PROPARACAINE EPIPHORA STUDY

PROJECT SUMMARY

Purpose: It is unknown whether instillation of a drop of anesthetic ophthalmic solution into the eye such as Proparacaine hydrochloride 0.5% prior to probing and irrigation of the lacrimal drainage system improves patient comfort during the procedure. To date, there have been no formal studies evaluating the possible benefit of this pretreatment.

Methods: Patients 18 years and older who present to our outpatient oculoplastics based practice with a chief complaint of epiphora who necessitate bilateral lower lid probing and irrigation of the lacrimal drainage system will be enrolled in the study after obtaining full informed consent. Exclusion criteria: a known allergy to topical -caine anesthetics, known pre-existing scarring, surgery, radiation to the nasolacrimal system, the presence of blockage and or reflux on probing and irrigation of either side, any cognitive impairment. One eye will be randomized to receive a drop of Proparacaine hydrochloride 0.5% and the other eye will receive a control drop of balanced salt solution (BSS). Probing and irrigation will then be performed in the usual fashion. Patients will then be given a simple one question survey asking: "Which side was more uncomfortable during probing and irrigation: right or left?" and the results will be recorded.

Expected Results: We expect patients' eyes that have received a drop of Proparacaine hydrochloride 0.5% prior to performance of probing and irrigation will experience statistically significantly less pain compared to the eyes which have received the control drop.

GENERAL INFORMATION

Title: Does Administration of Proparacaine Hydrochloride 0.5% Ophthalmic Solution Prior to Canalicular Probing and Irrigation Decrease Patient Discomfort?

Primary investigator

Austin Pharo, M.D

Co-investigators:

Jonathan S. Williams, M.D.

Jawad Ahmad, M.D.

Marlene Azar, M.D.

Zachary Davis, M.D.

Martine Domangue, M.D.

Benjamin Lee, M.D.

Nicole Legare, M.D.

Kush Patel, M.D.

Recruitment of patients and performance of trial will be at the following sites:

LSU Healthcare Network
3700 St. Charles Ave
New Orleans, LA 70115

University Medical Center New Orleans
2000 Canal St.
New Orleans, LA 70112

University Hospital and Clinics
401 St. Julien St
Lafayette, LA 70506

Our Lady of the Angels – Bogalusa
433 Plaza Street/2nd Floor
Bogalusa, LA 70427

Eyelid & Facial Consultants
3715 Prytania St, Suite 504
New Orleans, LA 70115

RATIONALE AND BACKGROUND INFORMATION

Rationale: It is common for male and female adult patients of all races with a chief complaint of epiphora to express discomfort either verbally or through body language while undergoing canalicular probing and irrigation even when no pathology is detected. Use of a topical anesthetic during canalicular probing and irrigation is seen in pediatric patients[1] but has yet to be formally investigated in adults to date. The goal of this study is to identify whether or not instillation of a drop of Proparacaine hydrochloride 0.5% ophthalmic solution into a patient's eye prior to performance of probing and irrigation will improve patient comfort during the procedure and is therefore recommended.

Hypothesis: Administration of a drop of Proparacaine hydrochloride 0.5% ophthalmic solution into the eye prior to probing and irrigation of the lower lid canalicular system will decrease patient discomfort as compared to a control drop of BSS ophthalmic solution into the opposite eye prior to the same procedure.

Null hypothesis: Administration of a drop of Proparacaine hydrochloride 0.5% ophthalmic solution does not have an effect on patient discomfort during canalicular probing and irrigation.

Medication: Proparacaine hydrochloride ophthalmic solution, USP 0.5% is a local anesthetic drug intended for topical ophthalmic use. Proparacaine Hydrochloride ophthalmic solution is a

fast-acting anesthetic lasting 10-20 minutes.[2] Proparacaine hydrochloride ophthalmic solution, USP 0.5% is FDA approved for this indication.

