR-QOL. Given these benefits, it is passable to conclude that the concept of personalised and adaptive QOL questionnaires are better in comparison to traditional pre-determined items on a questionnaire.

## 7.10 Summary

Questionnaires in ophthalmology are increasingly being required for assessing visual function in patients. Traditional psychometric VR-QOL questionnaires items lack brevity and do not take into consideration the individuality of the patient's visual function needs therefore VR-QoL questionnaire has the potential to accurately assess patients by means of direct active interaction with each patient.

## CHAPTER 8: DISCUSSION AND CONCLUSION

This body of work has sought to assess the impact of anatomical variations in visual axis, pupil size and ocular surface pathologies upon the QOV achieved during both multifocal IOL surgery along with other forms of refractive laser surgery. It has also sought to explore both:
-how these issues can impact VR- QOL, and
-assess if the traditional VR-QOL questionnaires can be improved.

A comprehensive set of pre-assessment equipment was used to investigate the pupil size, centroid shift, preoperative aberrations, and a photographic methodology developed to assist in the visualization of IOL centration. Improved IOL centration with regards to the centre of the photopic was demonstrated to improve a patient's overall QOV. A novel methodology of placement of the near add was developed. This enabled patients to increase the likelihood of high level of postoperative QOV and improved VR-QOL. This new methodology has now been advocated by the IOL manufacturer (Lenstec, UK) for common usage of these IOLs throughout the world. The results obtained with regards to the optimal pupil size can guide surgeon to preoperatively stratify patients and determine whether asymmetric multifocal IOLs should be used.

The human eye is not symmetrical and therefore in some patients a large deviation in the form of angle kappa. If this angle kappa coincides with a large centroid pupil shift, this combination can result in a significant encroachment of the pupil upon the near or distance section of an asymmetric multifocal IOL. This results in a significant reduction of QOV for either distance or near vision. A similar problem can also occur for different reasons:

Asymmetric fibrosis of a capsular bag can significantly decentre an IOL. For this reason, the authors have advocated the routine use of CTR in all routine IOL implantation surgery.

Another common cause of IOL decentration encountered was due to the periphery of the capsular bag not being centred upon the centre of the photopic pupil. This was found to be relatively consistent with 70% of the centre of the IOLs decentred superotemporal from the centre of the photopic pupil. With this knowledge, placing the near section of the asymmetric multifocal IOL in a superoptemporal position to enhances distance vision in the dominant eye. In the non-dominant eye placing the near section in the inferionasal position enhances near vision.

The preoperative assessments of angle kappa, pupil size and pupil centroid shift should be done in all eyes when using asymmetric multifocal IOLs. These assessments allow preoperative patient stratification for optimal visual outcome and postoperative patient satisfaction. The importance of multifocal IOL centration stated on this thesis is in line with findings of Werblin *et al*. (2001). Therefore, the findings of chapter 2, 3 and 4 of this thesis all reinstate the value of preoperative planning and accurate placement of asymmetric multifocal IOL. Additionally, chapter 3 of this thesis demonstrated the difficulty of centering the asymmetric multifocal IOL within a pharmacologically dilated intraoperative pupil. As there are no reference to where the photopic pupil centre would be postoperatively. The accurate depiction of the position of photopic pupil centre intraoperatively could allow bespoke positioning of asymmetric IOLs which took into account any unexpected malposition due to capsular bag positional anomalies.

The causation of photopic phenomena is multifactorial and our study suggests that angle kappa may possibly be one of the factors influencing it. However, it was also demonstrated that if the photopic pupil was greater than 3.2 mm postoperatively that angle kappa had less of an impact upon the overall QOV.

Less optimal QOV in asymmetric multifocal IOLs can arise from inadequate pupil size as a smaller pupil (< 3.00 mm) does not allow adequate exposure of both the optical sections of the asymmetric multifocal IOL. In other words, small pupils do not allow enough light to enter and fall on asymmetric multifocal IOL leading to poor QOV. Therefore, this poor exposure of the asymmetric multifocal IOL within a pupil can be alleviated by preoperatively selecting patients who have pupil diameter of a minimum of 3.00mm.

