Journal of Clinical & Experimental Ophthalmology

Aditi et al., J Clin Exp Ophthalmol 2016, 7:4
DOI: 10.4172/2155-9570.1000576

Research Article Open Access

The Effects of PASCAL Panretinal Photocoagulation on the Peripapillary Retinal Nerve Fiber Layer

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Received date: June 19, 2016; **Accepted date:** July 18, 2016; **Published date:** July 22, 2016

Abstract

Purpose: To investigate the effects of Pascal (Topcon Medical Laser Systems, Inc. Oakland, NJ) pan-retinal photocoagulation (PRP) on the optic nerve head (ONH).

Method: This was a prospective case control study comparing 3 groups of patients seen in the diabetic retinopathy (DR) clinics, without any coexistent optic nerve pathology.

Group A patients had proliferative or severe non proliferative DR necessitating PRP during the study period. Group B patients had mild or moderate DR and did not require PRP throughout the study period. Group C patients had standard retinal laser (green argon or frequency doubled YAG) PRP at least 2 years ago. All the 3 Groups had retinal oxygenation measurements and retinal vessel caliber readings by Oxymap T1(Oxymap, Reykjavik, Iceland), optic disc stereophotographs, high definition optical coherence tomography (HD-OCT) scans of the ONH by both Cirrus (Carl Zeiss Meditec Inc, Dublin, CA) and Spectralis (Heidelberg Engineering, Heidelberg Germany). These were performed prior to PRP at baseline, then at 3, 6, and 12 months post PRP for group A and at baseline, 3, 6, and 12 months for groups B and C. Paired t-test was used to assess the mean changes in parameters from baseline for each group.

Results: A total of 90 patients were recruited including 27 in Group A, 31 in Group B and 32 in Group C. At baseline, the average retinal nerve fibre layer (RNFL) was significantly thicker in group A compared to group B (102.0 ± 16.8 vs. 89.5 ± 11.6 μm, p=0.001) and group C (88.6 ± 11.2 μm, p=0.001) respectively. At 3 months, Group A exhibited a significant increase in the Cirrus average RNFL thickness (5.60 ± 8.54 μ, p=0.003) when compared to baseline. At 6 months, the average RNFL reverted to baseline values (p=0.89), and remained stable at 12 months (p=0.85). There was no significant change noted in the average Cirrus RNFL thickness at 3 and 6 months in Group B. At 12 months, the average RNFL was significantly thinner compared to baseline (-6.68 ± 8.10; p=0.005). In Group C, the average RNFL remained stable from baseline through to month 12 (p>0.05 at the three timepoints). No significant changes were noted in the average Spectralis RNFL thickness at any timepoints in each of the three groups.

Oxygen saturation dropped in all 3 groups at 3 months, being significant only in group B (-2.05 ± 4.20%, p=0.03).

Conclusion: In eyes treated with Pascal PRP, there was an initial increase in the retinal nerve fibre layer at the optic nerve head at 3 months followed by a thinning back to baseline values at 6 months which then remained stable up to 12 months. Hence the Pascal PRP did not have a significant effect on the nerve fibre layer at 12 months.

Keywords: Pascal panretinal photocoagulation; Optic nerve head; Retinal nerve fibre layer thickness; Retinal oximetry; Diabetic retinopathy

Summary

In this study, we investigated the effects of Pascal (Topcon Medical Laser Systems, Inc. Oakland, NJ) pan-retinal photocoagulation (PRP) on the optic nerve head (ONH). This was a prospective case control study comparing 3 groups of patients seen in the diabetic retinopathy (DR) clinics, without any coexistent optic nerve pathology. In eyes treated with Pascal PRP, there was an initial increase in the retinal nerve fibre layer at the optic nerve head at 3 months followed by a thinning back to baseline values at 6 months, which then remained stable up to 12 months. Hence the Pascal PRP did not have a significant effect on the nerve fibre layer at 12 months.

We believe this is the first SD-OCT study looking at our preferred PRP modality, Pascal and its effects on the optic nerve head by two modalities, the Cirrus and the Spectralis. It will be of importance to the

literature on the effects of panretinal photocoagulation on the retinal nerve fibre layer (RNFL). Pascal is the newer modality and our study suggests that at least at 12 months, there is no significant effect on the retinal nerve fibre layer thickness. Hence any thinning of the ONH RNFL cannot be attributed to the Pascal PRP alone. This is important for clinicians who manage patients with diabetic retinopathy and 'glaucomatous' looking optic discs. Both conditions often co-exist.

