

# Effect of primary selective laser trabeculoplasty on tonographic outflow facility - a randomised clinical trial.

Saurabh Goyal, Laura Beltran-Agullo, Safina Rashid, Shaheen Shah, Remin

Nath, Adanna Obi, Kin Sheng Lim

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#### Authors:

Saurabh Goyal, FRCOphth, FRCS.[i]

Laura Beltran-Agullo, MBBS [i]

Safina Rashid, BMEDSCI Orthoptist.[i]

Shaheen P Shah, MSc, MRCOphth.[ii]

Remin Nath, MBBS, MRCOphth.[i]

Adanna Obi, MBBS, FRCOphth.[i]

K. Sheng Lim, MD, FRCOphth.[i]

i Department of Ophthalmology, St Thomas' Hospital, London, UK.

ii International Centre for Eye Health, London School of Hygiene & Tropical Medicine, London, UK

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1 Abstract

Purpose: To investigate the effect of 180° versus 360° primary Selective Laser Trabeculoplasty (SLT) on
tonographic outflow facility (TOF) and intraocular pressure (IOP).

4 **Design:** Prospective, single masked randomised clinical trial.

5 Participants: Patients with untreated primary open angle glaucoma or ocular hypertension both with IOP

6 >21-35mmHg.

7 **Methods:** Forty patients randomly treated with 180° or 360 ° SLT after baseline TOF (electronic Schiøtz

8 tonography) and IOP measurements were repeated after one month. One eye from each patient was randomly
9 selected for analysis. Eight untreated eyes were included as a control group.

Main Outcome Measures: TOF and IOP difference. Responders were defined as having at least a 20%
 reduction in IOP.

12 **Results:** Three patients were excluded due to poor tonography. There were eighteen eyes in 180° group and

13 nineteen eyes in the 360° group. TOF increased significantly (180° p=0.003, 360 ° p=0.005) and IOP

14 decreased significantly (180° & 360° p<0.001) from baseline. There were no significant differences between

15 the two groups as regards the increase in TOF (180° group 37.5%, 360° group 41%, p=0.23) and decrease in

16 IOP (180° group 24%, 360° group 35%, p=0.35). There were similar number of responders in 180° group

17 (72%) as compared to 360° group (89.5%, p=0.23). TOF and IOP did not change significantly from baseline

18 in the control group (TOF-8% increase p=0.48, IOP-4% decrease p=0.33).

19 **Conclusions:** Primary SLT significantly increased the tonographic outflow facility and decreased IOP in

20 patients with primary open angle glaucoma and ocular hypertension but no statistically significant differences

21 were found between the 360° and 180° groups. The level of IOP reduction due to primary SLT treatment

22 could not be explained by the increase in TOF alone.

1 Intraocular pressure (IOP) reduction remains the only therapeutic means for treating ocular hypertension 2 (OHT) and primary open angle glaucoma (POAG). Argon laser trabeculoplasty (ALT) popularized by Wise 3 & Witter in 1979 became an acceptable form of treatment for open angle glaucoma with its use peaking in 4 the mid 1990s, however, the visible thermal damage, late pressure rise and treatment failure reduced its 5 subsequent use.[1] [2] ALT is usually performed using 50-100 applications of a 50µm spot size, 0.1 second 6 duration and average power setting of between 400 to 1000mW. It is a relatively high energy level treatment 7 causing visible damage to the trabecular meshwork.[3] Selective laser trabeculoplasty (SLT) was developed 8 by Latina in 1995 and FDA approved in 2001.[4, 5] It delivers over 100 times less energy than ALT while 9 providing a similar IOP lowering effect. [6-9] SLT uses a frequency-doubled, O-switched, neodymium: 10 yttrium aluminium garnet (Nd:YAG) laser and delivers a 400µm diameter treatment spot in three 11 nanoseconds. The power ranges from between 0.4–1.2 mJ with up to 120 applications per eye. This lower 12 energy treatment produces minimal or no visible damage to the trabecular meshwork with a potential for 13 repeat treatment.[3]

