

Automated Direct Selective Laser Trabeculoplasty: First Prospective Clinical Trial

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Received: October 15, 2020

Accepted: January 21, 2021

Published: March 5, 2021

Keywords: intraocular pressure; glaucoma laser; selective laser trabeculoplasty; open-angle glaucoma

Citation: Goldenfeld M, Belkin M, Dobkin-Bekman M, Sacks Z, Blum Meirovitch S, Geffen N, Leshno A, Skaat A. Automated direct selective laser trabeculoplasty: First prospective clinical trial. *Trans Vis Sci Tech.* 2021;10(3):5. <https://doi.org/10.1167/tvst.10.3.5>

Purpose: Direct selective laser trabeculoplasty (DSLTL) is a rapid, noncontact automated procedure performed directly through the limbus without gonioscopy. In this first nonrandomized clinical trial we assessed its safety and ability to reduce intraocular pressure (IOP).

Methods: Fifteen patients (15 eyes: 10 with open-angle glaucoma [OAG], 4 with ocular hypertension, and 1 with pseudoexfoliation glaucoma), naive or after medication washout, with an IOP ≥ 22 mm Hg, underwent DSLTL by irradiation with 100 or 120 sequential noncontact 532-nm, Q-switched laser shots (0.8–1.4 mJ) automatically applied during 1.5 or 2.3 seconds on the limbus, guided by image analysis and eye tracking. Results were assessed at 1 and 3 hours, 1 day, 1 week, and 1, 3, and 6 months.

Results: The mean \pm standard deviation baseline IOP (mm Hg) in all eyes was 26.7 ± 2.3 . At 1, 3, and 6 months, this value was significantly reduced to 21.7 ± 4.2 (by 18.1%), to 20.8 ± 2.5 (by 21.4%), and to 21.5 ± 4.1 (by 18.8%), respectively. In six patients treated with 1.4 mJ/shot, the mean IOP at 6 months decreased from 26.7 ± 3.2 to 19.3 ± 2.0 (27.1%, $P = 0.03$). There was a significant reduction in hypotensive medications (from 1.6 ± 1.0 to 0.4 ± 0.7 , $P = 0.03$). No serious adverse events occurred.

Conclusions: Automated DSLTL appears to be an effective and safe noncontact, rapid modality for reducing IOP in patients with OAG. Higher energy usage led to better results.

Translational Relevance: Studying laser transmission through sclera enabled laser irradiation of the trabeculum without gonioscopy.

Introduction

Glaucoma is a progressive multifactorial disease in which the optic nerve is damaged, causing visual field loss. The disease is closely associated with elevated intraocular pressure (IOP), but it may also occur with IOP within the normal range. Glaucoma is the leading cause of irreversible blindness worldwide¹ and among the leading causes of moderate or severe visual impairment,² causing reduced health-related quality of life and a very significant economic burden.³ The global prevalence of glaucoma for the aged population is

3.5%, and it has been estimated that the number of patients with glaucoma worldwide will increase to 111.8 million by 2040.³

Selective laser trabeculoplasty (SLT), a Q-switched 532-nm, frequency-doubled low-energy Nd:YAG laser applied to the trabecular meshwork (TM), is a widely used, safe, and cost-effective procedure for reducing IOP in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) and has been recommended as a first-line therapy.^{4,5} It can also be used to reduce the number of required antiglaucoma medications and to avoid or delay incisional surgery.⁶ Successful SLT has a twofold advantage over hypotensive

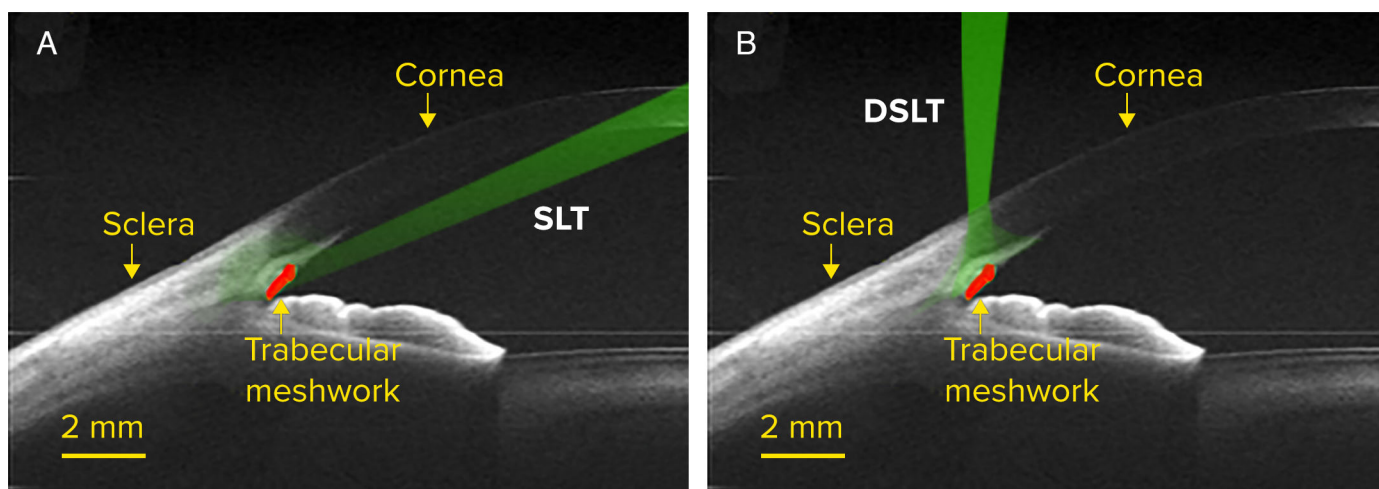


Figure 1. Optical coherence tomography (OCT) image of the eye with conceptual representation of the laser beam's position on the trabecular meshwork during (A) SLT and (B) DSLT. The 400- μm diameter DSLT laser beam on the sclera is shown to scale. Not shown is the gonioscopy lens used on the cornea in SLT. (The concept is adapted from Sacks et al.,¹⁶ and the OCT image is adapted from Li et al. 2013,³⁵ both under CC by 4.0 license <https://creativecommons.org/licenses/by/4.0/legalcode>).

