A retrospective case-series to assess the effectiveness of Selective Laser Trabeculoplasty in the management of open angle glaucoma in black patients.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfillment of the requirements for the degree of Master of Medicine in Ophthalmology
Plagiarism Declaration

I, G. A. Fernandes as a post graduate student registered for a MMed in Ophthalmology at the University of the Witwatersrand declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source
- I am aware plagiarism is wrong
- I confirm that this work is my own work except where I have stated otherwise
- I have followed the required conventions in referencing the thoughts and ideas of others
- I understand the University of the Witwatersrand may take disciplinary actions against me if there is belief that this is not my own unaided work or if I have failed to acknowledge ideas or writings of others.

7 June 2016

[Signature]

7 June 2016
Ethics approval

Ethics approval was obtained through the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Clearance certificate number: M120455

The clearance certificate is in addendum 1 of this document.

Hospital permission

Permission to conduct research at St John's Eye Hospital was obtained from the Medical Advisory Committee of Chris Hani Baragwanath Hospital
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The staff at St. John's Eye Hospital.
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Abstract

Aims

This study aims to evaluate the efficacy of SLT as a treatment option in black patients with open angle glaucoma and to distinguish which patients are most likely to respond to SLT.

Methods

The study is a retrospective case-series of black patients collected at St. John’s Eye Hospital in Johannesburg. Data from 46 eyes were collected from the files of patients who had had SLT at least six months previously. The data collected included demographic factors, ocular characteristics and intraocular pressure (IOP) before and at each visit after selective laser trabeculoplasty (SLT). The data were analysed statistically firstly by comparing the pre-SLT IOP with the average post-SLT IOP, and secondly by Kaplan-Meir analysis of the duration of IOP control post-SLT.

Results

The mean age of participants was 58,3 years. The mean follow up time was 8 months (range 1 week to 33 months). The mean pre-SLT IOP was 20,7mmHg and the mean post–SLT IOP was 17,8mmHg. The change in IOP was statistically significant (p<0,001). The mean reduction in IOP was a 12% reduction from baseline. The mean duration of IOP control by Kaplan-Meier analysis was 13 months. The only demographic or ocular factor associated with a greater reduction in IOP was trabecular meshwork pigmentation. Patients with higher pigmentation had a median IOP reduction of 23,0% and those with low pigmentation a median reduction of 3,5%.
Conclusion

SLT resulted in a statistically significant but modest reduction in IOP in black glaucoma patients. The average reduction in IOP was 12% from baseline. High trabecular meshwork pigmentation was associated with a statistically significantly greater reduction in IOP.

Introduction

Glaucoma is a disease of the optic nerve characterised by progressive visual field loss and characteristic structural changes. The structural changes include thinning of the retinal nerve fibre layer and excavation of the optic nerve head. The most important risk factor for progression of glaucoma is raised intraocular pressure (IOP). IOP can be controlled by medication, laser trabeculoplasty, surgery or a combination of treatments.

The level of IOP is the result of a balance between aqueous production by the ciliary body and aqueous drainage mostly through the trabecular meshwork (TM). The outflow resistance of the TM is increased in open angle glaucoma, so that aqueous drainage is only able to match aqueous production at a raised IOP. The raised IOP in turn leads to progressive visual field loss and structural changes to the optic nerve. Laser trabeculoplasty aims to reduce the outflow resistance at the TM resulting in reduced IOP and preservation of visual field.

Laser trabeculoplasty was first described by Wise and Witter in 1979. They used an argon laser to place thermal burns on the TM. Although the mechanism of action of argon laser trabeculoplasty (ALT) is controversial, the glaucoma laser trial established the efficacy and limitations of ALT.

Latina and Park developed selective laser trabeculoplasty (SLT) in 1997. SLT uses a...
laser with very low energy settings and a very short pulse duration. The energy is only absorbed by pigmented cells and causes photolysis. As the laser is selective unlike ALT there is no thermal coagulation of tissues. Only the pigmented cells of the TM are affected so SLT is less destructive to the surrounding tissues than ALT.³

Glaucoma is the second most common cause of blindness worldwide, including Africa where glaucoma accounts for up to 30% of cases of blindness. The annual incidence of glaucoma in Africa is estimated to be 400 cases per million population.³ The burden of glaucoma in Africa is exacerbated by difficulties with its management in part due to difficult social circumstances. Management of glaucoma in this setting using medication can be difficult due to long distances and the cost of travel to collect medication. The cost of medications and lack of a regular supply of medications to health care facilities add to problems with medical treatment. It can also be difficult to convince patients of the need to use medications despite no improvement in their vision.⁵ SLT in these circumstances has significant advantages over medication as compliance is easier, and the patient does not have to collect medication on a monthly basis.

In light of the above information, further information regarding the effectiveness of SLT in patients of African descent and in a hospital serving many patients with difficult social circumstances would be useful for clinicians as well as health care managers in decision making in order to reduce the burden of glaucoma in Africa.
Literature review

The most widely accepted theories for the mechanism of action of ALT are the mechanical and the cellular theories. According to the mechanical theory, ALT causes thermal coagulation of the treated potion of the TM. This leads to scarring and contraction of the treated portion of the TM, which pulls on the untreated portion of the TM opening the inter-trabecular spaces, facilitating outflow through the untreated portion of the TM. ALT causes shrinkage of collagen, separation of trabecular sheets and traction on Schlemm's canal. According to the cellular theory, the laser burns recruit macrophages which phagocytose debris in the TM and de-bulk the extracellular matrix, decreasing outflow resistance.

