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Original Article

Aqueous Flare and Intraocular Pressure in the Early Period Following Panretinal Photocoagulation in Patient with Proliferative Diabetic Retinopathy

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Abstract

Objectives: The aim of the study was to investigate the effect of panretinal photocoagulation (PRP) on aqueous flare and intraocular pressure (IOP) in the early period.

Methods: Eighty-eight eyes of 44 patients were included in the study. The patients underwent a full ophthalmologic examination including the best corrected visual acuity, IOP measured by Goldmann applanation tonometry, biomicroscopy, and dilated fundus examination before PRP. Aqueous flare values were measured by the laser flare meter. Aqueous flare and IOP values were repeated in both eyes at the 1st and 24th h after PRP. The eyes of the patients who underwent PRP were included in the study as the study group, and the other eyes as the control group.

Results: In eyes treated with PRP, 1st h (19.44 pc/ms) and 24th h (18.53 pc/ms) aqueous flare values were statistically higher than before PRP (16.66 pc/ms) ($p<0.05$). In the study eyes which were similar to the control eyes before PRP, the aqueous flare was higher at the 1st and 24th h after PRP compared to control eyes ($p<0.05$). The mean IOP at the 1st h (18.69 mmHg) after PRP in study eyes was higher than both pre-PRP (16.25 mmHg) and post-PRP 24th h (16.12 mmHg) IOP values ($p<0.001$). At the same time, the IOP value at the 1st h after PRP was higher than the control eyes ($p=0.001$). No correlation was observed between aqueous flare and IOP values.

Conclusion: An increase in aqueous flare and IOP values was observed after PRP. Besides, the increase in both values starts even in the 1st h, and the values at 1st h are the highest values. At the 24th h, while IOP values return to baseline, aqueous flare values are still high. In patients who may develop severe intraocular inflammation or cannot tolerate increased IOP (such as previous uveitis, neovascular glaucoma, or severe glaucoma), control should be performed at the 1st h after PRP to prevent irreversible complications. Furthermore, the progression that may develop in diabetic retinopathy due to increased inflammation should also be kept in mind.

Keywords: Aqueous flare, diabetic retinopathy, intraocular pressure, laser flare cell photometry, panretinal photocoagulation

Introduction

Diabetic retinopathy (DRP), one of the leading causes of preventable blindness, is the most common microvascular complication of diabetes mellitus (1). Panretinal photocoagulation (PRP) has been the mainstay therapy in proliferative DRP (PDR) since the 1970 s, and it is effective in the regression of neovascularizations. It is thought that the mechanism of PRP efficacy is to suppress the release of vascular endothelial growth factor by destroying the hypoxic retina and to improve oxygenation from the inner retina to the choroid by thinning the retina (2).

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Laser flare cell photometry is a non-invasive device that determines the amount of protein in the aqueous humor objectively and quantitatively (3). Aqueous flare value, which is an indicator of intraocular inflammation and blood-aqueous barrier damage, has many clinical uses such as uveitis, postoperative inflammation, and the effectiveness of anti-inflammatory drugs (4).

In this study, we aimed to investigate the effect of PRP on intraocular inflammation in the early phase by monitoring aqueous flare values with a laser flare meter in eyes with PDR. In addition, other purposes of our study were to examine the change in intraocular pressure (IOP) after PRP and the correlation between aqueous flare and IOP.

Methods

The records of 352 patients who underwent PRP due to PDR in one eye Department of Retina Beyoglu Eye Training and Research Hospital between January and March 2021 were reviewed retrospectively. Patients who underwent PRP in one eye but not in the other eye were included in the study. Patients who had previous ocular surgery, patients using steroids or other anti-inflammatory drugs, patients who received anti-VEGF therapy in the past month, patients with a history of ocular trauma/uveitis, and patients with vitreous hemorrhage, macular edema, tractional retinal detachment, and patients with HbA1c higher than 8.0 were excluded from the study. PRP applied eyes were taken as the study group and the other PRP-naive eyes were taken as the control group.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee with the decision number 13/2 on May 13, 2022. Informed consent was obtained from all patients in the study.

All patients underwent a full ophthalmologic examination before retinal photocoagulation. The best corrected visual acuity, IOP measured by Goldmann applanation tonometry, biomicroscopy, and dilated fundus examination findings were recorded. The other systemic/ocular diseases, surgeries, and drug use were questioned.

