180 Degree vs. 360 Degree Selective Laser Trabeculoplasty as Initial Therapy for Glaucoma

NCT02628223

Document Date: 11/13/16

Date Uploaded: 11/3/2020

INSTRUCTIONS:

1) Abstract of the study

Selective laser trabeculoplasty (SLT) is a well-recognized way to lower eye pressure in treatment of glaucoma. This treatment is performed for 180 degrees or 360 degrees, and studies at academic centers have shown mixed results when comparing the success rates of 180 degrees or 360 degrees. Both protocols are now typically done by comprehensive ophthalmologists. However, there is no data that compares success rates of 180 degrees and 360 degrees in the community setting. This study is designed as a prospective evaluation of the two treatment algorithms for SLT by measuring intraocular pressure (IOP) after treatment.

2) Protocol Title

A Randomized Trial of 180 Degree vs. 360 Degree Selective Laser Trabeculoplasty as Initial Therapy for Glaucoma

3) IRB Review History

Not applicable.

4) Investigator

Primary Investigator: Jeffrey D. Henderer, MD.

Drew Chronister, MD

Steve Luminais, MD

Richard Sherry, MD

Sophia Siu, MD

Daohai Yu, PhD

5) Objectives

The purpose of this study is to compare the efficacy of two treatment algorithms (180 vs 360 degrees) of SLT as initial therapy for glaucoma in two comprehensive ophthalmology practices.

The hypothesis is that 360 degrees of SLT will produce a greater reduction in IOP than 180 degrees of SLT at 3 months follow up.

6) Background

Glaucoma is a leading cause of blindness in the United States and in the world. It is a chronic, degenerative optic neuropathy characterized by optic-nerve cupping and loss of retinal ganglion cell axons. Patients with glaucoma lose peripheral

vision initially, but because the disease is often not diagnosed until extensive visual field loss has already occurred, all vision may be lost if untreated.[1] Primary open angle glaucoma (POAG) is the most common form of glaucoma. It is often associated with an elevated intraocular pressure but may also occur in the presence of a normal IOP. Elevated IOP is considered the only modifiable and causative risk factor for POAG; other risk factors include older age, black race, family history, myopia, and low diastolic perfusion pressure.[1] Randomized clinical trials suggest that reducing IOP in patients with ocular hypertension or glaucoma can slow the onset and progression of disease and can reduce the long term risk of visual field loss.[2,3]

Treatment of glaucoma is aimed at reducing intraocular pressure by decreasing aqueous production or increasing aqueous outflow using medical, laser, or surgical treatments. Evidence suggests that a greater reduction of IOP offers a larger protection against visual field loss.[3] Topical therapies with prostaglandin analogues, α-adrenergic agonists, β-adrenergic blockers, cholinergic agonists and carbonic anhydrase inhibitors are often used for IOP reduction. Surgical treatments can also enhance aqueous humor drainage.

Laser trabeculoplasty has been proven to lower IOP. Although results may be variable or gradually lose effect, laser therapy may allow decrease of medical therapy or postponement of surgery. Argon laser trabeculoplasty (ALT) has been shown to be a safe and effective means of lowering IOP in patients with POAG possibly by coagulative thermal damage to the trabecular meshwork, allowing improved outflow.[4] In more recent years, selective laser trabeculoplasty (SLT) has been used as an alternative means to lower IOP in patients with open angle glaucoma. Unlike ALT, SLT selectively targets pigmented trabecular meshwork cells. Because SLT uses much less energy than ALT, it does not cause the same thermal burn to the entire trabecular meshwork and does very little mechanical damage.[5] The exact mechanism by which SLT lowers intraocular pressure is unknown, but some theories postulate that thermal energy from the laser stimulates macrophage remodeling of the extracellular matrix in the trabecular meshwork, improving aqueous outflow. Release of cytokines involved in certain

metalloprotease expression may further contribute to remodeling of the extracellular matrix.[5,6]

SLT appears to be a safe and effective therapy in lowering IOP in glaucoma. Studies suggest that SLT appears to be equivalent to ALT in terms of lowering IOP with the added benefit of less pain and anterior chamber inflammation compared to ALT.[6] The IOP-lowering effects of SLT also appears to be comparable to medical therapy, with the added benefit of better compliance. Potential adverse effects of SLT treatment include a transient elevation of IOP and mild uveitis associated with transient ocular discomfort for the first few days after treatment.

