A (randomized/prospective/pilot) study comparing the efficacy of Selective Laser Trabeculoplasty versus Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) in lowering intraocular pressure as adjunct therapy in Primary Open Angle Glaucoma.

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Title: A (randomized/prospective/pilot) study comparing the efficacy of Selective Laser Trabeculoplasty versus Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) in lowering intraocular pressure (IOP) as adjunct therapy in Primary Open Angle Glaucoma.

Purpose: To compare Selective Laser Trabeculoplasty (SLT) to the beta blocker and alpha-2 adrenergic agonist combination medicine Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) in their ability to lower intraocular pressure while serving as an adjunct therapy in patients with Primary Open Angle Glaucoma who are not controlled on a prostaglandin analog alone.

Objective: The primary endpoint is the intra ocular pressure reduction of SLT and Brimonidine tartrate 0.2%/Timolol maleate 0.5% at 8 weeks.

Background: SLT has been shown to be a safe and effective treatment to reduce IOP and because of this, several authors have advocated its use as first line therapy in primary open angle glaucoma or high risk ocular hypertension. 1, 2 Currently, however, it is being used mostly as adjunct therapy, either second or third line, for glaucoma. There is no consensus on the optimal timing of when to perform SLT in primary open angle glaucoma nor is there any evidence that directly compares SLT to a fixed combination topical therapy such as Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergen inc.). This study aims to determine which treatment is most effective at lowering IOP when primary open angle glaucoma patients are not well controlled on a branded prostaglandin analog alone.

Study population: Adult patients with uncontrolled primary open angle glaucoma. Consecutive patients based on the inclusion criteria will be selected for the study.

Study design: Prospective

Masking: The investigator(s) assigned to measure intraocular pressure will be masked to the patients treatment. This will be accomplished by scheduling follow up visits with a different investigator than the one that performed the SLT.

Randomization: Yes, this study will have two arms. Patients will be randomized by selecting a prepackaged envelope with the either the number one or two in it. Patients that select number one will be assigned to group one and will received 360 degrees of SLT in one eye. Patients that select number two will be assigned to group two and receive Brimonidine tartrate 0.2%/Timolol maleate 0.5% bid in one eye.

Method: Primary Open Angle Glaucoma patients that are currently taking a prostaglandin analog and are not controlled on mono therapy alone will be enrolled in this study. Patients that are enrolled will have their baseline IOP determined. This will consist of two IOP measurements taken 30 minutes apart and averaged together. Patients will then be randomized into one of two arms to determine which second line

therapy is most effective at lowering intraocular pressure. The first group will receive 360 degrees of SLT in one eye and the second group will receive Brimonidine tartrate 0.2%/Timolol maleate 0.5% bid in one eye.

Patients in the SLT group will be seen 1 hour following the procedure to ensure there is no IOP spike and started on Prednisolone acetate 1% qid x 4 days in the study eye to improve patient comfort. No other postoperative drops will be permitted unless there is a pressure spike of 10 mmHg or greater from their baseline IOP at the 1 hour post operative visit. If a pressure spike following the procedure occurs, one drop of rescue alphagan will be given. If this does not control the IOP spike then treatment to control the IOP will be at the doctor's discretion. All complications and adverse events will be recorded and closely monitored. Patients in the Brimonidine tartrate 0.2%/Timolol maleate 0.5% will be started on the topical medication. Each group will be scheduled for a follow up visit 8 weeks (+/- 2 weeks) after their respective therapy is initiated to assess the intraocular pressure reduction of the adjunct therapy. All patients will continue taking their current prostaglandin analog throughout the study.

If patients need treatment in both eyes the second eye will receive the same treatment as the first however only one eye will be eligible for the study. The eye with the higher baseline IOP will be included in the study, if the baseline IOP is equal in both eyes the right eye will be chosen as the study eye.

Compliance: Subjects will be given a patient diary to monitor compliance with their medication. The diary will be a log that includes the date and time of each drop, the eye and number of drops administered, and any problems encountered. A contact number with questions about drop dosing will be given.

