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Leveraging Aqueous Humor Dynamics and Ocular Biometrics for Improving Therapeutic Outcomes in Glaucoma

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Leveraging Aqueous Humor Dynamics and Ocular Biometrics for

Improving Therapeutic Outcomes in Glaucoma

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Along any path when you turn around and look, it often gives you great perspective. As I near the milestone of submission of this dissertation and completion of this doctoral degree, a look back at the past several years fills me with humility and gratitude. I am appreciative of having had the opportunity to add a new dimension to my prior role as a glaucoma care provider, to help me along my path as a clinician scientist. I am grateful to the UNMC Clinical and Translation Research Mentored Scholars Program for providing this opportunity to UNMC faculty. I am thankful to the current and past Program Directors of the program and my advisory committee members for their help and guidance along the way. I would like to acknowledge the support I have received from the National Eye Institute K23 award EY023266, without which this work would not have been possible. I am grateful for the additional support I have received from American Glaucoma Society, Glaucoma Research Foundation, University of Nebraska Medical Center, Nebraska Tobacco Settlement Biomedical Research Development Fund and Research to Prevent Blindness.

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About 21 years ago, I defended a thesis towards a doctoral degree. The print version dedication said 'To My Teachers'. Little did I know then that I was yet to meet the greatest teacher of my life, Carl B Camras. I am grateful every day for having met him and having had the opportunity to learn from him as a resident and a fellow. He is the foundation beneath what I do and the eternal inspiration and guiding light for all that I aspire and pursue in the field of medicine and glaucoma. With my deepest gratitude, I dedicate this body of work to Carl.

Leveraging Aqueous Humor Dynamics and Ocular Biometrics for Improving Therapeutic Outcomes in Glaucoma

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University of Nebraska, 2020

Glaucoma laser and incisional surgical treatments are associated with a known risk of complications. The ability to better predict treatment outcomes and individualize treatment recommendations can enhance the benefit to risk ratio of a treatment option. The work presented in this dissertation explores the interplay of biometrics, race and aqueous humor dynamics and their influence on treatment outcomes. In the first chapter, we demonstrate that pre-operative aqueous humor dynamics (higher aqueous flow, lower outflow facility and lower uveoscleral outflow) are predictive of greater intraocular pressure lowering after selective laser trabeculoplasty. The second chapter describes significant race-based differences in aqueous humor dynamics and biometrics between a Chinese and Caucasian study set, each compromised of two different age groups. Overall, Chinese subjects had a higher intraocular pressure, higher aqueous flow, lower uveoscleral outflow, higher outflow facility, lower anterior chamber volume and higher central corneal thickness as compared to Caucasian subjects. The final chapter demonstrates that the intraocular pressure lowering effects of a trabecular bypass procedure (iStent) are much less apparent in non-Caucasian patients and in patients with higher axial lengths. Cataract surgery done without iStent, had greater success in eyes with flatter keratometry, deeper anterior chamber and shorter axial lengths. This work thereby identifies significant interplay between race, biometrics and aqueous humor dynamics and describes their influence on glaucoma treatment outcomes.

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List of Abbreviations

ACd   anterior chamber depth

ACV   anterior chamber volume

AHD   aqueous humor dynamics

ALT   argon laser trabeculoplasty

C   outflow facility

CCT   central corneal thickness

CE   cataract extraction

CE-IS   cataract extraction with iStent

CI   confidence interval

EVP   episcleral venous pressure

Fa   aqueous flow

FDA   food and drug administration

Fu   uveoscleral outflow

GEE   generalized estimating equations

HR   hazard ratio

ICC   intraclass correlation coefficient

IOL   intra ocular lens

IOP	intra ocular pressure
Kv	cornea volume
MIGS	minimally invasive glaucoma surgery
Nd:YAG	neodymium: yttrium aluminum garnet
OHT	ocular hypertension
PACG	primary angle closure glaucoma
PH	proportional hazards
POAG	primary open angle glaucoma
SAS	statistical analysis system
SLT	selective laser trabeculoplasty
SOPs	standard operating procedures

Background

Glaucoma is a one of the leading causes of blindness in the US and worldwide. It affects over 2 million people in the US[1] and over 60 million globally.[2] More than half of glaucoma is undiagnosed.[3-6] Unlike cataract, vision loss from glaucoma is irreversible with lasting functional consequences for the patients.[7-9]

Glaucoma can be broadly divided into open angle and angle closure types, depending largely upon whether there is a mechanical obstruction to the flow of aqueous humor to the trabecular meshwork. Presence of such an obstruction, most commonly with iris tissue implies the angle closure mechanism. According to the American Academy of Ophthalmology definition, primary open-angle glaucoma (POAG) is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons.[10] Even though IOP is just a risk factor for glaucoma, currently it is the only treatable clinical parameter that can prevent further vision loss in glaucoma.[11-14] The modified Goldmann equation (Eq 1) summarizes the relationship between the parameters of aqueous humor dynamics (AHD) that determine the IOP in health and disease states.

IOP = (Aqueous inflow-Uveoscleral outflow)/outflow facility + episcleral venous pressure

(Eq 1)

Aqueous humor is produced by the ciliary body and egresses the eye through trabecular and uveoscleral outflow. The pressure head required to maintain outflow through the trabecular pathway to maintain the equilibrium between aqueous inflow and outflow translates into the IOP. Outflow facility is the inverse of the resistance in the trabecular outflow pathway, also

referred to as the conventional outflow pathway. All these parameters can be measured using techniques utilized in the research included in this dissertation.

Aqueous inflow (or aqueous flow as is the traditional label) is measured by fluorophotometry. This technique entails administration of fluorescein drops to the eye in preparation for the experiments and waiting enough time (4-6 hours) to reach a stable level in the cornea and anterior chamber. Hourly measurements of fluorescein levels in the cornea and anterior chamber using a scanning fluorophotometer can be used to plot a decay curve over time and calculate the aqueous flow in the eye. [15]

Episcleral venous pressure is the downstream pressure for aqueous flow through the trabecular pathway and is believed to represent the outflow recipient pressure in the conventional outflow flow system of the eye. It is measured using a episcleral venomanometer whereby a silicon membrane connected to a variable pressure chamber is used to apply pressure to a visible episcleral vein on the eye under direct visualization.[16] Somewhat similar to blood pressure measurement, the episcleral venous pressure is deemed to be the pressure required to initiate the visible collapse of a selected episcleral vein on the ocular surface.

Outflow facility can be measured using 2 different techniques: fluorophotometry and tonography. Both methods were used in the research described herein. In the fluorophotometric method[17], baseline aqueous flow and IOP are measured. An aqueous suppressant medication such as topical timolol or systemic acetazolamide is administered followed by a repeat assessment of aqueous flow and IOP. The use of these drugs is driven by the fact that they are believed to have no effect on any of the other parameters of AHD. Outflow facility is calculated as the ratio of change in aqueous flow to the change in IOP. In the tonographic method, gentle pressure is applied to the eye using a weighted tonometer probe

for a period of 2-4 minutes. The decrease in IOP under artificially raised pressure is captured during the 2-4 minutes. Using the change in IOP and from known pressure/volume data for the eye (published elsewhere), the additional fluid expressed out of the eye is estimated and outflow facility is calculated using mathematical formulas. [18]

Uveoscleral outflow, also known as unconventional outflow, is a poorly defined aqueous egress pathway in the eye. This outflow is described as pressure independent because the flow rate does not change in the pressure range of normal to high. The flow occurs across the ciliary body face and in many directions thereafter including the suprachoroidal space. It cannot be directly measured noninvasively. It is mathematically calculated using the above Goldmann equation by plugging in all variables other than uveoscleral outflow.

Elevated IOP in primary open angle glaucoma is believed to be a consequence of increased resistance in the outflow pathways at the level of the juxtacanalicular tissue.[19,20] In terms of parameters of AHD, elevated IOP in ocular hypertensive patients is related to lower outflow facility and slower uveoscleral outflow.[21] Medical therapy lowers IOP by targeting one or more of the parameters of AHD. An assessment of AHD can provide valuable information on the mechanism of action of medications and some surgical interventions.

Ocular Biometrics

Like AHD, ocular biometrics can play a role in the mechanism of certain types of glaucomas and can have a potential effect on therapeutic outcomes as well. For example, shorter eyes are more likely to have narrow angle glaucoma and longer myopic eyes are more likely to have a type of glaucoma called pigmentary glaucoma. The biometrics parameters that can be measured clinically, include the curvature of the cornea, thickness of the cornea, distance between the

cornea and the anterior lens surface (anterior chamber depth) and the total antero-posterior length of the eyeball (axial length). Research included here explores the racial differences in biometric parameters and the influence of these parameters on surgical outcomes.

Laser Surgery for Glaucoma

Besides topical medications laser trabeculoplasty is another option for treatment of elevated IOP.[22,23] Laser trabeculoplasty delivers laser energy to the trabecular meshwork using a gonioprism in an attempt to lower the IOP. An earlier iteration of this procedure used argon laser, which has photocoagulative effects on the target tissues. Using the argon laser, the Glaucoma Laser Trial (GLT) has shown laser trabeculoplasty to be better than topical medications at visual field preservation and IOP lowering as primary therapy.[24,25] Currently most trabeculoplasties are performed using frequency doubled Nd:YAG laser rather the argon laser used in the GLT study. Trabeculoplasty performed using this laser, also known as selective laser trabeculoplasty (SLT), does not have any photocoagulative effects unlike argon laser and can be speculated to have a mechanism of action entirely different from argon laser trabeculoplasty. The research reported here is the first comprehensive study of the mechanism of action of SLT.

Baseline AHD and Therapeutic Outcomes

There are no prior reports on the influence of baseline AHD on IOP lowering outcomes by any medical or surgical intervention. One of the objectives of this research was to evaluate if preoperative AHD can be predictive of treatment outcomes after selective laser trabeculoplasty. Any associations seen may help leverage baseline AHD to guide treatment to maximize the efficacy and minimize the exposure to unwanted adverse events associated with the laser procedure.

Race and AHD

There is a scarcity of prior reports on racial differences in AHD. The prevalence of different types of glaucoma can vary across different racial backgrounds.[26-30] Primary open-angle glaucoma is much more prevalent in subjects of African and Latino descent whereas angle closure glaucoma is more prevalent in Asian subjects. If treatment outcomes are influenced by race and AHD it will be useful to study the systematic racial differences in AHD. These racial differences in AHD and their effect on treatment outcomes can then be targeted to better understand the mediators of treatment success and improve treatment outcomes in glaucoma. Part of the research described herein evaluates age and race-based differences between Chinese and Caucasian study populations.

Race and Surgical Treatment Outcomes

Conventional glaucoma procedures include trabeculectomy and glaucoma drainage devices. Trabeculectomy creates a fistula between the anterior chamber and the space under the conjunctiva and Tenon's capsule. Drainage devices involve placing a plate made of silicone or other material in this space connected to a tube that communicates between the anterior chamber and this plate. Both these procedures can fail as a result of scarring in the subconjunctival space. A higher rate of failure with traditional glaucoma surgeries such as trabeculectomies and glaucoma drainage devices among blacks is well known.[31-33] The difference may be due to different healing and scarring responses in the conjunctiva and Tenon's space among different races.[31] Newer glaucoma procedures such as the iStent[34] and Hydrus implant[35] do not involve the subconjunctival space and should not be subject to the perils of scarring in the subconjunctival space. The last study described herein evaluates if the

success of trabecular bypass procedures is affected by race. Specifically, we aim to evaluate if there is a difference in the IOP lowering outcomes with an FDA approved trabecular bypass device (iStent) between Caucasian and non-Caucasian subjects. The said device is only approved for use in conjunction with cataract surgery which by itself is well known to lower IOP for years after the procedure.[36] To control for the IOP lowering effect of cataract surgery and its interaction with race, a race based comparison is also performed for the IOP lowering effect of standalone cataract surgery. In addition, other clinical and demographic variables were utilized in the multivariate models to explore potential predictors of surgical success and failure.

A future goal of this research is to study the effect of aqueous humor dynamics on the outcomes of trabecular bypass surgical procedures. This research provides evidence supporting the influence of aqueous humor dynamics and race on IOP lowering procedures. It also demonstrates that aqueous humor dynamics and ocular biometrics, that influence surgical outcomes, are themselves affected by race. Therefore, a comprehensive race-based study of ocular biometrics and AHD can provide valuable insights into the mediators of success after surgical IOP lowering interventions.

Research included in this dissertation has the following 3 sections:

1. The first paper describes the mechanism of IOP lowering for selective laser trabeculoplasty and provides evidence that preoperative aqueous humor dynamics can be predictive of treatment outcomes.

2. The second paper compares aqueous humor dynamics and biometrics between a Caucasian and a Chinese population to provide evidence that biometrics, AHD and changes therein with aging vary across different racial backgrounds.

3. The third paper provides evidence that race and other biometric parameters correlate with IOP lowering outcomes of cataract surgery and a novel trabecular bypass procedure.

Impact

At this time there are no known clinical or physiological parameters that correlate with the IOP lowering effect of laser and surgical procedures. Practice patterns vary widely among clinicians. This approach is not only inefficient but may also be cost ineffective. It may expose some patients to the risk of an additional procedure without a potential benefit or may miss the one-time opportunity for potential IOP lowering using stents with less or no medications.

This work addresses several unmet needs to lay the groundwork for personalization of surgical management of mild to moderate glaucomas. This study is a step forward in the direction of precision medicine. Future predictive models evolving from the results of this work can help guide treatment choices for individual patients based on their individual risk factors.

Chapter One: Mechanism of Action of Selective Laser Trabeculoplasty and Predictors of Response

At the time of this research there were no prior comprehensive studies on the mechanism of action of selective laser trabeculoplasty. The assumptions of mechanism of action of SLT were derived from prior work on argon laser trabeculoplasty. SLT unlike ALT does not have any photo-coagulative effects and may have a completely different effect on AHD as compared to ALT. Additionally, to the best of our knowledge there were no prior reports on any association between pre-operative AHD and post-operative outcomes. The following research was directly supported by the American Glaucoma Society Clinician Scientist Award and has been published in Investigative Ophthalmology and Visual Sciences.[37]

Abstract

Purpose: This study was designed to evaluate the changes in aqueous humor dynamics (AHD) produced by selective laser trabeculoplasty (SLT) and to explore if baseline AHD parameters are predictive of intraocular pressure (IOP) response to SLT.