The role of pupil size and pupil centroid shift in multifocal lens is further verified by the fact that in a study conducted on monofocal IOLs concluded that pupil size and IOL decentration did not correlated with the postoperative visual outcome, contrary to the belief that decentration in all IOLs can lead to degradation of visual image and refractive error Werblin (2001). The plausible explanation to this finding may be due to the fact that monofocal IOLs have single optical design, unlike in multifocal IOLs where under exposure of light to a specific optical region of the IOL can occur. The role and importance of adequate exposure of the asymmetric multifocal IOLs within the pupil was further supported by the IOL rotation study where postoperative patients with poor QOV with pupil centroid shift had their IOLs rotated to compensate the pupil shift for a better centration of the IOL. This resulted in significant improvement of QOV. We have therefore incorporated these findings to our daily clinical practice and recommend preoperative pupil assessment in all patients opting for asymmetric multifocal IOLs.

The importance of tear lipid layer and its role in vision is underlined by the definition of DE (Lemp, Baudouin and Baum, 2007a). Observation and analysis of interferometry patterns of the tear lipid layer has been used by various studies to measure and quantify the severity of DE with relatively good agreement among different researchers where the thickness was measured to be 102 ± 3 nm using an interference microscopy (Norn, 1979), 68 nm by interference microscopy (Lemp and Marquardt, 1992), 13–70 nm by specular reflectometry(Guillon, 1982), 70–80 nm by specular reflectometry (Olsen, 1985) and 32–46 nm by photometric reflectometry (Yokoi, Takehisa and Kinoshita, 1996). The value to using these techniques to assess tear lipid layer lies is their simplicity of use and non-invasiveness nature. TF instability due to poor or lack of meibomian gland function can precipitate optical disturbances resulting in reduced QOV which is generally reported by DE and post laser surgery patients (Goto *et al.*, 2002; Savini, Barboni and Zanini, 2006). This direct relationship between interference patterns and the amount of lipid layer on the TF make it an attractive technique. It also offers researcher the opportunities to relate tear lipid layer with other tests and DE symptomology. The short coming of TF interferometry assessment for now is that it does not yield direct quantitative data and relies on a grading scale. The tear lipid layer chapter showed a strong correlation with the postoperative glare in SMILE and glare and fluctuations in vision in fs-LASIK patients. It also demonstrated that the immediate

effects of laser refractive surgery had the tendency to disrupt the TF. However, additional work is required to understand the dynamics and recovery of lipid layer disruption after laser refractive surgery. The understanding from this chapter highlights the importance of tear lipid layer in post laser refractive surgery visual recovery. Along with other DE tests tear lipid layer interferometry allows for holistic and comprehensive ocular surface assessment approach to preoperative stratification and selection of patients considering refractive laser surgery treatment.

In CXL the removal of the corneal epithelium is an essential step that allows the penetration, homogenous absorption and distribution of riboflavin solution into the stroma of the cornea. The inadequate removal of the epithelium has been documented by Kymionis *et al*. (2012) to result in reduced biomechanical stiffening effect of the treatment. Additionally, corneal imaging using anterior segment OCT and corneal confocal microscopy have revealed clear distinction between CXL performed with and without epithelial debridement. These findings support the comparative study between CXL with manual epithelial debridement and CXL combined with trans-PTK excimer mode in chapter 6. The findings of chapter 6 demonstrate that combining trans-PTK with CXL led to an earlier functional improvement of vision and stabilises the ectatic disorder. Trans-PTK smoothens the anterior corneal stroma by masking effect of the epithelium to partially eradicate some of the underlying irregular stroma astigmatism. This leads to an overall improvement in the corneal topography of the keratoconic eye (Kymionis *et al.*, 2014). Although the clinical utility and success of CXL alone has been well documented there are multiple different forms of additive treatments called ‘CXL plus’ and ‘CXL extra’. These methodologies are designed to stabilise the ectatic disorder and improve VA. However, since every individual patient has different level of disease severity. It is important to evaluate these methodologies to gain a better understanding on how varying levels of KC severity responds to these added treatments. The findings in chapter 6 suggests that larger levels of preoperative maximum K could be a positive preoperative factor in determining a beneficial improvement in postoperative visual outcomes. The extension of this research would be to examine the implication of preoperative maximum K values on a larger cohort for a longer period time. This will help us validate our initial findings.