Sample size: 30 patients will be enrolled in the study

Length of study: 12 months

SLT technique: 360 degrees of the angle will be treated with 100 spots (+/-10 spots) evenly spaced apart. The pigment in the angle is graded and the initial power for grade 1 or 2 pigment is set as 1.0 mj. The power is titrated in .1 mj steps until there is a visible response of cavitation bubbles or pigment blanching. For grade 3 or 4 pigment the initial power is set at .8 mj. The maximum energy is 2.0 mj and the minimal energy is .4 mj.

Posterior trabecular meshwork pigment grading system: Pigment in the posterior trabecular meshwork will be graded on a scale from 0-4. Standard photos will be provided to help guide the clinician as needed.

Inclusion Criteria:

- Uncontrolled primary open angle glaucoma
- Open angle on gonioscopy
- Patients aged 25 to 90 years old

Exclusion criteria:

- Best corrected visual acuity worse than 20/40 in the study eye (meaning 20/50 or worse)
- Hx of angle closure or an occludable angle on gonioscopy
- Untreated IOP less than or equal to 21 mmHg
- Patients who have used a second IOP lowering medication in the past 2 months
- Angle recession on gonioscopy
- Pseudoexfoliation glaucoma
- Pigment dispersion glaucoma
- Prior incisional glaucoma surgery
- Prior Microinvasive Glaucoma Surgery (MIGS, istent, Endocyclophotocoagulation)
- Previous SLT or Argon Laser Trabeculoplasty (ALT)
- Previous Laser Peripheral Iridotomy (LPI)
- Previous refractive surgery
- Inflammatory eye disease
- Contraindication to any of the topical medicines including asthma, chronic obstruction pulmonary disease, bradycardia, or a hypersensitivity reaction.
- A change in dosage, or addition of, a systemic medication that could effect IOP during the study
- Women who are pregnant or who intend to become pregnant in the next 4 months (as verbally asked during the medical history and consenting process, no formal pregnancy test will be administered for this study)
- Patients with significant dementia who are not able to fully comprehend the informed consent

Wash out period: none

Baseline IOP: Baseline IOP will be the average of 2 IOP measurements taken 30 minutes apart during the baseline exam. If the IOP measurements are greater than +/- 2 mmHg, a third IOP measurement will be taken 30 minutes later. All follow up exams will be within +/- 2 hour from the initial baseline exam to best control for diurnal fluctuations. Additionally, at each IOP measurement, 2 IOP readings will be taken and averaged together.

Examinations:

- Baseline exam
- Follow up 1 hour (SLT group only)
- Follow up 8 weeks (+/- 2 weeks) after SLT or starting additional topical therapy

Baseline exam (-30 to 0 days):

- Ocular history
- Family history

• Social history
• Blood pressure
• Pulse
• Pupils
• EOMs
• Visual acuity
• Goldman IOP
• Slit lamp exam
• Gonioscopy
• Pachymetry

1 hour follow up exam (SLT group only):

• Intraocular Pressure check (Goldman, tonopen, or icare) to ensure no IOP spike

8 week Follow up examination:

• Visual acuity
• Goldman IOP at same time as preoperative IOP to help control for diurnal IOP fluctuations, +/- 2 hours
• Blood pressure
• Pulse
• Pupils
• EOMs
• Slit lamp exam

Risk/Safety Information:

A. Potential risks:

Selective Laser Trabeculoplasty: Risks include mild pain, discomfort, red eye, blurred vision, photophobia, inflammation inside the eye, and an elevation in intraocular pressure immediately following the procedure.

Prednisolone Acetate 1%: Risks include increase in intraocular pressure, cataract, and drug hypersensitivity. Additionally, Prednisolone Acetate 1% may cause delayed wound healing, acute anterior uveitis (inflammation inside the eye), perforation of the globe (a full thickness hole in the eye), keratitis (inflammation of the cornea), conjunctivitis, corneal ulcers, mydriasis (pupil dilation), conjunctival hyperemia (red eye), loss of accommodation, ptosis (dropping eye lid) and ocular infections (bacterial, fungal and viral), although theses side effects are rare.

Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.): Risks include allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, stinging, and drug hypersensitivity. Additionally, Brimonidine

tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.), may exacerbate Chronic Obstructive Pulmonary Disease (COPD), asthma, uncompensated heart failure, 2nd or 3rd degree atrioventricullar block, sinus bradycardia, or cariogenic shock and should not be used in patients with these conditions.

B. Potential benefits to be gained by the subject:

Increased patient compliance for those in the SLT study arm. The potential for decreased cost of future glaucoma treatments. Contributing to the scientific body of knowledge. Additionally, since there is no placebo group, both groups will receive a treatment that has been shown to lower intra ocular pressure, this would be a direct benefit to research subjects with uncontrolled glaucoma.

C. Potential benefits or information which may accrue to science or society in general, as a result of this work.

Evidence to determine if topical Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) or SLT is more effective as adjunct therapy in treating primary open angle glaucoma.

D. Potential risks to subjects are reasonable in relation to anticipated benefits.

The risks associated with Selective Laser Trabeculoplasty are minor and transient in nature. However, there is a possibility of discomfort and eye pain associated with the procedure. Furthermore, the cost benefits of Selective Laser Trabeculoplasty compared to the current adjunct treatments of glaucoma is substantial. As Selective Laser Trabeculoplasty becomes more accepted as second line glaucoma therapy patients will stand to save money.

The risks of Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) are also minor and are mainly related to hypersensitivity to the topical medicine. This almost always resolves with discontinuation of the medicine.

Monitoring/Reporting Adverse Events:

SLT has been shown to be a safe and effective treatment to reduce IOP and several authors have advocated its use as first and second line therapy in primary open angle glaucoma or high risk ocular hypertension. Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.) is also widely used in treating primary open angle glaucoma, mostly as adjunct therapy. Additionally, Prednisolone Acetate 1% is a very common ophthalmic medication and is used routinely following cataract surgery. The risk profile for short term use in this study is limited only to drug hypersensitivity by the patient.

Adverse events will be monitored by the primary and sub-investigators at each study site. Adverse events will be documented and properly reported to the study IRB when

indicated. The adverse events for this study are minimal and transient in nature, however all investigators will have direct phone access to the lead investigator 24/7 for emergency situations. Data on adverse events will be reported and checked monthly by the primary investigator at each site as well as the lead investigator to ensure that there is no increased risk to the study subjects.

Study Oversight: The risks and adverse events for this study are minor and transient in nature, however this study will be prematurely terminated if the procedure or medications are found to have a risk profile that outweighs their benefit for the study. This determination will be made by the lead investigator/sponsor in conduction with the primary investigators and IRB. The study will provide direct access to the study data for the purposes of monitoring, auditing, IRB review, and regulatory inspection.

Data Management and Safety Monitoring:

A. Who will be responsible for the data and safety monitoring?

The lead investigator and the primary investigator at the research site will be responsible for data safety monitoring. The investigators are not independent from the study.

B. What will be monitored?

Only subjects who meet the study eligibility criteria will be enrolled in this study. Additionally the informed consent process will be conducted appropriately and informed consent will be obtained prior to any study procedure being performed. Data will be collected and analyzed by the guidelines set forth by the study protocol and adverse events will be reviewed promptly and reported as required to the IRB. HIPPA will be complied with at all times throughout the study and all patients will be assigned unique identifying numbers. The number of study dropouts will also be closely monitored.

C. What are the procedures for analysis and interpretation of data, the actions to be taken upon specific events or endpoints, the procedures for communication from the data monitor to the IRB and site, and other reporting mechanisms?

