COMIRB Protocol
COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

Protocol #: 18- 1713
Project Title: Enhanced Pupil Dilation in Patients Taking Alpha-Blockers for Potential Treatment of Intraoperative Floppy Iris Syndrome using Brimonidine Tartrate
Principal Investigator: Cristos Ifantides, MD
Version Date: 02/22/2019

I. Hypotheses and Specific Aims:

Hypothesis: In patients who have poor pupillary dilation secondary to α-1 blocker use (ex: tamsulosin), treatment with an α-2 agonist, such as brimonidine tartrate .2%, 7 days prior to standard pharmacological dilation will lead to improved pupillary dilation.

Primary Aim: To determine the average increased pupillary dilation in the α-2 agonist treated eye compared to the untreated eye in patients with a history of taking tamsulosin (or another systemic α blocker).

Secondary Aim: To determine the increased pupil dilation of the treated eye after bromidine tartrate .2% for 7 days compared to the initial dilation prior to brimonidine treatment.

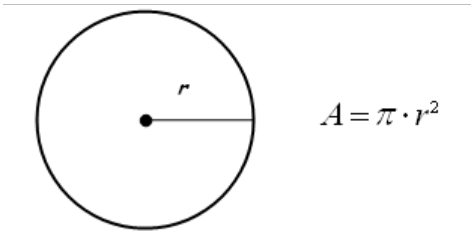
II. Background and Significance:

Each year, millions of people suffer from poor pupillary dilation during eye exams and eye surgery. Poor pupil dilation leads to inadequate visualization of pathology by an eye care specialist during clinic-based exams. Even more importantly, the surgical work area of the eye is severely diminished in these patients. Narrowing a surgeon's work area has significant implications for surgical safety and patient outcomes and contributes to higher rates of complications.[1,2,3] Capsular rupture is one of the many complications that can occur and is estimated to cost the U.S. up to $35 million annually.[4]

One cause of poor pupil dilation is due to secondary systemic effects of α blockers. Poor pupil dilation in these patients has been newly termed Intraoperative Floppy Iris Syndrome (IFIS) . This class of drugs is often prescribed in middle-aged to older men diagnosed with Benign Prostate Hyperplasia (BPH). IFIS is composed

of a triad of intraoperative characteristics: 1) a floppy iris that “billows” in response to irrigation and aspiration, 2) tendency of the iris to prolapse out of the wound, and 3) progressive pupil constriction during surgery despite standard pharmacological dilation measures. IFIS was first identified as problematic in patients taking tamsulosin in 2005[1]. Previous studies have indicated that the incidence of Intraoperative Floppy Iris Syndrome is 2% of all total patients undergoing eye operations (3.6 million cataract surgeries are performed in the United States each year)[5]. In patients taking tamsulosin the incidence of IFIS is up to 90%[6]. Simply discontinuing the α-blocker does not resolve the symptoms, which means any patient who has taken a tamsulosin at any point in their life is at high risk for having IFIS and suffering surgical complications. Complications include capsular rupture, loss of vitreous, iris prolapse, iris stroma atrophy, capsulorhexis tear, or anterior chamber hemorrhage. History of tamsulosin use in operative patients has an associated 2.3-fold increase risk of complications compared to patients who have never taken tamsulosin[7].

For surgical ophthalmologists, poor pupil dilation is problematic because the smaller pupil results in less light entering the dilated eye and an obstructed view during surgery. This is highlighted by the following diagram and equation for the area of a circle:



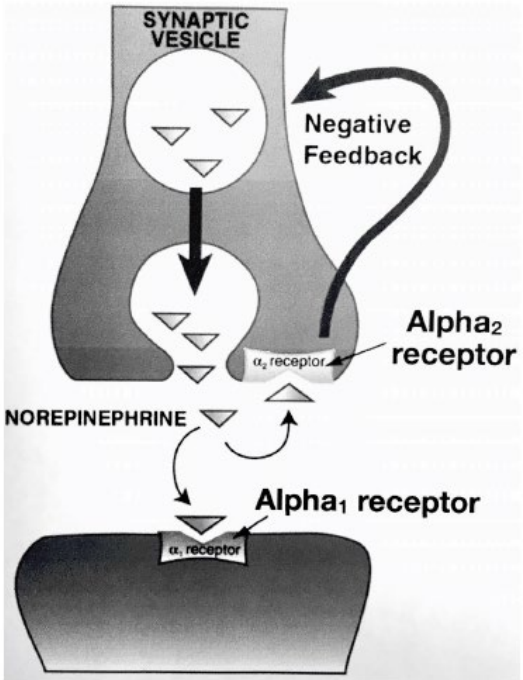
From the above equation, we can see that an eye surgeon’s work area (A) inside of a circular pupil is most influenced by the radius (r). As dilating eye drops are applied to the eye, the radius of the pupil increases and the surgical work area increases exponentially. If the radius of a pupil doubles, the surgical work area quadruples. Similarly, if the dilated pupil size decreases by one half from 8mm to 4mm, the surgical work area decreases by a factor of four.