14

A dose response effect of SLT treatment, depending on the degrees of angle treated has been previously suggested but the exact mechanism of action of ALT and SLT remains unclear.[10, 11] Most theories of mechanism of action of laser trabeculoplasty were developed for ALT and little data is available to suggest that SLT has the same mechanism of action, particularly taking into account marked differences between the two laser systems in terms of the energy fluence levels and the physical effects on the trabecular meshwork. Whatever the cellular effect, both ALT and SLT treatments are thought to eventually affect the trabecular outflow pathway.[7]

22

Previous aqueous dynamics studies on the effect of ALT suggest that it increases the tonographic outflow
facility (TOF) without any effect on aqueous production.[12-18] There is however no published report on the

1 effect of SLT on TOF. We performed this prospective randomised clinical trial to study to the effect of SLT

2 on TOF and also to determine whether differences existed between 180° and 360° treatment in newly

diagnosed and previously untreated primary open angle glaucoma (POAG) and ocular hypertension (OHT)
patients.

5

#### 6 Methods

7 Ethics approval for this prospective study was obtained from the St. Thomas's Hospital's local research

8 ethics committee. This research conformed to the recommendations adopted by the Helsinki declaration.

9 Consecutive patients attending the glaucoma clinic for the first time were invited to participate. A patient

10 information leaflet was provided at the initial contact and signed consent obtained before the measurements

11 and treatment.

#### 1 Inclusion/exclusion criterion

Inclusion criteria were previously untreated adult POAG patients (based on characteristic optic disc changes
with visual field changes) or high risk OHT patients which required treatment. All patients were required to
have an IOP greater than 21mmHg to be eligible. Exclusion criterion were secondary glaucomas
(pseudoexfoliation, pigment dispersion, uveitic, traumatic, etc.), primary angle closure, advanced POAG (cup
disc ratio ≥0.9 and/or visual acuity less than 6/36), very high IOP (>35mmHg), one eyed patients and any
previous intraocular surgery.

#### 8 Sample size calculation

9 The standard deviation of TOF was derived from a previous study by one of the authors.[19] The study was 10 powered at 80% with an alpha (two sided) of 0.05 to detect a TOF difference of 30% between the two 11 treatment groups. Including a 10% drop out rate the required sample size was 20 patients in each group.

#### 12 **Randomisation**

Patients were centrally randomized by a computer (random number method, odd number-180° and even number-360° treatment) to receive 180° or 360° SLT. The numbers were placed in non-transparent brown envelopes and shuffled. One envelope was opened on the day of the treatment for each patient.

16 If only one eye needed treatment then the contra-lateral eye was included in a 'control' group. If however
17 both eyes needed IOP lowering then both eyes were treated by SLT but only one eye was randomly selected
18 for analysis (coin toss).

19

#### 20 Measurements

All patients underwent a thorough clinical evaluation including ocular and systemic history. Examination
 included visual acuity, pupils, slit lamp examination, gonioscopy, central corneal thickness (CCT, Pachmate

DGH 55, DGH Technology, Inc. PA, USA), visual fields (VF) (Humphrey automated white on white, 24-2
SITA-standard) and dilated fundoscopy. On the day of treatment all patients had IOP measured by Goldmann
applanation tonometry (GAT) and tonography by an electronic Schiøtz tonographer (Model 720, Berkeley
Bioengineering Inc, USA) between 9.00 and 11.00am. Three consecutive IOP measurements were recorded
by SR and the mean was used as the baseline IOP. Both eye tonography measurements were done by KSL.
Both SR and KSL were masked to the treatment and the randomisation.

7

8 The facility of outflow was measured from the rate of decay of intraocular pressure in the supine position 9 during application of a recording Schiøtz tonometer over a period of four minutes with various weights 10 depending on the starting IOP. The "R" values of the curve at every 30-second time point was manually 11 entered into the McLaren tonography computer program.[20] This program fits a second-degree polynomial 12 by least squares to the nine data points and determines the best-fit values for time zero and time four minutes 13 by extrapolation. The measurement unit for outflow facility was expressed as µl/min/mmHg.