Methods: Thirty-one consecutive subjects diagnosed with ocular hypertension or primary open-angle glaucoma scheduled to undergo SLT as their primary IOP lowering therapy were enrolled in this prospective observational study. Subjects underwent baseline assessment of AHD in both eyes. Variables assessed were IOPs at 9AM and noon, aqueous humor flow rate(fluorophotometry), episcleral venous pressure (EVP, venomanometry), outflow facility (pneumatonography and fluorophotometry) and uveoscleral outflow (calculated using modified Goldmann equation). All subjects underwent 360 degrees SLT and AHD measurements were repeated 3 months later.

Results: Compared to baseline, IOPs after SLT were significantly lower at 9AM (22.9±5.1mmHg vs. 19.7±3.0 mmHg; p=0.001) and noon (23.4±4.6 mmHg vs. 20.0±3.5 mmHg; p<0.001). Outflow facility by fluorophotometry was significantly increased from 0.17±0.11 μl/min/mmHg at baseline to 0.24±0.14 μl/min/mmHg at 3 months (p=0.008). Outflow facility by tonography (baseline: 0.16±0.07 μl/min/mmHg vs. 3-months: 0.22±0.16 μl/min/mmHg; p=0.046) was similarly increased. No change in aqueous flow or EVP was observed. There were no changes in IOP or AHD in the contralateral untreated eye. Using multiple linear regression models, higher baseline aqueous flow, lower baseline outflow facility and possibly lower uveoscleral outflow were associated with more IOP lowering with SLT.

Conclusions: The IOP lowering effect of SLT is mediated through an increase in outflow facility.

There is no contralateral effect. Higher aqueous flow and lower outflow facility may be

predictive of better response to SLT.

Introduction

Lowering of intraocular pressure (IOP) is currently the only well-established treatment strategy for management of ocular hypertension (OHT)[38] and glaucoma.[12-14] Laser trabeculoplasty is extensively utilized as a primary or adjunctive therapy for lowering the IOP in OHT, glaucoma suspects, and patients with primary and several secondary open angle glaucomas. Introduction of selective laser trabeculoplasty (SLT) in the late 1990s[22] has resulted in a significant increase in the number of trabeculoplasties performed in the past decade.[39-41] The IOP lowering effect of argon laser trabeculoplasty (ALT) is mediated through an increase in conventional outflow facility,[42] which in turn may be mechanically or biologically mediated after the delivery of laser to the anterior chamber angle structures.[43-45] As SLT delivers about 1% of total energy used by a typical ALT and does not have any thermal coagulative effects like ALT,[46] it purportedly can have a mechanism of action different from ALT. Prior reports have shown an increase in conventional outflow facility at 1 and 3 months and no effect on aqueous humor inflow rate at 3 months after SLT.[47,48] These are two important parameters of aqueous humor dynamics (AHD), changes in which alter IOP. Other parameters important in regulating IOP but with unknown roles in the IOP responses to SLT treatment are episcleral venous pressure (EVP) and uveoscleral outflow. This is the first comprehensive study of the effects of SLT on all parameters of AHD in the same patients. Additionally, this study presents a multiple regression analysis of patient, treatment, and AHD variables to identify potential predictors of IOP response to SLT.

Methods

This prospective study, conducted at a tertiary care academic practice, enrolled consecutive patients undergoing primary SLT with a clinical diagnosis of either OHT, glaucoma suspect or primary open angle glaucoma. The study followed the tenets of the Declaration of Helsinki and

was approved by the Institutional Review Board of the University of Nebraska Medical Center.

Primary therapy for the purpose of the study was defined as SLT being considered as the only

IOP lowering modality whether or not patients have used IOP lowering medications in the past.

Subjects considered for the study were those interested in SLT as primary 1st line therapy, those

with a preference to discontinue current medication(s) for concerns such as side effects and

medication cost and those who were recommended SLT due to past poor compliance with

medication use. After the patient agreed to proceed with SLT, they were approached for

participation in this study. A total of 31 of 35 consecutive subjects agreed to participate in the

study and gave informed consent.

Participating subjects underwent a screening visit comprising of a detailed anterior segment

examination including dynamic gonioscopy, and a dilated fundus examination. A subjective

assessment was made of angle pigmentation on a scale of 0 to 4. Inclusion criteria consisted of

subjects with a clinical diagnosis of OHT, glaucoma suspect or primary open angle glaucoma

undergoing primary SLT (as defined above) who were either not on any medications or could be

safely washed out of a single topical medication. Subjects were excluded if they had a history of

prior ocular incisional surgical procedures, known history of past laser trabeculoplasty, corneal

opacity precluding fluorophotometry, use of topical or systemic steroids within 3 months of the

study, narrow angle (scleral spur not visible for greater than 180 degrees without pressure on

dynamic gonioscopy), secondary open angle glaucoma (exfoliation, pigment dispersion or angle

recession glaucoma), and known allergy to fluorescein, proparacaine or sulfa medications.

Subjects with a diagnosis associated with potential retinal ischemia (diabetic retinopathy or

retinal arterial or vein occlusion) also were excluded from the study.

 Of the 31 enrolled subjects, none were excluded from participation at the screening visit.

Enrolled subjects on a topical medication at the time of screening started a washout in both eyes, after approving the safety of the washout with the treating physician. For subjects who had stopped the topical medication prior to the screening visit, washout was deemed to start at the reported time point of stopping the medication. Of the eight subjects that underwent washout before baseline measurements were made, 7 were using a prostaglandin analog in both eyes and one was using a carbonic anhydrase inhibitor in both eyes. Washout for a prostaglandin analog was a minimum of 4 weeks and that for the carbonic anhydrase inhibitor was 1 week. During the washout period IOP was monitored every 2 weeks. The actual median washout in the study was 7 weeks (range 4 to 11 weeks).

Subsequent to the screening visit and any required washout, subjects underwent a baseline assessment of AHD. Standard techniques for AHD measurement and the underlying assumptions have been reported previously.[15] For the purpose of fluorophotometry, subjects self-instilled 8 drops of sodium fluorescein at 10 pm the night before each scheduled visit. On the study day, central cornea thickness and anterior chamber depth were measured by ultrasound pachymetry and A-scan respectively. Seated IOP was measured by pneumatonometer (performed by SF, CBT or DGN, masked to treatment plan) at 9 AM, followed by hourly fluorophotometry scans until noon. IOP measurement was repeated at noon. EVP was measured at 10 am using an episcleral venomanometer.[49] For both EVP and IOP, 2 measurements were obtained for each eye. A third measurement was obtained if the first 2 differed by more than 2 mm Hg. The median value for each eye was used for analysis. The rate of fluorescein decay in the cornea and anterior chamber was used to calculate the aqueous humor flow rate.[15] Subjects were given 500 mg of acetazolamide at noon. Three additional hourly fluorescein scans and IOP measurements were obtained after acetazolamide administration. Outflow facility was calculated as the ratio of change in flow to change in IOP accomplished by acetazolamide. Two minute

pneumatonography was performed at 3 pm after all other measurements were completed. IOP data during tonography was captured digitally at 40 Hz using Powerlab and Lab Chart 7 software. The starting and ending IOP were deduced using regression techniques previously described.[50,51] Pressure volume relationship data for the human eye were thereby used to calculate the outflow facility by tonography.[18] Uveoscleral outflow was calculated with the modified Goldmann equation, by using the outflow facility obtained by fluorophotometry and tonography, respectively. Data were obtained from all study eyes and the contralateral untreated eyes that met the inclusion and exclusion criteria.

The study eye underwent SLT within 1 week of obtaining baseline measurements. Preoperatively, all subjects received one drop each of pilocarpine 2% and brimonidine 0.2%. Goldmann lens was used to perform all trabeculoplasties. A total of 80 spots were placed over 360 degrees of the anterior chamber angle. Laser power was titrated starting at 0.8 mJ (with the exception of one case with excessive angle pigment), to 0.1mJ below the minimum required to generate 'champagne bubbles' at the application site. A subjective estimate of the percentage of applied laser spots associated with champagne bubbles was recorded by the treating physician (VG) in the patient chart. IOP was checked one hour after the laser treatment and the patients were provided with a non-steroidal anti-inflammatory drop to use if needed for relief of ocular pain and discomfort.

Following SLT two subjects required topical IOP lowering medications in the study eye (1 prostaglandin analog, 1 carbonic anhydrase inhibitor), and 4 subjects required IOP lowering medications in the fellow control eye (3 prostaglandin analogs, 1 carbonic anhydrase inhibitor) in the post-operative period. All medications were washed out using the protocol described above prior to obtaining the 3 months follow up study measurements.

Three months after the SLT, the subjects underwent repeat assessment of all AHD variables obtained at the baseline visit.

Statistical Analysis

Descriptive statistics were calculated for all data. Data are presented as mean ± standard deviation unless indicated otherwise. The primary comparison was made for the IOP and AHD data obtained in the study eye between baseline and 3 months after the laser treatment using paired t-tests. Sample size was calculated based on changes in outflow facility which was the leading hypothesis prior to the conduct of the study. With an expected change in outflow facility of 0.05 μl/min/mmHg and presumed standard deviation of 0.09 μl/min/mmHg for the change,[42] a sample of 27 subjects would have 80% power to detect such a difference at an alpha of 0.05. Multiple linear regression was used to study the association between baseline AHD, demographic and treatment parameters and IOP response. Three separate regression models were constructed; one based on parameters of aqueous humor dynamics (aqueous flow, EVP, outflow facility and uveoscleral outflow), the second based on patient demographic variables (age, sex, race and central corneal thickness) and the third based on variables relevant to laser tissue interaction (angle pigmentation, total laser energy used and percentage of spots with bubble formation). A stepwise backward elimination approach was used to develop the model, discarding associations with p value less than 0.05 until all remaining covariates in the model had a p value less than 0.05. Interactions were not included in the model to limit the covariates given the small sample size. The outcome variable for both models was mean change (mean for 9 AM and 12 noon) in IOP. Multiple regression analysis also was performed using the percentage change in IOP as the outcome variable (rather than absolute change in IOP). A P value of less than 0.05 was consider statistically significant.

Results

A total of 31 subjects who consented for the study, underwent a screening visit. Eleven subjects had opted for SLT as first line therapy, 12 had used medications in the past but were pursuing SLT because of issues with medications such as cost and side effects and 8 were recommended to undergo SLT because of poor compliance with recommended medications. In terms of the clinical profiles, enrolled subjects included 5 subjects with 2 or more IOPs above 24 with no glaucomatous cupping or visual field defect, 16 with glaucomatous cupping (as determined by the treating physician) without any visual field defect, and 10 with repeatable (2 or more occasions) visual field defects with supportive optic nerve head appearance. The IOP targets set by the treating physician for the subjects consented for the study were mid-teens (n=1), high teens (n=7), low 20s (n=10) and mid 20s (n=13).

Of the 31 subjects enrolled, 29 completed all study related measurements, one was lost to follow up after the SLT and one was unable to adequately administer fluorescein for fluorophotometry on scheduled baseline visits on two different days. The latter subject was withdrawn from the study and underwent SLT as planned. Four contralateral eyes also were excluded from analysis. Three of these were pseudophakic and one had previously undergone laser trabeculoplasty. Data were analyzed for 29 subjects, comprising 29 study eyes and 25 contralateral eyes.

Mean age of the study population was 64.0 ± 9.3 years (range 48-79 years). Eleven subjects were females. Based on self-reported race, 15 subjects were Caucasian, 12 were African Americans and 1 each were Hispanic and Asian.

Baseline and 3 month AHD data are summarized in **Table 1**. Post SLT, there was a significant decrease in both the 9 am and 12 noon IOP in the SLT treated eye, with no change in IOP in the

contralateral control eye. There was no change in aqueous flow or EVP in either the treated or

contralateral eye, 3 months after treatment. Outflow facility (by fluorophotometry) was

significantly increased from 0.17 ± 0.11 µl/min/mmHg at baseline to 0.24 ± 0.14 µl/min/mmHg

at 3 months after treatment (p=0.008). The outflow facility in the contralateral eye was

unchanged. The change in outflow facility was reproducible on tonography increasing from 0.16

± 0.07 µl/min/mmHg at baseline to 0.22 ± 0.16 µl/min/mmHg at 3 months (p=0.046).

Table 1: Aqueous humor dynamics parameters at baseline and 3 months after selective laser trabeculoplasty in the treated eye and contralateral control eye.

Variable	Treated Eye (n=29)		p	Control Eye (n=25)		p	Treated vs Control (n=25)	
	Baseline	3 months		Baseline	3 months		Baseline	3 months
IOP (9 AM, mmHg)	22.91 ± 5.12	19.67 ± 3.00	0.001	21.60 ± 4.80	21.83 ± 3.20	0.79	0.01	0.001
IOP (Noon, mmHg)	23.43 ± 4.60	20.00 ± 3.45	<0.001	21.53 ± 4.61	21.42 ± 3.49	0.87	0.01	0.01
Aqueous flow (µl/min)	2.51 ± 1.11	2.27 ± 0.84	0.16	2.60 ± 1.45	2.33 ± 1.00	0.28	0.47	0.51
EVP (mmHg)	9.74 ± 1.46	9.61 ± 1.12	0.64	9.89 ± 1.09	9.35 ± 1.30	0.07	0.62	0.54
Outflow facility (fluorophotometry, µl/min/mmHg)	0.17 ± 0.11	0.24 ± 0.14	0.008	0.24 ± 0.16	0.22 ± 0.20	0.74*	0.01*	0.85
Outflow facility (tonography, µl/min/mmHg)	0.16 ± 0.07	0.22 ± 0.16	0.046	0.18 ± 0.07	0.20 ± 0.12	0.53	0.18	0.73

*n=24 (subject excluded because of undetectable change in IOP with acetazolamide precluding outflow facility calculation). P values obtained using paired t-test.
IOP=intraocular pressure; EVP=episcleral venous pressure

Three months after SLT treatment, uveoscleral outflow in the treated eye was lower by

0.36 ± 0.94 µl/min when calculated using fluorophotometry data (p=0.05), but not when

using tonography data (Δ=-0.26±2.15 µl/min, p=0.52). At the same time, no change in

uveoscleral outflow was detected in the contralateral untreated eye. These results are

summarized in **Figure 1**.

