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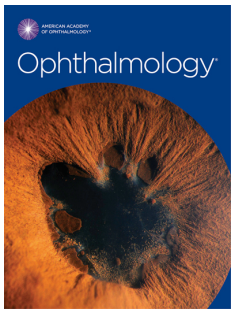

Primary Selective Laser Trabeculoplasty for Open Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success and Safety from the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial

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PII: S0161-6420(19)30162-9

DOI: https://doi.org/10.1016/j.ophtha.2019.04.012

Reference: OPHTHA 10751

To appear in: *Ophthalmology*

Received Date: 19 January 2019

Revised Date: 21 March 2019

Accepted Date: 8 April 2019

Please cite this article as: Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, Bunce C, Wormald R, Barton K, Gazzard G, on behalf of the LiGHT Trial Study Group, Primary Selective Laser Trabeculoplasty for Open Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success and Safety from the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial, *Ophthalmology* (2019), doi: https://doi.org/10.1016/j.ophtha.2019.04.012.

TITLE

Primary Selective Laser Trabeculoplasty for Open Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success and Safety from the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial

Anurag Garg[1, 2], Victoria Vickerstaff[3, 4], Neil Nathwani[1], David Garway-Heath[1, 2], Evgenia Konstantakopoulou[1, 2], Gareth Ambler[5], Catey Bunce[1,2, 6, 7], Richard Wormald[1, 2, 7], Keith Barton[1, 2], Gus Gazzard[1, 2]* on behalf of the LiGHT Trial Study Group**

1. Moorfields Eye Hospital NHS Foundation Trust, 169 City Road, London, EC1V 2PD, UK
2. UCL Institute of Ophthalmology, 11-43 Bath St, London, EC1V 9EL, UK
3. Marie Curie Palliative Care Research Department, UCL Division of Psychiatry, University College London, 6th Floor, Maple House, 149 Tottenham Court Road, London W1T 7NF, UK
4. The Research Department of Primary Care and Population Health, University College London, Rowland Hill Street, London NW3 2PF, UK
5. Department of Statistical Science, University College London, Gower Street, London, UK
6. School of Population Health and Environmental Sciences, Faculty of Life Sciences and Medicine, King's College London. 4th Floor, Addison House, Guy's Campus, London UK
7. London School of Hygiene and Tropical Medicine, London, UK

***Corresponding author:** Gus Gazzard FRCOphth, NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust, London, UK, 162 City Road, EC1V 2PD, London UK.

****A listing of the LiGHT Trial Study Group is provided as an Appendix:** (available at www.aaojournal.org)

Meeting presentation: Presented in part at the American Academy of Ophthalmology Annual Meeting, 2018

Funding: The research was supported by the National Institute for Health Research, Health and Technology Assessment Programme. Trial registration: ISRCTN32038223.

Conflict of Interest: GG received a research grant from Lumenis 8 years prior to the submitted work.

Running head: Primary SLT in treatment naïve OAG & OHT patients

This article contains additional online-only material. The following should appear online-only: List of LiGHT Trial Study Group members, Table 13, Table 14, Figure 2 and Figure 3

ABSTRACT

Purpose: To report clinical efficacy, predictors of success and safety of primary selective laser trabeculoplasty (SLT) used in treatment-naïve open-angle glaucoma (OAG) or ocular hypertension (OHT) patients.

Design: Post-hoc analysis of a multicentre prospective randomized-controlled-trial.

Participants: Treatment-naïve OAG or OHT patients.

Methods: Patients randomized to SLT or topical medication and treated to pre-defined target IOPs requiring ≥20% IOP reduction from baseline for all disease severity levels.

Outcome Measures: Initial ("early") absolute IOP-lowering at 2-months. Achievement of "drop-free disease-control": meeting target IOP without disease progression or need for additional topical medication over 36-months following SLT. Predictors of early absolute IOP-lowering and drop-free "disease-control" after single initial SLT. Frequency of laser-related complications.

Results: 611 eyes (195 OHT & 416 OAG) of 355 patients received SLT and 622 eyes (185 OHT & 437 OAG) of 362 patients received topical medication at baseline. Early absolute IOP-lowering following SLT was no different between OHT and OAG eyes (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85). No difference was noted in early absolute IOP-lowering between topical medication and primary SLT (adjusted mean difference = -0.1mmHg; 95% CI, -0.6 to 0.4mmHg; p=0.67). Early absolute IOP-lowering with primary SLT was positively associated with baseline IOP (Coefficient 0.59; 95% CI, 0.54 to 0.64; p<0.001) and negatively with female gender (Coefficient -0.63; 95% CI, -1.23 to -0.02; p=0.04). At 36-months, 536 eyes (87.7% of 611 eyes) of 314 patients (88.5% of 355 patients) were available for analysis. 74.6% of eyes (400 eyes) treated with primary SLT achieved drop-free "disease-control" at 36-months; 58.2% (312 eyes) following single SLT. Total SLT power and 2-month IOP were predictors of drop-free "disease-control" at 36-months following single SLT. 6 eyes of 6 patients experienced immediate post-laser IOP spike (>5mmHg from pre-treatment IOP) with 1 eye requiring treatment.

Conclusion: Primary SLT achieved comparable early absolute IOP-lowering in OHT vs OAG eyes. Drop-free "disease-control" was achieved in ~75% eyes at 36-months following 1 or 2 SLTs; the majority of these following single SLT. These analyses are exploratory, but support primary SLT to be effective and safe in treatment-naïve OAG and OHT eyes.

INTRODUCTION

Over the past two decades, selective laser trabeculoplasty (SLT) has become an established treatment to lower IOP for primary open angle glaucoma (POAG) and ocular hypertension (OHT). Introduced by Latina and Park in 1995, SLT uses a 532nm Q switched, frequency-doubled Nd:YAG laser that delivers a short pulse duration (3 nanoseconds) (1) to reduce IOP by increasing aqueous outflow through the trabecular meshwork (TM) (2). The procedure is short and outpatient-based, with quick recovery and good safety profile (3). SLT has the potential advantage of avoiding issues associated with topical IOP lowering medications such as local and systemic side effects and variable patient adherence. Since FDA approval in 2001, SLT increasingly has been adopted into practice. In the USA, 75,647 trabeculoplasties were performed in 2001 and this increased to 142,682 procedures in 2012 (4).

