Clinical outcomes of patterned laser trabeculoplasty as adjuvant therapy in open angle glaucoma and ocular hypertension

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Abstract

• AIM: To assess the efficacy and safety of patterned laser trabeculoplasty (PLT) as an adjunctive treatment in open angle glaucoma (OAG) or ocular hypertension (OHT) patients who were under antiglaucoma medical treatment.
• METHODS: This study was a retrospective review of primary or secondary OAG patients and OHT patients with medically uncontrolled (≥18 mm Hg) intraocular pressure (IOP) who underwent 360º PLT from June 2016 to August 2016. Follow-up visits at week 1, and 1, 3 and 6mo were performed. IOP, best corrected visual acuity (BCVA), complications and eye drop glaucoma medication were recorded at each follow-up visit. Success was defined as IOP reduction ≥20% from baseline.
• RESULTS: Forty-one eyes of 25 patients were included in this study. Pre-treatment mean IOP was 20.2±1.6 mm Hg. After PLT, IOP was 19.3±5.2, 16.1±2.7, 17.1±3.7 and 16.3±3.5 mm Hg, at 1wk, 1, 3 and 6mo, respectively. IOP reduction from baseline was statistically significant from the first month, remaining stable at 6mo (P<0.001). PLT success at 6mo of follow-up was 48.78%. The number of glaucoma medication per eye (P=0.10) and the mean BCVA both remained constant (P=0.37). Complications included transient IOP spikes in 4 eyes (9.8%) and peripheral anterior synchiae in 7 eyes (17.1%).
• CONCLUSION: PLT is an effective and safe method for the management of patients with OHT or OAG as an adjunctive therapy. Additional larger studies should be designed to verify the long-term stability of IOP reduction with this laser technology.

• KEYWORDS: glaucoma; intraocular pressure; laser; ocular hypertension; trabeculoplasty

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INTRODUCTION

Glaucoma is a major public health problem. It is estimated that 64 million people around the world suffer from this disease[1]. Some studies show that its prevalence increases as intraocular pressure (IOP) levels increase[2-3]. Elevated IOP is the only treatable risk factor for glaucoma[4]. Ophthalmologists can lower IOP with medications, laser therapy, or incisional glaucoma surgery. One of the major problems with the medical treatment is the patient’s lack of compliance. The most frequent reasons for this are race, socioeconomic income and level of education[5-6].

Argon laser trabeculoplasty (ALT) was first described by Wise and Witter[7] and has been accepted as a treatment option for primary open angle glaucoma (POAG). The argon laser, wavelength (λ) =488-514 nm, improves the outflow of aqueous humor through the trabecular meshwork. However, histological studies have shown that this laser can lead to coagulative damage of this structure[8]. At present, ALT has been mostly replaced by selective laser trabeculoplasty (SLT) due to its ease of application and the possibility of repeat treatments. SLT uses a 532 nm Q-switched Nd:YAG laser that releases less energy and is selectively absorbed by the pigmented cells of the trabecular meshwork[9]. SLT results in terms of efficacy and safety are comparable to those of ALT[10-12].

In 2006, PASCAL pattern scan laser photocoagulator was introduced with a 532 nm laser used for standard photocoagulation procedures that can apply a uniform pattern of many laser spots at one time[13]. The PASCAL laser allows ophthalmologist to perform macular grid treatments effectively
and panretinal photocoagulation more rapidly with less pain than conventional laser due to its short pulse duration and less thermal damage.\(^{[14-15]}\)

Recently, the patterned laser trabeculoplasty (PLT) has been described as a novel alternative used for the management of POAG. In this modality, PASCAL laser is used to generate a sub-visible treatment on trabecular meshwork. The device uses a sequence of 11.25° patterns that engages the angle and automatically rotates after each application in a 32-step series. Consequently, this avoids a treatment with significant gaps or overlaps.\(^{[16]}\) Another advantage of this technology is the reduction of tissue damage since it uses a relatively short pulse duration (5ms). It has been shown that when using sub-threshold powers, PLT produces less thermal damage on the trabecular meshwork than ALT.\(^{[17]}\)

Several studies have shown that PLT is just as effective and safe as ALT and SLT in treating IOP.\(^{[16-19]}\) However, in these studies all patients underwent a medication washout period prior to treatment. The aim of this study was to assess the efficacy and safety of PLT as an adjunctive treatment in open-angle glaucoma (OAG) or ocular hypertension (OHT) patients who were already using hypotensive drop treatment.

