ORIGINAL ARTICLE

Retinal Nerve Fiber Layer Thickness Post-Laser Treatment in Diabetic Retinopathy: Argon versus Pattern Scanning Laser

MAIMUNAH M[1], ROPILAH AR[2], OTHMALIZA O[2], MUSHAWIAHTI M[2]

[1]*Department of Ophthalmology, University Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.*
[2]*Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.*

ABSTRAK

Rawatan konvensional laser argon menyebabkan ketebalan sementara pada lapisan saraf retina (RNFL). Tetapi kesan dari 'pattern scanning laser' (PASCAL) tidak banyak diketahui. Kajian ini dilakukan untuk membandingkan kesan selepas konvensional laser argon dibandingkan dengan PASCAL pada pesakit yag mengalami masalah diabetik retinopati. Sebanyak 32 subjek telah terpilih dalam kajian ini. Seramai 16 pesakit dalam kumpulan argon dan 16 pesakit dalam kumpulan PASCAL. Pesakit yang terlibat diambil dari klinik mata, Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Pemeriksaan mata yang lengkap dan gambar fundus dilakukan pada awal kajian, selepas 2 bulan dan 4 bulan dilaser. RNFL diukur menggunakan domain masa tomografi koheren optikal (OCT). Kedua kumpulan mempunyai ciri klinikal yang sama sebelum rawatan (p= 0.323). RNFL selepas laser argon tidak berubah secara signifikan dalam semua kuadran pada bulan ke 2 dan 4 selepas rawatan. Namun, untuk kumpulan PASCAL, perubahan sigifikan telah ditemui pada bulan ke 4 rawatan pada 'average RNFL' dan RNFL 'inferior' (p<0.05). Bahagian lain menunjukkan kenaikan ketebalan RNFL tetapi tidak signifikan secara statistik. Sebagai kesimpulan, kenaikan RNFL berlaku pada kedua-dua kumpulan. Pesakit PASCAL mengalami lebih ketebalan. Dengan itu, adalah perlu mengambil kira kejadian laser yang baru berlaku jika mahu menganalisa ketebalan RNFL.

Kata kunci: fotokoagulasi, optikal koheren tomografi, retinopati diabetes, sel retinal gaanglion, tomografi

Address for correspondence and reprint requests: Mushawiahti Mustapha, Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +60391455981 Fax: +60391456673 E-mail: drmusha@yahoo.com/drmusha@gmail.com

ABSTRACT

Conventional argon laser causes transient thickening of retinal nerve fibre layer (RNFL). The effect of pattern scanning laser (PASCAL) has not been well described. We compared the immediate changes in peripapillary RNFL thickness post-panretinal photocoagulation between conventional argon lasers and PASCAL in patients with diabetic retinopathy changes. A total of 32 subjects were recruited. There were 16 patients in the argon group and 16 patients in PASCAL group. Diabetic patients were recruited from Ophthalmology Clinic, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Complete eye examinations and fundus photographs were performed at baseline prior to laser treatment, and post-laser treatment at two and four months. RNFL thickness was measured using time domain optical coherence tomography. Both groups were comparable with respect to clinical characteristics and demographics. There was no significant difference in average RNFL thickness between the two groups prior to treatment (p= 0.323). RNFL post-laser treatment for patients receiving conventional argon laser remained unchanged with no significant differences in all quadrants at any time-point (two and four months). However, for the PASCAL group, significant thickening occurred at four months for average RNFL and the inferior quadrant (p <0.05). The other quadrants similarly demonstrated increasing thickness at four months but this did not reach statistical significance. Transient RNFL thickening occurs in both conventional and PASCAL laser patients. The PASCAL laser induces a greater increase in RNFL thickness than the argon laser group. Important events, such as laser eye treatments and even type of laser used, are worthy of consideration when evaluating RNFL.

Keywords: diabetic retinopathy, optical coherence, photocoagulation, retinal ganglion cells, tomography

INTRODUCTION

Microvascular complications of diabetes dominated as the leading cause of preventable blindness in working aged people in many developed countries (Cheung et al. 2010). Over the past 30 years, pan retinal photocoagulation (PRP) has remained as the gold standard for treating ischemic and neovascular diseases of the retina. PRP reduces the risk of severe visual loss by 50% in patients with high risk proliferative diabetic retinopathy (DRSRG 1978).