Studies investigating SLT as a primary treatment have found a similar IOP lowering efficacy and success rate to topical medication using various success criteria (3). However, several of these studies include patients taking IOP lowering topical medications that were stopped for a variable duration prior to receiving SLT (5-8). Despite a washout period to mitigate against residual effects of prior topical treatment, SLT can be less effective following topical treatment (6). Few studies have evaluated primary SLT in true treatment-naïve patients (9-11) and there is limited knowledge of predictors of IOP lowering response, treatment success and safety in such patients.

The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial was a multi-centre randomized controlled trial (RCT) conducted to establish whether initial treatment with SLT is superior to initial treatment with medication for treatment-naive OAG or OHT patients in relation to health-related quality of life (HRQL), cost-effectiveness and clinical efficacy at 36 months (12). Eyes in the primary SLT arm were at target IOP over more clinical visits during 36-month follow up compared to drops, with fewer eyes demonstrating disease progression and fewer cataract and trabeculectomy surgeries. Primary SLT was found to be more cost-effective than initial medication over the course of 36 months, despite a lack of HRQL differences between the two arms (13).

This report characterizes the IOP lowering, drop-free “disease-control” and safety achieved by primary SLT in treatment-naïve OAG and OHT patients as part of LiGHT, in which eyes were treated to pre-defined target IOPs based on disease severity. We also investigated predictors of initial (“early”) IOP lowering and predictors for achieving drop-free “disease-control” at 36 months following single initial SLT. We hypothesized that primary SLT would demonstrate effective IOP lowering in treatment-naive OHT and OAG eyes with a comparable effect to topical medication. We anticipated that absolute IOP lowering could be greater in OHT vs OAG eyes due to higher pre-treatment baseline IOPs and that drop-free “disease-control” would be more readily achieved in eyes with less advanced disease because target IOPs were higher.

METHODS

The study was conducted in accordance to good clinical practice (GCP) guidelines and adhered to the tenets of the Declaration of Helsinki. Institutional Review Board (IRB)/Ethics Committee approval was obtained. All patients provided written informed consent before participation to the trial. The LiGHT Trial is registered at www.controlled-trials.com (registration number ISRCTN32038223).

This study was a post hoc analysis of the LiGHT trial, the design and baseline characteristics of which have been previously described (12, 14). Briefly, consecutive eligible patients were identified at the clinics of six participating centres in the UK from October 2012 until October 2014. Eligible patients had newly diagnosed, untreated OAG or OHT in one or both eyes and qualified for treatment according to National Institute of Clinical Excellence (NICE) guidelines (15), open angles on gonioscopy, visual field loss with mean deviation (VF MD) not worse than -12 dB in the better eye or -15 dB in the worse eye and, for OAG, corresponding damage to the optic nerve head. Patients were 18 years or older and able to read and understand English, had a visual acuity of 20/120 or better in the treated eye(s) and no previous intraocular surgery, except uncomplicated phacoemulsification at least one year before entering the trial. Patients were excluded if there were any contra-indications to SLT, if they were unable to use topical medical therapy, if they had visually symptomatic cataract and wanted to undergo cataract surgery, or were having active treatment for another ophthalmic condition. Patients with one or both eyes eligible were treated. All measurements influencing treatment escalation decisions: automated visual field using Humphrey Field Analyzer Mark II Swedish interactive threshold algorithm standard 24-2 programme (Carl Zeiss Meditec, Dublin, CA, USA), Heidelberg Retina Tomography (HRT) disc imaging (Heidelberg Engineering, Heidelberg, Germany) and IOP (Goldmann applanation tonometry with daily calibration verification) were performed by masked observers. Patients were monitored for 3 years.

Disease category and severity were defined using pre-set objective severity criteria from the Canadian Target IOP Workshop (16) with additional central VF loss criteria (17) – see Table 1.

Severity stratification (OHT, ‘mild’, ‘moderate’ or ‘severe’ OAG) determined an eye specific 'Target IOP' and follow-up intervals. Target IOP was objectively defined using both percentage reduction from untreated IOP and an absolute value, with the final target IOP being the lower of the 2 values (see Table 2). Achievement of target IOP thus required a minimum IOP reduction of >20% from baseline IOP, irrespective of disease severity.

Standardised criteria to escalate treatment were used according to a protocol following international guidelines by the European Glaucoma Society, (18) American Academy of Ophthalmology Preferred Practice Pattern (19) and the South-East Asia

Glaucoma Interest Group (20). These were incorporated into a real-time web-based clinical decision support software, based on optic disc analysis (HRT), automated visual fields analysis (Humphrey Visual Field, HVF) and IOP measurements. Criteria for defining IOP not at target and disease progression by HRT and VF have been reported previously (12).

Standardisation of SLT delivery was achieved by protocol-defined settings and clinical endpoints. The protocol advised 360-degree TM treatment, 100 non-overlapping shots (25 per quadrant) of a pre-set 3 nanoseconds duration and pre-set 400µm spot size, with the laser energy varied from 0.3 to 1.9mJ by the clinician according to just observable bubble formation. IOP was checked 60 minutes following SLT procedure. One SLT re-treatment was permitted during the study, if/when a treatment escalation was recommended by the decision support software and confirmed by the treating clinician. To allow time for the full effects of laser to occur, the earliest interval at which repeat SLT was permitted was following the first scheduled visit 2 months post initial SLT. SLT was not repeated if significant complications of laser treatment occurred, if there was a lack of IOP lowering response following initial SLT (judged by the treating clinician – not protocol defined) or other new medical conditions prevented repetition. In such cases, treatment escalation with topical medication rather than repeat SLT was permitted. In eyes that underwent repeat SLT, if further treatment escalation was required, the next step was topical medication. The earliest planned interval at which this could be initiated was following the first scheduled visit 2 months post repeat SLT.

Follow-up intervals were initially set at entry to the study according to NICE guidance (21) and subsequently adjusted on the basis of IOP control, glaucoma progression or adverse reactions. The routine schedule of appointments and assessments for patients has been published previously (14). At follow up, patients underwent visual acuity testing (ETDRS logMAR), slit-lamp examination, visual field testing (Humphrey Field Analyzer (HFA) Mark II SITA standard 24-2), HRT optic disc imaging, IOP measurement (Goldmann applanation tonometry) and clinical assessment of the optic discs, maculae and fundi.