Figure 1: Change in uveoscleral outflow at 3 months after selective laser trabeculoplasty in the treated (n=29) and contralateral control eyes (n=24 for fluorophotometry, 25 for tonography)
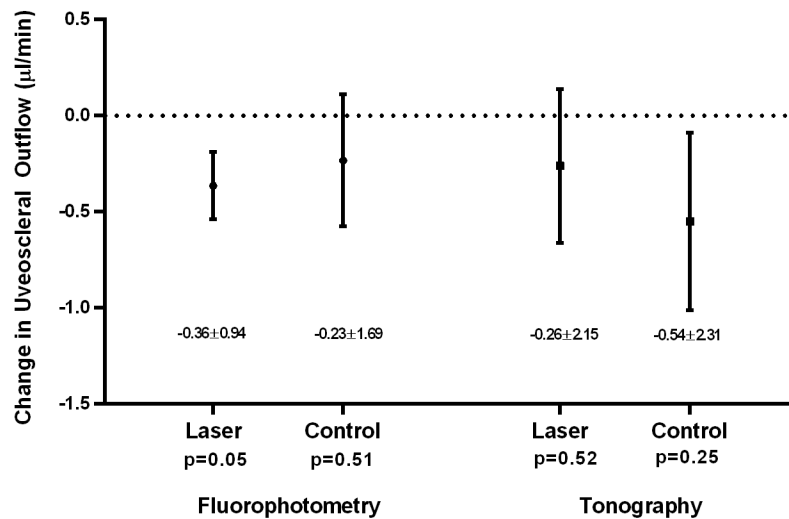
Values on the plot indicate mean ± SD. Error bars = one standard error.
p-values calculated using paired t-test

Responder Analysis

To further validate the 'cause-effect' hypothesis of change in fluorophotometric outflow

facility being the mediator of IOP lowering seen with SLT, secondary analysis of the

variable was conducted using a binary categorization of subjects as responders and non-

responders (**Figure 2**). When IOP response was defined as 10% or more IOP lowering at

either 9 AM or noon, a statistically significant increase in outflow facility was
reproducible with greater confidence (p=0.004) in IOP responders (n=20). The outflow
facility in IOP non-responders was unchanged (n=9, p=0.90). If the definition of response
was changed to 10% or greater IOP lowering for both the 9AM and noon IOP, the
confidence in increase in outflow facility increased further in IOP responders (p=0.0003,
n=15). The outflow facility was unchanged in IOP non-responders by this definition as
well (p=0.84). Scatter plot of change in IOP plotted against change in outflow facility for
the lasered and contralateral eye (**Figure 3**) was suggestive of a linear relationship in the
lasered eye and no correlation in the contralateral eye. The Spearman correlation
coefficient was statistically significant for lasered eyes (σ =-0.41, p=0.03) but not for
control eyes (σ =0.21, p=0.34).

Figure 2: Change in outflow facility at 3 months in lasered and contralateral control eyes categorized based on percentage IOP lowering from baseline with selective laser trabeculoplasty.
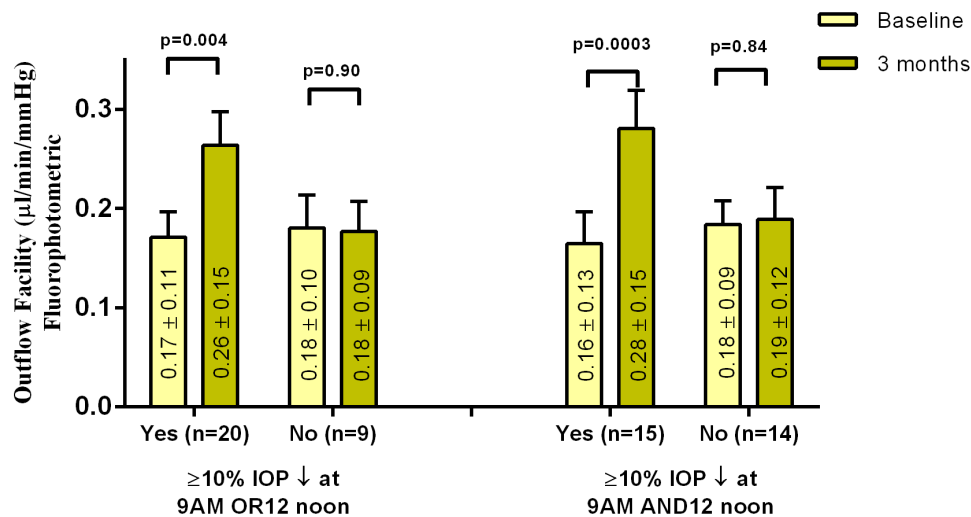
Values on the bars are mean ± SD. Error bars = one standard error.
p-values calculated using paired t-test

Figure 3: Scatter plot of change in intraocular pressure against change in fluorophotometric outflow facility in lasered and contralateral eyes. Scatter plot of change in intraocular pressure against change in fluorophotometric outflow facility in lasered and contralateral eyes. IOP change is the average of change at 9 am and noon for each subject. The Spearman σ for the correlation in lasered eyes was -0.41 (p=0.03) and that in contralateral untreated eyes was 0.21 (p=0.34).
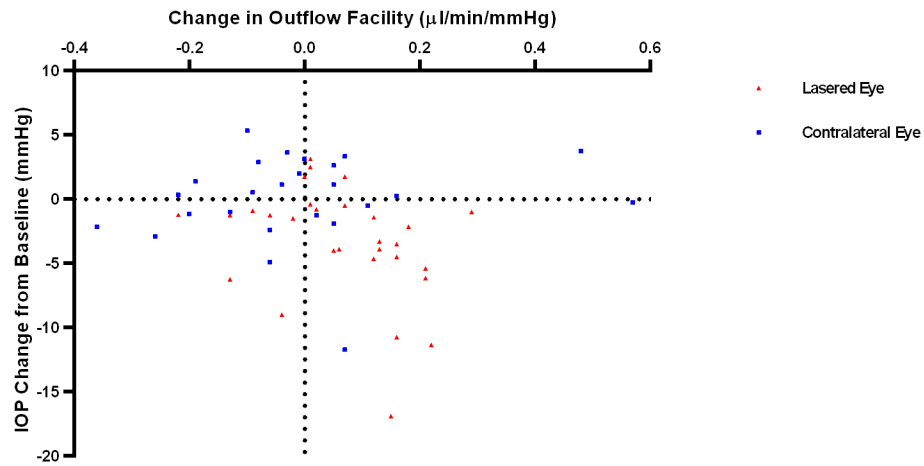
Predictors of Response

Using change in IOP as the outcome variable, baseline demographic, treatment and AHD variables were analyzed as covariates using multiple linear regression models (**Table 2**).

Table 2: Results of multiple linear regression analysis with IOP response (IOP at 3 months-baseline IOP) as outcome variable.

	Coefficient (SE)	P value	ANOVA p
Model 1a Fluorophotometry Data			0.003
Aqueous Flow	2.377 (0.749)	0.004	
Outflow Facility	-26.822 (7.684)	0.002	
Model 1b Tonography Data			<0.001
Aqueous Flow	4.170 (0.966)	<0.001	
Outflow Facility	-51.509 (11.383)	<0.001	
Uveoscleral outflow	-3.003 (0.735)	<0.001	
Model 2 Patient Variables			0.08
Age	-0.182 (0.090)	0.052	
CCT	-0.044 (0.024)	0.076	

SE=standard error
IOP response (outcome) was the average of the response at 9 am and 12 noon.
Model 1a included episcleral venous pressure (p=0.64) and uveoscleral outflow (fluorophotometric) (p=0.48) in the initial model.
Model 1b included episcleral venous pressure (p=0.06) in the initial model.
Model 2 included sex (p=0.41) and race (p=0.69) in the initial model.

Outflow facility and uveoscleral outflow were assessed in this study using 2 different methods, fluorophotometry and tonography. Therefore, the multiple regression model using AHD parameters was run separately for the fluorophotometry and tonography data for these variables (Models 1a and 1b respectively). The same values for aqueous flow and EVP were used for the two models. In the model with fluorophotometry data, the change in IOP was significantly associated with aqueous flow and outflow facility. Specifically, higher baseline aqueous flow was associated with a greater reduction in IOP (p=0.004). Lower baseline outflow facility also was associated with greater reduction in IOP (p=0.002).

Similarly, in the model with tonographic data, both higher aqueous flow and lower outflow facility were associated with a greater reduction in IOP. In addition, a lower baseline uveoscleral outflow also was associated with a greater IOP reduction (p<0.001). When percentage IOP reduction was used as the outcome variable there was no change in substantive conclusions (data not presented).

In the patient demographics-based model (model 2), none of the variables were found to be significantly associated with IOP response at an alpha of 0.05. However, a weak association was seen between IOP response and age (p=0.052) and IOP response and CCT (p=0.076). Specifically, the regression analysis approached significance for a greater IOP response being associated with younger age and thinner corneas. None of the treatment variables; angle pigmentation, percentage spots with visible bubbles or total laser power were associated with IOP response (model 3, data not presented).

Discussion

Similar to ALT, the IOP lowering effect of SLT appears to be mediated through an increase in outflow facility with no substantial effects on any of the other parameters of AHD. Using Shiotz tonometry based tonographic assessment, other authors[47,48] have reported an increase in outflow facility after SLT. This study has an expanded design as compared to any prior similar study. Both techniques used to assess outflow facility in our study are different from the ones reported in the past. Episcleral venous pressure and uveoscleral outflow calculations were included in the design to address all parameters in the modified Goldmann equation. Contralateral eyes were also studied for the first time and the negative results are important considering past speculations

on the contralateral effects of SLT. The primarily Caucasian composition of our study was different from any of the prior publications. The follow up measurement was done at a consistent time after the laser allowing 3 months for laser effects to be established prior to making repeat measurements. Given the fairly low baseline outflow facility in the two prior reports (0.08 μl/min/mmHg and 0.09 μl/min/mmHg),[47,48] our study perhaps represents a more moderate degree of trabecular pathology, more representative and generalizable to what is likely to be encountered in clinics.

In our study, as the criteria for IOP response was made more robust, the statistical significance of increase in outflow facility became greater. Even though this is not a true dose-response relationship, it does imply that for subjects with more IOP lowering, increase in outflow facility was more obvious. At the same time there was no change in outflow facility in subjects that did not have a good IOP response to SLT, adding credence to the hypothesis that IOP changes after SLT are mediated through an increase in outflow facility.

The overall magnitude of IOP response in our study subjects (approximately 15%) can be considered to be modest compared to the expectation from SLT for primary therapy. The mean clinic IOP, at which a decision was made to proceed with SLT was 26.05 ± 4.40 mmHg. This was considerably higher than the baseline visit's IOP of 22.91 ± 5.12 mmHg at 9 AM and 23.43 ± 4.60 mm Hg at 12 noon in the treated eye. The difference is reflective of the regression to the mean that affects clinical glaucoma management, where treatment decisions are typically made at IOP values on the higher end of the tonometry measurement error or inherent diurnal IOP variability. This also highlights

the potential overestimation of IOP response with the typical design of a retrospective

analysis where the most recent pretreatment IOP is considered the baseline IOP. The

modest IOP response seen in the study theoretically could be related to lower total

energy used for treatment as compared to some other studies of primary SLT.[47,52] It can

be speculated that higher total energy levels could have affected additional parameters

of AHD besides outflow facility or may have shown greater changes in outflow facility.

However, we feel that the magnitude and particularly the range of responses seen in

the study served the purpose of the study well. We had a fair number of 'non-

responders' with either of the 2 criteria used to make such comparisons and multiple

regression analysis meaningful. Additionally, within the range of laser energy used in

this study, a correlation between the total laser energy used and IOP response was not

detectable. This study did not find any IOP or AHD effects in the contralateral untreated

eye. However, one prior study has raised the possibility of a crossover effect of laser

trabeculoplasty on the contralateral untreated eye.[53]

A direct comparison of baseline parameters between responders and non-responders

based on more robust criterion 2 (at least 10% IOP lowering at both measurement time

points) is presented in **Table 3**. Subjects with a greater response had a higher IOP at

baseline. Other than IOP, the difference between the parameters of AHD between the 2

groups was not significant. In other words, in such an arbitrary binary comparison, the

parameters of aqueous humor dynamics were not evidently predictive of treatment

response. IOP can be considered to be an outcome of the complex interplay between

parameters of AHD. Therefore, examining and contrasting these parameters between

groups as covariates without controlling for others, is likely to yield limited information. Multiple linear regression facilitates such evaluation of a covariate while controlling for others in the model. Use of multiple regression revealed the significant influence of baseline AHD parameters on IOP outcomes (**Table 2**).

Table 3: Comparison of baseline aqueous humor dynamics parameters in lasered eyes with at least 10% IOP lowering at both 9 am and 12 noon to those that did not have such a response.

Baseline Parameters	≥10% IOP lowering(n=15)	< 10% IOP lowering (n=14)	p*
IOP (9 AM, mmHg)	25.38 ± 5.63	20.25 ± 2.77	0.005
IOP (12 noon, mmHg)	25.61 ± 4.91	21.08 ± 2.85	0.006
Aqueous Flow (µl/min)	2.82 ± 1.20	2.17 ± 0.92	0.11
Outflow Facility (fluorophotometry, µl/min/mmHg)	0.16 ± 0.13	0.19 ± 0.09	0.60
Outflow Facility (tonography, µl/min/mmHg)	0.15 ± 0.09	0.17 ± 0.07	0.52
Episcleral Venous Pressure (mmHg)	9.91 ± 1.82	9.55 ± 0.98	0.53
Uveoscleral Outflow (tonography, µl/min)	0.55 ± 1.64	0.18 ± 1.08	0.29
Uveoscleral Outflow (fluorophotometry, µl/min)	0.61 ± 1.02	0.15 ± 0.85	0.46

*p-value using paired t-test
IOP=intraocular pressure

To the best of our knowledge, this is the first report using regression modelling identifying what does and does not matter for laser response. This is perhaps the first report to identify any pretreatment AHD predictors of response to any IOP lowering

treatment.   Our study found a significant association between IOP response and AHD

parameters of aqueous flow rate and outflow facility. This association seen between

aqueous humor flow rate and IOP response for a fixed change in outflow facility is to be

expected based on Goldmann equation. Similarly, lower baseline outflow facility can

also expected to be more amenable to improvement after laser trabeculoplasty. The

results of multiple linear regression of the AHD data from this study experimentally

confirm these intuitive expectations. Based on the estimated coefficients in our

regression models we can speculate that for every 1 µl/min higher baseline aqueous

flow rate (approximately 40% higher than the study mean), the predicted IOP reduction

from SLT treatment was more by 2.38 ±0.75 mmHg (fluorophotometry based model) to

4.17 ± 0.97 mmHg (tonography based model). For every 0.1 µl/min/mmHg lower

baseline outflow facility, the predicted IOP reduction from SLT treatment was more by

2.68 ± 0.77 mmHg (fluorophotometry based model) to 5.15 ± 1.14 mmHg (tonography

based model). The application of this information to clinical care of patients currently is

limited by the techniques used to measure these variables. Aqueous flow determination

is a fairly time consuming exercise and difficult to incorporate into clinical practice.