Introduction

Glaucoma and diabetic retinopathy are both common ophthalmic conditions and often co-exist. Due to rising life expectancies and the growing prevalence of diabetes, the incidence of DR is expected to grow by more than 70% by 2020 [1]. Pan retinal photocoagulation (PRP) is the accepted gold standard treatment for proliferative diabetic retinopathy and whilst necessary, may lead to unwanted collateral retinal damage. Often, in PRP treated eyes, the disc may eventually display some typically glaucomatous features such as an increased cup to disc ratio (CDR) and pallor. DR related retinal and optic disc ischemia may also result in disc pallor and increase in CDR. As the visual fields may anyway be affected by the laser PRP, this can make a diagnosis of progressive glaucoma more challenging. After primary laser injury, the laser scar lesions may coalesce, leading to functional damage such as visual field defects and if involving the macula, visual disturbance [2-4]. There may be discernible changes to the optic nerve head [1,4-9]. Consequently, it is difficult to ascertain whether an increasing CDR in post PRP treated eyes is due to glaucoma, diabetes related ischemia or simply a non-progressive injury secondary to the PRP itself. Past studies used unsophisticated or non-dedicated imaging to measure retinal nerve fiber layers (RNFL) [1,4,5,7-17]. Ours is the first to use highly reproducible High Definition Spectral Domain Optical Coherence Tomography (SDOCT) of the optic nerve head (ONH) by both Cirrus (Carl Zeiss Meditec Inc, Dublin, CA) and Spectralis (Heidelberg Engineering, Heidelberg Germany).

There is currently conflicting evidence on the state of the RNFL post PRP.

Two studies by Lim et al. [1] and Cankaya et al. [12] proposed that PRP treated eyes had a thinner RNFL than their non-diabetic counterparts at baseline, placing them in an even more susceptible position for future glaucomatous damage [1]. Likewise, ONHs in eyes treated with PRP are more likely to be graded as abnormal, but their appearance is not necessarily glaucomatous and may be related to thinning of the RNFL [10]. In contrast, Kim et al concluded that there was no detectable change to the optic nerve following PRP [18].

Application of conventional argon or FD Yag laser photocoagulation uses laser energy of 100-200 ms duration per shot. It usually takes much longer to complete PRP using this mode of laser, and is more painful than Pattern scattered laser. PASCAL (Topcon Medical Laser Systems, Inc. Oakland, NJ) is the new laser modality used for PRP which is gaining popularity due to its ease of use, speed and reduced pain. It delivers a predetermined array of multiple laser shots (4-56) in a grid pattern simultaneously with a single foot pedal depression. Pulse durations are reduced by nearly a log unit to around 20-30 ms [4]. Whilst it is purported that this PRP is less destructive to the retinal layers, Muqit et al. reported thinning of the macular nerve fiber layer [6]. Although, one may assume that this may, with time, translate into peripapillary RNFL loss, they did not examine for this [4,6]. Cankaya et al. also suggested that PRP-treated eyes were found to have a significantly thinner mean peripapillary retinal nerve fibre layer compared with the eyes in the control group [12]. They used confocal scanning laser ophthalmoscopy to measure the RNFL. There are currently no SDOCT studies which investigate the effects of Pascal PRP on the optic nerve head, however, two recent Korean articles using the older time domain Optical Coherence Tomography (TDOCT) reported that Pascal is less destructive to the RNFL than conventional PRP [8,13].

Retinal oximetry is a new ocular imaging technology that measures oxygen saturation levels in retinal vessels, acting as a surrogate marker for the metabolic demands of the eye [14,19]. We used a noninvasive spectrophotometric retinal oximeter (Oxymap Retinal Oximeter T1; Oxymap ehf, Reykjavik, Iceland) in both eyes as a patient acceptable method rather than fluorescein angiongraphy in detecting retinal ischaemia. This was used to determine if any RNFL changes were mediated via changes in retinal oxygenation or more likely by direct thermal damage.

Method

This prospective case control study was approved by the institutional review board of the Singapore Eye Research Institute and was conducted in adherence with the tenets of the Declaration of Helsinki.

Patients were recruited by retina specialists in the diabetic retinopathy screening clinics. A detailed explanation was given to patients and written informed consent was obtained.