Retinal photocoagulation was performed with the pattern scan laser (PASCAL) system (PASCAL Synthesis, Topcon Medical Laser Systems, Santa Clara, CA) with a 200 micron spot size and an exposure time of 20–30 ms. The laser power was started with 200 mW and increased until a gray-white lesion was formed on the retina. 1000–1200 numbers of pulse were made in a single session. Any medication was not administered after PRP.

The laser flare meter (FC-700, Kowa Co. Ltd, Tokyo, Japan) was used to measure flare of aqueous humor. Measurements were performed by the same clinician. The mean of five consecutive reliable measurements was taken as the aqueous flare value. The values of flare meter were expressed as photon counts per millisecond (pc/ms).

Laser flare photometry and Goldmann applanation tonometry were both performed just before PRP and at the 1st and 24th h after PRP. At each visit, measurements were performed in both eyes consecutively and the other eye was accepted as the control eye.

"Statistical Package for the Social Sciences" version 20 software was used for statistical analysis. Continuous variables were reported as mean, standard deviation, and range. Categorical variables were expressed as absolute numbers and percentages. After evaluating the normality of the data with the Shapiro–Wilk test; the repeated measures analysis of variance (ANOVA) test with Greenhouse-Geisser correction was used to compare the values before and after retinal photocoagulation. If there was a significant difference with the repeated measures ANOVA test, Bonferroni correction was used to adjust of pairwise comparisons. Comparisons with the control eyes were made using an independent sample t-test. The correlation between variables was evaluated with the Pearson correlation coefficient. If $p<0.05$, the difference between values was considered statistically significant.

Results

Eighty-eight eyes of 44 patients (14 female–30 male) were included in the study. Sixteen right and 28 left eyes were study eyes. The mean age of the patients was 57.0±5.35 years (Range: 49–70 years). The mean best corrected visual acuity was 0.29±0.28 (Snellen).

Before PRP, the mean aqueous flare value of the eye to be treated was 16.66±6.77 pc/ms. The mean aqueous flare value was 19.44±7.40 pc/ms at the 1st h after the PRP; 18.53±7.76 pc/ms at the 24th h in study eyes. An average of 2.97 pc/ms (Range: −3.10–11.70 pc/ms) change was observed in aqueous flare values at 1 h. There was an increase in aqueous flare values in 33 (75%) patients at 1st h after PRP. The aqueous flare values of 11 (25%) patients did not change at the 1st h after PRP. Both 1st h and 24th h aqueous flare values were statistically significantly higher than the pre-photocoagulation value ($p<0.001$, $p=0.03$; respectively). There was no statistically significant difference between the mean aqueous flare values at the 1st h and at the 24th h ($p=0.83$) (Table 1). No patient had posterior synechiae and clinically detectable anterior chamber reaction after PRP. The mean aqueous flare values in the other eyes were 16.89±7.19 pc/ms before photocoagulation, 16.48±7.89 at 1 h, and 16.06±7.19 at 24 h. These values were found to be statistically similar ($p=0.27$) (Table 1). The mean aqueous flare value of study eyes was similar to

Table 1. Aqueous flare values and changes in study eyes and control eyes

Aqueous flare (pc/ms)	PRP applied eyes (study eyes)	Other eyes (Control eyes)	p
Before PRP	16.66±6.77	16.89±7.19	0.754
1st h	19.44±7.40	16.48±7.89	0.032*
24th h	18.53±7.76	16.06±7.19	0.037*
P' value	0.001*	0.27	
PRP applied eye before photocoagulation-1st h			p<0.001*
Before photocoagulation-24th h			0.03*
1st h–24th h			0.83

PRP: Panretinal photocoagulation, P values based on independent sample t-test (comparisons of control eyes and study eyes) and multiple comparisons with Bonferroni correction (post-hoc test- comparisons of data of study eyes at different times). P' based on repeated measures analysis of variance (ANOVA) test with Greenhouse-Geisser correction.

the control eyes before PRP (p=0.75); but higher in study eyes at the 1st h and 24th h (p=0.03, p=0.04; respectively).

The mean IOP values were 16.25 ± 3.36 mmHg before PRP, 18.69±4.55 mmHg at 1st h after PRP, and 16.12±4.27 mmHg at 24th h in study eyes. The mean IOP value at the 1st h after PRP was statistically significantly higher than both pre-photocoagulation and 24th h IOP values (each p<0.001). There was no statistically significant difference between the IOP values before PRP and at the 24th h after PRP (p=0.98). The mean IOP value in the other eyes was 15.47±2.67 mmHg before photocoagulation, 15.00±3.26 mmHg at 1 h, and 14.53±2.54 mmHg at 24 h. These values were found to be statistically similar (p=0.06) (Table 2). The mean IOP of eyes treated with PRP was statistically significantly higher than the control group at the 1st h after PRP (p=0.001). There was no statistically significant difference between control eyes and study eyes at the 24th h after PRP and before PRP (p=0.08, p=0.61; respectively).

