Effect of Diabetes Duration on Proliferative Disease Regression after Panretinal Photocoagulation Using a Conventional Laser Versus Pattern Scan Multispot Laser

Tamer Ahmed*, Ahmed Howaidy, Abd Allah El-Amin, Khalid Selim

Department of Ophthalmology, Faculty of Medicine, Aswan University, Egypt

*Corresponding author: Tamer Ahmed Ali Ahmed; **Mobile:** +201006508312; **Email:** tamerahmedali@yahoo.com

ABSTRACT

Background: Panretinal photocoagulation (PRP) is considered the gold standard for first line therapy in proliferative diabetic retinopathy (PDR). The aim of PRP is to prevent visual loss following vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma, by leading to regression of neovascularization.

Objective: The purpose of this study was to compare the effect of diabetes duration on proliferative disease regression after pan-retinal photocoagulation using a conventional green laser versus a multispot pattern scan laser.

Subjects and Methods: Eighty eyes with newly diagnosed proliferative diabetic retinopathy were randomly divided in to two groups each composed of 40 eyes: group (A) in which patients were received standard argon laser panretinal photocoagulation and group (B) in which patients were received pattern scan multispot panretinal photocoagulation. Changes in central macular thickness and BCVA at 1st, 4th, 12th week and 6th month follow-up were compared to baseline measurements. Fundus fluorescein angiography was performed at 4 weeks, 12 weeks and 6 months to assess regression of PDR.

Results: by the end of the study, complete regression occurred in 37 (92.5%) of patients in conventional laser group and 36 (90%) patients in PASCAL group, while persistence of the disease occurred in 3 (7.5%) patients in each group and recurrence occurred 1 (2.5%) in PASCAL group. There was no statistically significant correlation in each study group between clinical outcome and age or duration of DM.

Conclusion: There was no statistically significant correlation in each study group between duration of DM and proliferative disease regression.

Keywords: proliferative diabetic retinopathy, panretinal photocoagulation, pattern scan Multispot Panretinal Photocoagulation, Conventional argone laser.

INTRODUCTION

Diabetes mellitus (DM) is a major emerging clinical and public health problem in Egypt with a prevalence of 5–10% in the 1990s. It has been estimated that by the year 2025, nearly 9 million Egyptians (over 13% of the population over 20 years of age) will have DM [1, 2]. Epidemiological studies of DM and diabetic retinopathy (DR) in Middle Eastern countries including Egypt have shown a substantial heterogeneity in the reported prevalence of DM (3.4–29%) and its complications especially DR (7.6–60%), even within the same country [3, 4].

The prevalence of DR in Egypt was found to be 20.5%. Most patients (82%) were not aware of the hazards of diabetes mellitus for the eyes. The prevalence of DR was statistically significantly higher in females (22 vs.17%, p < 0.05), with longer diabetes disease duration (p < 0.001), hypertension (p < 0.001) and absence of hypertension control (p < 0.001), especially proliferative DR. Increasing age and poor glycemic control were associated with a nonsignificant increase in the rate of DR (p = 0.340 and p = 0.444, respectively) [5].

There is a strong positive relationship between the duration of diabetes and prevalence and progression of DR. Almost all type I diabetic patients and over three fourths of type II diabetic patients will have some form of DR after 20 years of the disease [6].

Since the Early Treatment Diabetic Retinopathy Research Study, panretinal photocoagulation have been the standard of care for treating patients with diabetic retinopathy. The first lasers were argon and krypton gas in blue-green wavelengths. Their use was limited because they had short wavelengths, causing light scatter, using high levels of energy inducing photochemical damage [1].

Tunable dye lasers were the next development in laser technology, maintaining the tunable lasers, however, was expensive and difficult. Further research resulted in the introduction of infrared (810 nm) and green (532 nm) wavelengths. The benefits of these lasers include reduced scatter, ease of delivery in dense ocular media, lower cost, and reduced maintenance [7]. Further development of solid-state technology brought about the production of 577-nm wavelength lasers [8].

The Pattern Scan Multispot Laser uses a proprietary, semiautomated pattern generation technique that allows rapid delivery of laser pulses, with durations of 10 ms to 20 ms at each spot, as opposed to 100 ms to 200 ms with conventional laser [9].