To investigate the IOP lowering efficacy of primary SLT for OHT vs OAG, we evaluated the initial ("early") absolute IOP reduction at 2-months for all eyes receiving primary SLT. This was the first scheduled visit (after 'safety' IOP check visit at 2 weeks post laser) following laser at baseline. To contextualize the early IOP lowering efficacy of primary SLT in treatment-naïve eyes, we compared early absolute IOP reduction at 2-months following primary SLT with 2-month absolute IOP reduction in eyes from the Medication-1st arm of LiGHT that had commenced topical medication at baseline. To investigate if early absolute IOP lowering following primary SLT was predicted by clinically relevant baseline factors, a linear regression analysis was performed (see Statistical Methods).

LiGHT followed a 'Treat in Pursuit of Control' design (TPC) and hence, following the first scheduled visit at 2-months, the web-based clinical decision support software began to monitor and escalate treatment (if required) for each eye based on achievement of "disease-control" i.e. achievement of predefined target IOP with no objective evidence of disease progression. OAG eyes had lower predefined target IOPs than OHT eyes (see Table 2) and thus were more likely to require greater treatment intensity compared to OHT eyes to achieve "disease-control". IOP comparisons between OHT vs OAG eyes at later time points would be confounded by differences in treatment intensity and hence were not performed.

We evaluated treatment intensity of primary SLT in OHT vs OAG eyes by assessment of drop-free "disease-control" achieved by primary SLT at 12, 24 and 36 months. The LiGHT treatment protocol permitted a single SLT retreatment (if required) and we therefore determined drop-free "disease-control" achieved by 1 or 2 SLTs collectively and by initial, single SLT alone.

In the SLT literature, the most commonly defined measure of 'success' is a minimum IOP reduction of ≥ 20% from baseline IOP following SLT at a specified time point, without need for further intervention (22). In LiGHT, the predefined target IOPs required a minimum IOP reduction of > 20% from baseline IOP for all disease severities (see Table 2) and thus, eyes achieving drop-free "disease-control" at 36 months following a single, initial SLT would serve as a useful (albeit much more stringent) 'success' comparator with pre-existing SLT studies. A logistic regression analysis of factors to predict eyes achieving drop-free "disease-control" at 36 months following initial, single SLT was performed.

To determine safety of primary SLT, the frequency of laser related complications and adverse events over 36 months was collated.

STATISTICAL METHODS

The sample size for LiGHT was based on analyses planned to assess HRQL in treatment-naïve OAG/OHT patients treated initially with either primary SLT or topical medication. The sample size was 718 patients, calculated to detect a difference of 0.05 in EQ-5D-5L between the two arms at 36 months using a two sample *t*-test at the 5% significance level with 90% power, assuming a common standard deviation of 0.19 (23) and 15% attrition.

In this report, the unit of analysis was the eye. All eligible study eyes that received SLT at baseline were included in the analysis with appropriate measures taken to account for correlation amongst paired eyes within a subject.

Summary statistics of the demographic and clinical characteristics are presented for all eligible study eyes. Descriptive statistics are presented as means and standard deviations. Analysis comparing baseline demographics of eyes available to those

unavailable to analyze at 36-months was performed. T-test or Wilcoxon Rank Sum test was used for comparison of continuous data and Chi squared test was used for categorical data.

To compare absolute IOP reduction at 2 months between OHT and OAG eyes, a mixed effects model using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes was performed. The model also controlled for pre-treatment baseline IOP and treating centre (to control for centre effects in a multicentre trial). To compare absolute IOP reduction at 2 months between primary SLT vs topical medication, a similar mixed effects model was also used.

To examine baseline predictors of early absolute IOP reduction at 2 months in eyes receiving primary SLT, univariate mixed effect linear regression analyses were performed using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes. Patient related baseline characteristics considered for univariable selection were age, gender, ethnicity, phakic status, baseline IOP, central corneal thickness (CCT), TM pigmentation, pseudoexfoliation (PXF), hypertension (HTN) & diabetes mellitus (DM). Laser related characteristics included total SLT power and total number of SLT shots of initial SLT at baseline. Covariates that achieved $p<0.10$ in the univariable selection regression analyses were entered in a mixed effect multivariable linear regression model controlling for LiGHT stratification factors (disease severity and treating centre). The regression model was then run, with non-significant variables removed one by one until only significant ($p<0.05$) variables remained.

A similar approach involving logistic regression was used to look for predictors of drop-free “disease-control” at 36 months. For the logistic regression analysis, a ‘success’ criterion defined as eyes that achieved drop-free “disease-control” following initial, single SLT at baseline was used. This was a more stringent criterion than used elsewhere. We also considered the 2-month IOP to assess if this was a post treatment predictor of drop-free “disease-control” at 36 months.

Statistical significance was defined as a 2-sided P value <0.05. Analyses were carried out using Stata15 (StataCorp, 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

RESULTS

356 patients (613 eyes) were randomized to the Laser 1st arm of LiGHT. One patient (2 eyes) withdrew consent prior to receiving SLT at the baseline visit and thus 355 patients (611 eyes) received primary SLT. At 36 months, 536 eyes of 314 patients were available for analysis. Of the 75 remaining eyes, 22 eyes (of 13 patients) were formally lost to follow up (withdrew, died, illness, or moved) during the course of the 3-year trial. The remaining 53 eyes (of 28 patients) were still returning HRQL questionnaires in the main LiGHT study, but clinical data were not available at the 36-month time-point. Analysis comparing baseline demographics of eyes available vs unavailable to analyze at 36-months (536 eyes vs 77 eyes) demonstrated no clinically or statistically significant differences in age, baseline IOP, ethnicity, gender, disease severity and VF mean deviation. A statistically but not clinically significant difference in baseline visual acuity was noted between groups (mean difference LogMAR -0.06 ,95% CI, -0.1 to -0.01, p=0.02) (see Appendix: available at www.aaojournal.org).