Patients were then categorised into the following 3 groups:

Group A: Patients with diabetic retinopathy who required PRP, with no other optic nerve co morbidity.

Group B: Patients who had mild to moderate non proliferative diabetic retinopathy that did not require PRP and with no other optic nerve co morbidity.

Group C: A control group of patients that had PRP in the past, at least two years prior to recruitment.

This was a prospective case control study comparing the three groups of patients.

Inclusion criteria

All patients who required PRP and underwent PASCAL photocoagulation, as suggested by a retinal specialist. These were patients with either proliferative diabetic retinopathy or severe non proliferative diabetic retinopathy and were included in Group A. Patients who had some diabetic retinopathy but did not require PRP were included in Group B. Patients who had Argon laser PRP at least two years ago were included in Group C. All patients had informed consent

Exclusion criteria

Patients with other ocular co morbidity example, glaucoma, ocular hypertension, retinal vein occlusion, macular degeneration, ischemic optic neuropathy.

Patients with clinically significant macular oedema requiring treatment ie intravitreal anti VEGF therapy and/or laser therapy.

Patients with dense cataracts or media opacity as this would have an effect on the quality of the fundus images, disc photos and OCT scans.

Patients with suspected glaucomatous discs who are being monitored in a glaucoma clinic. Patients with a strong family history of glaucoma, i.e., 1st degree relative.

Patients were seen at baseline, then at 3 months, 6 months and 12 months. For Group A patients baseline visit was prior to initiating PRP and then 3 months, 6 months and 12 months post PRP.

All patients underwent standardized ocular examination including visual acuity measurement, auto-refraction, intraocular pressure (IOP) measurement by Goldmann Applanation Tonometry, digital fundus photos and stereo disc photographs to assess for retinal vasculature and disc changes induced by the PRP, OCT of the optic discs for assessment of retinal nerve fibre layer thickness using two OCT instruments namely, Cirrus OCT(Carl Zeiss Meditec Inc. Dublin, US) and Spectralis OCT (Heidelberg Instruments Inc. Heidelberg, Germany), and Oxymap T1(Oxymap, Reykjavik, Iceland), a novel non-invasive device which measures oxygen saturation in retinal vessels. All patients had the retinal oxymap scan to quantify retinal ischaemia as a baseline. Oxymap uses spectrophotometric retinal oximeter in the dark to measure oxygen saturation in the retinal vessels. A trained Oxymap reader who was masked, read all the Oxymap images and did all the measurements. This provided uniformity and eliminated the risk of subjectivity in evaluating the Oxymap images.

During the follow up period, the retina specialists assessed the status of the DR. If the retinopathy was still active, it could imply there is a persistent state of retinal ischaemia despite PRP. This may influence changes if any on the optic nerve head. All fundus photos were also independently graded by a masked retina specialist to ascertain if there was any progression of the diabetic retinopathy.

Disc stereophotographs were graded by a glaucoma specialist who was masked to clinical data.

Sample size calculation and statistical analysis

The sample size calculation was based on previously published data in which patients who did not undergo laser treatment presented a mean RNFL thickness of 135.8 μm in the inferior region and a standard deviation of 29.8 μm. Assuming that group A lost 20% of RNFL thickness after laser treatment *vs* 1% for the control group, a sample size of 15 patients per group would be necessary to reach a power of 80% and a significance level of 5%. Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (Version 21.0; IBM Corp. Armonk, NY, USA). The time points for the study were baseline, 3 months, 6 months and 12 months. Paired t-test was used to assess the mean changes in parameters from baseline. An appropriate Bonferroni correction (α/4) was applied to correct for the number of time-point evaluated resulting in a P value threshold of 0.0125 to be considered statistically significant.

Results

A total of 90 patients participated in our study, 27 in Group A, 31 in Group B and 32 in Group C. We included only one eye of each patient for our study analysis. If there was bilateral involvement, only the right eye was included. Table 1 illustrates the number of patients that were included for the data analysis during the one year period; the remainder was lost to follow up.

	Group A	Group B	Group C
Baseline	27	31	32
3 Months	25	22	28
6 Months	16	21	14
12 Months	18	16	16

Table 1: Showing the number of patients at each time point.

