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ORIGINAL PAPER

Efficacy and safety of pop-titrated versus fixed-energy trans-scleral diode laser cyclophotocoagulation for refractory glaucoma

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Abstract

Purpose To compare the efficacy and safety of pop-titrated versus fixed-energy diode laser trans-scleral cyclophotocoagulation (DLTSC) for refractory glaucoma.

Methods This is a prospective, interventional, longitudinal, and comparative case–control study. Patients with refractory glaucoma treated with pop-titrated DLTSC were compared to a fixed-energy DLTSC control group. Variables analyzed included: age, gender, diagnosis, pre- and post-treatment intraocular pressure (IOP). Success rate, anti-glaucoma medications reduction, and complications were analyzed at day 90 post-treatment. Primary success criterion consisted of eyes with a postoperative IOP ≤ 22 mmHg or a 30% reduction of pre-treatment IOP and managed with topical anti-glaucoma medications only.

Results A total of 68 eyes from 67 patients were included for analysis: 30 in the pop-titrated group and 38 in the fixed-energy group. Therapeutic success was achieved in 56–72% of the pop-titrated group versus 47–52% in the fixed-energy group considering the 3 different criteria analyzed ($p = 0.23$–0.4). There was a 22% (from 4.1 to 3.2 drugs) reduction of anti-glaucoma medications in the pop-titrated group, compared to 32% (from 3.5 to 2.4 drugs) in the fixed-energy group ($p = 0.42$). Five eyes (13.1%) developed hypotony, all of which belonged to the fixed-energy group ($p = 0.048$).

Conclusions Pop-titrated DLTSC represents an effective and safe option for the management of refractory glaucoma. We found no statistically significant difference in success rates among both groups. However, there was a significantly higher risk of hypotony in eyes treated with the fixed-energy protocol.

Keywords Diode laser · Cyclophotocoagulation · Refractory glaucoma · Intraocular pressure · Hypotony

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Introduction

The management of refractory glaucoma represents a serious challenge that may be approached by filtration surgery, or cyclodestructive procedures. Filtration surgery, including Baerveldt and Ahmed shunt implants, is considered the preferred method;

however, in patients with multiple ocular surgeries, chronic ocular surface disease with conjunctival scarring, poor visual prognosis, or low economic income, cyclodestructive procedures may be more suitable [1]. Such procedures involve the destruction of the ciliary processes by different modalities. Nowadays, endoscopic and trans-scleral diode laser cyclophotocoagulation (DLTSC) are most popular and have shown the best results [2–5]. A prospective study comparing Ahmed valve implantation with DLTSC as primary therapy for neovascular glaucoma showed similar efficacy and visual outcome at 24 months [6]. The intraocular pressure (IOP) reduction rate reported with DLTSC goes from 12.3 to 66% [2, 7], and the percentage of patients achieving an IOP < 21 mmHg ranges from 54 to 92.7% [8]. Demographic, etiologic, and pathologic variables may explain the correlation differences and disagreements among literature reports with respect to IOP reduction rates and the amount of laser energy applied to the eye [9, 10].

Today, no standardized DLTSC protocol exists, but several have been proposed with variable results [10]. Developing an effective and safe customized DLTSC protocol for a determined population is ideal for the management of refractory advanced glaucoma in patients with a poor prognosis for filtration surgery. During DLTSC, a "pop" sound is frequently heard during laser application. This sound represents micro-explosions of the ciliary process after enough laser energy has been absorbed by the tissue [11]. The purpose of the present study was to compare the success rate and the safety profile of "audible pop-titration" (1100–2000 mW) DLTSC with fixed-energy (2000 mW, 72 J) laser delivery DLTSC in patients with refractory glaucoma in whom filtration surgery was not considered the first-choice.