III. **Preliminary Studies/Progress Report:**

There is currently no FDA approved cure or treatment to prevent or lessen the symptoms associated with IFIS. Current research is targeted at identifying patients most at risk for surgical complications by determining which characteristics of IFIS are associated with the

highest complication rates. Previous attempts to solve the problem of small pupil size during examination and surgery have not yet showed promising results as they only improve pupil dilation modestly. A solution not yet explored is to create a temporary, pharmacologically induced Horner's Syndrome, resulting in the temporary upregulation of α-1 receptors on the iris. This temporary upregulation of α-1 receptors would lead to moderate pupil constriction at rest, but in the presence of α-1 selective dilating drops such as phenylephrine, the result would be a "supersensitive" response and substantial pupil dilation in an eye that would otherwise not dilate adequately for surgical intervention.

Through disease mimicry, our method uses topical α-2 agonists to create a pharmacological Horner's Syndrome. Since activation of pre-synaptic α-2 receptors activates the negative feedback mechanism, this treatment will decrease the release of norepinephrine (NE) into the synaptic cleft. The lack of NE in the synaptic cleft will upregulate the post-synaptic α-1 receptors on the iris dilator muscle, which in turn will result in supersensitivity to any topical α-1 receptor agonist such as phenylephrine or epinephrine:



Synaptic influences of α-1 and α-2 receptors. Postjunctional α-1 receptors mediate effects on target tissues whereas prejunctional α-2 receptors inhibit neurotransmitter release and provide negative feedback.

Our initial research shows promising results. Preliminary data collected in one healthy human showed that pre-treatment with brimonidine

tartrate, a commercially available topical α-2 agonist prescribed for glaucoma treatment, resulted in increased dilation when compared to the non-treated eye. Specifically, after 4 days of pre-treatment with brimonidine in only one eye, the brimonidine-treated eye had an 84.4% greater surgical working area compared to the non-treated eye ($11.16mm^2$ vs $20.59mm^2$).

A preliminary IRB-approved study is currently under way looking at pupil dilation in patients with Horner's Syndrome who have previously been on a systemic α-1 blocker. This study titled "Exploration of Pupil Dilation in Horner's Patients Taking Flomax" studies the hypersensitivity that the effected Horner's eye has to α-1 receptor agonists.

Horner's Syndrome represents the classical triad of unilateral miosis (pupil constriction) and anisocoria (asymmetric pupil size), ptosis (abnormal low-lying upper eyelid), and anhidrosis (loss of sweating ability). This unilateral syndrome results from the destruction of autonomic sympathetic nerve axons leading to the loss of sympathetic innervation to one of the eyes and surrounding skin and subsequently, supersensitivity to α agonists (such as norepinephrine). This supersensitive state can be described through the Law of Denervation Supersensitivity (Cannon's law) first described in 1939. Specifically, for the eye, the iris is covered in α-1 and α-2 receptors. These receptors result in pupil dilation via the bonding to the sympathetic neurotransmitter norepinephrine. In a normal physiologic state, there is a set level of norepinephrine released that serves to keep the population of α-1 receptors at a normal level. In Horner's Syndrome, however, there is a lack of norepinephrine release secondary to the denervation upstream from the iris. The absence of the sympathetic neurotransmitters in Horner's syndrome results in an upregulation of alpha receptors onto the muscle fibers responsible for pupil dilation. The increased number of alpha receptors on the iris is responsible for the supersensitive state that results in an exaggerated dilation of the pupil.

The final results of this ongoing study will serve as the proof of concept study to evaluate how pharmacologic mimicry of an induced Horner's state for the eye may result in the ability to offset poor pupil dilation in patients with IFIS.

IV. Research Methods

A. Outcome Measure(s):

The primary hypothesis for this study is that application of routine dilating medications (Phenylephrine Hydrochloride 10%, tropicamide 1%, and

cyclopentolate 1% ophthalmic solutions) will dilate the brimonidine tartrate pre-treated eye more than the non-treated eye in patients previously treated with tamsulosin.