The principle by which the laser exerts its therapeutic effects relies on the destruction of the outer retina. This reduces the oxygen demand while maintaining a constant oxygen input. Laser burns may also serve as physiological windows through which oxygen diffuses from the choroid, increasing vitreous oxygenation and induced vasoconstriction (Velez-Montota et al. 2010). However, despite the efficacy for preventing severe visual loss, laser PRP is often associated with substantial ocular side effects, such as

difficulty with light–dark adaptation, a slight decrease in vision, and peripheral visual loss (Pender et al. 1981; Henson & North 1979).

The energy of a conventional argon laser is transformed to heat at the level of the retinal pigment epithelium (RPE) and the outer retinal layer. However, longer laser wavelengths will penetrate deeper than the RPE and cause more destructive changes to the retina, RPE, and choriocapillaris (Maeshima et al. 2004; Nagpal et al. 2010). Pattern scanning laser (PASCAL) is a novel device that has radically changed traditional laser parameters. Normal conventional laser requires an average duration of average of 100 ms compared to only 20 ms for PASCAL. Velez-Montoya et al. (2010) demonstrated short duration of PASCAL laser allows lower total energy used to produce a desired burn. This consequently limits the spreading of choroidal heating and elicits a more uniform energy distribution with less inner retinal injury (Muqit et al. 2010a). Another major advantage of PASCAL is the ability to distribute the laser treatment over a wider area of the retina in a single session with less collateral damage (Nagpal et al. 2010). At the same time, retinopathy regression was similar to the conventional argon green laser (Nagpal et al. 2010).

Argon laser has long since been known to cause a significant reduction in RNFL thickness over time (Kim & Cho 2009). Transient thickening post-PRP with the conventional argon laser has also been described by many authors (Kim & Cho 2009). However, the effect of PASCAL on peripapillary RNFL thickness has not been well described.

Therefore, this study was designed to compare the immediate changes in peripapillary RNFL thickness post-PRP between conventional argon lasers and PASCAL.

MATERIALS AND METHODS

This was a hospital based, randomized clinical trial study. It was conducted at UKMMC, Kuala Lumpur, Malaysia. Ethical approval was obtained from the Research and Ethics Committee of Faculty of Medicine, Universiti Kebangsaan Malaysia. The study was conducted from March 2011 to December 2012. Written consent was obtained from all the participants.

PARTICIPANTS

Recruited patients included those with proliferative diabetic retinopathy (PDR) or very severe non-proliferative diabetic retinopathy (NPDR) requiring PRP laser treatment. An experienced ophthalmologist clinically graded the stages of diabetic retinopathy and diagnosis was made based on the early treatment diabetic retinopathy study (ETDRS) classification. Patients were randomized into two groups based on the treatment received: conventional argon laser or PASCAL.

Inclusion criteria were: i) type 2 diabetes mellitus with very severe NPDR or PDR requiring laser treatment; ii) clear media without clinically significant amount of cataract; iii) age of diabetes mellitus diagnosis >35 years; iv) and best corrected vision of 6/18 or better to ensure good signal strength on optical coherence tomography (OCT). Exclusion criteria were: i) type

1 diabetes mellitus; significant media opacity; ii) co-existing glaucoma; iii) previous laser treatment or eye surgery; iv) degenerative myopia or uveitis; v) or any history of other vascular diseases, such as retinal artery or vein occlusion.

DATA COLLECTION

Complete eye examinations, fundus photographs,and OCT (Carl Zeiss Meditec Inc., Dublin, CA) measurement of the peripapillary RNFL were performed prior to laser and post-treatment at two and four months. A 3.4 mm peripapillary scan mode was used to measure peripapillary RNFL thickness. Patients with good signal strength on OCT (>5) were included.

A single, medically trained person performed the PRP. A total of 900 to 1,500 laser spots were generated at each sitting. Time interval of one to two weeks was maintained between two sittings. A laser spot size of 200 or 300 m was used for both modalities. Pulse duration of 20 ms was used for PASCAL and 100 ms for the argon laser. The power was adjusted to achieve gray burns. Spots were placed one spot distance apart. Topical anesthesia was used in all eyes. Among completing the treatment, total number of laser spots in each eye ranged from 2,000 to 3,000 shots. Treatment was considered complete once there was clinical evidence of regression of neovessels, and intraretinal hemorrhage, improvement in venous dilatation, and no new pre-retinal bleed. Pallor of the disc was unlikely to be observed at four months post-laser. Therefore, it was not used as an indication of disease regression.

