Selective laser trabeculoplasty v argon laser trabeculoplasty: a prospective randomised clinical trial

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Abstract

Aims—To compare the effectiveness of selective laser trabeculoplasty (SLT, a 532 nm Nd:YAG laser) with argon laser trabeculoplasty (ALT) in lowering the intraocular pressure (IOP) in patients with medically uncontrolled open angle glaucoma.

Methods—A prospective randomised clinical trial was designed. Patients were randomised to treatment with either SLT or ALT and were evaluated at 1 hour, 1 week, 1, 3, and 6 months post-laser.

Results—There were 18 eyes in each group. Baseline characteristics were similar in both groups. In the SLT group the mean IOP at baseline, 1, 3, and 6 months was 22.8 (SD 3.0), 20.1 (4.6), 19.3 (6.0), and 17.8 (4.8) mm Hg, respectively. In the ALT group, the mean IOP at baseline, 1, 3, and 6 months was 22.5 (3.6), 19.5 (4.7), 19.6 (5.6), and 17.7 (3.3) mm Hg, respectively. There was a greater anterior chamber reaction, 1 hour after SLT v ALT (p<0.01). Patients with previous failed ALT had a better reduction in IOP with SLT than with repeat ALT (6.8 (2.4) v 3.6 (1.8) mm Hg; p = 0.01).

Conclusion—SLT appears to be equivalent to ALT in lowering IOP during the first 6 months after treatment. There is a slightly greater anterior chamber reaction 1 hour after ALT. Patients with previous failed ALT had a significantly greater drop in IOP when treated with SLT v ALT. These results need to be confirmed with a larger sample size.

Patients and methods

A prospective randomised clinical trial was approved by the research ethics board of Ottawa Hospital. The patients included in this trial were those referred to the glaucoma clinic at the University of Ottawa Eye Institute. Patients were included if they had open angle glaucoma (to increase the generalisability of the trial, pigmentary and pseudoexfoliation glaucoma were also included) with uncontrolled IOP (>16 mm Hg) on maximal medical therapy or failed previous 180/360 degree ALT (>6 months previously), were over 18 years of age, had two sighted eyes, and were willing to participate. Patients were excluded if there was any evidence of glaucoma other than open angle glaucoma (if the TM could not be visualised), or split fixation on Humphrey visual field 24-2, full threshold program) was present in the eye being considered for treatment; if the patient had previous glaucoma surgery done (other than ALT or peripheral laser iridotomy (PI)), or required any ocular surgery within 6 months post-laser in the study eye; if there was corneal disease precluding an adequate view of the trabecular meshwork; or if the patient was on systemic steroids or had a concurrent condition warranting treatment with systemic steroids within the study period.

Baseline examinations included variables such as age, sex, history of any risk factors for glaucoma (myopia, hypertension, diabetes,
Selective laser trabeculoplasty v argon laser trabeculoplasty

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>SLT</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) (years)</td>
<td>69 (9.3)</td>
<td>65 (10.6)</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Diagnosis: POAG*</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Pigmentary glaucoma</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>OAG status post PI†</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Aphakic glaucoma</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>No risk factors</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Eye treated: R</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>L</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>No of glaucoma medications:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Failed previous ALT</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>TM pigmentation (SD)</td>
<td>2.5 (0.9)</td>
<td>2.4 (1.0)</td>
</tr>
</tbody>
</table>

*POAG = primary open angle glaucoma.
†PI = peripheral iridotomy.

race, thyroid disease, and family history of glaucoma), a history of past and present ocular medication, and history of any ocular surgeries done including any laser therapy (ALT/PI) to the study eye.