### SUBJECTS AND METHODS

#### Subjects

This study was a retrospective review of primary or secondary OAG patients and OHT patients who underwent PLT at Santander Ophthalmologic Foundation from June 2016 to August 2016. All patients provided written informed consent prior to inclusion in the study. The nature and possible consequences of the study were explained fully in accordance with the principles of the Declaration of Helsinki. This study was approved by the Santander Eye Foundation Research Ethics Committee.

Inclusion criteria were POAG, pigmentary glaucoma or OHT patients aged 18 years or older, with uncontrolled IOP (>18 mm Hg), using antiglaucoma medical treatment. Among the exclusion criteria were advanced visual field defects within 10° of fixation (1 point with sensitivity of 0 dB or 2 points with sensitivity less than 15 dB in the same hemifield) and/or mean deviation lower than -12 dB in a 24-2 SITA Standard Humphrey visual field (Heidelberg Engineering, Heidelberg, Germany); previous glaucoma surgery; presence of corneal disease that affected visualization of the trabecular meshwork; treatment with systemic steroids.

#### Examination

The ophthalmological examination included Snellen best corrected visual acuity (BCVA) that was converted to the logarithm of the minimum angle of resolution (logMAR) BCVA for analysis, slit-lamp examination of the anterior segment and indirect gonioscopy with 4-mirror lens. IOP was determined by Goldmann applanation tonometer (GAT). Stereoscopic evaluation of the optic nerve was performed with a Volk (Volk Optical Inc., Mentor, Ohio, USA) lens of 78 D or 90 D.

Patients were followed up at 1wk and 1, 3 and 6mo. At each follow-up visit IOP was measured by GAT (IOP measurements were averaged and used in data analysis) by the same observer. Biomicroscopy, BCVA, gonioscopy, funduscopy, and the presence of complications were registered.

Antiglaucoma medical therapy was continued after the laser treatment and was only modified if the IOP deteriorated significantly from its preoperative level or if there was a significant decrease in more than 2 consecutive controls (IOP<12 mm Hg). In the case of post-treatment IOP spikes (increase ≥10 mm Hg compared to the preoperative IOP), additional glaucoma treatment was started and an extra follow-up assessment visit was performed at one week.

#### Laser Treatment Procedure

Indications for laser procedure were medically uncontrolled IOP and/or intolerance to medical IOP treatment. All the patients were treated using the PASCAL laser (Pascal Streamline 577; Topcon Inc., Tokyo, Japan) in a single 360° session by the same surgeon (Espinoza G). Patients were pre-treated with 1 drop of pilocarpine 2% in the eye to be treated 10min before PLT. Subsequently, 1 drop of topical anesthetic (proparacaine 0.5%) was used in both eyes of the patient.

The pattern parameters were set using a touch screen. PASCAL laser shots were focused onto the trabecular meshwork using a Latina gonioscopy contact lens (Ocular Instruments, Bellevue, WA, USA). Titration of the power to be used (starting with a pre-set power of 550 mW) was carried out by applying 10ms laser pulses until visible light blanching of trabecular meshwork in the inferior quadrant occurred. The exposure time was then reduced to 5ms to decrease the applied energy by half, producing sub-visible treatment spots. After titration the laser was set up to begin with the pattern in the inferior angle (12 o’clock). After each shot the pattern rotated automatically so it could engage with the trabecular meshwork avoiding overlapping shots. As the laser pattern was changing its angle the Latina gonioscopy lens was rotated. The treatment was administered in 32 steps to cover the 360° of trabecular meshwork. The total number of pulses and total amount of energy were recorded. Postoperatively, patients were prescribed prednisolone acetate 1% eye drops 4 times daily for 7d.

