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Long-term incidence of dry eyes and visual aberrations after corneal refractive surgery

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Thesis

LONG-TERM INCIDENCE OF DRY EYES AND VISUAL ABERRATIONS AFTER CORNEAL REFRACTIVE SURGERY

by

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ABSTRACT

Introduction/Purpose

Billions of people world wide suffer from refractive errors requiring glasses, contact lenses, or other means of correction to enable them to see better. Many people seeking permanent means to correct their vision consider undergoing corneal refractive laser surgeries (CRLS), photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy (LASEK), or laser *in situ* keratomileusis (LASIK). These surgeries have been shown to improve vision, but are not without risks for complications intra-operatively and postoperatively. Few studies have looked at the long-term incidence of postoperative complications such as dry eyes and visual aberrations and the associated preoperative risk factors. It is the aim of this study to examine the long-term incidence of dry eyes and visual aberrations (starbursts, halos, glare) after CRLS, and assess for preoperative risk factors associated with the persistence of these symptoms after surgery.

Methods

This study consisted of 319 patients identified for undergoing PRK, LASEK, or LASIK, at Boston Laser between December 2009 and January 2014. The participants in this study completed a novel online questionnaire consisting of questions to assess dry eye and visual aberration symptoms, and included questions adapted from the Ocular

Surface Disease Index (OSDI). Postoperative dry eye symptoms were measured based on the OSDI score and a new dry eye measurement score created for this study's questionnaire. Presence or absence of visual aberration symptoms postoperatively were measured based on a score created for this study and derived from the calculation of the OSDI score. Additionally, a retrospective chart review was conducted of the 319 participants' medical charts to gather and assess for preoperative risk factors related to the long-term incidence of both dry eye and visual aberration symptoms.

Results

Our data found a significant association ($p < 0.05$) that suggests a relationship between development of long-term dry eye symptoms and the following preoperative variables: pupil size, flap thickness, and dry eye risk assessment (including: Zone Quick test values ≤ 9.0mm, contact lens use, and dry eyes with and without contact lenses). No significant association ($p > 0.05$) was found between the novel dry eye score and the preoperative factors, but it did approach significance with two variables, necessitating further investigation: gender and actual ablation. No significance ($p > 0.05$) was found in the association between the preoperative dry eye risk assessment and severity of postoperative symptoms as gathered using the OSDI score.

Our data found a significant association ($p < 0.05$) that suggests an increased risk for development of long-term visual aberrations symptoms postoperatively with the following preoperative variables: cylindrical manifest refraction, flat K, and greater actual flap thickness. As well as identifying two other possible variables that approached significance requiring further investigation: steep K and preoperative visual aberrations

risk (including: spherical manifest refraction ≥ -6.00, astigmatic manifest refraction ≥ -2.00, and pupil diameter ≥ 7.0). The data showed a significant association ($p < 0.05$) between postoperative symptom presence and the aforementioned preoperative visual aberrations risk. Our data showed no significance ($p > 0.05$) when comparing the difference between mean OSDI, dry eye, and visual aberration scores between participants grouped by years since surgery.

Discussion/Conclusion

Our data found a significant relationship between long-term dry eye risk after CRLS and preoperative pupil size, flap thickness, and dry eye risk assessment. Similarly the data also displayed a significant association between long-term visual aberration risk after CRLS and greater preoperative cylindrical manifest refraction, flat K, and flap thickness. These findings contribute to the risk factors identified in similar short-term follow-up studies, and support the need for increased research into the risk factors and long-term incidence of dry eyes and visual aberrations after CRLS. While the data showed no significance between participants grouped by years since surgery and reported postoperative symptoms, the OSDI mean scores did approach significance ($p = 0.088$), suggesting that further research with a greater survey population is required.

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LIST OF ABBREVIATIONS

BCVA ..... Best corrected visual acuity

cc-Dva ..... Corrected distance visual acuity

CRLS .....Corneal Refractive Laser Surgery

D.....Diopters

DES .....Dry Eye Syndrome

flat K ..... Flattest keratometry measurement

IOP .....Intraocular pressure

LASEK.....Laser-assisted subepithelial keratectomy

LASIK.....Laser in Situ keratomileusis

MMC..... Mitomycin C

NSAID ..... Nonsteroidal anti-inflammatory drug

OSDI .....Ocular Surface Disease Index

PRK..... Photorefractive keratectomy

sc-Dva ..... uncorrected distance visual acuity

sc-Nva ..... uncorrected near visual acuity

steep K .....Steepest keratometry measurement

TBUT .....Tear breakup test time

INTRODUCTION

It has been estimated that 670 million people worldwide have visual impairment due to uncorrected refractive errors (Naidoo & Jaggernath, 2012). Refractive errors occur due to improper focusing of light as it is bent or refracted when it enters the eye through the cornea, passes through the lens, and stimulates the retina at the back of the eye. An emmetropic, normal eye causes light rays to be focused directly onto the retina allowing for optimal distance vision (Chang, 2011). In a hyperopic eye the shorter length of the eye causes the light rays to reach a focal point that is at an imaginary point behind the retina, which is known as farsightedness (Chang, 2011). Conversely, the myopic eye has a longer length than the emmetropic eye causing the light rays to reach a focal point in front of the retina, which is known as nearsightedness (Chang, 2011). While these are the major classifications of refractive error there are many variants to these errors including several categories of astigmatism, which refers to situations when the light entering the eye results in multiple focal points (Riordan-Eva, 2011). Refractive errors can also be due to the irregularities in corneal curvature (Riordan-Eva, 2011).

Visual impairment due to refractive errors can be corrected via non-permanent methods, such as glasses and contact lenses, and permanent measures, such as implantable contact lenses and corneal refractive surgeries. However, there are limitations associated with all types of refractive error corrections. Glasses can be inconvenient and costly to repair or replace; contact lenses have recurring costs and associated health risks such as: corneal infections, corneal abrasions, neovascularization, corneal edema, and allergic responses (Cochrane, Toit, & Mesurier, 2010). Due to the

daily regimen of care and risks associated with non-permanent methods of correction, it is of no surprise that the permanent methods of correction are increasing in popularity, as shown by the estimate that around 16 million people worldwide have already undergone corneal refractive surgery (Riordan-Eva, 2014).

Corneal Refractive Surgeries

There are two common techniques for corneal refractive laser surgery (CRLS) performed today to correct refractive error: surface ablation and lamellar (Figure 1). Both techniques involve the use of an excimer laser, which causes photodecomposition to ablate and reshape the cornea to correct for the irregular shape of the eye (Chong, 2011). The difference between the two methods is the depth at which the ablation occurs. In the surface ablation procedures, laser-assisted subepithelial keratectomy (LASEK) and photorefractive keratectomy (PRK), the laser is fired after the thin corneal epithelium is displaced, with LASEK, or removed, with PRK (Biswell, 2011; Figure 1). These two procedures are similar except that in LASEK the corneal epithelium is replaced after ablation, and some studies have suggested that this epithelial replacement can decrease pain, decrease corneal haze, and allow for better visual acuity earlier in the recovery process as compared to after PRK surgery (Lee et al., 2001; Shah et al. 2001). However, other studies have disagreed with this idea, showing no significant differences in these factors between LASEK and PRK (O'Doherty et al. 2007). In the lamellar procedure, laser *in situ* keratomileusis (LASIK), the laser is fired after a flap has been created at a

specific depth in the corneal epithelium and folded away from the operative part of the cornea (Biswell, 2011; Figure 1).

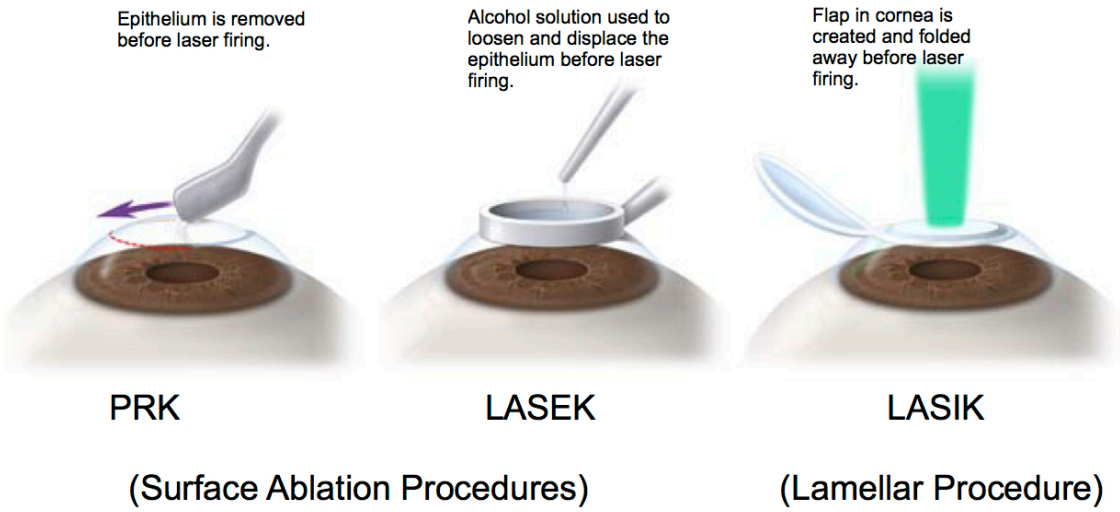


Figure 1. Three common CRLS procedures: PRK, LASEK, and LASIK. Common CRLS procedures (PRK, LASEK, and LASIK) and the management of the cornea before laser ablation ("LASIK vs LASEK, PRK y epi-LASEK - Operación de Ojos," n.d.; Biswell, 2011).

Surface ablation and LASIK can be used to treat varying degrees of myopia, hyperopia, and astigmatism. According to a report by the American Academy of Ophthalmology, depending on the excimer laser used, the FDA has approved surface ablation treatments of myopia up to -13.00 diopters (D), astigmatism up to -4.50 D, and hyperopia between +0.50 D to +6.00 D ("Refractive Errors & Refractive Surgery PPP - 2013 - American Academy of Ophthalmology," n.d.). Additionally, the same report indicated that, depending on the excimer laser used, the FDA has approved LASIK treatments of myopia up to -14.00 D, astigmatism up to -6.00, and hyperopia between +0.50 D to +6.00 D ("Refractive Errors & Refractive Surgery PPP - 2013 - American Academy of Ophthalmology," n.d.). Although the FDA has approved large ranges of treatment, studies have shown that a more conservative degree of treatment will lead to

more predictable visual outcomes: less than -8.00 D of myopia, less than -5.00 D of astigmatism, and less than +4.00 D of hyperopia (O'Keefe & Kirwan, 2010; Sutton, Lawless, & Hodge, 2014).

While the range of refractive errors is an important determinant of whether a patient is a good candidate for surgery, many other factors affect the treatment decision. The following factors must be evaluated before a patient is approved for CRLS: refractive stability (less than 0.50 D of change in the past year), corneal thickness, corneal curvature, pupil size, tear production, and medical diagnoses history (Sutton, Lawless, & Hodge, 2014). These elements are used to rule out contraindications for surgery and determine if a patient is eligible for LASIK or LASEK. As shown in Table 1, many of the indications for LASEK instead of LASIK are due to the flap created in LASIK and ensuring stable corneas after LASIK. For LASIK, corneal thickness should be measured to ensure that it is above 500 μm (normal: 530μm-560μm) and that the residual stromal bed after ablation is greater than 250-300 μm (Sutton, Lawless, & Hodge, 2014). Corneal thickness less than 500 μm is an indication that a surface ablation procedure should be selected to decrease risks associated with thin corneas (O'Keefe & Kirwan, 2010). Corneal curvature is assessed to ensure that the steepest and flattest corneal lines are within the normal range between 39 D and 47 D, which would aid in ruling out patients with keratoconus or irregular corneal topography (Sakimoto, Rosenblatt, & Azar, 2006). Additionally, pupil size (for laser optical zone selection), tear production (to assess dry eye symptoms), and complete medical diagnosis history should be collected to rule out conditions that are contraindications for CRLS, such as: Dry Eye

Syndrome (DES), glaucoma, or keratoconus, among others. (Table 2) (Sutton, Lawless, & Hodge, 2014).

Table 1. Indications for LASEK surgery. Reasons that a patient undergoing CRLS would select LASEK surgery as opposed to LASIK. Adapted from O'Keefe & Kirwan, 2010.

Corneal thickness <500μm
Recurrent corneal erosions
Post-LASIK flap complications
Retreatment after LASIK
Contact sports
Occupation

Table 2. Contraindications for CRLS. Conditions that could cause a patient to be ineligible to undergo CRLS. Adapted from Sutton, Lawless, & Hodge, 2014.

Unstable Refractions (>0.50 D change in year prior)
Inadequate central corneal thickness or thin corneas (dependent on required ablation depth)
Abnormal or irregular corneal topography
Inadequate tear production, dry eye symptoms, or Dry Eye Syndrome diagnosis
Significant corneal scarring
Recurrent corneal erosions (may be more suitable for PRK procedures)
History of herpes simplex keratitis or herpes zoster ophthalmicus
Atopic Disease
Autoimmune Disorders (such as Sjögren's Syndrome)
Glaucoma (LASIK procedures, due to the pressure created on the eye during flap creation)
Pregnancy (due to inability to take pre-/postoperative medications)
Keratoconus
Visually significant cataract
Uncontrolled ocular or systemic disease
Unrealistic patient expectations

After ruling out contraindications and deciding on a type of treatment, LASIK or LASEK, a final factor that must be discussed before surgery is type of ablation: traditional ablation or custom (wave-front guided) ablation. Both traditional and custom treatments are possible with LASIK and LASEK; however the visual results of each have been shown to vary depending on the degree of correction needed (Sakimoto, Rosenblatt, & Azar, 2006). While traditional treatments correct vision using the spherical and

astigmatic portions of the patient's dilated and non-dilated (manifest) refractions, custom treatments use other measurements specific to each eye to help correct for higher order aberrations, which might improve visual results and reduce the likelihood of visual aberrations after surgery (Sakimoto, Rosenblatt, & Azar, 2006). However, custom treatments aimed at correcting a wider scope of visual symptoms beyond the refractive data will inevitably necessitate a larger degree of ablation (Sakimoto, Rosenblatt, & Azar, 2006). A review by Sakimoto, Rosenblatt, and Azar (2006) analyzed results from multiple studies, both independent investigator and FDA studies, showing the differences between custom and traditional treatments and between myopia and hyperopia in LASIK, LASEK, and PRK procedures (Table 3). This review showed that in myopic treatments (0.00 D to -7.00 D) the uncorrected distance visual acuity (sc-Dva) was better than 20/40 in 96% of patients and 20/20 or better in 72% of patients receiving traditional LASIK (Sakimoto, Rosenblatt, & Azar, 2006). The sc-Dva was better than 20/40 in 98% of patients and 20/20 or better in 89% of patients receiving custom LASIK (Sakimoto, Rosenblatt, & Azar, 2006). Similarly, hyperopic treatments (0.00 D to +6.00) showed improvements from 90% to 97% in sc-Dva of better than 20/40 when comparing traditional LASIK to custom LASIK, but the percent of patients with sc-Dva of 20/20 or better dropped from 63% to 60% when comparing traditional LASIK to custom LASIK for hyperopia (Sakimoto, Rosenblatt, & Azar, 2006). Additionally, the data gathered in the review showed similar results when comparing both PRK and LASEK to LASIK for myopia and hyperopia (Table 3); however, high myopic LASIK patients showed a reduction in the percentage of patient who attained sc-Dva of 20/20 or better, which

supported previously mentioned suggestions regarding less predictable visual outcomes with higher degrees of treatment (Sakimoto, Rosenblatt, & Azar, 2006).

