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Two-Year Clinical Results After Selective Laser Trabeculoplasty for Normal Tension Glaucoma

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Abstract: This article aims to investigate the clinical results at 2 years after selective laser trabeculoplasty (SLT) for normal tension glaucoma (NTG).

This prospective cohort study recruited NTG patients taking anti-glaucoma medication. Subjects were excluded if they had previous glaucoma surgery/laser or corneal pathologies. All subjects underwent a 1-month washout. A single session of SLT was performed to 360° of the trabecular meshwork. Medication was resumed at 1 month to achieve a targeted 30% intraocular pressure (IOP) reduction from the post-washout/pre-SLT IOP. IOP was measured every 3 months and medication use was recorded at 3, 6, 12, and 24 months. Subjects with a secondary SLT or cataract extraction were excluded from IOP and medication analyses.

At 24 months, 34 of the initial 45 right eyes were eligible for analyses. There were significant IOP reductions at all time intervals (except at 1 week) following SLT when compared to the prestudy (without medication) or pre-SLT (post-washout) IOP ($P < 0.0001$). Medications were likewise significantly reduced at all time intervals following SLT ($P < 0.0001$). At 24 months, the IOP was 11.5% lower than the prestudy IOP, 22.0% lower than the pre-SLT IOP, and medication use was reduced by 41.1% ($P < 0.0001$). Six out of 45 eyes (13.3%) required a secondary SLT. Absolute success (IOP reduction $>20\%$ from pre-SLT, without medication) was achieved in 11.1% (5/45).

Reductions in IOP and medication use were evident at 2 years following SLT for the treatment of NTG whereas 11% remained medication free.

Trial Registrations: The Clinical Trials Register of the University of Hong Kong HKCTR1847. The European Clinical Trials Database 2014-003305-15 (August 11, 2014).

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Abbreviations: ALT = argon laser trabeculoplasty, IOP = intraocular pressure, NTG = normal tension glaucoma, POAG = primary open-angle glaucoma, SLT = selective laser trabeculoplasty.

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INTRODUCTION

Normal tension glaucoma (NTG) has a high prevalence in Asian countries.^{1,2} Selective laser trabeculoplasty (SLT) is safe and as effective as medication in the treatment of primary open-angle glaucoma (POAG).^{3–5} More recently, SLT was also found to be effective for the treatment for NTG, reducing the intraocular pressure (IOP) anywhere from 12% to 15% for up to 1 year.^{6–8} The effect of SLT is not permanent and a proportion of treated patients may continue to require additional medication, secondary lasers, or even glaucoma filtration procedures throughout the course of their disease.^{8,9} The objective of this study was to investigate the 2-year clinical results of using SLT in the treatment of NTG.

METHODS

This study adhered to the tenets of the Declaration of Helsinki. Informed patient consent and approval by the Institutional Review Board of The Hospital Authority of Hong Kong were obtained prior to study commencement.

The study was registered with the following publicly accessible registries: the Clinical Trials Register of the University of Hong Kong (trial registration number: HKCTR1847) in April 2012 and retrospectively registered with the European Clinical Trials Database (trial registration number: 2014-003305-15) on August 11, 2014.

The methodology of this study has been previously described in parts in earlier publications reporting the short-term clinical results.^{8,10} This was a prospective cohort study from July 2012 to July 2014, conducted at a university hospital in Hong Kong. The study recruited cases of unilateral or bilateral NTG subjects who were currently on topical antiglaucoma medications. NTG was defined by open angle on gonioscopy, glaucomatous visual field loss on Humphrey visual field analyzer as per the Hodapp–Parrish–Anderson criteria,¹¹ progressive thinning of the retinal nerve fiber layer (RNFL) on optical coherence tomography (OCT), and Goldmann applanation-measured IOP <21 mm Hg on all documented clinical visits prior to study recruitment. Cases were excluded if they had received prior surgery or laser for the treatment of glaucoma or taking any systemic medications that may affect IOP. Patients were also excluded if there were contraindications for SLT such as corneal pathologies or scars, not completing the 24-month follow-up, or if any intraocular surgery or repeated SLT was performed within 24 months of the first SLT treatment.