glaucoma medications. On the one hand, it avoids the progressive ocular surface disease associated with long-term exposure to preservatives and to active pharmaceutical agents of topical medications.^{7,8} On the other hand, it solves the problem of noncompliance to medications, a major cause of visual loss in patients with glaucoma.^{9,10}

The conventional SLT procedure is performed with a gonioscopy lens, which enables the physician to visualize the TM and direct the laser beam at it.¹¹ Visualization of the angle with a gonioscopy lens requires sufficient angle width, and the entire procedure requires training and experience.¹² It is possible, however, that the availability of a simpler SLT procedure would make general ophthalmologists and other trained allied health professionals more inclined to use it and would thus increase access to laser treatment for patients who need it. Moreover, during SLT, a gonioscopy lens is in direct contact with the corneal surface, potentially creating the hazard of transmitting infections¹³ or inducing corneal side effects, such as superficial punctate keratopathy, erosions, and ocular discomfort.¹⁴ Geffen et al.¹⁵ recently reported the results of a randomized controlled 6-month trial that compared a manual, nonautomated, translimbal direct SLT approach (DSLST) with a standard SLT unit. Their results demonstrated that SLT applied directly to the perilimbal sclera is as efficacious as the conventional procedure.

The clinical application of an automated image-processing controlled device for a noncontact translimbal DSLST was developed to provide a rapid, easy-to-use

laser trabeculoplasty procedure. The automated procedure is much faster than the manual procedure and ensures accurate target location and safe treatment by implementing eye tracking. Here, we report the results of the first-in-human clinical study that evaluated its safety and ability to reduce IOP in patients with OAG or OHT.

Patients and Methods

An Automated Device for DSLST

The principle underlying translimbal (external) DSLST, whose description and effectiveness were described by Geffen et al.¹⁵ SLT (Fig. 1A) is a procedure that is dependent upon the amount of energy reaching the TM and not upon any other laser beam characteristics. As such, while the DSLST laser beam is scattered during its passage through the limbal structures, sufficient energy reaches the TM to achieve an IOP-lowering effect. This is similar to conventional SLT procedures in which much of the energy is lost before reaching the TM.¹⁶ Geffen et al.¹⁵ demonstrated that direct application of DSLST to the limbus was as effective as the conventional SLT procedure.

A dose-response trial is performed at different energy levels to determine the beam energy level with the highest efficacy and safety. The automated DSLST device (BELKIN Laser Ltd., Yavne, Israel) employs a Q-switch, frequency-doubled Nd:YAG laser with a wavelength of 532 nm. It directs the 7-ns pulse, 400- μm