Tonography has better potential as a clinical tool to predict treatment response prior to

laser treatment. However, the technique has substantial measurement noise, whereby

the repeatability at the individual level is low despite a very good reproducibility for

large sample means. Further advances in these techniques may allow for better

estimation of likelihood of individual treatment response and aid in patient selection

based on these baseline variables.

This study did not find any statistically significant association between IOP response and patient demographic variables or treatment variables possibly relevant to laser-tissue interactions such as total laser energy, angle pigmentation or percentage of laser spots with visible response. The association between younger age and greater IOP response did approach statistical significance (β=-0.18, p=0.052). This translates into a possible 1.8 mm Hg (95% confidence interval of 0.0 to 3.6 mmHg) additional IOP response being associated with a 10-year younger age of patient. The association with central corneal thickness also approached statistical significance (β=0.04, p=0.076), implying a possible additional 1.0 mm Hg (95% CI 0.0, 2.0) IOP response associated with 25 μ thinner cornea. Thinner corneas have previously been shown to be associated with better IOP lowering efficacy of topical medications.[54] Even though the association between these variables and IOP response did not reach statistical significance in this study, the authors recommend controlling for these variables in future studies exploring the predictors of response to laser trabeculoplasty.

Our study limitations are largely related to the limitations of the techniques available for the assessment of AHD. Both fluorophotometry and tonography have several assumptions that need to be taken into account when interpreting the data. The select population required for the study such as exclusion of pseudophakic patients, and those that could not be washed off meds safely, limits the generalizability of the results to such subjects, who form a large part of any glaucoma practice.

Currently, the only way to assess uveoscleral outflow non-invasively is by mathematical calculation. The result shows a fair amount of variability depending upon the EVP value

used in the calculation.[55] However, change in uveoscleral outflow is more robust to errors in EVP estimation.[56] Therefore, we have reported the changes in uveoscleral outflow in this study, which is more meaningful than absolute values. A statistically significant decrease in uveoscleral outflow was noted after SLT by the fluorophotometric method but was not replicable with tonographic method. Therefore, the strength of evidence to support any changes in uveoscleral outflow is weak. We speculate that any small decrease in uveoscleral outflow after SLT, may merely reflect more aqueous flowing through the trabecular than uveoscleral pathway. Proparacaine drops were administered to measure the IOP and EVP in the same 7-hour period when the fluorophotometry scans were obtained. These measurements can potentially dislodge additional fluorescein and thereby result in an underestimation of the aqueous flow rate. With the assumption that any systematic error will affect the two measurement time points equally and thereby have negligible effect on the calculated change in flow, we proceeded to obtain all IOP and EVP measurements on the same day, to allow for chronologic proximity of all variables entered in the Goldmann equation.

In summary, this comprehensive study of changes in AHD three months after SLT found the IOP lowering effects of SLT to be mediated through an increase in outflow facility. No meaningful effects on any of the other parameters of AHD or the contralateral eye were detected. A higher baseline aqueous flow and a lower baseline outflow facility were found to be predictive of IOP response to SLT. Future advances in techniques for the assessment of AHD may make these parameters useful for patient selection for trabeculoplasty.

Chapter Two: Differences in Ocular Biometrics and Aqueous Humor Dynamics Between Chinese and Caucasian Adults

In this paper, through collaborative work with investigators at Tenth People's Hospital of Tongji University, Shanghai Hospital aqueous humor dynamics were compared between healthy young and older adult Chinese and Caucasian volunteers.[57] The motivation behind the research was to explore if there are systematic race-based differences in biometrics and AHD between 2 populations known to have different profile for the glaucoma sub type distribution. By enrolling 2 different age groups for each race group the study also explores potential differences in age related changes in the 2 racial groups.

Abstract

Background: Glaucoma prevalence and subtype profile varies across different racial and ethnic groups. This study provides a comparative evaluation of differences in aqueous humor dynamics (AHD) and ocular biometrics in healthy Chinese and Caucasian adults of 2 different age groups.

Method: Data from two independent studies with identical designs were compared. Cohorts included young adults (20 to 30 years old, 32 Chinese and 39 Caucasians) and older adults (>50 years old, 37 Chinese and 46 Caucasians). Parameters of aqueous humor dynamics and ocular biometrics were evaluated. Group comparisons were made by generalized estimating equation methods.

Results: Differences in young adult Caucasians compared to similarly-aged Chinese were thinner central cornea (-29.27µm, p<0.001); lower intraocular pressure (IOP) (-2.33 mmHg, p<0.001); larger anterior chamber volume (ACV) (28.78 µL, p<0.001) and faster uveoscleral outflow rate (Fu) (0.82 µl/min, p<0.001). Differences in older adult Caucasians compared to similarly-aged Chinese were slower aqueous flow rate (Fa) (-0.28 µl/min, p=0.042); lower IOP (-1.97 mmHg, p<0.001); and larger ACV (33.15 µL, p<0.001). Considering all subjects together by race, Caucasian subjects had slower Fa (-0.22 µl/min, p=0.035); thinner corneas (-0.52 µm, p=0.003); lower IOP (-2.11 mmHg, p<0.001); higher ACV (30.39 µl, p<0.001); and faster Fu (0.63 ul/min, p<0.001).

Conclusion: Differences in AHD and biometrics between Caucasian and Chinese adults include larger anterior chamber volumes that may contribute to the wider angles

reported in Caucasians; and slower aqueous flow rates coupled with faster uveoscleral

outflow rates that may contribute to their lower IOP and lower overall risk of glaucoma.

Introduction

Race and ethnicity are significant determinants of the prevalence of different subtypes of glaucoma in populations across the globe. Numerous studies have provided evidence that primary open-angle glaucoma (POAG) is more common in people of European or African descent while primary angle-closure glaucoma (PACG) is more prevalent in Asians.[28-30,58,59] Differences in ocular biometrics may underlie the differences in glaucoma subtype profile between Caucasian and Asian adults. These differences in ocular biometrics may translate into clinically relevant differences in variables of aqueous humor dynamics (AHD). For example, ocular biometrics such as central cornea thickness (CCT) may affect response to IOP lowering medications;[60] and changes in parameters of aqueous humor dynamics are associated with response to IOP lowering treatments including drugs and procedures like laser trabeculoplasty.[37] A study of differences in biometric and AHD parameters in people across different ethnic backgrounds can provide insights into the pathophysiology of glaucoma subtypes. It also can help elucidate the mechanisms of variance in treatment response as it may relate to these biometric and AHD differences. As IOP lowering, usually accomplished by altering one or more parameters of AHD, remains the only available treatment for glaucoma, exploring such differences across various racial and ethnic backgrounds is of clinical value. This report is a comprehensive comparative evaluation of biometric and AHD parameters between Caucasian and Chinese adults.

Methods

The data in this study were compiled from two separate studies of the same design. The studies were performed at the University of Nebraska Medical Center, Omaha, NE, USA and Tenth People's Hospital, Tongji University, Shanghai, China. During planning meetings among the investigators, detailed study schedules were prepared and standard operating procedures (SOPs) were written. Both centers followed the same SOPs and schedules. To the extent possible, most of the equipment used in the two institutions were of the same makes and models. Two groups of healthy volunteers were enrolled at each site. The 'young' group included subjects 20 to 30 years of age, and the 'older' group included subjects 50 years of age or older.

Subject demographics are summarized in **Table 4**. Those with a history or evidence of ocular hypertension, glaucoma, uveitis, ocular trauma, intraocular or refractive surgery, or ocular infection within the past 3 months were excluded from the study. Exclusion criteria also included use of medications that affect aqueous humor production such as β-adrenergic antagonists and/or carbonic anhydrase inhibitors, history of hypersensitivity to fluorescein, abnormalities preventing reliable IOP or fluorophotometric readings; such as severe dry eye, and serious cardiovascular or respiratory diseases. The young groups included 32 Chinese and 39 Caucasian adults, and the older groups included 37 Chinese and 46 Caucasian adults. Eligible subjects underwent a comprehensive ocular examination including gonioscopy and fundus examination. Study approval was obtained from the research ethics committees at the University of Nebraska Medical Center and the Tenth People's Hospital of Tongji

University. Written informed consent was obtained from each volunteer before the

start of any study-related activity.

Table 4: Baseline Demographic Characteristics of Chinese and Caucasian study subjects

	Chinese		Caucasian	
Demographics	Young	Old	Young	Old
Mean age (years ± SD)	22.8±1.4	60.2±7.3	25.8±2.1	66.8±5.2
Age range (years)	20 – 28	50 – 78	21– 30	50 – 79
Male	13	8	16	15
Female	19	29	23	31
Total subjects enrolled	32	37	39	46
Number of subjects taking systemic medications	0	8*	4*	9*

* 21 Subjects were taking non-ophthalmic systemic medications such as birth control pills; calcium channel blockers and angiotensin-II receptor antagonists for systemic hypertension, proton pump inhibitors, sulfonylurea for type II diabetes mellitus and warfarin for anti-coagulation.

Measurements

Volunteers self-administered 8 to 10 drops of 2% fluorescein sodium ophthalmic

solution topically into both eyes at 5-minute intervals starting at six to nine hours before

the first fluorophotometric measurement. The number of drops and time of

administration depended on the subject's age.[61] Study related measurements

commenced at approximately 8AM the following morning. CCT was measured by

ultrasound pachymetry (A-Scan ultrasonography (Pacscan Series 300, Sonomed, Lake

Success, NY at UNMC and SP-3000, Tomy, Japan at Tenth People's Hospital). Anterior

chamber depth (ACd) was measured by Pacscan (Series 300; Sonomed, Lake Success,

NY) at UNMC and by IOL Master 500 (Carl Zeiss Meditec Inc., Dublin, CA) at Tenth People's Hospital. ACd and CCT were used to calculate the anterior chamber volume (ACV) and cornea volume (Kv).[62] Both volumes were used in the calculation of aqueous flow.[63] At both sites, IOP was measured with a pneumatonometer (Classic Model 30, Reichert, Depew, NY) and episcleral venous pressure (EVP) was measured with a venomanometer (Eyetech, Morton Grove, IL).[49] The reported values are the average of two or three measurements per eye.

Four sets of duplicate fluorophotometric scans of the cornea and anterior chamber at intervals of 45 minutes were collected using a scanning ocular fluorophotometer (Fluorotron Master; OcuMetrics, Mountain View, CA, USA) at both sites. The slope calculated from four averaged values was used to obtain a baseline flow rate of aqueous humor. IOPs were measured immediately after the first and fourth sets of fluorophotometer scans. Next, topical timolol 0.5% was applied to both eyes or oral acetazolamide (500 mg) was given to the subjects. These drugs are known to decrease the IOP by decreasing aqueous production.[62,64,65] One hour after the administration of the aqueous humor suppressants, three additional sets of fluorescein scans and IOP measurements were obtained at 45 min intervals to allow calculation of fluorophotometric outflow facility (C) as the quotient of change in aqueous flow divided by change in IOP.[66,67] Uveoscleral outflow (Fu) was calculated[42,66] from the modified Goldmann equation.

Sample size and Power

Computed were the minimum detectable differences between Caucasian and Chinese subjects for different major outcomes stratified by age groups. Intraclass correlation coefficient (ICC) was used to account for the clustering effect between the two eyes from the same individual. From the data were obtained ICC values of 0.65 for the young group and 0.28 for the old group, and standard deviations for different major outcomes. Based on the adjusted two-sample t test, the sample size of 32 for each young group (64 total) achieves 80% power to detect a minimum IOP difference of 0.97 mmHg between Caucasian and Chinese subjects with a significance level of 0.05. The sample size (39 Caucasian and 32 Chinese) provided more than 80% power to detect such a difference. The minimum detectable differences in other variables at an alpha of 0.05 and a power of 80% are presented in **Table 5**.

Table 5: The minimum detectable difference for different major outcomes for the young and older groups at an alpha of 0.05 with 80% power.

Outcomes	Young (N=32)		Older adults (N=36)	
	Standard Deviation	Minimum Detectable Difference	Standard Deviation	Minimum Detectable Difference
Intraocular pressure (IOP mmHg)	1.500	0.969	2.100	1.125
Aqueous flow (Fa µl/min)	0.700	0.452	0.800	0.429
Uveoscleral outflow (Fu µl/min)	1.000	0.646	1.000	0.536
Fluorophotometric C (C µl/min/mmHg)	0.300	0.194	0.300	0.161
Episcleral venous pressure (EVP mmHg)	1.100	0.711	1.200	0.643
Central corneal thickness (CCT µm)	27.100	17.513	36.100	19.337

Statistical Analyses

For all major outcomes and covariates, descriptive statistics such as mean, standard

deviation, frequency and percentage were calculated for Chinese and Caucasian adults

stratified by age groups (young and older adults, **Table 6**). For these tests, the

correlations between the two eyes were ignored. Generalized estimating equation (GEE)

methods with identity link for continuous data were used to incorporate the correlation

of two eyes from the same individual and to account for other potential confounders

(such as sex). To test for heterogeneous effects of race in difference age groups, an

interaction between race and age group was added into the model. P values less than

0.05 were considered statistically significant. All analyses were conducted using SAS

(version 9.4).