The amount of laser to use in a treatment session has traditionally been either 180 degrees or 360 degrees. For SLT, previous work has shown that about 80% of eyes that receive a 360 degree SLT can achieve a reduction of 20% and about 60% achieve a 30% reduction. There was no statistical difference between success rates between 180 and 360 degree treatment.[8] A different study found 90 degrees to be as effective as 180 degrees,[9] while yet a third showed that 180 degree treatment often failed to lower IOP.[10] A 360 treatment is associated with less IOP fluctuation compared with a 180 degree treatment.[11]

Because the previous SLT outcomes data was collected from academic center and since SLT is a treatment commonly performed in a private practice setting, we wish to see if SLT might have a similar effect as the previously published data. We have previously shown that repeat SLT has limited effect in a community setting and now wish to investigate the initial response to SLT in the same setting and see which treatment algorithm will be better.

References:

1. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. N Engl J Med. 2009 Mar 12;360(11):1113-24.

2. Maier PC; Funk J; Schwarzer G; Antes G; Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials.

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3. Heijl A; Leske MC; Bengtsson B; Hyman L; Bengtsson B; Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002 Oct;120(10):1268-79.

4. Zhao JC, Grosskreutz CL, Pasquale LR. Argon versus selective laser trabeculoplasty in the treatment of open angle glaucoma. Int Ophthalmol Clin. 2005 Fall;45(4):97-106.

5. Stein JD, Challa P. Mechanisms of action and efficacy of argon laser trabeculoplasty and selective laser trabeculoplasty. Curr Opin Ophthalmol. 2007 Mar;18(2):140-5.

6. *Murthy S, Latina MA. Pathophysiology of selective laser trabeculoplasty. Int Ophthalmol Clin. 2009 Winter;49(1):89-98.*
7. *Hong BK, Winer JC, Martone JF, Wand M, Altman B, Shields B. Repeat selective laser trabeculoplasty. J Glaucoma. 2009 Mar;18(3):180-3.*
8. *Nagar M, Ogunyomade A, O'Brart DP, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br J Ophthalmol. 2005;89:1413-7.*
9. *Chen E, Golchin S, Blomdahl S. A comparison between 90 degrees and 180 degrees selective laser trabeculoplasty. J Glaucoma. 2004;13:62-5.*
10. *Song J, Lee PP, Epstein DL, Stinnett SS, Herndon LW Jr, Asrani SG, Allingham RR, Challa P. High failure rate associated with 180 degrees selective laser trabeculoplasty. J Glaucoma. 2005;14:400-8.*
11. *Prasad N, Murthy S, Dagianis JJ, Latina MA. A comparison of the intervisit intraocular pressure fluctuation after 180 and 360 degrees of selective laser trabeculoplasty (SLT) as a primary therapy in primary open angle glaucoma and ocular hypertension. J Glaucoma. 2009;18:157-60.*

7) Setting of the Human Research

This research will be conducted at two comprehensive ophthalmology practices.

Steve Luminais, MD - Levin and Luminais, PC in Thorndale, PA

Rich Sherry, MD - Brandywine Eye Center in Wilmington, DE

8) Resources Available to Conduct the Human Research

Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

We anticipate enrolling 3 subjects per month in the study.

Describe the time that you will devote to conducting and completing the trial within the agreed trial period.

How many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Describe the number and qualifications of your staff, their experience in conducting research, their knowledge of the local study sites, culture, and society.

The ophthalmologists who will be performing the SLT have years of experience performing SLT, and will continue to follow their patients after the procedure.

Describe your facilities.

Two comprehensive ophthalmology offices.

Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the Human Research.

The patients will be monitored on a regular basis for adverse effects. The patients will receive appropriate follow up care and support.

Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and function.

All staff will be instructed on the study protocol, products, informed consent and protection of patient information.

9) Prior Approvals

None

10) Study Design

a) Recruitment Methods

Potential subjects at the ophthalmology clinic will be approached by the investigator. The study will be explained and consent will be requested.

Describe the amount and timing of any payments to subjects.