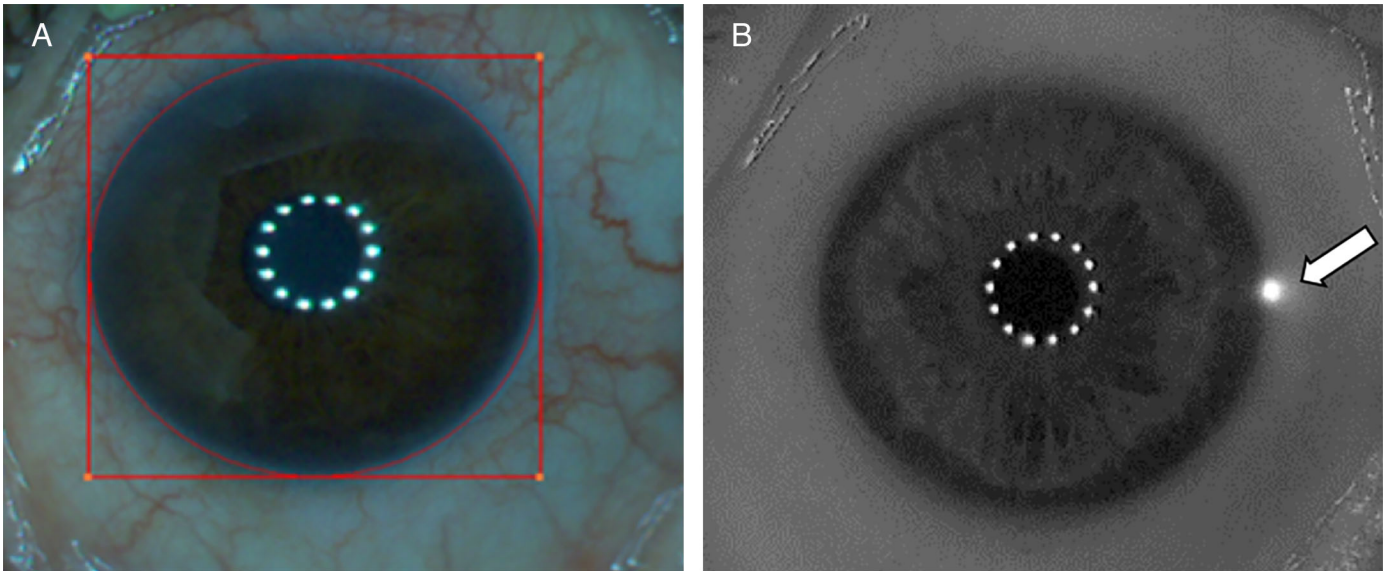


Figure 2. (A) Limbus target zone (red ring) is automatically located by the device software (as seen on the operator's screen). Touching and moving the corners or sides of the red rectangle allow additional target alignment. (B) The arrow points to the laser beam position on the targeted limbus area during treatment (as retrieved from the device, which automatically saves images for each laser shot during the treatment). Note the reflection of the light-emitting diode-illuminated ring at the corneal center.

laser beam to the limbus region (Fig. 1B) without the need for a delivery device (e.g., a gonioscope lens) or any contact with the patient's eye. An image-processing algorithm automatically locates the target area on the limbus (Fig. 2A and Supplementary Video Clip S1) and moves the scanner's mirrors to compensate for eye movement so that the laser spots will be delivered to the specifically intended location on the limbus. After the operator verifies the target, a predefined number of laser pulses with the preselected level of energy is delivered through a full 360 degrees around the limbus, resulting in fully automated treatment simultaneously with target tracking (Fig. 2B). The laser beam passes directly through the limbal area to the TM. Scattering of the beam during its passage through the limbal tissues ensures that all parts of the TM are impacted.

Since no dose-response curve was performed in the original study published by Latina and Park,¹¹ we were mainly concerned about the safety. We decided to start with 0.8 mJ, which is roughly equivalent to 0.3 to 0.4 mJ level of energy at the TM. As no serious adverse events were observed, we proceeded by dividing the rest of the limited patients' sample to two energy groups of six patients each (1 mJ and 1.4 mJ).

Study Design

This prospective, single-arm, assessor-masked clinical trial was conducted at a single institution (Chaim Sheba Medical Center, Tel Hashomer, Israel). All

laser treatments were performed by a single glaucoma specialist (M.G.) who used the herein described automated DSLT device (BELKIN Laser, Ltd.). The trial was approved by the Institutional Review Board of Sheba Medical Center and performed according to the Public Health Regulations (Clinical Trials in Humans) of the Israel Ministry of Health. Written informed consent was obtained for all patients. The trial was registered at ClinicalTrials.gov (NCT01383525).

The inclusion criteria for the trial were patients over the age of 18 years who had poorly controlled glaucoma and/or demonstrated noncompliance or intolerability to topical hypotensive treatment as well as naive patients. All patients had mild to moderate primary OAG (POAG), pseudoexfoliation glaucoma, or OHT. Another criterion for inclusion was an average IOP ≥ 22 mm Hg, measured at two pretreatment visits (after hypotensive medication washout). Excluded were patients with glaucoma other than OAG (as confirmed by gonioscopy), severe glaucoma as defined by the American Glaucoma Society,¹⁷ any ocular condition that precluded adequate visualization and treatment of the TM, and prior glaucoma surgery, laser trabeculoplasty, or any other ocular surgery during the 3 months prior to study recruitment. Also excluded were patients who could not understand the protocol and sign the informed consent form or comply with follow-up visits, as well as patients who were undergoing concurrent treatment with systemic steroids or were pregnant.

Primary outcome measures were mean percentage reductions in IOP from baseline, which were recorded 1 and 3 months after DSLT, as well as evaluation of the patient's DSLT profile of adverse events. Secondary outcome measures were the mean percentage IOP reduction from baseline as recorded at the 6-month post-DSLT visit and the number of medications needed after the laser treatment compared to the number being used at the time of the screening visit.

The recorded data during the comprehensive screening evaluation included age, sex, and the general medical and ocular history, the latter including previous ocular surgeries and the number and type of antiglaucoma medications. Each patient underwent a full ophthalmic examination of both eyes, including a best-corrected visual acuity (BCVA) evaluation on a Snellen chart, comprehensive biomicroscopy, fundus examination including optic disc, and gonioscopy. Humphrey 24-2 SITA-Standard visual field tests were performed at the screening and 6-month follow-up visits.

After the screening visit, the suitable patients underwent ocular medication washout for 14 days to eliminate carbonic anhydrase inhibitors and α -adrenergic agonists and for 28 days to eliminate β -blockers, prostaglandin analogues, and combined medications. The laser treatment window was 6 weeks starting from the initial screening. One patient, whose IOP at the screening visit was 26 mm Hg on one hypotensive medication, did not undergo washout at the discretion of the investigator. For medicated patients, IOP inclusion eligibility after washout (≥ 22 mm Hg) was confirmed twice before DSLT was administered.

An experienced ophthalmologist performed two IOP measurements by means of a calibrated Goldmann applanation tonometer (Haag Streit, Berne, Switzerland) at all time points of the study, and the average IOP was recorded. All posttreatment IOP measures were obtained in a masked fashion, wherein the IOP of both eyes was recorded by the examiner, who was unaware of the treated eye, or, alternatively, by a masked technique in which a nonmasked investigator took the measurement and a masked assistant read and recorded all IOP measurements. All follow-up visits took place between 08:00 and 13:00.