Table 6: Descriptive statistics for biometric and aqueous humor dynamics variables in different age and race groups

		Young Adults				Older Adults				All Subjects		
		Caucasian		Chinese		Caucasian		Chinese		Caucasian		Chinese
Variable	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
IOP	78	14.06±2.46	64	16.40±1.53	92	14.48±2.68	73	16.49±2.10	170	14.29±2.58	137	16.45±1.85
Fa	78	2.89±0.84	63	3.03±0.74	92	2.42±0.70	73	2.68±0.78	170	2.63±0.80	136	2.85±0.78
Fu	76	1.51±0.92	55	0.98±1.13	91	1.03±0.91	62	0.74±0.99	167	1.25±0.94	117	0.85±1.06
C	76	0.25±0.13	55	0.31±0.13	91	0.29±0.18	62	0.32±0.25	167	0.27±0.16	117	0.33±0.29
EVP	78	8.66±1.75	63	8.51±1.14	92	8.90±1.82	73	8.63±1.16	170	8.79±1.78	136	8.57±1.15
ACV	78	244.8±41.7	64	215.9±31.0	92	161.2±39.3	73	129.2±33.5	170	196.6±58.0	137	169.7±54.0
CCT	78	520.4±35.8	64	549.7±27.0	92	532.1±29.6	73	530.9±36.0	170	526.8±33.3	137	539.7±33.4

ACV, anterior chamber volume; C, outflow facility; CCT, central corneal thickness; Fa, aqueous flow; Fu, uveoscleral outflow; IOP, intraocular pressure; EVP, episcleral venous pressure; Data are represented as mean ± SD.

Results

When comparing young Caucasian with Chinese adults, IOP was lower (adjusted effect=-2.33 mmHg, p<0.001), Fu was higher (adjusted effect=0.82 µl/min, p<0.001), CCT was thinner (adjusted effect=-29.27µm, p<0.001) and ACV was larger (adjusted effect=28.78 µl, p<0.001) in Caucasian subjects. No difference was found in EVP (adjusted effect=0.17 mmHg, p=0.582), Fa (adjusted effect= -0.14 µl/min, p=0.367) and C (adjusted effect=-0.09µl/min/mmHg, p=0.057).

When comparing older Caucasian with Chinese adults, IOP was lower (adjusted effect=-1.97 mmHg, p<0.001), Fa was higher (adjusted effect=-0.28 µl/min, p=0.042), Fu was higher (adjusted effect=0. 60 µl/min, p=0.004) and ACV was higher (adjusted effect=33.15, p<0.001) in Caucasian subjects. No difference was found in EVP (adjusted effect=0.25 mmHg, p=0.4), C (adjusted effect=-0.03 µl/min/mmHg, p=0.4) and CCT (adjusted effect=1.26 µm, p=0.96).

When combining all data within racial groups and comparing Caucasians with Chinese, IOP was lower (adjusted effect=-2.11 mmHg, p<0.001), Fa was lower (adjusted effect=-0.22 µl/min, p=0.035); Fu was higher (adjusted effect=0.63 µl/min, p<0.001), CCT was thinner (adjusted effect=-30.5 µm, p=0.003) and ACV was higher (adjusted effect=30.4 µl, p<0.001). A lower outflow facility in the Caucasian group (adjusted effect=-0.06 µl/min/mmHg, p=0.05) approached statistical significance. No difference was found in EVP (adjusted effect=0.21 mmHg, p=0.304) between the 2 racial groups. These results are summarized in **Table 7**.

Table 7: The effect of race on different continuous outcomes based on GEE, controlled for gender. Values are presented as mean expected difference for Caucasian minus Chinese.

Outcomes	Young		Old		Overall	
	Adjusted Effect (95% CI)	Adjusted p-value*	Adjusted Effect (95% CI)	Adjusted p-value*	Adjusted Effect (95% CI)	Adjusted p-value*
IOP	-2.33 (-3.19, -1.48)	<0.001	-1.97 (-2.97, -0.96)	<0.001	-2.11 (-2.78, -1.44)	<0.001
Fa	-0.14 (-0.46, 0.17)	0.367	-0.28 (-0.54, -0.01)	0.042	-0.22 (-0.43, -0.02)	0.035
Fu	0.82 (0.45, 1.19)	<0.001	0.60 (0.20, 1.0)	0.004	0.63 (0.37, 0.90)	<0.001
C	-0.09 (-0.19, 0.0003)	0.057	-0.03 (-0.10, 0.04)	0.398	-0.06 (-0.12, 0.0004)	0.050
EVP	0.17 (-0.42, 0.76)	0.582	0.25 (-0.33, 0.83)	0.399	0.21 (-0.20, 0.62)	0.304
ACV	28.78 (13.40, 44.16)	<0.001	33.15 (18.01, 48.30)	<0.001	30.39 (18.89, 41.29)	<0.001
CCT	-29.27 (-43.29, -15.25)	<0.001	1.26 (-12.97, 15.50)	0.962	-30.52 (-50.50, -10.55)	0.003

*p-values represent the adjusted p value comparing Race and controlling for sex.
ACV, anterior chamber volume, µL; C, outflow facility, µL/min/mm Hg; CCT, central corneal thickness, µm; Fa, aqueous flow, µL/min; Fu, uveoscleral outflow, µL/min; IOP, intraocular pressure, mm Hg; EVP, episcleral venous pressure, mm Hg.

Discussion

This study describes numerous differences in aqueous humor dynamics and ocular biometrics between Chinese and Caucasian adults; differences that demonstrate additional change with aging. Independent of age, the main findings were that anterior chamber volume was larger and uveoscleral outflow was higher in Caucasian adults which may explain, at least in part, the lower IOP in Caucasian compared to Chinese adults.

A finding of interest in the current study is the apparent association between the volume of the anterior chamber and the drainage through the uvea. A putative point of egress of aqueous humor from the anterior chamber is at the ciliary body face which is devoid of any epithelial barrier. A wider ciliary body band may be associated with larger anterior chamber and may represent a larger area with access to aqueous humor. On a univariate analysis with the GEE model, anterior chamber volume was significantly associated with uveoscleral outflow (p=0.0004), implying that a faster uveoscleral outflow rate is indeed associated with a deeper anterior chamber. A narrowing of the anterior chamber angle may decrease the drainage through the uvea causing an IOP rise, thus providing a potential explanation for the higher prevalence of glaucoma in Asian populations.

One notable difference in the speculated effects of aging on AHD parameters between Chinese and Caucasians was the age-related slowing of aqueous humor flow. It was slower in older Caucasians compared to older Chinese, a difference that was not found

among the young groups. This may imply a greater age-related decline in aqueous

humor production in Caucasians as compared to Chinese subjects.

One noteworthy difference in the speculated effects of aging on ocular biometrics was

that CCT was thinner in young but not older Caucasians compared to Chinese. CCT is

genetically heritable and varies among racial groups.[68-73] The distribution of CCT in the

current study is similar to a multi-race population-based study, which showed that

Chinese adults had significantly thicker CCT compared with the other racial groups.[68] In

the current study, CCT increased with aging in Caucasians yet decreased with aging with

Chinese. This agrees with previous studies.[74] [69,75] Assuming there are no cohort effects

due to the convenience sample used in our study, our findings may corroborate

divergent effects of aging on CCT in Caucasian and Chinese subjects.

Differences in ocular biometric parameters may contribute to racial differences in

glaucoma risk, particularly for primary angle-closure glaucoma (PACG), which is found

with highest prevalence in Asians.[76] Anterior chamber depth is an inheritable trait which

is affected by age, sex and race.[77] Shallower anterior chambers and shorter axial lengths

are risk factors for PACG.[78,79] In the present study, Chinese adults have smaller ACV

compared with Caucasian adults possibly from a thinner ciliary body and a more

anteriorly positioned lens,[80] findings consistent with the differential risk for angle

closure among Asians and Caucasians.

The current study showed that outflow facility is not significantly different between

Caucasians and Chinese. When the racial groups were separated by age, both young and

older adult groups had a numerically smaller average C in Caucasians, but the differences were only marginally significant in young adults and not significant in older adults. No differences in outflow facility were found in a study comparing patients with glaucoma of Northern European and African descent.[81]

Trabecular outflow is driven by the outflow pressure (the difference between the IOP and EVP). The assessment and understanding of EVP are essential for a more complete picture of aqueous humor dynamics. The current study did not show significant differences in the EVP between Chinese and Caucasian adults but did find lower IOP in Caucasians. Hence, in Chinese, the outflow pressure and trabecular outflow rate are greater and the uveoscleral outflow pathway plays a lesser role in the drainage of aqueous humor compared to Caucasians.

Our study subjects were selected as a convenience sample from two very different health care systems. Despite meticulous attention to inclusion and exclusion criteria, the possibility of inherent systematic differences in the pool of subjects available for enrollment may exist. The potential for cohort effects being responsible for the differences seen in this study cannot be absolutely ruled out. Given the poor feasibility of random population-based sampling for the time and effort intensive data collection methods needed for AHD studies, such limitations are difficult to circumvent. Age-related changes in any parameter are perhaps best addressed using a longitudinal design. Even though feasible for some animal models, cross-sectional studies, such as this one, are the most feasible option when evaluating changes across the decades in

humans. Despite these limitations this study provides insights into race-based differences in AHD parameters and the effects of aging on the same.

A comparison of sex differences between the races found that differences were similar in males and females. However, significant differences were not reached in males because the study was neither designed nor powered to detect gender-based differences by race. These data may be misconstrued as lack of statistical significance rather than lack of power to detect sex differences. Therefore, the data are not reported. A future study with larger numbers and targeted enrollment of equal numbers of males and females can better address this issue.

Every effort was made to collect data at each research center with the same make and model of equipment. This was not possible for the measurement of anterior chamber depth. In Caucasians this parameter was measured with A-scan while in Chinese it was measured with an IOL Master. One published study[82] has reported that the measured AC depth from the two instruments are highly correlated. Other studies[83-85] found that the A-scan gives lower measurements than the IOL Master. The difference in anterior chamber depth between Chinese and Caucasians in the current study may be greater than reported here with greater statistical significance. Our conclusions regarding racial differences in AC depth remain valid.

In summary, differences exist in anterior chamber volume, IOP, aqueous flow and uveoscleral outflow between Caucasian and Chinese subjects. This study also provides limited initial evidence on possible differential effects of aging on CCT and aqueous flow in Caucasian and Chinese subjects. These results, with further validation and support,

may help explain differences in pathophysiology and prevalence of glaucoma in people

of different racial backgrounds. These parameters also may have future application as

target biomarkers for glaucoma diagnostics and therapeutics.

Chapter Three: Predictors of Intraocular Pressure Lowering after Phacoemulsification and iStent® Implantation

Traditional glaucoma surgery such as trabeculectomy and glaucoma drainage devices are associated with high rates of surgical complications.[86] There has been extensive interest of late in trabecular bypass implants such as iStent and Hydrus implants, as a potential lower risk option for IOP lowering. However, the IOP lowering success rate for these devices has been somewhat underwhelming. This paper evaluates the clinical and demographic factors associated with surgical success of iStent, the first trabecular bypass stent approved by the FDA, to be used in conjunction with cataract surgery. The study also explores factors associated with IOP lowering success of cataract surgery alone, where the addition of iStent to the procedure may not add much to the surgical success.

Abstract

Objective: To explore the demographic and clinical variables associated with intraocular pressure lowering after cataract extraction alone (CE) or in combination with iStent placement (CE-IS).

Design: Retrospective data extraction and survival analysis of consecutive patients identified over a 2-year period.

Subjects: Patients with mild to moderate glaucoma who underwent CE (48 eyes from 32 patients) or CE-IS (61 eyes from 37 patients) were analyzed.

Methods: Inability to reduce the number of medications or the IOP by at least 20% compared to baseline on 2 consecutive visits was considered surgical failure. Using Cox proportional hazards models, survival analysis was performed, and demographic and clinical variables were evaluated as risk factors.

Main Outcome Measures: Time to failure after surgical procedure.

Results: CE-IS had lower odds of failure than CE (HR=2.01, p=0.047). In Caucasian subjects, CE-IS had greater odds of success as compared to CE alone (HR=2.86, p=0.007). For non-Caucasian subjects there was no difference in the outcomes for the 2 procedures (HR 0.59, p=0.48). In the multivariate analysis, non-Caucasian race (HR=8.75, p=0.0002) and longer axial length (HR=1.61, p=0.03) were associated with greater hazard of failure after CE-IS. In the CE group, greater odds of failure were associated with steeper corneal curvature (HR=1.74, p=0.008), shallower anterior chamber (HR=0.22, p=0.008), and longer axial length (HR=1.58, p=0.01).

Conclusions: Addition of iStent to CE improved the survival of IOP lowering success in

Caucasians but not in non-Caucasians. Associations between IOP lowering after CE and

biometric parameters may allow for leveraging these clinical parameters for better case

selection for these procedures.

Introduction

Intraocular pressure (IOP) remains the strongest risk factor for development and progression of glaucomatous visual field loss. The management of glaucoma relies heavily on sustained reduction of IOP.[87] Topical ocular hypotensive medications or laser trabeculoplasty are typically considered first-line therapies for IOP lowering. In patients with inadequately controlled IOP, trabeculectomy or ab externo valve placement is considered. However, these procedures are associated with a high incidence of short and long-term complications, including infection, hypotony, scarring, and need for further surgeries.[86] Trabecular bypass and scaffolding implants that are typically placed at the time of cataract surgery constitute some of the minimally invasive glaucoma surgeries (MIGS), intended to avoid the complications associated with traditional aqueous shunting procedures. In 2012, the iStent implant (Glaukos Corporation, CA, USA) became the first FDA-approved ab interno device to be used for IOP lowering in combination with cataract extraction. Compared to cataract extraction alone, the addition of iStent improved IOP lowering or reduced the number of glaucoma medications in mild to moderate glaucoma patients.[34]

Since the introduction of the iStent, several studies have described its limitations, such as the surgical complexity of implantation, its need to be combined with cataract surgery, and its inability to lower IOP as well as ab externo procedures.[34,88-90] As a result, the lower rate of surgical complications is offset by lower efficacy in IOP lowering with MIGS procedures. To be able to identify the patient characteristics most likely to have an IOP lowering benefit from cataract extraction either with or without MIGS will have

significant value in guiding patient selection for these procedures. Even though the risk factors for failure such as race and prior procedures are relatively well known for conventional glaucoma procedures, these have not been well characterized for MIGS procedures. Additionally, ab interno trabecular bypass glaucoma procedures, in theory, should be able to minimize the perils of conjunctival scarring seen in conventional glaucoma surgeries.