Probing and irrigation: A common in-office ophthalmic procedure performed with a small gauge, blunt cannula on a syringe filled with BSS. The cannula is placed into the canaliculus of one eyelid, and the BSS is used to irrigate the lacrimal system. This procedure identifies whether or not obstruction of the lacrimal system is present. A patient with a patent system will taste the saline solution in the nasopharynx. A patient with a nasolacrimal duct obstruction (NLDO) or a more proximal canalicular obstruction will have reflux of the irrigant out of the opposite lid (on the same side) canaliculus, the probed canaliculus, or both and will usually not detect any irrigant within the nasopharynx.

Nasolacrimal drainage system: The physiologic apparatus which drains tears from the surface of the eye into the nose (i.e. the tear drain). It consists of (from eye to nose) the punctum (opening of the tube), the canaliculus (a thing tube within the eyelid), the lacrimal sac (a sac that hold the tears that lies within the bone of the nose) and finally the nasolacrimal duct (a duct that connects the lacrimal sac (-lacrimal) into the nose (naso-). A blockage anywhere along this pathway can cause epiphora.

Epiphora: The pathological process of tears overflowing from the ocular surface and rolling down the face. Commonly caused by obstructions of the lacrimal drainage system. Can cause significant patient irritation and loss of vision.

Relevant Literature:

1. Hung, CH. Chen, YC. Lin, SL. Chen, WL. "Nasolacrimal Duct Probing under Topical Anesthesia for Congenital Nasolacrimal Duct Obstruction in Taiwan" Pediatr Neonatol. 56. 2015: 402-7. 2015. https://www.ncbi.nlm.nih.gov/pubmed/26026949.
2. Alcaine (proparacaine hydrochloride 0.5%) [package insert]. Lake Forest, IL: Akorn Inc; 2016

STUDY GOALS AND OBJECTIVES

To identify if instillation of a drop Proparacaine hydrochloride 0.5% ophthalmic solution prior to performance of probing and irrigation of the lacrimal drainage system will decrease patient discomfort during the procedure.

STUDY DESIGN

A double-blinded, randomized, controlled clinical trial comparing the effects of Proparacaine hydrochloride 0.5% ophthalmic solution ocular surface instillation on patient discomfort during probing and irrigation of the lacrimal drainage system prior to performance of the procedure as compared to control BSS. Age range: 18 years and older. All races and sexes will be enrolled.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: Patients aged 18 and older who are having the signs and symptoms of epiphora which then would necessitate performance of a diagnostic probing and irrigation of the bilateral lower eyelid lacrimal drainage system at LSU Healthcare Network.

Exclusion criteria: a known allergy to topical proparacaine hydrochloride, known pre-existing scarring, surgery, radiation to the nasolacrimal system, the presence of blockage and or reflux on probing and irrigation of either side, any cognitive impairment.

METHODOLGY

Patients who present with epiphora can present with epiphora from both eyes or from only one side. A large proportion of those patients who present with epiphora only on one side, frequently have subclinical blockages that eventually will present clinically as epiphora. Thus, all patients who present with epiphora whether, bilateral or unilateral, undergo a bilateral diagnostic probing and irrigation in the office as the standard of care.

Procedure method: A patient who presents to the clinic with a chief complaint of epiphora who then necessitates probing and irrigation of the lacrimal drainage system to identify the cause of the epiphora will be marked for inclusion in the study. Informed consent to perform the procedure (as would be done normally) and full informed consent to participate in the study will be obtained by Dr. Pharo. Two identical 1 ml syringes will be prepared by Drs. Williams, Ahmad, Azar, Davis, Domangue, Lee, Legare, or Patel. One syringe containing control BSS, and the other containing Proparacaine hydrochloride 0.5% ophthalmic solution. Each of the patient's eyes will then be randomized. One eye to receive a drop of control BSS, and the other eye to receive a drop of Proparacaine hydrochloride 0.5% ophthalmic solution. Each syringe will be labeled with either left (L) or right (R) as randomized. Dr. Pharo will be the investigator performing the procedure with both syringes and will be blind to the solution in either syringe. These drops will be instilled by Dr. Pharo via the syringes into the patient's respective eyes. Thirty seconds will be given to allow for effect of the medication. Probing and irrigation with BSS will then be performed on each lower lid canaliculus as per normal exam protocol.