ETHICAL APPROVAL

The research was approved by the Ethics committee of UKMMC (FF-2010-347). The privacy and confidentiality of each individual was maintained and the respondents were given the rights to withdraw from participation.

DATA ANALYSIS

The statistical analysis in this study was presented descriptively. Univariate, bivariate, and multivariate analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp, Armonk, NY, USA). The differences in RNFL thickness were analyzed using paired t-tests (normal data), whereas the Chi-square test was used for categorical data and general linear models (repeated measurement analysis of variance [ANOVA]) were used for multivariate analysis. A p-value less than 0.05 was accepted as statistically significant.

RESULTS

DEMOGRAPHIC INFORMATION

A total of 32 subjects were recruited for the study; 16 patients in the argon group and 16 patients in the PASCAL group, and 27 patients had PDR and five had very severe non-PDR. The mean age for the argon group was 56.44 ± 7.87 yrs and Pascal group was 54.00 ± 7.94 yrs (p=0.390). The overall age range of both groups was 41 to 78 yrs. The duration of diabetes was comparable between the two groups with a mean duration for patients receiving argon laser of 7.31 ± 4.81 yrs and for the PASCAL

group 6.75 ± 3.75 yrs (p = 0.71). Table 1 summarised the demographic data and clinical characteristics of the study population.

PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS CHANGES IN THE CONVENTIONAL ARGON GROUP

Average RNFL before laser treatment was 108.64 ± 17.70 μm, and a slight increase was noted at two months post-treatment (112.64 ± 17.05 μm; p=0.127). Baseline RNFL before treatment was used as comparison. Subsequently, at four months, average RNFL was 106.55 ± 15.77 μm (p=0.457). Analysis of the individual quadrants (temporal,nasal,superior and inferior) showed similar transient thickening of the RNFL at two months, except for the nasal quadrant. Superior RNFL measurements prior to laser, at two and four months were 127.75 ± 22.12 μm, 132.38 ± 21.99 μm (p=0.200), and 126.69 ± 20.36 μm, respectively

(p=0.795). Nasal quadrant thickness was the only quadrant that showed a slight reduction in thickness from baseline after laser treatment: 86.31 ± 21.33 μm, 79.58 ± 24.41 μm (p= 0.404), and 80.63 ± 19.49 μm, respectively (p=0.366).

Although the transient thickening at two months was not statistically significant, there was a consistent trend of thickening observed in all quadrants except for the nasal region (Table 2, Figure 1). These changes were temporary and RNFL in all quadrants recovered to baseline thickness at four months.

PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS CHANGES IN THE PASCAL GROUP

Conversely in the PASCAL group, RNFL showed continuous significant thickening at two and four months post laser treatment. Significant changes were found for the average RNFL at two and four months, inferior RNFL at four

Table 1: Demographic and clinical characteristics at the baseline.

	Argon	Pascal	P-value
No. of eyes/patients	16	16	
Sex			
Male	8(53.3)	7(46.7)	
Female	8(47.1)	9(52.9)	
Age, years	56.44 ± 7.87 (range)	54.00 ± 7.94 (range)	0.390
Duration, years	7.31 ± 4.81	6.75 ± 3.75	0.71
Type of DR			
PDR	15(55.6)	12(44.4)	
Very severe NPDR	1(20.0)	4(80.0)	
Baseline RNFL pre-laser	108.64 ± 17.70	99.26 ± 13.96	0.107

Data are means ±SD (range), absolute values (%). PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; RNFL, retinal nerve fiber layer; SD, standard deviation.

Table 2: Peripapillary retinal nerve fiber layer thickness changes before and after laser
in the argon group.

