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Effect of Pan Retinal Photocoagulation on Retinal nerve fiber layer thickness, comparison with patients of NPDR and correlation with number of laser spots

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Abstract

Introduction: Pan Retinal Photocoagulation (PRP) is considered as gold standard treatment of proliferative diabetic retinopathy (PDR). The study was designed to objectively evaluate PRP in this era of pharmacotherapy by analysing its effect on Retinal nerve fiber layer thickness (RNFLT).

Aims: To evaluate effect PRP on RNFLT by Spectral Domain Optical Coherence Tomography and to compare RNFL loss with patients of nonproliferative diabetic retinoapathy (NPDR) and to correlate RNFL loss with number of PRP laser spots.

Materials and methods: Average RNFLT was measured by Spectral Domain Optical Coherence Tomography in 26 patients (52 eyes) with bilateral PDR or very severe NPDR before and after 1 year of PRP (group A) and in 26 patients (52 eyes) with bilateral mild, moderate or severe NPDR initially and after 1 year (group B). Pre and Post PRP RNFLT of patients in group A were compared using paired t test. RNFL thinning was calculated by subtracting average RNFLT at second visit 1 year apart from first visit in both groups. RNFL thinning in group A was compared with group B by unpaired t test. RNFL thinning in group A was correlated with number of PRP spots and Pearson correlation coefficient (r) was calculated.

Results: There was significant difference between pre and post PRP RNFLT after 1 year (p value < 0.0001). RNFL thinning was significantly more in group A as compared to group B (p value < 0.0001). RNFL thinning in group A strongly correlated with number of PRP spots and the value of Pearson correlation coefficient (r) was 0.87 (p value < 0.0001).

Conclusions: RNFL thinning occurs after PRP which can be detected as early as 1 year with SD-OCT and RNFL thinning correlate with number of PRP spots.

Keywords: Pan Retinal Photocoagulation, Retinal nerve fiber layer thickness, Spectral Domain Optical Coherence Tomography, Diabetic retinopathy

Introduction

Diabetes mellitus is a serious health problem worldwide. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[13] The overall prevalence of diabetic retinopathy (DR) was found to be 6.96% for proliferative diabetic retinopathy (PDR), 6.81% for diabetic macular edema, and 10.2% for vision threatening diabetic

retinopathy in individuals suffering from diabetes.[15]

The Diabetic retinopathy study (DRS) and Early treatment of diabetic retinopathy study (ETDRS) demonstrated the efficacy of panretinal photocoagulation (PRP) in reducing the risk of severe visual loss in severe non proliferative diabetic retinopathy (NPDR) and PDR.[9,2] Subsequently many studies have documented that PRP has side effects like decreased visual acuity[9,2], decreased visual fields[9], decreased contrast sensitivity[3], decreased colour vision[3] and decreased dark adaptation.[10]

Although photocoagulation primarily affects RPE and photoreceptors, laser burns may damage the inner retina and even nerve fiber layer as well.[11] Mild retinal edema may occur soon after the PRP as laser treatment triggers retinal inflammation. However in the long-term, reduction in retinal nerve fiber layer thickness (RNFLT) occurs due to ganglion cell loss.[5,8,7] Hence interest has been growing in evaluating the effect of panretinal photocoagulation on retinal nerve fiber layer thickness.

Studies have shown that diabetes mellitus decreases RNFL thickness. The RNFL thickness in patients with diabetes mellitus was reduced significantly as compared with age-matched normal control eyes. Moreover, all RNFL thickness parameters of the GDx VCC software were decreased significantly with exacerbation of diabetic retinopathy.[12]

OCT uses reflected and backscattered light to create images of various retinal layers. It is analogous to the use of sound waves in ultrasonography. Spectral-domain (SD) optic coherence tomography (SD-OCT) provides distinct advantages in signal-to-noise ratio permitting faster signal acquisition, optimal repeatability and reproducibility in measuring RNFLT. Previous studies have shown excellent reproducibility of RNFLT measurements with SD-OCT in both normal and glaucomatous eyes.[6,14]

Many newer drugs like anti vascular endothelial growth factor (anti-VEGF) drugs are being used in treatment of diabetic retinopathy along with PRP. Intravitreal bevacizumab (Avastin) was found to be effective in resolution of leakage from NVD and involution of neovascularisation.[1]

Hence in this era of pharmacotherapy, objective analysis of PRP is needed. Change in RNFL thickness after PRP is one such parameter. This study evaluated effects of PRP on RNFL thickness after 1 year, compared RNFL thinning in patients receiving PRP with patients suffering from mild, moderate or severe NPDR and have not received PRP to compensate for effect of diabetes and DR on RNFL thinning and correlated RNFL thinning with number of laser spots. The purpose of this study was to objectively analyze PRP in this era of pharmacotherapy by demonstrating its effect on RNFLT.