For study participants enrolled at Eyelid & Facial Consultants, the sub-investigators in this study will prepare 10 bags every 2 weeks containing two syringes for use by Dr. Pharo. Two identical 1 mL syringes will be prepared by Drs. Williams, Ahmad, Azar, Davis, Domangue, Lee, Legare, or Patel. One syringe will contain control BSS and the other will contain Proparacaine hydrochloride 0.5% ophthalmic solution. Each bag will be labeled #1 through #10 and the date the solutions were prepared. Each syringe will be labeled with either left (L) or right (R) as randomized. Upon enrollment of a patient in the study, one of the ten bags will be chosen. Dr. Pharo will be the investigator performing the procedure with both syringes and will be blind to the solution in either syringe. The drops from each syringe will be instilled by Dr. Pharo into the patient's respective eyes as labeled on the syringe (i.e. left and right eye). Thirty seconds will be given to allow for effect of the medication. Probing and irrigation with BSS will then be performed on each lower lid canaliculus as per normal exam protocol. Upon completion of the study on a patient enrolled at Eyelid & Facial Consultants, the bag number and date created will be reported with the other results as below. Ten (10) new bags will be created every 2 weeks or as needed

with the contents of each bag recorded on a master list (containing the creation date, bag number, and contents of each syringe). The master list will not contain any patient identifiable data. Dr. Pharo will be blinded to the contents of the master list. Any bags remaining after 2 weeks will be discarded.

A positive test on probing and irrigation is defined as the physical presence of blockage or reflux on performance of the test. A positive test on either side is exclusion criteria. Dr. Pharo be present in the exam room to perform testing. In those patients with noted blockages by the physician administering the test, Dr. Pharo will exclude them from the study.

In those patients with bilateral negative tests, after performance of the procedure, patients will then be given, by Dr. Pharo, a simple one question survey for each eye. The survey question is as follows: “Which side was more uncomfortable during probing and irrigation: right or left?” The patient’s demographic data (age and sex), medication list, and his/her responses to the survey will then be recorded on the assigned LSU research SharePoint site.

Randomization method: Randomization will be performed by Drs. Williams, Ahmad, Azar, Davis, Domangue, Lee, Legare, or Patel. A random number generator will be used to obtain either an even or odd number. Odd numbers mean the left eye receives Proparacaine hydrochloride 0.9% ophthalmic solution, even numbers mean the right eye does. These generated numbers will also be maintained on the assigned LSU research SharePoint site to maintain study validity. Drs. Williams, Ahmad, Azar, Davis, Domangue, Lee, Legare, or Patel will then label each syringe with an “L” or “R” depending on randomization result.

SAFETY CONSIDERATIONS

If during the course of the procedure and during close follow-up examinations, any adverse events are appreciated, the patient will be treated with the standard of care for that adverse event, the adverse event will be recorded into a spreadsheet which is encrypted and HIPPA compliant, the adverse event will be reported to the IRB in the required timeline, and the PI will frequently monitor for any patterns of unacceptably high rates of adverse events in which case the trial will be prematurely terminated. The study materials will be maintained on the clinic premises in a storage closet under lock and key.

The risks of use of proparacaine 0.5% include (obtained from package insert cited above):

NOT FOR INJECTION - FOR TOPICAL OPHTHALMIC USE ONLY. Prolonged use of a topical ocular anesthetic is not recommended. It may produce permanent corneal opacification with accompanying visual loss.

PRECAUTIONS:
Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenicity, or possible impairment of fertility in males or females.

Pregnancy: Animal reproduction studies have not been conducted with ALCAINE (proparacaine hydrochloride ophthalmic solution, USP) 0.5%. It is also not known whether proparacaine

hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Proparacaine hydrochloride should be administered to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when proparacaine hydrochloride is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of proparacaine hydrochloride ophthalmic solution in pediatric patients have been established. Use of proparacaine hydrochloride is supported by evidence from adequate and well controlled studies in adults and children over the age of twelve, and safety information in neonates and other pediatric patients.

