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THE ASSOCIATION BETWEEN VITREOUS VASCULAR ENDOTHELIAL GROWTH FACTOR LEVELS WITH VISUAL ACUITY BEFORE AND AFTER PARS PLANA VITRECTOMY IN PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT

Introduction: *Vascular endothelial growth factor (VEGF) plays a crucial role in the development of proliferative diabetic retinopathy. Elevated levels of VEGF in the vitreous have been found to be associated with the severity of ischemia and neovascularization, which can lead to a decline in visual acuity. This study aims to determine the association between vitreous VEGF levels and improvement in visual acuity before and after PPV in PDR patients.*

Methods: *This research is an analytic observational study with a pre-post single group design. The subjects of this study were all PDR patients who received PPV therapy at three hospital in Bali Province, Indonesia. Consecutive sampling method were conducted. The independent variable is vitreous VEGF, whilst pre and post-PPV visual acuity is the outcomes. We performed mean comparison and multivariable statistical test using IBM SPSS version 25.*

Result*: 45 people were included in this study. Improvement in visual acuity after PPV compared to before PPV with an average improvement of 0.54 logMAR (p=0.001). Based on the ANCOVA multivariate analysis, factors affecting visual acuity improvement after PPV were preoperative vision (p<0.001), postoperative vision (p<0.001), HbA1c level (p=0.036), and DM duration (p=0.024). There was no association between high vitreous VEGF levels and visual acuity improvement (PR=0.95; 95% CI=0.55-1.63;p=0.841).*

Conclusion*: This study concluded that there is an association between PPV and visual acuity improvement. However, clinicians should be aware of several confounding factors that affect visual acuity improvement, including pre-PPV visual acuity, post-PPV visual acuity, duration of DM, and HbA1c level. There is no relationship between vitreous VEGF and visual acuity before and after PPV in PDR, but it is necessary to keep good records of lens status and intraocular pressure status. Further research is needed and the research time is extended to evaluate a better visual outcome.*

Keywords: vascular endothelial growth factor, pars plana vitrectomy, proliferative diabetic retinopathy, visual acuity.
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INTRODUCTION

Diabetic Retinopathy (DR) is a vascular disorder of the retina that occurs due to diabetes mellitus (DM). Currently, at least 150 million people worldwide are affected by diabetic retinopathy, and it is estimated that this number will double by 2025. In Indonesia, about 42% of patients with DM have diabetic retinopathy, and 6.4% of them are proliferative retinopathy. About 50% of Non-Proliferative Diabetic Retinopathy (NPDR) patients become proliferative within 1 year.[1–3]

Proliferative Diabetic Retinopathy (PDR) is a more advanced level of DR. There is new blood vessel formation induced by retinal ischemia, which spreads either from the disc (neovascularization of the disc, NVD) or from other parts of the retina (neovascularization elsewhere, NVE). These new blood vessels will extend into the vitreous. PDR is characterized by retinal neovascularization, serum leakage, hemorrhage, and fibrovascular proliferation in the retinal vitreous fluid, which will result in vitreous hemorrhage and traction retinal detachment.[3]

Pars plana vitrectomy (PPV) is an effective surgical therapy for PDR. However, in some patients, PDR continues to develop after the surgical procedure. In recent studies, Anti-VEGF therapy is effective in inhibiting intraocular neovascularization and improving visual function. Intravitreal injection of antivascular endothelial growth factor (anti-VEGF) has been tested, although the results are still inconsistent.[4,5]

The process of neovascularization in the retina depends on the production of growth factors induced by hypoxic conditions. Vascular endothelial growth factor is the dominant proangionic factor in the development of PDR, triggering endothelial cell migration and proliferation and increased blood flow and microvascular permeability. Any pathological process affecting the retina, such as ischemia, inflammation, oxidative stress, vascular injury, or detachment, can cause an increase in vitreous levels in the retina.[6–9]

