Official Title: The Effect of Brimonidine on Intraocular Pressure When Dilating Routine Patients, Pressure Control and Pupil Effects

NCT03959176

IRB-Approved Date: 7/1/2019

Study Title: The Effect of Brimonidine on Intraocular Pressure When Dilating Routine Patients, Pressure Control and Pupil Effects.

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Sponsor or funding source: Wake Innovations

Background, Rationale and Context

Many biological parameters are dynamic and vary within a 24-hour cycle. Intraocular pressure (IOP) is one of these parameters. In addition to natural fluctuations, IOP can vary in relation to external factors such as exercise, medications, and eye movements [1]. Although patients experience daily IOP fluctuates, prolonged elevated IOP can be harmful. Sustained elevated IOP levels have been linked to optic nerve damage and diseases such as glaucoma. If IOP is not controlled, damage to the optic nerve can cause multiple disease states culminating in blindness. In patients with no disease, normal IOP ranges from 8-21 mm Hg, while glaucoma patients' have range 20 – 50+ mm Hg. Due to the damage that elevated IOP can have, it is highly important for physicians to monitor IOP.

Mydriatic eye drops that are routinely used to dilate pupils in patients presenting to ophthalmology clinics have also been shown to increase IOP [2]. Increased IOP has been seen with both parasympatholytic and sympathomimetic mydriatics [3-5]. In practice, a combination of tropicamide, an anticholinergic drug, and phenylephrine, an alpha-1-adrenergic drug, is used to achieve the pupil dilation needed for routine eye exams or perioperative situations [6, 7]. The combination of tropicamide 1% and phenylephrine 2.5% has been safe, effective and reliable in clinical use to adequately dilate the pupil for clinical examination and procedures [12]. However, these drugs have shown to increase IOP, and drugs such brimonidine, a selective alpha-2 agonist, have shown to reduce IOP [8, 9]**.** Brimonidine can lower IOP through a few methods. Chronic use of brimonidine acts through stimulating aqueous humor outflow, while using brimonidine in an acute setting will reduce IOP by reducing the amount of aqueous humor produce [10, 11].

We propose to observe whether pre-treating patients with Brimonidine 0.2% (brimonidine) prior to pupil dilation and/or post-treating will be effective in controlling the fluctuations in IOP seen when using mydriatics. In addition to observing IOP, we will also observe the effects of how differing the sequence of administration of **Tropicamide 1%/Phenylephrine 2.5% combined (standard dilation drops)** and brimonidine impacts pupil size and reactivity.

Objectives

Primary Objective: To observe how differing the sequence of administration of **Tropicamide 1%/Phenylephrine 2.5%** and Brimonidine 0.2% (brimonidine **0.2%**) influences intraocular pressure.

- *Hypothesis 1*: The administration of **Brimonidine 0.2%** prior to **Tropicamide 1%/Phenylephrine 2.5%** will result in lower intraocular pressure rise than when administering Brimonidine 0.2% after initiating dilation with **Tropicamide 1%/Phenylephrine 2.5%**.
- *Hypothesis 2*: The administration of both Brimonidine 0.2% and **Tropicamide 1%/Phenylephrine 2.5%** will result in lower intraocular pressure rise than when just administering **Tropicamide 1%/Phenylephrine 2.5% alone.**

Secondary Objective: To observe effect of differing the sequence of administration of **Tropicamide 1%/Phenylephrine 2.5%** and Brimonidine 0.2% on pupil size and pupil reactivity

- *Hypothesis 1*: The administration of Brimonidine 0.2% prior to **Tropicamide 1%/Phenylephrine 2.5%** will blunt or block, or delay pupil dilation compared to just using **Tropicamide 1%/Phenylephrine 2.5%** alone
- *Hypothesis 2*: The administration **Tropicamide 1%/Phenylephrine 2.5%** prior to Brimonidine 0.2% will lead to large pupil dilation with quicker reversal **in pupil size** than just **Tropicamide 1%/Phenylephrine 2.5%**.

Methods and Measures

- Design

An interventional study looking at what order of eye drops is more effective in reducing intraocular pressure with pupil dilation. We will recruit 10 volunteers in each of the two groups **(20 subjects total)**. In both groups, the participant's right eye will serve as a control with only **Tropicamide 1%/Phenylephrine 2.5%** given. In the first group, the left eye will receive Brimonidine 0.2% prior to **Tropicamide 1%/Phenylephrine 2.5%**. The second group will receive **Tropicamide 1%/Phenylephrine 2.5%** prior to Brimonidine 0.2%, in their left eye. We will observe and record the IOP lowering benefits of the addition of brimonidine over the **Tropicamide 1%/Phenylephrine 2.5%** alone and determine if pre-treating is any better than post-treating. In addition, we will monitor pupil response, as we know that brimonidine may have some effect on the pupil dilation.

We will collect the following demographic data: age, gender, and iris color. In addition, non-identifying color photos of the pupils may be recorded on a few representative patients in each group. Photos will be taken in a manner to protect patient confidentiality. Photos will be framed from the participants lower eyebrow, to the sides of their faces, and to the uppers nose. Photos will be stored on a password protected and encrypted computer or cloud-type website.

- Setting

The study will be performed at Wake Forest Baptist Hospital and/or Davie Medical Center. Each subject will be consented and have their measurements taken in a private exam room. They will be returned to a waiting area in between measurements. All concerns with measurements will be handled privately in the respective examination to ensure subject privacy.