Baseline characteristics of the patients are summarized in Table 2. Group B patients were significantly older than Group A patients (54.3 ± 10.6 vs. 60.6 ± 10.2, p=0.025). The Cirrus average RNFL was significantly thicker in Group A compared to Group B and Group C (p=0.001 for both) respectively. The Cirrus RNFL was significantly thicker in all 4 quadrants in Group A compared to Group B. This was similar in Spectralis except the nasal quadrant. The A-V difference is higher in Group C compared to Group A (p=0.04).

	Group A	Group B	P-value (A Vs B)	Group C	P-value (A Vs C)
Age	54.3 ± 10.6	60.6 ± 10.2	0.025	61.5 ± 7.9	0.005
Visual acuity	0.18 ± 0.12	0.15 ± 0.16	0.52	0.30 ± 0.36	0.21
Axial length	23.8 ± 1.3	23.7 ± 1.3	0.66	23.6 ± 1.2	0.43
Anterior chamber depth	3.46 ± 0.48	3.77 ± 0.80	0.08	3.65 ± 0.92	0.33
Arterial oxygen saturation	99.8 ± 10.1	98.3 ± 9.7	0.57	106.2 ± 16.2	0.10
Venous oxygen saturation	61.3 ± 9.4	61.8 ± 6.2	0.80	59.6 ± 12.1	0.59
Arterio-Venous difference	38.6 ± 11.1	36.5 ± 10.9	0.49	46.6 ± 15.4	0.04
Cirrus					
Average RNFL thickness	102.0 ± 16.8	89.5 ± 11.6	0.001	88.6 ± 11.2	0.001
Rim area	1.35 ± 0.25	1.31 ± 0.24	0.46	1.30 ± 0.22	0.39

Disc area	2.03 ± 0.45	1.99 ± 0.50	0.75	1.94 ± 0.39	0.44
Average CDR	0.50±0.15	0.50±0.17	0.92	0.50±0.17	0.99
Superior RNFL	122.5 ± 20.3	106.7 ± 23.1	0.008	101.5 ± 18.3	< 0.001
Nasal RNFL	81.6 ± 21.8	71.4 ± 14.8	0.04	74.5 ± 13.4	0.13
Inferior RNFL	127.7 ± 22.9	114.1 ± 18.9	0.02	109.5 ± 17.5	0.001
Temporal RNFL	79.9 ± 26.4	66.2 ± 11.0	0.01	68.8 ± 11.9	0.04
Spectralis					
Average RNFL	111.9 ± 20.7	95.6 ± 12.8	0.001	96.0 ± 13.4	0.001
Superior RNFL	130.8 ± 15.4	115.3 ± 22.6	0.004	113.7 ± 21.7	0.001
Nasal RNFL	88.2 ± 37.1	74.7 ± 16.9	0.07	80.9 ± 15.8	0.32
Inferior RNFL	141.9 ± 22.1	121.5 ± 20.7	0.001	120.1 ± 18.9	< 0.001
Temporal RNFL	86.8 ± 24.7	71.0 ± 14.1	0.004	69.4 ± 15.8	0.002

Table 2: The comparison of baseline characteristics.

At 3 months follow-up as summarized in Table 3, post PRP treatment in Group A resulted in a significant thickening of the Cirrus average RNFL and superior quadrant RNFL (pairwise P<0.0125 for both). The RNFL thickening was also observed in the Spectralis but the change was not found to be significant. There were no significant differences in the arterial and venous oxygen saturations (p>0.05 for both) post PRP treatment in group A. No significant changes were noted in the RNFL thickness in Groups B and C both on the Cirrus and the Spectralis (p>0.0125 for all measurements) as compared to baseline.