Patients and methods

This is a prospective, interventional, longitudinal, and comparative case–control study. Patients with refractory glaucoma defined as those on maximal topical anti-glaucoma therapy, with IOP levels ≥ 22 mmHg, and/or dependent on oral acetazolamide therapy, with or without previous glaucoma surgery and poor surgical prognosis, were included for DLTSC. Patients with previous DLTSC treatment or those with a postoperative follow-up time less than 3 months were excluded from the study. The study was conducted in mostly dark iris Mexican-mestizo patients at our clinic from April 2015 to January 2017. All patients read and signed an informed consent for laser treatment previously approved by the Research and Ethics Committees of our institution in compliance with the tenets of the declaration of Helsinki.

Patients treated with pop-titrated DLTSC were compared with those managed with a fixed-energy DLTSC protocol. The pop-titrated protocol consisted of 16 diode laser shots (Iridex® Oculight SLx Tri-mode 810-nm Diode Laser, Mountain View, CA, USA) delivered trans-sclerally with a G-probe under retrobulbar anesthesia (3 cc of 2% xylocaine). Laser shots were distributed along the 360º peri-limbal area at 1.2 mm from the corneo-scleral limbus in an axial orientation over the conjunctiva, avoiding the 3 and 9 o-clock positions due to potential damage to the long posterior ciliary nerves and arteries. In this protocol, the initial laser power was set to 1500 mW with a constant duration of 2000 ms. Then, the laser power was adjusted (range 1100–2000 mW) depending on the occurrence of an audible "pop." If after two consecutive shots delivered at baseline energy setting a "pop" sound was not heard, the energy was increased by 200 mW for another two consecutive shots. This operation was repeated until a "pop" sound was heard to a maximal energy power of 2000 mW. On the other hand, if a "pop" was heard after two consecutive shots at baseline energy settings, the energy was decreased by 100 mW to a minimum of 1100 mW. This procedure of rising or lowering the laser energy depending on the occurrence of an audible "pop" at a constant time of laser exposure was continued until the 16 shots were delivered. On the other hand, the fixed-energy protocol consisted of 16 laser shots at a constant power of 2000 mW for 2000 ms, regardless of the number of "pops" produced by the laser application in each eye. The shots distribution and the rest of the procedure were performed in the same manner as in the pop-titrated regimen.

After the procedure was ended, topical 1% prednisolone acetate was administered every 2 h for the first 3 days and weaned down to a stop by 2 weeks. Oral acetazolamide therapy was stopped, and topical anti-glaucoma drops were adjusted according to IOP reduction for the following 3 months. If therapeutic success was achieved, topical medications were

discontinued during the follow-up time. In case the postoperative IOP did not drop below 22 mmHg, oral acetazolamide therapy was restarted, or additional DLTSC was applied to the eye. Postoperative follow-up visits for all patients were performed at days 1, 7, 30, and 90, unless the patient required extra visits at the evaluator´s discretion. Variables analyzed included age, gender, glaucoma diagnosis, pre-treatment intraocular pressure (pre-IOP), pre-treatment anti-glaucoma medications, post-treatment intraocular pressure (post-IOP), and post-treatment anti-glaucoma medications. At day 90, therapeutic success, anti-glaucoma medications required, and hypotony (IOP ≤ 5 mmHg) were recorded. Primary therapeutic success was defined as post-treatment IOP ≥5 mmHg and ≤ 22 mmHg, or a 30% reduction from preoperative IOP; single DLTSC application; and need for postoperative topical anti-glaucoma medications only. For comparative analysis with previous similar reports, other two postoperative IOP cutoffs were also considered for analysis: IOP ≤ 22 mmHg alone (criterion 2) and IOP ≤ 25 mmHg (criterion 3). In addition, success criteria were only applied to eyes with preserved vision since blind eyes therapeutic goals are usually symptom-related only and not targeted on IOP reduction levels. Intraoperative and postoperative complications were also recorded. Results were analyzed with XLSTAT software (Addinsoft, 2015) using a Chi-squared test for categorical variables and a Student's *t* test for continuous variables.