Table 3. Comparison of visual outcomes of traditional PRK, LASEK, and LASIK for myopia and hyperopia. The percentage of patients with sc-Dva at better than 20/40 and equal to or better than 20/20 for myopic and hyperopic LASIK, LASEK, and PRK procedures. Adapted from Sakimoto, Rosenblatt, & Azar, 2006.

	Myopia				Hyperopia		
	PRK	LASEK	LASIK – Traditional	LASIK – Traditional	PRK	LASEK	LASIK – Traditional
Visual Range	-1 to -13.0 D	-1 to -12.5 D	0 to -7 D	-7 to -12 D	+1 to +5 D	+2 to +5 D	0 to +6 D
sc-Dva >20/40	94.3%	94.5%	96%	89%	87.1%	90.7%	90%
sc-Dva ≥20/20	61.1%	73.9%	72%	48%	75.2%	73.1%	63%

While the visual results have been shown to be similar between LASIK and LASEK procedures, the differences between treatments can cause variance in the major complications that can arise after surgery. As shown in Table 4, there are a number of complications specifically related to flap creation during LASIK, that are avoided by surface ablation techniques; however, the chance of these complications occurring is usually small and the continued popularity of LASIK procedures over surface ablation can most likely be attributed to the often faster and less painful visual recovery with less chance of postoperative corneal haze (Shah & Melki, 2014). Furthermore, beyond flap-associated complications there are similar complications that can occur with both LASIK and surface ablation techniques, albeit to varying degrees depending on type of procedure (Table 4). For example, it has been indicated that regression after surgery can occur with both types of treatments, but higher-order visual aberrations (halos, glare, rainbow glare, starbursts; Figure 2) and risk of corneal ectasia are higher after LASIK surgery as compared to LASEK surgery (O'Keefe & Kirwan, 2010). Postoperative haze, more

common in surface ablation techniques, can be reduced with the use of Mitomycin-C (MMC) during surgery (Hashemi et al. 2004). While there are varying frequencies of each type of complication listed in Table 4, dry eyes and visual aberrations, such as glare, are of the most common complaints following CRLS (Jabbur, Sakatani, & O'Brien, 2004).

Table 4. Complications of LASEK and LASIK surgeries. Intra-operative and Postoperative complications associated with LASIK flap creation and some common postoperative complications after LASIK and LASEK surgeries. (Jabbur, Sakatani, & O'Brien, 2004; Sakimoto, Rosenblatt, & Azar, 2006; Schallhorn, Amesbury, & Tanzer, 2006; O'Keefe & Kirwan, 2010; Na et al., 2012; Shah & Melki, 2014)

	LASIK	Reported Frequency (LASIK)	LASEK	Reported Frequency (LASEK)
Intra-operative flap-related complications (from primary treatments with femtosecond laser)	Loss of suction/Incomplete flaps	4.4%		
	Thin, buttonholed flaps with vertical gas breakthrough	0.33%		
	Flap tears	0.4% – 2.2%		
	Anterior chamber gas bubbles and opaque bubble layers	0.3%		
	Epithelial defect	0.6%		
	Bleeding at edge of flap	Unreported		
	Bleeding due to suction	68.9%		
	Flap interface debris	1.9% - 100%		
Postoperative flap-related complications	Dislocated flaps	1.1%		
	Striae and folds	1.6% – 15%		
	Epithelial ingrowth	0.14% – 9.1%		
	Diffuse lamellar keratitis	0.2% – 10.6%		
Non-flap-specific complications	Keratitis/infection	0.03%	Infection	= LASIK
	Dry eye	8% – 48%	Dry eyes	< LASIK
	Haze	0.50% – 22.6%	Haze	6.6% –63.6%
	Higher-order visual aberrations	5.8% – 26.7%	Higher-order visual aberrations	12% – 41%
	Regression	= LASEK after 2 years	Regression	2.1%
	Ectasia	0.2%	Ectasia	< LASIK
	Transient light-sensitivity syndrome	0.4%		

Dry Eyes

Dry eyes symptoms after LASIK have been reported by up to 50% of patients in some studies (Ambrósio, Tervo, & Wilson, 2008). Dry eye symptoms are highly varied in each individual and can include: foreign body sensation, itching, irritation, tearing, soreness, redness, blurry/fluctuating vision, photophobia, contact lens intolerance, symptoms that are ameliorated with artificial tear usage, and symptoms that vary depending on location or time of day ("Dry Eye Syndrome PPP - 2013 - American Academy of Ophthalmology," n.d.). Assessing for dry eye risk before surgery should be done by ocular and systemic medical history evaluation, visual acuity measurement, slit-lamp examination, as well as diagnostic tests such as: tear breakup time test (TBUT) (evaluates tear film stability), rose bengal, fluorescein dye or other ocular surface staining (evaluates ocular surface damage), and Schirmer test (evaluates aqueous tear flow) (Perry, 2008). Risk factors for dry eyes include: old age, female sex (greater risk after menopause), autoimmune disorder (e.g. Sjögren's Syndrome), or use of medications that can promote eye dryness (e.g. antidepressants and antihistamines) ("Dry Eye Syndrome PPP - 2013 - American Academy of Ophthalmology," n.d.). Additionally, assessing for dry eye risk before surgery is important because CRLS can worsen symptoms in preexisting dry eye conditions (Ambrósio, Tervo, & Wilson, 2008). It has been suggested that denervation of sensory neurons at the cornea during LASIK can reduce the eye's blink reflex and tear production resulting in the dry eye symptoms commonly reported after CRLS (Battat et al. 2001). While it has been stated that the denervation of sensory neurons is the most likely cause of dry eye symptoms, other theories include greater tear

evaporation and damage to "goblet cells and microvilli at the limbus" (Shah & Melki, 2014). Furthermore, studies have shown that LASIK surgery alters the results of many diagnostic tests used in evaluating dry eye symptoms, such that after LASIK there is a decrease in Schirmer test value, decreased TBUT, and decreased basal tear secretion (Yu et al. 2000). Studies have similarly shown decreases in Schirmer test and TBUT values following surface ablation procedures, PRK and LASEK (Horwath-Winter et al. 2004). Alternatively, it has been reported that there is a decrease in the subjective and objective presentation of dry eyes after LASEK and PRK as compared to LASIK with greater/quicker return to baseline, which could be explained by the idea that absence of flap creation allows for less damage to the corneal sensory neurons (Herrmann et al., 2005).

It has been demonstrated that dry eye risk after LASIK is specifically related to degree of correction for myopia, thus the higher degree of correction means a larger laser ablation depth and increased risk (De Paiva et al., 2006). However, a more recent study indicated that, for both LASIK and surface ablation procedures, there are no correlations between the subjective dry eye symptoms and the patients' age, ablation depth, and flap thickness (Murakami & Manche, 2012). While current literature is divided, in part due to small sample size, dry eyes after CRLS have also been correlated with contact lens use, preexisting dry eye conditions, hyperopic treatments, and Asian race (Raoof & Pineda, 2014). Additionally, studies have shown varying results regarding the length of time dry eye symptoms can persist after surgery, often approximately 20% of patients still experience symptoms at six months or more (De Paiva et al., 2006; Shoja & Besharati,

2007; Raoof & Pineda, 2014). A recent review by Raoof and Pineda (2014) highlighted a dry eye treatment progression, using some of the commonly prescribed treatments, beginning with artificial tears and, as the severity of symptoms increases or persists, to treat using punctal plugs, topical cyclosporine, autologous serum tears, and for the most severe cases consideration of scleral lenses or prosthetic replacement of the ocular surface.

Visual Aberrations

As discussed previously, visual aberrations are a common complication after CRLS. Examples of possible visual disturbances after CRLS, as seen in figure 2, show halos, starbursts, and glare on the left as some of the more common complaints after surgery. However, these symptoms are not specific to CRLS surgery, those who wear contact lenses and glasses have also reported these disturbances (Schallhorn et al. 2009). One additional symptom (not shown in figure 2), rainbow glare – glare with distinct bands of color, has been shown to be specific to femtosecond laser created flaps, as opposed to microkeratome created flaps, and presents within 3 months after surgery (Farjo et al., 2013). It has been reported that this symptom is likely due to the pattern made by the laser during flap creation and that no correlation has been shown between risk for rainbow glare and age, gender, or level of correction (Farjo et al., 2013).

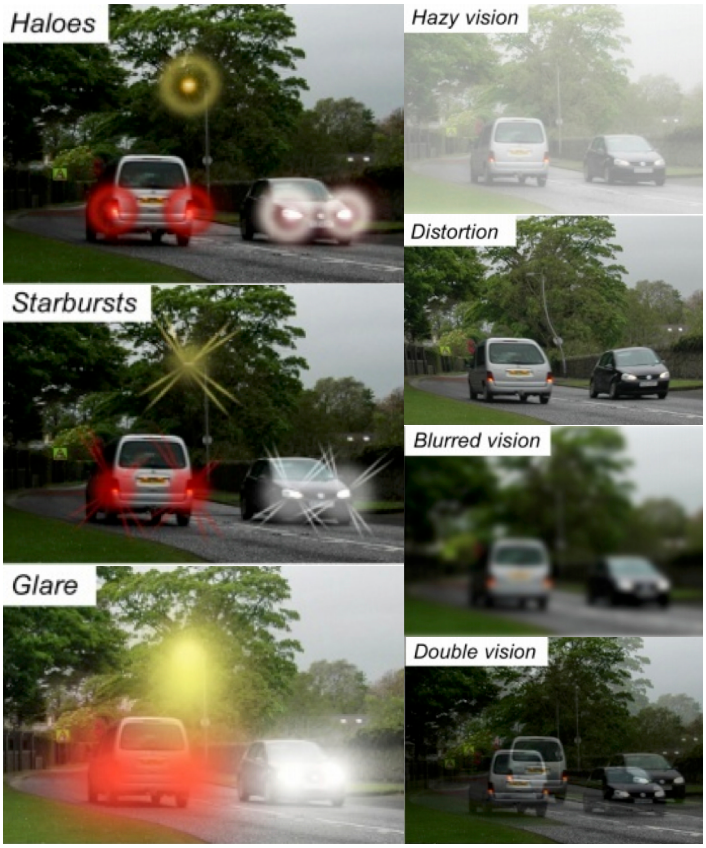


Figure 2. Examples of visual aberrations. Possible visual abnormalities that can be seen following CRLS. Adapted from (Boston Laser, 2014).

There have been varying results for the percentages of patients reporting the more common visual aberrations after surgery and the risk factors associated with them, including pupil size, arguably the most debated (Myung, Schallhorn, & Manche, 2013). In a 2003 study the results of a questionnaire mailed to patients who had surgery at least 6 months prior to answering the survey showed that, of the patients that did not report any symptoms before LASIK, 30.0% experienced halos, 24.5% experienced starbursts, and 27.2% experienced glare after surgery (Bailey et al. 2003). While that study did not show any correlation between the visual complications and pupil size or corneal asphericity, it did show a relation between glare and level of myopia, "preoperative

minimum corneal curvature and starbursts, and preoperative minimum and maximum corneal curvature and halos" (Bailey et al. 2003). Alternatively, another study reported that the results of a questionnaire given 6 months after surgery showed no correlations between level of correction and glare (Bamashmus et al. 2015). Risk factors for experiencing at least one of the three common visual aberrations include: enhancement surgeries, younger age, and increased depth of ablation (Bailey et al. 2003). Another risk factor for these visual aberrations could be the use of wave-front guided (custom) treatments versus the traditional treatments because, as mentioned previously, the custom treatments correct for higher-order aberrations instead of just spherical and astigmatic correction like in traditional treatments. There are decreased reports of glare after LASIK surgery using custom treatments as opposed to traditional surgery (Lee et al. 2006). One study analyzing wave-front data after LASIK surgery has shown that for the scotopic (dim-light) pupil size there is an association of both the spherical and total higher order aberration with both glare and starbursts, and the spherical aberration with halos (Chalita et al. 2004). Additionally it was shown that there was a positive correlation between starbursts and pupil diameter (Chalita et al. 2004).

There are also varying reports on the incidences of visual aberrations after CRLS. A study comparing the incidences of visual aberrations using a questionnaire before surgery and at 1, 3, 6, and 12 months after surgery showed no difference in the levels of glare or halo symptoms between LASIK and PRK eyes after one month, and for both types of procedures the severity of symptoms returned to near preoperative levels within one month of treatment (Manche & Haw, 2011). Another study also showed no

statistically significant difference between LASIK or PRK treatments in glare or halos in a six month follow-up questionnaire, but using the combination of glare and halo symptom scores showed that patients who underwent surface ablation treatment had more severe visual aberration symptoms after surgery than did LASIK patients (Hersh, Steinert, & Brint, 2000). Alternatively, a 1999 study using a questionnaire to assess incidence of visual aberrations two years after surgery showed that patients reported symptoms in 21% of eyes that received LASIK, where as symptoms were reported in 35% of eyes that received PRK treatment (El-Maghraby et al. 1999).

