Effect of pattern scanning laser on macular thickness in diabetic retinopathy

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Abstract

Purpose: This study investigates the effect of pattern scanning laser (PASCAL) panretinal photocoagulation (PRP) on central macular thickness (CMT) and visual acuity (VA) in patients with proliferative diabetic retinopathy (PDR).

Methods: This retrospective non-randomized comparative case series included 262 eyes (163 with macular edema) of 177 patients with PDR. Treatment was PRP alone (137), PRP + anti-vascular endothelial growth factor (VEGF) (69), PRP + focal laser (28), or all three (89). CMT and central macular volume 3 and 6 mm from fovea were analyzed before and 1, 3, and 6 months after PRP. Spot number was plotted against CMT, and linear regression analysis was performed.

Results: For each treatment group and time point, there was a non-significant relationship between spot number and CMT. In eyes receiving all three treatment modalities, a significant negative relationship was found between spot number and 3-mm volume at 6 months ($p = 0.04$) and 6-mm volume at 1 month ($p = 0.002$) and 6 months ($p = 0.011$). There was no significant change in VA in any treatment group at the 6-month time point.

Conclusion: PASCAL PRP ± focal laser or anti-VEGF was not associated with increased development of macular edema or change in VA. PASCAL PRP with focal laser and anti-VEGF may result in a decrease in macular edema.

Keywords: central macular thickness, diabetic macular edema, macular volume, pan retinal photocoagulation, pattern scan laser

Introduction

Since the 1985 Early Treatment Diabetic Retinopathy Study (ETDRS), photocoagulation therapy has become a staple treatment for eyes with severe diabetic retinopathy, producing significant reductions in vision loss and neovascularization.[1,2] Like any treatment, it is associated with certain risks. The most common cause of decreased visual acuity (VA) in eyes treated with panretinal photocoagulation (PRP) is macular edema.[3] As many as 11% of patients have a permanent decrease in VA of at least one line after argon laser PRP.[4]

The diabetic retinopathy study (DRS) and ETDRS evaluated the use of traditional single-shot argon laser photocoagulation in diabetic retinopathy.[5,6] In contrast to the single-shot laser, the PASCAL laser was designed to allow delivery of multiple spots simultaneously in a pattern array and is meant to allow for decreased pulse duration (10–20 ms vs 100–200 ms with traditional laser) and lower cumulative energies.[7] As it is a newer modality, few studies have looked at macular edema rates in PASCAL PRP specifically. One such prospective study of 38 eyes, compared conventional PRP plus ranibizumab with PASCAL PRP plus ranibizumab and found that PASCAL PRP plus ranibizumab had a statistically significant decrease in central subfield macular thickness as measured using optical coherence tomography (OCT), while conventional single-shot PRP did not.[8] However, this study did not

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examine PRP as a single treatment modality. Another small study of 28 eyes showed a reduction in central retinal thickness in eyes with proliferative diabetic retinopathy (PDR) after treatment with Optos-guided PASCAL retinal photocoagulation.[9] These studies provide evidence that PASCAL PRP may cause less macular edema than conventional single-shot PRP; however, these small studies need further validation.

The purpose of this study was to retrospectively evaluate the influence of PASCAL PRP on macular edema and VA in a larger population of patients with PDR.

Methods

This study was a retrospective non-randomized comparative case series from June 2011 to June 2017 including 262 eyes of 177 patients with PDR, 163 of which eyes had pre-existing macular edema identified on clinical exam. Patients with macular fibrovascular membrane, tractional retinal detachment, prior history of vitrectomy, retinal vein occlusion, or sickle cell retinopathy were excluded. logMAR VA prior to treatment ranged from 0.00 to 3.00.

Eyes were included in the study when treated with PASCAL frequency doubled Nd: 532-nm wavelength pattern scan laser, a set spot size of 200 μm and pulse duration of 20–40 ms. Thus, spot number served as an indicator of the total energy delivered to each eye. Eyes included received either PASCAL PRP alone, PASCAL PRP and anti-vascular endothelial growth factor (VEGF) injection, PASCAL PRP and focal laser, or all of the above. Choice of anti-VEGF agent was variable. While the majority received bevacizumab, a small minority received ranibizumab (17 eyes). The treatment plan was not pre-defined before PASCAL PRP.

Data were organized into separate groups according to the treatment received. Spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) images from 1, 3, and 6 months post-laser treatment (as available in the electronic medical record) were evaluated for central macular thickness (CMT), central macular volume at 3 and 6 mm from the foveal center. For each eye at each time point, CMT and central macular volume were calculated as a percentage of pre-laser baseline. Not every patient presented for measurement at every time point.

We defined significant (moderate or worse) loss of best-corrected vision as decreased vision from baseline ⩾3 lines on the ETDRS chart. Significant macular thickness change was defined as an increase in macular thickness change of more than 20% from baseline.

Statistical analysis

Data for each treatment was analyzed separately. For each data set, spot number was plotted against macular thickness (or volume) relative to baseline at a particular time point. Thus, linear regression analysis yielded a slope indicative of the relative magnitude of change in CMT produced by a given amount of PASCAL laser treatment (indicated by spot number).

A *t*-statistic was calculated from the slope of the regression line and the standard error of the slope of the regression line. This *t*-statistic was then used to produce a *p* value using a two-tailed *t*-test. The level of significance was $p < 0.05$. A $p > 0.05$ was taken to indicate *no significant relationship* between amount of laser and CMT or volume.