The basis of PDR progression is angiogenesis, and VEGF plays an important role in the process. Proliferative diabetic retinopathy (PDR) causes inflammation in the retina and vitreous, cytokine and matrix metalloproteinase imbalance, and retinal hypoxia which triggers an increase in VEGF levels. This is demonstrated by the finding of increased levels of VEGF in vitreous fluid and fibrovascular tissue in eyes with PDR. The progression of PDR can also cause deterioration of visual acuity due to recurrent vitreous hemorrhages, traction retinal detachment, fibrovascular membranes in the vitreous, and macular edema.[10,11]

Vitreous VEGF levels before the PPV process may be considered as a predictive factor for improvement in visual acuity. However, results from several studies regarding the role of vitreous VEGF levels in the pathogenesis and prognosis of PDR is still uncertain, and the optimal treatment strategy for PDR patients with high vitreous VEGF levels is still unknown.[10,12–15] We conducted this research to address this gap and to provide more insight into the factors that affect the visual acuity improvement after PPV in PDR patients. Therefore, this study aims to identify the association between VEGF levels with visual acuity before and after PPV in proliferative diabetic retinopathy.

The study result may help to identify the PDR patients who are most likely to benefit from PPV based on their preoperative visual acuity, HbA1c level, and DM duration. Additionally, the results may enhance our understanding of the role of VEGF in PDR development and progression.

METHODS

The research in this study used an analytical observational approach, utilizing a pre-post single group design. This study took place over a span of 6 months at Sanglah General Hospital, Bali Mandara Eye Hospital (RSMBM), and Ramata Eye

Hospital. Additionally, the Biochemistry Laboratory at the Faculty of Medicine, Udayana University, served as the reference facility for examining vitreous VEGF levels. Ethical clearance was obtained from the local review board with reference letter number LB.02.01/XIV.2.2.2/45707/2022.

The study focused on individuals diagnosed with Proliferative Diabetic Retinopathy (PDR) who underwent PPV therapy at Prof. I.G.N.G. Ngoerah General Hospital, Bali Mandara Eye Hospital, and Ramata Eye Hospital. The sample were selected through consecutive sampling, where all subjects fulfill the sample acceptance criteria were included until the required sample size was achieved. Minimum required sample was 43, which was calculated using correlation study sample size formula.[16]

The study's inclusion criteria encompassed individuals with type 2 DM, those diagnosed with PDR through VEGF panretinal photocoagulation, and individuals willing to provide informed consent. Conversely, the exclusion criteria consisted of patients with a history of vitreoretinal surgery, prior treatment involving anti-VEGF derivatives, history of retinal laser, history of uveitis or ocular inflammation, media opacity, corneal disorders, and vitreous opacity.

The independent variable in this research is vitreous VEGF, presented in numerical scale (ng/ml). The dependent variable is changes in pre- and post-operative best-corrected visual acuity (BCVA) measured in logMAR. Changes in BCVA were further categorized as improved if the difference was ≥0.3 logMAR, otherwise they were not considered improved. Furthermore, we controlled for other covariates such as patients' sex, age, HbA1c level, presence of cataract, macular edema, history of hypertension, hypercholesterolemia, and duration of DM.

The research commenced by conducting a comprehensive history and physical examination of PDR patients seeking PPV preparation at hospitals within the Denpasar city area. Patients who completed the history-taking and physical examination and met the inclusion criteria were then invited to provide informed consent, granting permission for their participation in the study. Before undergoing the PPV procedure, we conducted a visual acuity assessment using the Snellen chart and assessed the macula using macular optical coherence tomography. We then converted the visual acuity measurement unit using the Snellen chart to logMAR conversion table.

During the PPV procedure, a 1 ml vitreous fluid sample was extracted and stored in a sterile container, subsequently subjected to laboratory analysis to determine vitreous VEGF levels. A follow-up visual acuity assessment was performed six weeks post-PPV, again using the Snellen chart. Finally, data analysis was conducted as illustrated in Figure 1, outlining the overall research workflow.

