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LASER PHOTOCOAGULATION FOR PROLIFERATIVE DIABETIC RETINOPATHY, SINGLE-SPOT 532-nm vs MULTI-SPOT 577-nm: VERY SHORT TERM CLINICAL EFFICACY|

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ABSTRACT

***Introduction**: This study aimed to compare clinical efficacy of retinal laser photocoagulation using a 577-nm multi-spot laser with pulses of 20 ms versus conventional 532-nm single-spot laser treatment with pulses of 100 ms, on the same patient with proliferative diabetic retinopathy (PDR) during 6-weeks follow-up.*

***Methods:** We included 46 eyes of patients treated at the retina service of the Mexican Institute of Ophthalmology, Queretaro, Mexico. Pan-retinal photocoagulation (PRP) was performed on one eye (Group 1) using multi-spot PRP with the EasyRet® 577 diode laser (Quantel Medical, Cournon d'Auvergne, France). On the other eye (Group 2), laser treatment was performed by the conventional single spot method using the Oculight SL® 532 diode laser (IRIDEX Corporation, Mountain View, CA, The USA). The primary endpoint was absence of signs in which the disease was considered active at 6 weeks and the secondary outcomes included laser parameters, best-corrected visual acuity (BCVA), central macular thickness (CMT) at baseline, and 6 weeks and results of subjective pain analysis.*

***Result**: There was no significant difference between both treatment groups regarding age, gender, BCVA or CMT at baseline. At 6 weeks, PDR activity was similar between the groups (47.8 % versus 56.5%; p =0.55). No significant difference in CMT and BCVA was observed between the groups throughout the study period. Patient-reported pain scores were similar between the groups (5.0 versus 5.8; p = 0.30). However, total time of procedure was significantly shorter in group 1 (12.9 minutes [min] versus 22.3 min; p < 0.001). No major adverse events were identified*

***Conclusion**: Laser photocoagulation of the retina with the use of the multi-spot technology in patients with PDR has similar short-term efficacy to that of conventional single spot retinal photocoagulation. The multi-spot laser required less time to complete the procedure with more spots delivered to compensate its lower fluency, showing similar patient tolerance.*

Keywords: Diabetic retinopathy, Fluorescein Angiography, Laser Coagulation, Visual Acuity

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INTRODUCTION

Diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) are the most common causes of visual loss in individuals with diabetes.[1] Advanced PDR is characterized by tractional retinal detachment and vitreous hemorrhage; without promptly treatment approximately more than half of the patients will develop severe visual loss at five years.[2] Since the 1950 s, pan retinal photocoagulation (PRP) has been the standard of care for PDR, it destroys the peripheral retina to reduce the stimuli for neovascularization, preserving the central vision.[3] Its destructive nature leads to several side effects (transient vision loss, pain, loss of peripheral and/or night vision, worsening of macular edema and central vision loss) and does not always regress retinal neovascularization.[3]

Based on the Diabetic retinopathy study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS), conventional laser treatment is performed outside the vascular arcades, with pulse durations from 100 to 200 ms and a spot size of 100 to 500 µm, delivering at least 1500 burns and usually performed over several sessions.[2] New laser systems can produce shorter pulses (0.02 s and shorter). These pulses are also applied in fast sequences, one after another, called patterns. The Pattern Scanning Laser (PASCAL) was the first one of its kind. [4] and provided faster retinal photocoagulation facilitating the healing process by selectively targeting the retinal pigment epithelium (RPE) with minimal damage to photoreceptors and inner retina producing less retinal scarring with subsequent cell repopulation.[5] Newer machines also use different wavelengths, the 577-nm (yellow) wavelength has intrinsic biologic characteristics, such as better penetration and better absorbance by oxyhemoglobin and melanin with less absorbance by macular xanthophylls, and has been successfully used for macular and peripheral treatments. [6,7]

In the last years, a report (Protocol S) from the Diabetic Retinopathy Clinical Research Network (DRCR.net) [8] and the CLARITY study [9] supports the use of anti-angiogenic intravitreal drugs as monotherapy in patients with PDR, but the need for continuous injections, elevated costs and absence of data about long-term efficacy of this treatment compared to the known long-term efficacy of laser, make this treatment questionable. [10–12]

Emergence of newer, quicker and safer laser technologies and since PRP remains the standard of care for the treatment of PDR, we sought to compare clinical effectiveness of yellow (577 nm) multi-spot PRP with the standard Green (532 nm) single spot procedure.