#### Statistical Analysis

The mean IOP measured at each follow-up visit was compared with the pre-treatment level. In addition, percentage IOP reduction from baseline was assessed. Statistical analysis was done using the Stata 12.0 software (Stata Corp LLC, Texas, USA) and a P value <0.05 was considered to indicate statistical significance in all tests. The normal distribution of the data was evaluated by the Shapiro-Wilk test. Continuous data were presented in the form of mean±standard deviation. Absolute IOP and percentage IOP reduction from baseline (the IOP reduction rate) as well as the differences in the number of glaucoma medications were
analysed statistically using t-test. PLT success was defined as IOP reduction by 20% or more of pretreatment IOP without additional medications, laser or surgery.

RESULTS
Baseline Characteristics A total of 41 eyes of 25 patients (61% women and 39% men) were included in this study (53.7% left eyes). The mean age of the patients was 61.0±7.4y (range: 48-75y). The baseline characteristics of the patients are presented in Table 1.

Laser Treatment Outcomes In all cases, the PLT could be performed on the 360º of the trabecular meshwork in a single session. The mean power used for bleaching the trabecular meshwork with 10ms exposure time was 672.0±77.3 mW (range: 550-775 mW). The average of spots applied on the trabecular meshwork was 1044.7±206.3.

Intraocular Pressure Results The pre-treatment mean IOP was 20.2±1.6 mm Hg. As shown in Table 2, the IOP was 19.3±5.2, 16.1±2.7, 17.1±3.7 and 16.3±3.5 mm Hg, at 1wk, 1, 3 and 6mo after PLT, respectively. IOP reduction from baseline was statistically significant from the first month, remaining stable at 6mo (P<0.001). Four (9.8%) out of the 41 treated eyes, maintained initial IOP values (first post-operative IOP) at 6mo. Average relative changes in the IOP over time are shown in Table 2 and Figure 1. PLT success rate at 6mo of follow-up was 48.78%.

Visual Acuity Outcomes The mean pre-treatment BCVA was 0.10±0.22 logMAR, and the mean post-treatment BCVA at the last follow-up visit was 0.11±0.21 logMAR. There were no statistically significant differences (P=0.37, t-test).

Complications Complications included transient spikes (9.8%) and peripheral anterior synchiae (PAS) (17.1%). There were no serious adverse events. The 4 cases that had an IOP increase were controlled with medical therapy consisting of brimonidine 0.20% and none of them required filtering surgery. Regarding the 7 eyes that developed PAS, none developed PAS greater than 90º of trabecular meshwork or greater than 2 clock hours (Figure 2).

DISCUSSION
This study was aimed to evaluate the effectiveness of PASCAL PLT as an adjuvant treatment in the control of IOP in OHT and OAG patients. Our results show that during a 6-month follow-up period, this procedure proved to be effective with an adequate safety profile. Similarly to other studies with PLT, we observed similar results.

| Table 1 Baseline characteristics in patients who underwent patterned laser trabeculoplasty |
|-----------------|------------------|
| Characteristics | Data             |
| Age (y), mean±SD| 61.0±7.4         |
| Sex (F/M)        | 25/16            |
| Eye disease, n (%)|                 |
| Primary open angle glaucoma | 27 (66) |
| Pigmentary glaucoma | 1 (2)   |
| Ocular hypertension | 13 (32) |
| Visual acuity (logMAR), mean±SD | 0.10±0.22 |
| Intraocular pressure (mm Hg), mean±SD | 20.2±1.6 |
| No. glaucoma topical medication, mean±SD | 2.1±1.1 |

SD: Standard deviation.

| Table 2 Intraocular pressure distribution by follow-up visit after patterned laser trabeculoplasty |
|-----------|-----------------|
| Follow-up time | IOP (mean±SD) | Mean IOP reduction (%) | P   |
| Preoperative | 20.2±1.6 (18-25) | - | - |
| Week 1      | 19.3±5.2 (8-36)  | 4.0 | 0.287 |
| Month 1     | 16.1±2.7 (7-22)  | 19.7 | <0.001 |
| Month 3     | 17.1±3.7 (11-25) | 14.6 | <0.001 |
| Month 6     | 16.3±3.5 (8-22)  | 18.3 | <0.001 |

