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Comparison of 577-nm Multispot and Standard Single-Spot Photocoagulation for Diabetic Retinopathy

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Keywords
Diabetic retinopathy · Multispot laser · Panretinal photocoagulation · Standard photocoagulation

Abstract
Objective: To compare two different laser strategies of panretinal photocoagulation for diabetic retinopathy. ***Methods:*** Single-center, randomized study including 41 eyes treated with 577-nm multispot laser with a 20-ms pulse duration (group 1) or a 532-nm single-spot laser with a 100-ms pulse duration (group 2). The outcomes included best-corrected visual acuity (BCVA) and imaging changes at baseline, 6 and 12 months, laser parameters, and results of subjective pain analysis. ***Results:*** At 12 months, the treatments did not differ significantly in BCVA, central retinal thicknesses (CRTs), improved macular edema, vitreomacular interface changes, patient-reported pain scores, or angiographic responses. Group 1 had significantly fewer treatment sessions but used more laser spots ($p < 0.001$). ***Conclusion:*** The multispot laser required fewer applications with more spots delivered to compensate for lower fluency, showing similar patient tolerance to single-spot laser. Both groups maintained the initial visual acuities and CRTs; about 50% of cases had vitreomacular interface changes and improved macular edema, with similar angiographic improvements after 12 months.

Introduction

Panretinal photocoagulation (PRP) has remained the standard of care for advanced diabetic retinopathy (DR) since the late 1970s, when the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) [1, 2] reported their benefit in blindness prevention in the proliferative stages of the disease.

Recent studies such as the Protocol S of the Diabetic Retinopathy Clinical Research Network (DRCR.net) [3] and the CLARITY study [4] have found clear benefits supporting the use of anti-angiogenic intravitreal drugs in patients with proliferative DR (PDR). Both studies reported superior visual acuity (VA) gains, decreased visual field sensitivity loss, less progression to vitrectomy,

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and reduced macular thickness in patients treated with drugs compared to those treated with PRP. Therefore, those studies concluded that repeated anti-VEGF injections were not inferior and even superior in the CLARITY study to PRP for treating PDR. However, cost-effectiveness studies [5, 6] have reported that intravitreal ranibizumab as monotherapy for PDR incurred an estimated cost of USD 22,576 compared with USD 7,445 for those treated with PRP for only 2 years, among other calculations that concluded that ranibizumab was a non-cost-effective treatment. This is even more critical when assuming the necessity for life-long treatment [6]. Another concern is the questionable long-term efficacy of pharmacologic treatment compared with the well-known long-term efficacy of laser treatment [7, 8].

Conventional PRP has a wide array of undesirable side effects, i.e., early ones, such as patient pain/discomfort, worsening of macular edema, progression to vitreous hemorrhage, and vitrectomy; and late ones, such as confluent retinal scarring, visual field constriction, and optic disc atrophy [8]. These side effects can be minimized using less invasive treatment strategies such as short-pulse (10–20 ms) laser burns delivered through a pattern scanning method, i.e., multispot. The goal of this new laser technology is to achieve retinal photocoagulation that facilitates development of healing responses by selectively targeting the retinal pigment epithelium with minimal photoreceptor loss and subsequent cell repopulation, producing less retinal scarring [9, 10]. In addition, the 577-nm (yellow) wavelength has been used with good success and safety for macular and peripheral (PRP) treatments, due to its intrinsic physiobiologic characteristics, i.e., better penetration through media opacities, no absorbance by xanthophyll macular pigments, and excellent combined absorbance by melanin and oxyhemoglobin [11–14], where it has been reported to be a viable alternative to the 532- and 810-nm wavelengths [15, 16].

The current study is the first to compare the clinical efficacy (and noninferiority) of 577-nm multispot short-pulse PRP with the standard 532-nm single-spot PRP strategy for DR.

Material and Methods

After approval by the Federal University of São Paulo's ethics committee and adhering to all of Helsinki's statements of ethical principles for medical research involving human subjects, 41 eyes of 41 eligible patients were enrolled in this prospective, randomized, single-center clinical trial. The inclusion criteria included a diagnosis of type I or II diabetes mellitus and treatment-naïve severe non-PDR or PDR, minimal age of 18 years, and ability to understand and sign a written consent form. The exclusion criteria included a history of intravitreal injections during the previous 6 months, vitrectomy, or any ocular comorbidity.