Best-corrected visual acuity (BCVA) at distance was also evaluated using standard manual refraction before and after treatment at 1 and 6 months and converted to logMAR scale. A two-sampled *t*-test assuming unequal variances was used to compare mean BCVA before and after treatment, with significant *p* of <0.05.

Analysis of variance (ANOVA) testing was used to compare the percentage of patients with significant vision loss and significant CMT changes between the three treatment groups.

Results

Two hundred sixty-two eyes in 177 patients with PDR with and without pre-existing macular edema over a 6-year period were included. Patient's average age was 51.9 years old and mean hemoglobin A1c was 8.8. At the time of PRP, 76% of treated eyes were phakic. Thirty-nine percent of the 452 PRP sessions performed were first time treatments. The average spot number was 1395.

Effect of PASCAL PRP alone on CMT

In the 137 eyes receiving PASCAL PRP alone, the average relationship between spot number

Table 1. Slope of linear regression line relating number of spots to baseline (BL)-adjusted central macular thickness (CMT).

	1 month			3 months			6 months		
	% BL CMT	*p*	*n*	% BL CMT	*p*	*n*	% BL CMT	*p*	*n*
PRP alone	$2.63 \times 10^{-5} \pm 6.66 \times 10^{-5}$	0.445	28	$8.58 \times 10^{-5} \pm 1.45 \times 10^{-4}$	0.253	49	$6.00 \times 10^{-5} \pm 8.35 \times 10^{-5}$	0.168	36
PRP + injection	$-2.87 \times 10^{-6} \pm 2.89 \times 10^{-5}$	0.846	78	$3.97 \times 10^{-6} \pm 4.09 \times 10^{-5}$	0.85	78	$-1.48 \times 10^{-5} \pm 7.67 \times 10^{-5}$	0.707	69
PRP + focal laser	$2.35 \times 10^{-5} \pm 5.55 \times 10^{-5}$	0.454	6	$1.01 \times 10^{-5} \pm 7.18 \times 10^{-5}$	0.789	11	$-1.63 \times 10^{-6} \pm 1.18 \times 10^{-4}$	0.979	7
PRP + focal + injection	$-1.56 \times 10^{-5} \pm 2.70 \times 10^{-5}$	0.265	34	$5.17 \times 10^{-6} \pm 4.53 \times 10^{-5}$	0.824	38	$3.13 \times 10^{-5} \pm 5.97 \times 10^{-5}$	0.311	42

BL, baseline; CMT, central macular thickness; PRP, panretinal photocoagulation.

and % baseline (BL) CMT (defined as the slope of the linear regression line between the two) at 1, 3, and 6 months were found to be $2.63 \times 10^{-5} \pm 6.66 \times 10^{-5}$ ($p = 0.445$), $8.58 \times 10^{-5} \pm 1.45 \times 10^{-4}$ ($p = 0.253$), and $6.00 \times 10^{-5} \pm 8.35 \times 10^{-5}$ ($p = 0.168$), respectively (see Table 1). In eyes receiving PASCAL PRP alone, no significant correlation was found between spot number and CMT in the 6-month post-operative period.

Effect of PASCAL PRP and anti-VEGF injection on CMT

In the 69 eyes receiving PASCAL PRP and anti-VEGF injection, the average relationship between spot number and % BL CMT at 1, 3, and 6 months were found to be $-2.87 \times 10^{-6} \pm 2.89 \times 10^{-5}$ ($p = 0.846$), $3.97 \times 10^{-6} \pm 4.09 \times 10^{-5}$ ($p = 0.850$), and $-1.48 \times 10^{-5} \pm 7.67 \times 10^{-5}$ ($p = 0.707$), respectively (see Table 1). In eyes receiving PASCAL PRP and anti-VEGF injection, no significant correlation was found between spot number and CMT in the 6-month post-operative period.

Effect of PASCAL PRP and focal laser on CMT

In the 28 eyes receiving PASCAL PRP and focal macular laser, the average relationship between spot number and % BL CMT at 1, 3, and 6 months were found to be $2.35 \times 10^{-5} \pm 5.55 \times 10^{-5}$ ($p = 0.454$), $1.01 \times 10^{-5} \pm 7.18 \times 10^{-5}$ ($p = 0.789$), and $-1.63 \times 10^{-6} \pm 1.18 \times 10^{-4}$ ($p = 0.979$), respectively (see Table 1). In eyes receiving PASCAL PRP and focal laser, no significant

correlation was found between spot number and CMT in the 6-month post-operative period.

Effect of PASCAL PRP, anti-VEGF injection, and focal laser on CMT

In the 89 eyes receiving PASCAL PRP, anti-VEGF injection, and focal laser, the average relationship between spot number and % BL CMT at 1, 3, and 6 months were found to be $-1.56 \times 10^{-5} \pm 2.70 \times 10^{-5}$ ($p = 0.265$), $5.17 \times 10^{-6} \pm 4.53 \times 10^{-5}$ ($p = 0.824$), and $-3.13 \times 10^{-5} \pm 5.97 \times 10^{-5}$ ($p = 0.311$), respectively (see Table 1). In eyes receiving PASCAL PRP, anti-VEGF injection, and focal laser, no significant correlation was found between spot number and CMT in the 6-month post-operative period.

The change in CMT over 6 months is graphically displayed in Figure 1 and shows no significant change in CMT after PRP as compared to baseline (see Figure 1).