Baseline Characteristics

Baseline demographic data of the 611 eyes are given in Table 3. There was a greater proportion of males compared to females (56.1% vs 43.9%) at baseline. The most common ethnicities were White European (68.2%) and Black (21.7%). 72.1% of patients had both eyes in the study, 13.8% had only the right eye and 14.1% had only the left eye in the study; 31.9% of eyes had a diagnosis of OHT (195 eyes) compared to 68.1% of eyes with OAG (416 eyes). This is reflected in the average mean deviation (MD) value of -3.0 decibels (dB). Mean baseline IOP was 24.5mmHg (SD 5.2) for all eyes but was greater in OHT eyes (26.5mmHg (SD 3.5)) vs OAG eyes (23.5mmHg (SD 5.6)). During initial SLT, mean total power delivered was 90.4 (SD 23.5) mJ via a mean treatment of 99.2 (SD 5.1) shots. Baseline demographic data of the 622 eyes in the Medication 1st arm is also provided (see Appendix: available at www.aaojournal.org)

Early IOP lowering efficacy of Primary SLT

559 eyes (out of 611 eyes at baseline) were available for analysis at the 2-month time point in the primary SLT arm having undergone initial SLT at baseline (see Figure 1). Mean initial IOP lowering at 2 months was 8mmHg (SD 4.0) in OHT eyes and 6.5mmHg (SD 4.3) in OAG eyes. Mean percentage IOP reduction was 29.7% (SD 13.1) in OHT eyes and 26.1% (SD 14.7) in OAG eyes respectively. A clear trend was noted towards increasing absolute IOP reduction with higher baseline IOP in both OHT and OAG eyes (see Figure 1) but there was no significant difference in early absolute IOP lowering between OHT and OAG eyes having controlled for pre-treatment baseline IOP and centre effects (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85).

For comparison, 594 eyes (out of 622 eyes at baseline) were available for analysis in the Medication 1st arm at 2 months. Of these, 99.3% (590 eyes) were on a single medication (96.1% on topical prostaglandin, 1.9% on beta blocker, 0.3% on carbonic anhydrase inhibitor, 0.3% on alpha agonist, 0.7% on two medications). Mean initial IOP lowering at 2 months was 7.6mmHg (SD 4) in OHT eyes and 6.8mmHg (SD 4.4) in OAG eyes. Mean (SD) percentage IOP reduction was 27.9% (13.5) in OHT eyes and 27.9% (14.4) in OAG eyes respectively.

Overall, absolute IOP reduction at 2 months was no different between topical medication and primary SLT (adjusted mean difference = -0.1mmHg; CI -0.6 to 0.4mmHg; p= 0.67). There was no difference in absolute IOP reduction for OHT eyes (adjusted mean difference = 0.4mmHg; CI -0.4 to 1.2mmHg; p=0.31) or OAG eyes (adjusted mean difference = -0.2mmHg; CI -0.8 to 0.3mmHg; p=0.36) between the two treatment groups.

Predictors of early IOP lowering response following Primary SLT

For the predictors of initial IOP lowering response, covariates that achieved p<0.10 in the initial variable selection regression analyses were baseline IOP (p<0.001), gender (p=0.002) and age (p=0.05). Within group (OHT vs OAG) sub-analysis demonstrated that the trend noted towards increasing absolute IOP reduction with higher baseline IOP (see Figure 1) was significant in both OHT (Coefficient 0.68, 95% CI, 0.55 to 0.81; p<0.001) and OAG (Coefficient 0.58, 95% CI, 0.53 to 0.64; p<0.001). The final multivariable linear regression model showed that baseline IOP (p<0.001) and gender (p=0.04) were predictors of initial absolute IOP reduction.

"Drop-free Disease-control"

Eyes that met target IOP without disease progression or need for topical IOP lowering medication were deemed to have achieved drop-free "disease-control". At 12 months, 85.2% of eyes (518 eyes) achieved drop-free 'disease-control' after 1 or 2 SLTs. At 24 months and 36 months, 79.2% of eyes (456 eyes) and 74.6% of eyes (400 eyes) respectively, continued to achieve drop-free 'disease-control' (see Table 6). At all time points, drop-free 'disease-control' was achieved in a higher percentage of OHT and 'mild OAG' eyes compared to 'moderate' and 'severe' OAG eyes.

'Drop-free Disease-control' following initial single SLT

Assessing drop-free 'disease-control' achieved by *initial single SLT at baseline*, 75.5% of eyes (459 eyes) achieved this at 12 months, 66.5% of eyes (383 eyes) at 24 months and 58.2% of eyes (312 eyes) at 36 months. At all time points, drop-free 'disease-control' *after single initial SLT* was achieved in a higher percentage of OHT and 'mild OAG' eyes compared to 'moderate' and 'severe' OAG eyes (see Table 7).

Overall at 36 months, mean absolute IOP reduction in the 312 eyes achieving drop-free "disease-control" following single initial SLT at baseline was 8.1mmHg (SD 4.1). Mean absolute IOP reduction was similar between all disease severities (see Table 8).

By 36 months, 23 eyes had objective evidence of disease progression (19 eyes visual field progression, 2 eyes disc progression, 2 eyes disc and VF progression) and 26 eyes had an upward revision of target IOP, if IOP control was not initially achieved in the absence of disease progression (12). These results accounts for this, such that all eyes achieving drop-free "disease-control" met target IOP (achieving >20% IOP reduction from baseline IOP) without disease progression or need for topical medication. This is reflected in the number of eyes achieving drop-free "disease-control" at 36 months (74.6% eyes) and following single initial SLT (58.2% eyes) being slightly fewer compared to those solely achieving target IOP without topical medication at 36 months (78.2% eyes) and following single initial SLT (59.9%) as reported in the LiGHT main outcomes paper (13).

Predictors of drop-free 'disease-control' at 36 months

312 eyes achieved drop-free "disease-control" at 36 months following initial single SLT (Table 8). These eyes achieved >20% IOP reduction from baseline IOP and thus were a treatment 'success' (using conventional 'IOP lowering >20% from baseline IOP' definition of success). Baseline covariates that achieved p<0.10 in the mixed effects univariable logistic regression analyses were: total power of 1st SLT (p=0.08) and age (p=0.09) (see Table 9). Two month IOP (p<0.001) was a 'post' treatment covariate that achieved p<0.10 in the univariable logistic regression analysis. The final mixed effects multivariable logistic regression model of baseline factors showed that total power of 1st SLT (see Table 10) was a predictor of achieving drop-free "disease-control" at 36 months following single initial SLT (adjusted odds ratio 1.02, 95% CI, 1.01 to 1.04, p=0.01). Two month IOP was also a 'post' treatment predictor of drop-free 'disease-control' at 36 months when controlling for the other significant baseline factors (adjusted odds ratio 0.66, 95% CI, 0.57 to 0.79, p<0.001) (see Table 10).

