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Selective Laser Trabeculoplasty after Failed Trabeculectomy in Open Angle Glaucoma

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Abstract

Objective: To determine the efficacy of selective laser trabeculoplasty (SLT) for uncontrolled open angle glaucoma (OAG) on maximal tolerated medical therapy and with a history of previously failed trabeculectomy.

Methods: This was a prospective, non-randomized, interventional case series. Participants included 22 eyes of 20 consecutive glaucoma patients with a previously failed trabeculectomy and medically uncontrolled intraocular pressure, unable or unwilling to undergo further incisional surgery. A single SLT treatment was performed over 270° to 360°, and participants were followed for a minimum of 12 months. Success was defined in two separate analyses as 1) absolute IOP reduction ≥ 3 mm Hg and 2) percentage IOP reduction of 20% or 15% without additional laser or surgical intervention.

Results: The mean IOP dropped from 20.8 mm Hg to 16.3 mm Hg 12 months after SLT. The mean reduction in IOP was 19.5% or 4.5 mm Hg (95% confidence interval, 1.06-7.92, p<0.001). The cumulative success rate at 12 months (3 mmHg IOP reduction) was 16%. There was no statistically significant change in the number of medications (2.2 ± 0.8 to 2.0 ± 1.1).

Conclusions: In the short- and intermediate-term, SLT had mild to moderate success in achieving lower IOP in individuals with medically uncontrolled OAG with previously failed trabeculectomy.

Keywords: Glaucoma; Laser; Trabeculoplasty; Selective; SLT; Trabeculectomy

Introduction

Therapeutic options in persons with open angle glaucoma (OAG) include topical and systemic medications, laser trabeculoplasty, and incisional glaucoma surgery. Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) are approved for treatment of OAG and have documented efficacy [1-3] and therapeutic equivalency [2,3]. SLT was initially studied as a secondary modality in cases of failure of medical therapy or ALT [4]. It has more recently been shown to be effective as primary treatment in OAG [5,6] and as a replacement for glaucoma medications in medically controlled OAG [7]. The efficacy of SLT after failed trabeculectomy has not yet been studied, however.

The goal of the current study was to prospectively determine the 12 month success rate of SLT for uncontrolled OAG in persons with a history of previously failed trabeculectomy who were unwilling or unable to undergo further incisional glaucoma surgery.

Methods

Participants were recruited from consecutive patient visits to the clinical practice of an academic, tertiary-care glaucoma clinic at the Doheny Eye Institute. The Institutional Review Board at the University of Southern California approved the study protocol, and all study procedures conformed to Health Insurance Portability and Accountability Act and the Declaration of Helsinki for research involving human participants. All participants provided written consent prior to receiving laser trabeculoplasty treatment. Inclusion criteria were: 1) diagnosis of primary open angle (defined as a historical baseline IOP > 21 mmHg, with glaucomatous optic nerve appearance and characteristic visual field loss) or exfoliation glaucoma (same as POAG, also with exfoliation material evident on the anterior lens capsule or pupillary margin), 2) evidence of failed trabeculectomy (no functional bleb on clinical exam with flat or immobile, scarred conjunctiva over the scleral flap site) greater than 6 months post operatively after previous trabeculectomy, 3) poorly controlled IOP on maximum tolerated medical therapy (defined as failure to meet a predetermined target IOP based on optic nerve damage, visual field loss, baseline IOP, and stability of disease), and 4) the participants were unable or unwilling to undergo further surgery such as repeat trabeculectomy or aqueous tube shunt. Exclusion criteria included aphakia, corneal scarring, edema, or other abnormality that may affect applanation tonometry, topical or systemic corticosteroid use, more than one failed trabeculectomy, prior tube shunt or cycloablation procedure, and/or greater than 90 degrees of peripheral anterior synechiae noted on gonioscopic examination.

The glaucoma medications were initially started by monocular trial in order to determine efficacy. There was no attempt to washout medications or reestablish efficacy prior to intervention. In order to reduce diurnal variations, all IOP measurements were made at the same time of day (within 2 hours). Pre-operative IOP was calculated

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by the mean of the IOP on the visit prior to laser and the pre-operative IOP on the day of laser.