Study Rationale

There has been considerable debate, with study data supporting both sides, concerning those factors that put patients at increased risk for dry eyes and visual aberrations after CRLS; however, many studies fail to assess the persistence of symptoms beyond the one-year follow-up period after surgery. Additionally, those studies tend to have small sample sizes often considering the number of individual eyes rather than patients. Of those studies that consider long-term implications of refractive surgery, many do not mention or appear to assess dry eye symptoms or visual aberrations, or exclude candidates that report dry eye symptoms preoperatively (Autrata & Rehurek, 2003; Alió et al., 2008). A 4 year follow-up study after LASIK reports that for 22 PRK and 18 LASIK eyes there is a significant improvement in best corrected visual acuity (BCVA) in LASIK as compared to PRK from 6 months through 2 years, but this advantage was not maintained longer than 2 years after surgery due to myopic shift, and does not mention

visual aberrations or dry eye complications (Miyai et al., 2008). In a study examining 120 patients from one of the first PRK clinical trials at a 12 year follow-up, there were no significant changes reported from the 6 year follow-up of the same group, and much of the focus was on BCVA (Rajan et al. 2004). This study was one of few long-term studies that assessed visual aberrations and dry eyes. The data indicated that 12% of patients experienced night vision complications, including halos, at both 6 and 12-year follow-ups; furthermore, patients who had received more than 4 D of myopic correction experienced more severe symptoms than those that had underwent milder corrections, but none of the symptoms worsened and all patients claimed improvements over the 12 year follow-up period (Rajan et al. 2004). Additionally the study indicated that 3-6% of patients showed signs that could by related to dry eyes upon slit lamp evaluation (Rajan et al. 2004).

From this literature review it is evident that, while many studies report that objective measurements and subjective reports of dry eyes return to baseline within one year, few studies have evaluated dry eye symptoms and visual aberrations past that follow-up period after CRLS (Murakami & Manche, 2012). Our goal is to address this gap in literature and investigate the long-term incidence of these symptoms in CRLS patients and attempt to identify factors correlated with their persistence, if any. Additionally, an increased risk of regression has been correlated with persistent dry eyes after LASIK surgery, showing the importance of elucidating the risks for chronic dry eye after CRLS (Schallhorn, Amesbury, & Tanzer, 2006). Therefore, our study will also aim

to provide further insight into the risks associated with persistent dry eye and visual aberrations after CRLS.

SPECIFIC AIMS

The main objective of our study is to examine the long-term incidence of dry eyes and visual aberrations after CRLS, specifically:

1) Our study will select candidates that underwent CRLS at Boston Laser and whose date of surgery was at least one year prior to February 2015. Participants will be selected based on their affirmative response and consent to an electronic questionnaire e-mailed to all candidates.

2) Subjective data from the electronic questionnaire completed by participants will be examined. Pre-surgery data relating to risk for dry eyes and visual aberrations will be collected and matched with participant survey responses.

3) Statistical analysis between pre-surgery risk factors, time since surgery, and questionnaire responses will be determined.

We hope to show:

- A decrease in the persistence of dry eye symptoms and visual aberrations over time from 1-6 years post-surgery.
- A correlation between those patients that are still experiencing dry eye symptoms longitudinally after surgery through subjective responses on the study survey, and those that exhibited risk for dry eyes before surgery of: subjective reports of dry eyes with and without contact lenses before surgery, DES diagnosis before surgery, and Zone Quick test values less than or equal to 9mm before surgery.
- A correlation between patients that are still experiencing visual aberrations longitudinally after surgery and patients who before surgery had risk factors of:

pupil size greater than or equal to 7mm, spherical manifest refraction greater than or equal to 6.0, astigmatism greater than or equal to 2

METHODS

Study Design Overview

The design of our study consisted of three parts. The first part was a retrospective analysis of qualifying patient data. Data relating to the patients' surgery and those risk factors associated with dry eyes and visual aberrations were reviewed to determine eligibility from patient electronic medical records at Boston Laser. The second part entailed e-mailing an invitation to complete an online survey (Appendix A) to all qualifying patients who had LASIK, LASEK, or PRK surgery at Boston Laser during the period between December 2008 and January 2014. The survey consisted of 20 questions, and required approximately 3-5 minutes to complete. After the survey results were collected, the medical records of consenting participants were reviewed and the medical record data was associated with the survey results; then the study data was anonymized to protect patient information. The final portion consisted of a statistical analysis of the data from the survey results and the existing electronic medical record information to determine if there is any correlation between the pre-surgery risk factors and persistence of visual aberrations and dry eye symptoms after surgery.

Demographics / Patient Recruitment and Selection

The participants in this study were selected from a group of 2926 patients who were identified because their medical records indicated that they underwent CRLS with Dr. Samir Melki at Boston Laser between December 2008 and January 2014 and they met the inclusion and exclusion criteria for the study.

Participants included in the study also fit the following criteria: have an active e-mail address linked to their medical record in the Boston Laser electronic medical records, read and virtually agreed to the consent form included as the first page of the electronic questionnaire (Appendix A), and completed questions on the survey. Potential participants were excluded from the study if participant: failed to meet the inclusion criteria, underwent another corneal surgery after the original CRLS procedure, had a medical record that contained an incorrect, suspended, or non-existent e-mail address, or did not agree or failed to agree to the consent form. Patients were not excluded from the study on basis of gender, age, racial, or ethnic characteristics.

Electronic medical charts were reviewed of those 319 participants who consented to the study. During this retrospective review, demographic information, clinical data pertaining to each participant's specific CRLS, and known risk factors for dry eyes and visual aberrations were collected. Pre-surgery clinical data retrieved during the chart review included: contact lens wear history, glasses wear history, previous eye diagnoses, ocular medication history, manifest and cycloplegic refraction, BCVA, intraocular pressure (IOP) measurements, pupil diameter, Zone Quick measurement, keratometry (measurement of the radius of corneal curvature), and pachymetry (measurement of corneal thickness). Surgery specific data retrieved during the chart review included: optical zone size, actual ablation, target flap, actual flap thickness, spherical correction, target prescription, preablation bed (actual remaining bed underneath the flap when the flap is lifted), actual remaining bed (residual bed = pre-ablation bed – actual ablation),

MMC application, 1% cyclopentolate given after surgery, contact lens placement after surgery, and any complications with the flap or excimer laser during surgery.

Questionnaire

Qualifying participants were sent an e-mail with a link to the online questionnaire inviting them to participate in this study. The e-mail was sent confidentially using Constant Contact's e-mail service, such that each participant was not able to access the contact information of other participants. The e-mail was sent once and then resent six days later to all patients that had not yet completed the questionnaire.

The questionnaire used in this study contained twenty questions on six pages and was made using SurveyMonkey.com. The questionnaire was available to participants throughout the study duration, and, if a single participant submitted a questionnaire more than one time, the most recent complete submission was used. The first page of the study contained the consent form, detailing the participant's role and liabilities of participating in the study, and the first question asking the participant to acknowledge that they had read, understood, and agreed to the study terms. If a participant selected "yes", then they were directed to the second question, which began the survey; however, if the participant selected "no" then they were directed to a disqualification page and not allowed to participate in the study.

Questions six through eight of our questionnaire were adapted from the Ocular Surface Disease Index Questionnaire (OSDI), which has been validated for assessing dry

eye symptoms (Schiffman et al. 2000). Question sixteen was adapted from a study by Schallhorn et al. (2003) to be used as an assessment tool for evaluating visual aberrations.

Dry Eye and Visual Aberration Score Calculation

For this study we have developed new scoring methods for dry eyes and a visual aberration scoring method specific to the study's questionnaire. Both the dry eye score and visual aberration score were modeled after the OSDI Score calculation: total number of points from each question divided by the total number of questions answered and then multiplied by a modifier constant that enables the OSDI score to have a minimum of 0 and maximum of 100.

The Dry Eye Score created for this study incorporates the point values of the included OSDI questions (Questions 6-8, Appendix A) into the total point calculation. The total point range for the OSDI questions was 0-48. In questions 10, 12, 13, and 14, a response of "Yes" was considered 1 point, and a response of "No" was considered 0 points. The total point range for questions 10, 12, 13, and 14 for each question was 0-1. In question 9, a response of "None" was considered 0 points, and any other response besides none (i.e. "Artificial Tears", "Gel/Ointment Tears", "Restasis", "Other", "Punctal Plugs") was considered 1 point for each column that did not say none. Total point range for question 9 was 0-3. In question 11, a response of "I did not use this medication to treat dry eye symptoms in the last week" was considered 0 points, a response of "Occasionally (not everyday)" was considered 1 point, a response of "Once a day" was considered 2 points, and a response of "Three or more times a day" was considered 3

points. The total point range for question 11 was 0-12. In question 15, a response of "I am not experiencing dry eyes" was considered 0 points, a response of "No" was considered 1 point (because it indicated although they were experiencing dry eyes that it was not worse than it was prior to surgery), and a response of "Yes" was considered 2 points. The total point range for question 15 was 0-2. The points from all questions were summed into a total dry eye points value, which had a maximum value of 69 points. There were 24 total responses possible for the dry eye questions in this survey, 12 from the OSDI questions and 12 from questions 9-15. If a participant failed to answer a question or selected N/A, that question was not counted as part of the score for total questions answered. The final dry eyes score was calculated using the following formula: total dry eye points multiplied by 34.7827, and then divided by total dry eye questions answered. The 34.7827 constant allowed for the score to have a minimum of 0, maximum of 100, and to be significant to 2 decimal places.

The visual aberration score was calculated in a similar manner as the dry eyes score. In question 16 the total point range was 0-28. In questions 17 and 18, a response of "Yes" was considered 1 point, and a response of "No" was considered 0 points. Total point range for questions 17 and 18 was 0-1 for each question. In question 20, a response of "I am not experiencing halos, starbursts, or glare" was considered 0 points, a response of "No" was considered 1 point (because it indicated that although they were experiencing symptoms they were not worse than they were prior to surgery), and a response of "Yes" was considered 2 points. The total point range for question 20 was 0-2. The points from all questions were summed into a visual aberrations points total value,

which had a maximum value of 32 points. There were 10 total responses possible for the visual aberrations questions in this survey. If a participant failed to answer a question or selected N/A that question was not counted as part of the score for total questions answered. The final visual aberrations score was calculated using the following formula: total visual aberrations points multiplied by 31.25, and then divided by the total visual aberrations questions answered. The 31.25 constant allowed for the score to have a minimum of 0, maximum of 100, and to be significant to 2 decimal places.

Clinical CRLS Consultation Procedures

Each participant who had CRLS with Boston Laser went through the following practice standard consultation procedure before being scheduled for surgery. After information regarding referral, co-management, and participant's profession is gathered, the consultation begins by assessing glasses and contact lens wear history. Participants are asked whether they wear glasses and/or contact lenses and what percent of time on average is spent wearing their glasses, assuming that any non-glasses time would be with contact lenses or no correction. Additionally, if participants wear contact lenses, are asked first if they experience dry eyes with contact lenses and then if they experience dry eyes without contact lenses. Participants were questioned regarding their medical history, specifically if they have had any previous refractive surgeries, as well as ocular and systemic diagnostic history, allergies, and current medications.

The objective portion of the consultation begins by recording each participant's eye dominance, uncorrected distance and near vision (sc-Dva, sc-Nva), and distance

vision with present correction (cc-Dva) checked with glasses instead of contact lenses if possible. The current glasses prescription is recorded be performing lensometry using the Nidek LM-1200 Auto Lensometer (NIDEK Inc., Freemont, California).

Using either the Abbott Medical Optics WaveScan WaveFront System (Abbot Medical Optics Inc., Santa Ana, California) or Nidek TONOREF II (NIDEK Inc., Freemont, California), keratometry is performed and an objective refraction measurement is obtained. Keratometry data included: the flattest corneal curvature measurement (flat K) and steepest corneal curvature measurement (steep K). The objective refraction is next used as a basis for determining the participant's manifest refraction and recording the BCVA. Pachymetry information, such as the central and thinnest corneal thicknesses, and corneal topography images are gathered using the Ziemer Ophthalmology Galilei G4 (Ziemer USA, Inc., Alton, Illinois), Zeiss Atlas Topographer (Carl Zeiss Meditex, Inc., Dublin, California), or Oculus Pentacam (OCULUS Inc., Arlington, Washington).

An objective dry eye test is performed using the Oasis Medical Zone Quick (Oasis Medical Inc., San Dimas, California) phenol red thread tear test: one Zone Quick thread is hung for fifteen seconds from the participant's lower eyelid at a distance equal to one-third of the eye width from the temporal corners of each eye. The tear production is determined by measuring the length of string that turned from the original color yellow to red using the scale (mm) on the pack of the sterile packaging.

Pupil size (mm) is measured using the Oasis Medical Colvard Pupillometer (Oasis Medical Inc., San Dimas, California) in dim lighting with participants covering the opposite eye with the palm of their hand. The lighting is standardized so that

measurements are taken with the exam room door closed, all interior lights, including computer monitors, are turned off, and the shades of any windows are drawn closed. Technicians are instructed to measure the pupil within 0.5mm using the built-in scale, while the participant stares at the infrared light inside the pupillometer.

Participant IOP is measured via a non-contact method with the Nidek TONOREF II (NIDEK Inc., Freemont, California) or with the Reichert Technologies Tono-Pen (AMETEK Inc., Depew, NY) after administering 0.5% proparacaine hydrochloride ophthalmic solution. After checking IOP, participants' eyes are dilated with 1% tropicamide and 2.5% phenylephrine solution.

After full dilation is achieved a cycloplegic refraction as well as fundus and slit-lamp examination are performed. The treating surgeon discusses the procedure's benefits alternatives and risks after reviewing all the data gathered. A plan is then proposed in case the patient is deemed a candidate for surgery.