The prestudy IOP with antiglaucoma medication and the number of antiglaucoma medication used were recorded prior to study enrolment. Fixed combination eye drops were counted as 2 types of antiglaucoma medication. All patients then underwent a 1-month washout period in which all antiglaucoma medications were discontinued. A mean pre-SLT IOP without medication was then calculated after IOP phasing at 9 AM, 1 PM, and 5 PM. An individual target IOP was calculated as a 30%

reduction from the pre-SLT IOP, as per the findings from The Collaborative Normal Tension Glaucoma Study.¹²

All patients received a single session of SLT using a Q-switched Nd:YAG laser (Ellex Solo; Ellex Medical Pty. Ltd., Adelaide, SA, Australia) with an initial energy of 0.8 mJ. The power was titrated up or down until bubble formation was just visible. A single glaucoma specialist (J.W.Y.L.) delivered the SLT treatment and both eyes were treated in the same laser session for those with bilateral disease. In all treated eyes, a single drop of brimonidine tartrate (Alphagan P; Allergan Inc., Waco, TX) was instilled immediately after SLT. Dexamethasone 0.1% and neomycin 0.5% combination eye drop (Dexoptic-N by Ashford Laboratories Pvt. Ltd., Dheeraj Heritage, S.V. Road, Santacruz West, Mumbai, India) was used twice daily for 1 day and was continued for a few more days only if anterior chamber reaction was seen on day 1 after SLT. Subjects returned for follow-up on day 1, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months after SLT. At 1 month after SLT, IOP phasing (9 AM, 1 PM, and 5 PM) was repeated and a mean 1-month IOP was calculated. IOP phasing was only performed before SLT and again 1 month after SLT. Antiglaucoma medications were resumed and titrated based on clinical response to achieve the preset target IOP for each individual. The order of resuming antiglaucoma medications was as follows: α -adrenergic agonists or prostaglandin analogs followed by topical carbonic anhydrase inhibitors and, lastly, B-blockers. This order was based on the understanding from the Low-Pressure Glaucoma Treatment Study that NTG subjects treated with α -adrenergic agonists were less likely (9.1%) to develop visual field progression than those using B-blockers (39.2%).¹³ When multiple medications were required, fixed combination medications were given to simplify the drug regimen.

The primary outcome measure included IOP at the following time intervals: prestudy (with medication), pre-SLT (post-washout), 1 day, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months after SLT. Goldmann applanation tonometry was used to measure IOP.

The secondary outcomes included the following: the number of antiglaucoma medications used prestudy and at 3, 6, 12, and 24 months after SLT. Absolute success was defined as IOP reduction $\geq 20\%$ from the pre-SLT IOP without any additional antiglaucoma medication. The baseline and 24-month Snellen visual acuity, RNFL on OCT, as well as the pattern standard deviation (PSD) and visual field index (VFI) on Humphrey visual field were recorded.

Statistics

The D'Agostino and Pearson omnibus normality test was used to test for normality. Only the right eye was used for statistical analysis. Repeated measures ANOVA with Bonferroni multiple comparison test was used to calculate the following outcome measures over the study period:

1. IOP at prestudy, pre-SLT, and at 1 day, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-SLT.
2. Number of antiglaucoma eye drops at prestudy and at 1, 3, 6, 12, and 24 months post-SLT.

A paired *t* test was used to compare the following at baseline and 24 months:

1. Snellen visual acuity
2. RNFL on OCT

3. PSD on Humphrey visual field
4. VFI on Humphrey visual field

Those with a repeated SLT or phacoemulsification in the treated eye were excluded from the above statistical analysis on IOP and medication use as the IOP changes in these subjects would no longer be solely attributed to the effects of the initial SLT procedure. These subjects, however, will still be included in the calculation of the percentage of absolute success and the survival curve as described further.

A Kaplan–Meier survival curve was used to represent the “mortality” after SLT, which was defined as the need of a repeat SLT procedure to further lower IOP or medication load. All means were expressed as mean \pm standard deviation. Statistical significance was defined as $P < 0.05$.

RESULTS

In the initially recruited 46 NTG subjects (45 right eyes and 38 left eyes), 1 was deceased, 6 required a secondary SLT treatment, and 5 had a phacoemulsification with intraocular lens implantation within the 24-month period. In the remaining 34 subjects that completed the 24-month follow-up, the mean age was 65.1 ± 12.1 years. There were 18 males and 16 females with 34 right eyes and 28 left eyes. All subjects were ethnic Chinese with pigmented and open-angle configurations. The mean SLT shots delivered was 191.0 ± 27.3 at a mean energy of 1.0 ± 0.08 mJ.

The 34 right eyes were used for the statistical analyses on IOP and medication use. Whether using the prestudy IOP (with medication) or the pre-SLT IOP (post-washout, without medication) as the basis of comparison, there were significant IOP reductions at all time intervals following SLT (all $P < 0.0001$), except at 1 week, where there was no significant difference with the prestudy IOP or pre-SLT IOP ($P > 0.05$) (Table 1, Figure 1).

At 24 months, the IOP was 11.5% lower than the prestudy IOP ($P < 0.0001$) and 22.0% lower than the pre-SLT IOP ($P < 0.0001$). The number of antiglaucoma medications was also significantly reduced at all time intervals following SLT when compared to the prestudy level (all $P < 0.0001$). At 24 months, medication requirement was reduced by 41.1% compared to the prestudy level ($P < 0.0001$) (Table 2, Figure 2).