This study investigates the success in IOP lowering and medication reduction with cataract extraction with or without iStent implantation in mild to moderate glaucoma patients in an academic practice. With an exploratory analysis, clinical covariates were identified that were predictive of IOP lowering success with either of the 2 procedures evaluated.

Methods

This retrospective cohort study was approved by the University of Nebraska Medical Center Institutional Review Board. Subjects with a diagnosis of ocular hypertension or mild to moderate glaucoma who underwent cataract surgery with iStent implantation (CE-IS) or cataract surgery alone (CE) from 2015-2017 at the University of Nebraska Medical Center were included in this study. In patients with surgery performed on both eyes, each eye was included in the study.

All available IOP data from up to one year prior to the surgical procedure to the last available follow up visit were extracted from patient records. If more than one IOP was recorded on a given day, the one recorded by the attending or resident physician was

included for analysis. All IOPs were recorded using either Goldmann applanation

tonometry or pneumatonometry, though the method varied for the same patient from

visit to visit. Number of topical IOP lowering medications being used at each of these

visits was also recorded. Combination glaucoma medications were recorded as two

medications. Oral acetazolamide or methazolamide use was also counted in the study as

a single glaucoma medication. Demographic data including age, sex, and race/ethnicity

were recorded. Known history of prior laser trabeculoplasty and biometric data

including keratometry, anterior chamber depth, and axial length were collected as well.

Systemic comorbidities of hypertension, hyperlipidemia, and diabetes were recorded

from the patient problem list available in the electronic medical records. Operative and

clinic notes were reviewed to confirm the procedure performed (cataract surgery alone

or combined with iStent).

The average of all available IOPs up to one year prior to the surgical procedure was

considered the baseline IOP for that individual, and the median number of medications

in that period was used as the baseline number of medications. Eyes were evaluated for

failure on all visits after the first 30 days post operatively. This was done to allow for

resolution of any transient post-operative hyphema and effects of post-operative

steroids, as these would be considered the normal post-operative course for these

procedures. At each clinic visit after 30 days, IOP change was calculated as percentage

change from baseline and medication change was noted as numerical change from

baseline number of medications. Surgical failure was defined as inability to lower the

number of medications from baseline or reduce the IOP by at least 20% compared to

baseline on two consecutive visits. If the failure criteria were met on the last available

visit with no subsequent visit for confirmation, the eye was categorized as a surgical

failure. When the failure criteria were met on two consecutive visits, time to failure was

recorded as that of the first of these visits. Subjects who had less than 30 days of post-

operative follow-up (minimum required period to be at risk for failure) were excluded

from the analysis.

Primary data analysis was done using survival analysis methods with time to failure

being the primary outcome variable. Primary comparator groups were based on the

surgical procedure performed, namely cataract surgery with or without iStent. Effect of

covariates on surgical success was analyzed separately for each group. SAS version 9.4

(Cary, NC) was used for all data analysis. A p value less than 0.05 was considered

statistically significant. Descriptive analysis was performed on all variables. Summary

measures including mean, standard deviation, and quartiles were obtained for all

continuous variables. Frequency distributions were obtained for all categorical variables.

In this report, IOP and medication use data over time are presented as spaghetti plots of

individual subjects with a mean overlay plot using a fitted smoothed line using a spline

routine. Univariate effects of variables on time to failure was studied using Kaplan Meier

curves and log rank test and hazard ratios estimated using Cox proportional hazards

(PH) model. Quartiles of continuous variables and categories of categorical variables

were used for generating the Kaplan Meier curves. Quartile conversion of continuous

variables was not required for the Cox PH model. Variables with p value less than 0.05

on univariate analysis and those considered to be clinically relevant confounders on

secondary analysis were entered in the multivariate analysis. To account for the effect of inclusion of both eyes of some of the subjects in the analysis, robust sandwich estimate of Lin and Wei was used for the covariance matrix (using COVS(AGGREGATE) option in PHREG procedure in SAS).[91]

Results

A total of 64 eyes (39 subjects) undergoing CE-IS were initially identified for inclusion in the study. Three eyes (2 subjects) were excluded because of inadequate follow up (less than 30 days after surgery). In the CE group 65 eyes (44 subjects) were initially identified for inclusion in the study. Upon a further detailed review of the chart, 17 eyes of 12 subjects were excluded for the reasons as follows. In 3 eyes (3 subjects) iStent implantation was attempted after CE but was unsuccessful. In 4 eyes (3 subjects), there was history of past laser iridotomy with persistent angle closure, one due to peripheral anterior synechiae and 3 due to plateau iris configuration. Another 4 eyes (3 subjects) had a history of prior laser iridotomy with gonioscopy not available in the documentation. Of these 3 subjects, one (2 excluded eyes) was also using systemic prednisolone and another (one excluded eye) had proliferative diabetic retinopathy documented in the chart. Two subjects (4 eyes) were excluded as they had newly diagnosed narrow angles with iridotomy deferred due to planned cataract surgery. Two eyes (one subject) with a history of anterior uveitis and peripheral anterior synechiae on gonioscopy were also excluded from analysis. For the analysis presented in this report, 61 eyes from 37 patients were included in the CE-IS group, and 48 eyes from 32 patients were included in the CE group. Among the analyzed subjects, systemic comorbidities

data and biometry data was not available for one subject each in CE-IS group. Anterior

chamber depth data was not available for 2 additional subjects in the CE group.

A comparison of the baseline demographic and clinical characteristics of the 2 study

groups is presented in **Table 8**. There was no significant difference in age, sex, race or

ethnicity, preoperative IOP, or number of medications between the 2 study groups. A

higher proportion of CE-IS eyes had a history of prior laser trabeculoplasty.

Table 8: Baseline demographic and clinical characteristics of the study population

	CE-IS 61 eyes (37 patients)	**CE** 48 eyes (32 patients)	***p value**
Age (years)	71.0 ± 8.1	74.2 ± 7.2	0.09
Male sex % (n)	29.7% (11)	43.8% (14)	0.32
Caucasian race % (n)	86.5% (32)	71.9% (23)	0.15
Pre-operative IOP (mm Hg)	17.26 ± 3.1	17.64 ± 2.3	0.48
Pre-operative # of medications	1.5 ± 1.1	1.2 ± 1.1	0.22
Prior laser trabeculoplasty % (n)	31.1% (19)	8.3% (4)	**0.004**
Diabetes % (n)	19.4% (7)	18.8% (6)	0.99
Hypertension % (n)	55.5% (20)	75.0% (24)	0.13
Hyperlipidemia % (n)	38.9% (14)	43.8% (14)	0.81

* p value obtained using Student's t-test for continuous variables and Fisher's exact test for categorical variables. Data on systemic comorbidities was not available for one subject in the CE-IS group.

Figure 4 shows the IOP and medication trend over time for all individual subjects and

the overall trend for the same in the 2 study groups over time. Overall, there was a 2-3

mmHg reduction in IOP over the first year as compared to the IOP in the year preceding

the surgery. There was approximately 1 less medication used in the first year after the

procedure in both study groups.

Figure 4: Trends in intraocular pressure and number of medications over time in the CE-IS and CE groups. The plots show individual cases (light blue) with the trendline (dark blue) for overall trend generated using a smoothed curve with spline routine
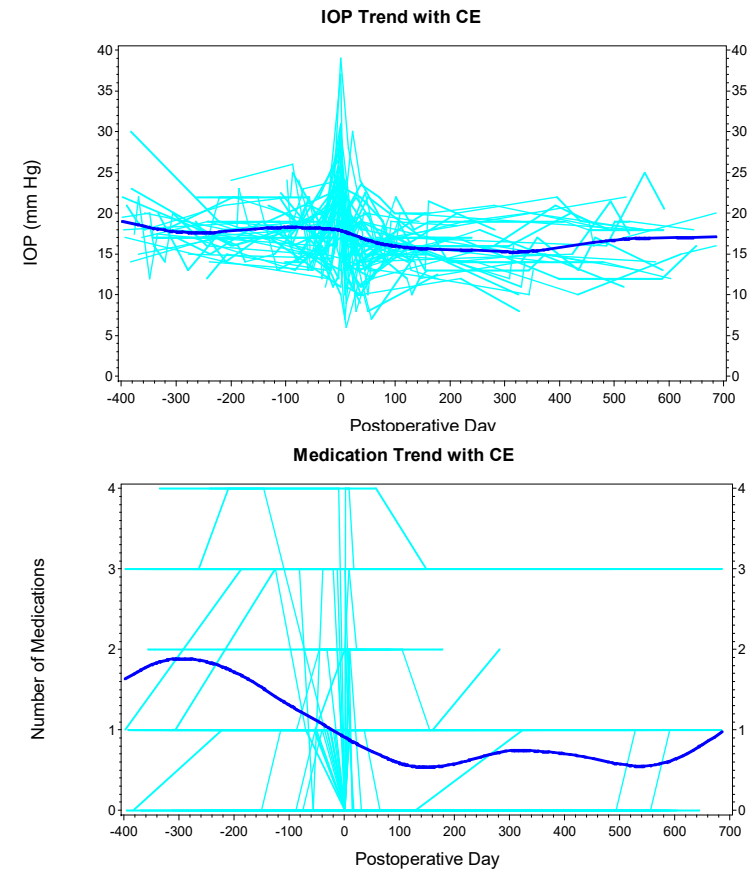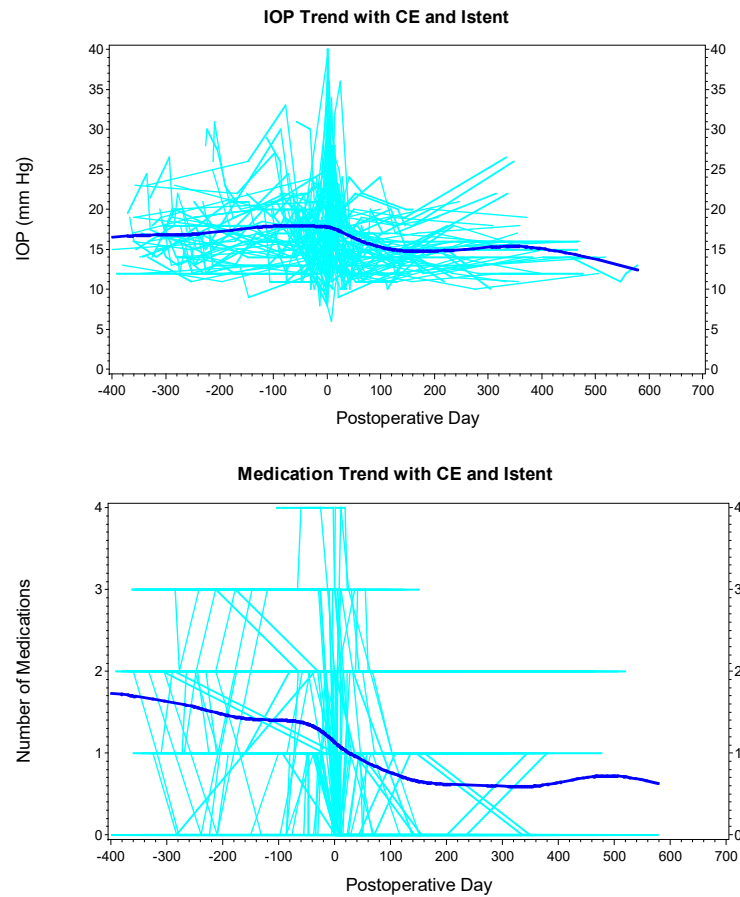
Kaplan Meier survival curves for the CE and CE-IS groups are shown in **Figure 5**. Patients

undergoing CE-IS had lower odds of failure as compared to patients in the CE group (HR

2.01, p=0.047).

Figure 5: Kaplan-Meier survival curves with 95% confidence interval comparing surgical
success among all patients between cataract surgery with iStent and cataract surgery
without iStent. Univariate Cox proportional hazard model based hazard ratio was 2.01
(CI 1.01-4.01, p=0.047).
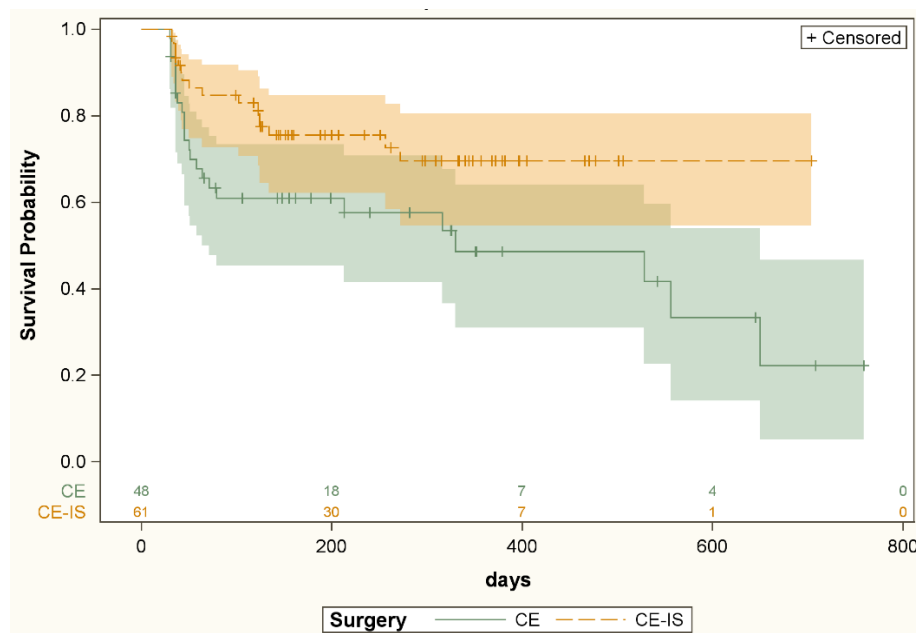
CE=cataract extraction; CE-IS = cataract extraction with Istent. Numbers above X axis indicates
number of eyes at risk at each time point.