Surgical Technique – LASIK

The LASIK surgical procedure at Boston Laser begins with flap creation in the operative eye(s) using a femtosecond laser: the Abbott Medical Optics Intralase FS Laser (Abbot Medical Optics Inc., Santa Ana, California). During flap creation the lasers were set to aim for a 9mm flap diameter; however, with the Intralase FS Laser there is some variation due to centration (centering of the flap on the pupil), but surgeries were not performed at less than 8.8mm. Theoretical flap depth with the Intralase FS Laser for most patients was between 90 and 100 microns. All flaps created had superior hinge-position.

After flap creation the patient bed moves under the Abbott Medical Optics Star S4 IR Excimer Laser (Abbot Medical Optics Inc., Santa Ana, California) microscope. The participant's upper eyelid of the operative eye is draped with a tegaderm and the eye is held open with a speculum. Next, the flap edge on the operative eye is marked with a McKesson Regular Tip Latex-Free Sterile Marker for flap repositioning purposes at the end of surgery. The eye is then washed with saline and dried with a LASIK PVA Spear (Beaver Visitec International Inc., Waltham, MA). Pachymetry is taken before and after the flap lift using external ultrasound pachymetry because the Star S4 IR Excimer Laser does not have a built-in pachymeter. After the flap is lifted, last minute centration is performed and the excimer laser is fired. During firing, the laser uses a pupil-tracking system, and uses Iris Registration to coordinate between the WaveScan measurement and the intra-operative laser parameters to ensure that the eye axis remains constant (is treated on the same plane). The flap is repositioned using Balance Saline Solution in a 25-gauge Yaghouti cannula with 33cc syringe. After repositioning and correct flap alignment using the ink mark made before lifting, the eye is rinsed with saline and dried with PVA Spear. Three intraoperative drops are then applied: a steroid, prednisolone [1.0%], a nonsteroidal anti-inflammatory drug (NSAID), either nepafenac [0.1%] or ketorolac [0.45%], and an antibiotic, any fourth generation fluoroquinolone such as Moxeza [0.5%]. After surgery it is the practice policy for participants to sit with eyes closed for thirty minutes followed by a flap check, and then scheduled for a one-day postoperative follow-up examination.

Surgical Technique – LASEK/PRK

The LASEK/PRK surgical procedure at Boston Laser begins with the patient bed under the microscope of the Abbott Medical Optics Star S4 IR Excimer Laser. The participant's upper eyelid of the operative eye is draped with a tegaderm and the eye is held open with a speculum. The edge of a 9mm LASEK trephine is coated using the McKesson Regular Tip Latex-Free Sterile Marker to mark the area the treatment zone and for epithelium replacement after ablation. The LASEK trephine is placed on the eye and filled with a 20% ethanol solution, made with 2cc medical grade 100% ethanol and 8cc sterile water using a 23-gauge cannula. The alcohol is left in the trephine for 40 seconds to loosen the epithelium before it is absorbed using a PVA Spear and the eye is washed with saline solution. For LASEK surgical procedures the epithelium is displaced outside the ablation zone using a LASEK spatula, and for PRK the epithelium is removed using a LASEK spatula and PVA Spear. Following epithelial displacement/removal the laser is fired and then a corneal light shield saturated with MMC [0.2mg/ml] is applied for a variable time depending on ablation depth (Table 5). After the MMC treatment is completed the eye is rinsed with cold saline solution, and for LASEK surgeries the epithelium is repositioned using the LASEK spatula. Hydro-silicone bandage contact lenses are placed on the operative eye at the end of surgery. Three intraoperative drops are then applied: a steroid, prednisolone [1.0%], a NSAID, either nepafenac [0.1%] or ketorolac [0.45%], and an antibiotic, any fourth generation fluoroquinolone such as Moxeza [0.5%]. Finally, the pupil of the operative eye(s) is dilated using 1% cyclopentolate.

Table 5. MMC application time. The Boston Laser practice standard for MMC application time based on ablation depth during LASEK or PRK surgeries.

Ablation Depth (μm)	MMC Time (seconds)
< 70	20
70-90	30
91-110	40
111-130	50
> 130	60

Statistical Analysis

Microsoft Excel software version 14.0.0 (Microsoft Corporation, Redmond, WA) and SPSS software version 13.0 (SPSS, Inc., Chicago, IL) were used for statistical analysis. A paired *t* test was used to compare continuous variables and Logistic regression was used to search for risk factors. Chi square test was used to compare qualitative proportions and ANOVA test was used to compare quantitative means. Probabilities of less than 5% were considered significant ($p < 0.05$), and probabilities less than 1% were considered to be highly significant ($p < 0.01$).

IRB approval

This study, its protocol, and the participant informed consent form was approved as an expedited review study by Sterling IRB (Sterling Institutional Review Board, Atlanta, Georgia) on February 6, 2015 under IRB identification number 4997-001 (Appendix B). Additionally, Sterling IRB approved a waiver of documentation of informed consent for this study on that same date (Appendix B).

RESULTS

Survey Invitation Response

There were 2926 patients who were identified because their medical records indicated that they underwent CRLS with Dr. Samir Melki at Boston Laser between December 2008 and January 2014, and met inclusion and exclusion criteria. Of the 2926 patients, CRLS was performed on both eyes of 2755 patients (94.2%), only the right eye of 103 patients (3.5%), and on the left eye of 68 patients (2.3%). From the electronic medical records of those 2,926 patients, 2,515 patients (86%) had e-mail addresses on file, some with multiple addresses.

In the first round of survey invitation e-mails, 2,644 e-mails were sent and 448 (16.9%) of those bounced because the e-mail address was incorrect, suspended, or non-existent. Additionally, 8 of those addresses opted-out of receiving further e-mails and 1 reported it as spam. Therefore, a total of 2,196 e-mails (83.1%) were successfully sent. Of these 2,196 e-mails, Constant Contact was able to track recipient interaction with the survey invitation e-mail and showed that 1,388 recipients (63.2%) opened the e-mail and 358 recipients (16.3%) clicked the survey link.

One week later, a second round of e-mails was sent to all those patients who had not yet responded to the survey. 2,324 e-mails were sent, 383 (16.5%) of those bounced, and 7 recipients opted-out of receiving further e-mails. Therefore, a total of 1,941 e-mails (83.5%) were successfully sent. Of these 1,941 e-mails, Constant Contact reported that 804 recipients (41.4%) opened the e-mail and 152 (7.8%) clicked the survey link.

Therefore, of the 2,926 patients that were eligible for this study, 510 e-mail recipients (17.4%) clicked the survey link and 380 participants (13.0 %) entered data in the survey; however only 319 (10.9%) participants answered questions pertaining to CRLS (Figure 3).

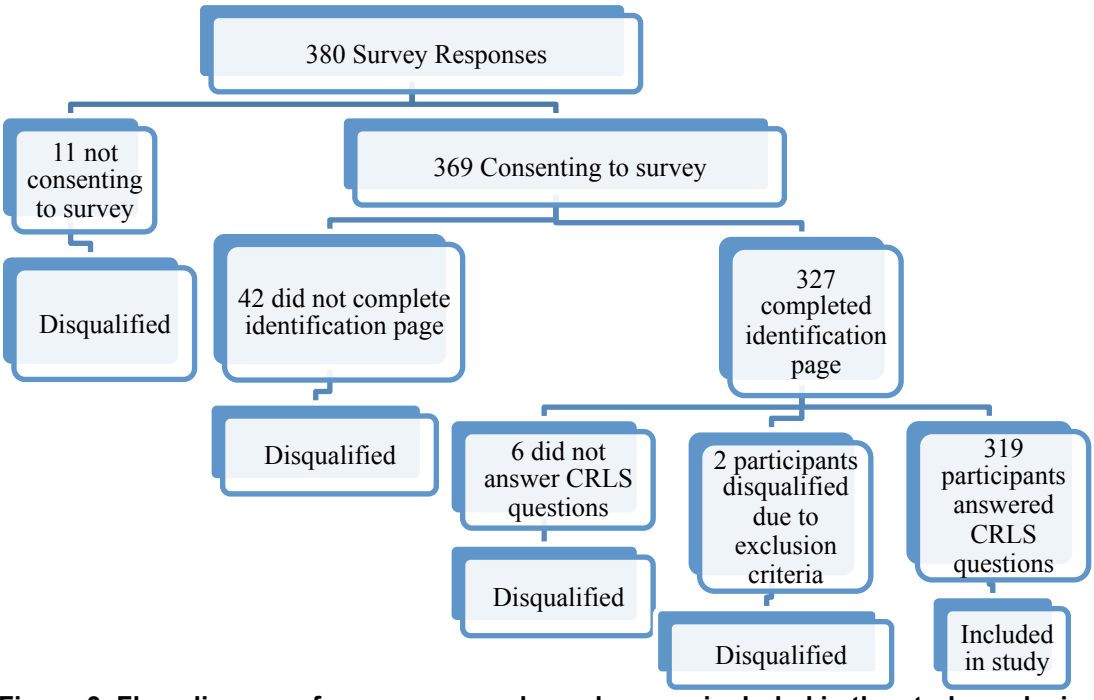


Figure 3. Flow diagram of survey responders who were included in the study analysis. Flow diagram showing the derivation of the 319 participants included in this study from the original 380 responses to the survey, including disqualification due to: lack of consent, incomplete identification page, missing CRLS question responses, exclusion criteria discovered within survey responses.

Preoperative Demographics

The majority of included participants (n=303; 95.0%), underwent CRLS in both eyes, while 9 participants (2.8%) received treatment in only the right eye and 7 participants (2.2%) received treatment in only the left eye. The 319 participants that underwent CRLS accounted for 622 treated eyes, which included: 94 eyes receiving LASEK with MMC (82 custom treatments, 12 traditional treatments), 44 eyes receiving

LASEK w/o MMC (35 custom treatments, 9 traditional treatments), and 484 eyes receiving LASIK (401 custom treatments, and 83 traditional treatments).

There were 31 hyperopic eyes (5.0%), 585 myopic eyes (94.0%), and 6 planar eyes (1.0%). Of the myopic eyes, 94 (16.1%) had a spherical manifest refraction greater than or equal to -6.0, which was considered a risk factor for visual aberrations. Additionally, 42 eyes (6.8%) had a cylindrical manifest refraction greater than or equal to -2.0; astigmatism greater than -2.0 was considered a risk factor for visual aberrations.

The preoperative BCVA of the majority of participants (97.0%) was 20/20 or better, with only 3.0% of participants recorded with a manifest BCVA of worse than 20/20, the worst being 20/30.

171 males (53.6%) and 148 females (46.4%) participated in this study (Table 6). Participant ages ranged from 20 years old to 70 years old with a mean of 37.88 ± 9.91. The average time since surgery was 2.5 ±1.24 years (range: 1-6 years). Mean pupil size, measured preoperatively, was 5.75 ± 0.89 mm, and equal to or larger than 7 mm was selected to indicate risk for visual aberrations. Schimer test value less than or equal to 9 mm was selected to indicate risk for dry eye symptoms and the mean preoperative test value was 20.54 ± 6.76 mm.

Table 6. Preoperative demographic factors and postoperative correlations. The means and standard deviations of relevant preoperative participant data and correlations from ANOVA logistic regression to postoperative survey scores: OSDI, dry eye, and visual aberration. (Not shown: Gender was correlated with Dry Eye Score at p = 0.071) (Bold text: significant values)

Preoperative Factor	Mean	Standard Deviation (±)	OSDI Score Significance (p)	Dry Eye Score Significance (p)	Halo Score Significance (p)
Age (years)	37.88	9.905	0.473	0.632	0.648
Time after surgery (years)	2.50	1.244	0.503	0.510	0.790
Manifest Spherical Refraction (D)	-3.41	2.346	0.324	0.158	0.303
Manifest Astigmatic Refraction (D)	-0.92	0.677	0.841	0.207	**0.025**
Pupil Size (mm)	5.75	0.892	**0.036**	0.385	0.438
Zone Quick Test (mm)	20.54	6.762	0.680	0.099	0.285
Flat K (D)	43.79	1.443	0.336	0.193	**0.016**
Steep K (D)	44.60	1.460	0.510	0.519	0.089
Intended Flap Thickness (μm)	94.53	5.069	**0.018**	N/A	0.495
Optical Zone (mm)	6.05	0.343	0.211	0.880	0.712
Pre-ablation Bed (μm)	458.66	30.187	0.227	N/A	0.939
Actual Flap Thickness (μm)	98.57	18.256	0.156	0.120	0.022
Actual Ablation (μm)	59.17	27.192	0.143	0.739	0.379
Remaining Stromal Bed (μm)	407.66	71.624	0.537	N/A	0.184
Preoperative Dryness Risk Assessment Consent	N/A	N/A	**0.047**	**0.037**	N/A
Preoperative Visual Aberration Risk Assessment Consent	N/A	N/A	N/A	N/A	0.175

Preoperative Risk Factors and Incidence of Dry Eyes

Preoperative dry eye risk was assessed based on: contact lens use, subjective dry eye complaints with and without contact lenses, and Zone Quick test value less than 9.0 mm. As previously indicated, the mean Zone Quick test was 20.54 ± 6.76 mm. 226 participants (70.9%) wore contact lenses prior to surgery, and subjective dry eye complaints were noted with contact lens in 76 participants (23.8%) and without contact lenses in 17 participants (5.3%)(Table 6). Using these preoperative data points as well as

slit-lamp examination findings, the doctor had 29 (9.1%) of participants sign a consent warning that they were at risk for dry eye symptoms postoperatively due to their preoperative measurements. From the survey data, the mean OSDI score and new dry eye score for participants were, 10.66 ± 14.02 and 11.27 ± 12.79, respectively.

Logistic regression ANOVA was performed on all of the preoperative factors gathered in Table 6 and the OSDI score and no significance was found ($p = 0.190$); however, there was an association found between the OSDI score and the following preoperative factors: those participants that consented to dry eye risk ($p < 0.05$), pupil size ($p < 0.05$), and actual flap thickness ($p < 0.05$). Logistic regression analysis was performed on the preoperative factors and the new dry eye score, which resulted in no significance ($p = 0.444$). An association was found between the new dry eye score and those participants that consented to having preoperative dry eye risk ($p < 0.05$). Additionally, the new dry eye score approached significance in showing an association between the score and the following risk factors: preoperative Zone Quick test value ($p < 0.1$), gender ($p <0.08$), actual ablation ($p <0.15$), and actual flap ($p <0 .16$).

