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"Study of outcome of Proliferative Diabetic Retinopathy patients treated by Panretinal Photocoagulation verses Intravitreal Anti Vascular Endothelial Growth Factor injections"

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Abstract
Aim
The purpose of this study was to assess and compare the outcome of different treatment modalities in PDR patients.
Methodology
This Prospective, comparative, Interventional study was conducted. All the patients who reported to ophthalmology Outpatient Department with PDR during the study period (Feb.2020-Aug.2021) were evaluated. Detailed ocular examination including Best corrected visual acuity (BCVA), indirect ophthalmoscopy, fundus photography and FFA was done. Patients were divided in two groups, Group A received Intravitreal Anti VEGF(Bevacizumab) injection and Group B treated by PRP. Outcome measure in term of visual improvement and regression of neovascularization.
Results
A total of 80 cases with PDR were enrolled in this study. Most of the patient show Improvement in vision (52.5% patients of Group A and 47.5% in Group B) and maintain of existing vision was found in 22.5% patient of Group A and 27.5% in Group B. Complete regression of neovascularization was found in 4 (10.0%) patients in Group A and 10(25.0%) in Group B.
Conclusion
For the regression of neovascularisation in PDR without macular oedema PRP is cost effective and better modality of treatment but visual acuity in the group treated by Anti VEGF was better than the group treated by PRP Based on our observation it can also be stated that the combined treatment with PRP and Anti VEGF results in regression as well as improved visual acuity in the patients with PDR.
Key word: *PDR, PRP, Anti VEGF, DME*

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I. Introduction

Diabetic retinopathy remains a major threat to sight in the working age population in the developed world. Furthermore, it is increasing as a major cause of blindness in other parts of the world especially in developing countries.[1]

Proliferative diabetic retinopathy (PDR), characterized by retinal neovascularization at the disc (NVD) or elsewhere in the retina (NVE), is the most common form[2]. Panretinal photocoagulation (PRP) has been the standard treatment for PDR during the past several decades. Although anti-VEGF agents have demonstrated a positive effect in regressing retinal neovascularization in recent years, PRP is still recommended by 98% of retina specialists as the primary management of PDR[3]

Recently, R.P. Center for Ophthalmic Sciences, New Delhi, conducted the National Diabetic Retinopathy Rapid Assessment of Avoidable Blindness (RAAB) Survey 2015–2019, under the aegis of the Ministry of Health and Family Welfare, Government of India has estimated that almost 16.9% of DR exists

among diabetes individuals and 3% has PDR that can progress to DR associated blindness[4]. Nearly 25% with type 1 DM and 15.5% with type 2 DM can develop PDR after 15 years of diabetes[5].

Pathogenesis of PDR

Hyperglycemia and metabolic changes from DM

↓

Alteration in retinal vasculature

↓

Reduced perfusion of the retinal tissue

↓

Relative retinal ischemia- primary stimulus for angiogenesis (angiopoetin, erythropoietin, basic firbroblast growth factor (bFGF), insulin like growth factor (IGF), protein kinase C (PKC), tumor growth factor (TGF), platelet derived growth factor (PDGF)

↓

Abnormal Retinal Neovascularization

Panretinal photocoagulation (PRP) and anti- vascular endothelial growth factor (anti-VEGF) are the two main treatment options for patients with PDR. For almost past three decades, patients with PDR had been receiving Panretinal Photocoagulation treatment (PRP) which remained as the gold standard treatment. In recent years, few clinical trials has concluded that the efficiency of intravitreal antiangiogenic agents (pegaptanib, ranibizumab and bevacizumab) is found to be more efficient than PRP.