The glaucoma laser trial (GLT) established the efficacy of ALT. The GLT demonstrated a mean drop in IOP of 9mmHg. At 2 years follow up, 44% of eyes had a controlled IOP after ALT alone, while 70% were controlled on ALT and Timolol drops. After 7 years, patients treated with ALT had a 1,2mmHg greater reduction in IOP than those treated with medication, as well 0,6dB better performance on visual field testing. Despite the encouraging results of the GLT there is debate about the long term effects of ALT. While some studies including the GLT show good efficacy at 7 years, other studies show loss of efficacy, with increasing IOP 2 years after treatment. Fink et al found that success rates fell from 71% at 33 months post ALT to 45% at 42 months. For patients who fail to maintain IOP control, re-treatment with ALT has been shown to be less successful than the initial treatment. There is also a risk of a rise in IOP after ALT, presumably due to coagulative destruction of a large part of the TM. The potential harmful effect of repeated ALT causing too much scarring of the TM is demonstrated by Gaasterland and Kupfer who induced glaucoma in monkeys by applying ALT to the entire TM.
The energy delivered by SLT is 1000 times less than that delivered by ALT due to the very short duration of the laser pulse. The 532nm wavelength and short pulse duration were chosen so that the energy is only absorbed by the pigmented cells of the TM, sparing the surrounding non-pigmented cells from any thermal effects. As there is no coagulative damage, crater formation, or disruption of trabecular beams or endothelial cells, the mechanical theory does not apply to SLT. The fine structure of the TM is preserved so SLT is less destructive than ALT. SLT works only by cellular mechanisms. The death of pigmented cells after SLT causes release of cytokines, which in turn cause release of gelatinases and metalloproteinases, macrophage recruitment, and repopulation of the TM by new cells. This results in remodelling of the TM, reducing IOP without observable mechanical or thermal damage to the recruited area.

The clinical efficacy of SLT in reducing IOP in patients with open angle glaucoma was first demonstrated by Latina et al in 1998. He treated 53 eyes and demonstrated a drop in IOP of at least 3mmHg in 70% of eyes and a mean drop of 5.8mmHg with a 6 month follow up. Other researches have demonstrated reductions in IOP, ranging from 3.9 to 8mmHg. A study of 460 eyes by Kaulen showed an average reduction in IOP of 23%.

SLT has been shown to produce similar reductions in IOP to ALT. Damji et al compared SLT to ALT in a randomised prospective trial of 176 eyes. They found no statistically significant difference in IOP between the two groups during a 1 year follow up period.
Similar conclusions have been obtained by Prinazar and Tabak.
SLT has similar efficacy to medical treatment with the prostaglandin analogue latanoprost in the primary treatment of POAG. Nager et al.11 performed a randomised prospective study comparing SLT with latanoprost 0.005%. The following table gives the percentage of patients achieving a 20% or 30% reduction in IOP after a mean follow-up of 10 months.11

<table>
<thead>
<tr>
<th></th>
<th>&gt;20% IOP reduction</th>
<th>&gt; 30% IOP reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>360 degree SLT</td>
<td>82.00%</td>
<td>59.00%</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>90.00%</td>
<td>78.00%</td>
</tr>
</tbody>
</table>

Table 1: Summary of the results of the study by Nager comparing response rates for SLT and latanoprost 11

The difference in IOP percentage reduction between the latanoprost group and the 360 degree SLT group was not statistically significant. The authors concluded that 360 degree SLT might be a useful primary therapy for ocular hypertension and open angle glaucoma.11 McIlraith et al.12 compared the efficacy of 180 degree SLT as initial therapy or as an alternative to medical therapy with latanoprost in a prospective trial with 100 patients. There was an average reduction in IOP of 8.3mmHg in the SLT group compared to 7.7mmHg in the latanoprost group. The difference was not statistically different. This study suggests that SLT is safe and effective as primary treatment for open angle glaucoma.12
SLT can also be offered to patients with medically controlled glaucoma in order to reduce the medication burden. Francis et al. did a prospective case-series of 66 eyes which were controlled on medical therapy. He applied 180 degrees of SLT and found the average number of medications required dropped from 2.8 at baseline to 0.7 at 6 months and 1.5 at 1 year.

SLT has also been used in patients with glaucoma that is not medically controlled on maximal topical medical therapy. In these cases, SLT can avoid surgical management and the risk and side effects that are associated with it. Geyer et al. performed SLT on 50 such patients. They found that 66% of patients had avoided surgery at 6 months, and 55% had avoided surgery at 12 months. Mean IOP reduction was 21% at 6 months and 20% at 12 months.

The side effects of SLT encountered by Latina and Park include mild anterior chamber inflammation in 83% of patients, which resolved after 5 days in all cases. They also found an IOP increase of 5mmHg or more in 25% of patients within 1 hour of SLT. The IOP spike resolved with medication in all cases within 24 hours and did not persist in any cases.

There are cases of persistent IOP elevation in patients with a hyperpigmented TM or pigment dispersion glaucoma. In these cases the IOP elevation is usually persistent, and these patients often require surgical management.