The OSDI scoring system generalizes the score into 4 categories: score less than or equal to 10 is considered normal eyes, score of 10-20 is considered mild dry eyes, score of 20-30 points is considered moderate dry eyes, and score greater than 30 is considered severe dry eye. Table 7 shows that 69.3% of participants who did not consent to dry eye risk preoperatively had normal OSDI scores, and 58.6% of those who did consent to dry eye risk preoperatively had normal OSDI scores. Furthermore, only 8.2% of the total population (26 participants) had severe dry eyes, although 24 of those

participants with severe dry eye were from the group that was not identified for dry eye risk preoperatively. Chi-square test of this data did not show significant relationship ($p > 0.05$) between the postoperative categories of dry eye symptom severity reported by OSDI scores and the consent to dry eye risk preoperatively (Figure 4).

Table 7. Cross-tabulation between patients consenting preoperatively to dry eye risk and severity of symptoms postoperatively. Participant OSDI dryness scores postoperatively were grouped into categories of normal (OSDI ≤10), mild (OSDI between 10-20), moderate (OSDI 20-30), and severe (OSDI >30), and cross-tabulated with those participants who were identified as and consented to having preoperative dry eye risk.

			OSDI Dryness Postoperatively				Total
			Normal	Mild	Moderate	Severe	
Dryness Risk Recognized Preoperatively	No	n	201	43	22	24	290
		Percent of participants without consent of dryness preoperatively	69.3%	14.8%	7.6%	8.3%	100.0%
	Yes	n	17	5	5	2	29
		Percent of participants with consent of dryness preoperatively	58.6%	17.2%	17.2%	6.9%	100.0%
Total		n	218	48	27	26	319
		Percent of total participant population	68.3%	15.0%	8.5%	8.2%	100.0%

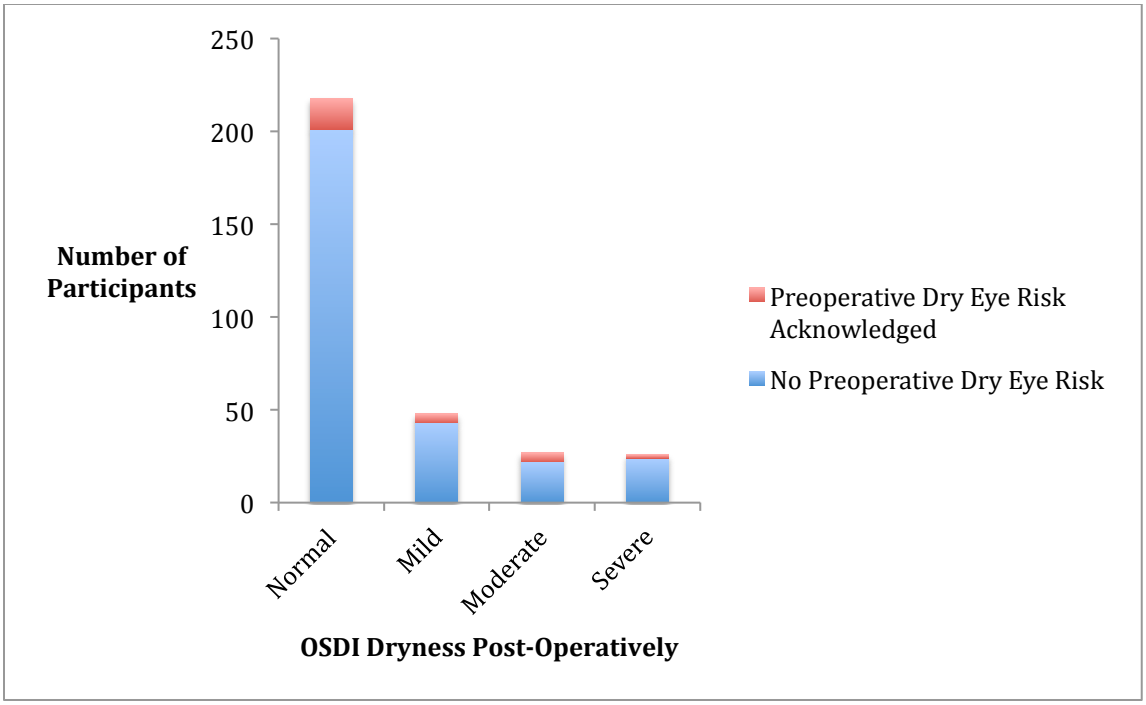


Figure 4. Preoperative dry eye risk and severity of postoperative dry eye symptoms. The severity of postoperative dry eye symptoms based on the OSDI scores (normal: <10; mild: 10-20; moderate: 20-30; severe: >30) of participants who were and were not advised of their preoperative dry eye risk. (p = 0.320; Pearson Chi-Square)

Preoperative Risk Factors and Incidence of Visual Aberrations

Preoperative visual aberrations risk was assessed based on the following preoperative factors: spherical manifest refraction greater than -6.00, cylindrical manifest refraction greater than -2.00, pupil diameter greater than 7.0 mm. As previously indicated, the mean pupil diameter was 5.75 ± 0.89 mm, and 6.8% and 16.1% of eyes were above the preoperative risk for visual aberrations due to spherical and cylindrical manifest refraction measurements, respectively (Table 6). Using these preoperative data points and other evaluation findings, the doctor determined that 70 participants (21.9%) were at risk for visual aberrations and had the participants sign consent forms

acknowledging their preoperative risk. From the survey data, the mean visual aberration score was 21.73 ± 25.16.

Logistic regression ANOVA was performed between the visual aberration score and the preoperative factors listed in Table 6 and found a significant association between them ($p < 0.05$). There was a significant association found between higher halo scores and greater cylindrical manifest refraction ($p < 0.05$), greater flat K value ($p < 0.05$), and greater actual flap thickness ($p < 0.05$). Additionally, the analysis approached significance in showing an association between the steep K value and visual aberration preoperative risk consent ($p < 0.09$ and $p < 0.18$, respectively).

Participant postoperative visual aberration scores were assessed and patients were identified for either presence of visual aberrations (score greater than 10) or absence of visual aberrations (score less than or equal to 10). As seen in Table 8, 60.0 % of participants that preoperatively acknowledge having visual aberrations risk reported in their survey responses as having postoperative symptoms, while only 47.0 % of those participants not identified as having preoperative risk reported having symptoms in their survey responses. A chi-square test of the data showed that there is a significant relationship ($p < 0.05$; Fisher's Exact Test) between those identified as having halo, starburst, or glare risk preoperatively and those patients that report visual aberration symptoms postoperatively (Figure 5).

Table 8. Cross-tabulation between patients consenting preoperatively to visual aberrations risk and incidence of symptoms postoperatively. Participant visual aberration scores postoperatively were assessed for presence (score >10) or absence (score ≤10) of symptoms, and cross-tabulated with those participants who were identified as and consented to having preoperative visual aberrations risk.

			Visual Aberrations Postoperatively		Total
			No	Yes	
Visual Aberrations Risk Consented Preoperatively	No	n	132	117	249
		Percent of participants without consent of visual aberrations preoperatively	53.0%	47.0%	100.0%
	Yes	n	28	42	70
		Percent of participants with consent of visual aberrations preoperatively	40.0%	60.0%	100.0%
Total		n	160	159	319
		Percent of total participant population	50.2%	49.8%	100.0%

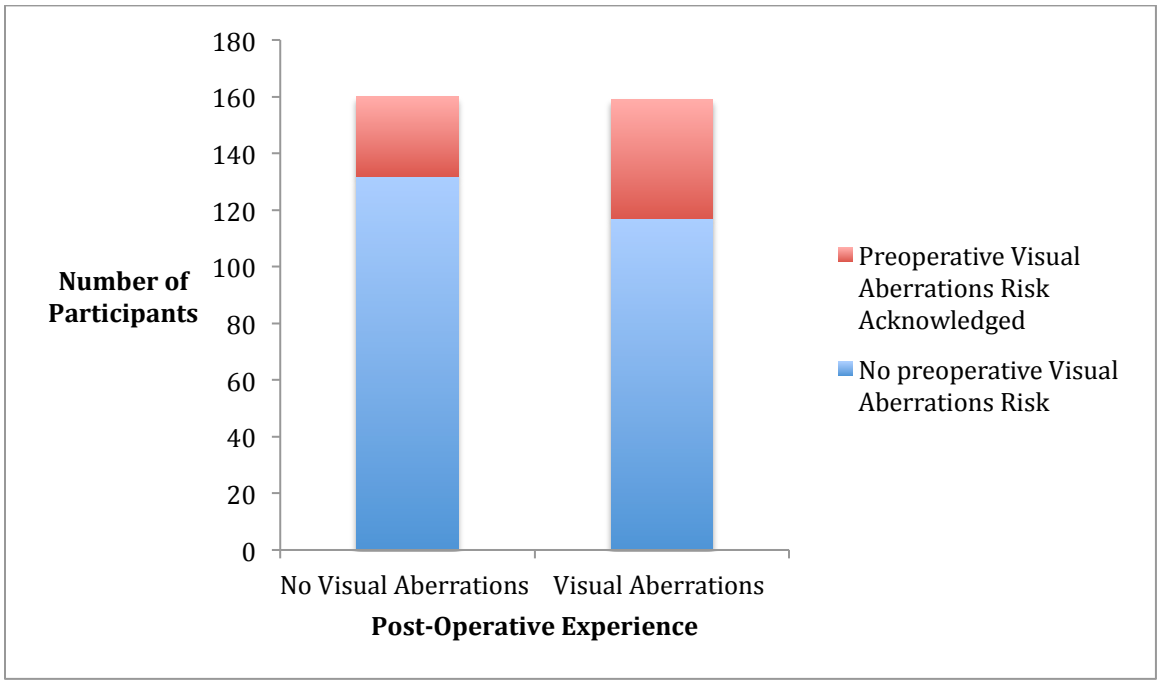


Figure 5. Preoperative visual aberrations risk and incidence of postoperative symptoms. Incidence of postoperative visual aberrations based on visual aberrations score (symptomatic >10; non-symptomatic ≤10) for patients who were and were not selected for consent documentation based on their preoperative risk for visual aberrations. ($p < 0.05$; Fisher's Exact Test)

Symptom Comparison Between Years

Participants were grouped by years since surgery and mean OSDI, dry eye, and visual aberration scores were calculated for each group (Table 9; Figure 6). ANOVA statistical testing was performed to determine if there were differences between the means of each group. No significant difference ($p > 0.05$) was found between groups for any of the scores tested; however, the OSDI score approached significance ($p = 0.088$).

Table 9. Mean OSDI, dry eye, and visual aberration scores grouped by years since surgery. Participants grouped by years since surgery and the mean OSDI, dry eye, and visual aberration scores for each group of participants. Significance for ANOVA between-groups testing is shown under each score.

	Years Since Surgery Groups	Number of Participants in Group	Mean Score Value	Standard Deviation (±)
OSDI Score (p = 0.088)	1	89	10.51	14.70
	2	77	12.20	13.77
	3	79	8.48	10.36
	4	54	9.35	13.61
	5	20	17.50	22.24
	Total	319	10.66	14.02
Dry Eye Score (p =0.134)	1	89	11.05	13.02
	2	77	12.93	13.80
	3	79	9.51	9.61
	4	54	9.84	11.68
	5	20	16.65	19.28
	Total	319	11.27	12.80
Visual Aberration Score (p =0.178)	1	89	18.33	25.43
	2	77	23.60	29.18
	3	79	17.12	23.83
	4	54	18.12	25.20
	5	20	30.92	34.18
	Total	319	20.06	26.67

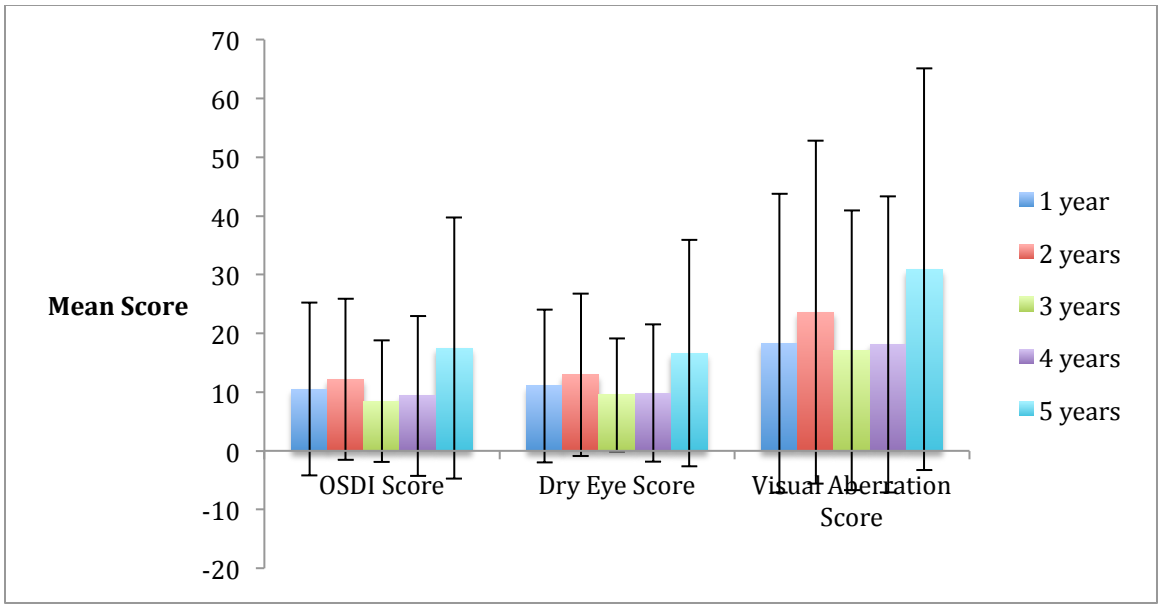


Figure 6. Mean OSDI, dry eye and visual aberration scores for participants whom are 1 to 5 years post-surgery. Mean OSDI, dry eye, and visual aberration scores for patients who were grouped based on years since surgery. Error bars show standard deviation. No significance was found for any of the scores ($p > 0.05$).