METHODS

Study design

This was a prospective, comparative clinical study conducted on 23 consecutive patients (46 eyes) in whom PDR was diagnosed recently, attending the retina service at the Mexican Institute of ophthalmology, Queretaro, Mexico from August , 2019, onward, on whom PRP was done for the first time. The study complied with the Helsinki Declaration and the ethics committee of the Mexican Institute of ophthalmology (22-CEI-003-2016215) approved this study. All participants gave a written informed consent before the procedure.

Eligibility and exclusion criteria

The eligibility criteria included patients with diagnosis of type I or II diabetes mellitus, age at least 18 years or more, best-corrected visual acuity (BCVA) of 6/60 or better, PDR recently diagnosed with good pupil dilatation and clear media to perform laser PRP, optical coherence tomography (OCT) and fluorescein angiography (FA). Monocular eyes, chronic renal failure or history of a renal transplant from diabetic nephropathy, application of anti-angiogenic intravitreal drugs (last six months), previous vitrectomy, cataract surgery or clinical evidence of prior PRP and any other associated vascular retinal disease were excluded from the study.

Subjects, follow up and measure outcome

Initial examination included BCVA using a Snellen chart (with later conversion to the logarithm of the minimal angle of resolution [logMAR] for statistical analysis) and complete ophthalmologic examination. FA and OCT were performed at baseline and 6 weeks. FA images were provided by the Zeiss Fundus Camera (FF 450 plus, Jena, Germany), and OCT was performed with the Spectral-domain (SD)-OCT Revo NX (Optopol Technology SA, Zawiercie, Poland). The central macular thickness (CMT) was defined as the mean thickness of the neurosensory retina in the 1 mm central area from the 3-D macular protocol with

high definition linear scans obtained by this method. Color fundus images (7 fields exam at 30° to 35°) and FA were performed on both eyes at the screening visit and 6 weeks. FA was used to evaluate presence of persistent neovascularization, increased on the extent or development of new vitreous hemorrhage and capillary leakage area. One author (A. A-G.) performed the OCT and FA analyses, while the two others (J. Q-M. and D. V-C.) did the laser treatments, reducing the observer bias. Examinations were conducted at baseline and 6 weeks after laser treatment.

Evaluation of patient pain

Pain was determined based on the patient's response. A face pain scale (FPS) was used with a numerical scale adapted from the FPS in adult patients.[13] The scale used ranged from 0 to 10, where 10 equaled to the greatest pain possible and 0 to no pain. The examiner annotated the scores without questioning.

Objectives

The primary endpoint was the absence of signs in which retinopathy was considered active (increased on the extent or develop of vitreous hemorrhage, or fluorescein leakage from retinal neovascularization) and It was defined as a complete absence of previous fluorescein leakage from the active neovascularization determined by the FA at 6 weeks. Secondary outcomes were differences in pain score between the procedures and mean change in BCVA and CMT (determined by the SD-OCT) at 6 weeks. All adverse events related to the treatment were reported.