SLT safety

There were no sight threatening adverse events related to primary SLT during or after the procedure (see Table 11). 6 eyes (of 6 patients) experienced immediate post laser IOP spike (>5mmHg from pre-treatment IOP) at 60 minutes, but only one of these eyes required medical treatment. No IOP spikes >10mmHg from pre-treatment IOP at 60 minutes post procedure were reported. In 4 patients (1.1%), there was difficulty in visualizing the angle and in 3 patients (0.9%) fewer laser applications than required by the protocol were reported to have been used. Following SLT, symptoms including ocular discomfort, headache, blurred vision and photophobia were reported by 34.4% of patients (122 patients). These were of a transient nature and self-limiting; all had resolved by the first scheduled visit. No IOP spikes (>5mmHg from Baseline IOP) were detected at the 2-week safety check visit post SLT; 6.2% of eyes (38 eyes) were noted to have a higher IOP at 2-week safety visit compared to baseline.

DISCUSSION

This report analyses the efficacy of primary SLT in one of the largest datasets of treatment-naïve OAG and OHT patients, with robust RCT-derived data.

There was no significant difference in early absolute IOP lowering between OHT and OAG eyes having controlled for pre-treatment baseline IOP and centre effects (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85). In addition, there was no significant difference in early absolute IOP lowering between topical medication and primary SLT (adjusted mean difference = -0.1mmHg, CI -0.6 to 0.4mmHg, p= 0.67).

We found that higher baseline IOP was a predictor of early absolute IOP lowering at 2 months in a mixed effects linear regression model. Increasing baseline IOP has already been reported as being associated with increased IOP lowering (3) and was also demonstrated in this study, in which OHT eyes had greater IOP lowering from baseline compared to OAG eyes. This is also reflected in NTG studies where baseline IOPs are lower and both absolute IOP reductions and success rates are lower compared to other subtypes (24, 25). Our study design minimized the effects of regression to the mean on IOP lowering: qualifying IOP measurements were made on a separate day to baseline assessments, and IOP level was an entry criterion only for OHT eyes (31.9% of eyes at baseline). There was no placebo arm in LiGHT to ascertain fully the regression to the mean, but a previous study has demonstrated a ~ 1.4mmHg (SD 3.1) absolute IOP reduction at first visit post placebo compared to 5mmHg (SD 3.6) in the topical latanoprost group (26). We also found in our analysis that female gender was associated with lesser initial IOP lowering, not a commonly reported predictor of IOP lowering (22).

Our results show that at 36 months follow up, 74.6% of eyes (400 eyes) treated with primary SLT achieved drop-free "disease-control", with 58.2% of eyes (312 eyes) doing so following a single initial SLT. All these eyes achieved IOP reduction > 20% from baseline IOP. IOP reduction >20% from baseline has been previously reported as occurring in between 38-74% of treated eyes at 36 months (7, 27-29). In our study, eyes with more advanced glaucoma had to meet more stringent target IOPs set according to previous published guidelines: 'moderate' or 'severe' disease had to achieve a minimum 30% reduction from baseline IOP to continue without further intervention (12). Thus, more severely affected eyes achieving >20% but <30% IOP reduction following first SLT would have undergone a further treatment (2^{nd} SLT or medication if non-response to 1^{st} SLT). This is reflected in our results with only 58.2% of eyes not receiving additional therapy. The relative proportion of eyes achieving drop-free "disease-control" at 36 months after initial single SLT at baseline (Table 7) was greater in OHT and 'mild OAG' eyes (with less stringent targets) than 'moderate' and 'severe OAG' eyes (with lower target IOPs), despite similar mean absolute IOP reductions for all levels of disease severity (Table 8). This does not mean SLT was ineffective in more advanced disease, merely insufficient in isolation.

The above was taken into account in the predictors of success mixed effects logistic regression model, with terms for baseline disease severity and site (to control for centre effects), whilst using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes. Our logistic regression model suggested a statistically significant but small increase in odds of achieving drop-free "disease-control" at 36 months with higher total power of 1^{st} SLT (adjusted odds ratio 1.02, 95% CI 1.01 to 1.04, p=0.01). On further analysis, mean total power of 1^{st} SLT in 'success' eyes was 92.6mJ (SD 21.8) vs 87.7mJ (SD 25.6) in 'non-success' eyes (adjusted mean difference = 2.37mJ, 95% CI -0.5, 5.2 mJ). The modest effect and overlap in treatment parameters between 'success' and 'non-success' eyes means that response prediction is not possible. The trend to a greater response with more power delivered would need confirmation in future studies. There is mixed evidence regarding the optimum power settings for SLT treatment. Tang et al compared 39 patients receiving 100 shots of 360^0 SLT using low energy settings (0.3-0.5mJ) with 35 patients who received 100 shots of 360^0 SLT using standard energy settings (0.6-1.0mJ) (30). No difference in IOP lowering between groups at all time points up to 1 year was noted. Furthermore, there was reduced incidence of adverse events in the lower energy group. Realini found total laser power *not* to be a significant predictor of 12-month success, with a mean (SD) of 86.0 (21.1) mJ in right eye and 87.7 (20.6) mJ in left (31) compared to a mean (SD) of 90.4 (23.5) mJ in our study (8). In contrast, Lee et al found greater total SLT energy was associated with a greater IOP lowering, but that study was limited by small sample size, short follow up (1 month) (32) and total energy powers that were considerably higher than those in this study ("optimum" total reported as 226.1mJ). Habib et al divided 360 degree SLT treatment patients into those who received low (<85 mJ), medium (85–105 mJ), or high (>105 mJ) energy SLT. At all time points up to 36-month follow-up, there was a significant positive correlation between greater energy and IOP lowering (33).

We wanted to establish whether IOP at first scheduled visit post SLT at 2 months was predictive of achieving "disease-control" at 36 months following initial single SLT at baseline. A previous study found that the only significant predictor of IOP lowering at 12 months across all eyes was time, with maximum IOP reduction seen at 3 months followed by a slow decline in effect subsequently (31). Whilst we found successful eyes achieving drop-free "disease-control" following initial single SLT at 36 months had a lower IOP at 2 months compared to non-successful eyes (adjusted mean difference = -1.9mmHg; 95% CI, -1.4 to -2.3mmHg), there may not be enough specificity in this observation (due to the standard deviation of IOP measurements) to be helpful in the individual case.