There are many racial differences in the incidence, age of onset, rate of progression and optic disc configuration. Black patients have a higher incidence of POAG than white patients, tend to develop glaucoma 10 years younger than white patients, and tend to progress more rapidly. These differences as well as differences in ocular pigmentation may lead to different responses and side effects after SLT in black patients. Studies on ALT have suggested that it is more effective in patients with
more pigment in the TM. Pigment in the TM may prevent laser/tissue interaction, reducing the efficacy of SLT in patients with hyperpigmented angles. Studies on Chinese eyes and African American eyes have shown similar response rates to white patients. This however needs further confirmation.

The Advanced Glaucoma Intervention Study (AGIS) looked at treatment options in uncontrolled glaucoma on maximal medical therapy. One cohort of patients received ALT and if unsuccessful a trabeculectomy first followed by another trabeculectomy if still uncontrolled (ATT cohort). The second cohort received a trabeculectomy first, followed by ALT if still uncontrolled, followed by another trabeculectomy (TAT cohort). Patients were followed up for between 4 and 7 years. They found a highly statistically significant difference in outcome between black and white patients in the two treatment groups. Black patients had a better outcome over the 7 years if they received ALT first (ATT group). White patients had a better visual outcome if assigned to the trabeculectomy first (TAT) group. This result highlights different responses in white and black patients to laser trabeculoplasty and trabeculectomy, and the need to assess the effectiveness of SLT in black patients.

**Study hypothesis**

SLT effectively lowers IOP in black patients.

**Study aims**

This study aims to evaluate the efficacy of SLT as a treatment option in black patients with open angle glaucoma and to distinguish which patients are most likely to respond to SLT.
**Study objectives**

The primary objective is to compare the pre-SLT IOP with the average post-SLT IOP in order to determine the overall effect of SLT on IOP, and to determine if the effect is statistically as well as clinically significant in black patients.

The secondary objective is to determine if any ocular or SLT treatment factors are associated with a greater or lesser response to SLT. The factors to be assessed include trabecular meshwork pigmentation, POAG versus PCE glaucoma, 180 versus 360 degrees of SLT, number of medications, glaucoma severity, corneal thickness and total SLT energy used.

**Methods**

**Study design**

The study is a retrospective case-series of patients collected at St. John's Eye Hospital in Johannesburg. Approval was obtained through the Medical Advisory Committee of Chris Hani Baragwanath Hospital and ethics approval was obtained through the Committee for Research on Human Subjects of the University of the Witwatersrand.

All doctors working at St. John's Eye Hospital were informed about the study and were asked to refer any patient who had had SLT at least 6 months prior for inclusion in the study, irrespective of the outcome after the treatment and the response to treatment in order the avoid referral bias. Patients who were referred for participation in the study were assessed for eligibility according to the inclusion criteria (see table 2). Prior to inclusion in the study patients were informed of the purpose of the study, were given an opportunity to decline to participate and were
made aware that their participation would in no way affect their treatment. Those who agreed to participate were asked to sign a consent form.

<table>
<thead>
<tr>
<th>6 months or longer post-SLT follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good compliance with reliable follow up and consistent use of prescribed medications</td>
</tr>
<tr>
<td>African decent and not of mix race</td>
</tr>
<tr>
<td>Good visualisation of the trabecular meshwork with clear media</td>
</tr>
<tr>
<td>Diagnosis of either primary open angle glaucoma or PCE glaucoma</td>
</tr>
<tr>
<td>No previous glaucoma filtration surgery</td>
</tr>
<tr>
<td>Age 18 years or older</td>
</tr>
</tbody>
</table>

**Table 2: Inclusion criteria**
Laser techniques

SLT treatment at St John's is generally administered by one of the registrars rotating through the glaucoma clinic. A Lumenis Coherent Selectra 7000 laser attached to slit lamp is used. This is a frequency doubled, q-switched Nd:YAG laser emitting at 532nm. The pulse duration is 3ns, the spot size 0.4mm and the energy can be set in 0.1mj increments between 0.2-1.7mJ.

After the application of a drop of local anaesthetic, a Latina SLT contact lens is applied to the cornea. After the trabecular meshwork has been visualised, 45-55 treatment shots are applied to each quadrant of the trabecular meshwork. The laser energy is initially set to 0.7mJ. If 'champagne bubbles' are seen, the energy is reduced in 0.1mJ increments until they are no longer seen. If no 'champagne bubbles' are seen, the energy is increased until they are seen and then reduced by 0.1mJ. Either 180 degrees or 360 degrees of the trabecular meshwork is treated, depending on the clinician. Post-SLT, the patients were instructed to continue their usual glaucoma treatment.

Data Collection

Data were collected from the patient's file directly onto the 'SLT Study patient record.' The first page of the record included ocular details and details of the SLT treatment itself. Ocular details included the patient's lens status, type of open angle glaucoma, and the amount of trabecular meshwork pigmentation. This information was obtained from the patient's file, except in cases where it was not recorded or not available. Trabecular meshwork pigmentation was not routinely recorded in the patient’s file. Gonioscopy was performed at the time of data collection in order to grade the amount of trabecular meshwork pigmentation. Trabecular meshwork pigmentation was graded on the Beker and Schaffer scale. 0 indicates no pigments, 1 indicated slight browning of the TM, 2 indicates definite browning of the TM, and 3
indicates heavy infiltration of the TM with dark brown pigment.

Patient’s stage of glaucoma was categorised into mild, moderate, or severe based on the best available information. If a visual field was available, those with a mean deviation (MD) greater than -10 were graded as mild, those with a MD between -10 and -15 were graded as moderate, and those with an MD less than -15 were graded as severe. If no visual field was available, the cup to disc ratio was used. A ratio less than 0.5 was graded as mild, between 0.5 to 0.8 was moderate, and greater than 0.8 was severe.