Patient Satisfaction

The last question of the survey asked participants whether they would repeat their decision to have surgery if they could do it all over again, and, if they selected no, to classify why they would not repeat their decision. Participants were able to select more than one reason for their dissatisfaction, if applicable. As shown in Table 10, 292 participants (88.48%) would choose to repeat their decision to have surgery, and only 14 participants (4.24%) would not repeat their decision to have surgery due to dry eyes or visual aberrations.

Table 10. Participant satisfaction with surgery. Participant satisfaction with surgery based on their willingness to repeat their original decision to have surgery, and if not, why they would not repeat their decision.

	Would you repeat your decision to have surgery if you could do it all over again?					
	Yes	No, because of:				
		Dry eyes	Halos, starbursts, or glare	Visual outcomes	Another reason	Total
Number of Responses	292	6	8	9	15	330
Percent of Total Responses	88.48%	1.82%	2.42%	2.73%	4.55%	100.00%

DISCUSSION

Study Implementation

Out of the 2926 patients originally identified as candidates only 319 (10.9%) qualified and participated in completing the questionnaire. Inability to reach participants (inaccurate or missing e-mail addresses) as well as less than 66.6% open rate accounted for much of the decrease from eligible patients to participants. The 319 survey participants allowed us to have 622 eyes available for study, but we were limited in our analysis because survey data did not individualize participants' symptoms for each eye. Surveying patients' symptoms for both eyes collectively made it difficult to analyze the effect of surgery type, LASIK versus surface ablation, on the long-term persistence of symptoms. Future studies should address whether LASEK patients continue to report less subjective symptoms than LASIK patients over long-term postoperative period, as has been noted previously during the follow-up period after CRLS (Herrmann et al., 2005). Additionally, many extended follow-up reports have focused on BCVA, regression, and refractive success after CRLS; however, our study did not consist of a clinical postoperative appointment, and therefore could not address those factors (Rajan et al. 2004).

Dry Eye Risk Factors

Our data was able to show an association between the previously established OSDI score for assessing dry eye symptoms and several risk factors for dry eyes (Schiffman et al. 2000). We found a significant association between the OSDI score and

flap thickness in patients who are more than 1 year post-surgery, which supports similar relationships found identifying those factors as risk for postoperative dry eye during the 6 months follow-up period (De Paiva et al., 2006). While those findings counter some associations made by Murakami & Manche (2012), our results support their findings that age was not shown to have a significant effect on postoperative dry eye symptoms. Our study also found a significant relationship between OSDI score for postoperative dryness and preoperative pupil size as a risk factor, which we believe has not been reported before. Future research should be done to address this finding and determine the reasoning behind this association. The OSDI score also had a significant association to the preoperative consent to dry eye risk that was performed per the Boston Laser practice standard. This assessment factor is based on many aspects of the preoperative evaluation including: contact lens use, dry eyes with contact lenses, Zone Quick tests ≤9mm, and individual slit-lamp findings by the doctor. This association between postoperative OSDI score and that evaluation could encompass all of those aspects, thus supporting current research claiming those factors as related to risk for developing persistent postoperative dry eyes (Raoof & Pineda, 2014). However, each patient evaluation is individualized and might not have all the aforementioned components of dry eyes, and therefore future studies must incorporate a more stringent classification of this consent to evaluate its usefulness of predicting postoperative dry eye risk. Additionally, the broad base of this preoperative risk factor and the limited patient population also likely contributed to the lack of statistical significance found between the OSDI score derived postoperative symptom severity and that preoperative factor.

While the dry eye score created for the survey in this study did not achieve significance for association to preoperative variables, it did approach significance in relation to several variables: Zone Quick test, gender, actual ablation, and actual flap thickness. These findings could lend further support to those studies that have already identified them as risk factors (Raoof & Pineda, 2014). More research needs to be done to evaluate the effectiveness of this score on larger populations to determine its accuracy at showing dry eye symptoms, and to determine if the risk factors suggested have significant bearing on postoperative dry eye symptoms.

Visual Aberration Risk Factors

This study found a significant association between the visual aberrations score and several preoperative risk factors: cylindrical manifest refraction, flat K value, and actual flap thickness. Previous studies have shown that increased ablation depth and level of myopic correction are related to increased risk for visual aberrations, while our data indicates that it might be the flap thickness and level of astigmatic correction that actually influence the incidence of visual aberrations (Bailey et al. 2003). These results could indicate new risk factors for development of halos, starbursts, and glare postoperatively, or could be due to the difference in time frame in which we attempted to associate symptoms with preoperative data. Additionally, the halo score approached significance with the preoperative steep K, which, combined with the significant associations of this score, suggests further studies are needed to examine the role of the keratometry measurements in preoperative risk for developing visual aberrations after CRLS. The

preoperative consent for visual aberration risk was shown to have significant association with those reporting starbursts, halos, or glare postoperatively using the visual aberration score. The preoperative consent for visual aberrations was based on spherical manifest refraction ≥ -6.00, cylindrical manifest refraction ≥ -2.00, and pupil diameter ≥ 7.0mm. While this significant association suggests that these factors might affect the risk for developing visual aberrations and thus contradict claims that pupil diameter, among other factors, do no affect visual aberration risk, it is difficult to determine exactly which of these factors affects long-term incidence of visual aberrations (Myung, Schallhorn, & Manche, 2013). Future investigations should be made with more stringent criteria for assigning this preoperative risk to enable researchers to determine what factors caused this association.

Long-term Persistence of Dry Eye Symptoms and Visual Aberrations

When evaluating the long-term incidence of both dry eye symptoms and visual aberrations symptoms by a comparison of the mean OSDI, dry eye, and visual aberration scores of the different years since surgery groups, our study data reached no significant difference between them. This result is not surprising given the relatively small population that completed the survey, and the fact that both the dry eye and visual aberration scores were new measures being tested for the first time in this study. The OSDI score means did approach significance ($p= 0.088$) in this between-group ANOVA testing, and thus further research should be done with larger sample populations and better supported measurements to assess this possibility. Another interpretation of these

results could revolve around the idea that previous studies have generally evaluated symptoms at most 6 months to 1-year postoperatively with a large proportion of dry eye and visual aberrations patients returning to preoperative baselines within 6-12 months in postoperative period, and only a small subset having chronic issues (Manche & Haw, 2011; Raoof & Pineda, 2014). This could suggest that the lack of difference in means between patients that are 1-5 years post-surgery shows that patients who have symptoms persisting beyond one year will for the most part continue to experience them chronically throughout at least five years postoperatively. While this would be an unfortunate conclusion for those that continue to experience symptoms postoperatively, it shows the importance of continued and more stringent research into the long-term persistence of both dry eyes and visual aberrations and the risk factors for developing those conditions.

Long-term Patient Satisfaction

While 31.7% of participant are still experiencing some severity of dry eye symptoms and 49.8% of participants are experiencing visual aberrations after more than 1 year postoperatively it does not seem to have affected patient satisfaction. As can be seen in our survey results: almost 90% of patients would still have decided to undergo their CRLS knowing their subjective results beforehand. Only 4.24% of all participants would not repeat their decision due to visual aberrations or dry eyes. Therefore, counter to some of the reported literature, we are led to believe that while these complications after CRLS are common, they do not significantly influence the subjective satisfaction of patients,

nor make them regret their decision to correct their vision through CRLS (Bailey et al. 2003).

CONCLUSION

Our study, one of the first to evaluate the long-term incidence of dry eyes and visual aberrations postoperatively, was able to introduce a number of suggested risk factors, supporting previous research, and therefore requiring further studies to confirm their roles. We found no reduction in the incidence of symptoms with longer follow up periods. While approximately 1/3 and 1/2 of participants experienced dry eyes and visual aberrations postoperatively, respectively, this did not affect patient satisfaction, as 88.48% of participants would repeat their decision to have surgery given their individual outcomes.

Limitations in our study design included: the lack of pre-surgery and postoperative interval questionnaires that would have been useful in comparing the progression of symptoms, clinical yearly follow-up appointments to address objective measurements of postoperative symptoms for comparison to pre-surgery data, survey questions individualized for right and left eye to allow for more robust data analysis on a per eye basis, and more thorough visual aberration questions in the survey that would address day and night time symptoms as well as addressing starburst, halos, and glare individually. Additionally, question 18 in the survey (Appendix A) did not include an option for “not currently experiencing visual aberration symptoms”, which made it hard to analyze the results of that question, and this might have affected statistical significance.

Future studies should address the above-mentioned limitations as well as create more stringent pre- and postoperative testing criteria. This would include changing the

evaluation procedures to allow for more accurate pupil measurements, as the Colvard measurement can be more subjective based on the technician evaluating the prospective patient, and adding a greater variety of dry eye assessment methods, such as TBUT and corneal fluorescein stain clearance rate among others.

As one of the few studies to evaluate long-term dry eye and visual aberration complications after CRLS, we have identified a number of preoperative risk factors and suggested associations. Given the limitations of our methods we have identified a number of important avenues that would benefit from being explored in the future to clarify the significance of the results and aid in providing better consultation procedures for prospective CRLS patients.

APPENDIX A – PARTICIPANT QUESTIONNAIRE

Welcome to our survey about your quality of vision since your surgery!

Below is a consent form that provides some information about our project and your role. If you would like to, please print a copy of the following consent form for your records or e-mail samuel@bostonlaser.com to request an electronic copy. After reading through the form and answering the question at the bottom of the page, you will be directed to the survey questions.

The survey questions on the following pages will take LESS THAN 5 minutes to complete!

Thank you in advance for your help.

PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE:	Long-term Incidence of Dry Eye and Halos after Refractive Surgery
STUDY DOCTOR:	Samir A Melki, MD PhD
STUDY DOCTOR E-MAIL:	melki@bostonlaser.com
STUDY SITE:	Boston Eye Group 1101 Beacon Street, Suite 6 Brookline, MA 02446
TELEPHONE:	617-556-0062 508-887-5320 (5:00pm – 10:00pm)
PRIMARY CONTACT:	Samuel G. Hilbert
PRIMARY CONTACT E-MAIL:	samuel@bostonlaser.com
SPONSOR:	Samir A Melki MD PhD

You are being asked to participate in a medical research study. Your participation in this research study is strictly voluntary, meaning that you may or may not choose to take part. To decide whether or not you want to be part of this research, the risks and possible benefits of the study are described in this form so that you can make an informed decision. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. This form explains how your medical information will be used and who may see it. You may have a copy of this form to review at your leisure or to ask advice from others.

The study doctor or study staff will answer any questions you may have about this form or about the study. Please read this document carefully and do not hesitate to ask anything about this information. This form may contain words that you do not understand. Please ask the study doctor or study staff to explain the words or information that you do not understand. The study doctor and primary contact are available both by phone and email.

BACKGROUND

You are being asked to take part in this study because you have had refractive surgery (LASIK, LASEK, or PRK) at Boston Eye Group between December 2008 and January 2014.

Some people who have refractive surgery experience a decrease in tear production that can cause eye discomfort and blurred vision. Almost half of all refractive surgery patients experience some degree of temporary dry eye syndrome. Dry eye problems usually disappear when healing of the eye is complete, which can take up to six months.

PURPOSE

The purpose of this research study is to investigate the incidence of dry eye symptoms and visual aberrations (halos) for longer than one year after refractive surgery. To do this we will gather patient data from December 2008 through January 2014 and ask all qualifying patients to complete a questionnaire regarding their experiences of dry eye symptoms and halos in the last month compared to before surgery, if applicable.

About 2,926 men and women will participate in this study at one location.

DURATION

Your participation in the study involves no visits to the study site. Your participation will last the amount of time it takes to complete one survey (about 3 – 5 minutes).

PROCEDURES

If you agree to take part in the study, you will be asked to complete an 20-question survey that should take approximately 3 – 5 minutes to complete. Your responsibility will be to click on the link to the survey provided in the e-mail and then complete the survey to the best of your knowledge.

You are also being asked for permission for the study staff to review your medical records and collect information in relation to your refractive surgery and incidence/risk factors of dry eye disease and halos. After the survey results have been collected and associated with your medical records, the study data will be anonymized (your name and identifying information will be removed) to protect your patient information.

POTENTIAL RISKS, SIDE EFFECTS, DISCOMFORTS, INCONVENIENCES

There are no foreseeable risks to participants in this study. The study may contain risks that are unforeseen or unknown.

POTENTIAL BENEFITS

Participants will benefit through completing the survey as their answers will contribute to the expanding body of knowledge about long term outcomes of refractive surgery.

ALTERNATIVE TREATMENTS

This study is not designed to treat any illness or improve your health. Your alternative is to not participate.

NEW INFORMATION

You will be informed in a timely manner if new information that may influence your willingness to continue participation in the study becomes available.

COMPENSATION TO YOU

There is no compensation provided for your participation in this study.

COSTS TO YOU

There are no costs to you for your participation in this study.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate is entirely voluntary. You may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which you are otherwise entitled. Your ongoing medical care will not be affected by your decision to be in this study or to withdraw from the study.

Your participation may be stopped without your consent by the study doctor for any reason. For example, your participation may be stopped:

- if you fail to follow instructions.
- If the study is cancelled.

CONFIDENTIALITY AND AUTHORIZATION TO COLLECT, USE AND DISCLOSE YOUR MEDICAL INFORMATION

As a part of this research, records that contain information or data about you and your health may be collected and used. These records may identify you and will be kept as confidential as possible. To the extent permitted by applicable laws and regulations, the records identifying you will not be made publicly available.

Under the privacy laws, you have the rights to decide who can use your protected health information (called PHI). When you sign this form, you are saying that you will allow the use of your protected health information for this study.

The information that will be collected about you as a part of this research includes:

- Name
- Address
- Telephone number
- Birth date
- Race
- Sex
- Family medical history
- Allergies
- Medications you take (current and past)
- Other information from other doctors' offices, clinics, and/or hospitals that is needed for the study

Information collected about you for the study will be kept in a research file that is separate from your medical chart. You will not be able to see your research file until after the end of the study.

The study team will know your identity; however, your records will be labeled with a code that is randomly assigned to you. The research staff are the only people who will have this code and its key.