The baseline IOP was recorded for each patient before undergoing DSLT. Based on the physician's judgment after assessment of the IOP and the general ocular and visual status, the eye with the higher IOP after washout was chosen for treatment (the exception would be when the same IOP was recorded in both eyes; in this case, the eye with more advanced disease was chosen). Postoperative examinations were performed by the masked observer or by the masked technique at

1 hour, 1 day, 7 (\pm SD 2) days, and 1 (\pm 7 d), 3 (\pm 7 d), and 6 (\pm 7 d) months after the procedure. They included BCVA testing, a complete biomicroscopic examination, and two Goldmann applanation tonometer IOP measurements. The mean IOP was recorded at each visit, as was the number of hypotensive medications being used in those cases in which medication had been reintroduced after treatment. Gonioscopy was performed at screening and immediately after DSLT treatment and at the 3- and 6-month follow-up visits.

Intraoperative and postoperative adverse events were recorded at each visit. Side effects were classified by the investigators as being either directly or incidentally related to the laser treatment. The investigators were allowed, at their discretion, to reintroduce hypotensive medications and to adjust the medication type, dosage, or frequency of use during the postoperative course. No repeat SLT was permitted. All changes in ocular medical treatments were recorded.

Treatment Procedure

Prior to DSLT, topical anesthesia with Localin (oxybuprocaine hydrochloride 0.4%; Fischer Pharmaceuticals LTD, Bnei Brak, Israel) was administered to the selected eye. At 30 to 60 minutes before treatment, each patient received one drop of pilocarpine hydrochloride 2% (Vitamed Pharmaceutical Industries, Binyamina, Israel) and one drop of apraclonidine hydrochloride 0.5% (Alcon, Couvreur, Puurs, Belgium). Artificial tear drops were applied immediately before the treatment. No eye drops were given after the treatment.

Preset parameters of the energy dose and the number of laser shots around the limbus in this limited dose-response study ranged from 0.8 to 1.4 mJ/shot. Patients treated with doses lower than 1.4 mJ/shot received a preset series of 100 shots, while those treated with doses of 1.4 mJ/shot received 120 shots.

Statistical Analysis

All measured variables and derived parameters were presented by descriptive statistics. Summary tables were provided for continuous variables, noting sample size, arithmetic mean, standard deviation, and the median, minimum, and maximum lower and upper limits for the 95% confidence interval (CI). Changes and relative changes from baseline were summarized in tables, and the statistical significance of those changes was tested by the Wilcoxon signed-rank test. A linear

Table 1. Baseline Patient Characteristics

Characteristic	Value
Mean age (years \pm SD)	66.2 \pm 8.4
Sex, No.	
Male	10
Female	5
Diagnosis, No.	
POAG	10
Exfoliation glaucoma	1
Medicated OHT	4
Hypotensive medications (at screening visit), No.	
Medicated	14
Naive	1

Table 2. Actual Mean Energy Delivered to the Limbus During Treatment

Energy Subgroups (Preset Energy)	Actual Mean Total Energy/Treatment, mJ
Total cohort ($n = 15$)	127.8
≥ 1 mJ/shot ($n = 13$) ^a	134.8
0.8 mJ/shot ($n = 2$)	82.7
1 mJ/shot ($n = 6$)	107.7
1.2 mJ/shot ($n = 1$)	119
1.4 mJ/shot ($n = 6$)	164.5

^aIncludes patients from 1-mJ/shot, 1.2-mJ/shot, and 1.4-mJ/shot subgroups.

regression model was applied to test the effect of time for each parameter. A χ^2 test was applied to ascertain the significance of the decrease in the number of medications. The exact CI for the proportion of success in IOP reduction (relative change $>20\%$) was calculated for each group by the Clopper-Pearson method. All tests were two-tailed, and a P value of 5% or lower was considered statistically significant. Data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Of the 30 patients who were recruited for this study, 15 were screen failures (9 failed to meet our IOP inclusion criteria after ocular washout, 2 failed to meet other inclusion criteria, and 4 withdrew for personal reasons), leaving 15 patients (15 eyes) who underwent DSLT. One of these patients dropped out after the 1-month follow-up visit. Relevant demographic data and baseline medical information on the study group of the 15 treated participants are summarized in [Table 1](#).

DSLTL Procedure

The total energy levels applied during DSLTL are summarized in [Table 2](#). Each laser treatment lasted around 2 seconds, depending upon the number of laser shots. Nine patients were treated with 100 preset shots around the limbus with energy levels of 0.8 mJ/shot (two patients), 1 mJ/shot (six patients), or 1.2 mJ/shot (one patient). We treated a subgroup of six patients with 120 preset shots of 1.4 mJ/shot to test the effect of applying an increase in overall energy. The actual energy received and the numbers of shots applied were automatically recorded by the device for each of the 15 patients. There were some deviations in delivered energy per treatment due to laser output deviations within the standard IEC60601-2-22 range,¹⁸ but deviations from the preset values did not exceed $\pm 20\%$. Deviations in the numbers of laser shots per treatment were attributable to the in-built safety algorithm of the device. Dynamic adjustments by the tracking system compensate for patient eye movement and ensure that the pattern of spots is delivered to the target position within an appropriate safety limits to ensure that laser spots are safely confined to the central limbus. The eye-tracking functionality also prevents laser exposure if the patient eye motion overall exceeds safety limits. The

current algorithm does not handle the patient blinking; the eye retractor is inserted before the procedure.

In two patients, the treatment was automatically arrested due to excessive eye movements deviating from the fixation light. The eye-tracking capability of the laser device terminated the laser irradiation, and thus a 360-degree treatment was not achieved in these patients, so they received 50 shots on the upper arc. The entire circumference of the limbus was treated in all of the other patients.