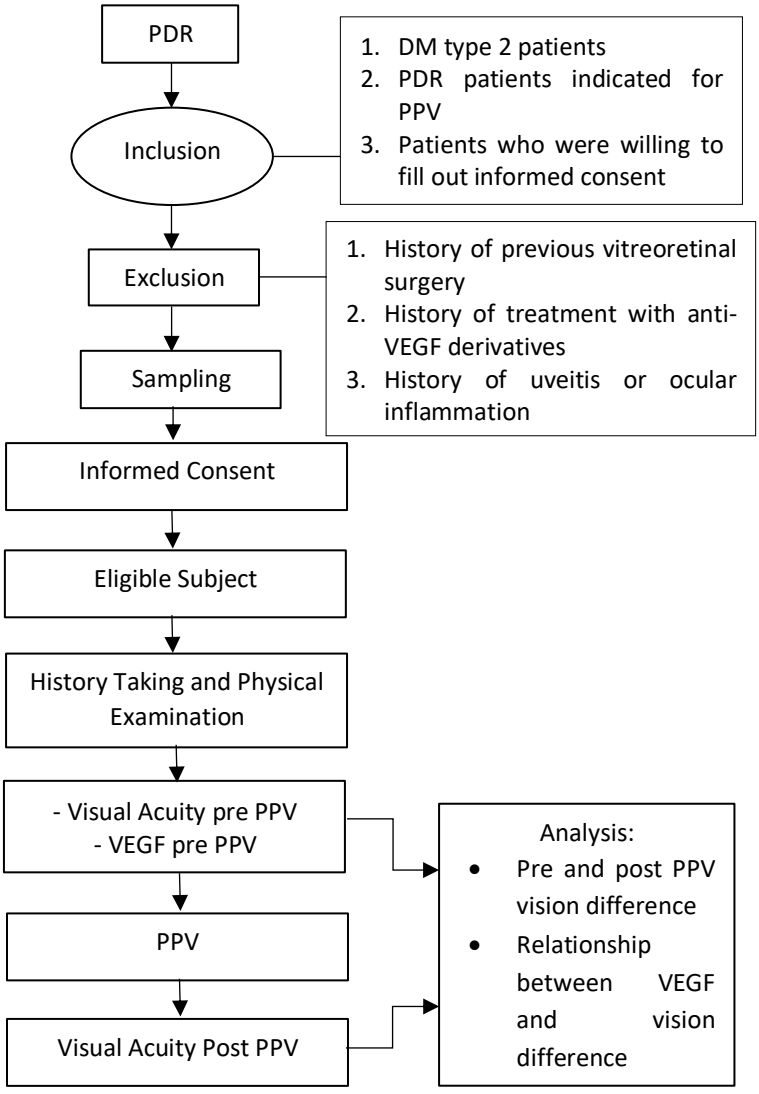

Figure 1. **Schematic of the Research Flow**

Data on patient characteristics were collected either through interviews or extracted from their medical records. The procedure for assessing vitreous VEGF levels involved the acquisition of research specimens and the subsequent VEGF level analysis using the ELISA method, which was conducted at the Biochemistry Laboratory within the Faculty of Medicine at Udayana University. The specimen obtained was vitreous fluid extracted from the patients' eye, following this process: Firstly, the designated area was thoroughly disinfected. Secondly, local anesthesia was administered through a retrobulbar and peribulbar injection of 2% lidocaine. Thirdly, 1 ml of vitreous fluid was aspirated from the mid-vitreous using a vitreous cutter and placed in a sterile Eppendorf tube. Lastly, the specimens were preserved at -20°C until the time of analysis.