SLT was well tolerated in this study, with no sight threatening adverse events and only 6 eyes (1% of total eyes receiving SLT) having an IOP spike (>5mmHg) immediately after SLT. This compares favorably with other studies, which have reported IOP spikes (>5mmHg) occurring in up to 28% of eyes (3). Post SLT, 34.4% of patients described mild laser related adverse events including ocular discomfort, headache, blurred vision and photophobia. These were of a transient nature and self-limiting. Anterior chamber inflammation is common post SLT with up to 83% of eyes demonstrating some degree of inflammation (34). Considering the biological changes that SLT induces (35), some regard transient self-limiting inflammation to be a predictable consequence of SLT, explaining the symptoms of ocular redness, photophobia and pain that patients may report. During the LiGHT trial overall, there were fewer drop-related ophthalmic and systemic adverse events reported by patients in the initial SLT arm vs the initial Medication arm(13).

Direct comparison between SLT studies is difficult. Differences in study design exist between studies, including patient demographics, disease subtypes investigated (OHT vs OAG), variations in topical IOP lowering medication usage prior to SLT (treatment-naïve vs medication washout period prior to SLT vs adjunct SLT in uncontrolled eyes on maximum tolerated medical therapy), differences in SLT treatment parameters (180-degree vs 360-degree treatments, variability in numbers of shots fired), variability in follow up intervals, total duration of follow up and variable definitions of success.

This report has several strengths. It utilizes data derived from a prospective multi-centre RCT with broad entry criteria that maximize its generalizability. Eyes were treated to pre-defined target IOPs based on disease severity with pre-defined treatment escalation criteria and SLT treatment parameters (12). An obvious limitation is that this analysis was post-hoc and the sample size of LiGHT was determined based on a power calculation to analyze the primary outcome of HRQL. We did not perform a post-hoc power calculation for the IOP lowering parameters considered in this report, since limitations have been reported with such calculations (36). Instead, the narrow (<1mmHg) confidence intervals for our pointwise estimates of differences in early IOP

lowering between OHT vs OAG eyes and primary SLT vs topical medication suggest that the study had an adequate sample size to detect a clinically important difference if it exists (37). For our logistic regression analysis, we had sufficient events based on the rule of thumb that 10-15 'events per variable' are required to develop an adequate prediction model (38). In this analysis, despite no clinically or statistically significant differences in gender or ethnicity being noted in eyes available vs unavailable to analyze at 36-months, relatively more females and black patients had eyes unavailable for analysis. Studies have shown disparities in the utilization of eye care services among different racial minorities, with socio-economic deprivation and differences in access to healthcare implicated as contributory to this (39, 40).

In conclusion, we report that primary SLT is an effective initial therapy for treatment-naive OAG and OHT patients. Primary SLT provides a comparable initial IOP lowering response in OHT vs OAG eyes and to topical medication. It achieves drop-free "disease-control" in ~75% of eyes at 36 months, with the majority of eyes (58.2%) doing so following a single, initial SLT. SLT had a good safety profile during our study, whilst avoiding the potential adherence issues associated with topical medication. Despite the exploratory nature of these analyses, our results are clinically valuable and add to the limited body of evidence on primary SLT in treatment-naïve OAG and OHT, supporting its' use as an effective and safe initial treatment for such conditions.

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529 LEGENDS:

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531 Figure 1: Scatter plot of absolute IOP reduction vs. baseline IOP in all eyes (559 eyes) at 2 months following initial SLT

532 Filled circles: OHT, Hollow circles: OAG

533

Severity	Definition of Severity for Treatment Target IOP				
	Optic Nerve		**VF MD**		**Central (10^{o}) Scotoma on VF**
OHT	Healthy		Any		No GON related VFL
Mild OAG	GON	**+**	> -6dB	**+**	None
Moderate OAG	GON	**+**	-6dB < and < -12dB	**or**	At least 1 central 5º point <15dB but none <0dB and only 1 hemifield with central point <15dB
Severe OAG	GON	**+**	< -12dB	**or**	Any central 5º point with sensitivity <0dB Both hemifields contain point(s) <15dB within 5º of fixation

Table 1: Severity criteria for setting Treatment Target IOP from the "Canadian Target IOP Workshop" (with central field criteria defined according to Mills). VF MD: Visual field mean deviation GON: Glaucoma optic neuropathy

Baseline Disease Severity	Treatment Target IOP
OHT	**>20% IOP reduction from baseline IOP *or* IOP< 25mmHg (whichever lower)**
'Mild' OAG	**>20% IOP reduction from baseline IOP *or* IOP< 21mmHg (whichever lower)**
'Moderate' OAG	**>30% IOP reduction from baseline IOP *or* IOP<18mmHg (whichever lower)**
'Severe' OAG	**>30% IOP reduction from baseline IOP *or* IOP<15mmHg (whichever lower)**

Table 2: Setting Treatment Target IOP

Characteristics	Value
Age (years), mean (SD)	63.4 (12.1)
Gender (patients), (%)	
Male	199 (56.1%)
Female	156 (43.9%)
Race/ Ethnicity (patients), (%)	
White European	242 (68.2%)
Black	77 (21.7%)
Asian	23 (6.5%)
Other	13 (3.7%)
Laterality (patients), (%)	
Bilateral Eyes	256 (72.1%)
Right Eye	49 (13.8%)
Left Eye	50 (14.1%)
Hypertension (patients), (%)	
Yes	131 (36.9%)
No	224 (63.1%)
Diabetes Mellitus (patients), (%)	
Yes	41 (11.6%)
No	314 (88.5%)
Disease Severity (eyes), (%)	
OHT	195 (31.9%)
'Mild' OAG	309 (50.6%)
'Moderate' OAG	67 (11.0%)
'Severe' OAG	40 (6.5%)
Mean Deviation (dB), mean (SD)	-3.0 (3.4)
Pattern Standard Deviation (dB), mean (SD)	3.7 (2.9)
Mean HRT area (mm2), mean (SD)	1.2 (0.4)
Baseline IOP (mmHg), mean (SD)	
Overall	24.5 (5.2)
OHT	26.5 (3.5)
OAG	23.5 (5.6)
Average Trabecular Pigmentation Grade (eyes), (%)	
0 -None	243 (39.8%)
1- Mild	264 (43.2%)
2-Moderate	101 (16.5%)
3-Dense	1 (0.2%)
Unknown	2 (0.4%)
Habitual VA (Logmar), mean (SD)	0.10 (0.2)
CCT (microns), mean (SD)	550.6 (38.1)
PXF (eyes), (%)	
Yes	5 (0.8%)
No	606 (99.2%)
Target IOP (mmHg)	
OHT	21.1 (2.4)
'Mild' OAG	17.9 (3.1)
'Moderate' OAG	15.9 (2.6)
'Severe' OAG	13.9 (1.6)

Table 3: Baseline characteristics of Primary SLT arm. OAG: Open Angle Glaucoma, OHT: Ocular Hypertension. Self-defined ethnicity; 'Asian' ethnicity refers to Indian, Pakistani, Bangladeshi and any other Asian background, 'Black' ethnicity refers to Caribbean, African and any other black background, 'Other' ethnicity refers to Chinese and any other ethnic groups.