The details of the SLT treatment were recorded. The total energy delivered was calculated by multiplying the number of treatment shots by the energy used per shot. The number of degrees of angle treated, either 180 degrees or 360 degrees was also recorded.

Where possible, data was collected for the 3 months prior to administration of the SLT in order to get a more accurate measure of the average pre-treatment IOP. In all cases the best estimate of average pre-treatment SLT was used. If the only available pre-treatment IOP was the IOP on the day of treatment, then that IOP was used. All IOPs collected were done so on the same medication that the patient was on at the time SLT treatment. If a medication was added, or removed, no further IOP measurements were collected.

The study had a minimum post SLT follow up of 6 months. However if a patient's medication was increased or they went for surgery within the 6 months, they were still included in the study, with the time which the SLT controlled the IOP recorded. It was important to include these patients, as excluding them would have biased the study.
Unfortunately as available medications in the hospital change, patient's medication was changed from time to time. During the assessment time for many patient the available prostaglandin analogue changed from latanoprost to bimatoprost. The effect of this change was assumed to be negligible if a medication was changed to a medication in the same class. Similarly, the supply of combination drops was variable so a change from two separate bottles of medication to a similar combination was also assumed to have a negligible effect on the IOP. If a patient defaulted treatment or was put on extra treatment for a period of less than 3 months, the IOPs while on the different treatment were disregarded, but were collected once the patient had been back on their pre-SLT treatment for at least a month.

**Data analysis-primary objective**

The data was captured onto a spreadsheet with one section allocated to demographic, ocular and laser treatment parameters, and one section allocated to the various IOP measurements at each time point after the SLT treatment.

As the study was retrospective and the follow up time periods varied with each patient, each time point contained different numbers of readings, and no time point had a reading for every patient. It was therefore not possible to draw a simple graph of IOP versus time. It was also not possible to use the percentage change of IOP at a time period (say 6 months) to assess the effect of the SLT treatment as those patients who did not respond were often started on additional medication within 1 month of SLT so their 6 month IOP was unknown. This limitation was overcome by analysing the data in two ways, firstly by determining the average post-SLT IOP, and secondly by defining IOP control in order to construct a Kaplan-Meier plot to assess the months of IOP control post-SLT.

The average post-SLT IOP gave a reasonable estimation of the overall effect of the
treatment for the full follow up period for each eye. Normality was assessed and a paired sample t test performed using Sofastats version 1.4.3 to compare the pre-SLT IOP with the average post-SLT IOP.

The clinical significance of SLT was further assessed by determining the average percentage change in IOP from baseline for each eye.

Secondly, a Kaplan-Meier analysis was performed. Control of IOP was defined as a 10% reduction of IOP from baseline at 75% or more of visits. Using this definition the time in months for which IOP was controlled was identified. The end point was the time post SLT where the patient did not meet the above definition of controlled. The patient was marked as censored if IOP was controlled through the entire available follow up period, and the time of follow up was recorded. These data was entered into MedCalc version 14.10.2 to obtain a Kaplan-Meier plot.

**Data analysis-secondary objective**

Ocular and laser factors were analysed using the percentage change in average IOP post SLT as an outcome measure, as well as by Kaplan-Meier plots of duration of IOP control as another outcome measure.

Continuous variables were converted into categorical variables in order to simplify statistical analysis. The amount of energy delivered during SLT was divided into less than 50mJ, 50-60mJ and more than 60mJ. The central corneal thickness was divided into corneas less than 510 microns and those greater than 510 microns.
Certain grades of TM pigmentation and had very few numbers in the group, so it was preferable to combine groups. TM pigmentation was categorised as either low (Becker and Schaffer grade 0-1) or high (Becker and Schaffer grade 2-3). The number of glaucoma medications also was categorised into two groups (those using 0-1 medications, and those using 2-4 medications) for similar reasons.

An independent samples t-test was used to analyse the average percentage change in IOP when comparing patient characteristics which fell into two categories with adequately normal data. A t-test was therefore used to compare pseudocapsular exfoliation (PCE) glaucoma with POAG; 180 degrees of treatment with 360 degrees; patients on 0-1 medications with those on 2-4 medications; and corneal thickness less than 510microns with corneal thickness greater than 510microns. When comparing low trabecular meshwork pigmentation with high pigmentation, a Mann Whitney test was used as the data was not sufficiently normal.

An analysis of variance (ANOVA) test was used to analyse the average percentage change in IOP when comparing patient categories with more than two variables and adequately normal data. ANOVA was therefore used to compare the average percentage change in IOP for each of the glaucoma stages (mild, moderate, or severe); and for each of the categories of SLT energy used.

Kaplan-Meier plots were used to assess the duration of IOP control post-SLT for each of the categories. IOP control was defined as an IOP decrease of at least 10% from baseline at 75% or more of clinic visits. A logrank test was used to analyse the Kaplan-Meier plots for statistically significant differences between categories.
Data analysis – SLT technique
The amount of energy used per spot was compared between the patients with low TM pigmentation and those with high TM pigmentation. The greater the pigmentation of the TM, the more energy is absorbed for each laser spot. A t-test was performed to assess if there was a difference in energy use between these two groups as the data was sufficiently normal.