During the 24-month period following SLT, 6 out of the initial 45 right eyes (13.3%) required a secondary SLT procedure at a mean of 17.8 ± 6.7 months after the initial laser. Absolute success was achieved in 11.1% (5/45) at 24 months following SLT (Figure 3).

In the SLT treated eyes, there was no significant progressive thinning in the RNFL (prestudy = 72.0 ± 14.0 μm , 24 months = 70.5 ± 13.1 μm , $P = 0.2$). Similarly, the PSD (prestudy = 6.7 ± 3.6 dB, 24 months = 7.4 ± 4.2 dB, $P = 0.2$) and VFI (prestudy = $74.9 \pm 22.7\%$, 24 months = 75.9 ± 20.4 dB, $P = 0.6$) on the Humphrey visual field were statistically similar before SLT and at 24 months after SLT. The visual acuity also remained unchanged prestudy versus 24 months (baseline = 0.6 ± 0.2 , 24 months = 0.7 ± 0.2 , $P = 0.2$).

DISCUSSION

Previously, the use of argon laser trabeculoplasty (ALT) in NTG resulted in IOP reductions lasting up to 21.6 months, but the scarring induced by ALT limited its repeatability when the laser effect worn off.¹⁴ In earlier studies involving the use of

TABLE 1. IOP Before and After SLT for NTG

| | Mean IOP | | Reduction From Pre-study Level | | Reduction From PreSLT Level, % | |
|------------------------------|----------|------|--------------------------------|----------|--------------------------------|----------|
| | mm Hg | SD | % | P Value | % | P Value |
| Prestudy (with medication) | 14.3 | ±3.6 | — | — | — | — |
| Pre-SLT (without medication) | 16.2 | ±2.3 | — | — | — | — |
| Day 1 post-SLT | 11.2 | ±2.5 | -21.8 | <0.0001* | -31.0 | <0.0001* |
| 1 wk post-SLT | 14.9 | ±3.3 | 4.6 | >0.05 | -7.8 | >0.05 |
| 1 mo post-SLT | 12.3 | ±2.1 | -14.0 | <0.0001* | -24.2 | <0.0001* |
| 3 mo post-SLT | 11.2 | ±2.1 | -21.4 | <0.0001* | -30.7 | <0.0001* |
| 6 mo post-SLT | 11.2 | ±1.7 | -21.2 | <0.0001* | -30.5 | <0.0001* |
| 9 mo post-SLT | 11.6 | ±2.1 | -18.9 | <0.0001* | -28.5 | <0.0001* |
| 12 mo post-SLT | 12.0 | ±2.1 | -15.6 | <0.0001* | -25.6 | <0.0001* |
| 18 mo post-SLT | 12.7 | ±2.1 | -10.7 | <0.0001* | -21.2 | <0.0001* |
| 24 mo post-SLT | 12.6 | ±2.7 | -11.5 | <0.0001* | -22.0 | <0.0001* |

IOP = intraocular pressure, NTG = normal tension glaucoma, SD = standard deviation, SLT = selective laser trabeculoplasty.
 * Statistically significant.

SLT in the treatment of a mixed population of NTG and POAG subjects, the IOP reduction ranged from 14% to 16.5% at 1 year.^{6,15} More recently, in a prospective study involving just NTG subjects, SLT was effective in lowering the IOP by 20% and 15% at 6 months and 1 year, respectively.^{8,10} Similarly, Nitta et al¹⁶ used SLT as the initial treatment in 42 NTG subjects and reported IOP reductions of 16.5% at 1 year and 14.6% at 2 years, which was in agreement with our finding of a 12% IOP reduction at 2 years.

The absolute success of SLT in our NTG population tapered off from 61%, at 6 months, to 22% at 1 year, to 11% at 2 years.^{8,10} At 1 year, 2 (4.3%) of the treated eyes required a secondary SLT.⁸ By 2 years, 6 (13.3%) eyes required a secondary SLT although the mean IOP reduction for the entire study population maintained at 22% lower than the pre-SLT IOP level while using 0.9 ± 0.9 medications at 2 years.

To the best of our knowledge, this is one of the largest and longest longitudinal studies reporting the effects of SLT in a homogenous NTG study population. Some of the limitations of our original study design have been previously described in

earlier publications.^{8,10} One of the most important limitations of this article is lack of a control group. In future studies, a randomized control trial composing of NTG patients continuing medical treatment would provide more robust results. In particular, relevance to this 2-year study, it should be pointed out that not all subjects were able to achieve the initial targeted 30% IOP reduction as per the Collaborative Normal Tension Glaucoma study¹² as in a realistic clinical environment, patient’s willingness to endure additional medication or secondary laser procedures were governed by individual goals, tolerances, and expectations to treatment. As NTG is asymptomatic with ‘‘normal pressures,’’ some patients were reluctant to receive additional medication or undergo additional laser in order to top up the few outstanding percentages in IOP reduction for statistical completeness. However, on a whole, the study population already enjoyed a mean IOP reduction of 22% from the pre-SLT level. Previous studies have demonstrated that SLT dampens the intervisit IOP variation and the IOP-related amplitude on 24-hour recordings, which may be related to NTG progression but analysis of IOP fluctuation was beyond the scope of this study.^{7,17} From the literature, while pretreatment IOP, number of preexisting medication, and the total SLT energy delivered seemed to influence the success of SLT, there is no effective formula to date that can predict the sustainability of SLT for an individual prior to laser.^{18–21} Future studies