Intervention

The operative technique for SLT was followed as previously described [7]. In brief, all operative eyes were pre-treated with topical apraclonidine 0.5% or brimonidine 0.15% to reduce risk of post-operative IOP spike. Topical proparacaine 0.5% was instilled in the operative eye for anesthesia, and the angle was visualized using a Latina gonioscopy laser lens coupled with methylcellulose 1% solution. The Coherent Selecta 7000 laser, a frequency-doubled q-switched neodymium-yttrium-aluminum-garnet laser that emits at a frequency of 532 nm with a standard spot size of 400μm and pulse duration of 3 nanoseconds, was used for all cases by a single surgeon (BAF). The pigmented trabecular meshwork (TM) was targeted using the helium-neon aiming beam, and 70 to 110 adjacent, but non-overlapping, laser spots were placed over the entire available TM. The energy level was initially set at 0.8 mJ (range 0.6 mJ – 1.0 mJ) and titrated up or down based upon the observed tissue effect. The power was decreased in 0.1 mJ increments if small cavitation bubbles were noted to form anterior to the trabecular meshwork until the bubbles were seen approximately 50% of the time.

The IOP was measured at 1 hour after the procedure. Post-operative medication consisted of a topical non-steroidal anti-inflammatory drug used twice to three times daily for up to 4 days as needed for post-operative pain. Glaucoma medications were continued after laser and discontinued one at a time after 1 month if warranted by IOP response. Specifically, medications were reduced if the IOP was at or below the target IOP level previously determined for that patient in the course of their management (prior to study), as previously described. They were restarted if IOP rose to greater than 2 mmHg over this target. If the patient was on multiple medications, those with greatest side effects or least patient acceptance due to other issues (cost, dosing frequency, etc) were stopped first, followed by those thought to have the least efficacy (topical CAI, then brimonidine, then beta blockers, then prostaglandin analogues).

All IOP measurements were made by Goldmann applanation tonometry by certified ophthalmic technicians who were not involved in the study but were not masked to the treatment, and at the same time of day (within 2 hours). IOP was measured at 1, 3, 6, 9 and 12 months post-SLT treatment in all participants.

Statistical analysis

The study was designed with an adequate sample size to detect a clinically meaningful difference of 3 mm Hg with 80% confidence given a standard deviation of 4 mmHg (nQuery Advisor). All analyses were conducted at a ≤ 0.05 significance level and utilized Statistical Analysis System programs (version 9.1, SAS Institute Inc., Cary, North Carolina). Paired *t*-test was performed comparing pre- and post-treatment IOP and # of glaucoma medications at 1, 3, 6, 9, and 12 months. The criteria for success of SLT after failed trabeculectomy was analyzed by 3 different definitions: ≥ 3 mm Hg reduction or 20% reduction or 15% reduction in IOP compared with baseline IOP without need for additional laser or surgical intervention. The outcome measures of this study were the mean change in IOP measurements and mean change in # of glaucoma medications at 1, 3, 6, 9, and 12 months after SLT. The Kaplan-Meier survival analysis was used to demonstrate cumulative success (with failure as defining endpoint) plotted as a function of time points after SLT treatment.

Results

Over the time period of recruitment, all patients that met the inclusion criteria were offered entry into the study. A total of 23 patients had at least one eye with uncontrolled IOP on maximal medical therapy and were unable or unwilling to undergo further incisional glaucoma surgery. Of these, 20 patients agreed to undergo SLT as an alternative, and all were included in this analysis. The pretreatment demographic characteristics of the participants are detailed in Table 1. SLT was performed on one eye in 18 individuals, and both eyes in two individuals for a total of 22 eyes. The mean number of spots was 99.8 ± 18.5 with a mean power setting of 0.95 ± 0.19 mJ.

The mean pre-treatment IOP was 20.8 ± 4.1 mm Hg, and a statistically significant reduction in mean IOP was noted at all follow-up times, except the one month post-treatment visit. The mean post-treatment IOP at one, three, six, nine, and twelve months after SLT was 17.0 ± 6.0, 16.6 ± 4.5, 17.1 ± 3.1, 16.3 ± 3.9, and 16.3 ± 3.4 mm Hg, respectively (Table 2).

The mean pre-treatment number of glaucoma medications was 2.2 ± 0.8, and no statistically significant reduction in the number of medications was noted at any follow-up time point ($p > 0.05$), except the one month post-treatment visit (1.9 ± 0.9, $p = 0.02$).