Not applicable.

b) Inclusion and Exclusion Criteria

Inclusion criteria are patients who have been diagnosed with open-angle glaucoma, including ocular hypertension, pseudoexfoliation, and pigment dispersion syndrome. Patients must be greater than 18 years of age, with an initial IOP ≥ 21mmHg,
Exclusion criteria include prior medical or laser therapy to lower IOP. Other exclusion criteria include previous incisional glaucoma surgery before the study period.

c) Local Number of Subjects

Indicate the total number of subjects to be accrued locally.

If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Each of the three comprehensive ophthalmologists is anticipated to recruit 37 patients, for a total of 111 patients. This also accounts for the possibility that approximately 5% of patients enrolled will be lost to follow up.

d) Study-Wide Number of Subjects

If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

We plant to enroll a total of 111 patients.

e) Study Timelines

Describe:

- The duration of a subject's participation in the study.

  One year

- The duration anticipated to enroll all study subjects.
- *Three years*
- The estimated date for the investigators to complete this study (complete primary analyses)
- *December 2017*

f) Study Endpoints

Describe the primary and secondary study endpoints. This is also called the primary outcome parameter. It is defined as the specific parameter or observation used to measure the effect of the intervention of interest. For example, a study may be conducted until the reoccurrence of disease, or change in blood pressure, or differences in proportions. Note that primary or secondary endpoints are not limited to clinical trials.

The primary endpoint is IOP at three months of follow up.

The secondary endpoint is 1 year of follow up or the point at which additional glaucoma therapy is required.

Describe any primary or secondary safety endpoints. Examples may include evidence of liver toxicity, an inability to tolerate further chemotherapy, or other side effects.

. Anticipated AE include spike in IOP and iritis, which will be treated accordingly.

g) Procedures Involved in the Human Research

Describe and explain the study design.

We will be conducting a prospective evaluation of two treatment algorithms for SLT. The first algorithm will be a 180 degree treatment and the second algorithm a 360 degree treatment. Treatments will be done by Drs. Steve Luminais, Drew Chronister, and Richard Sherry.

Patients will be pre-randomized to the 180 degree treatment or the 360 degree treatment by physician and by initial IOP (eg ≥ 21mmHg up to 30mmHg and ≥ 30mmHg.

Data that will be recorded for each patient include age, gender, race, glaucoma medications started during the study, the SLT protocol (number of spots, laser power setting and degrees of treatment). Baseline IOP before treatment will be recorded, in addition to measurement of IOP during a standardized follow up interval. Follow-up IOP measurements will also be recorded at one month, three months, six months and one year after laser. The physician will be masked as to the IOP result when measuring the IOP at each follow up visit Patients who require additional

glaucoma therapy will be censured from the study at that point. In addition, side effects and patient complaints will be noted.

For prospective studies:

Provide a description of all procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks. Include procedures being performed already for diagnostic or treatment purposes and differentiate between these and the procedures performed solely for the research.

We will be performing SLT on the trabecular meshwork of eyes.

Describe procedures taken to lessen the probability or magnitude of risks.

Patients will be monitored after the procedure for symptoms or a spike in IOP

Identify which procedures are being done as part of the Human Research and which are being conducted anyway for other reasons (standard of care).

Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Describe the source records that will be used to collect data about subjects. Attach all surveys, scripts, and data collection forms.

If you are unable to conduct your research using de-identified information, request a waiver of HIPAA authorization in section #13 ("privacy and confidentiality") by providing the following information as required by the HIPAA regulations:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

    a. an adequate plan to protect the identifiers from improper use and disclosure; You should describe the plan to protect identifiers. *For example: Data will be kept on a password-protected computer; data is only recorded electronically; Data will be saved on a secure server*;

    and

    b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law. For

example: once the data is recorded and verified for accuracy and completeness the link to the patient identifier will be destroyed;

and

c. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

and

2. The research could not practicably be conducted without the waiver or alteration. (The investigator should not claim a need for a waiver to allow recording of the patient's name or medical record number based on making it easier to go back to a medical record to verify information or obtain new information. A coding system should be developed and described in this protocol.);

and

3. The research could not practicably be conducted without access to and use of the protected health information.

The criteria for a waiver of HIPAA authorization can also be found in the CHECKLIST: HIPAA Waiver of Authorization.