Chapter 7 of this thesis initiated the investigation to test the validity and assumptions of VR-QOL questionnaires. Unfortunately, it has not been possible to attain a sufficient sample size to validate the proposed hypothesis that "asking the patient to choose two specific items that are relevant and meaningful to their VR-QOL for distance, intermediate and near vision (total 6 items) will generate a more accurate status and representation of their visual function in comparison to generic prechosen items on a questionnaire". Using Rasch analysis, initial findings of this chapter appears to demonstrate the weakness of generic pre-determined items on a questionnaire. Due to heterogeneity and variations in any given population regarding visual function, the static nature of pre-defined items on a questionnaire fails to be relevant to all or some participant (depending upon the sample population). This failure of relevancy in previously Rasch validated questionnaires was also been documented by Gothwal *et al*. (2010). Gothwal and colleauges administered the VF-14 questionnaire (validated and accepted) to a cohort of 210 cataract patients. Out of the 14 items, they found that only 8 items were considered ideally suited for measuring cataract surgery outcomes. Therefore, using Rasch analysis Gothwal *et al*. (2010) removed these irrelevant items and derived a shorter VF-8 questionnaire which had high precision in 'their' sample of cohort. In-order to mitigate such irrelevancy of items on a questionnaire, chapter 7 of the thesis devised a novel approach by allowing the participants to personally define VR-QOL items most relevant to them 'within' the domain of distance, intermediate and near vision. The findings of Gothwal *et al*. (2010) further supports the narrative that Rasch methodology of validation of psychometric questionnaires is based on the assumption that a given population is homogenous and does not take into account the possible heterogeneity. The follow-up to the findings of chapter 7 will be to test the hypothesis on a larger sample size and validate it against pre and postoperative VA readings.

**Limitations**

When comparing the effect of pupil size or angle kappa upon the QOV, one needs to recognise that QOV is a binocular impression which may be impacted more from one eye than another. There is usually little variation in angle kappa or pupil size between

eyes, to take into account any variation we initially averaged the pupil size and angle kappa between the left and right eyes.

One of the limitations to the interferometry and DE study was the lack of sex matching between the two groups, this might have influenced the results of the findings. In this study the tear lipid layer was interferometry patterns were captured 2 seconds after a complete blink as suggested by King-Smith *et al*. (2000), while other studies such as Monte´s-Mico´ *et al*. (2005) suggest measuring 5 seconds after a complete blink. As we know that TF in DE becomes unstable sooner than in normal eyes. Therefore by assessing the tear lipid layer after 2 seconds, the interferometry pattern was able to captured the patterns before the TF was destabilised. However, in the future, the TF assessment utilising various timings will be explored. This study also did not explore the assessment of tear lipid layer interferometry of different areas of the cornea and only focused on the central corneal region around the pupil. Since TF and tear lipid layer thickness is suggested to vary on the corneal surface (King-Smith *et al.*, 2000).

The primary limitation to CXL and trans-PTK study is that it is a retrospective in nature. And for valid comparison, patients in both mechanical group were matched to patients in the trans-PTK group on the parameters of keratometry and pachymetry prior to being included in the study sample. Therefore, this study suffers from selection bias.

**Conclusion**

Since the expectations of patients continues to grow. This demand can be met by improving technology and techniques to enhance examinations and treatments. Continued research is occurring throughout the world using different methodologies to improve the available treatments for presbyopia. The target of these technological enhancement is to better mimic true accommodation rather than iteratively improve upon the existing multifocal IOLs or other forms of monovision treatment. As the TF is the primary refracting surface of the eye, it is essential to ensure the ocular surface is consistently optimised to improve the quality of the TF. In our clinic, we aim to further explore the best processes to both improve the TF and monitor both the change in TF quality through interferometry and other methodologies. The goal to accurately

measure and monitor QOV and VR-QOL in laser refractive and cataract patients using the proposed hypothesis in chapter 7 will therefore continue to be pursued.

This body of work has currently attempted to understand various objective and subjective aspects of vision and their implications in vision rehabilitation. The future studies will be to validate the findings and examine long term changes.