Materials and methods

Approval for this study was obtained from the institutional review board. All research and data collection adhered to the tenets of the Declaration of Helsinki and Good Clinical practice guidelines. Written informed consent was obtained from all participants. This prospective clinical study involved 52 patients who were divided in 2 groups. Group A included 26 patients (52 eyes) with bilateral PDR or very severe NPDR and group B included 26 patients (52 eyes) of bilateral mild, moderate or severe NPDR who presented to our hospital. Patients suffering from glaucoma, degenerative myopia, age-related macular degeneration, hypertensive retinopathy, retinal dystrophies or who were prior lasered were excluded because these conditions affect baseline RNFL thickness or cause progressive RNFL thinning. Patients with significant media haze were also excluded. Patients not giving informed consent or not motivated for follow up were also excluded.

At the time of inclusion into our study, all subjects underwent a systemic evaluation, comprising a complete medical history and general physical examination. The ocular evaluation of cases comprised of visual acuity testing, slit lamp biomicroscopy of the anterior and posterior segment (with a +78 D lens). FFA and OCT were performed if indicated.

In both groups, average RNFLT was measured in both eyes using spectral domain OCT (*NIDEK RS-3000 OCT Retina Scan*) at first visit. RNFLT measurements were repeated in both groups after 1 year.

In 52 eyes of 26 patients with PDR or severe NPDR (group A), PRP was performed using 532 nm green laser *(Iridex OcuLight GL 532 Green Laser System)* done either by slit lamp delivery system with the help of widefield Mainster PRP lens *(Ocular Instruments, Inc.)* or Goldmann three-mirror lens *(Ocular Instruments, Inc.)* or by laser indirect ophthalmoscope *(Iridex TruFocus optical system)* with +20 D lens *(Volk Optical, Inc.).* The burns were intense enough just to produce medium white burn of the overlying retina, which usually required power of 200–600mW and duration of 0.1 – 0.2 second. Approximately 1200–2400 burns, 200 – 500µm in diameter were delivered one spot width apart in two to three sittings. Patients were examined after 6 weeks and 3 months of PRP and laser augmentation was considered if new vessels appeared to be active, fresh pre-retinal haemorrhage was present especially when previous scars appeared widely spaced or if there were skip areas. When laser augmentation was done, burns were placed between treatment scars or anterior to them.

Statistical analysis was done in three parts. In the first part of statistical analysis, pre PRP and post PRP average RNFLT of patients in group A were compared by paired t test to determine the effect of PRP on RNFLT.

For the second part of statistical analysis, RNFL thinning was calculated by subtracting average RNFLT at second visit 1 year apart from first visit in both groups. RNFL thinning in group A was compared with group B by unpaired t test. Results were considered statistically significant if the p-value was less than 0.05.

In the third part of statistical analysis, RNFL thinning in group A was correlated with number of PRP spots and Pearson correlation coefficient (r) was calculated. The value of Pearson correlation coefficient (r) ranges between +1 and −1 inclusive, where 1 is total positive correlation, 0 is no correlation, and −1 is total negative correlation.

Statistical analysis was done with the help of InStat 3.10 software (GraphPad Software Inc.).

Results

A total of 52 patients were recruited for this study and they were divided in 2 groups. Group A included 26 patients (52 eyes) with bilateral PDR or very severe NPDR and group B included 26 patients (52 eyes) with bilateral NPDR (mild, moderate or severe). There was no significant difference in the age and sex ratio in group A and group B. The mean age (SD) in group A and group B was 51.35 (9.64) years and 50.35 (9.48) years respectively (p value = 0.71). Male female ratio was 1.89 in both groups.

First part of statistical analysis compared RNFLT at first visit before PRP and RNFLT after 1 year of PRP in patients included in group A. Results showed that after 1 year there was significant difference between pre and post PRP RNFLT (p value < 0.0001). (Table 1)

Table 1: Comparison of Pre and Post PRP (after 1 year) RNFLT (p value < 0.0001).

	MEAN	**S.D.**
PRE PRP RNFLT	143.13	30.48
POST PRP RNFLT	108.23	27.92

Second part of statistical analysis compared RNFL thinning in group A with group B. RNFL thinning was calculated by subtracting average RNFLT at second visit 1 year apart from first visit in both groups. The mean (S.D.) RNFL thinning in group A and group B was 34.9 (19.51) and 14.62 (6.67) respectively. RNFL thinning was significantly more in group A as compared to group B (p value < 0.0001). (Table 2)

Table 2: Comparison of RNFL thinning in patients who received PRP (group A) with those who have not received PRP (group B), after 1 year of PRP laser therapy (p value < 0.0001).