The purpose of this study was to compare the effect of diabetes duration on proliferative disease regression after pan-retinal photocoagulation using a conventional green laser versus a multispot pattern scan laser

PATIENTS AND METHODS
This prospective randomized clinical trial study included eighty eyes with PDR eighty eyes of 60 patients, 20 patients had both eyes done. They were newly diagnosed as proliferative diabetic retinopathy (PDR). Patients were recruited from Aswan Ophthalmology Hospital Outpatient Clinic. This study was conducted between January 2017, to June 2019.

Ethical approval
Approval of the Ethical and Technical Review Committee of Aswan Faculty of Medicine was obtained. Informed written consents were taken from all patients for the specific procedure.

The included subjects were randomly divided into two groups each composed of 40 eyes; **Group (A)** in which patients received standard argon laser panretinal photocoagulation using single spots and **Group (B)** in which patients received pattern scan multispot panretinal photocoagulation.
After randomization, group A were treated in Aswan eye & laser center and group B were treated in Aswan university hospital.

Information was collected on age, sex, indication, pre-and post-laser procedure, best corrected visual acuities (BCVA) as well as outcome and complications of treatment and intra- and post-procedure pain sensation.

Inclusion criteria:
Patients with type I or type II diabetes mellitus who were newly diagnosed as proliferative diabetic retinopathy were enrolled if they met the following criteria:
1. Patients older than 18 years of age.
2. Patients with Snellen best corrected visual acuity of 6/60 or better.
3. Adequate pupil dilatation and clear media to perform laser photocoagulation, digital photography and optical coherence tomography scans.

Exclusion criteria:
1. Patients with previous laser photocoagulation or macular laser treatment prior to the study eye.
2. Patients underwent recent intra-ocular surgeries within the last three months prior to the procedure.

3. Patients with media opacities (e.g. corneal opacity, cataract, vitreous hemorrhage) that interfere with the proper evaluation of the posterior segment.
4. Mean Central macular thickness area more than 300μ as measured by optical coherence tomography scans.
5. Patients who are contraindicated to fluorescein angiography (pregnancy, allergy to fluorescein dye, renal failure).
6. Patients with poor glycaemic control, glycated haemoglobin (HbA1c) greater than 10.0 mg/dL.
7. Patients with uncontrolled hypertension, blood pressure greater or equal to 180/110 mmHg.
8. Patients with vitreo-retinal traction.
9. Patients who are planned for intra-ocular surgery within six month from the start of the treatment.

Chosen patients were subjected to the following:
(1) Counseling the patient about the procedure and the possible complications of panretinal laser photocoagulation; (2) Detailed general and ocular history; (3) Full ophthalmological examination including best corrected visual acuity, slit-lamb examination, IOP measurement using Goldmann applanation tonometer, and dilated fundus biomicroscopy;(4)Baseline fundus fluorescein angiography; (5) Baseline optical coherence tomography to measure central macular thickness

Treatment parameters
The pupils were dilated using 1% tropicamide and Cyclophrine (Cyclopentolate HCl 50 mg + Phenylephrine HCl 500 mg) drops, and used 0.5% proparacaine-hydrochloride drops is used as topical anesthetic before the procedure. Mainster wide-field lense were used for pan retinal photocoagulation. Treatment parameters including use of a pattern or single spot, type of pattern, power, burn duration, spot size and number of burns per session were noted. Prior to starting treatment, the operator chose whether or not to do Pascal based on the random distribution after informed consents from all patients. Eighty eyes with PDR were included in this clinical trial divided into two groups:

Group (A): patients were treated with pan laser photocoagulation for PDR using conventional laser photocoagulation (Ellex Medical Pty Ltd. Integre Pro) which is a 532 nm green-light Diode Solid State Photocoagulator laser.

Group (B): patients were treated with PRP for PDR with pattern scan multisport photocoagulation using a 532nm laser with computer-guided scanning technology (PASCAL Streamline Photocoagulator, Topcon Medical Laser Systems).