	Group A		Group B		Group C	
	Mean change	p-value	Mean change	p-value	Mean change	p-value
Arterial oxygen saturation	-0.86 ± 8.21	0.77	-2.05 ± 4.20	0.03	-3.30 ± 9.44	0.18
Venous oxygen saturation	2.96 ± 9.74	0.42	-0.94 ± 7.49	0.56	-1.76 ± 7.52	0.36
Arterio-Venous difference	-3.82 ± 13.1	0.43	-1.11 ± 8.40	0.54	-1.54 ± 13.13	0.65
Cirrus						
Average RNFL thickness	5.60 ± 8.54	0.003	-0.55 ± 7.27	0.73	0.57 ± 5.45	0.58
Rim area	-0.01 ± 0.11	0.75	0.01 ± 0.10	0.59	0.01 ± 0.13	0.65
Disc area	-0.03 ± 0.15	0.32	0.003 ± 0.25	0.95	0.002 ± 0.17	0.95
Average CDR	-0.002 ± 0.09	0.89	-0.007 ± 0.02	0.16	0.003 ± 0.03	0.62
Superior RNFL	5.40 ± 8.90	0.006	3.18 ± 18.51	0.42	2.71 ± 12.21	0.25
Nasal RNFL	4.68 ± 10.03	0.03	0.55 ± 5.27	0.63	0.18 ± 4.80	0.85
Inferior RNFL	2.08 ± 25.90	0.69	-6.05 ± 23.02	0.23	2.21 ± 7.04	0.10
Temporal RNFL	6.88 ± 14.67	0.03	-2.05 ± 7.15	0.19	-1.71 ± 6.16	0.15
Spectralis						
Average RNFL	4.61 ± 17.28	0.20	0.39 ± 5.50	0.75	0.77 ± 6.78	0.55
Superior RNFL	3.63 ± 26.64	0.51	0.82 ± 9.73	0.69	-1.21 ± 10.48	0.54
Nasal RNFL	2.42 ± 29.51	0.69	2.59 ± 6.42	0.07	1.11 ± 11.56	0.61
Inferior RNFL	-0.46 ± 24.24	0.92	-1.86 ± 8.65	0.32	4.39 ± 10.15	0.03

Temporal RNFL	12.87 ± 43.7	0.16	-0.86 ± 12.49	0.75	-1.21 ± 16.27	0.69

Table 3: Showing the change in parameters at 3 months compared to baseline in the 3 groups

The change at 6 months compared to baseline is demonstrated in Table 4. In Group A, the Cirrus average RNFL and superior quadrant RNFL thickness was similar to baseline values (p=0.89 and p=0.42 respectively). There were no significant changes in any other parameters including the oxymap parameters in Group A. We noted a significant decrease in the nasal and inferior Cirrus RNFL (p=0.01 for both); this was not reflected in the Spectralis.

	Group A		Group B		Group C	
	Mean change	p-value	Mean change	p-value	Mean change	p-value
Arterial oxygen saturation	-2.91 ± 8.76	0.63	0.37 ± 3.87	0.71	0.34 ± 10.20	0.94
Venous oxygen saturation	3.20 ± 1.78	0.09	0.09 ± 7.79	0.96	-1.64 ± 5.40	0.53
Arterio-Venous difference	-6.11 ± 10.55	0.42	0.46 ± 7.06	0.79	1.98 ± 9.21	0.65
Cirrus						
Average RNFL thickness	-0.63 ± 16.13	0.89	-2.57 ± 7.47	0.13	1.64 ± 4.56	0.20
Rim area	-0.004 ± 0.22	0.94	0.016 ± 0.20	0.72	0.02 ± 0.07	0.41
Disc area	-0.05 ± 0.15	0.18	0.03 ± 0.22	0.58	0.02 ± 0.09	0.33
Average CDR	0.001 ± 0.11	0.98	-0.01± 0.03	0.05	0.01 ± 0.03	0.09
Superior RNFL	-5.19 ± 24.94	0.42	-0.81 ± 19.44	0.85	3.57 ± 11.52	0.26
Nasal RNFL	-2.88 ± 19.23	0.56	-2.48 ± 4.00	0.01	-0.14 ± 4.64	0.91
Inferior RNFL	0.44 ± 26.20	0.95	-4.67 ± 7.64	0.01	0.86 ± 6.87	0.65
Temporal RNFL	-0.44 ± 18.78	0.93	-3.48 ± 8.68	0.08	1.71 ± 3.47	0.08
Spectralis						
Average RNFL	10.05 ± 16.38	0.07	-1.43 ± 3.49	0.07	0.00 ± 3.45	1.0
Superior RNFL	5.47 ± 16.80	0.23	-1.48 ± 6.04	0.27	-3.21 ± 8.13	0.16
Nasal RNFL	-1.67 ± 32.33	0.85	1.38 ± 6.99	0.37	3.36 ± 10.99	0.27
Inferior RNFL	16.73 ± 50.86	0.22	-2.29 ± 8.60	0.24	-0.79 ± 9.66	0.76
Temporal RNFL	15.40± 36.58	0.15	-3.33 ± 7.55	0.06	0.64 ± 11.51	0.83

Table 4: Showing the change in parameters at 6 months compared to baseline.