Correlation between aqueous flare and IOP was presented in Table 3. There was no correlation between aqueous flare and IOP values. However, IOP and aqueous flare values were correlated within themselves (Table 3).

Discussion

Inflammation, which has essential role in the pathophysiology of DRP, is thought to be the cause of the deterioration of the blood aqueous barrier. Any procedure applied in the presence of blood-aqueous barrier break-down can accelerate further blood-aqueous barrier deterioration and increase flare values. In this study, we aimed to examine the effect of PRP, which is one of the main treatment of PDR, on aqueous flare and IOP in early period. Thus, we tried to find the answers to the questions of whether patients at risk for anterior chamber inflammation and IOP increase should be checked in the early period after PRP and when the control visit should be.

Inflammation in PDR has been investigated in many studies before, and an increase in the level of inflammatory mediators in both serum and ocular fluids in DRP has been proven (5-7). The previous studies have identified an

Table 2. Intraocular pressure values and changes in study eyes and control eyes

Intraocular pressure (mmHg)	PRP applied eyes (study eyes)	Other eyes (control eyes)	p
Before PRP	16.25±3.36	15.47±2.67	0.611
1st h	18.69±4.55	15.00±3.26	0.001*
24th h	16.12±4.27	14.53±2.54	0.076
P' value	<0.001*	0.06	
PRP applied eye before photocoagulation-1st h			p<0.001**
Before photocoagulation-24th h			0.98
1st h–24th h			<0.001**

PRP: Panretinal photocoagulation, P values based on independent sample t-test (comparisons of control eyes and study eyes) and multiple comparisons with Bonferroni correction (post-hoc test- comparisons of data of study eyes at different times). P' based on repeated measures analysis of variance (ANOVA) test with Greenhouse-Geisser correction.

Table 3. Correlation between aqueous flare and intraocular pressure values

	Flare^{1}	**Flare^{2}**	**IOP^{0}**	**IOP^{1}**	**IOP^{2}**
Flare^{0}	P=<0.001r=0.889**	P=<0.001 r=0.855**	P=0.519 r=<0.100	P=0.783 r=<0.043	P=0.403 r=0.153
Flare^{1}		P=<0.001 r=0.816**	P=0.450 r=0.117	P=0.334 r=0.149	P=0.162 r=0.253
Flare^{2}			P=0.803 r=0.046	P=0.361 r=0.167	P=0.861 r=0.032
IOP^{0}				P=<0.001 r=0.845**	P=<0.001 r=731**
IOP^{1}					P=<0.001r=0.795**

Flare^{0}: Aqueous flare before photocoagulation, Flare^{1}: Aqueous flare at 1st h after photocoagulation, Flare^{2}: Aqueous flare at 24th h after photocoagulation, IOP^{0}: Intraocular pressure (IOP) before photocoagulation, IOP1: IOP at 1st h after photocoagulation, IOP^{2}: IOP at 24th h after photocoagulation, **: Statistically significant at the p<0.01, r: Pearson correlation coefficient.

increase in inflammatory mediators in both vitreous, tear, and aqueous humor. Increased acute phase response components and complement system elements in the vitreous, and increased levels of apolipoprotein and glycoprotein in the aqueous humor are just a few examples (8). This well-known inflammation in PDR patients leads to increased vascular permeability and disruption of the blood-retina barrier. As a result of all these, the development of macular edema and a decrease in visual acuity occur (9). While PRP is an important treatment option for neovascularization, the fact that PRP also increases inflammation may paradoxically trigger diabetic macular edema. Therefore, DRP patients may need to be followed closely in terms of macular edema and decreased vision after PRP. In addition, increased inflammation may lead to complications such as fibrin formation and posterior synechia in patients with existing anterior chamber inflammation, such as uveitic patients and neovascular glaucoma patients. Or the activation/progression in uveitis patients may be the result of increased inflammation.

