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Original research article

PANRETINAL PHOTOCOAGULATION PLUS INTRAVITREAL BEVACIZUMAB VERSUS PANRETINAL PHOTOCOAGULATION ALONE FOR PROLIFERATIVE DIABETIC RETINOPATHY

RIAZ S[1*], AHMED N[2], KHAN A[3], JABRAN A[4], RAZA I[5], AFZAL T[6]

[1]*Allama Iqbal Medical College Jinnah Hospital Lahore, Pakistan*
[2]*Department of Ophthalmology Nishtar Medical University Multan, Pakistan*
[3]*Department of Ophthalmology, Abbottabad International Medical Institute, Pakistan*
[4]*Department of Ophthalmology LGH/PGMI, Lahore, Pakistan*
[5]*Department of Ophthalmology Govt. Shahbaz Sharif DHQ Hospital Multan, Pakistan*
[6]*Department of VitreoRetina Al-Shifa Trust Eye Hospital Rawalpindi, Pakistan*
**Correspondence author email address:* drsara_ch@yahoo.com

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Abstract: *Proliferative diabetic retinopathy (PDR) is a severe and advanced stage of diabetic retinopathy, a major microvascular complication of diabetes mellitus.* ***Objective:*** *The basic aim of the study is to compare the panretinal photocoagulation plus intravitreal bevacizumab versus panretinal photocoagulation alone for proliferative diabetic retinopathy.* ***Methods:*** *This randomized control trial was conducted at various tertiary care hospitals of Lahore and Rawalpindi from September 2023 to August 2024. Data include 40 patients, 80 eyes according to the study's criteria. Participants were randomly assigned into two equal groups using a computer-generated sequence. The first group, consisting of 20 patients, received PRP treatment alone and served as the control group. The second group, also consisting of 20 patients, received PRP combined with a single intravitreal injection of bevacizumab, forming the intervention group.* ***Results:*** *Both groups had a mean age of 54 ± 8 years and a male-to-female ratio of 3:2. Baseline best-corrected visual acuity (BCVA) was similar, with 0.4 ± 0.1 logMAR in the PRP group and 0.42 ± 0.1 logMAR in the combination group ($p > 0.05$). Central macular thickness (CMT) at baseline also showed no significant difference, with 310 ± 25 µm in the PRP group and 312 ± 27 µm in the combination group ($p > 0.05$), indicating well-matched groups for the study. Improvement in BCVA was significantly higher in the combination group (0.10 ± 0.03 logMAR) than in the PRP group (0.04 ± 0.02 logMAR, $p = 0.02$). Similarly, the reduction in central macular thickness (CMT) was more pronounced in the combination group (-22 ± 4 µm) compared to the PRP group (-5 ± 3 µm, $p = 0.01$).* ***Conclusion:*** *It is concluded that the combination of panretinal photocoagulation and intravitreal bevacizumab offers superior outcomes in managing proliferative diabetic retinopathy compared to PRP alone.*

Keywords: Bevacizumab, Diabetic Retinopathy, Intravitreal Injections, Panretinal Photocoagulation, Proliferative Diabetic Retinopathy.

Introduction

Proliferative diabetic retinopathy (PDR) is a severe and advanced stage of diabetic retinopathy, a major microvascular complication of diabetes mellitus. PDR is characterized by the formation of new thin-wired blood vessels on the retina and posterior vitreous surface due to overexpression of VEGF by ischemic retina (1). These abnormal vessels are predisposed to complications such as vitreous hemorrhage TRD, and neovascular glaucoma which lead to severe vision loss. Management of PDR clinical burden therefore depends on these prompt and efficient therapeutic attempts aimed at discouraging progression and preserving vision. Until recently, panretinal photocoagulation (PRP) has been the only treatment modality for PDR (2). This laser treatment includes making burns around the peripheral part of the retina, which in turn lowers the degree of retinal ischemia and VEGF. Even if PRP successfully reduces the chance of the occurrence of a severe visual impairment due to neovascularization regression, it has several disadvantages (3). The treatment has been linked with complications such as, loss of the peripheral visual field, decreased contrast sensitivity, a decline in night vision, as well as DME which also affects the cone photoreceptors leading to loss of central vision. All these limitations call for the use of adjuvant or complementary therapies to enhance a patient's clinical condition but at the same time minimizing on complications arising from treatment (4).