The following groups may review and use your study information. They may review your study information to make sure that it is correct. They may also review your information to make sure that the study is being conducted properly.

- The study sponsor (or sponsor representatives such as monitors and/or auditors)
- The U.S. Food and Drug Administration (FDA)
- Sterling Institutional Review Board (IRB)
- The Department of Health and Human Service (DHHS)
- Other government agencies in other countries
- Other doctors, health care professionals or research staff who are involved in the study

Your study information may be released to the groups listed above. If your study information is reviewed by these people, they may need to see your entire medical record; it is possible that your Social Security number may be included in the records reviewed. Because of this, it cannot be assured that your confidentiality will always be protected. It is possible that your information will be shared (re-disclosed) in a way that it would no longer be protected. However, this access to your records will be granted without violating your confidentiality to the extent permitted by applicable laws and regulations. By signing this form, you are authorizing this access to your records.

The results of the study, including your information, may also be presented at meetings or in articles written about the study (publications). If the results of the study (including your research or health information) are published, your identity will remain confidential.

This permission (also called an authorization) will last until the end of the study

You have a right to see your study records; however, you will not be able to see your study records until after the study has ended.

You may also take away (or withdraw) your permission for the use of your protected health information at any time. If you choose to withdraw your permission, you must write your study doctor a letter.

The study doctor's mailing address is Boston Laser, 1101 Beacon Street, Suite 6, Brookline, MA, 02446. The study doctor will still be able to use the health information collected about you before you withdrew your permission. Information that has already been sent to the sponsor of the study cannot be taken back.

If you withdraw your permission after you have entered the study, you cannot continue participating in the study. If you refuse to give permission or withdraw your permission, your

medical care and your relationship with the health care providers at the study center will not be affected.

QUESTIONS

If you have questions, concerns or complaints about the research study, please contact Dr. Melki or the study staff at 617-556-0062 or 508-887-5320 (5:00pm – 10:00pm).

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact the Sterling Institutional Review Board Regulatory Department, 6300 Powers Ferry Road, Suite 600-351, Atlanta, Georgia 30339 (mailing address) at telephone number 1-888-636-1062 (toll free).

PARTICIPANT STATEMENT AND AUTHORIZATION

I have read the Participant Informed Consent Form and Authorization to Use and Disclose Medical Information and I agree to participate voluntarily in this study. I give my permission to the study doctor to use and disclose my protected health information as described in this consent form.

I am able to print a copy of this form, which has 5 pages.

All my questions have been answered.

I have not waived any of my legal rights by signing this document.

*** 1. By clicking yes, you acknowledge that you are virtually signing the above written consent form, and that you have read, understand, and agree to all terms outlined above.**

- ○ Yes, I have read and understand the consent form, voluntarily agree to the terms outlined above, and consent to participating in this study.
- ○ No

Next

*** 2. First Name**

*** 3. Last Name**

*** 4. Date of Birth**

MM DD YYYY

MM/DD/YYYY ___ / ___ / ____

*** 5. Have you had any other eye surgeries since your corneal refractive surgery (LASIK,LASEK, PRK) at Boston Laser?**

- Yes
- No

IF YES, please specify

Prev Next

Long-Term Quality of Vision after Refractive Surgery

Please answer the following questions regarding dry eye symptoms DURING THE LAST WEEK compared to BEFORE surgery: (These questions pertain to situations where you can assume you would be wearing your glasses, if they would help)

*** 6. Have you experienced any of the following DURING THE LAST WEEK:**

	4 - All of the time	3 - Most of the time	2 - Half of the time	1 - Some of the time	0 - None of the time
Painful or sore eyes?	○	○	○	○	○
Poor Vision?	○	○	○	○	○
Blurred vision?	○	○	○	○	○
Eyes that feel gritty?	○	○	○	○	○
Eye that are sensitive to light?	○	○	○	○	○

Comments (if necessary)

*** 7. Have problems with your eyes limited your performance of any of the following DURING THE LAST WEEK:**

	4 - All of the time	3 - Most of the time	2 - Half of the time	1 - Some of the time	0 - None of the time	N/A
Driving at night?	○	○	○	○	○	○
Reading?	○	○	○	○	○	○
Watching TV?	○	○	○	○	○	○
Working with a computer or bank	○	○	○	○	○	○

machine (ATM)?

Comments (if necessary)

*** 8. Have your eyes felt uncomfortable in any of the following situations DURING THE LAST WEEK:**

	4 - All of the time	3 - Most of the time	2 - Half of the time	1 - Some of the time	0 - None of the time	N/A
Windy conditions?	○	○	○	○	○	○
Areas that are air conditioned?	○	○	○	○	○	○
Places or areas with low humidity (very dry)?	○	○	○	○	○	○

Comments (if necessary)

Prev Next

*** 9. WITHIN THE FIRST YEAR following your refractive surgery, did you experience dry eye symptoms for AT LEAST a three month period AND receive treatment/medication for those symptoms?**

	Eye Drops	Medications	Plugs
Treatment Type:	Artificial Tears Ointment/Gel Tears Other None	Restasis Other None	Punctal Plugs Other None

IF OTHER, please specify

*** 10. Have you used any eye drops to treat dry eye symptoms IN THE LAST WEEK? (Examples: artificial tears, Restasis, etc.)**

- Yes
- No

IF YES, which one(s)?

*** 11. If you used eye drops to treat dry eye symptoms IN THE LAST WEEK, how often did you use them?**

	Three or more times a day	Once a day	Occasionally (not everyday)	I did not use this medication to treat dry eye symptoms in the last week.
Artificial Tears (such as: Refresh, Systane, etc.)				
Ointment/Gel Tears (such as: Genteal, Thera Tears)				

Restasis	○	○	○	○
Other	○	○	○	○

IF OTHER, please specify

*** 12. Have you had punctal plugs (micro inserts to block tear drainage canals) placed since your surgery?**

- ○ Yes
- ○ No

IF YES, do you still have them?

*** 13. Have you been diagnosed after the surgery with a condition that could PROMOTE eye dryness? (Menopause, Sjogren disease, Ocular rosacea, Blepharitis, ...)**

- ○ Yes
- ○ No

IF YES, please specify

*** 14. Are you taking medications that could PROMOTE eye dryness? (antihistamines, antidepressants, blood pressure medicines, Parkinson's medications, birth control pills, ...)**

- ○ Yes
- ○ No

IF YES, please specify

*** 15. If you are experiencing dry eyes, are they worse than BEFORE surgery?**

- ○ Yes
- ○ No

I am not experiencing dry eyes

Please explain (if necessary)

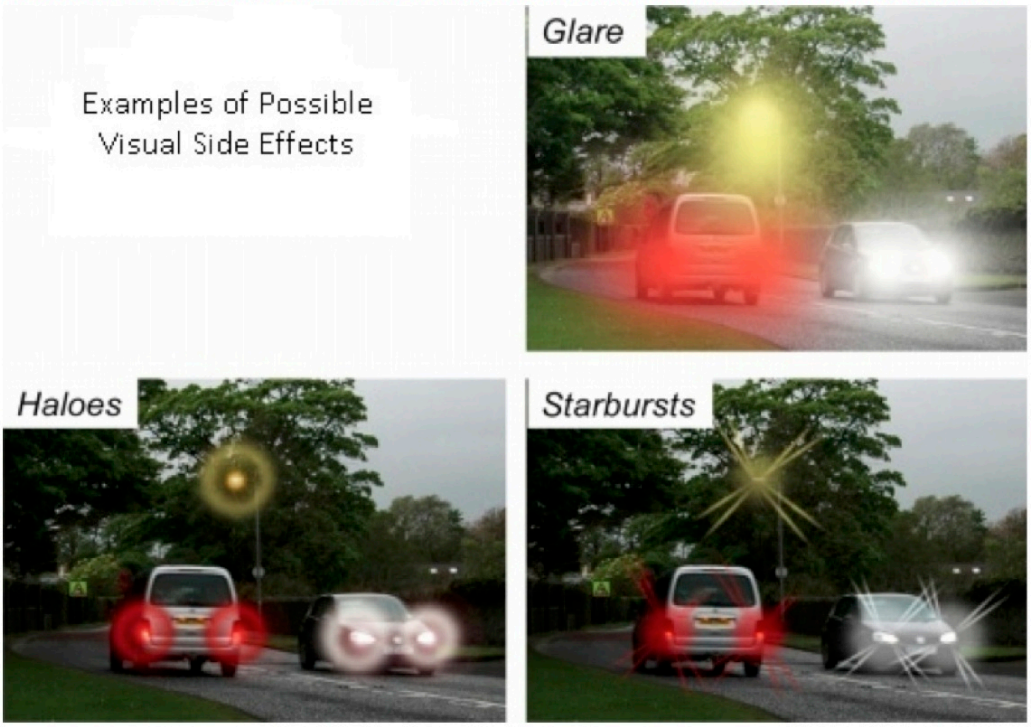
Prev Next

BOSTON LASER
YOUR EYES. OUR VISION.

Long-Term Quality of Vision after Refractive Surgery

Please answer the following questions regarding visual disturbances during the last week compared to BEFORE surgery

Please refer to these examples of visual disturbances as needed while answering the following questions.



*** 16. Have you had problems with halos/starbursts/glare around lights in any of the following conditions DURING THE LAST WEEK:**

	4 - All of the time	3 - Most of the time	2 - Half of the time	1 - Some of the time	0 - None of the time	N/A
From oncoming car headlights at night?	○	○	○	○	○	○
Reading a brightly	○	○	○	○	○	○

illuminated road sign at night?	○	○	○	○	○	○
At night?	○	○	○	○	○	○
To the extent that you slow down when driving at night?	○	○	○	○	○	○
Reading a road sign at night using your car headlights?	○	○	○	○	○	○
To the extent that you feel unsafe driving at night?	○	○	○	○	○	○
From car taillights at night?	○	○	○	○	○	○

Comments (if necessary)

Prev Next

Long-Term Quality of Vision after Refractive Surgery

*** 17. WITHIN THE FIRST YEAR following your refractive surgery, did you experience visual aberrations (halos, starbursts, glare) for AT LEAST a three month period AND receive treatment for those symptoms?**

- ○ Yes
- ○ No

IF YES, please specify the treatment(s) you received

*** 18. Do your symptoms improve if you wear glasses to help with difficulties due to halos, starbursts, or glare around lights?**

- ○ Yes
- ○ No

Please explain (if necessary)

*** 19. If you are experiencing halos, starbursts, or glare, are the visual aberrations worse than before surgery?**

- ○ Yes
- ○ No
- ○ I am not experiencing halos, starbursts, or glare

Please explain (if necessary)

*** 20. Given your current results from refractive surgery, would you still choose to have**

the surgery if you could do it all over again? If not why? (you may select more than one option if applicable)

- [ ] Yes, I would repeat my decision to have surgery
- [ ] No, I would not repeat my decision to have surgery because of dry eyes
- [ ] No, I would not repeat my decision to have surgery because of halos, starburst, or glare
- [ ] No, I would not repeat my decision to have surgery because of my visual outcomes
- [ ] No, I would not repeat my decision to have surgery because of another reason, (please specify)

Prev Done

APPENDIX B – IRB DOCUMENTS

Sterling IRB
Achieve More.

office 770.690.9491 **toll free** 1.888.636.1062 **fax** 770.690.9492
6300 Powers Ferry Road Suite 600-351 Atlanta, Georgia 30339
www.sterlingirb.com **e-mail** info@sterlingirb.com

NOTICE OF APPROVAL OF WAIVER OF AUTHORIZATION

Approval Date:	February 6, 2015
Study Expiration Date:	February 5, 2016
Principal Investigator:	Samir A Melki MD PhD
Protocol:	Long-term Incidence of Dry Eye and Halos after Refractive Surgery
IRB ID:	4997-001
Sponsor:	Samir A Melki MD PhD
Description of the PHI:	Each individual's type of surgery and specifics to that procedure, as well as information from their presurgery assessments that related to risk factors for dry eyes and visual abberations, such as halos and starbursts, after surgery.

ACTION: Approval for Waiver of Authorization

Sterling IRB reviewed your request for waiver of authorization for your above captioned research project via **Expedited review** and has found that your requested waiver of authorization, in the context submitted, meets the following criteria for approval:

1. The use or disclosure of protected health information involves no more than minimal risk to the individuals.
2. The alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals.
3. The research could not practicably be conducted without the waiver of authorization.
4. The research could not practicably be conducted without access to and use of the protected health information.
5. The privacy risks to the individuals whose protected health information is to be used or disclosed is reasonable in relation to the anticipated benefits if any to the individuals, and the importance of the knowledge that may reasonably be expected to result from the research.
6. There is an adequate plan to protect the identifiers from improper use and disclosure.
7. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
8. There are adequate written assurances that the protected health information will not be reused or redisclosed to any other person or entity, except as required by law, for the authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by regulation.

Sterling IRB
Achieve More.

office 770.690.9491 **toll free** 1.888.636.1062 **fax** 770.690.9492
6300 Powers Ferry Road Suite 600-351 Atlanta, Georgia 30339
www.sterlingirb.com **e-mail** info@sterlingirb.com

No alteration to the procedures described in the study protocol as reviewed on February 6, 2015 may be instituted unless this Board has reviewed and approved the continuation of the waiver of authorization.

Accounting rules apply to this waiver.

Sterling IRB reserves the right to report any violation of this approval to the Office for Civil Rights of the U.S. Department of Health and Human Services.

Signature Chairman or designee

Copy: Sponsor and/or CRO

Sterling IRB
Achieve More.

office 770.690.9491 **toll free** 1.888.636.1062 **fax** 770.690.9492
6300 Powers Ferry Road Suite 600-351 Atlanta, Georgia 30339
www.sterlingirb.com **e-mail** info@sterlingirb.com

Date Issued: February 10, 2015

Study Expiration Date: **February 5, 2016**

Site Continuing Review Status Report Due: **January 5, 2016** (form available at www.sterlingirb.com)

Principal Investigator: Samir A Melki MD PhD
Sites(s): Boston Eye Group
1101 Beacon Street, Suite 6
Brookline, MA 02446

Protocol: Long-term Incidence of Dry Eye and Halos after Refractive Surgery

IRB ID: **4997-001**

Sponsor: Samir A Melki MD PhD

TYPE OF REVIEW: Expedited Review – Study Approval – Initial

- Protocol (Date and version of the protocol 02/05/15 – Version 3)
- Participant Informed Consent Form and Authorization to Use and Disclose Medical Information (Version Date: 1/16/15)
- Waiver of Documentation of Informed Consent for the Consent Form under 45 CFR 46.117 (c)
- See Attachment A for Additional Approved Materials, including Recruitment Materials if applicable
- Investigator's Qualifications

APPROVED WITHOUT MODIFICATION

This study was reviewed and approved on February 6, 2015.