Age (years)	76.6 ± 10.1
Gender (M:F)	9 (41%): 13 (59%)
Race (Caucasian:Latino:Asian)	17 (77%): 3 (14%): 2 (9%)
Lens Status (Phakic:Pseudophakic)	15 (68%): 7 (32%)
Cup/Disk Ratio	0.92 ± 0.07
Visual Acuity (logMAR)	0.48* ± 0.40
Humphrey Visual Field Mean Deviation (dB)	-14.36 ± 9.18
Central Corneal Thickness (microns)	551.8 ± 22.5
Glaucoma Diagnosis	POAG = 17 (77%)
	Exfoliation Glaucoma = 5 (23)%

*Corresponds to mean visual acuity of approximately 20/60 on Snellen chart
POAG = primary open angle glaucoma
Data is represented as Mean ± Standard Deviation or Number (%)

Table 1: Patient Demographics: Selective Laser Trabeculoplasty after failed Trabeculectomy.

	n Mean (sd)	*% Reduction Mean (sd)*	*Paired t-test p-value*
IOP			
Pre laser	22 20.77 (4.07)		
1 hour	22 19.77 (5.14)	3.33 (25.18)	0.54
1 day	21 17.90 (5.05)	14.43 (13.27)	<0.001
1 week	22 17.86 (5.35)	14.00 (17.98)	0.002
1 month	22 17.00 (5.97)	18.16 (24.65)	0.002
3 months	22 16.55 (4.50)	19.31 (19.58)	<0.001
6 months	21 17.10 (3.06)	14.90 (18.87)	0.002
9 months	19 16.26 (3.94)	17.57 (22.40)	0.003
12 months	18 16.28 (3.43)	19.50 (18.47)	<0.001
Medications	Mean (sd) Median	Mean (sd) Median	
Meds pre laser	2.2 (0.8) 2		
Meds 1 week	1.9 (0.9) 2	15.5 (28.7) 0	0.02
Meds 1 month	1.9 (1.1) 2	9.5 (38.9) 0	0.27
Meds 3 months	1.9 (0.9) 2	4.4 (44.5) 0	0.66
Meds 6 months	1.9 (1.0) 2	6.8 (50.8) 0	0.55
Meds 9 months	2.0 (1.1) 2	0.8 (55.7) 0	0.95
Meds 12 months	2.0 (1.1) 2	5.8 (51.9) 0	0.62

Table 2: Selective Laser Trabeculoplasty after failed Trabeculectomy: Intraocular Pressure and Medications.