Table 1. Baseline characteristics and laser parameters

	577-nm multispot (n = 21)	532-nm single-spot (n = 20)	p
Age, years	56.2±10.4	61.2±7.4	0.091
Right eye, n (%)	13 (61.9)	11 (55.0)	0.654
Neovascularization, n (%)	18 (85.7)	18 (90.0)	1.000*
Lens, n (%)			0.283*
Transparent	8 (44.4)	4 (22.2)	
Cataract 1+ or 2+	7 (38.9)	12 (66.7)	
Cataract 3+ or 4+	0 (0.0)	0 (0.0)	
Intraocular lens	3 (16.7)	2 (11.1)	
Hemoglobin A1c, %	8.9±1.6	8.5±2.2	0.542
BCVA, logMAR	0.2±0.2	0.5±0.4	0.003
CRT, μm	259.5±92.1	333.0±186.4	0.267†
Power, mW	451.4±138.0	356.3±136.5	0.032
Spots, n	2,504.7±377.3	1,287.6±187.6	<0.001
Sessions, n	2.7±0.6	3.9±0.7	<0.001†
Pain (score 0–10)	4.9±2.4	5.9±2.2	0.172
Photophobia (score 0–10)	5.0±3	5.6±2.1	0.477

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness. $p < 0.05$ is considered statistically significant. * The χ^2 or Fisher's exact test was performed to compare the distributions. † Student's t test or the Mann-Whitney U test was performed to compare the means.

The baseline examination included measurement of the best-corrected VA (BCVA) using a Snellen chart and later conversion to logMAR for statistical analysis, complete ophthalmologic examination, fluorescein angiography (FA) using widefield (55°), high-quality angiograms provided by scanning laser technology (HRA 2 Spectralis, Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT). OCT was performed with the Spectralis SD-OCT instrument (Heidelberg Engineering, Heidelberg, Germany). The central retinal thickness (CRT) was defined as the mean thickness of the neurosensory retina in a central 1-mm-diameter area obtained by a 20 × 20° (5.7 × 5.7 mm) macular volume cube. Structural changes were analyzed through high-definition linear scans. The eye-tracking feature of the Spectralis SD-OCT was used to evaluate the same area during the follow-up visits. All examinations were performed at baseline and 6 and 12 months after treatment.

Laser Treatment Techniques

The patients were randomized to 1 of 2 treatments. In group 1, multispot PRP was performed using the Supra Scan® 577 Photocoagulator (Quantel Medical, Cournon d'Auvergne, France)

Table 2. Main clinical outcomes over time

	Time			*p**
	baseline	6 months	12 months	
BCVA, logMAR				0.938
577-nm multispot	0.3±0.2	0.3±0.3	0.3±0.3	
532-nm single-spot	0.5±0.4	0.6±0.4	0.6±0.4	
CRT, μm				0.207
577-nm multispot	275.8±96.3	262.6±83.1	258.4±62.1	
532-nm single-spot	334.2±191.5	350.4±200.7	246.8±102.0	

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness. * *p* values were obtained through analysis of variance for comparison of temporal behavior of BCVA and CRT between the two groups. *n* = 16 and 19 for groups 1 and 2, respectively, for patients who were seen at the final 12-month visit.

with a 577-nm wavelength. The following settings were used: pulse duration 20 ms; spot size 200 μm selected on the laser panel (doubled to 400 μm at the retinal level with Super Quad 160 lens [Volk Optical, Mentor, OH, USA]); and power titrated until a grayish/white lesion was attained (moderate burn, as defined by the ETDRS). Laser was applied using the multispot method of delivery through pattern grids of 3 × 3, 4 × 4, or 5 × 5 regularly spaced spots (0.75 burn width). The number of spots delivered per session was based on surgeon discretion and respected the patient's tolerance level. The number of laser spots, maximal power used, and number of sessions required to complete the PRP were recorded (when necessary, sessions were split 2 weeks apart). In group 2, treatment was performed using the Pascal Streamline® Photocoagulator (Topcon Medical Laser Systems, Livermore, CA, USA) set in the single-spot mode and using a 532-nm wavelength. The following standard ETDRS settings were used: pulse duration 100 ms; spot size 200 μm selected on the laser panel (doubled to 400 μm at the retinal level); and power titrated until a grayish/white lesion was attained. Laser burns were applied in a standard single-spot fashion, under repeat mode, and additional sessions were scheduled 2 weeks apart until the PRP was completed.

Evaluation of Patient Tolerance

Following each laser session, the patient was asked to provide feedback on the degree of pain experienced. The method chosen was a numerical pain scale adapted from the McGill Pain Questionnaire [17]. Using this scale, pain is graded using an imaginary scale ranging from 0 to 10, where 0 equaled no pain and 10 equaled the strongest pain possible. A similar subjective scale ranging from 0 to 10 was presented regarding the degree of photophobia during the treatment. The scores were annotated without questioning or prompting by the examiner.

