Effect of Topical Phenylephrine 2.5% on Episcleral Venous Pressure in Normal Human Eyes

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General Study Information

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Study Title: Effect of Topical Phenylephrine 2.5% on Episcleral Venous Pressure in Normal Human Eyes

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Research Question and Aims

Hypothesis: Topical phenylephrine 2.5% can change episcleral venous pressure (EVP) in normal human eyes.

Aims, purpose, or objectives: Phenylephrine hydrochloride ophthalmic solution is an alpha-1 adrenergic receptor agonist commonly used topically for dilation prior to ocular fundus examination. In the eye, phenylephrine acts locally as a potent vasoconstrictor and mydriatic by constricting ophthalmic blood vessels and the radial dilator muscle of the iris.[1,2,3] Episcleral venous pressure (EVP) is a determinant of intraocular pressure (IOP) and can be measured non-invasively by venomanometry. Since phenylephrine is a vasoconstrictor, it may affect episcleral venous tone, but the effect on EVP is unknown. The purpose of this study is to assess the effect of topical phenylephrine on EVP by using a custom slit-lamp mounted venomanometer.

Background: Phenylephrine eye drops are frequently used in ophthalmology for dilation of pupils, usually in combination with tropicamide 1% for routine clinical fundus examination, as well as in preoperative regimens for intraocular surgeries. Both concentrations of 2.5% and 10% phenylephrine have been used for this purpose. Maximal mydriasis occurs in 60 to 90 minutes with recovery after 5 to 7 hours. The time lag for response is about 15 minutes.[4] In prospective randomized trials in Caucasians, phenylephrine 2.5% has been found to be as effective as phenylephrine 10%, with fewer systemic side-effects but in darkly pigmented irises phenylephrine 10% appears to be more effective than phenylephrine 2.5% in pupillary dilation.[2,5,6] Phenylephrine also is used as a decongestant by constricting conjunctival vessels, therefore decreasing eye redness. Gaynes[7] reported of decrease in conjunctival venous diameter and blood velocity, and reduction of blood flow in rabbit conjunctival vessels.

Several studies have been carried out to measure the effects of phenylephrine on IOP and facility of aqueous humor outflow in normal and glaucomatous human eyes. In several studies, phenylephrine was found to cause a mild reduction in IOP in both normal eyes[8,9] and eyes with open- angle glaucoma.[9,10] Other studies have indicated that no change or a slight increase in IOP may occur in normal eyes or eyes with open-angle glaucoma

after treatment with Phenylephrine.[11-15] Tonographic studies have also been carried out with a range of results. Some have shown phenylephrine to increase[8, 9], some to decrease[13], and some to have no effect on outflow facility[9, 13, 14, 16] in normal and glaucomatous eyes.

Lee and Brubaker[17] reported that topical phenylephrine 2.5% did not cause a clinically significant change in aqueous humor flow, IOP, or anterior chamber volume. Marchini[18] showed that phenylephrine 10% did not cause any statistically significant change in IOP in patients with glaucoma and normal subjects. The effect of phenylephrine on the aqueous flow in normal human eyes is considered to be negligible as a result of either an insufficient concentration of phenylephrine in the ciliary body or the lack of influence of an α-receptor system on the aqueous flow.[17, 19] A pharmacokinetic analysis of topical phenylephrine in the human eye revealed that phenylephrine is lost fairly rapidly from the anterior chamber.[4]

Systemically administered phenylephrine can cause pronounced cardiovascular adverse effects, including increases in both systolic and diastolic blood pressure (BP) and change in heart rate (HR).[20, 21] However, there is no conclusive evidence regarding the cardiovascular adverse effects of phenylephrine, 2.5% or 10%, eye drops alone or in combination with tropicamide. The largest randomized clinical trial that compared phenylephrine 10% (n = 100) against tropicamide 1% (n = 50) did not find an increase in BP or HR up to 30 minutes after administration in either group.[22] No change was seen with phenylephrine 2.5% at 20 to 30 minutes or at 60 minutes or longer after topical application. Phenylephrine 2.5% is considered safe for routine use in ophthalmic examinations.[23]