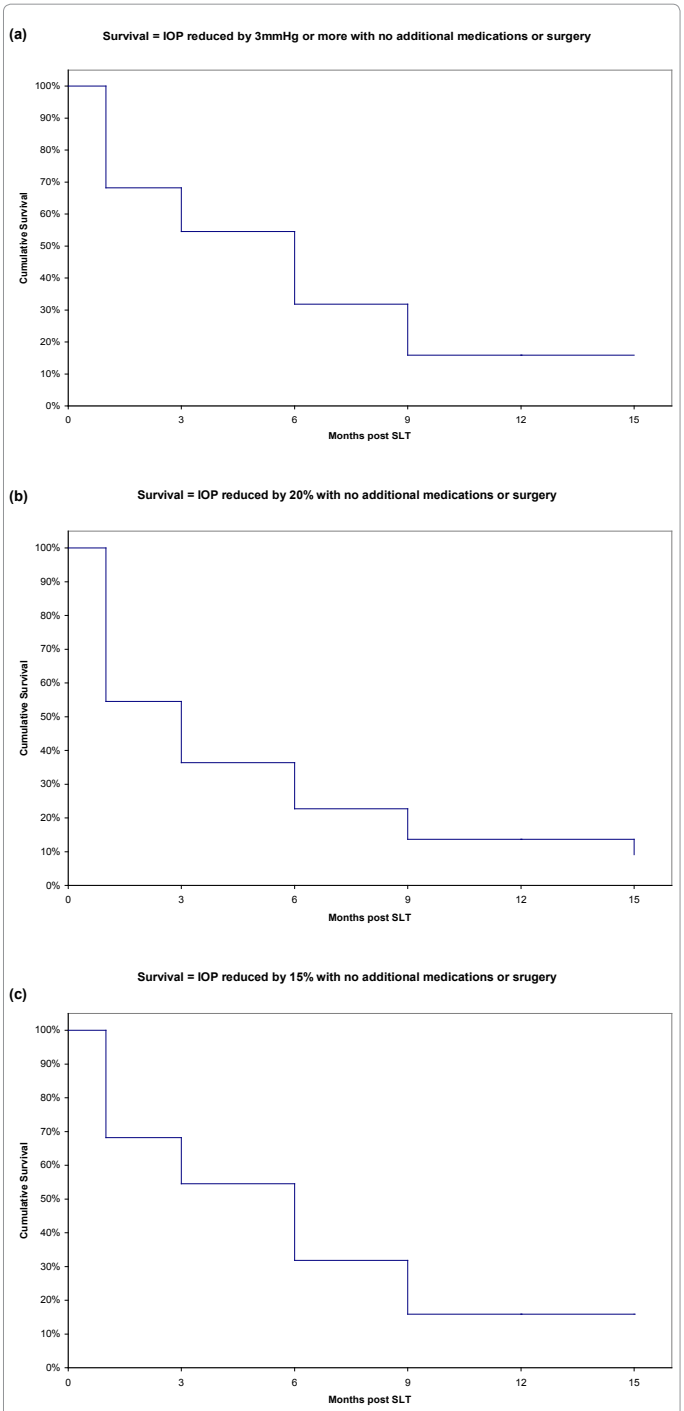

Figure 1: Kaplan-Meier survival curve showing the proportion of eyes at 1, 3, 6, 9 and 12 months that underwent successful selective laser trabeculoplasty treatment in the setting of prior failed trabeculectomy. The definition of success is **a)** 3 mmHg IOP reduction, **b)** 20% IOP reduction, and **c)** 15% IOP reduction, with no further surgical or laser procedure and no additional glaucoma medications.

A separate analysis was performed using only one eye of each participant, choosing the eye at random in those that had the procedure in both eyes, with a total of 20 subjects. The mean pre-operative IOP was 20.7 ± 4.3 mmHg and 16.8 ± 2.7 mmHg at 12 months after laser. These results were not statistically different compared to the larger data set, and justified our pooling the data from subjects in whom both eyes were included.

The cumulative success rate of SLT after failed trabeculectomy using our success criteria (≥ 3 mm Hg IOP reduction with no additional medications or interventions) was 16% at twelve months post-treatment (Figure 1). The success rates were similar for the definitions of 20% or 15% reduction in IOP.

Out of the 22 eyes, 12 maintained the same vision at 12 months when compared to their pre-operative vision. There were three eyes that had an increase or decrease of only one line, there were four eyes that had improved vision of two lines or more, and there were three eyes that had a decrease in vision of two or more lines. In the perioperative period after SLT, no complications were noted in any participant including IOP spike (defined as IOP rise ≥ 10 mm Hg after laser procedure).

Discussion

Selective laser trabeculoplasty has been used successfully to lower IOP in treatment of open angle glaucoma as initial therapy, and after previously failed argon laser trabeculoplasty or maximally tolerated medical therapy. To our knowledge, no previous reports have examined the efficacy of SLT after previously failed trabeculectomy. This study supports the conclusion that SLT appears to offer a therapeutic option in a select group of persons who would require IOP lowering but have already had a failed trabeculectomy and are unwilling or unable to tolerate incisional glaucoma surgery.

The IOP reduction seen in this study was smaller than that reported in the initial clinical trial of SLT by Latina et al. [4]. Their participant population included persons with failed prior treatment for OAG with maximal medical therapy and/or prior ALT with a refractory IOP > 22 mm Hg, but excluded those with previous trabeculectomy. In that study, the mean IOP reduction was 23% with a rate of response ≥ 3 mm Hg in more than 70% participants at 26 weeks after treatment. In our study, the IOP reduction was approximately 20%, but with a success rate of 33% at 6 months. The current study shares most of the inclusion criteria with the Latina study, but has the additional criteria of previously failed trabeculectomy, which likely explains the lower response rate and less effective IOP reduction.

For the purpose of analysis, all available data points were used to calculate mean IOP and medications after laser, including those considered failures. The Kaplan-Meier survival analysis censored subjects for dropout or failure. The Kaplan Meier survival curves for the absolute IOP reduction (3 mmHg) and percentage IOP reduction (20% and 15%) were comparable.