Data recorded on the data collection sheet, which had been meticulously organized, processed, and analyzed, was analyzed using SPSS version 25.0 software on a Windows computer. Descriptive data analysis was utilized to examine general characteristics and variable distributions such as age, gender, duration of diabetes mellitus (DM), metabolic diseases, and intraocular VEGF levels. The Shapiro-Wilk method was employed to perform a data normality test, determining the distribution of VEGF levels and visual acuity before and after PPV. If the data exhibited normal distribution, a dependent t-test was employed, while Wilcoxon's test was used for non-normally distributed data to compare pre-PPV and post-PPV outcomes. We conducted receiver operating characteristic (ROC) curve analysis to determine the cut-off for vitreous level. This cut-off will be used to classify the samples into high and low categories. Correlation and multiple linear regression tests were conducted to ascertain the association between vitreous VEGF levels and changes in visual acuity before and after PPV. A simple logistic regression test was utilized to investigate the association between vitreous VEGF levels and the occurrence of post-PPV visual improvement. Co-variate analysis (ANCOVA) was employed to compare control variables, such as age, sex, other metabolic diseases, DM duration, cataracts, corneal status, and macular edema. The significance level was set at a p-value of <0.05.

RESULTS

This study obtained a total of 45 samples of PDR patients who received PPV therapy. The study subjects had a mean age of 51.82 ± 10.8 years and were dominated by male gender (62.2%).

Table 1. **Characteristics of the Research Subjects**

Variabel	n=45
Age (year), mean ± SD	51.82 ± 10.8
Gender, n (%)	
Male	28 (62.2)
Female	17 (37.8)
Hypertension, n (%)	
Yes	23 (51.1)
No	22 (48.9)
Cataract, n (%)	
Yes	6 (13.3)
No	39 (86.7)
Corneal disorders, n (%)	
Yes	0 (0.0)
No	45 (100)
Macula edema, n (%)	
Yes	36 (80.0)
No	9 (20.0)
Hypercholesterolemia	
Yes	7 (15.6)
No	38 (84.4)
Tamponade, n (%)	
Silicone Oil (SO)	11 (24.4)
Gas	34 (75.6)
Macula, n (%)	
On	36 (80.0)
Off	9 (20.0)
Redetachment, n (%)	
Yes	1 (2.2)
No	44 (79.8)
Glaucoma, n (%)	
Yes	6 (13.3)
No	39 (86.7)
Rebleeding, n (%)	
Yes	1 (2.2)
No	44 (97.8)
Intraocular pressure, mean ± SD	16.1 ± 8.3
HbA1c, mean ± SD	8.25 ± 1.96
DM duration (year), mean ± SD	7.02 ± 7.1

Only 13.3% of subjects had cataracts, none had corneal abnormalities, 80% of subjects had macular edema, 24.4% used silicon oil tamponade, only

2.2% had redetach and rebleeding with 80% macula on and average intraocular pressure 16.1 ± 8.3 mmHg. The characteristics of the study subjects can be seen in Table 1.

Before and after PPV, the visual acuity was not normally distributed based on the Shapiro-Wilk normality test, so the Wilcoxon test was used. Based on the Table 2, the results showed that there was an improvement in visual acuity after PPV with a mean improvement of 0.54 logMAR.

Table 2. **Difference in Visual Acuity Before and After PPV**

Visual Acuity Pre-PPV (logMAR)	Visual Acuity Post-PPV (logmar)	Mean Difference	95% CI	p
1.78 (1.3-2.4)	0.7 (0.49-2.1)	0.54 ± 0.93	0.26-9.82	0.001*

*Wilcoxon Test

Based on ANCOVA multivariate analysis, factors that affect the improvement of visual acuity after PPV are pre-operative visual acuity, post-operative visual acuity, HbA1c levels, and duration of DM. Among of these confounding variables, HbA1c level with p=0.036, pre-operative vision and post-operative vision with p<0.001, and DM duration with p=0.024, were found significantly influence the improvement of visual acuity (Table 3).

Table 3. **Factors that Affecting Improvement in Visual Acuity After PPV Compared to Before PPV**

Variabel	f	p
Pre-Operation Visual Acuity (logMAR)	34.293	<0.001
Post-Operation Visual Acuity (logMAR)	35.676	<0.001
Gender	0.667	0.420
Age (year)	0.023	0.880
HbA1c (%)	4.758	0.036
Hypertension (yes)	0.321	0.575
Cataract (yes)	0.120	0.732
Macula Edema (yes)	0.319	0.576
Hypercholesterolemia (yes)	0.614	0.439
DM Duration (year)	5.581	0.024

The correlation between VEGF and visual acuity after PPV was analyzed using the spearman test, with the result that there was no correlation between VEGF and visual acuity after PPV (r=0.029; p=0.848). Simple linear regression test also showed no relationship between VEGF and improvement in visual acuity (p=0.541).