Statistical Analysis

For normally distributed quantitative variables, the standard values were used, i.e., the mean, standard deviation, and 95% confidence intervals, and for categorical variables, the absolute and relative frequencies (percentages). Numerical variables were compared with Student's *t* test after confirmation of data normality using the Kolmogorov-Smirnov test. In case this condition was not met, the Mann-Whitney U test was applied instead. Comparisons between categorical variables were done using the χ^2 test or, in the case of small samples, Fisher's exact test. To compare the BCVAs and CRTs over time between the groups, ANOVA with repeated measures was performed. The level of significance was 5% (p = 0.05) for all statistical tests, which were carried out with SPSS 20.0 (IBM, New York, NY, USA) and Stata 12 (StataCorp, LLC, College Station, TX, USA).

Results

Forty-one patients were included in the study and underwent PRP, 20 in group 1 and 21 in group 2. Thirty-five patients were evaluated at the final 12-month visit; 4 were lost to follow-up because of health issues or inability to attend, 1 developed a dense vitreous hemorrhage and underwent vitrectomy, and 1 died. Table 1 shows that at baseline the two groups did not differ significantly in age, eye laterality, incidence of neovascularization, lens status, or HbA_{1c}. The BCVA was better in group 1 (0.2 ± 0.2 vs. 0.5 ± 0.4; p = 0.003), while the difference in the CRT was not significant (259 ± 92 vs. 333 ± 186 μm; p = 0.267). Regarding the laser parameters, the multispot group used increased laser power (451 ± 138 vs. 356 ± 136 mW; p = 0.032), more laser spots were needed to complete the PRP (2,504 ± 377 vs. 1,287 ± 187; p < 0.001) and required fewer treatment sessions (2.7 ± 0.6 vs. 3.9 ± 0.7; p < 0.001). Patient tolerance levels measured by the subjective pain scale and perception of photophobia were not statistically different (p = 0.172 and 0.477, respectively).

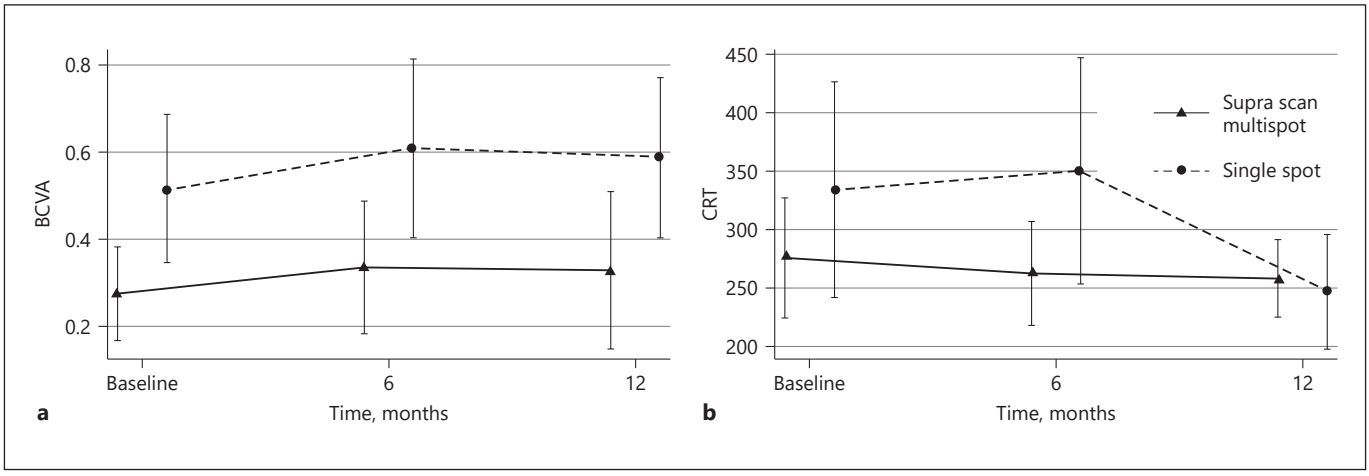

Fig. 1. Changes in the best-corrected visual acuity (BCVA) (**a**) and central retinal thickness (CRT) (**b**) over time. The dots indicate the means with 95% confidence interval bars. $n = 16$ and 19 for groups 1 and 2, respectively, for patients evaluated at the final 12-month visit. p values are shown in Table 2.

Table 3. Clinical outcomes and OCT qualitative changes at the final 12-month visit

	577-nm multispot ($n = 16$)	532-nm single-spot ($n = 19$)	p
BCVA, logMAR	0.3±0.3	0.6±0.4	0.043
CRT, μm	258.4±62.1	246.8±102	0.696
Vitreomacular interface change	9 (56.3%)	10 (52.6%)	0.830
Macular edema			0.677*
No	5 (31.3%)	3 (15.8%)	
Worsened	4 (25.0%)	6 (31.6%)	
Improved	7 (43.8%)	10 (52.6%)	

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness. Student's t test was performed to compare the means. * The χ^2 or Fisher's exact test was performed to compare the distributions. $p < 0.05$ was considered statistically significant.