IOP: Intraocular pressure; SD: Standard deviation. P value by the t-test.

| Table 3 Success rate and number of glaucoma topical medications in treated eyes during 6mo of follow-up |
|-----------------|-----------------|
| Follow-up time | Success rate (%) (n) | No. of glaucoma topical medications (mean±SD) | P   |
| Preoperative   | - | 2.2±1.2 | - |
| Week 1         | 31.71 (13) | 2.0±1.2 | 0.16 |
| Month 1        | 58.54 (24)  | 2.0±1.2 | 0.15 |
| Month 3        | 41.46 (17)  | 2.1±1.2 | 0.08 |
| Month 6        | 48.78 (20)   | 2.1±1.1 | 0.10 |

SD: Standard deviation. P value by t-test.
Patterned laser trabeculoplasty in glaucoma

Turati et al\textsuperscript{[16]} in 2010 performed a prospective pilot study in 47 eyes of 25 patients using the PASCAL laser with a wavelength of 532 nm. The PLT results with this PASCAL model showed a mean IOP reduction from 21.9±4.1 mm Hg preoperatively to 15.5±2.7 mm Hg at 6mo after treatment. An IOP reduction >20% was evident in 67% of eyes. However, at 6-month follow-up visit only 30 out of the 47 eyes were evaluated, and 8 eyes were excluded (4 of which IOP returned to its pre-laser values and the other 4 eyes were impossible to evaluate due to viral conjunctivitis). In those patients, no transient IOP spikes or other early complications were found.

Nozaki et al\textsuperscript{[20]} conducted a retrospective study in 11 eyes of 9 patients achieving an IOP reduction of 31% (from 20.5±4.7 to 13.4±3.7 mm Hg) at 6mo follow-up. In that study only a transient increase of IOP in one eye (9%) was reported. Barbu et al\textsuperscript{[18]} conducted a prospective, randomized clinical trial in 2014 comparing the effectiveness of PLT and ALT. Forty-two eyes were evaluated, showing an IOP reduction in the PLT group from 20.2±1.1 to 15.6±0.8 mm Hg at 8wk follow-up visit. Those results were similar (22.8% IOP reduction in the PLT group and 17.7% in the ALT group), and the comparison between both laser methods was not significant ($P=0.26$). Mansouri and Shaarawy\textsuperscript{[19]} designed a prospective, randomized clinical trial comparing the efficacy of PLT and SLT. The IOP levels in the PLT group dropped from 17.3±4.0 to 14.0±2.7 mm Hg (19.1%), and from 16.8±3.6 to 13.7±3.1 mm Hg (18.5%) in the SLT group, showing no statistically significant difference between both groups. The >20% IOP decrease in the PLT and SLT groups at 6mo follow-up was achieved by 37% and 26% of the evaluated eyes, respectively. The authors explained the low IOP reduction rate suggesting that the lower the baseline IOP is, the lower the post-treatment reduction rate might be. Ten eyes in the PLT group had conjunctival hyperaemia and anterior chamber flare within 24h postoperatively.

Similarly to other laser trabeculoplasty studies, we found an IOP reduction in patients with medically uncontrolled glaucoma. Shibata et al\textsuperscript{[21]} carried out a retrospective study in 2012 comparing the results of SLT as an adjuvant treatment in 2 groups: 180° treatment and 360° treatment. During follow-up both groups showed a significant IOP reduction. At 6mo the IOP reduction had been 5.6 mm Hg in the 360° group and 2.6 mm Hg in the 180° group, which represented a statistically significant difference in favor of the 360° group.

An interesting finding of our work was the presence of PAS in 17% of treated eyes (7 eyes). This can probably be explained by the learning curve that is required for the proper use of the equipment considering that these patients represented our first experiences with this type of technology. As this device uses a pattern of laser spots, it may involve a larger space of the trabecular meshwork, leading to a possible laser application at its posterior area. This mechanism has been described as a risk factor for the development of this complication in ALT patients\textsuperscript{[22]}. It is also important to emphasize that patients who developed PAS presented borderline open angles in the affected areas, which may be a particular condition to perform this type of procedure. Another interesting finding was that the most affected area was the inferior portion of the angle (5/7 eyes) making possible the idea that the titration site could lead to PAS due to more delivered energy. Finally, it is not easy to estimate the appropriate energy for the power titration on the trabecular meshwork, being this a determining effect in the development of PAS, as described by Rouhainen in eyes treated with ALT, the risk of PAS was higher as long as the laser power increased\textsuperscript{[21]}.

