Study Title: The Wearing-Off Period of Pharmacological Dilation: An Addendum to the Management of Anisocoria

NCT Number: NCT05238233

Date: April 8, 2022

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Protocol Version: 2.0

A. SPECIFIC AIMS

According to the Section 5 - Neuro-Ophthalmology in the *Basic and Clinical Science Course* textbooks, the workup for anisocoria, or unequal pupil size, is to be done according to a flow-sheet[appx.1]. For anisocoria that is greater in bright light than dim light, a low-dose pilocarpine test is indicated to determine if the anisocoria is due to either Adie's tonic pupil or pharmacological dilation versus third cranial nerve palsy. If the pupil constricts to low-dose pilocarpine, the patient is determined to have Adie's tonic pupil, or parasympathetic denervation. However, if the pupil does not constrict with low-dose pilocarpine, a high-dose pilocarpine test is the next step in the work-up. If the pupil constricts to high-dose pilocarpine, the patient is determined to have a third cranial nerve palsy which then needs to be further evaluated with imaging including CT angiogram due to concern for aneurysm rupture. However, if the pupil does not constrict to high-dose pilocarpine, the patient likely has anisocoria due to pharmacological dilation. Suspected iatrogenic anisocoria does not require further evaluation with imaging as it should resolve as the pharmacological substance causing the dilation is metabolized. The flow chart in the *BCSC* books does not consider a phenomenon that may occur as the pharmacological substance causing dilation wears off. We propose that there is a period of time in which a pharmacologically dilated pupil may constrict to high-dose pilocarpine, but still appear dilated, and thus anisocoric. In this case, the patient would require additional imaging with CT angiogram, even though their history may not support any findings concerning for third nerve palsy due to aneurysm. Depending on the patient's history, conducting further imaging may have greater risks and financial burden that are unlikely to provide valuable information. If a patient has history of possible pharmacological dilation in absence of aneurysm symptoms including headache, nausea, vision changes, loss of consciousness, then the patient should not be further evaluated with imaging. We aim to demonstrate the period in which a pharmacologically dilated eye may appear anisocoric on exam, but still respond to 1% pilocarpine.

B. BACKGROUND AND SIGNIFICANCE

Proper workup of anisocoria that is greater in bright light is extremely important given the potentially dangerous causes of an inappropriately dilated pupil. Particularly, the reaction of the anatomically intact, inappropriately dilated pupil to 1% pilocarpine can be essential in distinguishing pharmacologic dilation from dilation caused by a third nerve palsy. Although third nerve palsies are often associated with ophthalmoplegia in addition to mydriasis, isolated mydriasis of the affected pupil can be seen in the early stages of compressive damage to the nerve.[1] Whereas pharmacologic dilation is a benign condition that involves no further workup, compressive third nerve palsy is a common presenting sign of conditions such as subarachnoid hemorrhage, intracranial mass, intracranial aneurysm, or cavernous sinus aneurysm.[1-3]

If the current algorithm is followed, any anatomically intact, yet inappropriately dilated eye that contracts to 1% pilocarpine, but not to 0.1%, will be considered suspicious for a third nerve palsy. Our proposal to clarify the “wearing-off” period of pharmacologic dilation will provide those utilizing this algorithm with an alternative etiology for a pupil that constricts to 1% pilocarpine. This addition will help to avoid unnecessary and expensive workup for a suspected third cranial nerve palsy.

Currently, there is not any literature that describes the “wearing-off” period of pharmacological dilation as a cause of anisocoria in respect to acute clinical workup. Although there are examples of recent studies describing the potential use of constricting agents to reverse pharmacologically induced mydriasis, these studies have been limited in scope to symptomatic relief from the dilated eye and thus have not influenced the BCSC algorithm for the treatment of anisocoria in the acute setting.[4] We believe that this study has the potential to save money and time, as well as reduce the stress that may be associated with consideration of a more serious diagnosis. These benefits will be applicable to the provider, as well as the patient, thus advancing patient-centered high-quality care.

C. PRELIMINARY STUDIES

There are no preliminary studies that are pertinent to this protocol.

Dr. John D. Siddens, DO is a board-certified ophthalmic plastic & reconstructive surgeon. He will be overseeing the project’s academic and clinical aspects. He has completed CITI training through Prisma Health to conduct human subjects research.

G. Brandon Caudill is a fourth-year medical student who is currently in good standing to graduate from the University of South Carolina School of Medicine Greenville in 2022. He has completed CITI training through the University of South Carolina to conduct human subjects research.

D. RESEARCH DESIGN AND METHODS AND DATA ANALYSIS

Recruitment of participants for this study will be done at the University of South Carolina School of Medicine Greenville. We will be recruiting 15 otherwise healthy participants with no significant ophthalmological history. Data collection will be done at the Prisma Health Eye Institute - Greenville. Data analysis will be performed by Alex Ewing at Prisma Health.