Variable	Coefficient	95% confidence Interval	P-value
Baseline IOP (mmHg)	**0.59**	**(0.54, 0.64)**	**<0.001***
Race/ Ethnicity			**0.17**
Black	**1.18**	**(0.08, 2.29)**	
Asian	**0.89**	**(-0.87, 2.66)**	
Other	**0.70**	**(-1.75, 3.15)**	
reference White European			
Sex			
Female	**-1.42**	**(-2.29, -0.54)**	**0.002***
Age (years)	**-0.04**	**(-0.08, 0.00)**	**0.05***
CCT (microns)	**0.01**	**(0.00, 0.02)**	**0.15**
PXF (Y/N)			
No	**-1.62**	**(-4.94, 1.69)**	**0.34**
Average TM Pigmentation Grade			**0.12**
1- Mild	**-0.12**	**(-1.04, 0.81)**	
2-Moderate	**0.03**	**(-1.16, 1.23)**	
3-Dense	**6.51**	**(1.06, 12.0)**	
reference No Pigmentation			
Phakic Status (Y/N)			
Phakic	**0.70**	**(-0.90, 2.29)**	**0.39**
Hypertension (Y/N)			
No	**0.05**	**(-0.87, 0.96)**	**0.92**
Diabetes Mellitus (Y/N)			
No	**0.82**	**(-0.51, 2.15)**	**0.22**
Total Power 1st SLT (mJ)	**0.01**	**(-0.01, 0.03)**	**0.29**
Total Number of shots 1st SLT (shots)	**0.04**	**(-0.03, 0.11)**	**0.26**

Table 4: Univariable Linear Regression Analysis for Absolute IOP Reduction

**Covariates that achieved p<0.10 in the initial variable selection linear regression analyses were: baseline IOP (p<0.001), gender (p=0.002) and age (p=0.05)*

Variable	Coefficient	95% confidence Interval	P-value
Baseline IOP (mmHg)	**0.58**	**(0.53, 0.63)**	**<0.001**
Sex Female	**-0.63**	**(-1.23, -0.02)**	**0.04**

Table 5: Multivariable Logistic Regression Analysis for Absolute IOP reduction

Disease Severity	12 months Total eyes available for analysis (n)	12 months Eyes achieving drop-free 'disease-control' % (n)	24 months Total eyes available for analysis (n)	24 months Eyes achieving drop-free 'disease-control'% (n)	36 months Total eyes available for analysis (n)	36 months Eyes achieving drop-free 'disease-control'% (n)
ALL EYES	**608**	**85.2% (518)**	**576**	**79.2% (456)**	**536**	**74.6% (400)[a]**
OHT	***192***	***92.7% (178)***	***174***	***92% (160)***	***158***	***88.6% (140)***
'Mild' OAG	***315***	***87.3% (275)***	***293***	***81.2% (238)***	***269***	***76.6% (206)***
'Moderate' OAG	***54***	***63% (34)***	***69***	***56.5% (39)***	***57***	***56.1% (32)***
'Severe' OAG	***47***	***65.9% (31)***	***40***	***47.5% (19)***	***52***	***42.3% (22)***

Table 6: Eyes achieving drop-free "disease-control" using 1 or 2 SLT. a: one eye was protocol deviation - received 3 SLT

Disease Severity	12 months Total eyes available for analysis (n)	12 months Eyes achieving drop-free 'disease-control' after single SLT % (n)	24 months Total eyes available for analysis (n)	24 months Eyes achieving drop-free 'disease-control' after single SLT % (n)	36 months Total eyes available for analysis (n)	36 months Eyes achieving drop-free 'disease-control' after single SLT % (n)
ALL EYES	**608**	**75.5% (459)**	**576**	**66.5% (383)**	**536**	**58.2% (312)**
OHT	***192***	***85.9% (165)***	***174***	***80.5% (140)***	***158***	***72.8% (115)***
'Mild' OAG	***315***	***79.4% (250)***	***293***	***70.6% (207)***	***269***	***64.3% (173)***
'Moderate' OAG	***54***	***46.3% (25)***	***69***	***42% (29)***	***57***	***33.3% (19)***
'Severe' OAG	***47***	***40.4% (19)***	***40***	***17.5% (7)***	***52***	***9.6% (5)***

Table 7: Eyes achieving drop-free 'disease-control' after single, initial SLT at baseline

	Drop-free 'disease-control' using single SLT at 36 months (eyes)	Mean(SD) absolute IOP reduction (mmHg)	Mean (SD) % IOP reduction from baseline
ALL EYES	**312**	**8.1 (4.1)**	**31.4 (11.7)**
OHT	***115***	***8.8 (3.6)***	***32.7 (11.5)***
'Mild' OAG	***173***	***7.5 (4.3)***	***29.9 (11.7)***
'Moderate' OAG	***19***	***8.6 (3.9)***	***36.4 (11.7))***
'Severe' OAG	***5***	***8.2 (4.6)***	***34.4 (13.1)***

Table 8: Mean IOP reduction and Percentage IOP reduction at 36 months in eyes achieving drop-free "disease-control" after single initial SLT

Variable	Odds Ratio	95% confidence Interval	P-value
Baseline IOP (mmHg)	**1.01**	**(0.95, 1.09)**	**0.69**
Race/ Ethnicity			**0.74**
Black	**1.55**	**(0.57, 4.20)**	
Asian	**0.74**	**(0.16, 3.41)**	
Other	**1.78**	**(0.23, 13.64)**	
****reference White European***			
Sex			
Female	**0.57**	**(0.26, 1.28)**	**0.17**
Age (years)	**0.97**	**(0.94, 1.00)**	**0.09***
CCT (microns)	**1.00**	**(0.99, 1.01)**	**0.62**
PXF Status			
Nil PXF	**18.9**	**(0.28, 1294.66)**	**0.17**
Average TM Pigmentation Grade			**0.98**
1- Mild	**1.1**	**(0.47, 2.57)**	
2-Moderate	**1.1**	**(0.34, 3.26)**	
3-Dense	**1[a]**		
****reference No Pigmentation***			
Phakic Status			
Phakic	**0.52**	**(0.10, 2.67)**	**0.44**
Hypertension(Y/N)			
No	**0.63**	**(0.28, 1.43)**	**0.27**
Diabetes Mellitus (Y/N)			
No	**1.07**	**(0.30, 3.80)**	**0.91**
Total Power 1st SLT (mJ)	**1.01**	**(1.00, 1.03)**	**0.08***
Total Number of shots 1st SLT (shots)	**1.02**	**(0.96, 1.10)**	**0.41**
2 month IOP post treatment (mmHg)	**0.71**	**(0.61, 0.82)**	**<0.001***