Strengths of this study include that it is the first attempt to analyze SLT in this population (post-failed trabeculectomy), and that it is a prospective trial with one year of follow up. Success was analyzed both by absolute IOP reduction (3 mmHg) and by percentage IOP reduction (20% and 15%). There are several weaknesses, including the fact that it is a non-comparative, interventional case series. In our opinion, it is not feasible to design a randomized controlled trial to determine the efficacy of SLT after failed trabeculectomy, as it is not clear what treatment options would be involved. Since further filtration surgery is the accepted standard of practice, it would be difficult to randomize patients to receive laser instead of surgery. Our population is special in that they are not able to undergo, or have refused further incisional surgery, and therefore have laser trabeculoplasty as the only option for additional treatment.

We did not include a comparison arm, as it can be very misleading to do so when the study is not designed as a randomized trial. A comparison arm in a non-randomized study is very susceptible to selection bias, as the investigators usually decide on a treatment for specific reasons, which leads to systematic bias. We therefore believe that it is more beneficial to describe results of a case series as is rather than to make a comparison to a group that is not comparable.

Although we attempted to minimize error by measuring IOP at the same approximate time of day, and using the average of two measurements for pre-operative IOP, there is still a potential for regression to the mean error and diurnal variation. While medications were started by a monocular trial to demonstrate efficacy, there is still the possibility for tachyphylaxis and loss of effect over time. This would lead to bias towards success in lowering number of glaucoma medications. However, in this population, we did not feel it was safe to wash out medications and restart them individually.

This study demonstrates mild to moderate success of SLT in lowering IOP in the short- and intermediate-term in persons with open angle glaucoma after previously failed trabeculectomy. The mean IOP reduction was 20% at one year with no further interventions or additional glaucoma medications. The comparatively low success rate, however, may be explained by the fact that this group of patients had already undergone incisional filtration surgery and were on maximum tolerated medications. The reduction of glaucoma medications was not included in the success criteria. Thus the criteria for success in this refractory population is quite stringent.

Although this study is the first to analyze the response of SLT in persons with previously failed trabeculectomy, the use of laser trabeculoplasty after trabeculectomy is not without precedent. The Advanced Glaucoma Intervention Study (AGIS) tested the hypothesis that argon laser trabeculoplasty was more beneficial than immediate trabeculectomy after failure of maximally tolerated medical therapy [8]. The two treatment arms were 1) ALT followed by trabeculectomy and another trabeculectomy if the previous treatment failed (labeled ATT); and 2) trabeculectomy followed by ALT, and then another trabeculectomy if the previous treatment failed (labeled TAT). The 2nd intervention in the TAT group of AGIS can be considered analogous to our population, where trabeculoplasty was performed after a failed trabeculectomy. The AGIS reported a 10-year failure rate in the TAT arm of 65% (95% CI, 35% – 95%) in blacks, and 72% (95% CI, 31 – 100) in whites. The success rate was therefore, respectively, 35% and 28% at 10 years. Although the AGIS success/failure criteria differed from our study, the AGIS concurs with our study in demonstrating mild to moderate success of laser trabeculoplasty after failed trabeculectomy.

The proposed mechanism of action of laser trabeculoplasty based on basic science research [9-12] may help explain the clinical effects observed in this study. An induction of interleukin-1 was observed in cultured human trabecular meshwork cells after treatment with ALT and SLT. The maximal effect was seen with SLT at 1.0 mJ with treatment of the melanin in the cultured cells. Level of tumor necrosis factor and interlukin-1 also increased in a dose-dependent fashion after SLT. The combination of the induction of cytokines, reduction in glycosaminoglycans, and increased macrophage recruitment are proposed to modulate the remodeling of the cellular matrix in the trabecular meshwork or Schlemm's canal tissues resulting in increased outflow facility and lower IOP. If enough of the angle remains open and available and sufficient trabecular outflow function remains after failed trabeculectomy, then laser trabeculoplasty may be expected to reduce IOP.

In summary, SLT appears to be a moderately effective, short to intermediate-term modality for lowering IOP in persons with medically uncontrolled open angle glaucoma after previously failed trabeculectomy, who are either unable to tolerate or reluctant to undergo additional invasive glaucoma surgery.

Conflict of Interest

Brian Francis is a consultant for Lumenis, the manufacturers of the SLT laser. All other authors have no proprietary or commercial interest in any materials discussed in the manuscript.

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