After participants are recruited, they will be brought into the ophthalmology clinic where they will first be consented for the study by a physician[appx.5]. Following consent, participants will complete paperwork such as demographics[appx.2], contact information[appx.3] and exclusion/inclusion criteria forms[appx.4]. They will then be screened for hyperopia using a phoropter, have their intraocular pressures measured using a Reichert Tono-Pen Avia , and have their iridocorneal angle measured with a gonio lens. The purpose of this exam is to screen out participants with hyperopia > +1 diopter, iridocorneal angles where trabecular meshwork cannot be seen for greater than half of the angle, and/or intraocular pressures of > 22 mm Hg, as these conditions may increase the risk for mydriatic agent-induced angle closure glaucoma[appx.4]. An additional ophthalmic medication, proparacaine hydrochloride 0.5%, will be used to numb the eyes before measuring intraocular pressures and prior to gonio lens examination. This medication is commonly used as an ocular surface analgesic during routine eye examinations. This screening exam will take place at least one day prior to administration of any dilating drops, as examination of the angle with gonio lens may affect pupillary dilation through corneal contact. The initial exam will be performed by a physician licensed to practice ophthalmology.

After screening, participants will be asked to return to the clinic on a scheduled day (within a week of screening) to have their left eye dilated. At this visit, the diameter of their left pupil will be measured using a Near card in a windowless room with a set light-level. Tropicamide will be our agent of choice for pharmacological dilation. Tropicamide is widely used in ophthalmology clinics to dilate the pupil of the eye and has a suspected effect time of 4-8 hours of dilation.[5] Participants will receive one drop of tropicamide in the left eye and, after the drops have had time to take effect, about 20-30 minutes, the diameter of the participant's pupil will be measured again. After measurement of baseline pupillary response to tropicamide, participants will be dismissed and asked to return to the clinic in 3-4 hours. At this time, we will record the diameter of the left pupil again and compare it to the participant's baseline as well as post-dilation diameter. One drop of 1% pilocarpine will then be administered to the participant's left eye. Pilocarpine 1% is a miotic agent that is the current standard for workup of anisocoria of unknown cause according to the 2021-2022 Basic and Clinical Science Course[appx.1]. After the pilocarpine has been given 10-15 minutes to take effect,

any change in pupillary diameter will be measured. Following this measurement, participants will be dismissed. A positive result will be indicated by a constricting response of the pupil after administration of pilocarpine of > 1mm in diameter, while still appearing anisocoric on exam (clinically significant difference in pupillary diameter between right and left eyes). Application of dilating and constricting eye drops, as well as measurement of pupillary response will be performed by medical student volunteers. These volunteers will receive training on sterile eye-drop application technique as well as pupillary measurement using a Near card.

In the event that no response to 1% pilocarpine is observed at the initial post-dilation visit, or if pupillary diameter has returned to baseline prior to the administration of 1% pilocarpine at any point, we will ask this participant to return to the clinic on another day to have the process repeated in their right eye, with the modification of either shortening or lengthening the interval of reassessment based on their left eye's response to the drops. This is to avoid any confounding from the administration of subsequent pilocarpine eye drops in the same eye. If the left pupil returned to baseline pupillary diameter prior to the 3-4 hour reassessment, we will have them return 2-3 hours following dilation of their right eye to have their pupillary diameter checked and the administration of Pilocarpine 1% repeated. If the left pupil remained dilated with no response to 1% pilocarpine at 3-4 hours, we will have them return 4-5 hours following dilation of their right eye to have their pupillary diameter checked and the administration of Pilocarpine 1% repeated. Repeating the protocol with varied assessment times in the contralateral eye will be in an effort to compensate for expected variation in each participant's response to tropicamide and 1% pilocarpine. Despite this, it is possible that we will not be able to capture this critical window in each participant, if one exists. However, we do not believe it will be necessary to demonstrate the phenomenon in all participants, and a minimum of 2 positive results should be sufficient to demonstrate our proposed concept for this preliminary study.

E. PROTECTION OF HUMAN SUBJECTS

1. TARGET POPULATION:

We plan to conduct the study with 15 medical student volunteers at the University of South Carolina Greenville. Exclusion criteria include a history of angle closure glaucoma, any other type of glaucoma, or any elevated eye pressure readings as well as any history of intraocular surgery or procedure. Exclusion will also occur if the participant is found to be hyperopic to >+1 diopter, has an intraocular pressure of > 22 mm Hg in either eye, or displays an iridocorneal angle where trabecular meshwork cannot be seen for greater than half of the angle in either eye, as these features are known to increase the risk of angle closure glaucoma when using dilating eye drops.

Finally, those with a known allergy to natural rubber latex will be excluded from the study.

We chose a sample size of 15, as this is a proof of concept, and thus we would like to demonstrate a minimum of 2 instances of pharmacologically dilated eyes that constrict > 1mm to 1% pilocarpine. We feel that at least 15 participants will be necessary to guarantee that we witness at least 2 instances of the proposed phenomenon, assuming that we test both of their eyes independently with varying timeframes of reassessment. If we limited the study to < 15, we may not be able to witness the desired effect without subjecting participants to multiple rounds of testing.