Out of 24 patients who experienced visual acuity improvement after PPV, 13 patients (54.2%) had high VEGF levels and 11 patients (45.8%) had low VEGF levels. Out of 21 patients who did not experience visual acuity improvement after PPV, 12 patients (57.1%) had high VEGF levels while 9 patients (42.9%) had low VEGF levels. The results of the chi-square test showed no association between high vitreous VEGF levels and visual acuity improvement (Table 4).

Table 4. **Association of High Vitreous VEGF levels (≥51.9 ng/dl) with Improvement in Visual Acuity**

VEGF Level	Improvement in Visual Acuity		PR	95%CI		p*
	Yes	No		Upper Limit	Lower Limit	
High (≥51.9 ng/dl)	13 (54.2%)	12 (57.1%)	0.95	0.55	1.63	0.841
Low (<51.9 ng/dl)	11 (45.8%)	9 (42.9%)				

*Chi-Square Test

The VEGF cutoff based on ROC analysis was 51.9 ng/dl with a sensitivity of 45.8%, specificity of 57.1% for predicting visual acuity improvement after PPV and an area under the curve (AUC) of 0.493 (Figure 2).

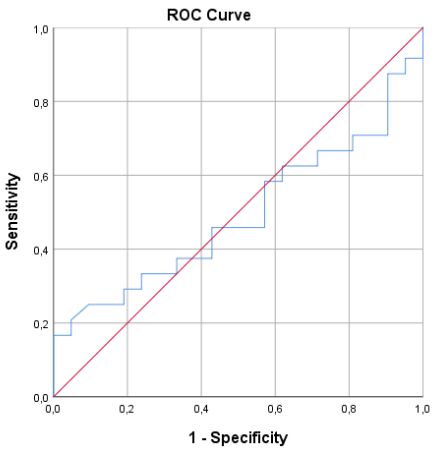

Figure 2. **Receiver Operating Characteristic Curve with Optimal Cutoff Value of VEGF 51.9 ng/dl for Predicting Visual Acuity Improvement after PPV (Sensitivity 45.8%; Specificity 57.1%; AUC= 0.493; p=0.937)**

Multiple linear regression analysis revealed no association between VEGF and post-PPV visual acuity after confounding variables were controlled (p=0.713). There was also no association between gender, age, HbA1c, cataract, macular edema, dyslipidemia, and duration of DM with improvement in post-PPV visual acuity (Table 5).

Table 5. **Association of VEGF Levels with Visual Acuity Improvement Post-PPV After Controlling Other Variables**

Variables	B	SE	95%CI (B)		p
			Lower Limit	Upper Limit	
VEGF levels (ng/dL)	0.002	0.006	-0.009	0.013	0.713
Gender (male)	0.135	0.148	-0.165	0.435	0.366
Age (year)	-0.003	0.007	-0.019	0.012	0.650
HbA1c (%)	0.031	0.039	-0.048	0.111	0.429
Hypertension (yes)	0.207	0.168	-0.133	0.548	0.225
Cataract (yes)	0.072	0.210	-0.354	0.499	0.733
Macula edema (yes)	-0.110	0.179	-0.474	0.253	0.541
Hypercholes-terolemia (yes)	-0.215	0.219	-0.660	0.231	0.334
DM duration (years)	0.020	0.014	-0.009	0.049	0.168

DISCUSSION

This study found no association between vitreous VEGF and visual acuity before and after PPV in PDR. However, this research indicated a link between PPV and the enhancement of visual acuity before and after PPV. Several significant confounding factors, such as the visual acuity before and after PPV, the duration of DM, and HbA1c levels, influenced the changes in visual acuity.