The primary outcome measure for this single arm study is pupil diameter size post dilation (using standard dilating medications of phenylephrine 10%, tropicamide 1%, and cyclopentolate 1%) of the brimonidine tartrate pre-treated eye compared to the non-treated eye.

The secondary outcome is the change in pupil diameter of each eye after dilation at the start of the study, compared to pupil post dilating drops at the end of the study.

B. Description of Population to be Enrolled:

This study will recruit from the Denver Health Medical Center Eye Clinic. Adult subjects who have any history of taking tamsulosin and do not meet one of the exclusion criteria will be approached for consent. .Adult patients must be able to consent for study participation by themselves. Exclusion criteria that will eliminate potential subjects for enrollment includes:

1) Subjects with untreated hypertension, baseline BP >160
2) Subjects with thyrotoxicosis
3) Pregnant women
4) Prisoners
5) Inability to consent
6) Subjects with anatomical narrow angles who have never had a dilated exam
7) Subjects currently prescribed brimonidine tartrate for glaucoma
8) Subjects who require topical or systemic α agonists
9) Any eye disease that would alter pupil dilation

C. Study Design and Research Methods

Single Arm, Superiority Trial

This is a single arm study. All enrolled subjects will receive the interventional drug, Brimonidine tartrate 0.2%, to be applied to ONE eye only. Brimonidine is currently an FDA approved drug with a favorable safety profile, thus an internal pilot efficacy trial is the next step to evaluate the off-label use of Brimonidine to treat IFIS. The internal pilot (i.e., pilot data are part of the final sample size) data will be used to improve the estimation of variance in response to these medications, since the therapy approach is novel and there are no published data. In addition, the internal pilot will be used to re-assess recruitment methods, as well as patient satisfaction and adherence.

This study will investigate the resulting difference in pupil dilation in the treated eye (Brimonidine Tartrate .2% for 7 days) eye compared to the non treated eye. The

investigators hypothesize that in patients with IFIS, brimonidine tartrate .2% is superior to the current standard of care for pupil dilation for surgical preparation.

The primary outcome is pupil dilation sized of the treated eye compared to the non-treated eye, and the secondary outcome is pupil dilation of the treated eye compared to the pre-treatment pupil dilation size of that same eye.

Patients will be screened at their annual Denver Health Eye Clinic examination. Clinical examinations will involve a medication history and baseline vitals, as per standard of care, and any patient taking a systemic α blocker (such as tamsulosin) will be approached for consent if they do not meet any exclusion criteria.

For all patients, consent will occur in person in the Denver Health Eye Clinic in a private setting at the first study visit, or at a standard of care visit which will include study procedures. Consent will be obtained by a member of the research team. Once consent has occurred, the principal investigator (PI) will examine the patient's anterior eye segment and measure the subject's pupil diameter prior to instilling the dilating drops. Pupil measurements will occur with the use of a Digital Pupillometer (NeuroOptics Inc, Irvine, California, USA). The Digital Pupillometer measures objective pupil size and reactivity data independent of the examiner and allows changes in pupil reactivity to be trended over time.

The PI will then instill the pupil dilation drops using the pre-operative dilating cocktail given in the pre-operative phase of cataract surgery. The dilating cocktail is composed of phenylephrine 10%, tropicamide 1%, and cyclopentolate 1% drops. All of these drugs have a well known safety profile and thus we expect minimal side effects during this clinical trial. Measurement for post dilation pupil size will occur at 15, 30, and 45 minutes after instillation of these medications. After the pupil measurement with the pupillometer, the study related activity for the initial visit will be complete. If patients are in the clinic for their regular examination, the clinic specialists will commence the exam at that time.

After this initial visit, a 20-day washout period will ensue. During this time, the patient will be asked to not use any topical or systemic α-agonists. They may continue to use systemic α-receptor blockers such as tamsulosin. After this 20-day washout period, patients will begin treatment using brimonidine tartrate 0.2% three (3) times per day in the right eye. This dose and frequency is the FDA approved dose for glaucoma patients, and at this dose the side effect profile is well tolerated.

After 7 days of treatment, the patient will return to the Denver Health Eye Clinic. Again, the PI will examine the patient's anterior eye segment and measure the subject's pupil diameter prior to instilling dilating drops. Pupil measurements will occur with the use of the NeurOptics Digital Pupillometer. After measurement of both pupils in the clinical examination room, the routine eye drop cocktail for

dilation prior to cataract surgery (phenylephrine 10%, tropicamide 1%, and cyclopentolate 1% drops) will be placed on both of the subject's eyes by the PI. Measurement post dilation will occur 15, 30 and 45 minutes after instillation of these medications. After the pupil measurement with the pupillometer, the study related activity will be complete.