Primary Endpoints

Table 2 and the associated Figure 1 show that the BCVAs remained stable in both groups throughout the study (ANOVA with repeated measures, $p = 0.938$), with no statistical effect of time ($p = 0.216$) but a significant effect of laser modality, meaning that visual acuity was better in group 1 compared to group 2 in all time periods ($p = 0.019$), even though they were already from baseline. The CRT also had a similar temporal pattern between the groups, showing stability of the macular thickness measured by OCT throughout all time periods ($p = 0.207$), revealing no statistical effect of time or laser modality ($p = 0.105$ and 0.185, respectively).

OCT Qualitative Findings

Besides the objective CRT measurement, other OCT qualitative aspects were also observed and summarized in Table 3. The vitreomacular interface was analyzed in all high-definition scans obtained in the central macular region and compared before and after treatment to determine the position of the posterior hyaloid membrane, status of vitreomacular adhesion, or development of epiretinal membranes. At the 12-month visit, about 50% of eyes in both groups ($p = 0.830$) developed some degree of vitreomacular interface change but not necessarily a complete posterior vitreous detachment (PVD). Other ways of evaluating PVD such as ultrasound or enlarged OCT

scans around the vascular arcades and the optic disc (where most traction actually happens) were not performed, so the relevance of such a finding should be taken into account carefully. The presence of macular edema in the form of intraretinal or subretinal fluid was evaluated, and a similar response was seen in the groups (p = 0.677), with improvement occurring in about 50% of eyes and worsening in about 30% of eyes by the final 12-month visit.

FA Findings

One author (J.B.-N.) performed all OCT and FA analyses, while another (R.M.P.) did the laser treatments, avoiding any type of observer bias. At the 6-month visit, in cases in which the disease was considered active (persistent neovascularization, vitreous hemorrhage, or intense capillary leakage), the patients received additional laser treatment using the same strategy according to the initial group (group 1, 68.8%; group 2, 52.6%; p = 0.332). These extra treatment sessions were not included in the data shown in Table 1. Besides neovascularization regression, we evaluated the number of microaneurysms and microhemorrhages in selected retinal quadrants and the posterior pole, capillary leakage and vascular staining in the late phases (markers of inflammatory tissue response), size of retinal nonperfusion areas, and the presence of vitreous or preretinal hemorrhages. These variables (summarized in Table 4) showed similar behavior after PRP in the two groups, with improvement rates ranging from 40 to 75% (except for vitreous hemorrhage, which was not present at baseline in most eyes), but they were not equally responsive, with neovascularization regression having a worse angiographic response (37.5 vs. 42.1% improvement rates in groups 1 and 2, respectively; p = 0.634). In fact, numerous eyes had worsening of retinal or optic disc neovascularization (31.3 vs. 15.8% in groups 1 and 2, respectively; p = 0.634).

Table 4. Fluorescein angiography changes at the final 12-month visit

	577-nm multispot (n = 16)	532-nm single-spot (n = 19)	p
MA/MH[a]			0.555
Same	3 (18.8%)	7 (36.8%)	
Worsened	1 (6.3%)	1 (5.3%)	
Improved	12 (75%)	11 (57.9%)	
Capillary leakage[b]			0.891
Same	5 (31.3%)	8 (42.1%)	
Worsened	2 (12.5%)	2 (10.5%)	
Improved	9 (56.3%)	9 (47.4%)	
New vessels[c]			0.634
Same	5 (31.3%)	8 (42.1%)	
Worsened	5 (31.3%)	3 (15.8%)	
Improved	6 (37.5%)	8 (42.1%)	
Nonperfusion areas[d]			0.277
Same	4 (25.0%)	9 (47.4%)	
Worsened	3 (18.8%)	1 (5.3%)	
Improved	9 (56.3%)	9 (47.4%)	
Vascular staining[e]			1.000
Same	5 (31.3%)	7 (36.8%)	
Worsened	1 (6.3%)	1 (5.3%)	
Improved	10 (62.5%)	11 (57.9%)	
Vitreous hemorrhage[f]			0.795
Same	10 (62.5%)	12 (63.2%)	
Worsened	3 (18.8%)	5 (26.3%)	
Improved	3 (18.8%)	2 (10.5%)	

MA, microaneurysm; MH, microhemorrhage. $p < 0.05$ with Fisher's exact test was considered statistically significant. [a] Number of microaneurysms and microhemorrhages were counted manually in corresponding fields (wherever they were more significantly present) in angiograms obtained at baseline and 12 months. [b] Capillary leakage was observed in the late-phases angiograms in the macular area and subjectively compared regarding the amount of blurring of retinal details due to fluorescein leakage through the capillary vessels. [c] New vessels were observed and compared regarding the initial size of the neovascular lesions in the initial and late phases of the angiograms, considering the total area of leakage around them. [d] Nonperfusion areas, defined as hypofluorescent areas due to capillary nonperfusion, were measured manually and compared. [e] Vascular staining, defined as hyperfluorescence of medium and small vessels in the late phases of the angiogram, due to staining or leakage along the vessel walls. [f] Vitreous hemorrhage (or preretinal hemorrhage) could be present at baseline and improve over time (improved), or could be absent at baseline and develop over time (worsened). When it was not present during any time period, it was labeled as "same."