The results of this study showed no association of vitreous VEGF with visual acuity before and after PPV in PDR. This result is similar to the study by Petrovic et al. who stated there was no association between vitreous VEGF levels and visual acuity after PPV in PDR (p=0.94). Variables that were found to be associated with visual acuity after PPV based on multiple logistic regression tests in the study were IL-8, macular detachment, and panretinal photocoagulation (PRP).[17] Given the low sensitivity and specificity in detecting improvement in visual acuity after PPV and the high cost, vitreous VEGF assessment may not be useful in the clinical setting.

In Petrovic et al's study, out of seven eyes with PDR that showed regression of active neovascularization without laser treatment, five patients had poor visual acuity after vitrectomy. In one patient, visual acuity was logMAR 0.1, while the other was 0.3. All seven eyes had significantly lower vitreous VEGF levels and higher vitreous IL-8 levels compared to the PDR eyes that had visual improvement after vitrectomy. The study concluded that it appears that the inflammatory component manifesting as elevated vitreous IL-8 levels is more important in predicting visual acuity than ischemia-induced angiogenesis showing increased vitreous VEGF.[17]

These results were also supported by a 4-year prospective, randomized, multicenter clinical trial of 328 adults (399 eyes) with moderate to severe NPDR but without center-involved diabetic macular edema (CI-DME). Eyes were randomized to the intravitreal aflibercept or placebo group (200 vs 199 eyes, respectively) where participants received 8 injections for the first 2 years followed by quarterly injections for 2 years unless eyes improved to mild NPDR or better. The results showed the 4-year probability of developing proliferative diabetic retinopathy or CI-DME with vision loss was 34% with aflibercept, which was significantly lower than the 57% probability seen

with placebo. However, there was no significant difference in the change in visual acuity between the two groups, signaling anti-VEGF administration did not provide any benefit on visual acuity. The 34% of patients who went on to develop PDR or CI-DME in the aflibercept group also highlights the importance of non-VEGF mediated aspects of diabetic retinopathy progression.[18]

Smith JM and Steel DHW reviewed RCTs published in recent years and cautiously concluded that anti-VEGF (bevacizumab) can reduce the incidence of early bleeding in the postoperative vitreous cavity, suggesting that VEGF may play an important role against vitrectomy complications for PDR patients. Prevention of PPV complications may indirectly prevent visual decline in PDR patients post PPV.[19]

VEGF has a central role in mediating microvascular and macrovascular pathologies in diabetes. VEGF is a major mediator of diabetic retinopathy, capable of inducing the changes observed in proliferative retinopathy, macular edema, and possibly also nonproliferative diabetic retinopathy. VEGF was found to be increased in the vitreous of patients with iris neovascularization, active neovascularization, and macular edema. In highly progressive ischemic cases of the natural course of DR, the angiogenic potential is already reduced, active neovascularization regresses, and visual acuity is poor.[18,20,21]

This study shows many patients have high VEGF levels even after PPV. This could be due to the phenomenon of 'metabolic memory', where the development of chronic inflammatory mediators including VEGF does not stop when good metabolic control is re-established after a period of poor metabolic control.[22,23]

Multivariate analysis showed no association of VEGF levels and macular edema with visual acuity improvement after PPV. This result is consistent with the study by Jahn et al. that PPV is almost always associated with a reduction or even disappearance of macular edema, thus affecting post-PPV visual improvement. Macular edema can indeed cause a decrease in pre-operative visual acuity, but it turns out that patients with poor pre-operative visual acuity due to macular edema can still experience visual acuity improvement after PPV. Conversely, patients who do not have macular edema will not necessarily experience improvement in visual acuity after PPV. This shows that PPV surgery can still be performed even if there is macular edema or high VEGF levels in patients.[24]

The mean intraocular pressure in this study was 16.1 ± 8.3 mmHg. The study by Sharma et al. (2011) stated that IOP ≥ 30 mmHg on the first postoperative day is a significant risk factor that jeopardizes the visual outcome of patients undergoing PPV. Postoperative IOP elevation can be caused by factors such as viscoelastic residue, widespread use of SO tamponade, bleeding, pupillary block, ciliary body edema, inflammation, or response to topical corticosteroid therapy.[25]

A total of 53.3% of PDR patients who underwent PPV in this study had improved vision, while the remaining 46.7% did not improve. In the study by Petrovic et al., 33.3% of PDR patients did not improve their vision after PPV. The main causes of poor visual outcomes after vitrectomy have been found to be related to ischemic changes in the macula, traction macular detachment, preoperative iris neovascularization, and neovascular glaucoma,[17] which would have been excluded in this study.