At 12 months (Table 5), in Group A, the Cirrus average RNFL remains stable with no significant difference noted when compared to baseline values. In Group B, there is a significant thinning of the Cirrus average RNFL and superior quadrant RNFL compared to baseline (p=0.005 and p=0.001 respectively). These changes were not reflected in the Spectralis. In Group C, the nasal RNFL was significantly thinner compared to baseline in both the Cirrus (p=0.009) and Spectralis (p=0.005) respectively.

	Group A		Group B		Group C	
	Mean change	p-value	Mean change	p-value	Mean change	p-value
Cirrus						
Average RNFL thickness	0.56 ± 12.70	0.85	-6.68 ± 8.10	0.005	-0.69 ± 4.74	0.57
Rim area	0.03 ± 0.14	0.33	0.04 ± 0.20	0.49	0.02 ± 0.12	0.46

Disc area	0.02 ± 0.13	0.56	0.03 ± 0.25	0.64	-0.07 ± 0.09	0.009
Average CDR	-0.02 ± 0.56	0.16	-0.004± 0.03	0.62	0.03 ± 0.08	0.25
Superior RNFL	-3.78 ± 17.96	0.38	-13.0 ± 13.0	0.001	-1.31 ± 9.83	0.60
Nasal RNFL	-0.78 ± 25.72	0.89	-12.72 ± 25.17	0.06	-9.63 ± 12.86	0.009
Inferior RNFL	-1.39 ± 23.97	0.81	-10.36 ± 35.32	0.25	2.13 ± 6.63	0.22
Temporal RNFL	8.17 ± 18.46	0.08	-8.72 ± 26.41	0.21	6.13 ± 12.05	0.06
Spectralis						
Average RNFL	5.66 ± 13.56	0.11	-4.43 ± 11.13	0.13	0.33 ± 7.22	0.86
Superior RNFL	-0.94 ± 22.32	0.86	-13.16 ± 35.15	0.16	0.69 ± 11.75	0.82
Nasal RNFL	6.65 ± 27.52	0.33	-3.00 ± 17.89	0.51	-15.31 ± 18.90	0.005
Inferior RNFL	6.17 ± 21.81	0.26	-0.25 ± 12.91	0.94	3.18 ± 22.59	0.58
Temporal RNFL	10.76 ± 26.0	0.11	-1.31 ± 18.85	0.78	12.75 ± 19.22	0.02

Table 5: Change in parameters at 12 months compared to baseline

Figure 1 illustrates the progressive change in RNFL from baseline to 12 months. In Group A, there is an initial thinning of the RNFL post PRP, followed by a return to the pre-PRP baseline levels and remains stable until 12 months. In Group B, interestingly, there is a thinning of the RNFL noted at month 12. The RNFL thickness in Group C remained stable throughout the study period. There was no significant change noted in the diabetic retinopathy status in these patients during the study period. All optic disc photos were reviewed by a masked Glaucoma specialist and none of the photos were graded as having any discernible change or being frankly glaucomatous according to the ISGEO guidelines. All the fundus photos, posterior pole and periphery were graded again by a masked medical retina specialist. There was no progression noted in the diabetic retinopathy status for all patients when compared to baseline grading.

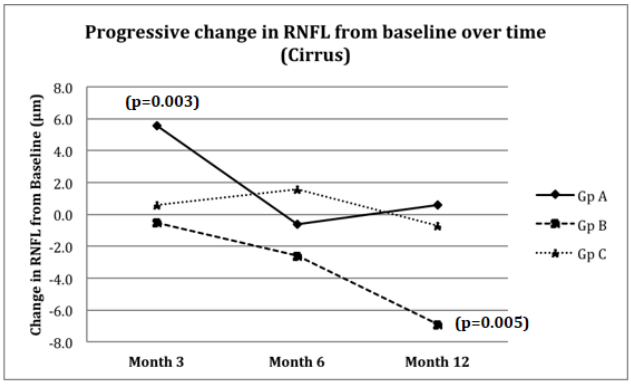

Figure 1: Graph illustrating the change in RNFL from baseline in the three study groups.