Study Design and Methods

Visit Schedule:

Description	Visit 0 (Screening)	Visit 1
Time	0.5 – 1 hour	1.5 - 2 hours
Purpose	1. Informed consent 2. Eligibility ophthalmic examination, medical and ophthalmic history. 3. Review protocol.	Measurements of systemic and ocular parameters, and response to topical phenylephrine
Compensation	0$	50$

Tests performed:	1. Height, weight, blood pressure, pulse rate 2. Routine eye examination	1. Blood pressure and pulse rate 2. IOP measurement with pneumatonometer 3. EVP measurement with venomanometer Topical phenylephrine 2.5% will be instilled in one eye after all baseline measurements. 4. Blood pressure and pulse rate repeated at 15 & 60 min 5. IOP measurement repeated at 15 & 60 min 6. EVP measurement repeated at 15 & 60 min

Medications:

The subjects will be treated with the following FDA-approved topical medications: proparacaine 0.5% and phenylephrine 2.5%. All the eye drops will be provided from Mayo pharmacy stock supplies available in every ophthalmology clinic exam room. Proparacaine will be stored in a secure refrigerator that is monitored for medication storage. Phenylephrine will be stored in a secure area at room temperature.

Clinical Methods:

Visit 0 (Screening):

After obtaining informed consent, we will examine each subject for general eye health to determine eligibility for the study, including visual acuity, slit lamp biomicroscopy, IOP measurement, gonioscopy, fundoscopy including optic disc and macula characterization. We will also record current medications, medical and surgical histories, and obtain routine physical measures (height, weight, blood pressure and pulse rate). A urine pregnancy test will be performed for all women who are sexually active and able to become pregnant.

Visit 1:

1. Intraocular Pressure:

IOP will be measured after topical anesthesia by using the pneumatonometer (Model 30 Classic, Medtronic Solan, Jacksonville, FL), the instrument used in research and clinical care at Mayo Clinic. There will be a minimum of three IOP measurements and a mean will be accepted as IOP. The difference between the three valid measurements should be no more than 2 mmHg.

2. Episcleral Venous Pressure:

EVP will be measured non-invasively using a custom-modified slit-lamp mounted venomanometer[24], with modifications designed and constructed by the Mayo Clinic Division of Engineering.[25] This device utilizes the pressure chamber technique, in which a clear flexible balloon is placed against the conjunctival surface of the eye, and the pressure is increased until an episcleral vein is noted to blanch. Our system for pressure-chamber based venomanometry includes a computer-controlled motor drive to increase pressure automatically, a transducer to record pressure, and a high-definition video camera to record vein collapse. Pressure measurements are synchronized with the video stream and image analysis software is used to determine the pressure required to collapse the vein to a specific pre-determined degree.

3. Blood Pressure & Pulse Rate:

All blood pressure and pulse measurements will be taken with the subject in sitting position using an automated blood pressure monitor. An appropriate cuff size will be used for each subject.

Topical proparacaine will be instilled in each eye for anesthesia before IOP measurement and EVP measurement. After determining eligibility of subjects, baseline IOP, EVP, blood pressure and pulse rate will be measured in both eyes prior to instillation of phenylephrine eye drop. Each subject will then receive three consecutive drops of phenylephrine 2.5% instilled into the lower conjunctival sac of one eye at 1 minute intervals based on an Excel randomization table. The other eye won't receive any eye drop. Subjects will be instructed to close their eyelids gently after instillation of each drop and to maintain closed eyes for 1 minute. They will be instructed to press a finger over medial canthal area against nasal bone to close nasolacrimal duct and reducing systemic absorption of phenylephrine. No placebo will be used for the other eye as a control. Blood pressure and pulse rate, IOP, and EVP will then be measured 15 minutes and 60 minutes after instillation of phenylephrine. For each parameter, a mean of 3 measurements will be accepted as a final value. On the day of the study the subjects will be asked to maintain a regular schedule with normal activities.