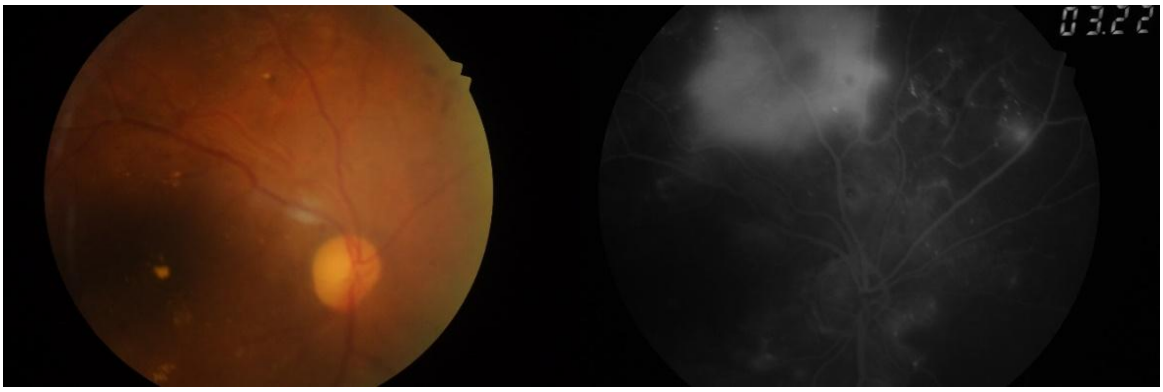


Figure 1: Fundus photograph and FFA showing PDR (NVE)

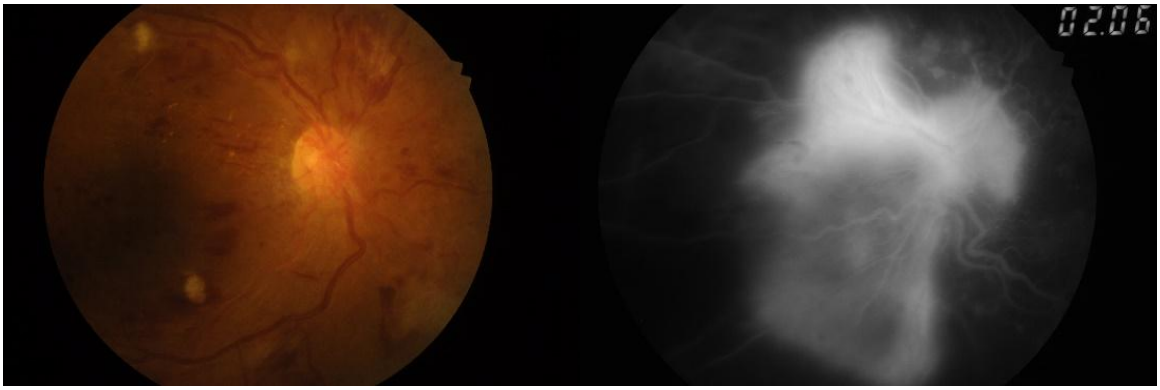


Figure 2: Fundus photograph and FFA Showing PDR (NVD)

II. Matetraial and Methods

A prospective interventional study was conducted at the Upgraded Department of Ophthalmology of J.L.N. Medical College, Ajmer (Rajasthan), India. The study was conducted from Feb 2020 to August 2021 and 80 patients who came to Ophthalmology outpatient department (OPD) were included. Ethical clearance was obtained from institutional review board.

Inclusion criteria

1. Both males & female patients of proliferative diabetic retinopathy.
2. Patients of all adult who has given informed & written consent to receive Panretinal Photocoagulation or intravitreal Anti VEGF injections.

Exclusion criteria

1. Advanced stage of proliferative diabetic retinopathy.
2. Visual acuity adversely affected by opacities of the media
3. History of ocular surgery within past 6 month
4. Cases with nephropathy and extra ocular complications
5. Cases of Diabetic Macular oedema or Previous Photocoagulation

After informed and written consent, all the subjects were asked a detailed ocular and systemic history and then a thorough ophthalmic examination was done, which included Best-Corrected Visual Acuity using Snellen's Visual Acuity Chart, intraocular pressure using Schiotz Tonometer, slit lamp examination and retinal examination using direct ophthalmoscopy, indirect ophthalmoscopy and Slit Lamp Biomicroscopy with +90D lens(when needed), Optical Coherence Tomography, Fundus Fluorescein Angiography was done in all cases before therapy.

OCT (Optical Coherence Tomography) was performed by sd-OCT Topcon model (if required) through a dilated pupil. Patient was explained about the procedure and after proper positioning of patient for each eye, scans were taken. Fluorescein Angiography was carried out using a fundus camera KOWA VX-10α wherever possible and required. After proper consent and dilatation of pupil with tropicamide and phenylephrine, 3cc of 20% Na-fluorescein injected into the antecubital vein and fundus photographs were taken, both early and late phases of angiography were captured.