Schedule of Events

	Baseline Visit, Day 0	Week 1, Days 1-7	Week 2 Days 8-14	Week 3, Days 15-21	Week 4, Days 22-28	Final Visit, Day 29
Screening	**X**					
Medical History	**X**					
Consent	**X**					
Vital Signs	**X**					**X**
Anterior Eye Exam	**X**					**X**
Pre-Dilation Pupil Measurements	**X**					**X**
Dilating Cocktail	**X**					**X**
Post-Dilation Pupil Measurements	**X**					**X**
Washout Period		**X**	**X**	**X**		
Brimonidine Tartrate .2% TID, Right Eye					**X**	
Side Effect Questionnaire						**X**

All subjects will be paid for their participation in this study. A ClinCard with $25 will be distributed to each subject after each one of the two visits as reimbursement for their time and travel, for a total of $50 for study duration.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Risks to Subjects:
Brimonidine Tartrate will be prescribed for 7 days TID at the FDA approved dose for glaucoma. There are some risks associated with this drug, but it is a very well tolerated topical medication approved for long term use:

- Most common side effects associated with this medication (10-30%), in descending order: oral dryness, ocular hyperemia, burning adn stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, ocular pruritus.
- Less common side effects (3-9%) of patients: corneal straining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain

- Adverse reactions that were reported in less than 3% of patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope
- Post-marketing side effects reported (unknown frequency): bradycardia, hypotension, iritis, miosis, skin reactions (including erythema, eyelid puritis, rash, and vasodilation), tachycardia, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence.

The other drugs included in the protocol will be applied twice, 21 days apart, by the PI only; the following side effects have been reported in these drugs, but frequency are not listed.

- Side effects of Phenylephrine 10% (not in known frequency order): pre-existing cardiovascular disease with use of phenylephrine 10% can result in serious adverse reactions. Other more common, but less serious side effects: rebound miosis, elevation in blood pressure, eye pain, stinging, temporary blured vision, photophobia, conjunctival sensitivity

- Side effects of cyclopentate 1%: increased intraocular pressure, burning, photophobia, blurred vision, irritation, hyperemia, conjunctivities, blepharoconjunctivitis, punctate keratitis, synechiae

- Side effects of tropicamide 1%: transient stinging, blurred vision, photophobia and superficial keratitis; increased intraocular pressure; dryness of the mouth, tachycardia, headache, allergic reactions, nausea, vomiting, pallor, central nervous system, disturbances, and muscle rigidity

The PI will monitor for side effects at study visits and all side effects will be captured for data analysis. Any serious adverse events will be reported to COMIRB.

Data Collection:
The pupil measurements will be stored in a private, password protected Excel database for this study. This database will contain patient's name, MRN, age, sex, past medical history, and current medications, along with the each pupil measurements in time (for a total of 8 pupil measurements). The PHI from this database will be deleted after the study concludes, but the pupillometer readings will remain paired with de-identified medical data.

We are seeking Investigational New Drug (IND) application exemption for brimonidine tartrate 0.2% for the following reasons:

1. Brimonidine tartrate 0.2% is an α adrenergic agonist lawfully marketed in the United States indicated for lowering intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.
2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product.
3. The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product.
4. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. Dosage and administration in this study will be exactly the same as is indicated and FDA approved for open angle glaucoma or ocular hypertension: “One drop in the affected eye(s), three times daily, approximately 8 hours apart”. Furthermore, we will only be using this medication for 7 days. This is far shorter of a treatment course than is typically used. Typically, this medication is used continuously for many years/decades to treat the above eye conditions.
5. The investigation will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50. We are seeking IRB approval for this study and all patients must give consent in order to enroll.
6. The investigation will be conducted in compliance with FDA regulations 21 CFR 312.7: Promotion and charging for investigational drugs. We will not represent the off-label use of the drug for this study as safe and effective or otherwise promote it. The medication used in this study will be obtained and paid for by the investigator, and will not be charged to the subject or subject's insurance.

F. Data Analysis Plan:

Cases and Controls: Each treated eye (Case) has two Controls: 1) the baseline measurement of the treated eye prior to commencing pre-treatment and 2) the left, untreated eye after pre-treatment is completed. The two controls (baseline and untreated eye) are necessary to assess the possible role of systemic effects of the α-2 agonist (which could affect the untreated eye). Our primary and secondary endpoints are the change in pupil diameter of the treated right eye compared to the pre-treated pupil dilation size, and compared to the untreated left eye pupil dilation size.