Ocular assessment included corrected visual acuity, slit lamp assessment of the anterior segment of the eye, and gonioscopy of the angle. Trabecular meshwork pigmentation was graded according to a standard scale provided by Coherent Medical (graded from 0 to 4+ where 0 = no pigment and 4+ = dense homogeneous pigment). IOP was measured with a Goldmann applanation tonometer at approximately the same time of day (plus or minus 1 hour) for all follow up visits to minimise diurnal variation of IOP. Stereoscopic optic nerve examination was performed with a Volk 90D lens. On the day of laser trabeculoplasty, IOP was checked and one drop of 1% apraclonidine was instilled in the study eye. Patients were then treated with either SLT or ALT according to a blocked randomisation schedule using blocks of six. The allocation schedule was computer generated. The generator of the random allocation (WGH) did not participate in generating the schedule in any way. The clinicians (KFD, WJR) who administered the laser were not masked as to the treatment allocation. The clinicians (KFD, WJR) did not participate in generating the schedule in any way.

The inferior 180° of the angle was generally treated unless the patient had previous ALT to the inferior half in which case the superior 180° was treated. ALT was performed using 50 non-overlapping applications of 50 µm spot size, 0.1 second duration, and an average power ranging from 400 to 600 mW directed through an antireflection coated Goldmann lens to produce blanching or occasional bubble formation in the anterior TM. SLT was performed with Selecta 7000 (Q switched, frequency doubled, 532

Nd:YAG laser) using 50 non-overlapping applications, with a spot size of 400 µm (centred on the TM) and pulse duration of 3 ns. The initial energy used was 0.8 mJ. The energy was increased or decreased until bubble formation appeared and was then decreased by 0.1 mJ for the remainder of the treatment. Average power during treatment ranged from 0.8 to 1.4 mJ. A drop of 1% apraclonidine was instilled in all treated eyes post-laser. One hour post-laser IOP was checked and the anterior chamber reaction was assessed (cells and flare graded on a scale from 0 (no reaction) to + 4 (very marked reaction)). If pressure was high, 500 mg of acetazolamide was given to the patient and pressures were checked after an additional hour. When stable, patients were sent home on prednisolone acetate 1% to be instilled in the treated eye four times a day for 5 days. An attempt was made to keep the patient on the same glaucoma medications prescribed at the study inception for the duration of the study. The medication was changed only if the pressure worsened significantly from preoperative status, or if an adequate drop in IOP was not seen. Patients were evaluated at end of 1 week, then at approximately 1, 3, and 6 months. At all follow up examinations, the best corrected vision, anterior chamber reaction, IOP, grade of trabecular pigmentation, presence of any peripheral anterior synchia, and cup to disc ratio were noted.

STATISTICAL ANALYSIS

The distribution of baseline characteristics was compared between the two groups for all potential confounders (age, sex, type of glaucoma, glaucoma risk factors, number of glaucoma medications, past ocular surgery, and amount of trabecular pigmentation). For continuous variables, the mean was compared using a non-paired t test after checking for normality using an inverse normal plot. For binary variables, proportions were compared using the χ² test. Given that no differences were found among baseline variables, we took the liberty of comparing the outcome between groups in both a univariate and multivariate manner.

For univariate analysis, we used the same tests as for the baseline characteristics. For the multivariate analysis continuous outcomes were compared using multiple linear regression controlling for the above mentioned covariates. As expected the results were very similar given the equal distribution of baseline characteristics, hence only the univariate p values are provided. In order to calculate sample size, the expected difference between the two groups and an acceptable type I and type II error must be known. Because no long term clinical trial had ever been performed comparing these two laser modalities, the expected difference was unknown. Hence a priori it was decided to enrol between 35–40 patients in this phase I clinical trial.

All statistical analyses were performed with the software STATA (College Station, TX, USA). Significant p values were considered to
be less than or equal to 0.05. All tests were performed two tailed.

The primary outcome variable was a change in IOP from baseline. Secondary outcomes were anterior chamber reaction and Snellen visual acuity. All patients who were randomised were analysed in an intent to treat analysis.

Results
In all, 36 eyes of 34 patients were included; 15 eyes had previously received ALT. The average follow up time for 1, 3, and 6 months visit was 34.2 (SD 7.8), 90.6 (10.3), 184.7 (17.0) days, respectively. At the start of the study there were 18 eyes in each group. All baseline characteristics including IOP were similarly distributed in the two groups. The baseline characteristics of these patients are summarised in Table 1. It was noticed that ALT caused blanching and occasional bubble formation around the laser spot while during SLT, there was nil to mild reaction of the trabecular meshwork at most exposed sites. Both treatments were free of bleeding. Patients did not complain of any pain during treatment with either laser.