Discussion

Considering the classic studies [1, 2] and recent cost-effectiveness studies [5, 6], PRP remains the standard cost-effective treatment of choice for PDR, reducing the risk of severe visual loss over the long term by 50% [1]. New laser techniques have recently emerged [9, 18, 19] to decrease the side effects associated with PRP. Among these, the 577-nm multispot laser combines the benefits of yellow wavelength [20, 21] with the benefits of shorter pulse duration and automated patterns of delivery (predictable and adjustable burn spacing, less thermal diffusion to the choroid leading to less pain, and faster treatments, among others) [22].

Palanker et al. [23] pointed out that while the exact mechanisms of laser treatment are unknown, the following factors are important: ablation of a fraction of highly metabolically active photoreceptor cells to decrease retinal oxygen consumption, creation of photoreceptor-free glial "windows" to improve oxygenation and metabolic transport, and thermal stimulation of adjacent retinal pigment epithelium cells. The clinical effect of these mechanisms is likely to be proportional to the total treated area. Thus, after performing a series of measurements of burn sizes using various laser parameters, the authors concluded that full-scatter PRP using short-pulse (20 ms) light burns must deliver 2,111 spots to be equivalent to standard PRP with 100-ms pulse duration delivering 1,093 spots [23]. In the current study, the number of laser spots was doubled in group 1 compared to group 2, which reinforced this recommendation. The number of laser sessions necessary to complete the treatment was also smaller with the multispot laser. Using this strategy, because of better patient tolerance and a faster delivery system, more spots can be applied during the same time frame (927 burns/session in group 1; 330 burns/session in group 2) (data not shown), improving patient tolerance and adherence to treatment.

Patient discomfort and pain during PRP are critical issues, possibly leading to low patient adherence and sometimes undertreatment. Thermal diffusion of laser energy to the choroid stimulates pain receptors and is related with larger pulse durations and laser wavelengths with deeper penetration to the choroid, while less painful approaches have been described with shorter pulse durations and 532- and 577-nm wavelengths [24–28]. This has been studied in clinical trials mainly using the visual analog scale [29] or a numerical pain scale adapted from the McGill Pain Questionnaire [17]. Despite all these validated methods of pain assessment, patients' self-reported information will always be prone to subjective and social-educational differences between subjects, which may explain the lack of statistical significance in the present study regarding this outcome.

The two treatments were equivalent in terms of visual acuity stability and improvement of macular edema (of 50% in both groups), while the mean CRT also remained stable and tended toward improvement in group 2, suggesting a beneficial effect of PRP for controlling macular edema and visual stability over the long term, probably by decreasing the retinal VEGF and other proinflammatory cytokines in the photocoagulated retina and vitreous cavity. The incidence of severe visual loss at the 12-month follow-up was low in this study, with only 1 patient in group 1 developing severe vitreous hemorrhage in the 6th month and necessitating vitrectomy.

We also evaluated the status of vitreous adhesion through high-definition linear OCT scans on the central macular region at baseline and after PRP. Sebag and Nguyen-Cuu [30] reported that the risk of PDR is lower in eyes with PVD than in eyes with an attached vitreous, a well-established finding [31, 32]. It was hypothesized previously that PRP might provide therapeutic benefit by inducing a PVD, and studies have shown that the incidence of PVD was greater in patients treated with PRP than in those who did not, supporting this hypothesis. In the current study, 56.3% of eyes in group 1 and 52.6% in group 2 developed some degree of change in the vitreomacular interface at the final 12-month visit, ranging from a mild change in the position of the posterior hyaloid to a partial PVD seen on the OCT (ultrasound or extended OCT scans in the peripapillary area or around the vascular arcades were not performed). This result indicated that the interaction of laser treatment with posterior vitreous adhesion is not dependent on the laser strategy or parameters used.

