Version 11/1/2018 Study Protocol

Project Title: A Prospective Randomized Control Trial of Pilocarpine use After Combined Cataract/Trabectome Surgery

Principal Investigator: Wen-Jeng (Melissa) Yao MD
Co-investigators: Matthew S. Wieder MD, PGY-2; Ana Rubin Panvini MD, PGY-3

Site(s) where study will be performed: Montefiore Medical Center, Ophthalmology Department

Background

Glaucoma is the leading cause of irreversible blindness worldwide, and its treatment consists of lowering intraocular pressure to prevent damage to the optic nerve and loss of vision[1]. Current methods for lowering intraocular pressure (IOP) include topical and oral medications, laser trabeculoplasty, microincisional glaucoma surgery (MIGS), and traditional incisional surgeries such as trabeculectomy and aqueous tube shunts. MIGS have become more popular in recent years as less invasive methods than traditional surgeries that effectively reduce IOP and help reduce the medication burden on patients[1]. There are multiple available MIGS procedures, most of which act by increasing trabecular outflow. One such procedure is the Trabectome, which is usually performed in combination with cataract surgery. Trabectome is an FDA approved device used to perform a trabeculectomy via an internal approach. A strip of 60-120 degrees of the nasal angle trabecular meshwork and the inner wall of Schlemm's canal are removed providing a direct pathway for aqueous outflow from the anterior chamber into the collector channels[2].

Pilocarpine, a parasympathomimetic agent, is a glaucoma medication that works by causing contraction of the ciliary muscle leading to opening of the trabecular meshwork[3]. Due to its frequent dosing requirement and large number of ocular and systemic side effects, pilocarpine has largely fallen out of favor for the treatment of primary open angle glaucoma (POAG), except in patients for whom few other alternatives exist. However, pilocarpine is often used after trabectome surgery. The rational for its use after Trabectome procedure is for its miotic effect, which theoretically may prevent the formation of peripheral anterior synechiae. Formation of peripheral anterior synechiae can lead to the closure of the cleft that is generated and the possibility of failure of the procedure. While the theoretical benefit of pilocarpine has been proposed, its actual benefit has never been proven. In this study, we aim to evaluate whether Trabecome / Cataract surgery without pilocarpine is non-inferior to Trabecome / Cataract surgery procedure followed by treatment with pilocarpine. The outcomes to be evaluated are the degree (percentage) of IOP lowering from baseline after the procedure, the mean post-operative IOP, the number of IOP lowering agents required to achieve goal IOP, and the rate of progression towards further glaucoma surgeries.

Key Questions

1. What are the demographics and characteristics of patients undergoing combined cataract/trabectome surgery at Montefiore Medical Center?
2. What is the post procedure percent IOP drop at 1 month, 6 months and 1 year after surgery.

3. What is the number of pre and post procedure drops required to achieve goal IOP at 6 months, 1, 2 and 3 years after combined cataract/trabectome surgery in patients treated with post-op pilocarpine vs control?
4. What is the rate of progression towards further surgery in patients treated with post-op pilocarpine vs control over a 3 year follow up period?
5. What is the rate of pilocarpine related side effects and drug discontinuation due to adverse effects?

Objectives

1. To determine whether Trabectome/cateract surgery without pilocarpine is non-inferior to Trabecome / Cataract surgery procedure followed by treatment with pilocarpine in decreasing IOP at 1 year after surgery.
2. To determine the incidence and characteristics of pilocarpine induced side effects in this population.

Selection of Patients

1. Inclusion Criteria: Patients with ocular hypertension or open angle glaucoma undergoing combined cataract surgery with trabectome in a single surgical center at Montefiore Medical Center with a single provider between March 1st 2018 and July 1st 2020
2. Exclusion Criteria: Patients with previous history of eye surgeries (including laser procedures).
3. Age Range: 30 to 100 years old

Study Design

Prospective randomized controlled trial

Study Methods

140 consecutive patients with POAG who are planned for combined cataract/trabectome surgeries will be consented for inclusion in this study. Patients will be randomized to one of two study arms, using an online computer randomizer; the first group labeled “treatment group” and the second “control group.” The treatment group will receive post-operative treatment with pilocarpine 2% for 1 month postoperatively, in addition to the standard post-operative surgical drops including topical steroids and topical antibiotic drops. The control group will receive the usual post-operative drop schedule without pilopcarpine. Most surgeons who do combined trabectome/cataract surgery will include the use of pilocarpine besides steroid and antibiotic. However, it is also acceptable for patients to only receive steroid and antibiotics (without pilocarpine) after such surgery. Patients in both groups will be followed for 1 year with the primary endpoint of percent decrease in IOP after surgery at 1 year. Secondary outcome measures will include: progression of glaucoma on OCT and HVF testing, medication side effects, number of pre and postoperative drops the patient was using before and after surgery, and need for further glaucoma surgery. All subsequent visits will be according to routine post-operative monitoring, where visual acuities, intraocular pressures, gonioscopy measurements will be performed at the slit lamp. These visits will coincide with standard of care post op follow up visits.