Table 2 shows the individual data for each patient at all time periods. It shows the change in IOP along with any intervention or change in medication performed in individual patients. Although we tried to keep the patients on a constant regimen of medications during the study period, in 12 eyes (six eyes in each group) a change in medication occurred to control the IOP. The average number of medications at baseline and 6 months was 2.3 and 2.5 respectively in the SLT group, and 1.8 and 2.1 respectively in the ALT group. Table 3 shows the mean intraocular pressure at baseline and after laser trabeculoplasty at 1 hour, 1 week, 1, 3, and 6 months whereas Table 4 shows the mean reduction in IOP at these time intervals. IOP measurements obtained 1 hour after treatment were higher with SLT than with ALT, although the results were not statistically significant (p=0.13). At 1 month there were 16 patients in the SLT and 17 patients in the ALT groups. Patient number 30 (Table 2) belonging to the SLT group had trabeculitis post-laser surgery. Trabeculitis was done in his eye at the end of 1½ months. This patient had developed a similar reaction to ALT in the fellow eye 1 year earlier also necessitating filtering surgery. At 3 months, there were 18 patients in the SLT group and 17 patients in the ALT group. At 6 months, there were 17 patients in the ALT group and 18 patients in the SLT group. Figure 1 shows the trial profile summarising the participant flow, numbers, intervention, and completeness of the follow up. Table 5 shows the mean intraocular pressures at 6 months in eyes (n=15) with a previous failed ALT. In this group, eyes treated with SLT had a significantly better final outcome in terms of drop in IOP compared with those treated with repeat ALT. When we eliminated the “previous ALT” subgroup from our analysis, the mean 6 month IOP was 19.6 (4.9) mm Hg in the SLT group and 16.7 (2.62) mm in the ALT group. This difference was not statistically significant (p=0.69).

A multivariate analyses was done at 6 months taking all baseline characteristics and the type of laser used into consideration and analysing their effect on the final intraocular pressures. It was found that the only predictor of final intraocular pressure at 6 months was the baseline intraocular pressure—that is,
Selective laser trabeculoplasty v argon laser trabeculoplasty

Figure 1  Trial profile.

Table 6  Anterior chamber reaction 1 hour post-laser

<table>
<thead>
<tr>
<th>Mean flare</th>
<th>Mean cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLT 1.0 (0.6)</td>
<td>1.6 (0.8)</td>
</tr>
<tr>
<td>ALT 0.8 (0.6)</td>
<td>0.9 (0.6)</td>
</tr>
<tr>
<td>p Value* 0.39</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*By non-paired t test.

Discussion

In this study we compared the standard continuous wave argon laser and a Q switched frequency doubled (523 nm) Nd:YAG laser. Our results showed that over 6 months' duration there was no statistically significant difference in the intraocular pressures in the two groups. To the best of our knowledge, no prospective randomised clinical trial with 6 months' follow up comparing these two lasers has been reported previously in the literature. Tabak et al. conducted a prospective randomised trial simultaneously treating one eye of a patient with SLT and the other with ALT. They found an equivalent decrease in IOP at 4 weeks (ALT n=17, SLT n=22) in both the groups. Longer follow up was not reported. Pirnazar et al. conducted a retrospective study comparing ALT (27 eyes) with SLT (30 eyes) and found no difference in IOP drop at 1, 6, and 12 months post treatment. ALT has been a standard therapeutic intervention in open angle glaucoma. The 5 year success rate with ALT is reported to be 50%, with a decrease of 6% to 10% per year. The drawbacks of argon gas laser, however, include high cost, large power supply system, large size, low electrical to optical efficiency, and plasma tube degradation with time. As a possible alternative to this laser a number of other wavelengths are being tested. The laser used in this study is a Nd:YAG laser, which is a solid state laser. It has the advantages of less cost, smaller size, longer duration, and high electrical to optical efficiency. Although a number of previous studies have been done using Nd:YAG laser trabeculoplasty in animal models and in human glaucomatous eyes, these studies used Nd:YAG either in the continuous wave or free running mode with a wavelength of 1064 nm. We used a Q switched, frequency doubled Nd:YAG (532 nm) which combines the advantage of solid state lasers with the emission of monochromatic green wavelength light. In this system, infrared radiation is filtered and only the visible component (532 nm) is used. This uses an effect similar to monochromatic argon green light (514 nm). An additional advantage of 532 nm laser over 1064 nm laser is that optical absorption by melanin increases with the decrease in wavelength, thus lower threshold energy is required for a similar effect.