A similar study by Liao et al. in 2020 followed PDR patients post PPV for 24 months, with the results of BCVA improving in 70.7% of eyes, stabilizing in 15.5% of eyes, and worsening in 13.8% of eyes.[26] The difference in the results of this study with Liao et al. may be due to differences in follow-up time, where the study by Liao et al. followed patients for 24 months while this study was only 6 weeks.

Factors affecting the improvement of visual acuity after PPV in this study were pre-postoperative visual acuity, HbA1c levels, and duration of DM. These results are similar to the study by Flaxel et al. (2010) which stated that there is a significant association between pre-operative visual acuity and post-PPV visual acuity improvement. Eyes with worse pre-operative visual acuity are more likely to experience better visual acuity improvement than eyes with good visual acuity. Another factor that was found to influence post-PPV visual acuity in the study was eyes with

the epiretinal membrane removed. This relationship is likely due to the ceiling effect, which is the inability of a measure or test to show valid differences above a certain point. Thus, PPV no longer causes visual acuity improvement when pre-operative visual acuity is as good as a certain point, although the limit is unknown.[27]

Seong-Su et al. reported that pre-operative visual acuity, diabetes duration, traction membrane, SO tamponade, and vitreous hemorrhage were associated with post-PPV visual acuity outcomes.[28] The study by Kumagai et al. found that post-PPV visual acuity was inversely related to HbA1C levels. This means that better blood sugar control, indicated by lower HbA1c levels, resulted in better post-PPV visual acuity.[29] Similar results were obtained in a retrospective study by Shah et al. (2008), which also found a correlation between HbA1c levels and visual acuity outcomes after PPV.[30]

HbA1c levels in the blood indicate the level of glycemic control of DM patients. Chronic hyperglycemia conditions, in addition to initiating many other biochemical and functional abnormalities and altering the expression of genes associated with them, it also increases oxidative stress. Increased production of cytosolic reactive oxygen species leads to mitochondrial dysfunction, and the compromised antioxidant defense system becomes overwhelmed to neutralize free radicals. With the extended duration of diabetes, mitochondrial DNA (mtDNA) is also damaged, and the transcription of mtDNA-encoded genes, which are essential for electron transport chain function, is impaired. This triggers a vicious cycle of 'self-propagating' free radicals, and retinopathy continues.[22,23]

This study has some limitations. Firstly, we did not examine complications of PPV that could affect visual acuity, such as vitreous cavity bleeding. Secondly, we did not examine the pre-PPV optic disc and macular state, only post-PPV macular edema. Therefore, it cannot be concluded whether there is a relationship between macular edema and changes in visual acuity after PPV. Thirdly, we did not investigate the association between changes in visual acuity and other confounding variables, such as intraocular pressure, lens status, level of PDR, optic disc disorders, and the use of post-PPV tamponade. Additionally, the study duration was too short. Finally, we did not analyze inflammatory biomarkers, such as IL-8 in vitreous fluid, despite other studies demonstrating a significant relationship between IL-8 and changes in visual acuity.

CONCLUSION

In conclusion, this study demonstrated that there is no association between vitreous VEGF and pre- and post-PPV visual acuity in PDR. Vitreous VEGF has no significant clinical value in determining visual acuity improvement. However, PPV is associated with the improvement in visual acuity before and after PPV, including other confounders such as post-PPV visual acuity, duration of DM, and HbA1c levels. It is necessary to keep good records of lens status and intraocular pressure conditions, as they greatly affect pre- and post-PPV visual acuity.

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