Percentage of patients with significant CMT changes

Significant macular thickness changes in the PRP group were significant in 5.2%, 5.6%, and 8.7% of patients at months 1, 3, and 6, respectively. In the focal laser with injection group significant increased CMT changes were seen in 4.8%, 3.8%, and 11.5% at months 1, 3, and 6, respectively. In the injection only group, these changes were 14%, 18%, and 7% at months 1, 3, and 6, respectively. There were no significant changes
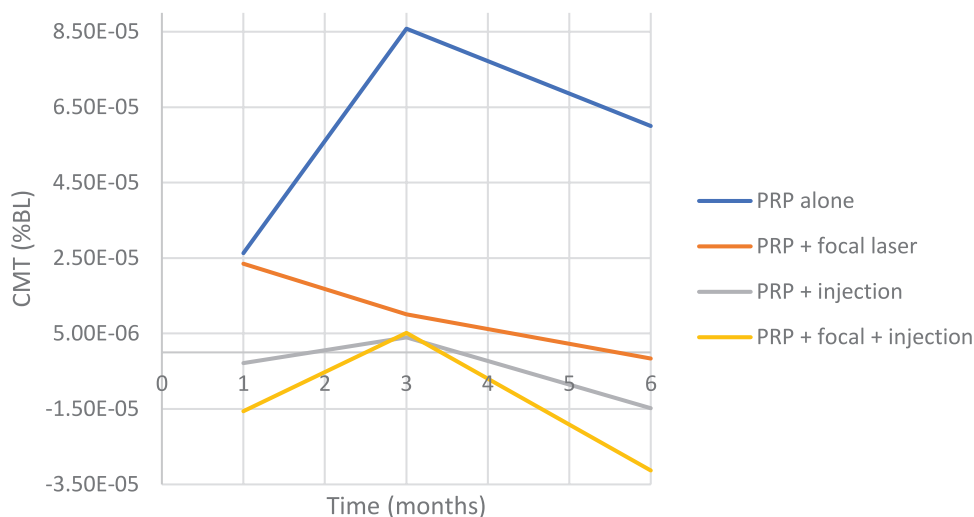
Figure 1. Change in central macular thickness (CMT) relative to baseline after PRP.

Table 2. Comparison of percentage of patients with significant central macular thickness changes (CMT > 20% from baseline (BL)) and *p* values (ANOVA) in the PRP, focal laser + injection, and injection only groups at months 1, 3, and 6 post-procedure.

Groups	PRP	Focal laser + injection	Injection only	*p* value between groups
CMT BL				
CMT 1 month	5.26	4.76	14	0.25
CMT 3 months	5.55	3.84	18	0.39
CMT 6 months	8.69	11.53	7.4	0.58

ANOVA, analysis of variance; BL, baseline; CMT, central macular thickness; PRP, panretinal photocoagulation.

between different groups at months 1, 3, and 6, respectively ($p = 0.25$, 0.39, and 0.58; Table 2).

Effect of PASCAL PRP alone on central macular volume at 3 mm

In the 137 eyes receiving PASCAL PRP alone, the average relationship between spot number and baseline-adjusted central macular volume at 3 mm (% BL 3 mm vol) at 1, 3, and 6 months were found to be $1.23 \times 10^{-5} \pm 4.49 \times 10^{-5}$ ($p = 0.596$), $3.38 \times 10^{-5} \pm 4.10 \times 10^{-5}$ ($p = 0.114$), and $2.98 \times 10^{-5} \pm 4.58 \times 10^{-5}$ ($p = 0.211$), respectively (Table 3). In eyes receiving PASCAL PRP alone, no significant correlation was found between spot number and 3 mm macular volume in the 6-month post-operative period.

Effect of PASCAL PRP and anti-VEGF injection on central macular volume at 3 mm

In the 69 eyes receiving PASCAL PRP and anti-VEGF injection, the average relationship between spot number and % BL 3-mm vol at 1, 3, and 6 months were found to be $-3.32 \times 10^{-6} \pm 1.72 \times 10^{-5}$ ($p = 0.706$), $-7.57 \times 10^{-6} \pm 2.27 \times 10^{-5}$ ($p = 0.516$), and $-1.37 \times 10^{-5} \pm 3.90 \times 10^{-5}$ ($p = 0.493$), respectively (Table 3). In eyes receiving PASCAL PRP and anti-VEGF injection, no significant correlation was found between spot number and central macular volume at 3 mm in the 6-month post-operative period.

Effect of PASCAL PRP and focal laser on central macular volume at 3 mm

In the 28 eyes receiving PASCAL PRP and focal macular laser, the average relationship between spot number and % BL 3-mm vol at 1, 3, and 6 months were found to be $2.68 \times 10^{-5} \pm 3.01 \times 10^{-5}$ ($p = 0.156$), $1.61 \times 10^{-5} \pm 3.15 \times 10^{-5}$ ($p = 0.416$), and $4.59 \times 10^{-5} \pm 4.72 \times 10^{-5}$ ($p = 0.115$), respectively (Table 3). In eyes receiving PASCAL PRP and focal laser, no significant correlation was found between spot number and central macular volume at 3 mm in the 6-month post-operative period.

Effect of PASCAL PRP, anti-VEGF injection, and focal laser on central macular volume at 3 mm

In the 89 eyes receiving PASCAL PRP, anti-VEGF injection, the average relationship between spot number and % BL 3-mm vol at 1, 3, and 6 months

Table 3. Slope of linear regression line relating number of spots to baseline (BL)-adjusted 3-mm macular volume.