Safety Analysis

All documented complications in this study were mild, and all resolved completely within 1 week after the procedure. No severe sight-threatening or other adverse events occurred during the study. The DSLT procedure was well tolerated. All 15 patients reported that they had experienced no pain during the treatment and had not felt disturbed by the green treatment laser light either during or following the procedure. There were no spikes in IOP and no incidence of corneal edema. Four patients experienced minor subconjunctival hemorrhages, and they all resolved without treatment within a few hours to 1 week after the procedure. Six patients received anticoagulant medications for nonocular conditions during the study, one of whom had sustained a subconjunctival hemorrhage. There were no significant changes in visual acuity or visual fields at the 6-month follow-up visits (Table 3).

IOP-Lowering Analysis

The mean IOP values in each subgroup are summarized in Table 4. Although transient reductions in IOP were observed at the 1- and 3-month follow-up visits in two patients who had been treated at the lowest energy level of 0.8 mJ/shot, their IOPs returned to the baseline values by the 6-month visit.

We evaluated the DSLT effect in patients treated at an energy level above 0.8 mJ/shot by analyzing the IOP reductions from baseline at 1, 3, and 6 months after DSLT in 13 patients who had been treated at energy levels ≥ 1 mJ/shot (6 patients at 1 mJ/shot, 1 patient at 1.2 mJ/shot, and 6 patients at 1.4 mJ/shot). Their mean percentage reductions from baseline were statistically significant ($P < 0.01$) (Table 4) at all three follow-up time points. The mean baseline IOP in the six patients treated with 1 mJ/shot was 27.3 ± 2.0 mm Hg, which was significantly reduced to 20.0 ± 4.2 ($P = 0.03$) at the 1-month follow-up (Table 4). The mean percentage reductions from the baseline in the six patients treated with an energy level of 1.4 mJ/shot were significant ($P = 0.03$) at the 3- and 6-month follow-up visits

(Table 4). Linear regression analyses of subgroups of patients treated with energy levels of ≥ 1 mJ/shot ($P = 0.019$) and of 1.4 mJ/shot ($P = 0.006$) revealed that the IOP reduction effect was sustained during the follow-up visit.

An IOP reduction of $\geq 20\%$ from baseline at each of the follow-up visits was taken to reflect a successful response to treatment. As shown in Table 5, this was achieved at the 6-month follow-up by 8 of the 14 study patients. The success rates of the subgroups of patients treated with different energy levels ranged from 40% to 83.3% (Table 5). All responders achieved IOP values ≤ 20 mm Hg.

The number of glaucoma medications used in each subgroup is shown in Table 3. The average number of ocular hypotensive drops was significantly reduced from 1.6 at baseline to 0.4 at 6 months ($P = 0.03$) for the entire cohort. Hypotensive drops were reintroduced in two patients during the study period, one of whom was the patient who had not undergone washout and had continued with his medication throughout the trial. Hypotensive drops were reintroduced at the 6-month follow-up visit in two other patients (one treated with 0.8 mJ/shot and the other with 1 mJ/shot) who displayed insufficient IOP reduction following treatment.

Discussion

The safety and efficacy of SLT have been demonstrated in various types of glaucoma as well as in ocular hypertension.⁴ Several studies have confirmed the cost-effectiveness of SLT treatment compared to treatment with medications.^{19–21} The recently published LiGHT (Laser in Glaucoma and ocular HyperTension) study established the efficacy of SLT as a primary single or repeat procedure for the treatment of OHT and POAG, validating its superiority over medical therapies as a primary treatment capable of providing better control of IOP at a lower cost and with fewer side effects.^{22–24} SLT, however, requires skills in performing gonioscopy and contact with the cornea by the rotating contact lens with resulting common epithelial complications. Given the efficacy of SLT in reducing IOP and visual field deterioration while overcoming adherence problems and being relatively free of side effects, we considered ways to simplify the procedure. We achieved this goal by irradiating the TM through the limbus. The limbus is the area of transition between the scattering sclera and the transparent cornea, and it transmits the laser beam at the 532-nM wavelength. This fact obviates the need for the gonioscopy lens that is rotated over the

Table 3. Ocular Characteristics at Screening and at 6-Month Visits (Mean ± SD) and Treatment-Related Ocular Adverse Events

Total Cohort and Subgroups	No. of Hypotensive Medications (Mean ± SD)				No. of Medicated Patients				Visual Field Mean Deviation, dB (Mean ± SD)				Visual Acuity, LogMar (Mean ± SD)				Adverse Events
	Screening		6 Months Postop		Screening		6 Months Postop		Screening		6 Months Postop		Screening		6 Months Postop		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total cohort (n = 15) ^a	1.6 ± 1.0	0.4 ± 0.7	0.4 ± 0.7	0.03	14	3	0.03	0.03	-2.0 ± 1.6	-1.6 ± 1.3	0.24	0.24	0.07 ± 0.06	0.07 ± 0.06	0.5	0.5	4 ^b
≥ 1 mJ/shot (n = 13) ^{a,c}	1.6 ± 0.9	0.4 ± 0.8	0.4 ± 0.8	0.06	13	3	0.08	0.08	-2.0 ± 1.7	-1.6 ± 1.3	0.17	0.17	0.07 ± 0.06	0.07 ± 0.06	0.5	0.5	4 ^b
1 mJ/shot (n = 6) ^a	1.8 ± 1.0	0	0	0.06	6	0	ND	ND	-1.2 ± 1.4	-1.7 ± 1.5	0.125	0.125	0.06 ± 0.07	0.04 ± 0.04	ND	ND	
1.4 mJ/shot (n = 6)	1.5 ± 0.8	0.5 ± 0.8	0.5 ± 0.8	0.25	6	2	0.4	0.4	-2.6 ± 1.8	-1.8 ± 1.3	0.063	0.063	0.09 ± 0.06	0.1 ± 0.06	0.5	0.5	3 ^b

ND, not determined; postop, postoperative.