Procedure -

Patients were divided into 2 groups, Group A was treated with intravitreal Anti VEGF injection and Group B with PRP

I. **Group A for Anti VEGF-**

After informed & written consent, 1.25 mg in 0.05 ml bevacizumab was injected intravitreally under complete sterile preparation in the operating theatre under topical anesthesia. Injection preferably given at inferotemporal location 4mm away from limbus in phakic eye (3.5mm away in pseudophakic eye). Topical antibiotic (moxifloxacin) was given for 5 days. 2nd dose of intravitreal bevacizumab was considered after at least one month of the first injection on basis of improvement.

II. **Group B for PRP-**

Patients were treated with PRP on OPD basis, using Visulas 532s Carl Zeiss machine. This involves applying laser burns over the entire retina sparing the central macular area. Patient was explained about the procedure and after proper positioning topical anesthesia was instilled then fundus lens (Mainster PRP lens) inserted and laser spots were applied 1 spot size apart, except in areas of neovascularization by using Diode Pumped Solid State Laser System with 532nm wavelength by slit lamp delivery system. If required Laser indirect ophthalmoscope was used to treat the retinal periphery with CNP areas.

Laser Parameters used for PRP

1. Total number of bums: 1400-1800.
2. Spot size: 300-500 µm.
3. Power: 200-400mW (Moderate intensity burns) gray-white burns.
4. Duration: 60mSec.

Sequence of application of laser burns

1. Below and along the inferior temporal arcades.
2. Nasally 1DD away from the disc.
3. Above and along the supero-temporal arcade.
4. Temporally at least 2 DD away form the fovea.
5. Peripheral treatment until completion.

This procedure was done in 2 to 3 settings.

Follow up-
After giving appropriate treatment to the patients, they were asked to follow up on day 1 and then at 1 week, 1 month, and 3 months after treatment. On every follow up we checked visual acuity, fundus examination by direct and indirect ophthalmoscope and OCT (if required). FFA was also repeated whenever required. Outcome of treatment was measured in term of improvement in visual acuity and regression in Neovascularization, clearance of vitreous haemorrhage, and complications related to disease progression.

Statistical Analysis
Data was represented in the form of tables and analysed with the help of descriptive statistical.

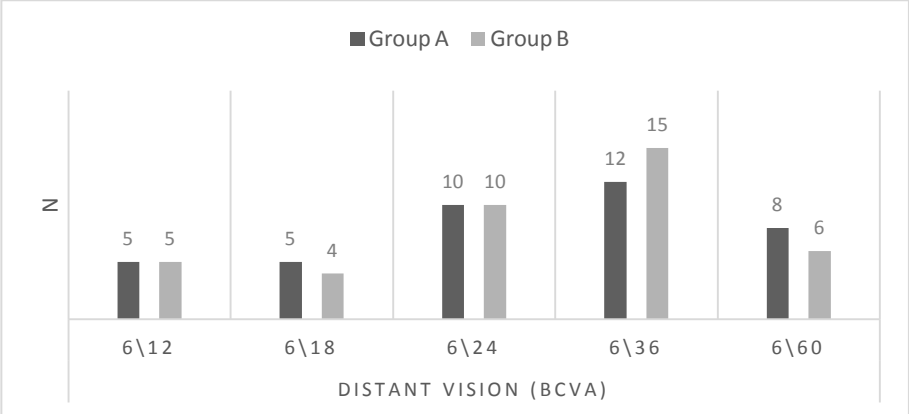
III. Result

Most of the patient's BCVA ranges in between 6/18-6/36 (67.5% in group A and 72.5% in group B) and near vision ranges in between N12-N8 (80% in group A and 70% in group B) at Presentation.