Frequency doubled Nd:YAG laser with pulse of short duration and low fluence (energy/area) has been found in tissue cultures, to selectively target pigmented TM cells while sparing adjacent cells and tissues from collateral thermal damage. It may thus have the advantage of better maintaining the architecture of the TM compared with ALT. The exact mechanism of action of this selective laser trabeculoplasty is not known. However, since minimal mechanical damage is thought to occur, a predominately cellular theory has been proposed to explain an improvement in outflow facility. According to Hollo, following ALT, the uveoscleral meshwork is severely destroyed in the area of the laser spots and the surrounding collagen fibres are heat damaged. A membrane is formed by migrating endothelial cells, which covers the meshwork between the laser spots and is responsible for the late pressure rise and treatment failure after ALT. This endothelial membrane and thermal damage was not seen after 532 nm Nd:YAG laser trabeculoplasty. Naecker et al. studied the morphological changes after SLT and ALT in human postmortem eyes. They found that there was no coagulative damage to the human TM after SLT compared with ALT. This may offer a theoretical advantage for treatment with laser or topical medications if needed in the future.

SLT uses a pulse duration of 3 ns compared with ALT which has a pulse duration in the range of 1 ms or greater. According to Latina and Park, at pulse duration between 10 ns and 1 µs energy is deposited within the target (pigmented TM cells) more rapidly than it can diffuse away, hence minimising damage to the surrounding non-pigmented TM cells. Hence with pulse duration of 3 ns, SLT selectively...
confines the energy to the pigmented cells, whereas in ALT, heat gets dissipated from the pigmented cells to the surrounding tissues, damaging the non-pigmented cells within the irradiation zone. One interesting observation in our study was almost nil to mild visible reaction on the TM in response to the SLT impacts. In contrast, after ALT there was a bubble formation or blanching seen. This may be the result of deeper tissue penetration of the Nd:YAG laser energy in comparison with argon laser energy, which is deposited near the TM surface.

We also found that the anterior chamber reaction 1 hour post-laser was significantly greater in the SLT group than in the ALT group. A possible explanation for this may be the large spot size used for SLT 400 µm v 50 µm in ALT. The large spot size in SLT is used to maintain a low fluence (energy/area) which is essential for the selectivity of this laser. Because of such a large spot size, the laser beam probably has an effect on the pigmented cells not only in the TM but also in the ciliary body and surrounding iris. This may be responsible for the increased anterior chamber reaction.

An intriguing finding in our study was that in patients with previous ALT there was a statistically greater drop in IOP after SLT than after repeat ALT. This could probably be explained on the basis that ALT may have a predominantly “mechanical” action while SLT may mainly have a “cellular” effect, thus adding an additional mechanism to further reduce the IOP.

In summary, SLT appears to be equivalent to ALT in lowering intraocular pressures in patients with open angle glaucoma. There is a slightly greater post-laser anterior chamber reaction at 1 hour after SLT. Interestingly, patients with previous failed ALT had a better outcome when treated with SLT v ALT. These results are encouraging and suggest that SLT should be investigated further as an IOP lowering treatment in open angle glaucoma, especially in patients with previously failed ALT. Nevertheless our results need to be verified with a phase III clinical trial.

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