	1 month			3 months			6 months		
	% BL 3-mm vol	*p*	*n*	% BL 3-mm vol	*p*	*n*	% BL 3 mm vol	*p*	*n*
PRP alone	1.23×10^{-5} $\pm 4.49 \times 10^{-5}$	0.596	28	3.38×10^{-5} $\pm 4.10 \times 10^{-5}$	0.114	48	2.98×10^{-5} $\pm 4.58 \times 10^{-5}$	0.211	35
PRP + injection	3.32×10^{-6} $\pm 1.72 \times 10^{-5}$	0.706	77	-7.57×10^{-6} $\pm 2.27 \times 10^{-5}$	0.516	77	-1.37×10^{-5} $\pm 3.90 \times 10^{-5}$	0.493	69
PRP + focal laser	2.68×10^{-5} $\pm 3.01 \times 10^{-5}$	0.156	6	1.61×10^{-5} $\pm 3.15 \times 10^{-5}$	0.416	10	4.59×10^{-5} $\pm 4.72 \times 10^{-5}$	0.115	7
PRP + focal + injection	-1.56×10^{-5} $\pm 2.07 \times 10^{-5}$	0.149	33	2.92×10^{-6} $\pm 2.76 \times 10^{-5}$	0.837	37	-3.94×10^{-5} $\pm 3.65 \times 10^{-5}$	0.04	41

BL, baseline; PRP, panretinal photocoagulation.

were found to be $-1.56 \times 10^{-5} \pm 2.07 \times 10^{-5}$ ($p = 0.149$), $2.92 \times 10^{-6} \pm 2.76 \times 10^{-5}$ ($p = 0.837$), and $-3.94 \times 10^{-5} \pm 3.65 \times 10^{-5}$ ($p = 0.0405$), respectively (Table 3). In eyes receiving PASCAL PRP, anti-VEGF injection, and focal laser, a *significant* negative correlation was found between spot number and central macular volume at 3 mm only at the 6-month time point.

The change in central macular volume at 3 mm over a 6-month period is displayed in Figure 2 and reveals the decline in macular volume in the combined group (PRP + focal laser + injection) at 6 months compared to baseline (Figure 2).

Effect of PASCAL PRP alone on central macular volume at 6 mm
In the 137 eyes receiving PASCAL PRP alone, the average relationship between spot number and baseline-adjusted central macular volume at 6 mm (% BL 6 mm vol) at 1, 3, and 6 months were found to be $2.31 \times 10^{-5} \pm 2.92 \times 10^{-5}$ ($p = 0.134$), $2.44 \times 10^{-5} \pm 3.79 \times 10^{-5}$ ($p = 0.214$), and $6.03 \times 10^{-6} \pm 2.78 \times 10^{-5}$ ($p = 0.673$), respectively (Table 4). In eyes receiving PASCAL PRP alone, no significant correlation was found between spot number and 6-mm macular volume in the 6-month post-operative period.

Effect of PASCAL PRP and anti-VEGF injection on central macular volume at 6 mm
In the 69 eyes receiving PASCAL PRP and anti-VEGF injection, the average relationship between spot number and % BL 6-mm vol at 1, 3, and 6 months were found to be $-3.89 \times 10^{-6} \pm 1.36 \times 10^{-5}$

($p = 0.578$), $-4.71 \times 10^{-6} \pm 2.56 \times 10^{-5}$ ($p = 0.719$), and $-6.54 \times 10^{-6} \pm 2.71 \times 10^{-5}$ ($p = 0.638$) (Table 4). In eyes receiving PASCAL PRP and anti-VEGF injection, no significant correlation was found between spot number and central macular volume at 6 mm in the 6-month post-operative period.

Effect of PASCAL PRP and focal laser on central macular volume at 6 mm
In the 28 eyes receiving PASCAL PRP and focal macular laser, the average relationship between spot number and % BL 6-mm vol at 1, 3, and 6 months were found to be $3.02 \times 10^{-5} \pm 1.41 \times 10^{-5}$ ($p = 0.0138$), $1.59 \times 10^{-5} \pm 3.78 \times 10^{-5}$ ($p = 0.433$), and $4.01 \times 10^{-5} \pm 4.36 \times 10^{-5}$ ($p = 0.131$), respectively (Table 4). In eyes receiving PASCAL PRP and focal laser, a significant positive correlation was found between spot number and central macular volume at 6 mm only at 1-month post-treatment.