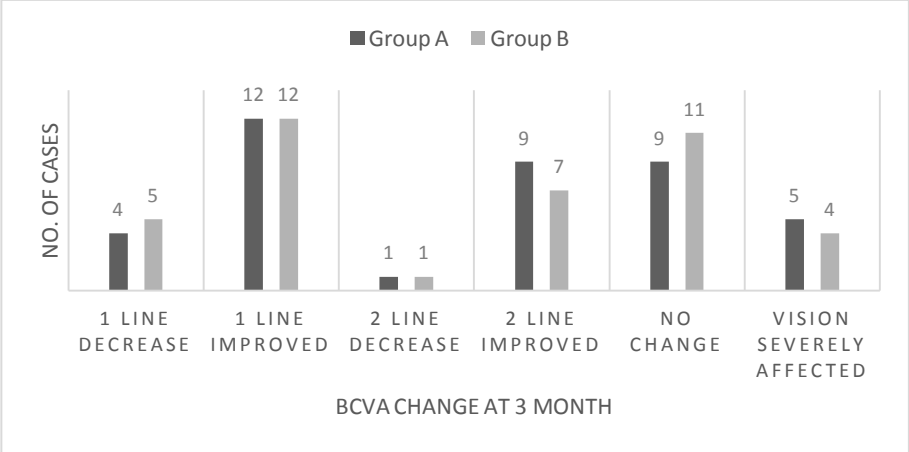
Distant Vision (BCVA) at 3rd month follow-up: Most of the patient's BCVA ranges in between 6/18-6/36 (50% in group A and 50% in group B). Most of the patient show Improvement in vision (changes from baseline) in both the groups, 21(52.5%) patients of group A and 19(47.5%) in group B. Maintain of existing vision were found in 22.5%(9) patients of group A and 27.5%(11) in group B. Vision severely affected more in group A 5(12.5%) then group B 4(10%). The data did not confer any statistical significance, but better visual improvement noted in group A (anti VEGF).

Final outcome of Neovascularization (NV) at 3-month follow-up on FFA finding: Complete regression of neovascularization was found in 4 (10.0%) patients in group A and 10(25.0%) in group B. No regression in 6(15.0%) and 2(5.0%) in group A and B respectively was reported. More patients were found with partial regression, 21(52.5%) patients in group B and 19(47.5%) patients in group A. It was observed that 6(15.0%) and 3(7.5%) patients had progression in group A and B respectively. 5 (12.5%) patients and 4(10.0%) patients had progression along with complications in group A and B respectively. The data has confirmed a statistical significance with p-value=0.03.

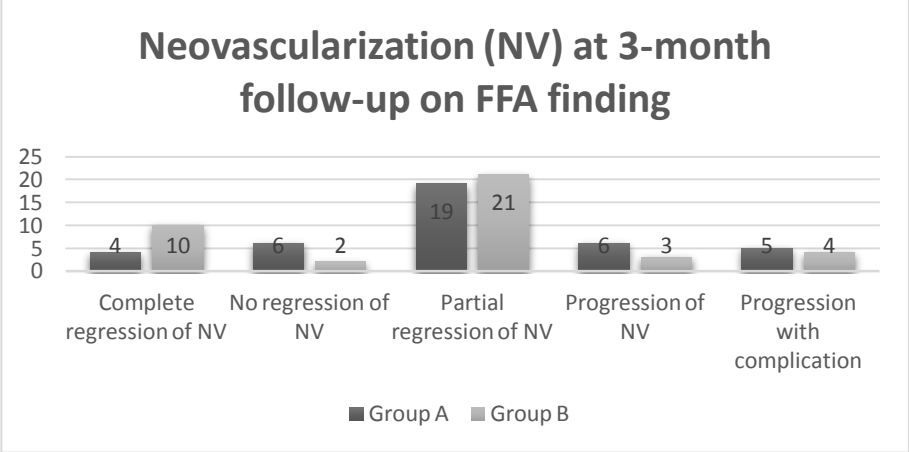
Complications: occurred in both the groups. In group A (Anti VEGF/Bevacizumab) none of the patients developed Diabetic macular edema (DME) and 2 (5.0%) and 3(7.5%) patients developed Tractional Retinal Detachment (TRD) and Vitreous Hemorrhage (VH) respectively. Similarly in group B (PRP) 1(2.5%) patient was found to have DME and 1(2.5%) had TRD and only 2 (2.5%) patients had VH. No complication was found in 35(87.5%) patients of group A and 36(90.0%) patients of group B. The overall data conferred a statistical significance with p-value=0.001. It can be stated that treatment given to group B (laser) could achieve better control in complications being caused by PDR.