Finally, we conducted a detailed analysis of the FA outcomes after laser treatment at the 6- and 12-month visits, using widefield (55°), high-quality fluorescein angiograms provided by scanning laser technology. Figure 2 depicts the clear differences between the laser burns between the two PRP strategies, with the single-spot burns being more intense, larger in size and sometimes confluent, which might affect visual fields while not improving the overall regression of neovascularization or reducing progression to vitreous hemorrhage and vitrectomy. Besides neovascularization regression, which is the most common feature observed and analyzed in similar studies and clinical practice, we decided to evaluate other angiographic markers such as microaneurysm and microhemorrhage count, capillary leakage and vascular staining in the late phases (markers of inflammatory tissue response), size of retinal nonperfusion areas, and the presence of vitreous or preretinal hemorrhages. A case with very good outcome is presented in Figure 3, where an improvement of all these angiographic parameters is well observed.

In general, regression of new vessels was seen less frequently than the other parameters. Besides, numerous eyes had worsening of retinal or optic disc neovascularization (31.3 vs. 15.8% in groups 1 and 2, respectively; $p = 0.634$), and this was seen more frequently in severely ischemic retinas at baseline, independent of the treatment strategy, a finding already described by the DRCR.net group [33]. In that study, the factors associated with

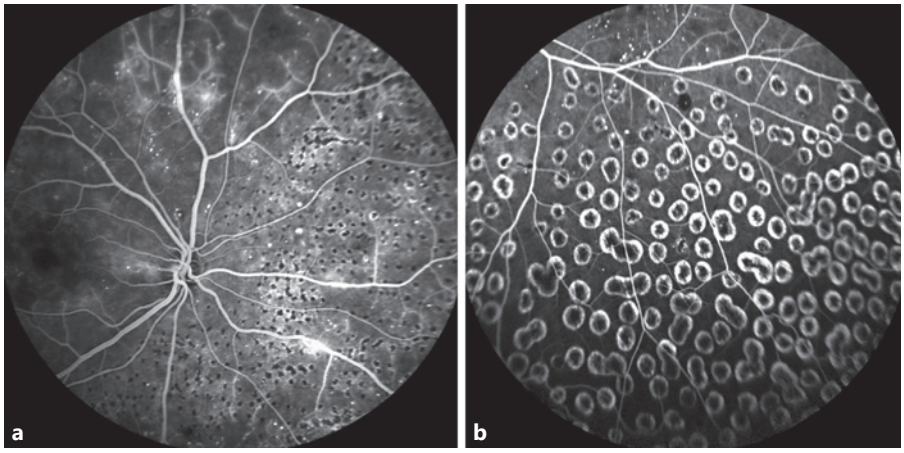

Fig. 2. Examples of laser burn scarring comparing the two panretinal photocoagulation (PRP) strategies. Fluorescein angiograms (from the Spectralis Scanning Laser Angiography® instrument, Heidelberg, Germany) from eyes treated with the two PRP strategies evaluated in the present study. **a** The image shows an eye treated with 577-nm multispot PRP and shows small, regularly spaced, and mostly nonconfluent laser scars due to the short pulse duration and pattern delivery system of the laser burns. **b** The image shows an eye treated with the standard single-spot PRP (100-ms pulse duration) and shows larger, irregularly spaced, and sometimes confluent laser scars.