Effect of PASCAL PRP, anti-VEGF injection, and focal laser on central macular volume at 6 mm
In the 89 eyes receiving PASCAL PRP, anti-VEGF injection, and focal laser, the average relationship between spot number and % BL 6-mm vol at 1, 3, and 6 months were found to be $-3.33 \times 10^{-5} \pm 1.97 \times 10^{-5}$ ($p = 0.00236$), $-4.48 \times 10^{-6} \pm 2.41 \times 10^{-5}$ ($p = 0.718$), and $-4.03 \times 10^{-5} \pm 3.00 \times 10^{-5}$ ($p = 0.0119$), respectively (Table 4). In eyes receiving PASCAL PRP, anti-VEGF injection, and focal laser, a *significant* negative correlation was found between spot number and central macular volume at 6 mm at the 1- and 6-month time points.
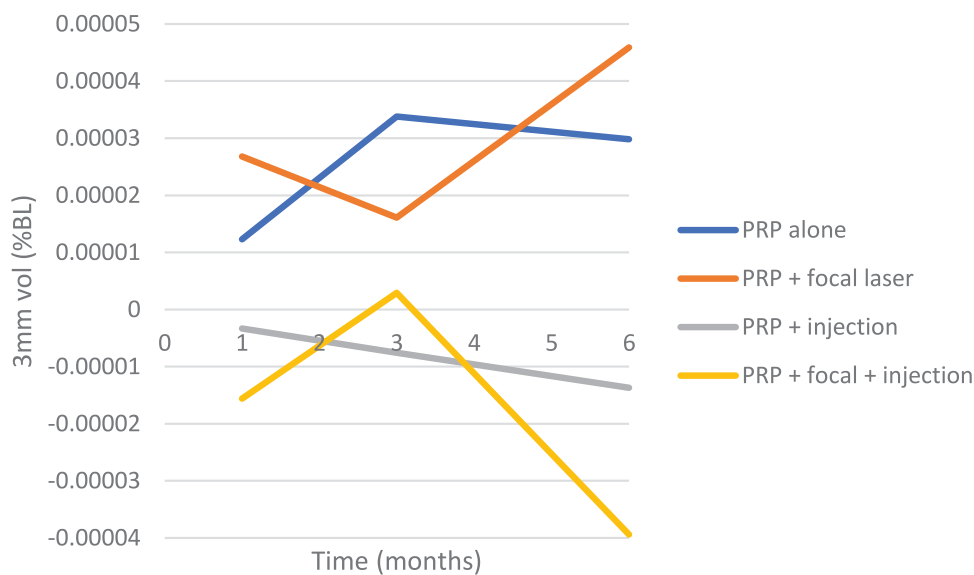
Figure 2. Change in central macular volume at 3 mm relative to baseline after PRP.

Table 4. Slope of linear regression line relating number of spots to baseline (BL)-adjusted 6-mm macular volume.

	1 month			3 months			6 months		
	% BL 6-mm vol	*p*	*n*	% BL 6-mm vol	*p*	*n*	% BL 6-mm vol	*p*	*n*
PRP alone	2.31×10^{-5} $\pm 2.92 \times 10^{-5}$	0.134	27	2.44×10^{-5} $\pm 3.79 \times 10^{-5}$	0.214	48	6.03×10^{-6} $\pm 2.78 \times 10^{-5}$	0.673	35
PRP + injection	-3.89×10^{-6} $\pm 1.36 \times 10^{-5}$	0.578	77	4.71×10^{-6} $\pm 2.56 \times 10^{-5}$	0.719	77	-6.54×10^{-6} $\pm 2.71 \times 10^{-5}$	0.638	69
PRP + focal laser	3.02×10^{-5} $\pm 1.41 \times 10^{-5}$	0.0138	6	1.59×10^{-5} $\pm 3.78 \times 10^{-5}$	0.433	10	4.01×10^{-5} $\pm 4.36 \times 10^{-5}$	0.131	7
PRP + focal + injection	-3.33×10^{-5} $\pm 1.97 \times 10^{-5}$	0.002	33	-4.48×10^{-6} $\pm 2.41 \times 10^{-5}$	0.718	37	-4.03×10^{-5} $\pm 3.00 \times 10^{-5}$	0.011	41

BL, baseline; PRP, panretinal photocoagulation.

The change in central macular volume at 6 mm over a 6-month period is shown in Figure 3, and the decline in macular volume in the combined group (PRP + focal laser + injection) at 6 months can be seen (Figure 3).

An example in our series of transient CMT and volume changes after PASCAL PRP for PDR is seen in Figure 4.

VA (logarithm of the minimal angle of resolution) after PRP

There was no statistically significant difference in mean logMAR VA before and 6 months after treatment with PRP. A two-sample *t*-test assuming unequal variances did trend toward a statistically significant decrease in VA at 1 month—0.460–0.522 ($p = 0.0968$). However, the difference at 6 months was not statistically significant—0.460–0.502 ($p = 0.244$) (Figure 5).

Percentage of patients who developed significant loss of vision (≥3 lines) after PRP