Univariate Cox proportional hazards model analysis of risk factors for failure in the CE-IS

group is displayed in **Table 9**. A greater hazard of failure was associated with non-

Caucasian race (HR 3.65, p=0.01) and lower number of pre-operative medications (HR

0.58, p=0.03).

Table 9: Univariate and multivariate Cox proportional hazards model analysis of risk factors in patients undergoing cataract surgery with iStent

Variable (reference)	Univariate			Multivariate		
	Hazard Ratio	Confidence interval	p value	Hazard Ratio	Confidence interval	p value
Age (1 year)	0.99	0.92-1.07	0.88	1.04	0.98-1.10	0.22
Sex (female)	1.60	0.60-4.27	0.35			
Race (Caucasian)	3.65	1.29-10.33	**0.01**	8.75	2.80-27.31	**0.0002**
Pre-operative IOP (1 mmHg)	1.09	0.95-1.26	0.22	1.06	0.88-1.29	0.52
Pre-operative # of medications (1 medication)	0.58	0.36-0.95	**0.03**	0.63	0.33-1.21	0.16
Selective laser trabeculoplasty	0.40	0.13-1.21	0.10			
Corneal curvature (1 diopter)	0.86	0.68-1.09	0.22			
Axial length (1 mm)	1.29	0.93-1.78	0.13	1.61	1.05-2.47	**0.03**
Anterior chamber depth (1 mm)	1.53	0.52-4.53	0.45			
Hypertension	1.44	0.45-4.63	0.54			
Diabetes	1.77	0.60-5.27	0.30			
Hyperlipidemia	1.37	0.48-3.96	0.56			

A comparison of Kaplan-Meier curves demonstrating the surgical success of CE-IS

between Caucasian and non-Caucasian subjects is presented in **Figure 6**.

Figure 6: Kaplan-Meier survival curves with 95% confidence intervals comparing success of cataract surgery with iStent implantation between Caucasians and non-Caucasians. Univariate Cox proportional hazard model based hazard ratio was 3.65 (CI 1.29-10.33, p=0.01)
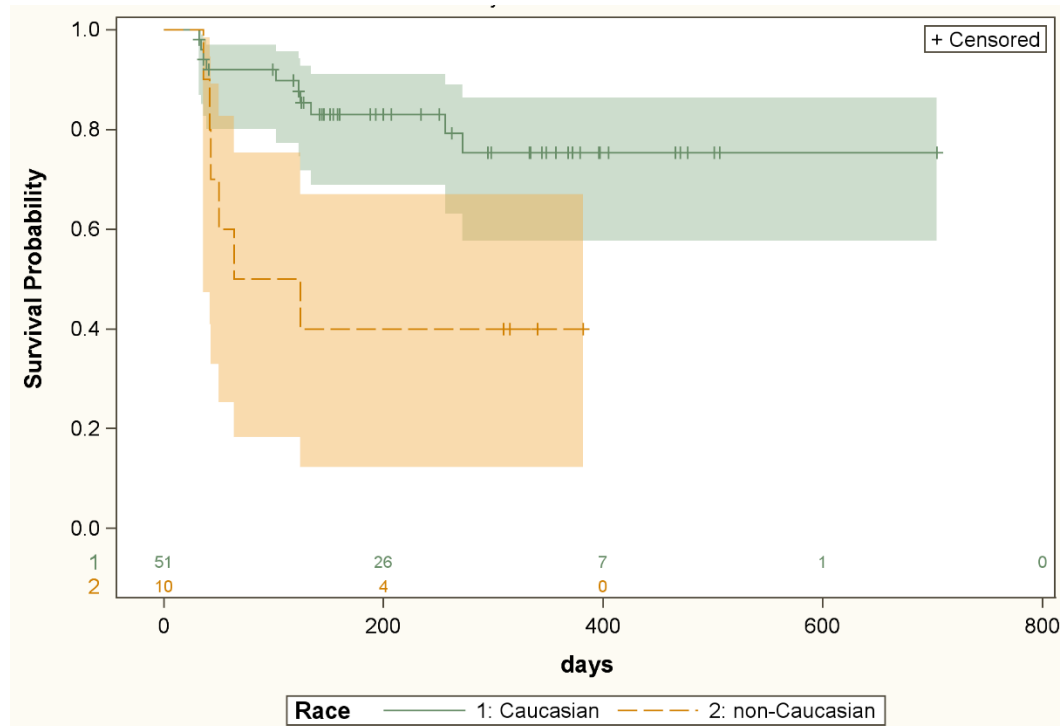
Numbers above X axis indicates number of eyes at risk at each time point.

To evaluate for systematic differences between the Caucasian and non-Caucasian population, baseline demographic and clinical variables were compared between the two groups (**Table 10**). Caucasians subjects had lower pre-operative IOP (16.9 ± 3.2 vs 19.0 ± 1.7, p=0.009). Nearing significance were older age (71.9 ± 7.4 vs 65.7 ± 11.2 years, p=0.07) and longer axial length (25.0 ± 1.6 vs 23.9 ± 1.4 mm, p=0.07) in the Caucasian subjects. No other variable was different between the 2 groups. Variables entered in the multivariate analysis were those that were statistically significant in the univariate analysis and others that needed to be controlled for because of possible different distributions in the 2 race-based groups.

Table 10: Comparison of demographic and biometric variables between Caucasian and non-Caucasian subjects in the CE-IS group.

	Caucasians 51 eyes (32 subjects)	Non-Caucasians 10 eyes (5 subjects)	p value*
Age (years)	71.9 ± 7.4	65.7 ± 11.2	0.07
Corneal curvature (D)	43.7 ± 1.8	43.9 ± 1.5	0.72
Axial length (mm)	25.0 ± 1.6	23.9 ± 1.6	0.07
Anterior chamber depth (mm)	3.23 ± 0.4	3.11 ± 0.6	0.72
Pre-operative # of medications	1.6 ± 1.2	1.2 ± 0.7	0.43
Pre-operative IOP (mm Hg)	16.9 ± 3.2	19.0 ± 1.7	**0.009**
* p values calculated using Mann-Whitney test			

In the multivariate analysis, non-Caucasian race was associated with increased odds of surgical failure compared with Caucasians (HR 8.75, p=0.0002). A greater axial length was also associated with higher risk of surgical failure (HR 1.61, p=0.03) after controlling for other variables in the model. Results of multivariate analysis in the CE-IS group are included in **Table 9**.

Univariate Cox proportional hazards model analysis of patients in the CE group (**Table 11**) found a greater hazard of failure associated with lower pre-operative IOP (HR 0.81, p=0.04), steeper corneal curvature (HR 1.42, p=0.03), shallower anterior chamber depth (HR 0.28, p=0.01), and presence of systemic hypertension (p=0.008). No failure events

were encountered in the non-hypertensive group. This precluded calculation of a hazard

ratio based on application of the proportional hazards model to this variable. Therefore,

log rank test was used to determine statistical significance of effect of hypertension on

the survival curves, and the variable was not used in the multivariate model.

Table 11: Univariate and multivariate Cox proportional hazards model analysis of risk
factors for failure in patients undergoing cataract surgery alone

Variable (reference)	Univariate model			Multivariate model		
	Hazard Ratio	Confidence interval	p value	Hazard Ratio	Confidence interval	p value
Age (1 year)	0.98	0.92-1.04	0.48			
Sex (female)	1.35	0.52-3.47	0.54			
Race (Caucasian)	0.91	0.22-3.67	0.89	0.50	0.13-1.91	0.31
Pre-operative IOP (1 mmHg)	0.81	0.65-1.00	**0.04**	0.87	0.74-1.02	0.09
Pre-operative # of medications (1 medication)	0.55	0.24-1.26	0.15			
Selective laser trabeculoplasty	0.81	0.30-2.16	0.68			
Keratometry (1 diopter)	1.42	1.03-1.95	**0.03**	1.74	1.15-2.62	**0.008**
Axial length (1 mm)	0.98	0.73-1.30	0.88	1.58	1.10-2.29	**0.01**
Anterior chamber depth (1 mm)	0.28	0.11-0.74	**0.01**	0.22	0.07-0.68	**0.008**
Hypertension*	-	-	**0.008**			
Diabetes	0.68	0.21-2.20	0.52			
Hyperlipidemia	1.32	0.55-3.15	0.53			

In the multivariate model (**Table 11**), greater hazard of failure was associated with a

longer axial length (HR=1.58, p=0.01), steeper corneal curvature (HR=1.74, p=0.008) and

shallower anterior chamber (HR=0.22, p=0.008). There was no difference in survival of

surgical success between Caucasian and non-Caucasian subjects in the CE group. A

Kaplan-Meier curve demonstrating comparable CE surgical success between Caucasians

and non-Caucasians is shown in **Figure 7**.

Figure 7: Kaplan-Meier survival curves with 95% confidence intervals comparing IOP lowering success of cataract surgery between Caucasians and non-Caucasians. Univariate Cox proportional hazard model based hazard ratio was 0.91 (CI 0.22-3.67, p=0.89).
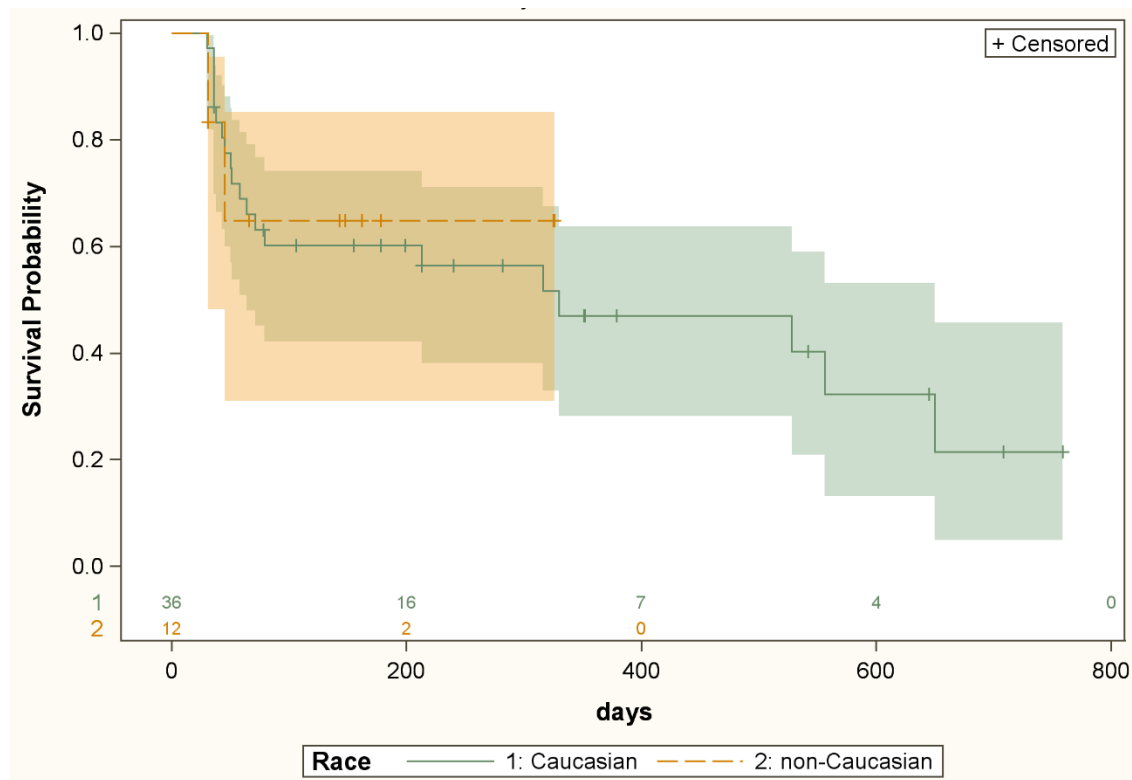
Numbers above X axis indicates number of eyes at risk at each time point.

Surgical success for the 2 procedures was compared separately in the 2 race groups.

Kaplan-Meier curves comparing surgical success of CE-IS and CE among Caucasians is

shown in **Figure 8**. Patients in the CE-IS group were more likely to maintain surgical

success compared to CE alone (HR 2.86, CI 1.33-6.14, p=0.007).

Figure 8: Kaplan-Meier survival curves with 95% confidence intervals comparing IOP lowering success of CE and CE-IS in Caucasian subjects only. Univariate Cox proportional hazard model based hazard ratio was 2.86 (CI 1.33-6.14, p=0.007).

CE=cataract extraction; CE-IS = cataract extraction with Istent
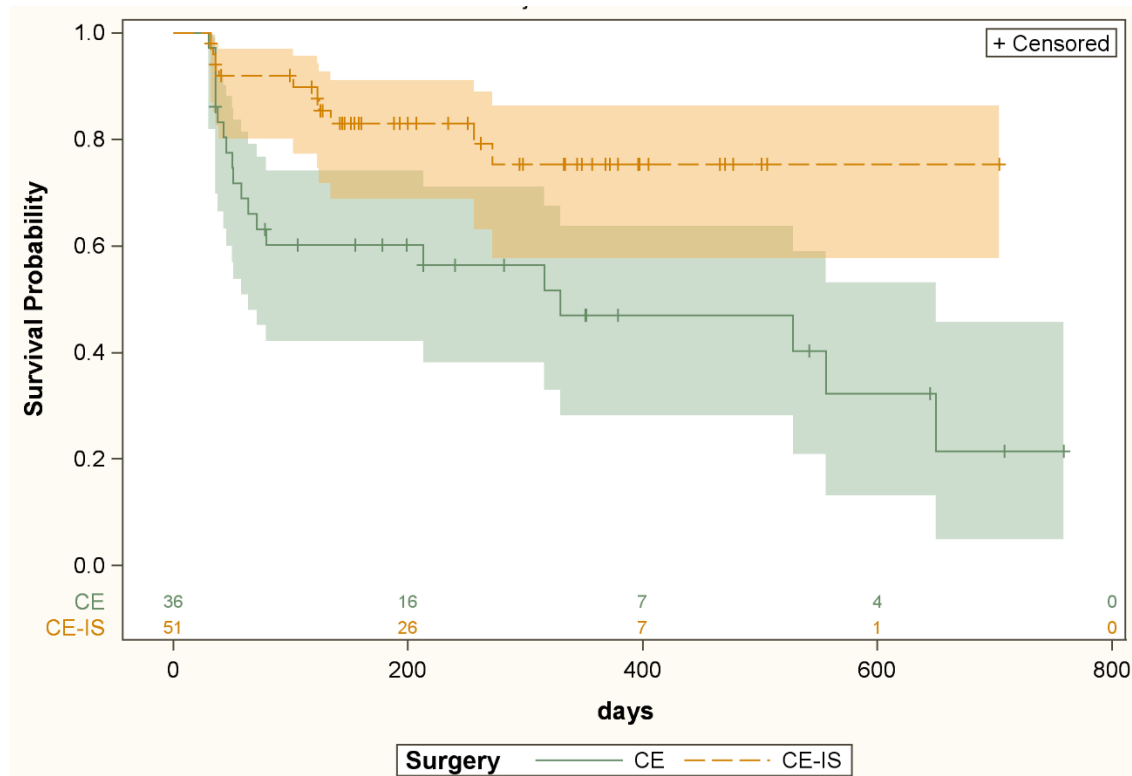Numbers above X axis indicates number of eyes at risk at each time point.