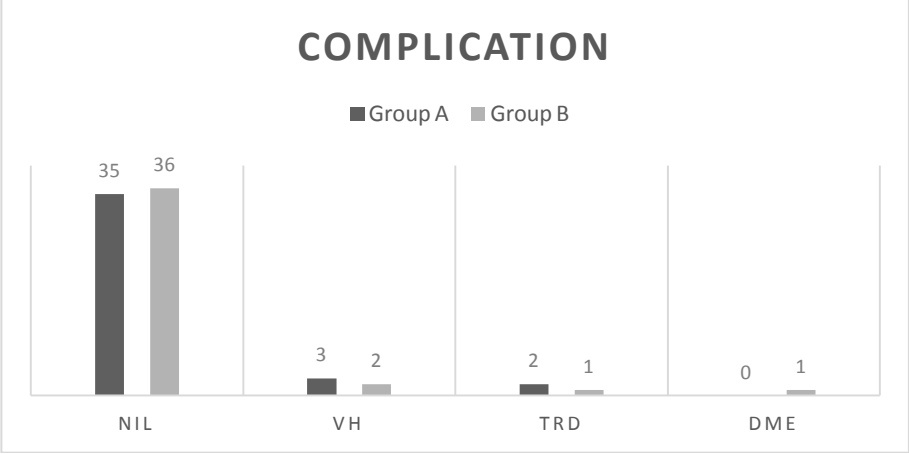
Graph no. 1: Distant vision (BCVA) at presentation



graph no. 2: Distant vision (BCVA) change from baseline in Snellen's chart at 3rd month



Graph no. 3: Final outcome of Neovascularization (NV) at 3-month follow-up on FFA finding