Results
Subjects
Mean age was 58.3 years (standard deviation 13.6). Mean central corneal thickness was 0.509mm (standard deviation 0.041). The mean number of glaucoma medications used was 1.8 (range 0-4). Mean pre-SLT IOP was 20.7mmHg (standard deviation 4.3). 4 eyes had PCE glaucoma while 41 had POAG.
16 eyes had 180 degrees of SLT while 29 had 360 degrees.
The mean follow up time was 8 months, but ranged from 1 week (for a patient who did not respond) to 33 months.
Primary objectives

Analysis of pre-SLT IOP and average post SLT IOP

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% Confidence interval</th>
<th>Standard deviation</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-SLT IOP</td>
<td>20,7 mmHg</td>
<td>19,4 to 21,9</td>
<td>4,3</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>Average post-SLT IOP</td>
<td>17,8 mmHg</td>
<td>16,7 to 18,9</td>
<td>3,7</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Change in IOP</td>
<td>-2,8 mmHg (-12,1%)</td>
<td>-4.2 to -1.5</td>
<td>4.5</td>
<td>-13,8</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3: Summary of the results of the effect of SLT on IOP

A histogram of the pre-SLT IOP and post-SLT IOP is shown. The skew and kurtosis of the graphs are within acceptable ranges so the data is sufficiently normal for an analysis with a paired sample t-test.
Fig 1: Histogram of the pre-SLT IOP. The horizontal axis shows the pre-SLT IOP. The vertical axis shows the proportion (P) of eyes with a particular IOP measurement.
The results of the paired sample t test is shown graphically with a histogram of the change in IOP as well as with a dot and line plot of the pre-SLT and post-SLT IOP.
Fig 3: The results of the paired sample t-test. The horizontal axis indicates the change in IOP post-SLT in mmHg. The vertical axis shows the proportion (P) of cases which experienced a particular change in IOP.
The paired samples t test showed that the difference between pre-SLT IOP and average post-SLT is statistically significant (p<0.001).

The percentage change in IOP was assessed to determine the clinical significance of SLT treatment. A graph of the results is shown in figure 5. The average percentage change in IOP after SLT ranged from a 49% decrease to a 29% increase. The mean change in IOP was a decrease of 12.1%, while the standard deviation was 19.3%.
Fig 5: Histogram of the percentage change in IOP.

In terms of responder rates, 17% of patients achieved a 30% or greater reduction in IOP. 39% of patients achieved a 20% or greater reduction in IOP. 4% of eyes experienced a 20% or greater increase in IOP.

The overall Kaplan-Meier survival curve for all patients is shown in figure 6. IOP control was defined as a 10% or greater decrease in IOP from baseline at 75% or more of clinic visits. The total sample size was 46 eyes. 27 (59%) of cases were uncontrolled at a time point and so were labelled as an 'event.' 19 cases (41%) were controlled at all points of the study and so were censored. Mean duration of IOP control was 13 months (95% confidence interval 8.5-17.8 months).
Fig 6: Kaplan-Meier plot showing the percentage of patients with controlled IOP at each time point in the study. The area between the grey curves indicate a 95% confidence interval. Censored data (i.e. patients who were controlled until the end of the follow up period and who therefore have an unknown duration of IOP control) are indicted by a vertical tick on the main curve. The number at risk table below the graph indicates the number of patients remaining in the study at each time point.
**Secondary objectives**

The following tables summarise the results of the analysis of the various ocular and laser factors. The Kaplan-Meier graphs are included only when the results are of special interest.

<table>
<thead>
<tr>
<th></th>
<th>Analysis of average percentage change in IOP post -SLT</th>
<th>Analysis of months of IOP control post SLT (IOP reduction of 10% from baseline at 75% of clinic visits) by Kaplan-Meier analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low trabecular meshwork pigmentation (14 cases)</td>
<td>Median -3.6%</td>
<td>Mean duration of IOP control = 8.5 months (95% CI = 2 to 15 months)</td>
</tr>
<tr>
<td></td>
<td>Average rank 19.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P=0.011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Mann Whitney U test)</td>
<td></td>
</tr>
<tr>
<td>High trabecular meshwork pigmentation (15 cases)</td>
<td>Median -23.0%</td>
<td>Mean duration of IOP control = 15.4 months (95% CI = 7 to 24 months)</td>
</tr>
<tr>
<td></td>
<td>Average rank 11.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P = 0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(logrank test)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Results of statistical analysis comparing the high TM pigmentation group and the low TM pigmentation group**
Fig 7: Kaplan-Meier plot comparing months of IOP control post-SLT for patients with low and high trabecular meshwork pigmentation.
### Table 5: Summary of statistical analysis comparing POAG with PCE glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Analysis of percentage change in IOP post -SLT</th>
<th>Analysis of months of IOP control post SLT (IOP reduction of 10% from baseline at 75% of clinic visits) by Kaplan-Meier analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POAG</strong> (41 cases)</td>
<td>Mean -15.3% (SD 19.0%)</td>
<td>Mean duration of IOP control = 12.9 months (95% CI = 8 to 18)</td>
</tr>
<tr>
<td></td>
<td>P=0.187</td>
<td>P =0.8275 (logrank test)</td>
</tr>
<tr>
<td><strong>PCE glaucoma</strong> (4 cases)</td>
<td>Mean -24.0% (SD 21.0%)</td>
<td>Mean duration of IOP control = 3.1 months (95% CI = 0.4 to 6 months)</td>
</tr>
<tr>
<td>180 degrees of SLT (16 cases)</td>
<td>Mean -14.1% SD 22%</td>
<td>P = 0.659 (Independent samples t test)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>360 degrees of SLT (29 cases)</td>
<td>Mean -16.7% SD 16.8%</td>
<td>P = 0.0351 (logrank test)</td>
</tr>
</tbody>
</table>