^aOne patient from 1-mJ/shot subgroup was lost to follow up after the 1-month visit.

^bMinor subconjunctival hemorrhage during treatment.

^cIncludes patients from 1-mJ/shot, 1.2-mJ/shot, and 1.4-mJ/shot subgroups.

Table 4. IOP Dynamics, mm Hg (Mean \pm SD), and Mean IOP Reductions at Follow-Up Visits

Total Cohort and Subgroups	Baseline IOP ^a	1 Month Postop			3 Months Postop			6 Months Postop		
		IOP	% Reduction	<i>P</i>	IOP	% Reduction	<i>P</i>	IOP	% Reduction	<i>P</i>
Total cohort (<i>n</i> = 15) ^b	26.7 \pm 2.3	21.7 \pm 4.2	18.1	0.005	20.8 \pm 2.5	21.4	<0.001	21.5 \pm 4.0	18.8	0.003
\geq 1 mJ/shot (<i>n</i> = 13) ^{b,c}	26.8 \pm 2.5	21.5 \pm 4.4	19.4	0.001	20.7 \pm 2.7	22.1	0.001	20.7 \pm 3.8	22	0.002
0.8 mJ/shot (<i>n</i> = 2)	26 \pm 0.7	23.5 \pm 0.7	9.6	ND	21.5 \pm 0.7	17.0	ND	26 \pm 2.8	0	ND
1 mJ/shot (<i>n</i> = 6) ^b	27.3 \pm 2.0	20.0 \pm 4.2	26.4	0.03	22.0 \pm 2.4	18.4	0.06	22.7 \pm 5.1	15.2	0.3
1.4 mJ/shot (<i>n</i> = 6)	26.7 \pm 3.2	21.2 \pm 2.3	19.9	0.06	19.8 \pm 2.9	24.9	0.03	19.3 \pm 2.0	27.1	0.03

^aAfter washout of hypotensive medications.

^bOne patient from 1-mJ/shot subgroup was lost to follow-up after the 1-month visit.

^cIncludes patients from 1-mJ/shot, 1.2-mJ/shot, and 1.4-mJ/shot subgroups.

Table 5. Treatment Response Rate During Follow-Up

Total Cohort and Subgroups	1 Month Postop		3 Months Postop		6 Months Postop	
	Response Rate, %	CI	Response Rate, %	CI	Response Rate, %	CI
Total cohort (<i>n</i> = 15) ^a	46.7	21.3–73.4	57.1	28.8–82.3	57.14	28.8–82.3
\geq 1 mJ/shot (<i>n</i> = 13) ^{a,b}	53.8	25.1–80.8	58.3	27.6–84.8	66.7	34.9–90.0
1 mJ/shot (<i>n</i> = 6) ^b	66.7	22.2–95.7	40.0	5.3–85.3	40.0	5.3–85.3
1.4 mJ/shot (<i>n</i> = 6)	50.0	11.8–88.1	66.7	22.3–95.7	83.3	35.9–99.6

Treatment response is \geq 20% reduction from baseline intraocular pressure.

^aOne patient from 1-mJ/shot subgroup was lost to follow up after the 1-month visit.

^bIncludes patients from 1-mJ/shot, 1.2-mJ/shot, and 1.4-mJ/shot subgroups.

cornea in conventional SLT. Theoretical calculations using Monte Carlo simulations showed that the energy reaching the TM by translimbal application from the treatment laser is 2.8 times lower for DLST than for SLT.¹⁶ This reduction in energy is due to scattering of the beam and absorption of energy upon transmission through the nontransparent tissues. Thus, the highest DSLT energy used in this trial (1.4 mJ/shot) would be equivalent to 0.5 mJ/shot of SLT.

This report describes the findings of the first clinical trial of automated DSLT for patients with OAG. Although we found a trend toward improvement of IOP reduction in the higher-energy subgroup, this dose dependence on energy level did not reach a level of significance. A dose-response trial with larger numbers of patients will be required to establish optimal energy levels.

The laser we selected for the automated DSLT device has pulse parameters similar to those of standard nanosecond SLT lasers, with the exception that our laser is capable of emitting tens to hundreds of pulses per second. As a result, we are able to use laser-scanning galvanometer mirrors to guide the laser beam to deliver 100 to 120 laser pulses around the limbus in about 1.5 or 2.3 seconds. This delivery regimen enables us to obtain full automatization of the procedure, with the operating physician's confirmation of the target points and eye-tracking functions. Once the target is defined by the algorithm and approved by the operator, a specially developed electronic system is

put into operation to deliver the laser pulses automatically. Controlled by the software, the system images the eye before each shot, analyzes the image to track the eye's motion, adjusts the position of the laser's steering mirrors, and then fires a single laser shot. The process is then repeated for all of the remaining shots. Importantly, the system's architecture and software prevent laser delivery through the pupil to avoid potential exposure of the retina.