Results

A total of 78 eyes from 77 patients were initially considered for the study. Ten patients did not complete the minimum 3-month postoperative follow-up time and therefore were excluded from the study, leaving a total of 68 eyes of 67 patients who were finally analyzed. The pop-titrated group consisted of 30 eyes and the fixed-energy group of 38 eyes. Clinical and demographic characteristics of all patients are presented in Table 1. The mean age of the pop-titrated group was 54 years (range 17–87 years) and in the fixed-energy control group was 60 years (range 20–83 years). The male-to-female ratio was 2:1 in the pop-titrated group and 3:1 in the fixed-energy dose group. The most frequent preoperative diagnosis was diabetic neovascular glaucoma (DNVG) seen in 56% eyes of the pop-titrated group and 68% eyes from the fixed-energy control group, followed by secondary glaucoma seen in 10 and 21% eyes, respectively (Table 1). The only representative difference between groups was the proportion of vitrectomized eyes (33%) in the fixed-energy group, compared to 10% in the pop-titrated group ($p = 0.55$).

The total amount of laser energy delivered to eyes in the pop-titrated group was significantly lower (49 ± 7 J) compared to a total of 72 J per session/eye delivered to the fixed-energy control group ($p < 0.0001$). The mean preoperative IOP was 42.6 ± 10 mmHg for the pop-titrated group, compared to 41.13 ± 12.8 mmHg for the fixed-energy group ($p = 0.60$). Pre- and post-treatment IOP levels at day 90 for both groups are presented in Table 2.

The mean number of pre-treatment anti-glaucoma medications, including acetazolamide, was 4.1 for the pop-titrated group and 3.5 for the energy-fixed control groups ($p = 0.21$). At day 90, the number of medications was reduced to 3.2 in the pop-titrated group and 2.4 in the fixed-energy group ($p = 0.42$). This represents a 22% reduction in the pop-titrated group and a 32% reduction in the fixed-energy group. Considering only the topical medications, the mean reduction was from 3.23 to 2.07 (36%) in the pop-titrated group and from 3.46 to 2.53 (27%) in the fixed-energy control group ($p = 0.22$). The primary therapeutic success rate of eyes with preserved vision was 72% in the pop-titrated group compared to 52% in the fixed-energy control group ($p = 0.23$). Similar results were observed in the other two postoperative IOP cutoffs considered for analysis. Overall, there was a trend for a better therapeutic success rate in the pop-titrated group (Table 3).

With respect to postoperative complications, only 5 (13%) eyes, all from the fixed-energy group, developed hypotony by day 90, compared to none from the pop-titrated group ($p < 0.048$, Fisher's exact test). Most of these eyes had neovascular glaucoma (3 out of 5) related to diabetic retinopathy, and three of them were pseudophakic and vitrectomized with silicon oil in the vitreous cavity. Other complications associated with the procedure included: transient anterior uveitis, pigment dispersion, mild to moderate ocular pain, and transitory hyphema. All these complications were resolved by day 30 of follow-up and were not significantly different between therapeutic groups.

Table 1 Demographic and clinical characteristics of study groups

Characteristic	Pop-titrated $N = 30$ eyes	Fixed-energy $N = 38$ eyes	p value
Age (years)	54.9 ± 16.8	60 ± 14.6	0.18
Gender	No. (%)	No. (%)	
Male	19 (63)	29 (76)	0.24
Female	11 (37)	9 (23)	
Diagnosis (DLTSC indication)			
DNVG	17 (56)	26 (68)	
CRVO-NVG	3 (10)	2 (5)	
POAG	5 (16)	1 (2)	
PCAG	2 (6)	1 (2)	0.18
SecG	3 (10)	8 (21)	
Phakic	19 (63)	26 (68)	0.9
Vitrectomized	3 (10)	12 (31)	0.55

DNVG diabetic neovascular glaucoma, *CRVO-NVG* neovascular glaucoma associated with central retinal vein occlusion, *POAG* primary open angle glaucoma, *PCAG* primary closed angle glaucoma, *SecG* secondary glaucoma