There were 7.8% of patients in PRP group that lost vision significantly at month 1 and 7.8% at month 6 after PRP. In the focal laser + injection group, 4% and 14% of patients had significant vision loss at months 1 and 6, respectively. In the
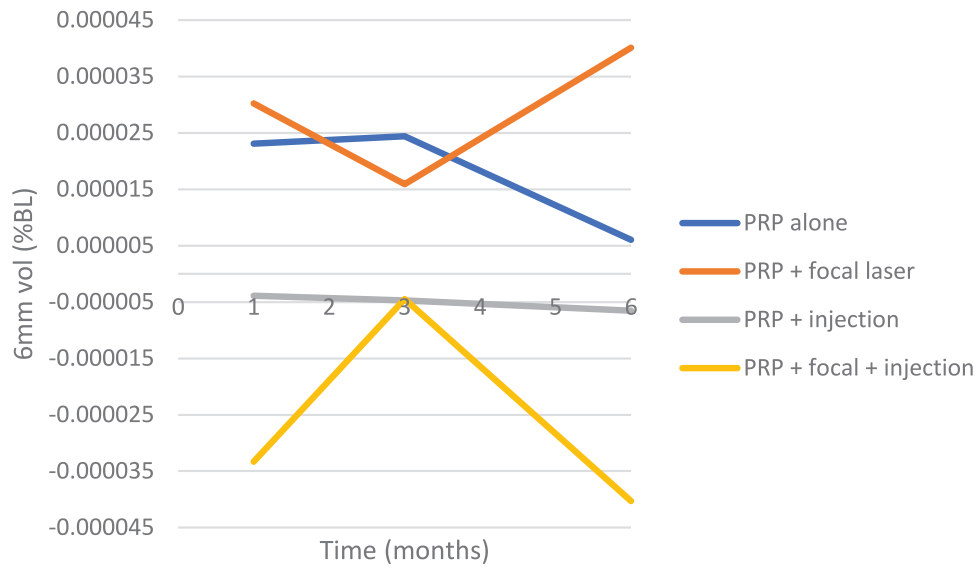
Figure 3. Change in 6-mm central macular volume relative to baseline after PRP.
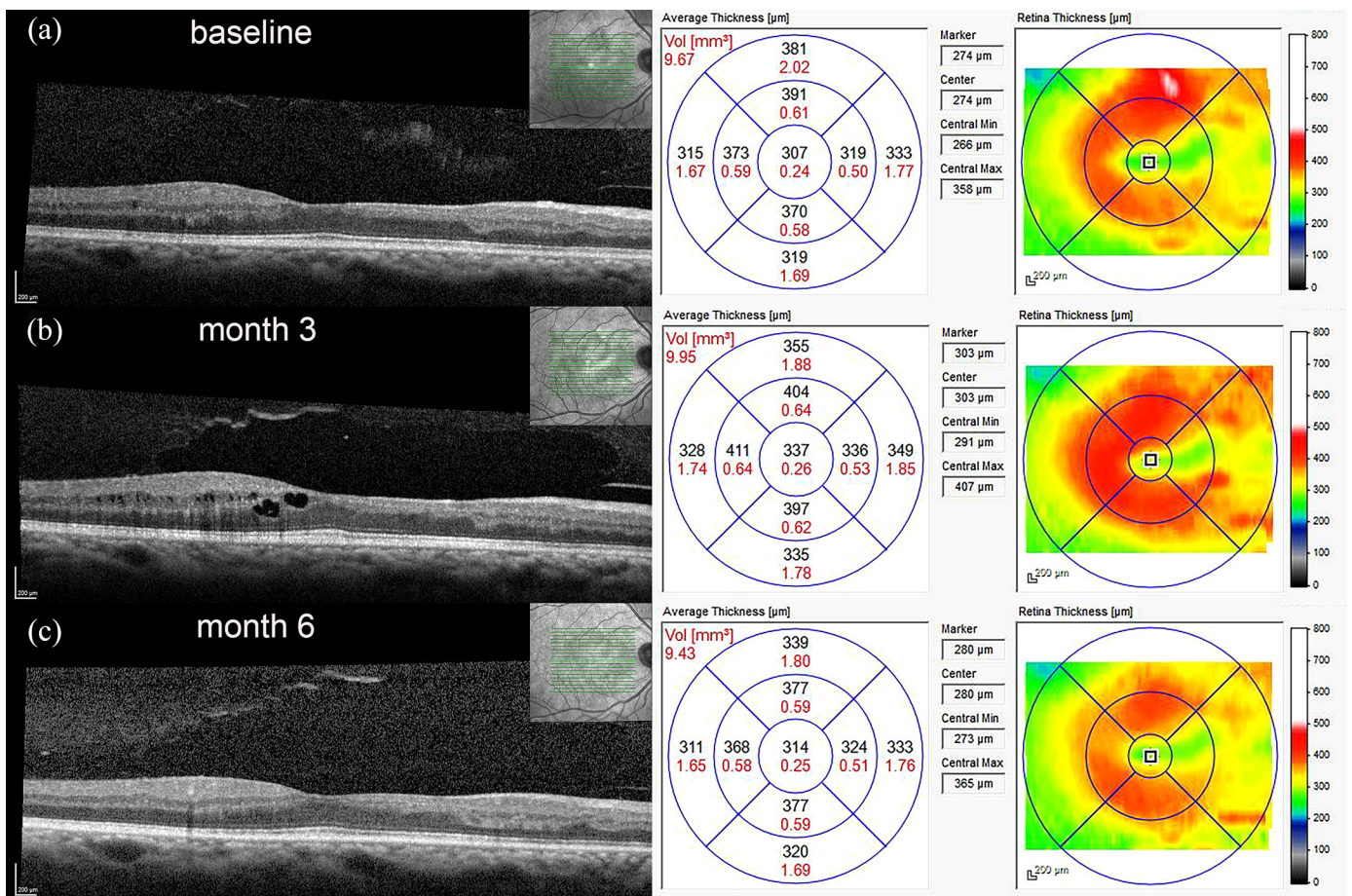

Figure 4. A representative example of spectral-domain OCT testing showing baseline macular thickness and volume (a), a subsequent increase in thickness and volume at month 3 after PASCAL PRP (b), and then a return to approximate baseline levels at month 6 (c) with observation only (no anti-VEGF or focal laser treatment).

Table 5. Comparison of percentage of patients with significant vision loss (baseline ⩾ 3 lines on the ETDRS chart) and *p* values (ANOVA) in PRP, focal laser + injection, and injection-only groups at months 1 and 6 post-procedure.

Groups	PRP	Focal laser + injection	Injection only	*p* value between groups
VA 1 month	7.80%	4.878	12.6582	0.08
VA 6 months	7.80%	14.6341	18.9873	0.11

ANOVA, analysis of variance; ETDRS, Early Treatment Diabetic Retinopathy Study; PRP, panretinal photocoagulation; VA, visual acuity.

injection-only group, 12% and 18% of patients developed significant vision loss at months 1 and 6 from baseline. Vision changes were not significant between different groups at months 1 and 6 after the procedures (*p* = 0.08 and 0.11, respectively; Table 5).