If we are able to describe a period in which the pharmacologically dilated pupil responds to 1% pilocarpine with >1mm of constriction but maintains the appearance of anisocoria that is worse in bright light in two or more participants, this study will serve as a pilot study to demonstrate the need for further research on the concept in order to make an addendum to the current treatment algorithm for anisocoria.

2. RECRUITMENT PLANS:

Recruitment of subjects will be done in person at the University of South Carolina School of Medicine Greenville, via the school newsletter that is sent to the student body on a weekly basis, and with email correspondence via the Ophthalmology interest group at the school. Approval has been obtained from school administration to conduct recruitment onsite and via electronic correspondence[appx.6,7].

3. EXISTING DATA/SAMPLES:

There are not any existing data or samples for this study.

4. CONSENT/ASSENT:

The participants will be asked to sign a consent form prior to participation[appx.5]. The study doctor will consent the participants before any study procedures are completed. All communication will take place in a private setting. The participant will be given ample time to read the consent and have all questions answered prior to providing signature. The consent will be signed and dated by all parties and a copy will be provided to the participants at the time of consent. The consent will discuss risks of eye dilation including blurred vision for several hours following drop administration. Participants will also be informed of the risk of angle-closure glaucoma, and will be screened for any significant ophthalmological history, which will exclude them from the study. Participants will have ample opportunity to ask any questions concerning what to expect from and potential risks of dilating drops.

5. POTENTIAL RISKS:

Drug Tropicamide:

The risks of the study are largely limited to side effects from the dilating drops, which are mild (increased heart rate, headache, nausea, vomiting, dry mouth, allergic reactions, tense muscles, stinging of eyes (transient), eye surface injury) other than the rare, but serious, risk of inducing angle closure glaucoma. Participants will be instructed to monitor symptoms of angle closure glaucoma including headache, nausea, and eye pain, and participants with history of angle closure or any other type of glaucoma will be excluded from the study.

Drug Pilocarpine:

A possible side effect is retinal detachment, an emergency situation in which a thin layer of tissue (the retina) at the back of the eye pulls away from its normal position. This side effect is serious but extremely rare. Other side effects, which are less severe, but may occur more frequently include: brow ache, headache, blurred vision, eye irritation, eye pain, watery eyes and visual impairment (including dim, dark, or jumping vision).

Drug Proparacaine Hydrochloride:

Occasional temporary stinging, burning and conjunctival redness may occur with the use of proparacaine. A rare, severe, immediate-type, apparently hyperallergic corneal reaction characterized by acute, intense and diffuse epithelial keratitis, a gray, ground glass appearance, sloughing of large areas of necrotic epithelium, corneal filaments and Sometimes iritis with descemetitis has also been reported.

Therefore, the small likelihood of risks outweighs the benefit of improving understanding of the time parameters of the pharmacological effects of dilation drops. The participants will likely experience blurred vision, particularly near vision, for up to eight hours after administration of dilating drops. The participants will be asked to use dark sunglasses when in bright sunlight or when driving for at least twelve hours.

For precautionary measures, participants will be asked to contact the clinic if vision is moderately or severely blurred following the administration of Tropicamide, or if they experience any symptoms of acute angle closure glaucoma or retinal detachment. If angle-closure glaucoma or retinal detachment are suspected, we plan to adhere to standardized protocol for treatment.

Devices:

There is a small risk of corneal abrasion with handheld applanation tonometry and gonioscopy, as in both cases direct contact is made with the cornea. This is extremely rare, and we are mitigating this risk by having a trained physician (Dr. Oakman) perform these exams. These are both examination techniques used in the eye office daily.

The Reichert Tono-Pen Avia uses tips that contain natural rubber latex which may cause allergic reactions. Participants will be screened for a known allergy to natural rubber latex and will be asked to monitor for signs and symptoms of an allergic reaction following use of the Tono-Pen.

6. POTENTIAL BENEFITS:

This research study is not expected to directly benefit individual subjects but is likely to yield generalizable knowledge which contributes to the field. The information gained from this study may be useful and may help others who will be undergoing evaluations for anisocoria in the future.

7. CONFIDENTIALITY

Information obtained about participants during this research may be published, but they will not be identified. Information that is obtained concerning this research that can be identified will remain confidential to the extent possible within State and Federal law. The investigators associated with this study, the sponsor, and the Institutional Review Board will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law. Study information will be securely stored in locked files and on password-protected network storage.

8. COMPENSATION:

We plan to provide participants with a gift card (Clincard) for their time spent conducting the study. We plan to request $50 per participant. Potential medical student participants will be advised that their participation in the study will in no way affect their grades, evaluations or medical school standings.

9. WITHDRAWAL:

Participants may withdraw at any point, but the gift card will not be given as compensation unless participants complete the entire study. If participants fail to meet all inclusion criteria or meet any exclusion criteria during their initial visit and screening exam, they will not be able to proceed with the experiment and therefore will not receive compensation.

F. REFERENCES/LITERATURE CITATIONS

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G. APPENDIX

See Attached (Appx1-7)