Table 2 Mean postoperative intraocular pressure change from baseline at different intervals of follow-up time

Study group	Intraocular pressure change (mmHg)						
	Pre-IOP (baseline)	Day 1	Day 7	Day 30	Day 90	Total difference	Total mean change
Pop-titrated	42.6	26.3	24.1	23.4	26.5	16.3	36%
Fixed energy	41.1	28.6	24.1	23.5	23.3	17.4	40%
Difference	1.5	2.3	0.0	0.1	3.2*	1.1**	4.0†

Total difference: difference between pre-IOP and IOP at day 90; total mean change: percentage of IOP change taking into consideration pre-IOP and IOP at day 90. *($p = 0$ .20); **($p = 0.28$); †($p = 0$ .33)

Discussion

Trans-scleral diode laser cyclophotocoagulation represents one of various interventional alternatives to decrease the IOP in patients with refractory glaucoma [7]. Compared to other surgical techniques, DLTSC has several advantages; it is minimally invasive, technically easy, and low cost [1]. Until recently, cyclodestructive procedures had been only reserved for eyes with poor visual prognosis because of multiple reported complications including intraocular hemorrhage, cataract formation, pigment dispersion, uveitis, prolonged inflammation, hypotony, *phthisis bulbi,* visual loss, pain, IOP spikes, atonic pupil, necrotizing scleritis, and sympathetic ophthalmia [12, 13]. In an extensive literature review, Ishida K. [10] suggested that DLTSC protocols with energy levels above 80 J per session result in higher rates of hypotony and phthisis. However, hypotony and *phthisis bulbi* have been reported to occur in only 26 and 10% of neovascular glaucoma, respectively [14]. In the present study, hypotony was documented in 5 (13.5%) eyes, all from the fixed-energy group ($p < 0.048$), and 3/5 of them had diabetic neovascular glaucoma. While some studies have found a correlation between the rate of IOP reduction, hypotony and the amount of laser energy employed, [9, 13] others do not support this finding [12]. An explanation for this controversy may be related to differences in the type of glaucoma, pre-existing eye comorbidities, surgical background, as well as population studied. In the same manner, previous studies have demonstrated that post-treatment iridocyclitis has a close relation with the number of "pops" reported during the procedure [15, 16]. Many variables have been proposed to be responsible for differences in results among studies including: age,

Table 3 Comparison of success rates between study groups

Success criteria	Pop-titrated $N =$ eyes (%)	Fixed-energy $N =$ eyes (%)	p value
Primary success			
30% IOP reduction, or $<$ 22 mmHg w/o hypotony, only topical medications			
All eyes	18 (60)	19 (50)	0.41
Eyes with vision	13 (72)	13(52)	0.23
Criterion 2			
$<$ 22 mmHg w/o hypotony, only topical medications			
All eyes	17 (56)	18 (47)	0.4
Eyes with vision	12 (66)	13 (52)	0.4
Criterion 3			
$<$ 25 mmHg w/o hypotony, only topical medications			
All eyes	18 (60)	18 (47)	0.3
Eyes with vision	13 (72)	13 (52)	0.23

gender, pre-treatment IOP, glaucoma subtype, previous surgery, and iris pigmentation [10]. A study conducted in India found that patients with more pigmented iris required lower energy levels to achieve the same results, suggesting that a standardized treatment protocol may be inappropriate for all patients, races, and subtypes of glaucoma [16]. Most patients in this study were Mexican-mestizo with dark-pigmented iris, yet no significant differences were found in the postoperative IOP outcome between protocols despite major differences in the energy applied, with much less energy delivered to eyes in the pop-titrated group ($p < 0.0001$). Other studies have reported good results after DLTSC in eyes with good vision and prognosis [3, 17]. Murphy et al. [13] found a 91.2% efficacy and no major complications after DLTSC in patients with primary open angle glaucoma (POAG) refractory to medical therapy. Lai et al. [8] reported its use for primary closed angle glaucoma, also with good results. Such results may be related to lower energy settings or the use of DLTSC in eyes with good prognosis.