Laser Treatment Techniques

The laser treatment was performed in a darkened room. At first, 0.8% tropicamide with 5% phenylephrine (T-P Ofteno©, Sophia Laboratories, Guadalajara, Mexico) were used to dilate the pupil 20 minutes before the procedure. The eyes were anesthetized using topical 0.5% tetracaine hydrochloride (Ponti-Ofteno©; Sophia Laboratories, Guadalajara, Mexico) drops. The Mainster 165 PRP lens (Ocular Instruments Inc., Bellevue, Washington, USA) was used for all procedures, with a spot magnification factor of 1.96. The patient eyes were allocated as follows:

Right eye treatment was performed using the IRIS Medical Oculight SL® 532 diode laser (IRIDEX Corporation, Mountain View, CA, The USA) using a conventional single-spot therapy (532-nm wavelength). The laser energy was gradually titrated until a moderate laser spot (grayish/white) was achieved (moderate burn, as defined by the ETDRS). These settings (standard ETDRS) were used: pulse duration 100 - 200 ms and a spot size 400 µm. Laser pulses were applied in a conventional single-spot manner, under repeat mode and supplementary session was scheduled 1 week later, for the completion of the procedure. The number of burns was performed according to the recommendation from the International Council of Ophthalmology guidelines for diabetic eye care 2018 and were divided into two sessions.[14]

Left eye treatment was applied using the 577 EasyRet ® diode laser (Quantel Medical, Cournon d'Auvergne, France) with a wavelength of 577-nm. The power was titrated until a moderate laser burn (grayish/white) was attained. The settings were as follows; pulse duration of 20 ms; 390 µm of spot size. Treatment was applied using a multi-spot strategy that uses pattern grids of 3 x 3 to 5 x 5 (regularly spaced spots with 0.75 burn width). The number of spots per session depended on patient tolerance and surgeon discretion. The procedure was completed in two sessions with 7 days apart. The number of laser spots and maximal power used was recorded.

Rescue therapy

Clinical and angiographic signs of disease activity were assessed by the investigators at 6 weeks. Worsening of the disease activity and/or persistent severe disease were treated again, with prompt 1500 burns of the laser. Stable and eyes with reduced disease activity were observed. In cases of uncertainty regarding the treatment efficacy, the case was reviewed by the chief study investigator.

Statistics

Central tendency and dispersion values were defined for quantitative variables, as well as absolute and relative frequencies for categorical

variables. The normality of quantitative variables was evaluated using Shapiro-Wilk test, with a significance level of 5%. For comparison of the effects of PRP with a 577 nm multi-spot laser against the 532 nm single-spot laser, Paired student's T and Wilcoxon rank tests were used. Stata statistical package ® version 15.1 (StataCorp. 2015, Stata Statistical Software: Release 15. College Station, Texas, The USA, StataCorp LP) was used for the analyses. P value below 0.05 was considered as statistically significant.

RESULT

Forty-six (46) eyes were included. From 23 patients diagnosed with PDR, 13 (56.5%) were female, with a mean ± standard deviation (SD) age of 59.6 ± 11.2 (range; 42-88) years, all patients were phakic, with a mean ± SD glycated hemoglobin (HbA1c) of 8.24 ± 1% (range; 6.3-10.6%). Twenty-three eyes (23) were evaluated in the 577nm multi-spot laser group and 23 eyes in the 532nm single-spot laser group. Table 1 summarizes baseline characteristics of BCVA and CMT in each group, as well as the parameters used.

Table 1. **Baseline characteristics, and PRP parameters with 577 multi-spot yellow laser and 532 nm single-spot green laser in patients with PDR (n= 46 eyes)**

		Laser		
		577 Yellow Multi-spot (n=23)	532 Green Single-spot (n=23)	
Variable		mean±SD	mean±SD	p*
BCVA, LogMAR				
	Baseline	0.51 ± 0.3	0.48 ± 0.3	0.97
	6 weeks	0.52 ± 0.4	0.50 ± 0.4	0.96
CMT (µm)				
	Baseline	235.5 ± 33.0	245.0 ± 27.9	0.24
	6 weeks	247.2 ± 40.2	256.9 ± 42.3	0.64
		Laser Parameters		
Number of spots		3766.3 ± 933.9	2772.2 ± 819.6	**< 0.001**
Exposure time (ms)		20.9 ± 5.7	134.8 ± 46.3	**< 0.001**
Power (mW)		381.5 ± 102.3	333.7 ± 92.2	0.10