Resources:

Subjects will be brought to the Ophthalmology Clinic where the study will be explained and informed consent will be obtained. All measurements will take place in a standard examination room or the glaucoma clinical research area in the Ophthalmology Department and performed by the Principal Investigator or trained study personnel. All measurements for each subject are expected to take 120 minutes.

Subject Information

Target accrual: 20 normal adult subjects

Subject population: Participants will be recruited from local area residents, employees of Mayo Clinic, and prior study participants who have consented to be contacted for future research. All subjects will provide an ophthalmic history and receive a complete eye examination to ensure that they are eligible for the study.

INCLUSION CRITERIA	EXCLUSION CRITERIA

• Either gender.
• Adult subjects, 18 years of age and older.
• Any self-declared ethno-racial category.
• Medically healthy subjects.
• Subjects with two healthy eyes.
• Intraocular pressure (IOP) less than 22 mmHg in each eye.
• Best-corrected visual acuity (BCVA) in each eye 20/50 or better.
• Open angles in both eyes.
• Contact lens wear stopped at least 3 days prior to study, and during the study.
• Ability to cooperate for examinations required for study.
	• **Ophthalmic:**
	  • Chronic or acute ophthalmic diseases including glaucoma, wet type macular degeneration, uveitis and clinically significant cataract.
	  • Evidence of ocular infection, inflammation, clinically significant blepharitis or conjunctivitis.
	  • Cornea pathologic changes preventing reliable measurement.
	  • Narrow anterior chamber angle.
	  • Previous intraocular surgeries, laser procedures, and intravitreal injections.
	  • Previous corneal refractive surgeries.
	  • Myopia greater than -6.00 D spherical equivalent.
	  • Hyperopia greater than +2.00 D spherical equivalent.
	  • Lack of suitable episcleral vein for measurement.
	  • Ocular trauma within the past 6 months.
	  • Ocular infection or ocular inflammation in the past 3 months.
	  • Ocular medication of any kind within 30 days of study visit.
	  • Known hypersensitivity to Phenylephrine or topical anesthetic medication.
	• **Systemic:**
	  • Severe hypertension: Systolic blood pressure

	greater than 180 mmHg and/or diastolic blood pressure greater than 105 mmHg. • A known history of ischemic heart disease (angina or myocardial infarction), cerebrovascular accidents, cardiac arrhythmias, cerebral or aortic aneurysms. • Uncontrolled diabetes mellitus. • Uncontrolled hyperthyroidism. • Use of some systemic medications within 30 days prior to study including: β-adrenergic antagonists, α-adrenergic agonists and antagonists, calcium channel blockers, diuretics, vasodilators, monoamine oxidase inhibitors, and systemic steroids. • Participation in any interventional study within the past 30 days prior to study visit. • Women who are pregnant.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

3. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

4. ☒ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

Biospecimens – Categories 2 and 3

N/A

Review of medical records, images, specimens – Category 5

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be collected after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic		

images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Human Safety Aspects:

There is a minimal risk of corneal abrasion from measurement of IOP. This is similar to the risk of corneal abrasion during a routine eye exam, which is a very rare event. Any subject experiencing a corneal abrasion will be withdrawn from further study measurements and treated.

The risk of EVP measurement is negligible since the device only touches the conjunctiva, not the cornea.

There is a minimal risk of eye irritation from the use of topical anesthetic eye drops. However, these drops are used hundreds of times daily for routine clinical care in the Ophthalmology Department with adverse reactions occurring very rarely.

There is a minimal risk of systemic absorption of topical phenylephrine and raising the blood pressure. However we will use phenylephrine 2.5% eye drop that has been used routinely for pupil dilation and fundus examination in ophthalmology clinics and has been reported safe to use in clinical routine.

Data Analysis

Data Analysis Plan:

All baseline measurements before instillation of phenylephrine will be compared to corresponding ones 15 and 60 minutes after that by using two-sided t-test. There is also a comparison between treated and non-treated eyes for IOP and EVP measurements. Differences will be considered significant if *P* is less than 0.05.

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