**Table 6: Summary of statistical analysis of 180 degrees of SLT and 360 degrees of SLT**
Fig 8: Kaplan-Meier plot of the proportion of eyes with controlled IOP at each time interval showing a significant difference between patients who received 180 degrees of SLT compared to 360 degrees of SLT.
<table>
<thead>
<tr>
<th>Analysis of percentage change in IOP post -SLT</th>
<th>Analysis of months of IOP control post SLT (IOP reduction of 10% from baseline at 75% of clinic visits) by Kaplan-Meier analysis</th>
</tr>
</thead>
</table>
| **0-1 medications (17 cases)**              | Mean duration of IOP control = 4.9 months  
(95% CI = 2 to 8 months)  
P = 0.0739  
(logrank test) |
| -8.60%  
SD 19.7% | **2-4 medications (28 cases)**  
Mean duration of IOP control = 7.0 months  
(95% CI =5 to 9 months) |
| -14.10%  
SD 19.0% | **P = 0.351**  
(Independent samples t test) |

**Table 7: Summary of the statistical analysis comparing patients using 0-1 medications with those using 2-4 medications**
### Table 8: Summary of the statistical analysis comparing mild, moderate and severe glaucoma

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mean percentage change</th>
<th>SD</th>
<th>Mean duration of IOP control</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>-16,0%</td>
<td>20.8%</td>
<td>12.2 months</td>
<td>6 to 19 months</td>
</tr>
<tr>
<td>(22 cases)</td>
<td></td>
<td></td>
<td>P = 0.987 (ANOVA)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>-16.8%</td>
<td>24.3%</td>
<td>10.2 months</td>
<td>2 to 18 months</td>
</tr>
<tr>
<td>(8 cases)</td>
<td></td>
<td></td>
<td>P = 0.6278 (logrank test)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>-17.0%</td>
<td>14.6%</td>
<td>7.8 months</td>
<td>5 to 10 months</td>
</tr>
<tr>
<td>(16 cases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal thickness &lt;510 microns (19 cases)</td>
<td>Mean -6.8% SD 18.1%</td>
<td>P = 0.430 (Independent samples t test)</td>
<td>Mean duration of IOP control = 12.8 months (95% CI = 6 to 19 months)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------</td>
<td>---------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Corneal thickness &gt;510 microns (18 cases)</td>
<td>Mean -11.9% SD 20.8%</td>
<td>P = 0.3707 (logrank test)</td>
<td>Mean duration of IOP control = 10.0 months (95% CI = 4 to 16)</td>
<td></td>
</tr>
</tbody>
</table>

Table 9: Summary of statistical analysis comparing eyes with corneas less than 510 microns with those thicker than 510 microns
| Total SLT energy less than 50mJ (10 cases) | Mean -6,1% SD 19,7% | P=0,599 (ANOVA) | Mean duration of IOP control = 10,2 months (95% CI = 3 to 17 months) |
| Total SLT energy between 50 and 60 mJ (18 cases) | Mean -11,8% SD 16,3% | P = 0,9331 (logrank test) | Mean duration of IOP control = 12 months (95% CI = 5 to 19 months) |
| Total SLT energy greater than 60mJ (17 cases) | Mean -13,7% SD 20,8% | Mean duration of IOP control = 14 months (95% CI = 6 to 21 months) |

Table 10: Summary of statistical analysis of corneal thickness and total SLT energy used

SLT technique
Mean energy per treatment spot was 0,7mJ for patients with low TM pigmentation, and 0,67mJ for those with a high TM pigmentation (P=0,475)
Discussion

Primary objectives

This study found a statistically significant reduction in IOP after treatment with SLT. The mean absolute decrease in IOP in this study was 2.9mmHg and the mean percentage decrease in IOP was 12.1%. SLT is therefore a useful adjunct in the management of open angle glaucoma at St. John's Eye Hospital.

The following table summarises the reduction in IOP (both the absolute and the percentage reduction) of the most significant published studies on SLT.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pre-SLT IOP</th>
<th>Mean reduction in IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damji 1999</td>
<td>18</td>
<td>22.8mmHg</td>
</tr>
<tr>
<td>Damji 2006</td>
<td>36</td>
<td>23.8 mmHg</td>
</tr>
<tr>
<td>McIlraith 2006</td>
<td>74</td>
<td>26 mmHg</td>
</tr>
<tr>
<td>Hodge</td>
<td>72</td>
<td>23.8 mmHg</td>
</tr>
<tr>
<td>Song</td>
<td>94</td>
<td>17.6mmHg</td>
</tr>
</tbody>
</table>

Table 11: Summary of the IOP reduction in the major SLT trials
Although direct comparison of the IOP reduction across studies is not possible given the differences in study design, population groups, stage of glaucoma and baseline IOP, the substantial difference between this study outcomes and those in the literature needs consideration.

The mean pre-SLT of 20.7 is a relatively low in comparison to most of the studies so one would expect a lower drop in IOP. Similar to this study, the study by Song had a low pre-SLT IOP of 17.6 and also had relatively modest results, similar to this study.