Discussion and conclusion

Laser photocoagulation has previously been shown to be an effective treatment for diabetic retinopathy by reducing vision loss and neovascularization.[1,2] However, worsening of macular edema can be a side effect of laser treatment.[3] The PASCAL laser was designed to lower cumulative energies used via pattern array and decreased pulse duration (10–20 ms vs 100–200 ms with traditional laser).[7] There has been scarce investigation into how lower total energies of PASCAL PRP effect macular edema. A 2014 prospective study of 38 eyes compared conventional PRP + ranibizumab, PASCAL PRP + ranibizumab, and ranibizumab alone. In its 24-week follow-up period, the study found that both PASCAL PRP + ranibizumab and ranibizumab-alone groups had a statistically significant decrease in central subfield macular thickness as measured by OCT while conventional PRP + ranibizumab did not.[8] This provides some evidence that PASCAL PRP may produce less macular edema compared to its conventional laser counterpart. However, larger studies are needed to verify these results.

In addition, a recent 2019 study of 97 eyes compared conventional *versus* PASCAL PRP with regards to CMT. This study found no significant difference in CMT between conventional and PASCAL PRP.[10] However, it only examined patients without macular edema at baseline. While this provides valuable data on the rate and magnitude of macular edema formation after PRP, from these data we cannot assess the effect PRP may have on existing macular edema and is not generalizable to patients with macular edema, which is common in PDR.

In our study of 262 eyes, 163 of which had macular edema, receiving PASCAL PRP alone or in combination with focal laser and/or injection, there was found to be *no* positive correlation between amount of laser delivered during PRP and macular edema. PASCAL PRP, either alone or in combination with focal laser or injection, had *no* significant effect on CMT in the 6-month period after treatment. On the contrary, the evidence suggests that macular edema may be reduced by a combination of PASCAL PRP, focal laser, and anti-VEGF injection. In this group, the amount of PASCAL laser was found to negatively correlate with 6-mm macular volume at 1 and 6 months (Table 4, Figure 3) and 3-mm central macular volume at 6 months (Table 3, Figure 2). When evaluated as a whole, less than 20% of patients had significant changes in macular thickness compared to baseline after PASCAL PRP in each treatment group, and the differences between each group were not significant.

These results compare quite favorably with outcomes for conventional, non-pattern scan, PRP. For example, McDonald and Schatz reported that 43% of patients treated with PRP for PDR exhibited increased macular edema. Furthermore, 8% of their patients exhibited permanent visual loss >2 lines after PRP.[3] While DRS did not directly evaluate conventional PRP on macular edema, it was noted that VA loss soon after treatment was especially prominent in those patients with baseline macular edema. From this, we can infer that the macular edema was likely worsened in patients with pre-existing macular edema.[6] Similarly, in the ETDRS study, patients treated with early full conventional PRP treatment without focal laser had higher rates of moderate visual loss as compared to untreated patients at 6 weeks after treatment. This occurred regardless of the presence of macular edema at the time of treatment, but to a greater extent in those with pre-existing macular edema.[11]

With regards to rate of macular edema formation from the PASCAL laser in previous studies, in a cohort of 36 eyes, 8.3% of patients developed macular edema, which is significantly less than the 43% reported by McDonald and Schatz.[3,12]

However, this study was meant to assess the amount of PRP needed to cause regression of PDR in mild, moderate, and severe PDR requiring 2187, 3998, and 6924 burns, respectively.[12] It did not analyze which patients developed macular edema or the number of burns in each of those patients. It is difficult to draw conclusions beyond their rate of diabetic macular edema in a small study. A retrospective review of 35 patients treated with PASCAL PRP found it increased the CMT by 24.0 and 17.4 μm at 4- and 12-week follow-ups, respectively.[13] However, both these studies excluded patients with macular edema at baseline, thereby limiting its generalizability and skewing results, as PRP could not have a negative correlation with macular edema if there is none to begin with.

Our study is supported by evidence demonstrated by Mukhtar and colleagues,[14] who found decreased mean CMT in patients with macular edema compared to baseline in 67 eyes after receiving two PASCAL PRP treatments. This study did not examine the relationship of focal laser or anti-VEGF modalities. Their mean cumulative number of burns for both treatments was 2313, but they did not examine the relationship of number of burns or energy used to CMT.

No study to our knowledge has directly compared the amount of laser used to CMT or central macular volume. Previous studies focused on whether or not there was a significant change in macular edema as compared to baseline[8,14] but did not study the relationship of energy used. Previously, it has been shown that with conventional laser, increased power or duration are tied to complications of macular edema.[15] On the contrary, our evidence suggests that the amount of PASCAL laser used, when combined with focal and anti-VEGF injection, is negatively correlated with central macular volume at 3 mm at 6 months and central macular volume at 6 mm at 1 and 6 months. In addition, our evidence does *not* show a positive correlation between the amount of PASCAL laser used and CMT or central macular volume regardless if PRP is used as a primary modality or combined with focal laser and/or anti-VEGF injection.