Sterling IRB has determined that this study represents the following category(ies) of research eligible for expedited review:
research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)
research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation or quality assurance methodologies

Sterling IRB has approved this Principal Investigator to conduct this study at the above-listed site(s). Approval will expire on the study expiration date listed above, and if the study is to continue the Principal Investigator must receive Sterling IRB approval for study continuation prior to the expiration date. The Principal Investigator should submit the **Site Continuing Review Status Report** not less than one month prior to the last Sterling IRB meeting preceding the expiration date. If approval for study continuation is not obtained prior to the expiration date, the study will be considered to be in noncompliance with Federal Regulations and IRB requirements, may be suspended, and may be subject to termination.

A **Site Final Report** will be due at the conclusion of the study (form available at www.sterlingirb.com).

Any changes to the research must be submitted in writing to Sterling IRB for review and approval prior to implementation. Sterling IRB should be informed immediately of any serious adverse reaction or should any unanticipated problems involving risks to the subject or others occur or should the Sponsor provide safety information. Local prejudices or negative attitudes in the community toward the conduct of research projects must be reported immediately. State laws pertaining to Patient/Volunteer Bill of Rights and specific state laws concerning research which affect the conduct of clinical research must be enforced. Non-English speaking subjects enrolled in this study must be provided with an informed consent written in their fluent language, which must be approved by Sterling IRB before use.

As Principal Investigator you are responsible for following all policies of Sterling IRB as described in the Investigator's Compliance Agreement which you signed with study submission. It is your responsibility to ensure this research is conducted in accordance with applicable regulations (local, state and federal) as well as any requirements established by the IRB at the time of the approval. Refer to the Investigator Handbook at www.sterlingirb.com for details of these responsibilities.

Copy: Sponsor and/or CRO

Attachments (if applicable): Attachment A, Sterling IRB Membership List, Approved Informed Consent / Approved Recruitment Material(s)

Sterling Achieve More. IRB

office 770.690.9491 **toll free** 1.888.636.1062 **fax** 770.690.9492
6300 Powers Ferry Road Suite 600-351 Atlanta, Georgia 30339
www.sterlingirb.com **e-mail** info@sterlingirb.com

Date Issued:	February 10, 2015
Study Expiration Date:	**February 5, 2016**
Site Continuing Review Status Report Due:	**January 5, 2016** (form available at www.sterlingirb.com)
Principal Investigator:	Samir A Melki MD PhD
Protocol:	Long-term Incidence of Dry Eye and Halos after Refractive Surgery
IRB ID:	**4997-001**
Sponsor:	Samir A Melki MD PhD

ATTACHMENT A: ADDITIONAL APPROVED MATERIALS

Study Materials:

- Long-Term Quality of Vision after Refractive Surgery Survey

Recruitment Materials:

- Email Recruitment Advertisement (dated: 2/4/2015)

For these approved materials, you may insert or change site-specific information without resubmitting to the IRB.

The following may apply dependent upon approved item:

Federal Regulations require that Sterling IRB be supplied with an actual copy of the advertisement (MP3, CD, DVD, tear sheet, cassette, VHS, etc.), when applicable, for review and approval prior to use. Approved print advertisements are authorized for internet use without being resubmitted to the IRB provided that they remain true to scale and are in no way modified.

If the above-referenced recruitment and/or study material(s) contain(s) a reference or link to a website, Sterling IRB assumes that the link(s) provided do/does not contain any information which would violate either Sterling IRB requirements or applicable regulations. It is your responsibility to submit any research-related content, including any information which pertains to a study under the review of Sterling IRB, for review and approval prior to use.

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Sterling IRB Membership Roster

Term: July 25, 2014 – July 24, 2016 IRB Registration Number: 00001790

Primary Members	Area of Expertise / Representative Capacity
Steven L. Saltzman, M.D., F.A.C.O.G., Chairman Scientific	Obstetrics and Gynecology / College Educator Pregnant Women / Prisoners / General Participant Perspective
Jennifer R. McGaughey, RN, BSN, CIP, Vice-Chairman Scientific	Human Research Protection / Nursing Children / General Participant Perspective
Melody Palmore, M.D., Medical Director Scientific	Infectious Diseases / College Educator Pregnant Women / Cognitively Impaired Persons / Prisoners / General Participant Perspective
George A. Kramer, M.D., MPH Scientific	Cardiology Cognitively Impaired Persons / General Participant Perspective
Maziar Rezvani, M.D., F.A.A.A.A.I. Scientific	Allergy and Immunology Children / General Participant Perspective
Steven J. Feagin, M.D. Scientific	Internal Medicine
Arin Neely, BS, CIP Scientific	Human Research Protection / Biology Children / General Participant Perspective
Lisa K. Kuklinski, BBA, CPMSM, CPCS, CAP Non-Scientific	Credentialing / Medical Staff Management General Participant Perspective
Arthur J. Powell, PhD Non-Scientific	Ethics
Alternate Members	**Area of Expertise / Representative Capacity**
Mark Cavitt, M.D. Scientific	Psychiatry / Pediatric Psychiatry Children / Cognitively Impaired Persons
Harvey DuBiner, M.D. Scientific	Ophthalmology
Pat F. Bass III, MD, MS, MPH Scientific	Internal Medicine / Pediatrics Children
Paula S. Hickman, MHA, CPMSM, CPCS Non-Scientific	Health Information Systems & Technology / Credentialing General Participant Perspective
Lauren S. Surden, MSW Scientific	Clinical Research / Social Work Cognitively Impaired Persons / Children / General Participant Perspective

PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE:	Long-term Incidence of Dry Eye and Halos after Refractive Surgery
STUDY DOCTOR:	Samir A Melki, MD PhD
STUDY DOCTOR E-MAIL:	melki@bostonlaser.com
STUDY SITE:	Boston Eye Group 1101 Beacon Street, Suite 6 Brookline, MA 02446
TELEPHONE:	617-556-0062 508-887-5320 (5:00pm – 10:00pm)
PRIMARY CONTACT:	Samuel G. Hilbert
PRIMARY CONTACT E-MAIL:	samuel@bostonlaser.com
SPONSOR:	Samir A Melki MD PhD

You are being asked to participate in a medical research study. Your participation in this research study is strictly voluntary, meaning that you may or may not choose to take part. To decide whether or not you want to be part of this research, the risks and possible benefits of the study are described in this form so that you can make an informed decision. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. This form explains how your medical information will be used and who may see it. You may have a copy of this form to review at your leisure or to ask advice from others.

The study doctor or study staff will answer any questions you may have about this form or about the study. Please read this document carefully and do not hesitate to ask anything about this information. This form may contain words that you do not understand. Please ask the study doctor or study staff to explain the words or information that you do not understand. The study doctor and primary contact are available both by phone and email.

BACKGROUND

You are being asked to take part in this study because you have had refractive surgery (LASIK, LASEK, or PRK) at Boston Eye Group between December 2008 and January 2014.

Some people who have refractive surgery experience a decrease in tear production that can cause eye discomfort and blurred vision. Almost half of all refractive surgery patients experience some degree of temporary dry eye syndrome. Dry eye problems usually disappear when healing of the eye is complete, which can take up to six months.

PURPOSE

The purpose of this research study is to investigate the incidence of dry eye symptoms and visual aberrations (halos) for longer than one year after refractive surgery. To do this we will gather patient data from December 2008 through January 2014 and ask all qualifying patients to complete a questionnaire regarding their experiences of dry eye symptoms and halos in the last month compared to before surgery, if applicable.

About 2,926 men and women will participate in this study at one location.

DURATION

Your participation in the study involves no visits to the study site. Your participation will last the amount of time it takes to complete one survey (about 3 – 5 minutes).

PROCEDURES

If you agree to take part in the study, you will be asked to complete an 20-question survey that should take approximately 3 – 5 minutes to complete. Your responsibility will be to click on the link to the survey provided in the e-mail and then complete the survey to the best of your knowledge.

You are also being asked for permission for the study staff to review your medical records and collect information in relation to your refractive surgery and incidence/risk factors of dry eye disease and halos. After the survey results have been collected and associated with your medical records, the study data will be anonymized (your name and identifying information will be removed) to protect your patient information.

POTENTIAL RISKS, SIDE EFFECTS, DISCOMFORTS, INCONVENIENCES

There are no foreseeable risks to participants in this study. The study may contain risks that are unforeseen or unknown.

POTENTIAL BENEFITS

Participants will benefit through completing the survey as their answers will contribute to the expanding body of knowledge about long term outcomes of refractive surgery.

ALTERNATIVE TREATMENTS

This study is not designed to treat any illness or improve your health. Your alternative is to not participate.

NEW INFORMATION

You will be informed in a timely manner if new information that may influence your willingness to continue participation in the study becomes available.

COMPENSATION TO YOU

There is no compensation provided for your participation in this study.

COSTS TO YOU

There are no costs to you for your participation in this study.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate is entirely voluntary. You may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which you are otherwise entitled. Your ongoing medical care will not be affected by your decision to be in this study or to withdraw from the study.

Your participation may be stopped without your consent by the study doctor for any reason. For example, your participation may be stopped:

- if you fail to follow instructions.
- If the study is cancelled.

CONFIDENTIALITY AND AUTHORIZATION TO COLLECT, USE AND DISCLOSE YOUR MEDICAL INFORMATION

As a part of this research, records that contain information or data about you and your health may be collected and used. These records may identify you and will be kept as confidential as possible. To the extent permitted by applicable laws and regulations, the records identifying you will not be made publicly available.

Under the privacy laws, you have the rights to decide who can use your protected health information (called PHI). When you sign this form, you are saying that you will allow the use of your protected health information for this study.

The information that will be collected about you as a part of this research includes:

- Name
- Address
- Telephone number
- Birth date
- Race
- Sex
- Family medical history
- Allergies
- Medications you take (current and past)
- Other information from other doctors' offices, clinics, and/or hospitals that is needed for the study

Information collected about you for the study will be kept in a research file that is separate from your medical chart. You will not be able to see your research file until after the end of the study.

The study team will know your identity; however, your records will be labeled with a code that is randomly assigned to you. The research staff are the only people who will have this code and its key.

The following groups may review and use your study information. They may review your study information to make sure that it is correct. They may also review your information to make sure that the study is being conducted properly.

- The study sponsor (or sponsor representatives such as monitors and/or auditors)
- The U.S. Food and Drug Administration (FDA)
- Sterling Institutional Review Board (IRB)
- The Department of Health and Human Service (DHHS)
- Other government agencies in other countries
- Other doctors, health care professionals or research staff who are involved in the study

Your study information may be released to the groups listed above. If your study information is reviewed by these people, they may need to see your entire medical record; it is possible that your Social Security number may be included in the records reviewed. Because of this, it cannot be assured that your confidentiality will always be protected. It is possible that your information will be shared (re-disclosed) in a way that it would no longer be protected. However, this access to your records will be granted without violating your confidentiality to the extent permitted by applicable laws and regulations. By signing this form, you are authorizing this access to your records.

The results of the study, including your information, may also be presented at meetings or in articles written about the study (publications). If the results of the study (including your research or health information) are published, your identity will remain confidential.

This permission (also called an authorization) will last until the end of the study

You have a right to see your study records; however, you will not be able to see your study records until after the study has ended.

You may also take away (or withdraw) your permission for the use of your protected health information at any time. If you choose to withdraw your permission, you must write your study doctor a letter.

The study doctor's mailing address is Boston Laser, 1101 Beacon Street, Suite 6, Brookline, MA, 02446. The study doctor will still be able to use the health information collected about you before you withdrew your permission. Information that has already been sent to the sponsor of the study cannot be taken back.

If you withdraw your permission after you have entered the study, you cannot continue participating in the study. If you refuse to give permission or withdraw your permission, your

medical care and your relationship with the health care providers at the study center will not be affected.

QUESTIONS

If you have questions, concerns or complaints about the research study, please contact Dr. Melki or the study staff at 617-556-0062 or 508-887-5320 (5:00pm – 10:00pm).

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact the Sterling Institutional Review Board Regulatory Department, 6300 Powers Ferry Road, Suite 600-351, Atlanta, Georgia 30339 (mailing address) at telephone number 1-888-636-1062 (toll free).

PARTICIPANT STATEMENT AND AUTHORIZATION

I have read the Participant Informed Consent Form and Authorization to Use and Disclose Medical Information and I agree to participate voluntarily in this study. I give my permission to the study doctor to use and disclose my protected health information as described in this consent form.

I am able to print a copy of this form, which has 5 pages.

All my questions have been answered.

I have not waived any of my legal rights by signing this document.

BOSTON LASER

YOUR EYES. OUR VISION.

I hope you've been seeing well since your surgery and am curious to learn how your eyes have been.

I would like to thank you for choosing Boston Laser for your refractive surgery. I'd like to invite you to participate in a quick survey regarding your quality of vision since your surgery.

*Clicking the link below will re-route you to a survey that will take **less than 5 minutes to complete.***

I appreciate your feedback!

Your answers will be used in a research study, which will help prospective patients have an increased understanding about the successes and limitations of refractive surgery. Thank you in advance for taking a moment to ***share your experience with me!***

Help others!
Please Click

Approved by Sterling IRB
IRB ID 4997

Here for the Survey

If you have any questions, please do not hesitate to call or e-mail. You may contact Samuel Hilbert via either of the methods below. If calling, please mention that your call is in regards to the Refractive Surgery Outcomes Survey.

Samuel Hilbert
Email: samuel@bostonlaser.com
(Subject: Refractive Surgery Outcomes Survey)
Phone: 617-566-0062

Stay Connected

Approved by Sterling IRB
IRB ID 4997

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