Laser technique

The PASCAL PRP parameters were defined as 200 μm spot size, 20 ms pulse duration, and power was adjusted until a gray-white lesion was observed starting from 200 mW. The whole PRP treatment was performed in two sessions, for PRP, the 3×3, 4×4 and 5×5 arrays were most commonly used. Pattern array near-simultaneously setting was used with a single depression of the foot switch. All burns were placed one burn width apart. Conventional laser PRP parameters were defined as 200 μm spot size, 100 ms pulse duration, and power increased from 200 mW until a gray-white lesion was attained. Burns were placed one burn width apart. All of the patients completed the entire PRP treatment in two or three sessions. Burn distribution was greater than 2-disc diameters (DD) temporal to the fovea, no closer than one row within the arcades, and burn placement as close to the ora serrata as possible.

Pain score: A mean value between numerical rating pain score and The Wong-Baker Faces Pain Rating Scale was used to record the pain score.

Data extraction strategy

Data were extracted into a predesigned data extraction form. Information collected included age, sex, DM duaration, procedure, best-corrected visual acuity (BCVA), clinical efficacy and outcome, and complications following laser. Data were also collected on the parameters used for the treatment including power, pulse duration, number of burns per treatment session and retinal spot size.

Statistical analysis

The data was analyzed using IBM SPSS Statistics 24.0 program. Screening for extreme values in quantitative variables was done using independent t-test. Discrete and categorical variables were screened using frequency distribution, Chi-square test & Fisher Exact Test. Correlation with Pearson correlation. Visual acuities (VA) were converted from Snellen to log Mar to explore changes in vision pre- to post-laser. p value of <0.05 was considered significant and highly significant (p< 0.001).

RESULTS

Eighty eyes of 60 patients, 20 patients had both eyes done, were included in this clinical trial; of whom 26 (43.33%) were male, and 34 (56.67 %) were female with a mean age of 54.47 years (SD 8.72, range 31 - 75). There were 40 eyes in the conventional laser group (A) and 40 eyes in the PASCAL group (B).

For eyes in group A, the mean age of the patients was 52.8 (SD 8.78, range 31 - 69) of whom 18 (45%) were for males and 22 (55%) were for females. For patients in group B, the mean age of the patients was 56.14 (SD 9.55, range 35 - 75) of whom 17 (42.5%) were for males and 23(57.5%) were for females.

At baseline (table 1), there was no significant difference between the groups (p > 0.05, for all) in terms of age, sex, most recent glycated hemoglobin, DM duration, BCVA, or CMT. For patients in group A, the mean DM duration was 15 ± 9.75 (range 5 - 25), for patients in group B, the mean DM duration was 15 ± 9.25 (range 5 – 30).

Table (1): Comparison between the two studied groups regarding the demograhic data and baseline parameters.

Variables	Group A		Group B		P-value
Age	$52.8 \pm SD\ 8.78$		$56.14 \pm SD\ 9.55$		0.326
Sex	**Male**	18 (45%)	**Male**	17 (42.5%)	0.823
	Female	22 (55%)	**Female**	23 (57.5%)	
DM duration	15 ± 9.75		15 ± 9.25		0.529
Baseline HA1C	7.8 ± 1.75		7.95 ± 1.95		0.824
Baseline BCVA	0.3 ± 0.22		0.3 ± 0.21		0.596
Baseline CMT	250 ± 50		24.6 ± 45.25		0.725

Regarding laser parameters for the PASCAL group the mean power of PRP used was 525 mW (SD 125.4, range 350 - 950) and the mean number of spots used were 2820.63 (SD 394.18, range 2200 - 3700). All procedures were done in 2 sessions. For the conventional group the mean power of PRP used was 260 mW (SD 130.7, range 160 - 590) and the mean number of spots used were 2611.42 (SD 285.61, range 1782 - 3121). The majority of cases were done in 2 sessions and only in 5 cases the procedure was done in 3 sessions.

Regarding the correlation of demographic data and proliferative disease regression in both groups as shown in (table 2), there was no statistically significant correlation in each study group between clinical outcome and age or duration of DM.

Table (2): Correlation between demographic data and clinical outcome throughout the study period in each group.

		Conventional group		PASCAL group	
		r	P-value	r	P-value
Age	<50y	0.098	0.428	-0.060	0.580
	≥50y				

Duration of DM	-0.162	0.410	-0.199	0.220

- r = pearson correlation

DISCUSSION

Panretinal photocoagulation (PRP) is considered the gold standard for first line therapy in proliferative diabetic retinopathy (PDR) [1].