Another possibility which needs to considered is the possibility of racial differences in the response to SLT. Most of the studies mentioned earlier were performed on a Caucasian population. Given the racial differences in glaucoma recognised in the AGIS study, this possibility needs to be considered. Juzych did a retrospective review of 41 patient after SLT. He found no difference in the effectiveness between white patients and African Americans. Of Nager's study of 167 patients, 22% were of African descent. There were no racial differences in terms of IOP response in his study. The above studies suggest that racial differences are unlikely to be a factor in the modest IOP reduction in this study.

At St. John's SLT is usually performed by a registrar rotating through the glaucoma clinic. The registrars are usually new to SLT and are performing their first few treatments. As they are early in their learning curve, they may not be using the optimal energy level and may struggle to visualise the TM adequately to place the laser spots accurately. In order to assess the technique of SLT delivery, the energy used for the low TM pigmentation group was compared with that of the high TM group. Less energy is required in patients with a darkly pigmented trabecular meshwork to produce the ‘champagne bubble’ appearance which is used to find the optimal energy setting. The mean energy per spot was however found to be similar
in both groups (0.7mJ for low pigmentation vs 0.67mJ for high pigmentation, P=0.475) suggesting that the energy selection in patients in this study was not optimal. This may be one of the factors responsible for the relatively modest IOP reduction in this study.

Determining the target IOP or percentage drop in IOP required to prevent the progression of glaucoma is challenging, but this would give an indication of the clinical significance of the IOP reduction caused by SLT. The early manifest glaucoma trial was a large study of 255 patients with early glaucoma. The trial showed that a decrease in IOP of 25% reduced the risk of progression from 62% to 45%. The collaborative initial glaucoma treatment study had very low rates of progression. They decreased IOP by 38% in the medical group and 46% in the surgical group. The target IOP reduction therefore varies between 25% and 50%, depending on various patient factors. In this study the percentage of patients reaching a 30% or greater decrease in IOP was 17%, whereas a 20% decrease was reached in 39% of eyes. Although many patients may not meet the above target percentage decrease in IOP with SLT alone, the IOP reduction for those who did respond was achieved without the burden, side-effects, and costs of medications, or the risks of surgical treatment.

The Kaplan-Meier plot showed a rapid decrease in proportion of patients controlled in the first 3 months with only 48% of patients controlled at 3 months, dropping off to 39% at 5 months. This is best explained by there being a high proportion of patients who did not respond to the SLT. In the study by Nager, it was noted that most patients who are going to respond to SLT will respond within 3 months. The non-responders cause the steep initial decline in the Kaplan-Meier graph. However patients who do respond to the treatment tend to have a sustained benefit and remain controlled, causing a levelling off of the graph.
Secondary objectives

The change in IOP post-SLT was statistically significantly greater for patients with high TM pigmentation than for those with low TM pigmentation. In the Kaplan-Meier analysis, although there was a longer duration of IOP control for patients with high TM pigmentation the difference did not reach statistical significance. The effect of TM in other studies is inconsistent. Chen et al found a statistically significantly greater IOP reduction at 7 month for patients with higher TM pigmentation while Hodge and McIlraith found no difference. Considering that the mechanism of action of SLT is thought to occur by disruption and fragmentation of intracytoplasmic melanosomes, and the ensuing inflammatory response there is a reasonable theoretical basis for TM pigmentation to affect outcomes.

High TM pigmentation increases the absorption of SLT energy and so requires less energy per spot. This is important as patients with high TM pigmentation are at risk of a sustained increase in IOP after SLT as reported by Harasymowycz et al in a series of 4 patients. He recommended reducing the SLT energy and treating less of the angle at a session to avoid this complication. The reason for the greater response among high TM pigmentation patients may be related to the SLT technique. In this study registrars tended to use similar energy for all patients, regardless of TM pigmentation. The energy used may have been optimal for a highly pigmented TM, but insufficient for a less pigmented TM. The median 23.5% decrease in IOP in this study in the high TM pigmentation group is closer to the IOP reduction one would have expected from the studies in table 8. Differences in choice of energy selection between different centres, may also explain the inconsistencies between the studies mentioned earlier.

Due to the small sample size of the PCE group, the analysis between PCE and POAG groups should be interpreted with caution. Most studies however find equal efficacy
of SLT in PCE glaucoma and POAG as in this study.17

Although the percentage reduction in IOP between the 180 degree and 360 degree groups were similar, the Kaplan-Meier analysis suggests that the duration of IOP control was statistically significantly longer for the 180 degree SLT group than for the 360 degree group (mean 18.7 months vs 8.4 months). Chen compared 90 degree SLT and 180 degree SLT and found no statistically significant difference between the groups. Chen suggested that the low grade inflammatory response initiated by the SLT in the treated portion of the TM may spread through the aqueous to the untreated portion and increase the outflow through the entire TM.18 Nager et al11 compared the IOP reduction of latanoprost with 90, 180 and 360 degrees of SLT. The trend was for greater IOP reduction with increasing angle treated. The response rates for a 30% and 20% reduction in IOP are presented in the table.