Tertiary endpoints are noted side effects from the administration of topical brimonidine tartrate .2% TID for 7 days. Brimonidine tartrate has a well tolerated side effect profile, so at a shortened duration of 7 days we expect minimal

systemic effects by teaching the patients specific procedures (punctal occlusion) during drop instillation to minimize systemic effects.

Assumptions for sample size: All calculations assume two-tailed tests, with 80% power and 95% confidence. The overall sample size is initially calculated based on published data on healthy volunteers and patients on tamsulosin. After 50% enrollment in each arm, we will re-calculate the variance based on acquired data and re-estimate the final sample size.[8] This initial comparison will be considered as an interim look using the O'Brien-Fleming alpha spending function. All samples size calculations will be conducted using PASS Power Analysis and Sample Size Software (2015, NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). Based on Theodossiadis et al. (2), normal individuals show a 2.9 ± 0.5 (standard deviation) fold change in pupil minimum aperture after phenylephrine 10% compared to 2.7 ± 0.5 (standard deviation) fold change in patients taking tamsulosin for >=6 months. It should be noted that even minimal increases in pupil aperture result in large, clinically relevant improvements in the surgical field. With the above assumptions, maintaining a worst case scenario of a standard deviation of 0.45, and 30% attrition rate, 30 patients will be needed to detect a minimum difference in pupil aperture fold change of 0.3 (effect size=0.6).

G. Summarize Knowledge to be Gained:

BPH is the most commonly diagnosed condition for male patients age 45-74.[9] It is estimated that up to 90% of men between the age of 45 and 90 suffer from BPH.[10] The most common and effective treatment, recommended as first line therapy for BPH by the American Urological Association, is the selective α-1 blocker (e.g.: tamsulosin) that target α-1 receptors in the genitourinary (GU) system. The risk of IFIS among men taking tamsulosin was as high as 90% in 10 retrospective and prospective studies.

The scope of the unmet clinical need is staggering. 3.6 million cataract surgeries are performed each year in the USA alone, 20 million worldwide. An estimated 2% of these surgeries have IFIS (72,000 cases each year in the USA).[1] The cataract and BPH population is only expected to increase over the next 30 years due to population aging.[11]

This study will provide data on the potential treatment of IFIS. Currently no adequate treatment for IFIS exists. This potential treatment method creates a "pharmacologically induced Horner's Syndrome", resulting in an increased response to mydriatic medications. This is accomplished by blocking the sympathetic innervation, whseraich upregulates α-1 receptors on the iris. This supersensitivity to dilating medications counteracts the poor dilation that tamsulosin causes.

In the face of population growth and increasing IFIS prevalence, this could be a novel therapy in the fight against IFIS-related surgical complications.

H. References:

1. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg 2005; 31:664–673.
2. Lim LA, Frost A. Iris tears secondary to intraoperative floppy-iris syndrome associated with tamsulosin. J Cataract Refract Surg 2006; 32:1777.
3. Storr-Paulsen A, Jorgensen JS, Norregaard JC, Thulesen J. Corneal endothelial cell changes after cataract surgery in patients on systemic sympathetic alpha-1a antagonist medication (tamsulosin). Acta Ophthalmol 2014; 92:359–363.
4. Ryburn C, Lynch AM, Patnaik JL, Cathcart J, Alexander J, Davidson RS, Taravella MJ. The Financial Burden of Posterior Capsular Rupture (PCR) in America. Presentation. American Society of Cataract and Refractive Surgery Annual Meeting 2018. April 15, 2018.
5. Flach AJ. Intraoperative floppy iris syndrome: pathophysiology, prevention, and treatment. Transactions of the American Ophthalmological Society. 2009 Dec;107:234.
6. Chang, D.F., Osher, R.H., Wang, L. and Koch, D.D., 2007. Prospective multicenter evaluation of cataract surgery in patients taking tamsulosin (Flomax). *Ophthalmology*, *114*(5), pp.957-964.
7. Theodossiadis PG, Achtsidis V, Theodoropoulou S, Tentolouris N, Komninos C, FountasKN. The effect of alpha antagonists on pupil dynamics: implications for the diagnosis of intraoperative floppy iris syndrome. *American journal of ophthalmology*, 153(4), pp.620-622
8. Billingham SAM, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol. 2013;13(1):104.
9. Isaa MM, Marshall FF. Contemporary Diagnosis and Management of Disease of the Prostate. Newton, Pa: Handbooks in Healthcare Co.;200.
10. McVary KTet al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011 May;185(5):1793-803.
11. Manvikar S, Allen D. Cataract surgery management in patients taking tamsulosin staged approach. J Cataract Refract Surg 2006; 32:1611–1614.