Subject selection criteria

Subjects will be recruited through recruitment flyers and internet methods (email) (appendix 2) and selected to participate based on the following inclusion and exclusion criteria.

- Inclusion criteria: Ages 18-50. Healthy with no major medical conditions. Contact lens wear is ok but must be not worn on the day of the study.
- Females of childbearing potential must agree to use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence, oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation or vasectomy of the partner (with confirmed negative sperm counts) in monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or cervical cap or sponge. A pregnancy test is required at least 10 days from the last normal menstrual period, if the patient is a sexually active female of childbearing potential.

- Exclusion criteria: Diabetic, history of glaucoma, history of iris trauma, history of eye surgery except LASIK or PRK, pregnancy, anisocoria **(unequal pupils)**.

Sample size: 20 patients total.

Study Procedure

- Informed Consent Process: After the patient has been evaluated and meets all of the inclusion and exclusion criteria, Dr. Walte**r, or another investigator** will introduce the study. This will occur 10 min to 24 hours before pupil dilation. The study will be discussed in detail and consent (appendix 1) will only be obtained once the patient has been given time to fully understand the study. If the patient agrees, patients will be dilated and intraocular pressure and pupil size will be measured at 6 time points: Baseline (pre drop), 15 min, after last **Tropicamide 1%/Phenylephrine 2.5%** drop given, 30 min, 1 hour, 2 hours, 4 hours
- Study Procedure (Approximately 4 hours): Participants will be come to the ophthalmology clinic where the study will be completed. Participants will be randomized and separated into two groups. In both groups, the participant's right eye will serve as a control with only **Tropicamide 1%/Phenylephrine 2.5%** given. In the first group, the left eye will receive **Brimonidine 0.2%** prior to **Tropicamide 1%/Phenylephrine 2.5%**. The second group will receive **Tropicamide 1%/Phenylephrine 2.5%** prior to **Brimonidine 0.2**.
    - IOP will be measured using the iCare tonometer device
    - Pupil size and reactivity will be measured under bright lights using a pupil gauge, and slit-lamp micrometer**.**
- To prevent the dilution of the eye drops through tearing, 0.5% proparacaine hydrochloride (Alcaine®, Alcon Co., USA) will be delivered to each eye 5 minutes before administering the dilating drugs. All eye drops will be placed within the conjunctival sac of the lower eyelid, and patients will be directed to close their eyes approximately 1 minute after drop delivery to prevent loss of medication through the punctum in the conjunctival sac.

Study Schematic: 1 X 4 hour participant visit

Group 1		Group 2	
Right Eye	Left Eye	Right Eye	Left Eye
▪ **Sham drop (none)** ▪ Wait 5 minutes ▪ 1 drop **Tropicamide 1%/Phenylephrine 2.5%** ▪ 1 minute ▪ 2nd drop **Tropicamide 1%/Phenylephrine 2.5%**	▪ **2** drops Brimonidine 0.2% ▪ 5 minutes ▪ 1 drop **Tropicamide 1%/Phenylephrine 2.5%** ▪ 1 minute ▪ 2nd drop **Tropicamide 1%/Phenylephrine 2.5%**	▪ **1 drop Tropicamide1% /Phenylephrine 2.5%** ▪ **Wait** 1 minute ▪ 2nd drop **Tropicamide 1%/Phenylephrine 2.5%** ▪ **15 secs later** ▪ **Sham drop (none)**	▪ 1 drop **Tropicamide 1% /Phenylephrine 2.5%** ▪ **Wait** 1 minute ▪ 2nd drop **Tropicamide 1%/Phenylephrine 2.5%** ▪ 15 secs later ▪ **2** drops Brimonidine 0.2%
▪ **15 min. collect Data set**	▪ **15 min. collect Data set**	**15 min. collect Data set**	▪ **15 min. collect Data set**

Outcome Measures

- Intraocular pressure at 6 time points: Baseline (pre-drops), 15 min after last drop given, **then** 30 min, 1 hour, 2 hours, **and** 4 hours
- Pupil size at 6 time points: Baseline (pre drop), 15 min, 30 min, 1 hour, 2 hours, 4 hours. We will measure the pupils under bright light conditions (photopic) and dim light conditions (scotopic).
- Pupil's reaction to light will be measure at 6 time points: Baseline (pre drop), 15 min, 30 min, 1 hour, 2 hours, 4 hours. Pupil reaction will be measure either as none, poor, or brisk.

Analytical Plan

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Human Subjects Protection

Pregnancy testing will be done on all female patients, after consent and prior to enrollment to ensure no pregnant participates are included in the study.

Subject Recruitment Methods

Subjects will be recruited though placed recruitment flyers as well as electronically through an email with wordage directly from the flyer (appendix 2) and no students or residents will be recruited that are under the direct supervision of Dr. Walter. If any ophthalmology residents wish to volunteer (not recruited), no credit will be given for participating and their evaluations will not be affected. Participants will be compensated with a $30.00 Starbucks gift card.

Informed Consent

Signed informed consent will be obtained from each subject. The study will be introduced by both Dr. Walter and the study coordinator and informed consent will be obtained formally by Dr. Walter once the subject fully understands the study. Informed consent will be given 1-2 days or more prior to the subject eyes being dilated, giving them plenty of time to decide and fully understand the study. Final written consent will be obtained on the day the study.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 3 years after the study is published. They will be destroyed by deleting all files and shredding any documents consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events, or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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