- 14
- 15

#### 16 Treatment

17 SLT treatment in all patients was performed by SG. Pilocarpine 2% drops (Minims, Pilocarpine nitrate, 18 Chauvin Pharmaceuticals Ltd, Surrey, UK) were instilled half an hour prior to SLT. SLT treatment was 19 performed using the Ellex Solo machine (Ellex, Adelaide, Australia), spot size of 400um, duration three nano 20 seconds. Starting energy level was 0.6 mJ. Energy level was titrated at three o'clock position up to the point 21 where champagne bubbles or minimal blanching was visible. Magna view gonioscopy lens (Ocular 22 instruments, USA) was used to visualize the trabecular meshwork for treatment. Only the inferior half of the 23 angle was treated in patients undergoing 180° treatments. All patients had a standardised postoperative regime of Dexamethasone 0.1% eve drops (Maxidex, Alcon Laboratories, UK) four times a day for five days. 24 25 Patients were reviewed at one week and one month and in between as necessary. IOP and TOF

- 1 measurements were repeated at one month between 9.00 and 11.00am. If needed, additional glaucoma
- 2 medical treatment was started at one month to achieve the target pressure.

#### **3 Data collection and Outcome Measure**

- 4 Data including age, sex, race, IOP, TOF, CCT, VF, treatment details and adverse outcomes were recorded on
- 5 a datasheet. The primary and secondary outcome measures were TOF and IOP difference respectively.
- 6 Success (i.e. responders) was defined as at least 20% reduction in IOP from baseline.

#### 7 Data Analysis

- 8 The data was analyzed by statistical software STATA (StatCorp, USA) in a per protocol manner. Non
- 9 parametric methods of analysis (Wilcoxon signed-rank test and Kruskal Wallis test) were used after

10 distribution analysis for both TOF difference and IOP difference revealed non normal distributions. (Positive

skew, p=0.001 and p=0.04 respectively, Shapiro Wilk Test for normality).

12

#### 13 **Results**

Forty-two consecutive patients between August 2006 and July 2007 were invited to participate in the study, two declined (one was not available for follow up and the other opted for medical treatment). Forty patients were randomized to receive 180° or 360° treatment. All Schiøtz tonography tracings were graded by the examiners before the treatment was unmasked. Poor quality tracings were identified in three participants and they were excluded from the study.

19 Eighteen patients in the 180° treatment group and nineteen patients in the 360° treatment group were included

20 in the final analysis (Fig.1). Twelve patients (67%) in the 180° group and fifteen (79%) in the 360° group had

- 21 POAG (p=0.41). There were nine (50%) and ten (53%) women in 180° and 360° groups respectively. The
- 22 majority of patients in both groups were Afro-Caribbean/African in origin, nine (50%) in the 180° group and

1	seventeen (89.5%) in 360° group (p=0.01). There were six Caucasians in 180° and two in 360° group. One
2	patient each in the 180° group was from South East Asia and Latin America. The high number of Afro-
3	Caribbean/African patients in our study generally reflects the local at risk population in this part of London.