Surgical success for the 2 procedures among non-Caucasians is shown in **Figure 9**. There

was no difference between the survival curves for CE-IS and CE in this group (HR 0.59, CI

0.13-2.54, p=0.48).

Figure 9: Kaplan-Meier survival curves with 95% confidence intervals comparing IOP lowering success of CE and CE-IS in non-Caucasian subjects only. Univariate Cox proportional hazard model based hazard ratio was 0.59 (CI 0.13-2.54, p=0.48).
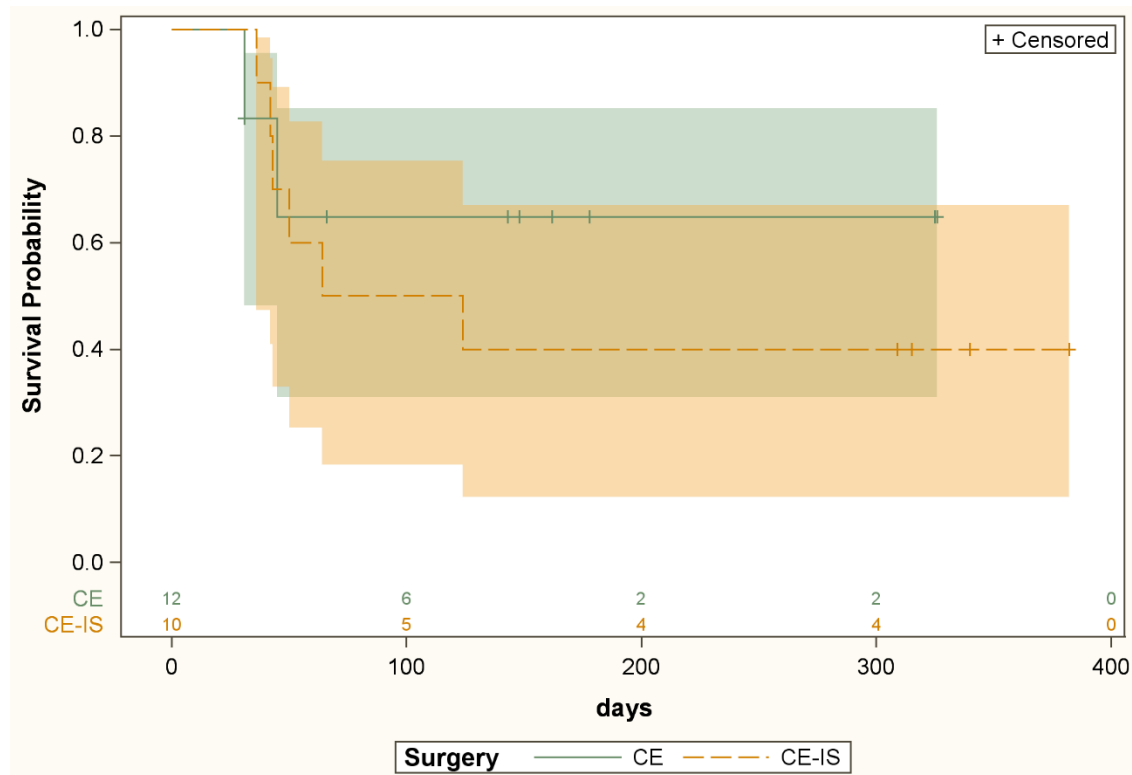
CE=cataract extraction; CE-IS = cataract extraction with Istent
Numbers above X axis indicates number of eyes at risk at each time point.

Discussion

Given our current understanding of pathophysiology of elevated IOP in glaucoma,

reducing the resistance in the trabecular outflow pathway should be a robust approach

to treatment. However, the real-world outcomes of this approach have not met the high

expectations based on the theory behind these procedures. A priori risk stratification of

patients undergoing cataract surgery with or without iStent can help enhance the

benefit to risk ratio and help with better case selection for either procedure. Our retrospective analysis presented here provides preliminary clues as to what demographic and clinical variables may be of value for such models in the future.

In this study, we demonstrated improved IOP lowering success in patients undergoing the combined CE-IS procedure compared to CE alone. However, we found that this advantage of iStent over cataract surgery alone was not seen in our small sample of non-Caucasian patients. The non-Caucasian group consisted of mostly Black subjects in both CE-IS and CE patients. The incremental benefit of adding an iStent to CE was much more apparent in the Caucasian group. This suggests that the reported IOP lowering outcomes of Schlemm's canal stenting and trabecular bypass procedures may be significantly affected by the racial composition of the study population, with predominantly Caucasian samples reporting higher success rates as compared to the ones primarily consisting of non-Caucasian subjects. The IOP lowering benefit of cataract surgery alone was equivalent in the 2 race-based groups in our study. To the best of our knowledge, an effect of race on outcomes after MIGS procedures has not been reported in the literature. In prior reports, patients were either not stratified by race or ethnicity, or all patients were noted to be Caucasian. In a prior report by Seibold et al, Caucasians tended to be more likely to achieve surgical success, however this difference did not reach statistical significance (HR 0.29, CI 0.06-1.29, p=0.10).[92] In comparison to that study, our study has a larger sample and longer follow up which may have helped reach statistical significance.

A higher failure rate of conventional filtration procedures in Blacks may be related to a greater number of fibroblasts and macrophages in the conjunctiva of Black patients.[31] Angle surgical procedures are mechanistically expected to avoid the familiar hazards of the subconjunctival space. The cause of failure of angle surgical procedures is not yet established. It is possible that post-operative downstream changes in the trabecular outflow may contribute to surgical failure despite successfully eliminating the resistance at the inner wall of Schlemm's canal. The likely mediators for such a mechanism can be humoral in nature, such as inflammatory markers in the aqueous humor. We are not aware of any known racial differences in the composition of aqueous humor. A prior study evaluating transforming growth factor beta 2 did not find any significant differences in its aqueous concentration between Caucasian and Black subjects.[93]

Systemic hypertension is more common and more severe in Black patients compared to the general population. Several mediators have been proposed for a greater vulnerability of Blacks patients to hypertension.[94] A greater propensity for vasoreactivity and vascular sclerosis, akin to vulnerability to systemic hypertension in Black patients, can potentially affect the distal outflow pathways. However, contrary to this speculation on a possible mechanism, our study did not find hypertension to be a risk factor for failure. A prior study by Irshad et al found the Schlemm's canal to be more posteriorly located in eyes of Black patients as compared to Caucasians.[95] Other than this report, there are no known race-based differences in the distal outflow pathways. A study comparing aqueous humor dynamics between Black and Caucasian patients with primary open angle glaucoma and ocular hypertension also did not find any significant

differences.[81] Future research into differences in aqueous humor composition and flow physiology between different race groups may provide greater insights into the causes for failure of trabecular stenting procedures.

In evaluating the effects of systemic comorbidities on surgical success, our study found hypertension to be a risk factor for failure to lower IOP in CE alone, but not for combined CE-IS. Diabetes and hyperlipidemia also were not found to be risk factors for failure. In the hypertensive subset of the study population, the lower hazard of failure with CE-IS was no different from that of the population as a whole (HR 2.35, CI 1.10-5.02, p=0.03). Further research may help determine if the lower odds of IOP lowering with CE in hypertensive subjects is related to some shared pathophysiological effects of hypertension itself or the medications being used to treat it.

Longer axial length was associated with an increased risk of failure after CE alone or with iStent implantation. Although all eyes included in this study had open angles on preoperative gonioscopy, shorter eyes may be more likely to have IOP lowering after cataract surgery, similar to eyes with narrow angles. Surprisingly, among patients with CE alone, greater corneal curvature and lower anterior chamber depth were associated with increased risk of failure. Empirically, one would expect a better IOP lowering effect of CE in eyes with shallower chambers, as seen in previous studies.[96,97] However, the results of the analysis were contrary to this expectation. This suggests that there may be more to IOP lowering with CE than a mere deepening of the anterior chamber. Consistent with this speculation, Coh et al evaluated the effect of preoperative biometric parameters on IOP lowering after cataract surgery in glaucomatous and non-

glaucomatous eyes.[98] At 4 months, they found shallower anterior chambers to be associated with greater IOP lowering only in non-glaucomatous eyes, but not in glaucomatous eyes. Also found was a significant effect of glaucoma diagnosis on the anterior chamber depth-IOP association with a modeled 2.19 mmHg lesser IOP lowering associated with glaucoma diagnosis. Glaucoma patients with certain lens positioning in the eye may have greater IOP lowering benefit from CE. Based on the results of this study's multivariate analysis, an eye with a combination of shorter axial length, flatter cornea and deeper anterior chamber is expected to have the most IOP lowering benefit from CE.

Our study has several limitations that need to be considered when interpreting the findings. This is a retrospective review of surgical success in a single academic center. However, the severity of pathology and practice patterns at this institution likely reflect those of any academic center in the United States. The sample size is small with a much larger proportion of Caucasian subjects as compared to non-Caucasians, reflective of the population demographics in the service area. To have a large enough sample to make meaningful comparisons, the non-Caucasian group consisted of several racial and ethnic groups. Future prospective studies can address this limitation by targeted enrollment of specific racial and ethnic groups of interest. The current study has all the limitations of a retrospective study with potential for selection bias and cohort effects. To minimize any potential systematic biases, the study had consecutive inclusion of all eligible cases and contemporary controls. The two groups were well matched for most demographic and clinical characteristics with the exception of history of prior SLT, which was as expected,

more prevalent in the CE-IS group. This likely reflects a selection bias for cases more in need of IOP lowering for both SLT and iStent. However, we did not find any effect of prior SLT on outcomes in either group in this study. Because of the retrospective design and the absence of any washout prior to surgery, the true IOP lowering effect of either procedure cannot be deduced from these data and could be much different from that reported here. However, outside of the setting of a clinical trial, such data is rarely available to a treating clinician, and treatment decisions and determination of success or failure must be made based on the available clinical data. In that sense, the current study is more reflective of the real-world effectiveness of the procedures evaluated rather than their true efficacy. The systemic co-morbidities were extracted from the problem list available in the patient's electronic medical records. Patient's general medical care notes were not reviewed, and current treatment was not controlled for. This was outside the primary scope of this preliminary study. Despite these limitations, the current study found clinically and statistically relevant variables associated with IOP lowering success of CE with or without iStent.

The reported findings suggest that there are significant differences in the success of CE-IS but not CE alone based on race. Further research into potential racial differences in wound healing processes at the surgical site or compensatory adjustments in distal outflow pathways may help explain the findings of this study. Certain anatomic configurations of the eye measurable by biometry are associated with success of CE with or without iStent implantation. These variables can be viable candidates for inclusion in possible personalized models for estimating success probability and thereby

individualize the surgical recommendations for either procedure. They also can be used

to prospectively evaluate and explore other local, humoral or genetic factors to help

optimize the IOP lowering outcomes with trabecular bypass procedures.

Conclusions

Selective laser trabeculoplasty (SLT) is one of the few treatment options in glaucoma that directly target the trabecular meshwork and conventional outflow. In the research presented in Chapter 1, we have shown that the IOP lowering effects of SLT are mediated through an improvement in outflow facility. We also demonstrated that in a multiple linear regression analysis model greater IOP lowering was associated with lower baseline outflow facility and higher baseline aqueous flow. Thinner corneas and younger age were of marginal association with additional IOP lowering with SLT at 3 months. This lays the groundwork for future work on using pre-operative AHD for case selection prior to surgical procedures.

In the second chapter we established that race can be a significant determinant of AHD. Specifically, differences in young adult Caucasians compared to similarly aged Chinese were thinner central cornea, lower intraocular pressure, larger anterior chamber volume and faster uveoscleral outflow rate. Differences in older adult Caucasians compared to similarly aged Chinese were slower aqueous flow rate, lower IOP and larger ACV. Considering all subjects together by race, Caucasian subjects had slower Fa, thinner corneas, lower IOP, higher ACV, and faster Fu. This research makes a case for using race as an important factor and as a leverage point for studying the effect of biometrics and aqueous humor dynamics in studies of therapeutic IOP lowering outcomes.

In the final chapter, using a retrospective study and survival methods, we demonstrated that race and biometrics do indeed influence the surgical outcomes after trabecular

bypass procedures. Overall, CE-IS patients had an increased chance of success in lowering IOP or reducing the number of medications. Non-Caucasian patients demonstrated a significantly higher risk of failure with CE-IS than Caucasian patients, which was not seen with CE alone. Longer axial length was also associated with an increased risk of failure in both surgeries in our study. Among CE patients, greater corneal curvature and lower anterior chamber depth were associated with increased risk of failure. Associations between IOP lowering with CE and biometric parameters may allow for leveraging these clinical parameters for better case selection for MIGS procedures in glaucoma patients.

Future work will use the lessons learned from this work to prospectively evaluate the effects of biometrics and AHD on the outcomes of iStent and other trabecular bypass procedures. This work will address the unmet needs to allow for personalization of surgical management of mild to moderate glaucoma, by helping case selection based on maximizing the potential IOP lowering benefit and minimizing the risk of complications.

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