The agreement for mean RNFL thickness between Spectralis and Cirrus showed that the mean difference was 7.7 microns (95% limits of agreement; -9.1, 24.5; Figure 2). A fixed bias was noted from the mean difference values. The regression slope for the agreement between instruments showed proportional bias (p=0.002), indicating a greater difference between the 2 measurements for thicker RNFL measurements by Spectralis.

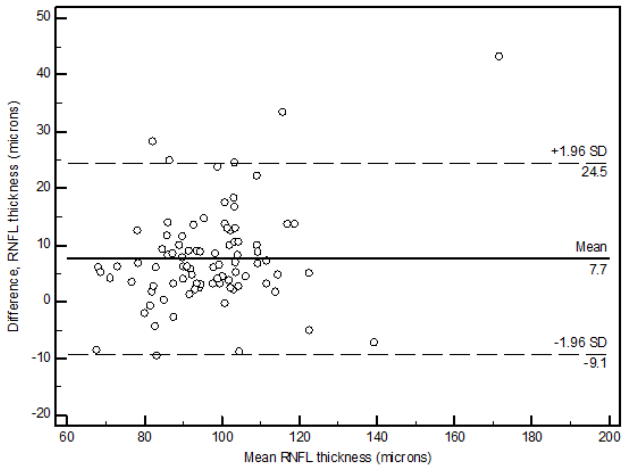

Figure 2: Bland-Altman plots show the mean difference and 95 % limits of agreement for intra-observer agreement for mean RNFL thickness for all patients.

Discussion

Panretinal photocoagulation remains the gold standard treatment for proliferative diabetic retinopathy. Our study aimed to improve our understanding of the changes at the optic nerve head following Pascal PRP. This is important in the management of patients with diabetic retinopathy as well as those who are considered to have 'glaucomatous optic discs' following PRP.

We found an initial significant increase in RNFL thickness post PRP, probably due to retinal oedema caused by the initial insult from PRP. This is consistent with other studies in the literature. [1,2,5,17]. This was followed by progressive resolution, back to baseline values at 6 months, maintained through to 12 months. This is in contrast to

previous studies with conventional Argon PRP which showed a progressive thinning in RNFL in PRP treated eyes [1-3,5] and concurs with recent TD-OCT studies [8,13].

In general, the SD-OCT RNFL changes were largely similar for both the Cirrus and Spectralis; although significant difference at the intermediate time-points were only detected on the Cirrus. The exact reason for our findings is not known. The disparity in RNFL measurements between the Cirrus and Spectralis concurs with previous published data where the Spectralis generates thicker RNFL thickness readings. Some of the explanations that have been suggested for the disparate findings include differences in RNFL boundary segmentation algorithms, signal strength, scan acquisition, data processing and/or software properties between the two devices [20,21].

Our study demonstrates that post Pascal PRP, there is no peripapillary RNFL thinning, at least up to 12 months. When the laser entry is documented in the notes, it is important to specify that PASCAL laser was used as in future if there is any optic disc RNFL thinning noted, our study shows that this may not be attributed to the PRP alone. Hence other pathology needs to be ruled out. This has an important effect on patient care as one can now better streamline the glaucoma referrals. In our study, Group B patients showed a progressive thinning of the RNFL after 6 months. We accept that this may be due to ischemia from worsening retinopathy at a microscopic (pre-clinical) level. Unfortunately, one limitation of our study was the absence of Oxymap data at 12 months to ascertain this.

Nevertheless, the fundus photos and optic disc stereophotographs graded by masked specialists revealed no significant change in the diabetic retinopathy grading or disc appearance.

Group C showed no significant change in RNLF thickness over 12 months (except in the nasal quadrant) indicating that after a given period of time the RNFL of PRP treated eyes seem to stabilize. This could represent a stabilization of the retinopathy. Longer follow up of our Group A patients would help adjudicate on this. It must be mentioned that Group C patients had received PRP at least 2 years prior to recruitment into the study and a majority of these patients had received conventional Argon PRP. Interestingly, while group C showed no change in RNFL thickness at 12 months, at baseline the RNFL was significantly thinner than group A. It is therefore likely that the conventional Argon PRP causes more retinal thinning compared to the Pascal. However, longer follow-up of patients in Group A may be needed to determine if progressive thinning beyond pre-laser baseline occurs after Pascal PRP. Interestingly, we noted significant thinning of only the nasal quadrant in Group C at 12 months when compared to baseline in both the Cirrus and the Spectralis. We are uncertain of the reason for the thinning. Since it was demonstrated in both the Cirrus and the Spectralis, it is less likely to be due to the inter-test variations.