	MEAN	S.D.
GROUP A	34.9	19.51
GROUP B	14.62	6.67

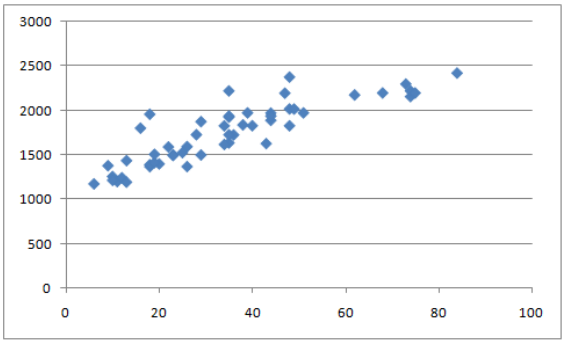

Fig. 1: Correlation of number of PRP spots with RNFL thinning (µm), r = 0.87 (p value < 0.0001).

In the third part of statistical analysis, RNFL thinning in group A was correlated with number of PRP spots. The mean number of PRP spots given was 1748.56 spots (range 1198 – 2419 spots). RNFL thinning strongly correlated with number of PRP spots and the value of Pearson correlation coefficient (r) was 0.87 (p value < 0.0001). (Figure 1)

Discussion

The total number of people suffering from diabetes is projected to rise to 366 million in year 2030.[13] The prevalence of PDR in individuals suffering from diabetes is 6.96%.[15]

PRP remains the gold standard treatment of PDR. DRS and ETDRS had demonstrated the efficacy of pan retinal photocoagulation in reducing the risk of severe visual loss in severe non proliferative diabetic retinopathy and proliferative diabetic retinopathy.[9,2] But PRP has its own set of adverse effects like decreased visual acuity[9,2], decreased visual fields[9], decreased contrast sensitivity[3], decreased colour vision[3] and decreased dark adaptation[10].

Avery et al (2006) had shown that after intravitreal bevacizumab (Avastin), there was complete resolution of leakage from NVD in 73% of eyes. Neovascularisation clinically appeared to involute in many patients. In 2 cases/45 cases subtle decreases of leakage in fellow untreated eye was noted.[1]

Hence, risk benefit analysis of PRP is needed. Change in RNFL thickness is a parameter which can be used for objective analysis of PRP. Although photocoagulation primarily affects RPE and photoreceptors, laser burns may damage the inner retina and even nerve fiber layer as well.[11] And previous studies had demonstrated reduction in RNFLT after 2 years.[5,8,7] Spectral-domain optic coherence tomography (SD-OCT) was found to provide excellent reproducibility of RNFLT measurements in both normal and glaucomatous eyes.[6,14]

Previous studies have shown that the average RNFL thickness increased slightly during the initial 3 to 6 months post-PRP and thereafter gradually decreased, showing statistically significant reductions at 2 years post-PRP.[5,7]

Our study had shown the significant difference between pre and post PRP RNFLT at the end of 1 year (p value < 0.0001).

Studies have shown that diabetes also decrease RNFL thickness. Takahashi et al (2006) had shown that RNFL thickness in

patients with diabetes mellitus was reduced significantly as compared with age-matched normal control eyes.[12] Lim et al (2009) had also showed that eyes that had been treated with PRP had thinner peripapillary RNFL compared with healthy individuals and diabetic patients who did not undergo PRP.[8]

Hence control group with patients of NPDR was taken to compensate the effect of diabetes and DR on RNFL thinning. Our study had shown that after period of 1 year, RNFL thinning was significantly more in patients receiving PRP (group A) as compared with patients with mild, moderate or severe NPDR (group B) who did not received PRP laser therapy (p value < 0.0001).

Previous studies have not found correlation between RNFL loss and number of PRP spots. Kim and Cho (2009) found that after 6 months, the relationship between the number of laser burns and changes in RNFL thickness was not significant.[4] But our study had shown that after period of 1 year, RNFL thinning strongly correlated with number of PRP spots with r value 0.87 (p value < 0.0001).

Based on the results of our study, we conclude that RNFL thinning occurs after PRP which can be detected as early as 1 year with SD-OCT. This RNFL thinning correlate with number of PRP spots given. We believe that number of PRP laser spots should be titrated in a way that although regression of neovascularisation is achieved but adverse effects are minimised. It will also be interesting to study the effects of combination of intravitreal Anti-VEGF agents and decreased number of PRP spots in achieving regression of neovascularisation with reduced adverse effects.

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