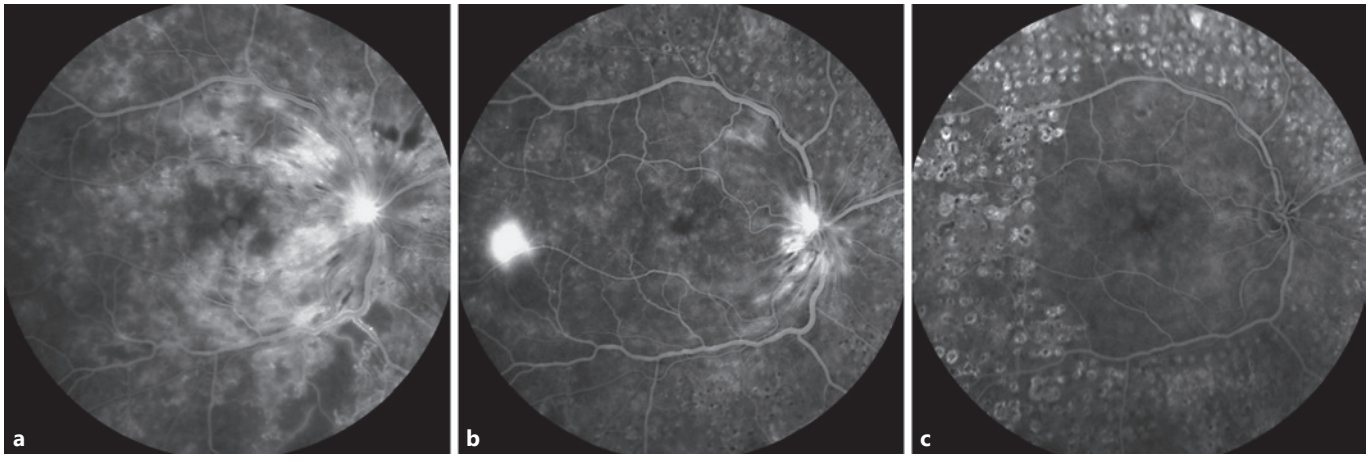

Fig. 3. Angiographic responses to panretinal photocoagulation (PRP) over time. Baseline (**a**), 6-month (**b**), and 12-month (**c**) fluorescein angiograms of an eye treated with 577-nm multispot PRP. The images show an initial picture of proliferative diabetic retinopathy with considerable vascular leakage in the macular area, a petalloid pattern of macular edema, nonperfusion areas, staining of the walls of medium-sized vessels in the temporal inferior quadrant, and optic disc neovascularization. Over time, a significant improvement is seen, with a complete remission of the inflammatory and neovascular changes at the final 12-month visit.

worsening of retinopathy after PRP included worse baseline levels of disease severity (ETDRS scale), eyes without center-involved macular edema not treated with ranibizumab, and eyes receiving pattern scan laser versus single-spot laser (regardless of the number of laser spots or number of sessions needed to complete PRP), a finding distinct from the one described in the present study. Such difference might result from an increased number of laser spots in our multispot group (2,504 ± 377) compared to that described by the DRCR.net protocol (1,800–2,400, with a median of 2,190, $n = 28$) or by Chappelow et al. [18] in a previous paper with even less burns in the multispot group (1,438 ± 67). These observations reinforce the importance of expanding the total treated area by increasing the number of laser spots with this PRP strategy for maintaining its efficacy. Protocol S of the DRCR.net [3] and CLARITY [4] studies were not designed to compare single-spot and multispot PRP strategies regarding their efficacy, describing only the percentages of patients that received one or the other treatment. So, the relevance of such a topic is still high and larger prospective studies are needed.

In conclusion, 577-nm multispot PRP was equally effective and not inferior to standard 532-nm single-spot PRP regarding BCVA stability and regression of DR, measured by angiographic responses. The OCT response

was also similar, with the macular edema improving in an average of 50% of eyes and induction of some degree of PVD also in 50% of eyes 12 months after treatment. Patient tolerance was similar between the two strategies. The fewer laser sessions needed to complete the treatment was a clear advantage of the multispot strategy, which in clinical practice may result in superior patient adherence.