In recent years, newer lasers for trabeculoplasty have been described. Micropulse diode laser trabeculoplasty (MDLT) delivers energy in repetitive microsecond pulses followed by an intermittent rest period, thereby reducing the build-up of thermal energy. In a phase II prospective interventional case series, Fea et al\textsuperscript{[24]} evaluated the efficacy of 180° MDLT in 20 eyes of 20 patients during 12mo of follow-up. They found that 66.67% of patients who reached the 12-months follow-up visit ($n=15$ eyes) achieved an IOP reduction of ≥20%. Only one eye developed IOP spike and flare, and no PAS or change in visual acuity was detected. Titanium-sapphire laser trabeculoplasty (TSLT) is another type of laser trabeculoplasty that uses a 790 nm wavelength laser, emitting near-infrared energy in pulses ranging from 5 to 10ms. This is thought to allow deeper penetration into the yuxtaanaculicular trabecular meshwork and the inner wall of Schlemm’s canal. A prospective randomized clinical trial with 37 subjects comparing TSLT versus SLT was published in 2016. After 2y, it demonstrated that TSLT treated eyes had a mean IOP reduction of 35%, while the ALT

Figure 2 Gonioscopy image of peripheral anterior synchiae

The PAS presented in a 70-year-old female patient 3mo after laser treatment. It has a wide base and inserts to the trabecular meshwork, extending along 2 clock hours (white arrows).

group achieve a 25% IOP reduction. There was no statistical difference between the two groups. Three patients in the TSLT group and three patients in the SLT group experienced IOP spikes ≥10 mm Hg[25].

SLT and ALT have been standard therapeutic interventions in OAG and OHT. The mechanism through which the laser trabeculoplasty works is not entirely clear. In tissue cultures, SLT has been found to selectively target pigmented trabecular meshwork cells while sparing adjacent cells and tissues from collateral thermal damage. The laser’s brief pulse duration confines heat to the pigmented cells within the irradiated zone. In contrast, ALT destroyed all cells (with and without pigment) in culture models. According to Latina and Park[26], at pulse duration between 10ns and 1 μs energy is deposited within the target (pigmented trabecular meshwork cells) more rapidly than it can diffuse away, hence minimising damage to the surrounding non-pigmented trabecular meshwork cells. Therefore with a pulse duration of 3ns, 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. Turati et al[26] mentioned that for a pulse duration of 5ms with PLT heat can diffuse to approximately 50 μm. Recently, Lee et al[27] conducted a study comparing morphologic changes between ALT and PLT in cat’s trabecular meshwork. They demonstrated that performing sub-threshold (250-350 mW) PLT resulted in thinning of the uveal meshwork and demudation of endothelial trabecular cells. Nevertheless, they also reported the late formation of a membranous covering on the trabecular meshwork. They also demonstrated that by applying supra-threshold powers (400-450 mW), thermal damage of the trabecular meshwork could be induced producing an extensive membranous obliteration that could lead to difficulty in later aqueous outflow as seen with ALT. Since trabecular collapse showed by them in ALT and supra-threshold PLT is a consistent finding in the glaucomatous eye, they speculate that supra-threshold PLT may have at least deleterious effects on the IOP behaviour.

Our study is limited by its retrospective design and short-term follow-up. Another possible limitation could be the difference of IOP measurement time of the day before and after laser treatment and the possible improvement of compliance with medical therapy after laser treatment.

In conclusion, we can emphasize that PLT is an effective and safe method for the management of patients with OHT or OAG as an adjunctive therapy. Patients described as having borderline open angles may be carefully selected in order to avoid complications such as PAS. Additional larger studies should be designed to verify the long-term stability of IOP reduction with this laser technology.

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