5	The baseline patient and treatment characteristics are shown in Table 1. Patients in the 180° group were
6	significantly younger (p=0.03) than the 360° group and had less mean deviation (MD) visual field score
7	(p=0.02). The rest of the baseline characteristics including the visual acuity, IOP, cup/disc ratio, CCT, TOF
8	and treatment parameters were comparable. Neither age nor MD were associated with outcome measures and
9	were therefore not regarded as confounders (Spearman's rank correlation age with TOF difference p=0.07
10	and IOP difference p=0.79 and MD with TOF difference p=0.60 and IOP difference p=0.82). The SLT
11	treatment was well tolerated. Two patients, one undergoing 360° SLT (0.95mJ, 110 shots) and one
12	undergoing 180° SLT (1.12 mJ, 56 shots) reported mild pain during the SLT treatment, which resolved
13	within one week. One patient had mild asymptomatic anterior uveitis at one week visit which resolved on its
14	own at the two week review.
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Parameter	Parameter180° SLT (n=18)		360° SLT (n=19)			P- value	
	Median	IQR	Range	Median	IQR	Range	
	(mean)	(SD)	(min-max)	(mean)	(SD)	(min-max)	
Age	57 (56.4)	50, 64 (11.8)	28-75	67 (65.30)	55, 71 (11.6)	46-88	0.03
VA	0.0 (0.05)	0, 0.17 (0.05)	-0.08-0.3	0.18 (0.15)	0, 0.18 (0.20)	0.08-0.60	0.17
ССТ	545 (546)	511, 565 (46.7)	465-657	565 (558)	528, 578 (31.50)	508-620	0.30
CD	0.63 (0.6)	0.4, 0.8 (0.23)	0.10-0.85	0.70 (0.66)	0.6, 0.8 (0.17)	0.3-0.85	0.59
VF (MD)	-1.96 (-5.4)	<sup>-</sup> 4.41, <sup>-</sup> 0.56 (8.7)	-30-0.69	<sup>-</sup> 4.40 ( <sup>-</sup> 7.40)	<sup>-</sup> 12.22, <sup>-</sup> 2.99 (6.39)	25-1.90	0.02
Number of shots	55 (56)	53, 57 (3.3)	52-63	102 (104)	101, 109 (4.75)	97-111	<0.01
Power	1.1 (1.0)	0.9, 1.1 (0.13)	0.80-1.20	1 (1)	0.94, 1.1 (0.12)	0.64-1.20	0.36
Tenergy	57.5 (57.5)	52, 65 (7.56)	44.40-69	108 (105)	98, 113 (12.60)	73.3-126	<0.01

2 n, number of treated eyes in each group; IQR, interquartile range; SD, standard deviation; age, in years; VA, visual acuity (logmar equivalent);

3 CCT, central corneal thickness (microns); CD, cup to disc ratio; VF (MD), visual field (mean deviation in decibels); power of each shot in mJ;

4 tenergy, total energy used in mJ.

- 1 Table 2 describes the effect of SLT on TOF and IOP in the two groups. Overall there was a 37.5%
- 2 (interquartile range 9.5%, 127.3%) increase in median TOF (p<0.001) and 29% (interquartile range 21.2%,
- $3 \quad 41.2\%$ ) reduction in median IOP (p<0.001).

# Table 2- Baseline and one month Tonographic outflow (TOF, μl/min/mm) and Intraocular pressure (IOP, mmHg) and differences between the 180° and 360° treatment groups.

P-**Parameter** 180° SLT (n=18) 360° SLT (n=19) value Median IQR Range Median IQR Range (mean) **(SD)** (min-max) (mean) **(SD)** (min-max) 0.08 0.06, 0.09 **Pre-SLT** 0.01-0.16 0.08 0.07, 0.11 0.05-0.31 0.35 TOF (0.08)(0.04)(0.11)(0.07)0.03#  $0.04^{\#}$ **Increase in** 0,0.06 0.02, 0.0 0.04-0.13 0.08-0.33 0.23 **TOF from** (0.04)(0.05)(0.06)(0.09)baseline **Pre-SLT** 24.4 23, 29.3 21.3-35 26 24.3, 26.7 22-30 0.76 IOP (26)(4.1)(25.54)(2.1)9\* 6.1\* 4.2, 8.3 2.66-19.33 5.7, 11 **Decrease in** 1.33-13.83 0.35 IOP (6.9) (4.1)(8.2)(3.52)

6

7 n, number of treated eyes in each group; SLT, selective laser trabeculoplasty; IQR, interquartile range; SD, standard deviation.

8 <sup>#</sup>Change in TOF from baseline (180°, p=0.003: 360°, p=0.005).

9 \*Change in IOP from baseline p<0.001.

1

Although there was a significant increase in TOF from baseline in both groups (180° p=0.003, 360° p=0.005)
the differences between the two groups were not statistically significant (180° group 37.5% and 360° group
41%; p=0.23).