Describe the data that will be collected, including long-term follow-up.

h) Data and Specimen Banking

Not applicable.

If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.

List the data to be stored or associated with each specimen.

Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

i) Data Management

Describe the data analysis plan, including any statistical procedures.

Multiple IOP values will be analyzed over the one year follow-up period. In addition to degrees of SLT, other covariates will be used to adjust the observed effects. These covariates will include age, sex, and baseline IOP. A multiple variable linear model (analysis of covariance for repeated measures) will be used to evaluate the effectiveness of SLT over time. In addition, change in IOP from baseline values to last follow-up will be calculated and compared.

Provide a power analysis.

A review of previous retrospective studies, and prospective studies performed at glaucoma specialists' offices found: on average 360 degrees of SLT lowers IOP by 6.33 +/-5mmHg and 180 degrees of SLT lowers IOP by 3.86 +/-5mmHg. Based on these results and a 5% loss-of-follow-up rate, our power analysis shows that we will need 55 patients in each arm of the study.

Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Patients will be assigned a number and that number will be entered in the database. No other patient identifying information will entered in the database

Describe how data and specimens will be handled study-wide:

- What information will be included in that data or associated with the specimens?
- Where and how data or specimens will be stored?

  The data will be stored on a Temple University password protected computer

- How long the data or specimens will be stored?
- *For the duration of the study*
-
- Who will have access to the data or specimens?

  Dr. Henderer and study investigators.

-
- Who is responsible for receipt or transmission of the data or specimens?

Dr. Henderer

j) Provisions to Monitor the Data to Ensure the Safety of subjects

This section is required when Human Research involves more than minimal risk to subjects.

Describe the plans to periodically evaluate the data collected regarding harms and benefits to determine whether subjects remain safe.

The patients will be followed closely to monitor for harms and benefits

Describe who will review the data.

Data will be reviewed by study investigators

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Primary and secondary endpoints, complications and demographics will be reviewed, including a comparison of 180 versus 360 degrees of SLT

Describe when data are reviewed.

Data will be reviewed after all patients have been followed for 1 year, or have reached another secondary endpoint

k) Withdrawal of Subjects

Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

This is not anticipated

Describe any procedures for orderly termination.

Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

11) Risks to Subjects

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to the subjects' participation in the research. Include the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Risks to the subjects include risks of SLT such as a spike in IOP, or mild anterior uveitis

If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

If applicable, indicate which procedures may have risks to an embryo or fetus if the subject is or becomes pregnant.

If applicable, describe risks to others who are not subjects.

12) Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

Benefits include lowering IOP and avoiding glaucomatous nerve tissue damage relating to elevated IOP.

13) Privacy and Confidentiality

Describe whether the study will use or disclose subjects' Protected Health Information (PHI).

If the study uses or discloses PHI, the PI must do one of the following:

a) Submit a HIPAA Authorization Form;

or

b) Justify a waiver of HIPAA authorization in this protocol. The criteria for a waiver of HIPAA authorization can be found in the CHECKLIST: HIPAA Waiver of Authorization.

Do not merely submit the checklist or state "I request a waiver" or "the criteria in the checklist are met." Instead, the PI must justify the waiver in this section of the protocol by referring to the checklist and explaining how each element of the waiver is met.

Additional information regarding PHI and HIPAA can be found in the "references" section of the Temple IRB website.

Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data).

The data will be transported and stored on password protected computers and encrypted USB drives.

Describe whether results (study results or individual subject results, such as results of genetic tests or incidental findings) will be shared with subjects or others (e.g., the subject's professor, teacher, advisor, counselor, or primary care physician) and if so, describe how it will be shared.

Every effort will be made to maintain the patient's privacy. The results of the research may be presented at meetings or in publications, however the patient's identity will not be disclosed in these presentations.

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information to.

Describe the steps that you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Study will be explained to the patients. Interview will take place in a private clinic room to ensure protection of the individuals' privacy and ease of the patient.

14) Compensation for Research-Related Injury

If the research involves more than minimal risk to subjects, describe the available compensation in the event of research-related injury.

Not applicable.

Provide a copy of contract language, if any, (e.g., clinical trial agreement) relevant to compensation for research-related injury.