Measurements in different quadrants	Pre -Laser (µm ±SD)	Post-Laser 2 months (µm ± SD)	Post-Laser 4 months (µm ± SD)	P-value*	P-value"
Average	108.64 ± 17.70	112.64 ± 17.05	106.55 ± 15.77	0.127	0.457
Superior	127.75 ± 22.12	132.37 ± 21.99	126.69 ± 20.36	0.200	0.795
Inferior	138.25 ± 28.21	140.69 ± 25.65	134.12 ± 25.29	0.659	0.385
Nasal	86.31 ± 21.33	79.58 ± 24.41	80.63 ± 19.49	0.404	0.366
Temporal	79.81 ± 14.37	90.81 ± 22.28	85.19 ± 13.44	0.053	0.102

Paired-sample *t*-test.
*P-value <0.05 corresponding to pre-laser and 2 monthspost-laser.
"P-value <0.05 corresponding to pre-laser and 4 monthspost-laser.
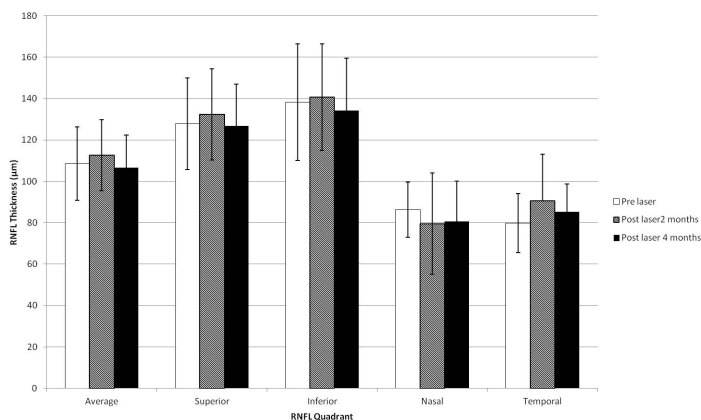

Figure 1: Peripapillary retinal nerve fiber layer thickness changes before and after laser in the argon group.

months and nasal quadrant at two and four months. Average RNFL thickness before laser treatment was 99.26 ± 13.96 µm, 105.52 ± 17.39 µm at two months (p=0.003), and 107.20 ± 12.14 µm (p = 0.001) at four months (Table 3, Figure 2).

Overall, in the PASCAL group, increasing trend of RNFL thickness occurred in all quadrants with time. Compared to the argon group, RNFL thickness failed to return to its baseline level at four months.

DISCUSSION

Histologically, Blumenkrantz et al. (2006) reported application of 100 ms threshold level of 514 nm argon green laser in rabbit eyes produced a complete loss of the photoreceptors as well as hyperplasia of the pigment epithelium). High powered lasers cause transmission of heat to adjacent tissue causing destructive effects and inflammatory response immediately after laser treatment. This transmitted

Table 3: Peripapillary retinal nerve fiber layer thickness changes before and after laser in the PASCAL group.

Measurements in different quadrants	Pre-Laser (µm ± SD)	Post-Laser 2 months (µm ± SD)	Post-Laser 4 months (µm ± SD)	P-value*	P-value″
Average	99.26 ± 13.96	105.52 ± 17.39	107.20 ± 12.14	**0.003**	**0.001**
Superior	118.81 ± 18.26	123.69 ± 26.48	122.19 ± 16.75	0.311	0.213
Inferior	130.88 ± 23.75	135.25 ± 23.95	140.06 ± 21.28	0.291	**0.021**
Nasal	66.44 ± 17.60	79.06 ± 22.10	80.69 ± 16.38	0.280	**0.00**
Temporal	82.75 ± 25.81	82.75 ± 17.95	85.38 ± 24.76	1.00	0.712

Paired-sample *t*-test.
 *P-value < 0.05 corresponding to pre-laser and 2 monthspost-laser.
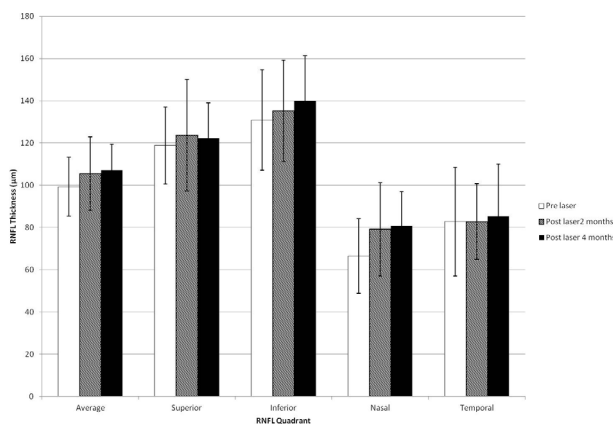 ″P-value < 0.05 corresponding to pre-laser and 4 monthspost-laser.