Previous studies have used pop-titrated algorithms with good results. Kaushik et al. [16] reported a success rate of 78% (IOP = 5–22 mmHg) using pop-titration with only 9% hypotony in an Asian-Indian population. On the other hand, Espino-Barros & Rodríguez-García [14] reported a success rate of 57% after one session of fixed-energy DLTSC in Mexican-mestizo neovascular glaucoma patients, but with a 26% hypotony rate. The latter is almost three times higher than Kaushik et al. [16] reported hypotony rate, suggesting that reducing the energy power to 1800 mW may be suitable in the fixed-energy protocol. And even though all hypotony eyes in the present study were pseudophakic and vitrectomized with silicone oil tamponade, other authors have found a higher frequency of hypotony (11 and 0%, respectively) among patients with silicone oil [18, 19].

In the present study, the therapeutic success rate in eyes with preserved vision ranged from 52 to 72% depending on the criteria analyzed, with no significant differences in IOP control between study protocols (Table 3). However, there was a consistent trend for better results no matter the criteria applied, in the pop-titrated group. In a study with no standardized laser energy applied, Murphy et al. [13] reported a much higher success rate (89%) than our study using the same primary success criterion in a miscellaneous group of patients with refractory glaucoma. These authors reported a 9.5% hypotony rate associated with high pre-treatment IOP, high energy delivered per session, and neovascular glaucoma. Bloom et al. [20] used a $<$ 22 mmHg postoperative IOP cutoff and reported a 71% success rate (criterion 2 in the present study). These authors also reported a partial treatment success, which they defined as IOP $\leq$ 25 mmHg (criteria 3 in the present study) in 84% of their patients without a standardized energy protocol. Although their population studied and diode laser treatment protocol were different from ours, both success rates using the $<$ 22 mmHg

and $<$ 25 mmHg postoperative IOP cutoffs were similar to what we found in our population [20].

With respect to vision preservation in patients with refractory glaucoma, it is very difficult to identify the cause of visual loss since progression of the disease will always have to be considered [17]. One prospective study used DLTSC as the primary therapy in eyes with POAG refractory to medical treatment; there was a visual acuity loss in only 23% of eyes, a similar percentage of visual loss seen in the fellow eye treated only with anti-glaucoma medications [2]. In that report, blind eyes were also isolated from analysis since IOP requirements are different from eyes in which the therapeutic goal is to preserve vision. Topical medications are usually avoided in blind eyes unless persistent and throbbing pain occurs. In the present study, vision was not taken into consideration for analysis since most patients had other pathologic contributors to visual loss (most commonly diabetic retinopathy).

Postoperative ocular complications of DLTSC seem to be less prevalent with pop-titrated laser delivery. In the present study, reported complications included 5 (13%) eyes with hypotony, but none of them went on to *phthisis bulbi* during the entire follow-up time. It is important to mention that all these eyes were part of the fixed-energy protocol ($p = 0.048$). The lower risk of hypotony in the pop-titrated eyes may be related to the lower energy level used (49 ± 7 vs 72 J in the fixed-energy group), but this cannot be proved from our results. No other major complications related to the procedure were reported.

In conclusion, both the pop-titrated and fixed-energy DLTSC protocols were comparable effective in lowering the pre-IOP of patients with refractory glaucoma. On the other hand, hypotony was only reported in the fixed-energy protocol which delivered a significantly higher cumulative energy than the adjustable pop-titrated protocol, somehow compromising the safeness of DLTSC. To the best of our knowledge, this is the first study that compares a "pop"-based adjustable laser energy delivered protocol versus a high fixed-energy one. Studies with a longer follow-up and a larger cohort of patients are necessary to confirm these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with respect to materials and equipment used in this study.

Informed consent Informed consent was obtained from all individual participants for whom identifying information is included in this article (materials and methods section).

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