* Paired T test or Wilcoxon rank test, as appropriate. P<0.05 in bold.
Abbreviations: N: number; BCVA: best-corrected visual acuity; LogMAR: logarithm of the minimum angle of resolution; CMT: central macular thickness; SD: standard deviation; PDR: proliferative diabetic retinopathy; PRP: pan-retinal photocoagulation; µm: micrometer; nm: nanometer; ms: millisecond; mW: milliwatt.

Regarding the primary outcome (disease activity determined by FA; figure 1 and 2), no statistically significant differences were found (p = 0.55) after the application of both types of lasers at 6 weeks (multi-spot 47.8% and single-spot 56%).

Table 2. **Disease activity, Pain score and procedure time among groups (n= 46 eyes)**

	Laser		
	577 Yellow	532 Green	
Variable	Multi-spot (n=23)	Single-spot (n=23)	p*
Inactive Disease, n (%)	11 (47.8)	13 (56.5)	0.55
Pain (FPS 0-10); mean±SD	5.0 ± 2.6	5.8 ± 2.5	0.30
Time of procedure (min); mean ±SD	12.9 ± 3.2	22.3 ± 4.2	**< 0.001**

* Paired Student T test, as appropriate. P<0.05 in bold.
Abbreviations: n: number; %: percentage; FPS: face pain score; SD: standard deviation, min: minutes.

However, less procedure time was found in the 577nm multi-spot laser (p < 0.001) compared to the 532nm single-spot laser group (Table 2).

There were no statistically significant differences in BCVA and CMT at baseline and 6 weeks in the both groups (Table 1). The number of shots was significantly higher (p < 0.001) in the group treated with 577nm multi-spot laser with less exposure time (p < 0.001); however, there were no differences in the power used compared to the 532nm single-spot laser group (p = 0.10). Similarly, pain levels measured subjectively with the FPS were not statistically different (p = 0.30).

Two eyes from the same patient developed choroidal detachment during the follow-up that was successfully managed and 2 eyes developed vitreous hemorrhage that ended up on vitreoretinal surgery.