Disclosure Statement

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References

1 The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophthalmology. 1981 Jul;88(7):583–600.
2 Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology. 1991 May;98(5 Suppl):766–85.
3 Diabetic Retinopathy Clinical Research Network. Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK, Beck RW: Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA. 2015;314:2137–46.
4 Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al.; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet. 2017 Jun;389(10085):2193–203.
5 Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR; Diabetic Retinopathy Clinical Research Network. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy. JAMA Ophthalmol. 2017 Jun;135(6):576–84.
6 Lin J, Chang JS, Smiddy WE. Cost evaluation of panretinal photocoagulation versus intravitreal ranibizumab for proliferative diabetic retinopathy. Ophthalmology. 2016 Sep;123(9):1912–8.
7 Li X, Zarbin MA, Bhagat N. Anti-vascular endothelial growth factor injections: the new standard of care in proliferative diabetic retinopathy? Dev Ophthalmol. 2017;60:131–42.
8 Silva PA, Cavallerano JD, Sun JK, Blodi BA, Davis MD, Aiello LM, et al. Proliferative Diabetic Retinopathy. In: Ryan SJ, Schachat A, Wilkinson C, Hinton D, Sadda S, Wiedemann P, editors. Retina Volume Two: Medical Retina. 5th ed. Atlanta (GA): Elsevier Saunders; 2013. p. 969–1000.
9 Muqit MM, Marcellino GR, Henson DB, Young LB, Patton N, Charles SJ, et al. Single-session vs multiple-session pattern scanning laser panretinal photocoagulation in proliferative diabetic retinopathy: The Manchester Pascal Study. Arch Ophthalmol. 2010 May;128(5):525–33.
10 Muqit MM, Gray JC, Marcellino GR, Henson DB, Young LB, Patton N, et al. In vivo laser-tissue interactions and healing responses from 20- vs 100-millisecond pulse Pascal photocoagulation burns. Arch Ophthalmol. 2010 Apr;128(4):448–55.
11 Hirano T, Iesato Y, Imai A, Toriyama Y, Kikushima W, Murata T. Effect of Laser wavelength on delivering appropriate laser burns through the opaque lens using a pattern scan laser. Ophthalmic Res. 2014;51(4):204–9.
12 Yadav NK, Jayadev C, Mohan A, Vijayan P, Battu R, Dabir S, et al.; Medscape. Subthreshold micropulse yellow laser (577 nm) in chronic central serous chorioretinopathy: safety profile and treatment outcome. Eye (Lond). 2015 Feb;29(2):258–64.
13 Kim JY, Park HS, Kim SY. Short-term efficacy of subthreshold micropulse yellow laser (577-nm) photocoagulation for chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2015 Dec;253(12):2129–35.
14 Kwon YH, Lee DK, Kwon OW. The short-term efficacy of subthreshold Micropulse yellow (577-nm) laser photocoagulation for diabetic macular edema. Korean J Ophthalmol. 2014 Oct;28(5):379–85.
15 Sramek CK, Leung LS, Paulus YM, Palanker DV. Therapeutic window of retinal photocoagulation with green (532-nm) and yellow (577-nm) lasers. Ophthalmic Surg Lasers Imaging. 2012 Jul;43(4):341–7.
16 Vujosevic S, Martini F, Longhin E, Convento E, Cavarzeran F, Midena E. Subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser in center-involving diabetic macular edema. Retina. 2015;35(8):1594–603.
17 Melzack R, Katz J. Pain Measurement in Adult Patients. In McMahon SB, editor. Wall and Melzack's textbook of pain. 6th ed. Atlanta (GA): Elsevier Saunders; 2013. p. 301–14.
18 Chappelow AV, Tan K, Waheed NK, Kaiser PK. Panretinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. Am J Ophthalmol. 2012 Jan;153(1):137–42.e2.
19 Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. Retina. 2010 Mar;30(3):452–8.
20 Mainster MA. Wavelength selection in macular photocoagulation. Tissue optics, thermal effects, and laser systems. Ophthalmology. 1986 Jul;93(7):952–8.
21 Vogel M, Schäfer FP, Stuke M, Müller K, Theuring S, Morawietz A. Animal experiments for the determination of an optimal wavelength for retinal coagulations. Graefes Arch Clin Exp Ophthalmol. 1989;227(3):277–80.
22 Blumenkranz MS, Yellachich D, Andersen DE, Wiltberger MW, Mordaunt D, Marcellino GR, et al. Semiautomated patterned scanning laser for retinal photocoagulation. Retina. 2006 Mar;26(3):370–6.
23 Palanker D, Lavinsky D, Blumenkranz MS, Marcellino G. The impact of pulse duration and burn grade on size of retinal photocoagulation lesion: implications for pattern density. Retina. 2011 Sep;31(8):1664–9.
24 Friberg TR, Venkatesh S. Alteration of pulse configuration affects the pain response during diode laser photocoagulation. Lasers Surg Med. 1995;16(4):380–3.
25 Al-Hussainy S, Dodson PM, Gibson JM. Pain response and follow-up of patients undergoing panretinal laser photocoagulation with reduced exposure times. Eye (Lond). 2008 Jan;22(1):96–9.

26 Muqit MM, Marcellino GR, Gray JC, McLauchlan R, Henson DB, Young LB, et al. Pain responses of Pascal 20 ms multi-spot and 100 ms single-spot panretinal photocoagulation: Manchester Pascal Study, MAPASS report 2. Br J Ophthalmol. 2010 Nov;94(11):1493–8.
27 Mirshahi A, Lashay A, Roozbahani M, Fard MA, Molaie S, Mireshghi M, et al. Pain score of patients undergoing single spot, short pulse laser versus conventional laser for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2013 Apr;251(4):1103–7.
28 González-Saldivar G, Rojas-Juárez S, Espinosa-Soto I, Sánchez-Ramos J, Jaurieta-Hinojosa N, Ramírez-Estudillo A. Single-spot yellow laser versus conventional green laser on panretinal photocoagulation: patient pain scores and preferences. Ophthalmic Surg Lasers Imaging Retina. 2017 Nov;48(11):902–5.
29 Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med. 2001 Dec;8(12):1153–7.
30 Sebag J, Nguyen-Cuu J. The effects of vitreous on proliferative diabetic retinopathy and the response to pan retinal photocoagulation. Graefes Arch Clin Exp Ophthalmol. 2017 Feb;255(2):421–2.
31 Akiba J, Arzabe CW, Trempe CL. Posterior vitreous detachment and neovascularization in diabetic retinopathy. Ophthalmology. 1990 Jul;97(7):889–91.
32 Sebag J, Buzney SM, Belyea DA, Kado M, McMeel JW, Trempe CL. Posterior vitreous detachment following panretinal laser photocoagulation. Graefes Arch Clin Exp Ophthalmol. 1990;228(1):5–8.
33 Bressler SB, Beaulieu WT, Glassman AR, Gross JG, Jampol LM, Melia M, et al.; Diabetic Retinopathy Clinical Research Network. Factors associated with worsening proliferative diabetic retinopathy in eyes treated with panretinal photocoagulation or ranibizumab. Ophthalmology. 2017 Apr;124(4):431–9.