The results of this clinical trial demonstrated that translimbal DSLT in patients treated with a preset energy level of \geq 1 mJ (mean IOP reduction, 6.0 mm Hg; CI, 3.2–8.9) did not differ significantly from the reported IOP reduction obtained 6 months posttreatment in prospective randomized clinical trials (the mean IOP reduction calculated for the SLT study arm was 5.76; CI, 5.28–6.24).^{25–29} A major limitation of the current study is its small patient sample and the lack of a control group. It should therefore be borne in mind that the difference in the CIs might be decreased with a larger multicenter randomized controlled study group (currently under way).

IOP spikes are known to be a possible early complication of SLT in up to 27% of the treatments.^{20,29,30} The fact that none of our current study patients had IOP spikes might be attributable to the exclusion of patients with pigment dispersion glaucoma, as well as to the relatively small number of participants, or, alternatively, due to the laser delivery method.

A potential problem with translimbal irradiation is its possible effect on the stem cells present in the beam path. The corneal endothelium stem cell niche may receive less irradiation by the DSLT approach than by SLT. These cells, however, were shown to be activated rather than damaged by the higher-energy argon laser trabeculoplasty in experiments on human anterior segments in organ culture.³¹ Some corneal epithelial stem cells might also be impacted by the DSLT beams. However, oligopotent stem cells are present throughout the corneal, limbal, and conjunctival epithelia.³² Furthermore, no corneal transparency problems were encountered in any of our study participants or in our proof-of-concept study,¹⁵ suggesting that the laser application has no deleterious effects on these cells.

The only adverse events documented in our study were mild subconjunctival hemorrhages, which resolved without treatment within 1 week in four patients. We assume that these events had resulted from direct laser hits on small conjunctival vessels on the perilimbal area on the sclera.

A significant increase in the future glaucoma workload can be expected as a result of the rising numbers of people affected by glaucoma worldwide. In parallel, more nonphysician personnel (optometrists, glaucoma nurses) are likely to provide eye care in the years ahead. Optometrists are already legally allowed to perform SLT in the United Kingdom and in several states of the United States. An automatic DSLT approach may achieve widespread acceptance as a rapid and simple glaucoma treatment not limited to professionals who are experts in gonioscopy or by the nonavailability of glaucoma medications or by adherence considerations. DSLT could prove highly beneficial, especially in communities lacking ophthalmologic services. Furthermore, since visualization of the angle is not required, DSLT may become an option for treating angle closure glaucoma as well.³³ Another advantage of the system in the era of the coronavirus disease 2019 (COVID-19) pandemic is the lack of contact with the treated eye and the potential for increasing the distance between the patient and operator, who does not have to use the gonioscope. Although the severe acute respiratory syndrome coronavirus 2 viral particles could be present in the tear film in one-third of ocular samples among patients with ocular manifestation, which in turn represents only 5% of the COVID-19–related patients,³⁴ we do not consider the laser plume effect could result in the release and dispersion of significant particulate matter into the atmosphere. In DSLT, the laser first passes through relatively transparent conjunctiva/epithelium above the limbus. If laser energy is absorbed, it is

expected to be subsurface—where the absorbers are located—resulting in minimal ejected particles. In fact, we reported on few subconjunctival hemorrhages, meaning that the ablation would have been mostly contained. In our study, there have been no reports of eye discomfort, which would be an indication of surface damage on the conjunctiva.

Given the low laser energy and the expected low concentration of the virus on the eye, the potential for dispersal is expected to be minimal.

In summary, our results suggest that DSLT applied directly to the limbus without a gonioscopy lens is an effective, safe, easily performed, and well-tolerated new modality to reduce IOP in patients with POAG and OHT. The findings that higher levels of energy result in better-sustained IOP reduction remain to be further evaluated in a larger patient sample. This novel noncontact technique simplifies and shortens the procedure, increasing accessibility to eye drop–free first-line glaucoma care while reducing cornea-related side effects. A multicenter, international randomized clinical trial is currently under way to verify the results reported herein.

Acknowledgments

Supported by the European Union's HORIZON 2020 Research and Innovation Program under Grant 720274 (to BELKIN Laser Ltd., study sponsor). The clinical trial was sponsored by BELKIN Laser Ltd.

Disclosure: **M. Goldenfeld**, Belkin Laser Ltd. (C); **M. Belkin**, Belkin Laser Ltd. (P, I, C), NovaSight Ltd. (I, C), Springvision Ltd. (I, C), Sclerax Ltd. (I), Ellex Ltd. (C), BiogenCell Ltd. (I, C), Wizepharm Ltd. (I, C); **M. Dobkin-Bekman**, Belkin Laser Ltd. (C); **Z. Sacks**, Belkin Laser Ltd. (C); **S. Blum Meirovitch**, None; **N. Geffen**, Belkin Laser Ltd. (C), Sanoculis Ltd (C), Allergen Inc (F); **A. Leshno**, None; **A. Skaat**, None

References

1. Quigley HA. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol.* 2006;90(3):262–267.
2. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Global Health.* 2017;5(12):e1221–e1234.

3. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology*. 2014;121(11):2081–2090.
4. Garg A, Gazzard G. Selective laser trabeculoplasty: past, present, and future. *Eye*. 2018;32(5):863–876.
5. Waisbourd M, Katz LJ. Selective laser trabeculoplasty as a first-line therapy: a review. *Can J Ophthalmol*. 2014;49(6):519–522.
6. Barkana Y, Belkin M. Selective laser trabeculoplasty. *Surv Ophthalmol*. 2007;52(6):634–654.
7. Barisic F. Prevalence of ocular surface disease in patients with glaucoma using topical antiglaucoma medications. *J Clin Exp Ophthalmol*. 2014;5(2):334–338.
8. de Jong C, Stolwijk T, Kuppens E, de Keizer R, van Best J. Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluorescence of the cornea in glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 1994;32(4):221–224.
9. Newman-Casey PA, Salman M, Lee PP, Gatwood JD. Cost-utility analysis of glaucoma medication adherence. *Ophthalmology*. 2020;127(5):589–598.
10. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol*. 2008;53(6):S57–S68.
11. Latina MA, Park C. Selective targeting of trabecular meshwork cells: in vitro studies of pulsed and CW laser interactions. *Exp Eye Res*. 1995;60(4):359–371.
12. Lieberman MF, Congdon NG, He M. The value of tests in the diagnosis and management of glaucoma. *Am J Ophthalmol*. 2011;152(6):889–899.e1.
13. Sood D, Honavar SG. Sterilisation of tonometers and gonioscopes. *Indian J Ophthalmol*. 1998;46(2):113.
14. Nguyen TP, Nishimoto JH, Nakamura CY, De Land PN. Comparison of carboxymethylcellulose vs. hydroxypropyl methylcellulose as a gonioscopic fluid. *Optom Vis Sci*. 1996;73(7):466–472.
15. Geffen N, Ofir S, Belkin A, et al. Transscleral selective laser trabeculoplasty without a gonioscopy lens. *J Glaucoma*. 2017;26(3):201–207.
16. Sacks ZS, Dobkin-Bekman M, Geffen N, et al. Non-contact direct selective laser trabeculoplasty: light propagation analysis. *Biomed Opt Express*. 2020;11(6):2889–2904.
17. Prum BE, Rosenberg LF, Gedde SJ, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern guidelines. *Ophthalmology*. 2016;123(1):P41–P111.
18. IEC60601-2-22:Medical electrical equipment. Part 2-22: Particular requirements for basic safety and essential performance of surgical, cosmetic, therapeutic and diagnostic laser equipment. IEC, Geneva, Switzerland, November, 2019, <https://webstore.iec.ch/publication/31111>.
19. Cantor LB, Katz LJ, Cheng JW, Chen E, Tong KB, Peabody JW. Economic evaluation of medication, laser trabeculoplasty and filtering surgeries in treating patients with glaucoma in the US. *Curr Med Res Opin*. 2008;24(10):2905–2918.
20. Taylor HR. Glaucoma: where to now? *Ophthalmology*. 2009;116(5):821–822.
21. Lee R, Hutnik CML. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. *Can J Ophthalmol*. 2006;41(4):449–456.
22. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet*. 2019;393(10180):1505–1516.
23. Garg A, Vickerstaff V, Nathwani N, et al. Primary selective laser trabeculoplasty for open-angle glaucoma and ocular hypertension. *Ophthalmology*. 2019;126(9):1238–1248.
24. Garg A, Vickerstaff V, Nathwani N, et al. Efficacy of repeat selective laser trabeculoplasty in medication-naïve open-angle glaucoma and ocular hypertension during the LiGHT trial. *Ophthalmology*. 2020;127(4):467–476.
25. Kent SS, Hutnik CML, Birt CM, et al. A randomized clinical trial of selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with pseudoexfoliation. *J Glaucoma*. 2015;24(5):344–347.
26. Gracner T, Falez M, Gracner B, Pahor D. Long-term follow-up of selective laser trabeculoplasty in primary open-angle glaucoma [in German]. *Klin Monbl Augenheilkd*. 2006;223(9):743–747.
27. Martinez-de-la-Casa JM, Garcia-Feijoo J, Castillo A, et al. Selective vs argon laser trabeculoplasty: hypotensive efficacy, anterior chamber inflammation, and postoperative pain. *Eye (Lond)*. 2004;18(5):498–502.
28. Almeida ED, Pinto LM, Fernandes RAB, Prata TS. Pattern of intraocular pressure reduction following laser trabeculoplasty in open-angle glaucoma patients: comparison between selective and nonselective treatment. *Clin Ophthalmol*. 2011;5:933–936.
29. Katz LJ, Steinmann WC, Kabir A, et al. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. *J Glaucoma*. 2012;21(7):460–468.

30. Ayala M. Long-term outcomes of selective laser trabeculoplasty (SLT) treatment. *TOOPHTJ*. 2011;5(1):32–34.
31. Samples JR, Bradley JMB, Bacon DR, Bylsma SS, Van Buskirk EM, Acott TS. Trabecular repopulation by anterior trabecular meshwork cells after laser trabeculoplasty. *Am J Ophthalmol*. 1989;107(1):1–6.
32. Sun T-T, Tseng SC, Lavker RM. Location of corneal epithelial stem cells. *Nature*. 2010;463(7284):E10–E11.
33. Narayanaswamy A, Leung CK, Istantoro DV, et al. Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial. *JAMA Ophthalmol*. 2015;133(2):206.
34. La Distia Nora R, Putera I, Khalisha DF, Septiana I, Ridwan AS, Sitompul R. Are eyes the windows to COVID-19? Systematic review and meta-analysis. *BMJ Open Opth*. 2020;5(1):e000563.
35. Li P, An L, Lan G, Johnstone M, Malchow D, Wang RK. Extended imaging depth to 12 mm for 1050-nm spectral domain optical coherence tomography for imaging the whole anterior segment of the human eye at 120-kHz A-scan rate. *J Biomed Opt*. 2013;18(1):016012.