Geriatric Use: No overall clinical differences in safety or effectiveness have been observed between the elderly and other adult patients.

ADVERSE REACTIONS: 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 been reported. Allergic contact dermatitis from proparacaine with drying and fissuring of the fingertips has also been reported.

FOLLOW-UP

Participants in the study will follow up as normally done after a probing and irrigation one month after the procedure. One month will be the total follow up period.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data and protected health information will be kept on the assigned LSU research SharePoint site. All statistical analysis will be performed by a professional statistician who will not have access to any identifiable patient data.

We will evaluate percent agreement between the eye identified as having the least discomfort and the eye in which proparacaine was administered. We will test whether the percent agreement is greater than 50%, the percent agreement expected based on random subject responses, using a score test for a single proportion. We will also calculate a 95% credibility interval for the percent agreement using the Jeffreys prior.

We determined sample size for this study based a test for a single proportion where the null hypothesis is that the proportion is 50%. A sample size of 145 provides ~95% power to detect at least 65% agreement.

QUALITY CONTROL AND QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s). Proparacaine Hydrochloride Ophthalmic Solution and BSS will be stored according to manufacturer's instructions. Manufacturer information such as Lot Number and expiration date will be documented by research staff for all Proparacaine Hydrochloride Ophthalmic Solution and BSS used.

EXPECTED OUTCOMES OF THE STUDY

Administration of a drop of Proparacaine hydrochloride 0.5% ophthalmic solution will decrease patient discomfort during lower lid canalicular probing and irrigation as compared to a control drop of BSS ophthalmic solution into the opposite eye prior to lower lid probing and irrigation. The answer to the question will be significant in that if the null hypothesis is found true, patients do not need to receive an unnecessary medication into their eye prior to the procedure. If the null hypothesis is rejected, then proparacaine can help alleviate some of the discomfort experienced by patients during this procedure which can occasionally be unpleasant.

DURATION OF THE PROJECT

Each subject undergoes one treatment period. Each trial lasts approximately three minutes in duration. The study will be concluded when a sample size of 90 eligible patients in the blockage group has been reached.

PROBLEMS ANTICIPATED

A potential source of error in this study is that patients with small unilateral blockages that might be missed on probe and irrigation may state the blockage side was more uncomfortable compared to the non-blockage side. Every effort will be made to mask the results of the probing and irrigation procedure until after the patient responds to the survey in order to decrease the chances of this occurring.

PROJECT MANAGEMENT

Collection of data, data analysis, writing, submission: Austin Pharo, M.D.

Identification, recruitment and treatment of patients: Jonathan S. Williams, M.D.; Jawad Ahmad, M.D.; Marlene Azar, M.D.; Zachary Davis, M.D.; Martine Domangue, M.D.; Benjamin Lee, M.D.; Nicole Legare, M.D.; Kush Patel, M.D.

DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Investigators will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections, and provide direct access to source data/documents.

ETHICS

Informed consent process

Patients with a chief complaint of epiphora who then necessitate bilateral lower lid probing and irrigation are identified. The presence of the study is then revealed to them.

Informed consent for participation in this study consists of explaining this pretreatment is an onlabel use of the ophthalmic topical anesthetic drug, Proparacaine hydrochloride 0.5% USP ophthalmic solution in an experimental method for reducing patient discomfort during lacrimal drainage system probing and irrigation. There have been no previous studies evaluating this question.

The process of the procedure will then be explained fully to the patient, along with the complete list of adverse effects that may be encountered.

All questions will be fully answered, and the informed consent form (or study information sheet) will not be signed until both the patient and physician are satisfied that both parties fully understand the details and concerns of the trial.

BUDGET

As probing and irrigation is an approved diagnostic modality for epiphora, probing and irrigation will be charged to the patient's insurance company or to the patient directly if the patient lacks insurance as per normal office procedure. No additional cost will be incurred to the patient for participation in the study. Any complications will be billed to the patient's insurance. Any unforeseen additional costs will be covered by LSU Healthcare Network.