Anti- VEGF agents have indeed dramatically shifted therapeutic paradigm in diabetic retinal diseases. PDR is also treated using intravitreal bevacizumab – a monoclonal antibody against VEGF. Through the suppression of VEGF, bevacizumab suppresses the formation of new blood vessels, induces better morphology of the retina and strengthens barrier function of the blood/retinal barrier (5). It is for these reasons that there has been growing interest in its use as a 'second wave' of treatment in combination with PRP principally in patients with active PDR along with its myriad complications. Introducing bevacizumab along with PRP offers the possibility of optimizing the limitations connected with the use of only PRP. Anti-VEGF injections can easily and effectively regress neovascularization, which perhaps lessens the ischemic stimulus before or during PRP (6). This might make it possible to perform narrower laser therapy; fewer extensive burns will be needed, which should help reduce unfavorable effects on the peripheral retina (7).

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Recommendations of early research prompt for this combination treatment may yield better results than PRP procedure only (8). It has been shown that current reports reflect the beneficial effects of using bevacizumab in neovascular regression; better visual acuity; and lower incidences of vitreous hemorrhage and macular edema. Therefore, the relative advantages and disadvantages of the synergistic action of PRP and intravitreal bevacizumab compared to the use of PRP alone still warrant further study (9). The specific issues of concern are do anti-VEGF injections have to be given frequently and at what kind of intervals? And secondly there is concern that complications developing much later may be caused by the administration of these drugs? Another crucial question to be addressed is whether combination therapy is cost effective or not in a low resource setting (10). Laser treatment can reduce moderate visual loss with little improvement in BCVA; and intravitreal triamcinolone gives short term BCVA gain and leads to cataract and glaucoma formation.5 Although ranibizumab is used in treatment of DME but this is somewhat expensive. Although off-label it is used extensively because of cost and approval as an anti-neoplastic agent.7 It has been observed that IVB along with PRP has reduced worsened visual acuity and regression of retinal new vessels (3). Thus the basic aim of the study is to compare the panretinal photocoagulation plus intravitreal bevacizumab versus panretinal photocoagulation alone for proliferative diabetic retinopathy.

Methodology

This randomized control trial was conducted fromSeptember 2023 to August 2024. Data include 40 patients, 80 eyes according to the criteria of the study.

Inclusion criteria

- Adults aged >18 years with a confirmed diagnosis of PDR based on fundus examination and fluorescein angiography.
- Absence of prior treatment for diabetic retinopathy, including PRP or anti-VEGF injections.
- Hemoglobin A1c (HbA1c) levels below 10%, ensuring stable glycemic control.
- No other significant ocular pathologies (e.g., advanced glaucoma or severe cataracts) that could interfere with the evaluation of outcomes.

Exclusion criteria

- History of intraocular surgery within the past three months.
- Coexisting conditions such as uveitis, retinal vein occlusion, or significant systemic illness (e.g., malignancies or advanced renal failure).

Data collection

Participants were randomly assigned into two equal groups using a computer-generated sequence. The first group of twenty patient who served as the control group had received only the PRP treatment. The second group involved 20 patients that received PRP alongside a single intravitreal injection of bevacizumab, making it the intervention group. Randomization was useful in making equal distribution between the two groups and allocation concealment maintained minor control against inherent biases. The PRP treatment was done using a standard 532 nm laser in about 1500 to 2000 burns to the peripheral retina over two to three sittings. Laser settings covered spot size of 200-500 microns, a power level to produce mild retical blanching and a pulse duration of 100-200 ms. For the intervention group the patients received a single intravitreal injection of bevacizumab 1.25 mg/0.05 ml, one week before starting PRP. The injection was made in a very sterile manner, and the needle used was 30-gauge, which was inserted to a 4.0 mm's distance from the limbus. This combination was expected to have the beneficial effect on neovascular regression and the worsening of treatment related complications, such as DME. Follow up was done on participants after one month, three months, and six months after completion of treatment. In each visit, participants received a comprehensive ophthalmic test using the same device. Visual acuity was assessed under optimal conditions in each eye with Snellen chart and the ABC of the condition was assessed using fundoscopy and with the help of OCT on macular regression of the new vessels. The fluorescein angiography was performed during the six-month visit to determine the condition of the retinal neovascularization.