Similarly the decrease in IOP in the 360° (35%) group as compared to the 180° group (24%) did not reach
statistical significance (p=0.35).

#### 7 **Control group**

8 Eight eyes of eight patients (average age- sixty-six years, six males, three white, three Afro-Caribbean, av.

9 CD ratio-0.48, av.VF MD score=-2.52, av. CCT=543µm) out of the forty patients in this trial did not require

10 treatment and were included as a no treatment 'control' group. There was no significant change in TOF

11 (median baseline: 0.12 µl/min/mmHg, one month; 0.129 µl/min/mmHg, 8% increase, p=0.48) or IOP

(median baseline: 19.7 mmHg, one month: 19.0 mmHg, 4% decrease, p=0.33) from baseline to one month in
these eyes.

#### 14 **Responders versus non-responders**

15 The overall success rate of SLT in reducing the IOP by at least 20% was 81%. SLT was successful in 89.5%

16 of patients in 360° treatment group as compared to 72% of patients in 180° treatment group (p=0.232). There

17 were no differences in baseline IOP between the responders and non-responders in the two groups (360°

18 group p=0.462, 180° group p=0.62).

19

#### 20 **Discussion**

21 This is the first study which investigates the effect of SLT on outflow facility in previously untreated

22 patients. Overall, we found a significant increase in TOF and a corresponding decrease in IOP with a success

rate of 81% one month after SLT. Although there was a tendency for the 360° treated arm to respond more
 than the 180° treatment arm both in terms of TOF increase and IOP reduction, these differences did not reach
 statistical significance.

4

5 We used the classic electronic Schiøtz tonometer to measure trabecular outflow facility as described in a
6 recent paper by the author and rejection rate of 7.5% (three out of forty) subjects due to 'poor' tonography is
7 comparable to that study by the same operator in a different population.[19]

8 The overall IOP reduction of 29% in this study is comparable to other studies of both SLT and ALT.[10-18]. 9 In our study this was associated with a 37.5% increase in tonographic outflow facility. Most studies on the 10 effect of ALT on outflow facility were done in patients who were already on medical treatment making a 11 direct comparison difficult.[12-17] The only study of the effect of ALT on outflow facility in medically 12 untreated eyes with POAG was performed over fifteen years ago by Bergeå et al.[18] A comparable level of 13 IOP reduction was found in those with POAG but this reduction was associated with a much higher TOF 14 increase (65%). Although Bergea's study used the same measurement technique, the results are limited by 15 the relatively small number of POAG patients. These patients also had much higher pre laser IOP than our 16 patients.[18]

Similarly, Brubaker and Liesegang's study found a higher increase in TOF (64%) after ALT treatment but similar IOP reduction (29%) in medically treated patients (n=17) using the same tonographic technique.[16] The authors did not find any effect on aqueous production. In another study of ALT treatment reported by Thomas et al there was a 29% average reduction in IOP and 64% increase in outflow in patients with different types of glaucoma who were on maximal tolerated medical treatment.[14] Although these two study patients were already on medical treatment they had a similar pre laser IOP as our previously untreated patients.

Our results differ significantly from these ALT studies, in that although a comparable level of IOP reduction
was achieved, the TOF increase following SLT was only about half of that observed with ALT.[14, 15, 16,
18] This is a curious finding which could indicate a difference in mechanism of action of SLT as compared to
ALT. This could also be due to differences in study populations including the different racial distribution.
Our study had a proportion of African/Afro-Caribbean patients who are also known to have lower CCT.
Although CCT is known to affect Goldmann applanation tonometry readings its exact effects on Schiøtz
indentation tonographic outflow facility are not well understood.

