Exploration of Pupil Dilation in Horner's Patients Taking Flomax

NCT03615508

July 17th, 2020

COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 18-0620
Project Title: Exploration of Pupil Dilation in Horner's Patients Taking Flomax

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Version Date: 7/12/2018

I. Hypotheses and Specific Aims:
Hypothesis: In patients who suffer from Horner's Syndrome and have used an alpha blocker at any time in the past, use of topical ophthalmic eye drops phenylephrine 10% will dilate the Horner's Syndrome affected eye more compared to the unaffected eye.

Primary Aim: To determine the average increased dilation size in the effected Horner's eye compared to the unaffected eye.

Secondary Aim: To provide proof-of-concept data for future studies validating that in patients who take tamsulosin (Flomax) or another less common alpha blocker and suffer from Floppy Iris Syndrome, inducing a temporary "pharmacologic Horner's Syndrome" can serve as treatment by increasing the effective pupil dilation of these patients.

IV. Research Methods

A. Outcome Measure(s):

The primary hypothesis for this study is that Phenylephrine Hydrochloride Ophthalmic Solution 10% will dilate the affected Horner's eye more than the non affected eye in patients previously treated with an alpha blocker).

The primary outcome measure for this single arm study is pupil diameter size status post phenylephrine 10% of the Horner's eye compared to the non-Horner's eye.

The secondary outcome is the change in pupil diameter of each eye post-intervention compared to pre-intervention dilating drops. The average change in pupil size between Horner's eye compared to the non-Horner's eye will be determined.

B. Description of Population to be Enrolled:

This study will recruit all adult patients seen at Denver Health or University of Colorado Hospital with a diagnosis of Horner's Syndrome who have any history of taking tamsulosin (Flomax). 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
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

C. Study Design and Research Methods

This is a single arm study investigating the difference in pupil dilation in Horner's Syndrome patients with a history of taking tan alpha blocker. Patients with a history of tamsulosin/ terazosin/doxazosin/alfuzosin/silodosin medication, even for short durations are at high risk for developing Floppy Iris Syndrome. This study will test the hypothesis that patients with Floppy Iris Syndrome have greater pupil dilation in the affected Horner's eye compared to the non-affected eye.

Through medical record chart review we will identify patients with a diagnosis of Horner's Syndrome and a history of taking Flomax. We anticipate some of these patients will be patients within the Denver Health Eye Clinic or the Rocky Mountain Lions Eye Institute whom the investigator has a clinical relationship. We anticipate some potential subjects will not be patients either of these clinics. These potential subjects will be contacted for participation, as well. If necessary, we will recruit using COMPASS if enrollment numbers from these two institutions are lower than expected.

Potential subjects will be contacted in one of two ways: 1) potential subjects who are eye clinic from one of the two centers patients will be approached in the Eye Clinic by a study member who has been notified by the clinic staff. 2) Potential subjects who are not current patients at these clinics will be contacted through the phone number in their medical record. These patients will be called a maximum of two times to inform them of potential study participation. HIPAA Waiver will be used to contact these potential subjects. In the initial phone call with these subjects, history of tamsulosin or similar alpha antagonist will be confirmed over the phone so as to prevent an unnecessary visit.

Once contacted, subjects will be informed of the study and the inclusion criteria will be reviewed with the subject. If contact occurs in person at the eye clinics, the consent will occur at that time and study procedures will occur at that eye exam appointment. If contact initially occurs over the phone, the patient will be invited in to the the clinic for face-to-face consent process and pupil dilation. They will be informed that this pupil dilation can occur as part of a yearly, standard eye examination if they are in need of one, but if they do not need an eye examination for the year, we will only dilate their eyes and measure pupil diameter, and limit the exam to only the anterior part of the eye.

For all patients, consent will occur in person in the eye clinics in a private setting. Consent will be obtained by a member of the research team. Once consent has occurred, the principal investigator (PI) or another member of the study team 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 a Digital Pupilometer (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.

After measurement of both pupils in a photopic light setting in the clinical examination room, 10% phenylephrine drops will be placed on the subject's eyes by the PI. Measurement post dilation will occur 30 minutes after instillation of phenylephrine. After the pupil measurement with the pupillometer, the study related activity will be complete. If patients are in the clinic for their regular examination, the clinic specialists will commence the exam at that time.

All subjects will be paid for their participation in this study. A ClinCard with $25 will be distributed to each subject as reimbursement for their time and travel.

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 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. Denver Health will serve as the coordinating site of data between the two sites; no PHI will be shared among the two sites.

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

This study will administer the standard dose of Phenylephrine Hydrochloride Ophthalmic Solution 10% (Akorn Inc, Lake Forrest, IL, USA) This solution is an α-1 adrenergic receptor agonist that is FDA approved for the indication of pupil dilation. We will be using this drug for the specific FDA approved indication and will use the standard accepted dosage. All patients will receive one drop of Phenylephrine Hydrochloride Ophthalmic Solution 10% strength to the conjunctival fornix.

Phenylephrine Hydrochloride Ophthalmic Solution 10% has a well known and accepted side effect profile. Some common side effects that patients may experience during the clinic eye examination, or as part of this study if not participating in a yearly eye examination, include eye pain and stinging upon instillation, temporary blurred vision and photophobia, and conjunctival sensitization during examination. Cardiovascular adverse reactions are rare but have been reported in hypertensive patients include an increase in blood pressure, syncope, myocardial infarction, tachycardia, arrhythmia and subarachnoid hemorrhage. For this reason, Phenylephrine Hydrochloride Ophthalmic Solution 10% is contraindicated in hypertensive patients. Phenylephrine Hydrochloride Ophthalmic Solution 10% is contraindicated in patients with a diagnosis of thyrotoxicosis as well. We will exclude these two patients from participation in the study.

Patient names and MRNs will be recorded in the database for the duration of this study. This database will be stored on the secure servers at each site under restricted access and password protected. There is a small risk for breach of confidentiality when storing PHI for research. The research team will do everything to ensure confidentiality of the subjects. At the completion of the study the names and MRNs will be deleted from the database and the remaining information (pupil diameters and medical history) will be unidentifiable.

The potential benefit of this study is to society and future ophthalmic surgical patients with a history of taking Flomax or another alpha blocker.

F. Data Analysis Plan:

This is a small pilot study exploring the potential pupil dilation change in eyes with an upregulated number of α receptors compared to normal irises. This study is not powered to determine the clinically significant change that occurs with pupil dilation after topical placement of Phenylephrine Hydrochloride 10% strength. Continuous variables will be analyzed using a linear regression model of covariates. Categorical predictor variables will be analyzed using chi square test.

H. References:

1. Chang, D.F. and Campbell, J.R., 2005. Intraoperative floppy iris syndrome associated with tamsulosin. *Journal of Cataract & Refractive Surgery*, *31*(4), pp.664-673.
2. Flach AJ. Intraoperative floppy iris syndrome: pathophysiology, prevention, and treatment. Transactions of the American Ophthalmological Society. 2009 Dec;107:234.
3. 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.
4. 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