15) Economic Burden to Subjects

Describe any costs that subjects may be responsible for because of participation in the research.

Not applicable.

16) Consent Process

Indicate whether you will you be obtaining consent, and if so describe:

- Where will the consent process take place

  In the private clinic room of the office

- Any waiting period available between informing the prospective subject and obtaining the consent.

  No

- Any process to ensure ongoing consent.
- *Subjects can opt out at any point*
- The role of the individuals listed in the application as being involved in the consent process.
- *The investigators will consent the patients*
- The time that will be devoted to the consent discussion.
- *Adequate time will be taken to discuss the study and address all concerns*
-
- Steps that will be taken to minimize the possibility of coercion or undue influence.
- Steps that will be taken to ensure the subjects' understanding.
  - *The investigators will ask the following questions to ensure the subjects' understanding:*
  - *What are your concerns regarding the procedure and its risk and benefits?*
  - *What are your concerns about the study?*
  - *Do you understand why are you are participating in the study?*
  - *Do you understand what the study entails?*
-

Non-English Speaking Subjects

- Indicate the language(s), other than English, that are understood by prospective subjects or representatives.
- If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language.
- *A certified translator will be used.*
-

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- Review the CHECKLIST: Criteria for Waiver or Alteration of the Consent Process to ensure you have provided sufficient information for the IRB to make these determinations. Do not merely submit the checklist or state "I request a waiver" or "the criteria in the checklist are met." Instead, the PI must justify the

waiver in this section of the protocol by referring to the checklist and explaining how each element of the waiver is met.

- If the Human Research involves a waiver of the consent process for planned emergency research, please review the CHECKLIST: Criteria for Waiver of the Consent Process for Planned Emergency Research to ensure you have provided sufficient information for the IRB to make this determination. Do not merely submit the checklist or state "I request a waiver" or "the criteria in the checklist are met." Instead, the PI must justify the waiver in this section of the protocol by referring to the checklist and explaining how each element of the waiver is met.
- If the Human Research involves a waiver of the consent process that includes use or disclosure of protected health information (PHI), please review the CHECKLIST: HIPAA Waiver of Authorization to ensure that you have provided sufficient information for the IRB to make these determinations. Do not merely submit the checklist or state "I request a waiver" or "the criteria in the checklist are met." Instead, the PI must justify the waiver in this section of the protocol by referring to the checklist and explaining how each element of the waiver is met.

Subjects who are not yet adults (infants, children, teenagers)

Not applicable.

Adults Unable to Consent

*Not applicable***.**

17) Special considerations when obtaining consent for genetic studies

*Not applicable***.**

18) Process to Document Consent in Writing

If the consent of the subject will not be documented in writing (consent will be obtained, but the subject or representative will not sign a consent document) review CHECKLIST: Criteria for Waiver of Written Documentation of Consent to ensure that you have provided sufficient information for the IRB. Do not submit the checklist or state "I request a waiver" or "the criteria in the checklist are met." Instead, justify the waiver in this section of the protocol by referring to the checklist and explaining how each element of the waiver is met.

19) Vulnerable Populations

If the Human Research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards to protect their rights and welfare.

Indicate whether you will include any of the following populations:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

The consent will be discussed with the subject, their guardians and their families.

If the Human Research involves cognitively impaired adults, review the CHECKLIST: Criteria for Research Involving Cognitively Impaired Adults to ensure you have provided sufficient information for the IRB.

If the Human Research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the CHECKLIST: Criteria for Research Involving Children to ensure you have provided sufficient information for the IRB.

If the Human Research involves pregnant women, review the CHECKLIST: Criteria for Research Involving Pregnant Women to ensure you have provided sufficient information for the IRB.

If the Human Research involves prisoners, review the **"CHECKLIST: Criteria for Research Involving Prisoners"** to ensure you have provided sufficient information for the IRB.

20) Drugs or Devices

Not applicable.

21) Multi-Site Human Research

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g., results, new information, unanticipated problems involving risk to subjects or others, or protocol modifications) among sites to protect subjects.

Efforts will be taken to manage information and ensure standardization across sites.

22) Sharing of Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or

incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Individual results with remain part of the subject's health record. Subjects will be aware of their IOP.