Table 9: Univariable Selection Logistic Regression Analysis

**Covariates that achieved p<0.10 in the initial variable selection logistic regression analyses were: total power of 1st SLT (p=0.08) and age (p=0.09)*

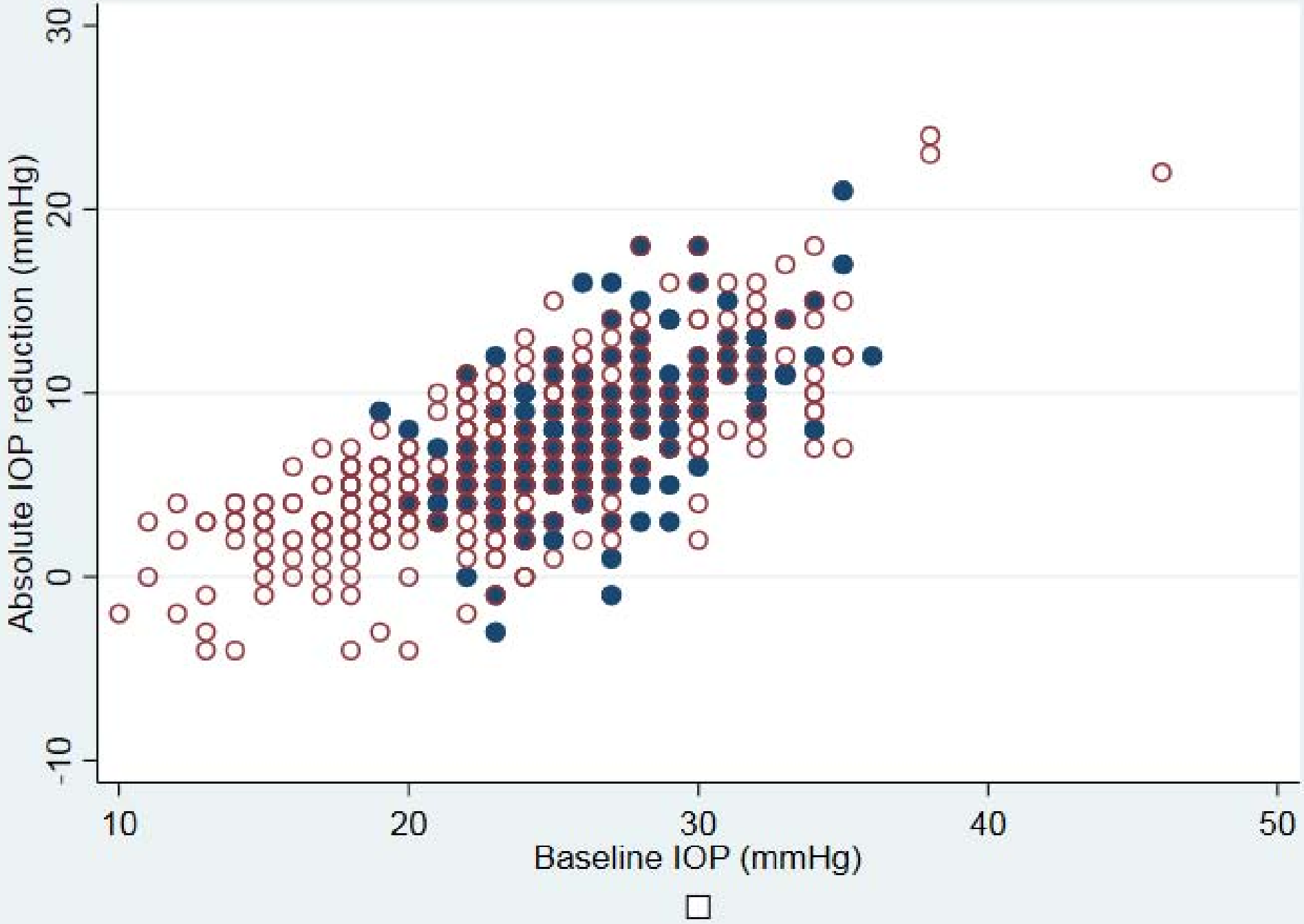
[a]model unable to converge due to insufficient data

Variable	Odds Ratio	95% confidence Interval	P-value
Total Power 1st SLT (mJ)	**1.02**	**(1.01, 1.04)**	**0.01**
***2 month IOP post treatment (mmHg)**	**0.66**	**(0.57, 0.79)**	**<0.001**

Table 10: Multivariable Logistic Regression Analysis Result of Baseline Factors
** 2 month IOP is a post treatment predictor*

Adverse Events during SLT	Total Number of Events (n=20)	Total Number of Patients reporting (N=19) (5.4%)
Discomfort (Ocular and/or Headache)	6	6 (1.7%)
IOP spike (>5mmHg)	6	6 (1.7%)
Other (specify): Fewer shots Visualization of angle	 3 5	 3 (0.9%) 4 (1.1%)
Adverse Events post SLT	**Total Number of Events Total (n=172)**	**Total Number of Patients reporting (N=122) (34.4%)**
Discomfort (Ocular and/or Headache)	92	82 (23.1%)
Blurred/ altered vision	23	21 (5.9%)
Change in Refraction	5	4 (1.1%)
Inflammation post SLT	1	1 (0.3%)
Other (specify): Photophobia Hyperaemia	51 21 3	47 (13.2%) 20 (5.6%) 3 (0.8%)

Table 11: Summary of Laser related Adverse Events


Absolute IOP reduction (mmHg)
30
20
10
0
-10
10
20
30
40
50
Baseline IOP (mmHg)

Post-hoc analysis of clinical outcomes, predictors of success and safety of primary SLT used in treatment-naïve primary open-angle glaucoma (POAG) and ocular hypertension (OHT) patients