A recently published similar study by Park and Jee examined the effects of PRP using a PASCAL system on the RNFL thickness in patients with diabetic retinopathy [13]. This was a retrospective study, however the design itself was very similar with three groups including a control group of patients with moderate or less non proliferative diabetic retinopathy. They found no significant differences in the four quadrants of RNFL thickness between the 3 groups at baseline. In our study, there were significant differences at baseline. These are summarized in Table 2. Group B patients were significantly older than Group A patients. The Cirrus average RNFL was significantly thicker in Group A compared to Group B and Group C ($p<0.05$ for both) respectively. The Cirrus RNFL was significantly thicker in all 4 quadrants in Group A compared to Group B. This was similar in Spectralis except the nasal quadrant. This likely suggests that ischaemia may play an important role as well. The chronicity of previous conventional argon laser may be an important factor and one of our control groups addressed this. Time may have an effect on the long term implications of conventional argon laser coupled with ischaemia. Both the studies had 1 year follow up and what needs to be done next is longer follow up post PASCAL to see if there are any long term effects of this type of laser. Certainly both studies suggest that up to 1 year post PASCAL, there is no significant change in the RNFL thickness.

The study by Park and Jee1 [5] did not assess 3 months data post PASCAL PRP, whilst our study showed an initial thickening of the RNFL. We deduced that this was probably due to oedema caused by the initial insult of the PRP. The unique features of our study were the inclusion of the Oxymap and serial fundus photos reviewed by a retina specialist to determine any progression in diabetic retinopathy. Both of these take into account ischaemia which is an important confounding factor that could potentially cause changes to the RNFL itself. Yip et al. concluded that the Oxymap allows reliable and repeatable retinal vessel oximetry measurements [14]. Our study showed that the Oxymap readings remained unchanged up to the 6 months period in Group A indicating that the observable changes in RNFL were independent of retinal oximetry.

Another recent study by Lee et al. looked at the effects of PASCAL panretinal photocoagulation on peripapillary RNFL thickness, central macular thickness and optic nerve morphology in patients with diabetic retinopathy [8]. The follow up period was relatively short i.e., 2 months and 6 months post PRP. They found that after PASCAL PRP, the inferior RNFL thickness had increased at 2 months, quite similar to our study findings at 3 months. However, the superior, temporal and nasal RNFL had decreased at 2 and 6 months respectively. These changes were not significant though and no explanation for this was given. Furthermore, we believe that 6 months may not be sufficiently adequate to evaluate for the long term changes caused by PASCAL panretinal photocoagulation on RNFL thickness. Our study showed no significant change in RNFL thickness post PASCAL PRP at 12 months. While the control group in the study by Lee did not have any laser intervention, our study had two control groups-one without laser intervention and the other composed of eyes that has had the conventional Argon laser. We were thus better able to compare assess and deduce the PRP induced changes.

Other studies by Lee et al. [22] and Hsu et al. [23] had similar findings as our study. However, they only used time domain OCT to assess RNFL thickness.

Our study has some limitations. Due to logistical issues, we could not collect the Oxymap data at the 12 month follow-up visit. Therefore we were unable to assess for the long term PRP induced ischaemic changes, although at 6 months post PRP, we noted no significant differences in the Oxymap data. It is likely that the PRP induced changes in ischaemia either occur after 6 months or the Oxymap may be incapable of detecting modest changes in ischaemia levels (if any). Few patients were also lost to follow-up at the different study visits. It would have been ideal to have data available for all patients at all study visits.

Our study addresses a relevant clinical question facing both retina and glaucoma specialists. It is the first SD-OCT study looking at our

preferred PRP modality, PASCAL and its effects on the optic nerve head by two modalities, the Cirrus and the Spectralis.

What we knew:

* PRP can cause retinal nerve fibre thinning

* Optic discs of PRP treated eyes can appear glaucomatous over a period of time

What our study has added:

* While conventional Argon PRP can cause retinal nerve fibre thinning, PASCAL PRP did not show any progressive thinning of the retinal nerve fibre layer at 12 months.

* We suggest that the use of Pascal PRP should be clearly documented and that any RNFL thinning in these eyes cannot be attributed to the PRP alone.

Grant Support

Singhealth Foundation Grant SHF/FG454P/2011.

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