Graph no. 4: Complication

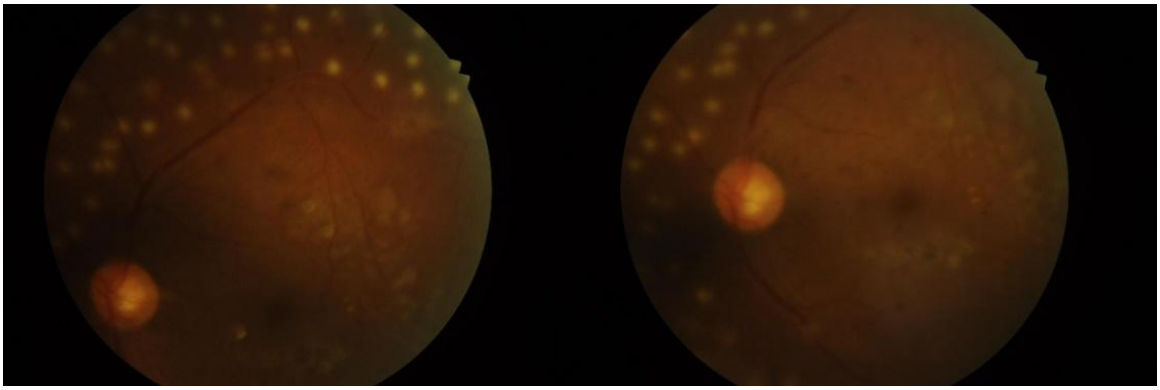


Figure 3: Fundus photograph showing regression in PDR after PRP

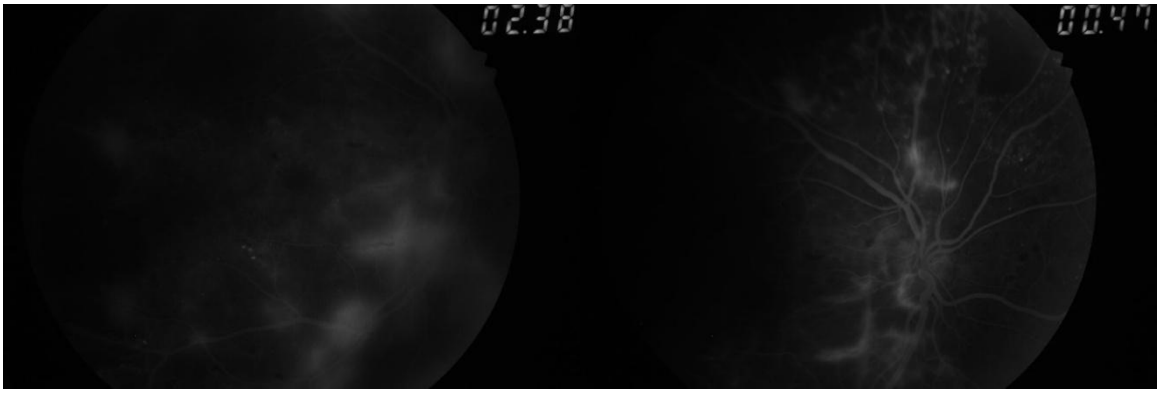


Figure 4: FFA showing partial regression in PDR after PRP

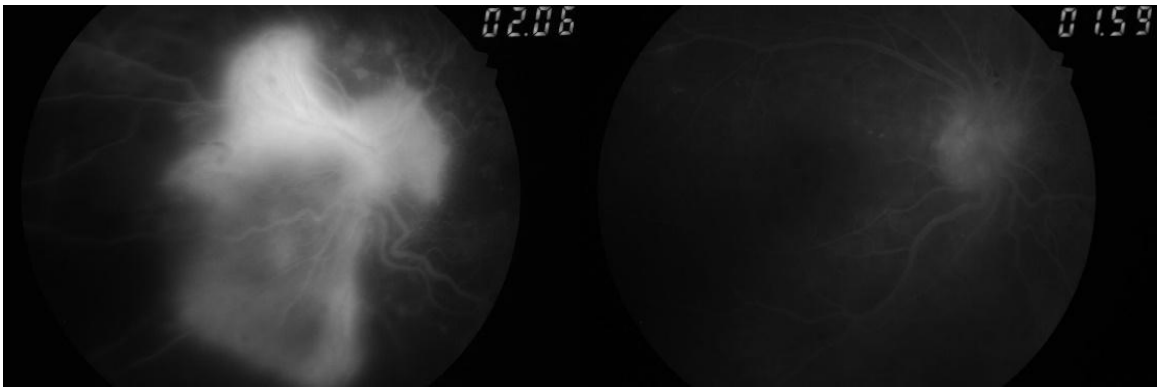


Figure 5: FFA showing partial regression in PDR after Anti VEGF injection

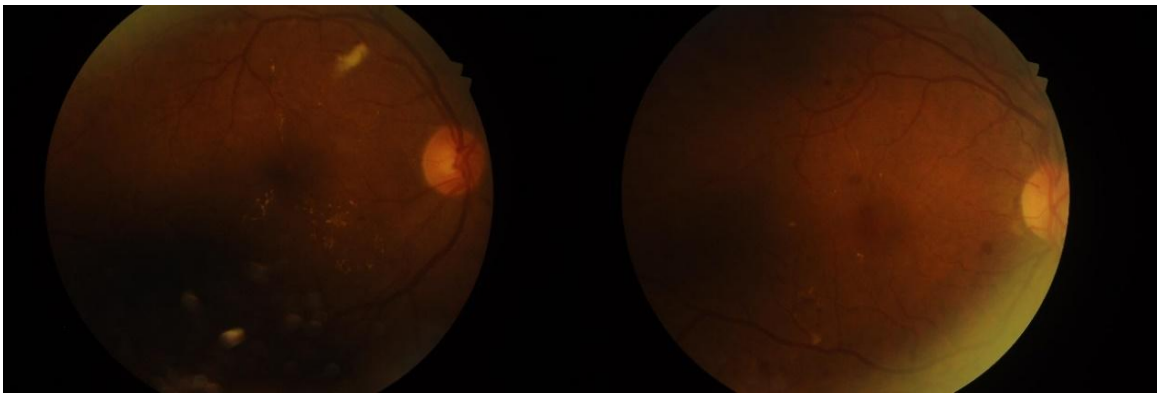


Figure 6: Fundus photograph showing regression in PDR after Anti VEGF injection

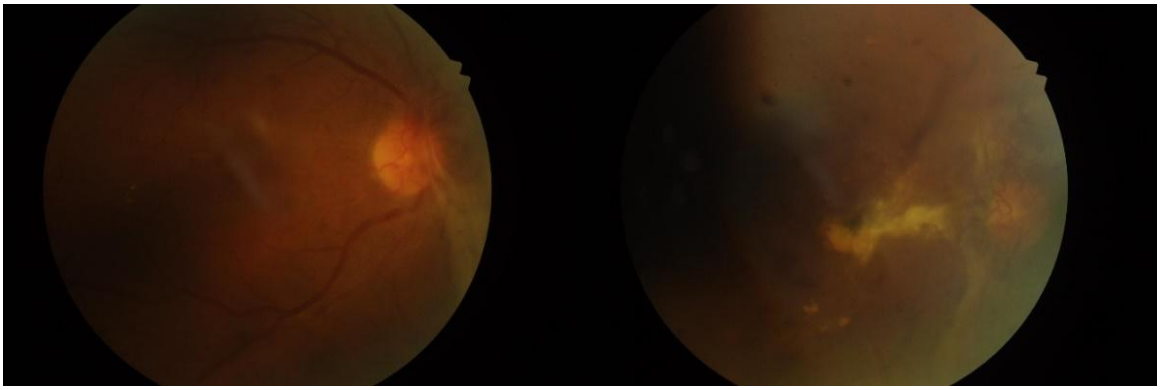


Figure 7: Fundus photograph showing progression in PDR after Anti VEGF injection

IV. Discussion

There has been a decline in the use of PRP and the increase in anti-VEGF monotherapy for PDR. Azad AD et al[6] have demonstrated a significant decrease in PRP rates since the publication of Protocol S, coupled with a sharp increase in anti-VEGF for PDR. Although the findings of our study suggest a benefit for anti-VEGF over PRP in PDR for the better outcomes. This suggests that the benefit of anti-VEGF over PRP (in terms of BCVA) occurs early but is not sustained in the longer term.

Sujatha RMA et al[7] in her study has evaluated the maintenance of existing vision after PRP for proliferative diabetic retinopathy (PDR) and assessed the causes of severe visual loss after PRP. She found that Visual acuity 6/12 – 6/36 after laser at 1st month was found in 22(44%) patients, these results are lower than our study results obtained.

A study performed by Rajendram R et. al.,[8]studied that during the 2-year follow-up visit, the bevacizumab arm maintained a median of +9 letters improvement, whereas laser-treated eyes showed better results at 1-year visit (+2.5, $p = 0.005$). In terms of percentage of patients who gained 15 letters or more compared to baseline, the bevacizumab arm showed superiority compared to laser (32% and 4%, resp., $p = 0.004$). Mean reduction in central macular thickness was 146 μm in the bevacizumab arm versus 118 μm in the MLT arm. Even though the follow-up was short, laser outcomes are slightly better during the second year compared with the first year.

Yates WB et al[9]in his study found that anti-VEGF monotherapy were less likely to experience moderate vision loss when compared with patients undergoing PRP (RD 0.12, 95% 0.21 to 0.03, p = 0.01) and for severe vision loss (logMAR 1.0 or VA 6/60 or less) there was no difference between anti-VEGF and PRP (RD 0.03, 95% CI 0.08 to 0.03, p = 0.93). When two clinical trials were considered (Protocol S and CLARITY), which included visual field outcomes, demonstrated significant benefits for anti-VEGF monotherapy over PRP. This suggests that the peripheral ischemic retina in PDR loses function over time, despite anti-VEGF treatment. There has been a decline in the use of PRP and the increase in anti-VEGF monotherapy for PDR.