The DRS study established that in patients with high-risk PDR, 20% of eyes treated with conventional PRP developed severe vision loss (5/200 or worse) as compared to 44% of untreated eyes at 4 years.[6] ETDRS showed that early PRP resulted in
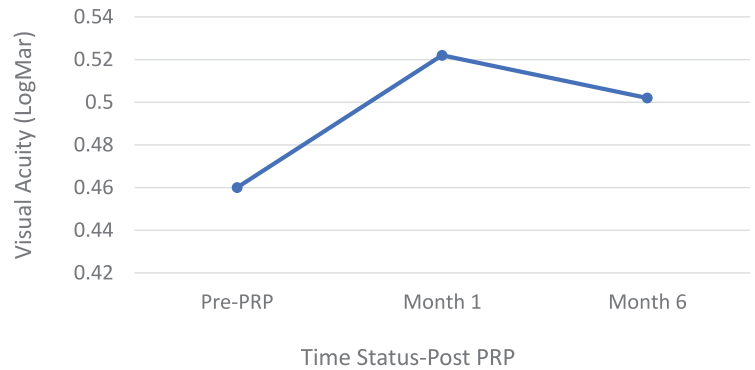

Figure 5. Change in visual acuity after PRP.

a small reduction in the risk of severe vision loss and that focal laser reduced moderate visual loss as compared to untreated eyes.[11] This was neither confirmed nor refuted by our PASCAL data. We found no statistically significant difference between logMAR VA before and 6 months after treatment (Figure 5). Published in February 2020, a study of the long-term follow-up data comparing conventional *versus* PASCAL PRP, also demonstrated that there was no difference in VA between the groups with a mean follow-up time of 743.5 and 719.8 days, respectively.[16] When we looked specifically at the percentage of patients who had significant vision loss after PASCAL PRP, it was less than 20% in each group. Interestingly, the percentage of patients who had significant vision loss and also changes in CMT was slightly higher in the injection only group (although it did not reach significance compared to the other groups). This suggests that the injection-only group may have had worse maculopathy compared to the other groups and was treated accordingly with anti-VEGF.

In summary, PASCAL PRP treatment for PDR, whether alone or in combination with focal laser or anti-VEGF injection, was not associated with increased development of macular edema or change in VA. PASCAL PRP when used in combination with focal laser and anti-VEGF injection may result in a decrease in macular edema.

Limitations of the study
Although total enrollment in our study was quite robust, totaling 262 eyes, some subgroup data sets were quite small, as not all measurements were available at all time points for all groups. However, to date, these data are the most extensive among published studies.

We did not differentiate between patients with or without pre-existing macular edema when grouping into treatment groups. This may have skewed our results toward increased mean CMT and central macular volume after treatment because one-third of our patients had no edema at baseline and there could be no decrease in their macular thickness or volume after treatment.

Our patient population had an average hemoglobin A1c of 8.8. As this population is not considered well controlled (as defined by HbA1c < 7.0%), our data may be skewed toward having increased macular edema compared to a population that is well controlled. However, as many patients are not well controlled while receiving treatment, this does improve our study's generalization to real-world populations.

This study is a retrospective analysis; as such, we have no ability to control certain factors, such as angiographic demonstration of macular ischemia, number of laser shots, power, or exposure time. In our study, exposure time did vary from 20 to 40 ms and our use of number of laser shots approximates total cumulative energy but is not an exact representation. The effect of macular ischemia on the development of macular edema was not assessed in this study, as patients did not routinely undergo intravenous fluorescein angiography prior to their treatment(s).

This is a single center study at the University of Florida, which over the course of study data collected involved multiple physicians at different levels of training who performed treatments. Therefore, there may have been variation in levels of total energy used, location of treatment, and modality of therapy based on the treating physician and resident. Treating physicians also decided when patients were to follow-up and whether or not to obtain an OCT. This negatively impacted our data collection as not all measurements were available for each follow-up time point.

Future directions

Analysis of PRP effects on individual retinal layers and choroid is now possible with newly developed OCT angiography. This may help increase our understanding of the effect photocoagulation has on the surrounding microvasculature to a greater extent than intravenous fluorescein angiography (IVFA) and OCT can provide. Sub-threshold PRP is currently being examined on its efficacy in treatment of PDR. If efficacious, it would be important to understand its relationship to macular edema and VA as well.

Newer treatment approaches exclusively with anti-VEGF, for example, can have good results for patients based on compliance with follow-up treatments, evaluations, and systemic diabetic control. The authors have had good experiences with this approach for both the resolution of neovascularization and improvement in macular edema; although patient selection is very important. Perhaps a hybrid approach of anti-VEGF with limited or directed photocoagulation is a reasonable consideration moving forward.

The relationship of macular edema in patients treated with IVFA-guided PRP, which limits the treatment area to active extra-macular neovascularization and retinal ischemia has yet to be established. In addition to VA, the preservation of visual fields in patients treated with IVFA-guided *versus* full PRP would also be important to study, as IVFA-guided PRP aims to preserve the most retina possible while inducing regression of neovascularization. It would be interesting to examine the quality of life between these two groups as well, such as the ability to drive.

Future studies of larger sample sizes may be able to power a study that subgroups the different types of anti-VEGF treatments as well as laser modality. We did not include steroid treatment modalities, but their impact on macular edema needs to be further investigated. Our study provides valuable information of a retrospective nature over a 6-year period. Further prospective studies are required to better understand the relationships that have been highlighted in this study.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics statement

The Institutional Review Board (IRB) of the University of Florida approved this study (approval id. IRB201701031). Given this was an IRB-approved retrospective review of medical records, informed patient consent was not required. This study followed the principles of Declaration of Helsinki.

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