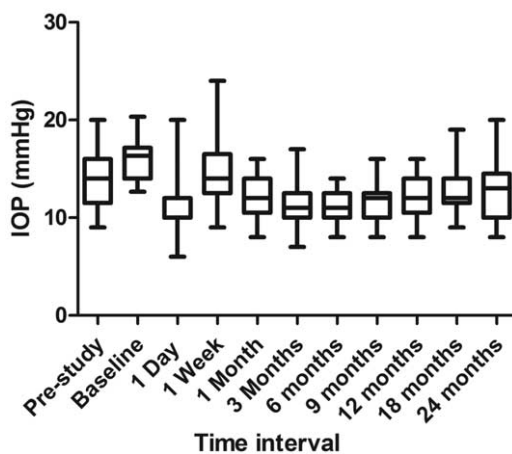


FIGURE 1. Changes in IOP before and after SLT for NTG, wherein whiskers represent the 2.5 to 97.5th percentile. IOP = intraocular pressure, NTG = normal tension glaucoma, SLT = selective laser trabeculoplasty.

TABLE 2. Medications Before and After SLT for NTG

| | Mean Number of Medications | | Reduction From Prestudy Level, % | |
|----------------|----------------------------|------|----------------------------------|----------|
| | n | SD | % | P Value |
| Prestudy | 1.5 | ±0.8 | — | — |
| 3 mo post-SLT | 0.9 | ±0.9 | -40.0 | <0.0001* |
| 6 mo post-SLT | 1.0 | ±1.0 | -55.6 | <0.0001* |
| 12 mo post-SLT | 1.0 | ±0.8 | -33.3 | <0.0001* |
| 24 mo post-SLT | 0.9 | ±0.9 | -40.0 | <0.0001* |

n = number, NTG = normal tension glaucoma, SD = standard deviation, SLT = selective laser trabeculoplasty.
 * Statistically significant.

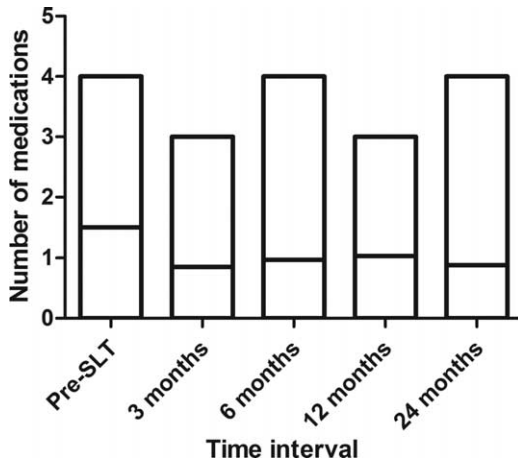


FIGURE 2. Changes in the number of antiglaucoma medications before and after SLT for NTG, wherein the boxes represent the minimum/maximum and the center line represents the mean. NTG = normal tension glaucoma, SLT = selective laser trabeculoplasty.

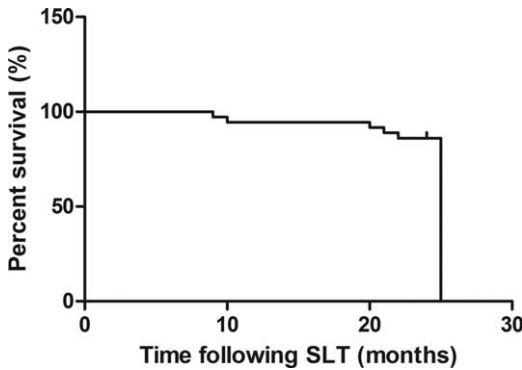


FIGURE 3. Kaplan–Meier survival curve following SLT, wherein mortality = need of a secondary SLT. SLT = selective laser trabeculoplasty.

investigating the parameters that influence or predict laser sustainability would be of great clinical relevance. The findings from this study are only applicable to NTG subjects previously receiving antiglaucoma medications with a 1-month washout period and may not generalizable to other populations.

CONCLUSION

At 2 years after a single session of SLT in the treatment of NTG, treated eyes benefited from a 12% IOP reduction with 41% fewer medication, whereas 11% were medication free.

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