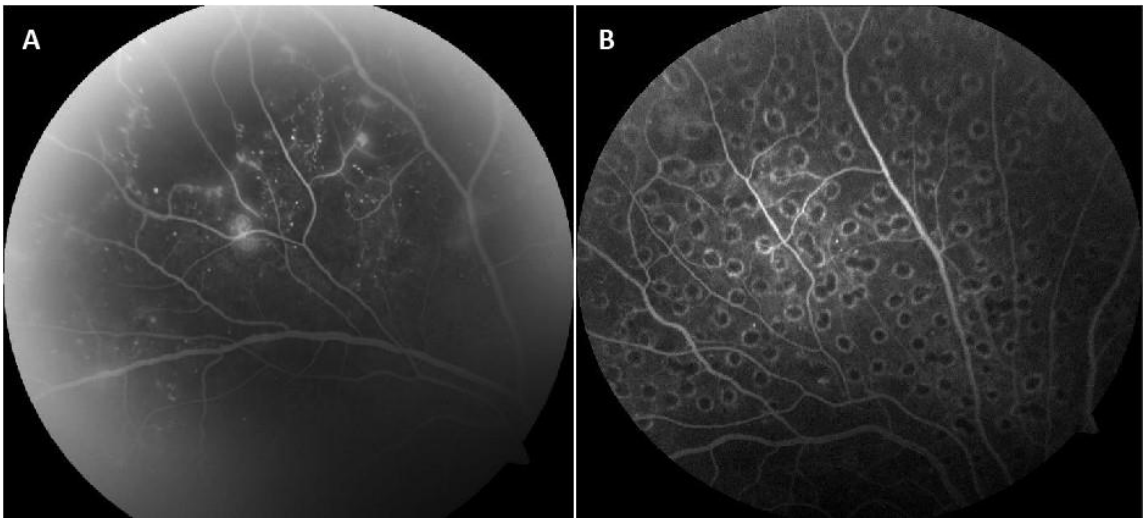

FIGURE 1 (A and B): **Fluorescein angiogram from right eyes at baseline (A) and after laser treatment (B) Representative images from different patients shows the treated retina with conventional 532-nm single-spot pan retinal photocoagulation (100-ms pulse duration) and larger, irregularly spaced and some confluent scars. Complete remission of disease activity at 6 weeks is shown.**

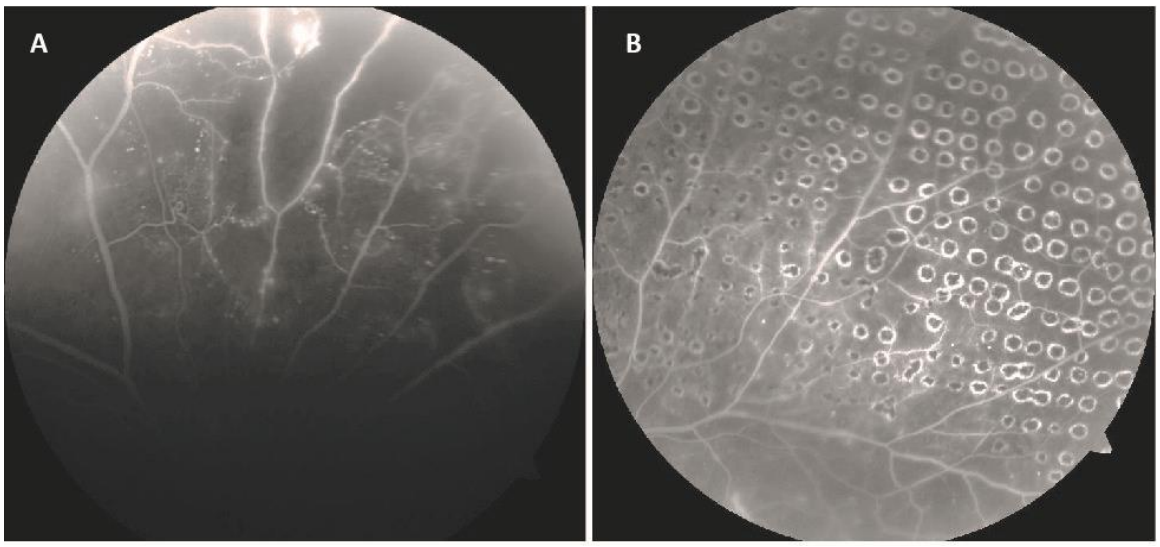

FIGURE 2 (A and B): Fluorescein angiogram from left eyes at baseline (A) and after laser treatment (B): Representative images from different patients shows the treated retina with 577-nm multi-spot pan retinal photocoagulation (20 ms pulse duration) and small, regularly spaced and mostly non-confluent scars owing to its short pulse duration and pattern delivery system. Complete remission of disease activity at 6 weeks is shown.

DISCUSSION

In the present study, both treatments were equally effective in achieving the primary endpoint (absence of signs in which the disease was considered active) at 6-week follow-up; a half of our patients (47.8% versus 56.5%) achieved it in the both groups, which is consistent with other reports. [15–18] Although some reports showed a less clinical effect with the multi-spot laser, this may be because a fewer number of laser spots were performed by the DRCR.net protocol (1,800–2,400) and by Chappelow et al. (1,438 ± 67). [19–22] These observations reinforce the importance of increasing the number of laser spots with this strategy by expanding total treated area, therefore, maintaining its efficacy. Data from the Protocol S and the CLARITY study are not relevant

to our outcome, since they were not designed to compare single-spot and multi-spot PRP strategies, and they described only the percentages of patients that received one of the treatments. [8,9,20]