8 If we assume that the increase in TOF is likely to be from the direct cellular effect of SLT on the trabecular 9 meshwork, leading to an increase in trabecular outflow, then according to Goldmann's equation (see 10 Appendix 1), a 29% reduction in intraocular pressure (Pi) should correspond to 100% increase in TOF (C). 11 As we found an increase of only 37.5%, this raises the possibility that other aspects of aqueous dynamics 12 parameters, such as aqueous production (F), uveoscleral outflow (U) or episcleral venous pressure (Pv) may 13 be affected by SLT. Previous aqueous dynamic studies of ALT have demonstrated that aqueous humour 14 production rates were not affected by ALT.[16, 17] Whether SLT treatment can cause a decrease in aqueous 15 production or a significant increase in uveoscleral outflow needs further investigation.

16

17 The overall responder rate of 81% in our study is similar to that of other studies of primary SLT.[8, 10, 21] 18 There was a trend favouring 360° SLT treatment in terms of more responders, which is consistent with 19 previous reports.[10, 11] Nagar et al. found progressively greater success rates with 90°, 180° and 360° 20 treatments (34%, 65%, 82% respectively).[10] One eighty degree and 360° treatments were significantly 21 more successful than 90° treatment but the differences between the 180° and 360° groups did not reach 22 statistical significance. Prasad et al also found a greater IOP reduction with 360° treatment as compared to 23 180° treatment in patients who had primary SLT but again the difference between the two groups was not 24 statistically significant.[11] It is likely that a smaller treatment effect exists when increasing SLT treatment 1 from 180° to 360° therefore in order to detect this difference a much larger study population than that of the
2 present study will be required (i.e. introducing the possibility of a type II error in the present study).

3

4 To our knowledge, this is the first study which systematically investigates the effect of SLT on outflow 5 facility as a step towards understanding its mechanism of action. Prior ocular hypotensive treatment can 6 affect the aqueous dynamics and for this reason we restricted eligibility to previously untreated patients. In 7 doing so, this study is the largest to investigate the effect of laser trabeculoplasty on TOF in previously 8 untreated primary open angle glaucoma. Although we did not have active controls in this study, the results 9 from our 'passive' control group suggest that all the changes seen in this study are due to treatment effect 10 rather than by chance. The slight caveat from this study is the over representation of the Afro-11 Caribbean/African population, which may mean that the findings are not applicable to other population 12 groups.

13

In conclusion, both 180° and 360° SLT treatments increase tonographic outflow facility and reduce intraocular pressure but no significant differences between the two groups were evident. Furthermore, the extent of IOP reduction cannot be explained by TOF increase alone, raising the possibility that SLT may affect other aqueous dynamics parameters.

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#### 1 Appendix 1

2

- <u>Goldmann's equation.</u> The aqueous production (flow) rate is equal to the sum of trabecular outflow and
   uveoscleral outflow:
- 5  $F_{f} = (P_i P_e)C + F_u$
- 6 Where,  $F_f$  is aqueous humour flow measured by fluorophotometry,  $P_i$  is pressure in the anterior chamber,  $P_e$ 7 is the episcleral venous pressure, *C* is trabecular outflow facility measured by tonography and  $F_u$  is 8 uveoscleral outflow. In this study,  $P_i$  and C were measured at baseline and at one month, while SLT 9 treatment is assumed to have no effect on  $F_f$ ,  $F_u$  and  $P_e$ . Therefore, a 30% drop in  $P_i$  should correspond to 10 100% increase in C.

1 Legends for figure.

## 

3	Figure 1 – Study flow chart. A top down flow chart outlines the study process, showing the number of
4	patients (n) with primary open angle glaucoma (POAG) or ocular hypertension (OHT) in each step from
5	participation in the study until last visit one month following selective laser trabeculoplasty (SLT).

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9

#### 10 **Competing Interest**

- 11
- 12 The SLT machine was provided by Ellex (NSW, Australia) on loan for the duration of the study. The
- 13 sponsor or funding organisation had no role in the design or conduct of this research. Dr Lim and Dr Goyal
- 14 have received travel grants from Ellex,



#### Figure legends

**Figure 1 - Study flow chart**. A top down flow chart outlines the study process, showing the number of patients (n) with primary open angle glaucoma (POAG) or ocular hypertension (OHT) in each step from participation in the study until last visit one month following selective laser trabeculoplasty (SLT).