<table>
<thead>
<tr>
<th></th>
<th>&gt;20% IOP reduction</th>
<th>&gt;30% IOP reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 degree SLT</td>
<td>34%</td>
<td>11%</td>
</tr>
<tr>
<td>180 degree SLT</td>
<td>65%</td>
<td>48%</td>
</tr>
<tr>
<td>360 degree SLT</td>
<td>82%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Table 12: Summary of the response rates for the study by Nager et al for success defined as a 20% and a 30% reduction in IOP11
Despite the higher response rates for 360 degree SLT, the difference between the 180 and 360 degree groups did not reach statistical significance. Nager however concluded that there is most likely an additional benefit in treating 360 degrees of TM rather than just 180 degrees. In the context of above information, this study's finding of a longer duration of IOP control with 180 degrees of treatment is difficult to explain. It is more likely the result of a confounding factor rather than a real finding. Such confounding factors may include clinician factors such as experience or techniques; or patient factors. The reasons for clinicians selecting 180 degrees or 360 degrees of treatment are unknown so selection may have led to patient differences between the two groups.

This result may also be due to the inherent limitations and assumptions of the Kaplan-Meier method. The number at risk table underneath the graph indicates that at 5 months, 8 of the 16 180 degree patients and 7 of the 29 360 degree patients remained in the sample. The low 'number at risk' early in the plot is due either to patients no longer being controlled or due to patients being censored early in the study. The plot after 5 months should be interpreted with caution as there are relatively few patients remaining 'at risk' in that portion of the graph.

The number of glaucoma medications was found to have no significant effect on the efficacy of SLT. Damji came to a similar conclusion in his study of 18 eyes. There are however few studies comparing the efficacy of SLT for patients on different numbers of medications. One of the commonest indications for SLT is for IOP control for patients already on maximal medical therapy. The finding of good efficacy of SLT, even for patients on high numbers of medication, supports the use of SLT in this context.

There is no study comparing the efficacy of SLT in various stages of glaucoma.
Realani after reviewing multiple studies, each on patients at various stages of glaucoma suggested that SLT is efficacious at all stages of glaucoma. This study supports his suggestion. One of the limitations of this study is that visual field information was not available for all patients, so staging in some patients was based on cup to disc ratio. This measurement is a subjective one and is subject to inter-observer error. Furthermore cup to disc ratio can be affected by disc size, which was not evaluated in this study. This may have led to patients being placed in the incorrect group as correlation between cup to disc ratio and visual field performance may not be adequate. However, given the very high p values obtained for both the analysis of post-SLT IOP and Kaplan-Meier analysis, these limitations are unlikely to have affected the results.

Interest in corneal thickness as a risk factor for glaucoma progression began with the ocular hypertension treatment study which showed that patients with ocular hypertension were more likely to progress to glaucoma if they had thinner corneas, independent of their IOP. This finding is more likely related to the effect of corneal thickness on IOP measurement, or to susceptibility of the optic nerve to damage in patients with thin corneas. As the values used in this analysis were a change in IOP rather than an absolute IOP value and optic nerve progression was not assessed, this study was unlikely to come across any differences between thin and thick corneas.

There were no significant differences in the efficacy between high, medium and low total SLT energy. The absolute amount of energy used is probably less important than using the appropriate energy for a particular patient. A relatively low energy level is appropriate for a highly pigmented TM and vice versa. Any correlation between the total energy is therefore masked by different TM pigmentations.

The major limitation of this study stems from its retrospective nature, and therefore
from the very heterogeneous patient and clinician mix. The large number of treating clinicians, each with different SLT techniques and experience introduced an important confounding variable. Clinician’s handling of patients after SLT was also varied greatly. Some clinicians increased medical treatment very soon after SLT. These patients may have responded if given some more follow up time, but were eliminated from further IOP collection as their medication was increased.

It was difficult to define a criterion for treatment success which would be appropriate for all the study patients as the indication for SLT was not always clear from the patient notes.

Variability in patients’ medical treatment was also a problem. Variability in supply of medications led to patients either going without a particular medication or using a substitute. This in turn could lead to IOP increases which may have affected the results.

Follow up intervals were different for each patient so it was not possible to analyse the IOP at a particular time point. The average post-SLT IOP therefore had to be used. This measure however also had its limitations as there was great variability in follow up time and follow up interval for each patient. For this reason the Kaplan-Meier analysis was also performed.
Conclusion

The analysis performed has shown that SLT results in a statically significant reduction in the IOP of black patients with glaucoma. The mean reduction in the IOP after SLT of in this study was 12% which is modest when compared to previously published SLT studies. The clinicians which performed SLT on the patients analysed in this study were relatively inexperienced compared to the clinicians that would have performed SLT on the patients analysed in the previously published studies. This inexperience has been highlighted by the observation that the energy used for SLT on the patients analysed in this study was not always appropriate for the level of TM pigmentation. This may account for the moderate IOP reduction observed in this study. Inappropriate energy selection may also account for the greater IOP reduction seen in patients with high trabecular meshwork pigmentation.

In conclusion SLT is effective in treating glaucoma in black patients. Clinicians and patients however should be cognisant of the possibility of no response whatsoever, and should be aware that a 30% reduction in IOP may only be seen in a minority of patients. In addition, this study has highlighted the importance of good technique and appropriate energy selection in order to get maximum benefit when SLT is performed.
References


Addendum 1: Ethics Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R1449  Dr GA Fernandes

CLEARANCE CERTIFICATE  MI20455

PROJECT
A Retrospective Review of the Effectiveness of Selective Laser Trabeculoplasty in the Management of Open Angle Glaucoma in Black Patients

INVESTIGATORS
Dr GA Fernandes

DEPARTMENT
Division of Ophthalmology

DATE CONSIDERED
04/05/2012

DECISION OF THE COMMITTEE*
Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04/05/2012  CHAIRPERSON

*Guidelines for written ‘informed consent’ attached where applicable
cc: Supervisor: H Kana

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...