Figure 2: Peripapillary retinal nerve fiber layer thickness changes before and after laser in the PASCAL group.

effect predisposes patients not only to macular edema due to transient choroidal thickening, but, in the long run, increases the risk of developing epiretinal membranes (Kim & Cho 2009). Moreover, the end point laser marks tend to exaggerate with time, which correlates well with reported histological data (Maeshima et al. 2004). Such effects are well tolerated in older age groups, but with the increasing number of young diabetics

(Geiss et al. 2014), these side effects may significantly affect their quality of life.

The aim of new laser technologies is to achieve retinal photocoagulation that causes healing responses by selectively targeting the RPE with minimal photoreceptor loss and scar expansion. PASCAL uses a special scanning pattern to permit rapid photocoagulation, and thus reduces burn session time, improving patient

comfort as well as ensuring excellent physician performance and efficiency (Blumenkranz et al. 2006; Muqit et al. 2012). PASCAL technology is a semi-automated pattern generation method using short laser pulse durations of typically 20 ms (five times shorter than conventional systems). Moreover, argon lasers and PASCAL have been proven to be equally effective for treating proliferative diabetic retinopathy (Naqpal et al. 2010). OCT observations by Inagaki et al. (2012) showed that the PASCAL laser reduces the vertical and horizontal spread of laser energy, thus producing shorter defect in the inner/outer segment line compared to the conventional laser group.

Apart from limited injury to the entire retina, PASCAL laser scars were not found to enlarge with time (Muqit et al. 2010b). Histopathology evaluation by Paulus et al. (2013) reported preservation of the inner nuclear layer of RNFL post PASCAL laser. Previous OCT study, describe transient RNFL thickening occurs immediately after argon laser treatment and may last for up to 6 months (Lee et al. 2013). As opposed to our study, transient thickening in our study did not last beyond four months. The cause of this transient thickening remained uncertain although many authors postulated the presence of upragulated inflammatory mediators occur post laser treatment. Nonaka et al. (2002) reported increase number of leukocytes and vascular permeability, which resulted in retinal edema post-lase).

To the best of our knowledge, there is no previous study reporting changes in peripapillary RNFL thickness after PASCAL laser in diabetic patients, let alone comparing conventional argon to PASCAL laser. It is interesting to note that, in the present study, the PASCAL laser produced more thickening of the peripapillary RNFL compared to the argon group immediately after multi-session PRP. Also, the increased thickening continued to progress even at four months post treatment. The common argon laser setting for retinal ablation was 100–200 ms duration and the power used ranged from 150–350 mW. The PASCAL laser, on the other hand, uses higher power to deliver the same amount of energy with extremely shorter pulse duration of 10 ms (Lee et al. 2013). Therefore, in general the amount of energy received by the lasered area is lower compared to the conventional argon treatment (Velez-Montoya et al. 2010). The possible explanation at this point is the probability of higher power used during PASCAL laser induces greater inflammatory responses compared to the argon laser. Paulus et al. (2011) in another study, described the histological changes of retina in rabbits post pascal laser. Spot size used was less than 60um with lacking of description on the power used. The authors observed accumulation of oedema between the outer segment and RPE layer. Resolution was seen as early as one month with persistent preservation of the inner retinal layer (Paulus et al. 2011). Similar observation might occur in vivo. However, direct comparison with our findings might not be feasible. Despite uncertain explanation for the persistent peripapillary retinal swelling in our study, it is important to note that the retinal cells react differently with PACAL

laser. Evaluation of peripapillary RNFL in such cases immediate post laser will not represent the actual RNFL thickness and has to be evaluated with caution.

Although the limitations of this study were due to the short duration of follow-up, our findings are significant enough to indicate a difference in tissue response between these two treatment modalities. Longer follow-up in larger study scale might help to determine the onset of RFNL thickening resolution that is known to occur with time. Another limitation involved the use of time domain OCT which is the earlier version of biomicroscope. Time domain OCT was the only machine available during the study period. Therefore, future study design the latest spectral domain OCT will be able provide additional biomicroscope changes and offer better explanation for such changes.

In conclusion, transient thickening of the RNFL occurs post-PRP in both conventional and PASCAL laser patients. However, the PASCAL laser seems to produce more cellular reaction, hence increases the RFNL thickness to a greater extent than the argon laser group. This is important as RFNL measurements have been incorporated as one of the gold standards of glaucoma evaluation. Important events, such as laser treatment to the eye and type of laser used worth of consideration during OCT evaluation of RNFL thickness in such cases.

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