While aqueous flare values are 2.9–3.9 pc/ms in the healthy subjects between 20 and 40 years of aged, it increases with aging and reaches 5.0–6.5 pc/ms in the subjects between 70 and 80 years of aged (10-13). The previous studies have shown increased aqueous flare values in diabetic background retinopathy, diabetic macular edema, and PDR (14-17). Noma et al. reported higher aqueous flare values in patients with diabetic macular edema than in patients with macular hole, respectively, 17.1 pc/ms, 4.5 pc/ms (14). While Moriarty et al. obtained higher flare values in diabetic eyes than control eyes, they also observed higher flare values in PDR than in background retinopathy (15). On the other hand, Çelik Büyüktepe et al. found higher aqueous flare intensity in diabetic eyes with retinopathy than in diabetic eyes without retinopathy (16). Diabetic eyes without retinopathy had higher flare values compared to the control group in the same study (16). Ikegami et al. found higher flare values in diabetic eyes than in non-diabetic eyes (7.42 pc/ms, 5.57 pc/ms; respectively) (17). In this present study, the aqueous flare values were quite high before PRP in both study and control eyes (16.66 pc/ms, 16.89 pc/ms; respectively).

It is a concern whether interventions that increase inflammation in DRP will cause further deterioration of the already impaired blood retinal and blood aqueous barriers. For example, Ikegami et al. showed that the increase in central macular thickness and aqueous flare were higher in diabetic eyes than controls after cataract surgery and the continued in the 3rd post-operative month (17). Since PRP is one of the main treatments in DRP, researchers have been wondering for many years whether it will further break down the already impaired blood-aqueous barrier in diabetic patients. The mechanism by which PRP disrupts the blood-aqueous barrier is still not fully elucidated. Protein release by causing blood-aqueous barrier damage with direct effect, increased anterior segment vascular permeability with the release of some mediators, and thermal damage are possible mechanisms suggested (18). Moriarty et al. observed an increase in flare values at the 3rd, 24th, and 48th h after the PRP (19). They did not encounter uveitis and synechia in any of the patients they followed (19). Larsson et al. evaluated the aqueous flare values of 20 patients at the 10th and 90th days after PRP (18). In that study, aqueous flare values at 10th and 90th day were statistically significantly higher than pre-PRP flare values (18). In our study, there was an increase in aqueous flare values similar to these studies. In addition to these studies, we would like to state that this increase started even in the 1st h. In fact, the 1st h values are numerically higher than the 1st day values, although not statistically significant (19.44 pc/ms, 18.53 pc/ms; respectively). However, no patient had posterior synechiae and significant anterior chamber reaction. Activation of uveitis may occur in patients with a previous history of uveitis attack. In our study, there was no patient with a previous history of uveitis. Although more studies are needed on this subject, especially in risky eyes, patients can be checked for inflammatory reactions in the 1st h.

There are studies showing an increase in IOP after the PRP in the literature. In their study, Lata et al. encountered a significant increase in IOP values at the 1st h and observed a return to the baseline on the 1st day (20). Similarly, Birinci et al. also observed an increase in the IOP values at the 1st h after the PRP (21). Again, on the 1st day, the IOP values returned to the baseline (21). In our study, the IOP values increased at the 1st h and returned to the baseline on the 1st day, which was consistent with these studies. These results suggest that IOP measurement at 1 h may be necessary to prevent irreversible optic disc damage in cases where acute IOP elevation is important, such as severe glaucoma and optic disc damage. At the same time, the strong correlation between pre- and post-photocoagulation IOP values indicates that pre- IOP values can be instructive.

There is no other study in the literature examining the correlation between aqueous flare and IOP after PRP. We did not observe any correlation between flare and IOP in this present study. We thought that the increase in IOP at the 1st h was secondary to inflammation. However, on the 1st day, although the anterior chamber inflammation continued, the increase in IOP ceased.

Lata et al., in their study comparing the effects of conventional laser and PASCAL laser on IOP, observed an increase at the 1st h and 6th h in IOP after both laser applications (20). Similar to our study, 1st day IOP values returned to normal levels (20). In their study, more increase of IOP values was observed with the PASCAL laser, which is less destructive on the retina and choroid, than with the conventional laser (20).

The major limitation of our study is the retrospective design of the study and short follow-up period. However, our main purpose is to determine when the flare and IOP increase starts. Therefore, we did not plan this study with a long follow-up period. Prospective studies examining when flare values return to pre-PRP values may contribute to the literature. In addition, although we excluded patients with HbA1c above 8.0 from this study, the results may have been affected by individual blood glucose and HbA1c levels.

Conclusion

Aqueous flare and IOP values increase in eyes with PDR following PRP in the early period. The increase in both values starts even at the 1st h. While IOP values return to the baseline; the increase in the aqueous flare still continues at the 24th h. Anterior chamber reaction and IOP monitoring at the 1st h after PRP may be important in terms of severe complications in patients in whom this increase poses a risk. At the same time, care should be taken in terms of the progression of DRP/macular edema that may occur as a result of increased inflammation.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (no: 13/2, date: 13.05.2022).