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## APPENDIX A

### Quality of Life Questionnaire

Quality of vision questionnaire

| Parameter | Subscale question and response scale |
|---|---|
| Glare | 1. How often do you experience glare? Never (0) – Very often (3) |
| | 2. How severe is the glare? Not at all (0) – Severe (3) |
| | 3. How bothersome is the glare? Not at all (0) – Very (3) |
| Haloes | 4. How often do you experience haloes? Never (0) – Very often (3) |
| | 5. How severe are the haloes? Not at all (0) – Severe (3) |
| | 6. How bothersome are the haloes? Not at all (0) – Severe (3) |
| Starbursts | 7. How often do you experience starbursts? Never (0) – Very often (3) |
| | 8. How severe are the starbursts? Not at all (0) – Severe (3) |
| | 9. How bothersome are the starbursts? Not at all (0) – Severe (3) |
| Hazy vision | 10. How often do you experience hazy vision? Never (0) – Very often (3) |
| | 11. How severe is the hazy vision? Not at all (0) – Severe (3) |
| | 12. How bothersome is the hazy vision? Not at all (0) – Severe (3) |
| Blurred vision | 13. How often do you experience blurred vision? Never (0) – Very often (3) |
| | 14. How severe is the blurred vision? Not at all (0) – Severe (3) |
| | 15. How bothersome is the blurred vision? Not at all (0) – Severe (3) |
| Distortion | 16. How often do you experience distortion? Never (0) – Very often (3) |
| | 17. How severe is the distortion? Not at all (0) – Severe (3) |
| | 18. How bothersome is the distortion? Not at all (0) – Severe (3) |
| Double or multiple images | 19. How often do you experience double or multiple images? Never (0) – Very often (3) |
| | 20. How severe are the double or multiple images? Not at all (0) – Severe (3) |
| | 21. How bothersome are the double or multiple images? Not at all (0) – Severe (3) |
| Fluctuation in your vision | 22. How often do you experience fluctuation in your vision? Never (0) – Very often (3) |
| | 23. How severe is the fluctuation in your vision? Not at all (0) – Severe (3) |
| | 24. How bothersome is the fluctuation in your vision? Not at all (0) – Severe (3) |
| Focusing difficulties | 25. How often do you experience focusing difficulties? Never (0) – Very often (3) |
| | 26. How severe are the focusing difficulties? Not at all (0) – Severe (3) |
| | 27. How bothersome are the focusing difficulties? Not at all (0) – Severe (3) |
| Difficulties judging distance or depth perception | 28. How often do you have difficulty judging distance or depth perception? Never (0) – Very often (3) |
| | 29. How severe are the difficulties judging distance or depth perception? Not at all (0) – Severe (3) |
| | 30. How bothersome are the difficulties judging distance or depth perception? Not at all (0) – Severe (3) |

**Notes:** The QoV questionnaire is a Rasch-tested, linear-scaled (0–3) 30-item instrument on three scales providing a QoV score in terms of symptom frequency, severity, and the degree to which the symptom is bothersome. McAlinden et al[4] developed the instrument and consider it suitable for measuring QoV in patients with all types of refractive correction, eye surgery, and eye disease. The instrument and further details pertaining to its development can be found in McAlinden et al.[4]
**Abbreviation:** QoV, quality of vision.

## APPENDIX B

VF-14 QOL questionnaire

Patient Name: _____ DOB: _____ Date of Visit: _____

**VF-14 QOL Questionnaire**

**Because of your vision**, how much difficulty do you have with the following activities?
Check the box that best describes how much difficulty you have, even with glasses.
If you do not perform the activity for reasons unrelated to your vision, circle "n/a"

| Activity | | None | A little | Moderate | Great deal | Unable to do |
|---|---|---|---|---|---|---|
| 1. Reading small print, such as medicine bottle labels, a telephone book, or food labels | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Reading a newspaper or a book | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Reading a large-print book or large-print newspaper or numbers on a telephone | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Recognizing people when they are close to you | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Seeing steps, stairs or curbs | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Reading traffic signs, street signs or store signs | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Doing fine handwork like sewing, knitting, crocheting, carpentry | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Writing checks or filling out forms | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Playing games such as bingo, dominos, card games, or mahjong | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. Taking part in sports like bowling, handball, tennis, golf | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. Cooking | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. Watching television | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. Driving during the day | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. Driving at night | n/a | ☐ | ☐ | ☐ | ☐ | ☐ |