The Primary and sub-investigator(s) at the testing site will be responsible for the collection and storage of all study data. Data will be stored in a password protected cloud storage site and organized into an excel spreadsheet. The identity of each patient will be protected using a unique identifying number. A second spreadsheet will match that unique number with that patient's name, and will be stored separately under password protection. The lead and principal investigators will evaluate the current data collection monthly to make sure it is in order and the study performance is progressing without incident. After study completion, all collected data will be analyzed by appropriate statistical tools.

D. What is the frequency of monitoring?

Study data will be grossly monitored on a monthly basis to ensure that the study is performing smoothly and that all data is being collected in accordance with the set study protocol. This will also allow for the groups to be balanced as needed to ensure that the baseline population in one group does not become skewed.

E. What information will be reported to the IRB?

All necessary data will be reported to the IRB in a prompt manner including but not limited to the frequency and dates of data monitoring, a cumulative summary of adverse events, an assessment of new research that could impact the safety of the subjects, a summary of privacy and data confidentiality breaches, and any changes to the procedures risk-benefit ratio.

Informed consent: The protocol, informed consent document, and relevant supporting information will be submitted to the IRB for review and will be approved before the study is initiated. In addition, any subject recruitment materials will be approved by the IRB prior to being used. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56 [add 312 for IND studies or 812 for device studies], applicable laws and the IRB requirements. Any change to the protocol will be submitted to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects will be implemented immediately provided the FDA and the reviewing IRB are notified within 10 working days.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

1. When and where will consent take place?

Informed consent will take place at the eye care facility during normal business hours in either a private office or exam room. If a patient meets the eligibility requirements as determined by the primary investigator or sub-investigator they will inform the patient of the study and the risks/benefits/alternatives of the procedure in English. The subject will be given adequate time to weigh their options and the risk/benefits/alternatives of the study. If after adequate time is given, and all questions are answered, the subject wishing to participate will sign the informed consent documentation and they will be enrolled in the study. At this time their baseline IOP will be evaluated and the subject will

be randomized. All primary and sub-investigators for the study will be required to pass the National Institute of Health Protecting Human Research Participants certification.

2. How will the subject's privacy be protected during the consent process?

Each testing site will comply with HIPAA guidelines at all times. Informed consent will be performed during normal business hours at the eye care facility. The informed consent will be conducted in a private office or exam room.

Subject Payment and Costs: Subjects will paid $125.00 dollars for their participation in this study. This will help compensate the patient for their time and transportations costs. Payment will be made in the form of a Visa Gift card upon completion of the study and will be mailed to the patient. Additionally, subjects taking part in this study may incur added costs to themselves or their insurance company. The subject or their insurance company will be responsible for the following costs: All standard of care procedures, exams, and testing including the Selective Laser Trabeculplasty, the baseline exam, gonioscopy, pachemetry, and the eight week follow up exam. The subject will not be responsible for these study-specific costs: Prednisolone Acetate 1% or Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.)

Confidentiality: Efforts will be made to keep each subject's personal information confidential. All electronic data will be password protected, all paper records will be kept in private locked rooms, and patients in the study will be identified by unique ID numbers. However, we cannot guarantee absolute confidentiality. Personal information may be disclosed if required by law. Subject’s identity will be held in confidence in reports in which the study may be published and databases in which results may be stored.

Organizations that may inspect and/or copy the research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the study sponsor, and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) [for FDA-regulated research and research involving positron-emission scanning], the National Cancer Institute (NCI) [for research funded or supported by NCI], the National Institutes of Health (NIH) [for research funded or supported by NIH], etc., who may need to access your medical and/or research records.

Intended Use of Data: After all the data has been collected and analyzed a scientific paper addressing which adjunct therapy, SLT or Brimonidine tartrate 0.2%/Timolol maleate 0.5% (Combigan, Allergan inc.), lowers intraocular pressure more effectively, will be written and submitted to a distinguished peer reviewed journal for publication.

References:

1. Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G; SLT/Med

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2. McIlraith I, Strasfeld M, Colev G, Hutnik CM. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. J Glaucoma. 2006 Apr;15(2): 124-30. PubMed PMID: 16633226.