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Conflict of Interest: None declared.

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References

1. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: Systematic review and meta-analysis. Ophthalmology 2021;128:1580–91. [CrossRef]
2. El Rami H, Barham R, Sun JK, Silva PS. Evidence-based treatment of diabetic retinopathy. Semin Ophthalmol 2017;32:67–74.
3. Ladas JG, Wheeler NC, Morhun PJ, Rimmer SO, Holland GN. Laser flare-cell photometry: Methodology and clinical applications. Surv Ophthalmol 2005;50:27–47. [CrossRef]
4. Tugal-Tutkun I, Herbort CP. Laser flare photometry: A noninvasive, objective, and quantitative method to measure intraocular inflammation. Int Ophthalmol 2010;30:453–64. [CrossRef]
5. Gerhardinger C, Costa MB, Coulombe MC, Toth I, Hoehn T, Grosu P. Expression of acute-phase response proteins in retinal Muller cells in diabetes. Invest Ophthalmol Vis Sci 2005;46:349–57.
6. Funatsu H, Yamashita H, Sakata K, Noma H, Mimura T, Suzuki M, et al. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. Ophthalmology 2005;112:806–16. [CrossRef]
7. Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW, et al. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes 2005;54:1559–65. [CrossRef]
8. Youngblood H, Robinson R, Sharma A, Sharma S. Proteomic biomarkers of retinal inflammation in diabetic retinopathy. Int J Mol Sci 2019;20:4755. [CrossRef]
9. Kempen JH, O'Colmain BJ, Leske MC, Haffner SM, Klein R, Moss SE, et al. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol 2004;122:552–63. [CrossRef]
10. Shah SM, Spalton DJ, Smith SE. Measurement of aqueous cells and flare in normal eyes. Br J Ophthalmol 1991;75:348–52.
11. Guillén-Monterrubío OM, Hartikainen J, Taskinen K, Saari KM. Quantitative determination of aqueous flare and cells in healthy eyes. Acta Ophthalmol Scand 1997;75:58–62. [CrossRef]
12. Oshika T, Kato S. Changes in aqueous flare and cells after mydriasis. Jpn J Ophthalmol 198;33:271–78.
13. Sawa M. Laser flare-cell photometer: Principle and significance in clinical and basic ophthalmology. Jpn J Ophthalmol 2017;61:21–42. [CrossRef]

14. Noma H, Mimura T, Yasuda K, Shimura M. Role of inflammation in diabetic macular edema. Ophthalmologica 2014;232:127–35.
15. Moriarty AP, Spalton DJ, Moriarty BJ, Shilling JS, Ffytche TJ, Bulsara M. Studies of the blood-aqueous barrier in diabetes mellitus. Am J Ophthalmol 1994;117:768–71. [CrossRef]
16. Celik Buyuktepe T, Özmert E, Demirel S, Batıoğlu F. Role of inflammation in retinal microcirculation in diabetic eyes: Correlation between aqueous flare and microvascular findings. Ophthalmologica 2020;243:391–8. [CrossRef]
17. Ikegami Y, Takahashi M, Amino K. Evaluation of choroidal thickness, macular thickness, and aqueous flare after cataract surgery in patients with and without diabetes: A prospective randomized study. BMC Ophthalmol 2020;20:102. [CrossRef]
18. Larsson LI, Nuija E. Increased permeability of the blood-aqueous barrier after panretinal photocoagulation for proliferative diabetic retinopathy. Acta Ophthalmol Scand 2001;79:414–6.
19. Moriarty AP, Spalton DJ, Shilling JS, Ffytche TJ, Bulsara M. Breakdown of the blood-aqueous barrier after argon laser panretinal photocoagulation for proliferative diabetic retinopathy. Ophthalmology 1996;103:833–8. [CrossRef]
20. Lata S, Venkatesh P, Temkar S, Selvan H, Gupta V, Dada T, et al. Comparative evaluation of anterior segment optical coherence tomography, ultrasound biomicroscopy, and intraocular pressure changes after panretinal photocoagulation by pascal and conventional laser. Retina 2020;40:537–45. [CrossRef]
21. Birinci H, Abidinoglu MR, Oge I. Anterior chamber depth and intraocular pressure following panretinal argon laser photocoagulation for diabetic retinopathy. Ann Saudi Med 2006;26:73–5.