***Patient Signature:*** _____

| ***Office use only:*** | (C) *# checked boxes in column* | | | | | |
|---|---|---|---|---|---|---|
| | (F) *factored amounts* | X4 = | X3 = | X2 = | X1 = | **0** |

**C** = total number of **C**hecked boxes in column

**F** = sum of the **F**actored amounts

**Final Score: (F _____ / C _____ ) x 25 = V**

**V** =Final **V**-14 score

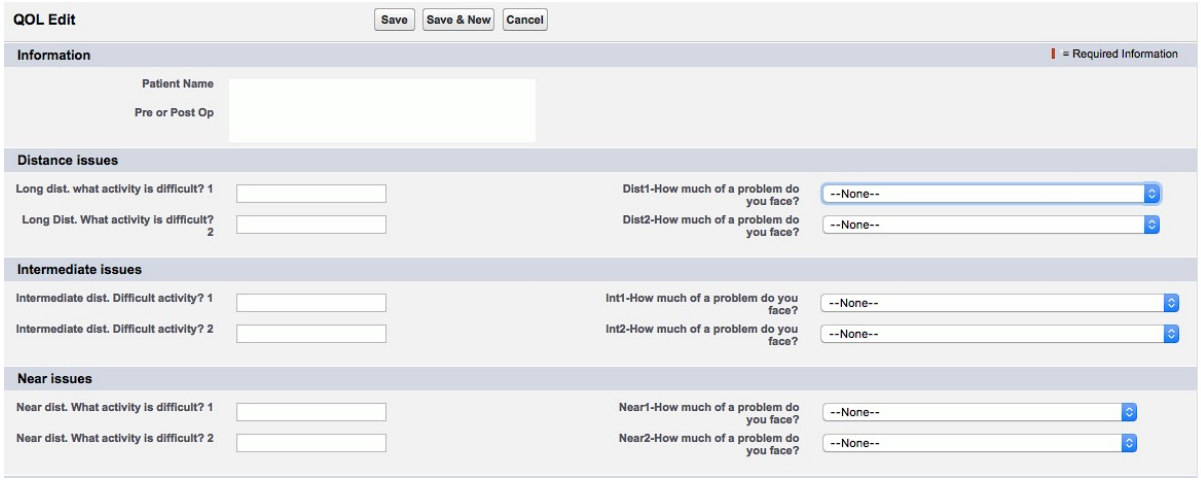
**V =** ☐

VF-14 QOL Questionnaire_10-28-09

*MD Signature:* _____

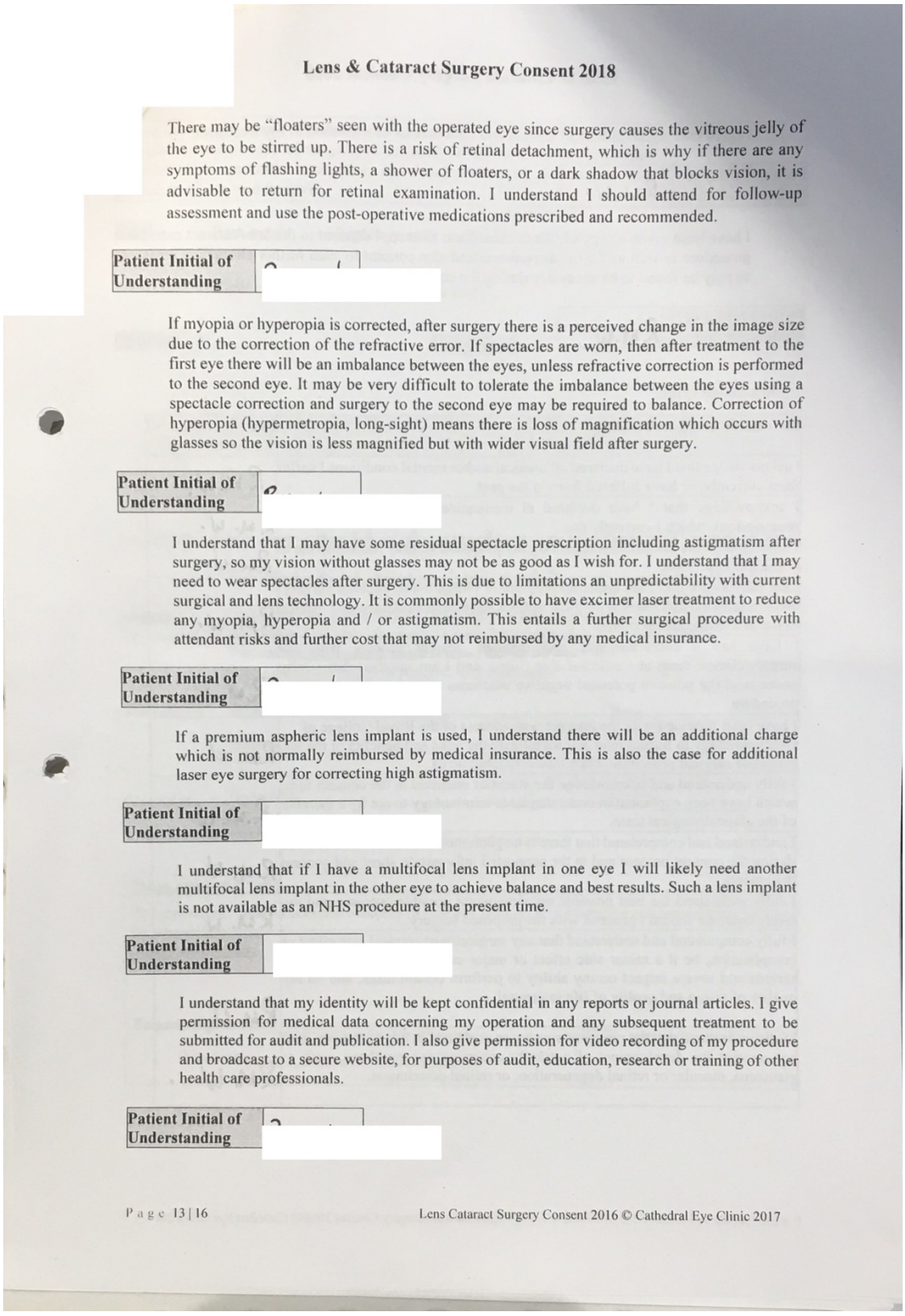
## APPENDIX C

Vision related QOL questionnaire



## APPENDIX D

Sample of patient consent form



**Lens & Cataract Surgery Consent 2018**

There may be "floaters" seen with the operated eye since surgery causes the vitreous jelly of the eye to be stirred up. There is a risk of retinal detachment, which is why if there are any symptoms of flashing lights, a shower of floaters, or a dark shadow that blocks vision, it is advisable to return for retinal examination. I understand I should attend for follow-up assessment and use the post-operative medications prescribed and recommended.

**Patient Initial of Understanding**

If myopia or hyperopia is corrected, after surgery there is a perceived change in the image size due to the correction of the refractive error. If spectacles are worn, then after treatment to the first eye there will be an imbalance between the eyes, unless refractive correction is performed to the second eye. It may be very difficult to tolerate the imbalance between the eyes using a spectacle correction and surgery to the second eye may be required to balance. Correction of hyperopia (hypermetropia, long-sight) means there is loss of magnification which occurs with glasses so the vision is less magnified but with wider visual field after surgery.

**Patient Initial of Understanding**

I understand that I may have some residual spectacle prescription including astigmatism after surgery, so my vision without glasses may not be as good as I wish for. I understand that I may need to wear spectacles after surgery. This is due to limitations an unpredictability with current surgical and lens technology. It is commonly possible to have excimer laser treatment to reduce any myopia, hyperopia and / or astigmatism. This entails a further surgical procedure with attendant risks and further cost that may not reimbursed by any medical insurance.

**Patient Initial of Understanding**

If a premium aspheric lens implant is used, I understand there will be an additional charge which is not normally reimbursed by medical insurance. This is also the case for additional laser eye surgery for correcting high astigmatism.

**Patient Initial of Understanding**

I understand that if I have a multifocal lens implant in one eye I will likely need another multifocal lens implant in the other eye to achieve balance and best results. Such a lens implant is not available as an NHS procedure at the present time.

**Patient Initial of Understanding**

I understand that my identity will be kept confidential in any reports or journal articles. I give permission for medical data concerning my operation and any subsequent treatment to be submitted for audit and publication. I also give permission for video recording of my procedure and broadcast to a secure website, for purposes of audit, education, research or training of other health care professionals.

**Patient Initial of Understanding**