Mitamura Y et al[10] discussed that Arevalo JF et al[11] reported that 11 (5.2%) of 211 eyes developed or had progression of TRD after intravitreal bevacizumab and that the mean time from bevacizumab injection to TRD was 13 days. Therefore, he suggested that intravitreal bevacizumab induced a rapid neovascular involution with accelerated fibrosis and posterior hyaloidal contraction that led to the MH–RD. Most patients who developed a TRD after intravitreal bevacizumab had poorly controlled diabetes (elevated HbA_1C), used insulin and their PDR were refractory to PRP.

Gross JG et al [12]studied the efficiency of ranibizumab vs PRP over 5 years for PDR and he observe that lower rates of development of vision-impairing DME and less visual field loss in Ranibizumab group.

In another study conducted by Moisseiev E et al [13]discussed that minimally invasive laser treatment has the large potential to reduce the burden of anti-VEGF injection under a combined use for the treatment of DME.

V. Conclusion

We observed in our study that an overall regression of neovascularisation and arrest of progression of diabetic retinopathy following PRP treatment were more than compared to the patients treated with Intravitreal Anti VEGF injections in patients with PDR. FFA provided quantitative information on vascular changes and may have an important role in monitoring the efficacy of treatment regimen in these patients.

It was also observed that the visual acuity in the group treated by Anti VEGF was better than the group treated by PRP, and lower rates of vision impairing DME and less visual field loss.

Therefore, we can conclude that for the regression of neovascularisation in PDR without macular oedema, PRP is cost effective and better modality of treatment. Based on our observation it can also be stated

that the combined treatment with PRP and Anti VEGF results in regression as well as improved visual acuity in the patients with PDR.

Patient specific factors, including anticipated visit compliance, cost and frequency of visit should be considered when choosing treatment for patient with PDR.

In order to prevent the development of diabetic lesion in the eye, it is necessary to carry out regular ophthalmic check-ups, to quantify patients for treatment as early as possible.

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