In our clinical trial, we prospectively investigated the clinical efficacy of a conventional panretinal photocoagulation versus PASCAL retinal photocoagulation in the treatment of PDR regarding DM duration. Eighty eyes with PDR were enrolled in our clinical trial; there were 40 eyes treated with conventional laser (group A) and 40 eyes treated with PASCAL laser (group B).

The mean power used in our present study was significantly higher with the Pascal system 525 mW (SD 125.4, range 350 – 950) than with the conventional system 260 mW (SD 130.7, range 160 – 590) (p 0.001). So higher power settings were needed with the Pascal system as compared with conventional photocoagulation.

However, these higher power levels required with the Pascal system did not result in any serious complications. This may be a reflection of the reduced laser energy per burn reaching the eye secondary to its shorter duration. Fluence is calculated as (power ×time/area), and provided that spot size remains unchanged, with a burn duration of 20 ms the fluence is less than with a 100 ms burn when titrating to the same burn intensity because of reduced diffusion of heat [10].

Another study **Blumenkranz et al.** [11] has demonstrated that 20 ms pulse durations represent an optimal compromise between reduced collateral damage and sufficient width of the therapeutic window [12].

The total number of laser spots applied to each eye was calculated for each group. In the conventional group, the mean number of PRP burns used was 2611.42 (SD 285.61, range 1782 – 3121) delivered on average over two sessions (range 2–3 sessions), and this was significantly lower than the PASCAL group 2820.63 (SD 394.18, range 2200 – 3700) delivered over two sessions, (P=0.03).

Laser parameters regarding power, spot size and number of burns that has been used in our present study was comparable to many studies like **Salamn et al.** [13], **Nagpal et al.** [14], **Muqit et al.** [15] and **Muraly et al.** [16].

In our study both groups showed favorable success rates. After 3 months complete regression occurred in 33 (82.5%) of patients in conventional laser group and 30 (75%) patients in PASCAL group, reduction of NV occurred in 5 (12.5%) patients in conventional group and 3 (7.5) in the PASCAL group, while persistence of the disease occurred in 2 (5%) patients in conventional laser group and 7 (17.5%) in PASCAL group. More laser photocoagulation was need for patients who developed partial regression or persistence of PDR.

The average power with the conventional photocoagulator for these 7 procedures was 346 mW (135.6 SD, range 250 – 590), and the mean number of burns was 725 (SD 235.2, range 410–850). The Pascal parameters used for these 10 procedures were as follows: mean power was 500 mW (150.2 SD, range 350 – 800), and the mean number of burns was 850 (SD 290.18, range 550–1400).

After 6 months complete regression occurred in 37 (92.5%) of patients in conventional laser group and 36 (90%) patients in PASCAL group while persistence of the disease occurred in 3 (7.5%) patients in each group and recurrence occurred in 1 (5%) in PASCAL group.

In a study by **Muraly et al.** [16] comparing PASCAL and 532 nm conventional laser, one eye of each patient was treated with single session PRP using the PASCAL system (mean 2,795 spots), while the other eye was treated with multi-sessions PRP using a conventional laser over 2 or 3 sessions (mean 1,414 spots). PASCAL PRP was 90% effective and conventional PRP was 64% effective at 1 month; both were 98% effective at 6 months.

In the Manchester Pascal Study, **Muqit et al.** [15] studied 40 eyes of 24 patients with PDR. Half of the eyes were treated with 1,500 single spots at 100 ms duration using PASCAL over the course of 3 sessions at 2-week intervals; the other eyes were treated with 1,500 spots in a single session of 20-ms multispot laser. Twelve weeks after treatment, single session PRP was 74% effective and multi-session PRP was 53% effective, although the difference was not statistically significant.

In this study regarding the correlation of diabetes duration and proliferative disease regression there was no statistically significant correlation in each study group between clinical outcome and age or duration of DM.

CONCLUSION

There is no effect of diabetes duration on proliferative disease regression after pan-retinal photocoagulation using a conventional laser versus pattern scan multispot laser

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