There was no statistically significant difference for BCVA between the treatment groups and both treatments were similar in terms of visual acuity stability, CMT, pain score and disease activity (around 50% for both groups). Mean CMT also remained in the both groups. Laser application induces cytokine release and retinal capillary hyperpermeability that explain why some studies reported transient increase in macular thickness after single-spot PRP.[23]

Our findings did not demonstrate any differences between the both groups (20 and 100 ms PRP) regarding the procedure pain. Even though our findings are not consistent with other authors, which demonstrated a lower pain perception in the multi-spot laser strategy in contrast to the conventional treatment. [15–19,24,25] We have to remember that, the retina is devoid of pain sensitivity and the ocular pain frequently reported after the procedure may be related to thermal effects in the choroid, thermal diffusion to the nerve fiber layer, stimulation of ciliary nerves in the suprachoroidal space or probably direct damage of the posterior ciliary nerve. [26]

A significant reduction in the procedure time with similar clinical outcomes compared with conventional laser treatment may have a greater implication in terms of hospital and office diabetic eye care. The main benefit is shorter time used for both the patient and physician allowing to increase the number of patients treated each day and earlier clinical reevaluation. More patients can potentially be treated with the multi-spot laser per clinic session with shorter waiting times in the waiting room and laser appointment on the treatment day.

The main limitations of our study were the small sample size and very short follow-up time to evaluate clinical outcomes. We also did not perform pre and post-operative visual field evaluation, because it was not included in the protocol. One strength of our study was the fact that we used the same patient (inter-eye comparison) to compare the effect of the procedure reducing some bias.

The increase in retinal oxygenation (increase in the diffusion of oxygen from the choroid) and elimination of hypoxic retinal area and vasoproliferative factors are the two main mechanisms by which PRP theoretically works. [27] Decades ago, more patient discomfort was observed with higher-wavelength lasers (810 nm, krypton), because of its deeper penetration and green (532 nm) and yellow (577 nm) diode lasers have become the dominant modality in the last years. Regardless of wavelength, up to 70% of eyes treated with conventional DRS-PRP for high-risk PDR experience some regression of neovascularization within 6 months.[28] Newer strategies are focused to produce less retinal tissue damage selectively targeting a specific retinal layer. This can be achieved with lower fluences, higher burn density and targeted approaches (treating only damaged areas of the retina).[29]

This type of new approach may achieve the same regression rates of disease without well-known complications of conventional PRP. Therefore, the idea of targeted retinal laser treatment for PDR emerged intending to treat only damaged areas of the retina (areas of ischemia and neovascularization) using wide-field imaging systems. Muqit et al. reported complete and partial regression of the disease on treated eyes in 37% and 33 %, respectively at 24 weeks with this technique. Visual acuity was also improved by three letters at 24 weeks. [30]

The idea to reduce fluence and increase density treatment area with minimal retinal damage (minimal traumatic PRP; MT-PRP) has been emerged. The MT-PRP strategy was designed to potentially minimize tissue trauma, as the laser

fluence and burn intensity are lower than conventional laser (the idea was to produce a light grey/barely-visible burn). A report using this strategy was performed and compared it with the conventional and targeted strategies showing positive clinical results regarding disease activity in 70% of patients in the MT-PRP and targeted PRP, while 90% achieved it in the conventional group. [25] These newer strategies have potential benefits since they do not increase macular thickness, maintain and improve visual field sensitivities, prevent visual loss and have good rates of disease regression.

CONCLUSION

Single standard 532 single-spot PRP was equally effective to 577 multi-spot PRP regarding disease activity and BCVA at 6 weeks with shorter application time with the latter. The multi-spot laser required less time to complete the procedure with more spots delivered to compensate its lower fluency, showing similar patient tolerance.

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