Participant recruitment

140 consecutive patients with POAG who are planned for combined cataract/trabectome surgeries with the principal investigator will be consented for inclusion in this study. Patients will be given a copy of the consent document to read over and they will be given time to ask any questions they have about the study. Participation in the study is completely voluntary and if they do not wish to participate in the study they can continue their care with the principal investigator and undergo their combined cataract/trabectome surgery without any remediation and their information will not be used in the study.

Confidentiality of data

Electronic data will be saved under a password protected computer in an anonymized fashion. Only the co-investigators will have access to the data for the duration of the study and only the co-investigators will be able to add data to the database. The data will be destroyed at the completion of the study.

Consent

Patients will provide written consent prior to participation in the study, as obtained by the investigators of this study. Once eligible patients are identified for the procedure at the pre-op visit, they will be asked to fill out the informed consent form and all questions will be answered. Patients will be informed of all risks and benefits of both the procedure and the use of pilocarpine as outlined further below. As no placebo will be utilized, patients will not be blinded to which group they are in.

Risks and Benefits:

1. Risks: Potential risks include the proposed risk of failure of the trabectome surgery secondary to scarring in both groups. Additional risk includes side effects of the use of pilocarpine, including but not limiting to: blurry vision, decrease night vision, headaches, browache, nausea, vomiting, diarrhea.
2. Benefits: Patients - the benefit to not using pilocarpine is a decrease in the medication burden and a decrease in the potential side effects that can occur with pilocarpine use. Additional benefits include for society and for the investigators due to the knowledge that will be gained from the study.

Statistical Considerations

1. Proposed sample size: 140
2. Proposed time period to be evaluated: 1 year of follow up
3. Feasibility of study – Over the time period 2/2016 – 9/2017, Dr. Yao completed 118 combined cataract/trabectome surgeries. Based on her historical usage and her usage of the combined procedure only increasing due to its success, we believe 140 patients can be recruited over a 1.5 – 2 year time frame.

Analytic Plan

All analyses will be based on the intent-to-treat approach (ITT). Standard descriptive statistics will be used to summarize the baseline characteristics and outcomes of the two treatment arms. The primary endpoint, percent decrease in IOP at 1 year after surgery compared to baseline, will be analyzed by computing the mean difference of this endpoint between treatment groups (pilocarpine - no pilocarpine) along with the corresponding two-sided 95% confidence interval. Non-inferiority of treatment without pilocarpine will be declared if the upper limit of the two-sided confidence interval is less than the margin of non-inferiority, which is deemed to be 5% in this study. Since the ITT approach can be anti-conservative in non-inferiority trials, a per-protocol analysis will also be performed. Two sample tests of the standard null hypothesis of no difference between groups will be conducted using the student T-test

for continuous variables or chi-square test for categorical variables (e.g., occurrence of side effects, need for further surgery). Linear or logistic regression models will be fit to the data to adjust for any baseline characteristics which are found to differ between treatment arms. In addition, generalized linear mixed models will be fit to the repeated measures obtained post-surgery, as part of every standard clinic encounter during follow-up. to assess whether the longitudinal trends in the outcomes differ between groups.

Sample size considerations

The sample size for this study is 140 subjects (70 per group). This sample size will yield greater than 95% power at a 1-sided Type I error rate of 2.5% (two-sided of 5%) to declare non-inferiority of the no pilocarpine group to the pilocarpine group with respect to the percent decrease in IOP after surgery, assuming an alternative hypothesis of no difference between groups, a non-inferiority margin of 5%, and a SD of 7.5% in both groups based on prior studies.

Data and Safety Monitoring Policy

As pilocarpine is an FDA approved medication with the overall risk level to the patient deemed to be mild, DSM will be undertaken by the investigator. At each office visit over the course of the life of the study (all visits as part of standard of care) specific attention will be made to reviewing whether the patient is having any potential side effects of the medication. If any side effects are noted and either the side effect cannot be tolerated by the patient or it is deemed to not be safe for the patient to continue to use the medication, the medication will be stopped and the patients inclusion in the study terminated.

1. Hu, K., et al., *Ab interno trabecular bypass surgery with Trabectome for open angle glaucoma.* Cochrane Database Syst Rev, 2016(8): p. Cd011693.
2. Mizoguchi, T., et al., *Clinical results of Trabectome surgery for open-angle glaucoma.* Clin Ophthalmol, 2015. **9**: p. 1889-94.
3. *Isopto Carpine (pilocarpine)[Package insert]*: Alcon, Inc. TX. 2010