Data were analyzed using SPSS v26 software. Continuous variables, such as BCVA and CMT, were reported as mean ± standard deviation and compared between the two groups using the Student's t-test or Mann-Whitney U test based on normality. A p-value of less than 0.05 was considered statistically significant.

Results

Data were collected from 40 patients. Both groups had a mean age of 54 ± 8 years and a male-to-female ratio of 3:2. Baseline best-corrected visual acuity (BCVA) was similar, with 0.4 ± 0.1 logMAR in the PRP group and 0.42 ± 0.1 logMAR in the combination group ($p > 0.05$). Central macular thickness (CMT) at baseline also showed no significant difference, with 310 ± 25 µm in the PRP group and 312 ± 27 µm in the combination group ($p > 0.05$), indicating well-matched groups for the study.

Table 1: Demographics and Baseline Characteristics

Characteristic	PRP Alone	PRP + Bevacizumab	p-Value
Mean Age (years)	54 ± 8	54 ± 8	-
Male-to-Female Ratio	3:2	3:2	-
Baseline BCVA (logMAR)	0.4 ± 0.1	0.42 ± 0.1	> 0.05
Baseline CMT (µm)	310 ± 25	312 ± 27	> 0.05

Complete regression of neovascularization was significantly higher in the combination group (75%) than in the PRP group (55%, $p = 0.03$). BCVA at six months improved to 0.32 ± 0.1 logMAR in the combination group, compared to 0.36 ± 0.1 logMAR in the PRP group ($p = 0.04$). Additionally, central macular thickness (CMT) was significantly lower in the combination group (290 ± 25 µm) versus the PRP group (315 ± 28 µm, $p = 0.01$). T

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Table 2: Primary and Secondary Outcomes

Outcome	PRP Alone	PRP + Bevacizumab	p-Value
Complete Regression of Neovascularization (%)	55	75	0.03
Partial Regression of Neovascularization (%)	45	25	-
BCVA at 6 Months (logMAR)	0.36 ± 0.1	0.32 ± 0.1	0.04
CMT at 6 Months (µm)	315 ± 28	290 ± 25	0.01
Vitreous Hemorrhage (%)	30	10	0.02

Improvement in BCVA was significantly higher in the combination group (0.10 ± 0.03 logMAR) than in the PRP group (0.04 ± 0.02 logMAR, p = 0.02). Similarly, the reduction in central macular thickness (CMT) was more pronounced in the combination group (-22 ± 4 µm) compared to the PRP group (-5 ± 3 µm, p = 0.01). Patient satisfaction was also notably higher in the combination group, with 90% reporting satisfaction versus 70% in the PRP group (p = 0.01), reflecting the perceived benefits of the combined treatment approach.

Table 3: Visual Improvement and Patient Satisfaction

Parameter	PRP Alone	PRP + Bevacizumab	p-Value
Improvement in BCVA (logMAR)	0.04 ± 0.02	0.10 ± 0.03	0.02
Improvement in CMT (µm)	-5 ± 3	-22 ± 4	0.01
Patient Satisfaction (%)	70	90	0.01

Exacerbation of diabetic macular edema (DME) was significantly less frequent in the combination group (5%) than in the PRP group (20%, p = 0.01). There were no cases of tractional retinal detachment in either group, reflecting the safety of both treatment modalities. Ocular discomfort was slightly lower in the PRP + Bevacizumab group (10%) compared to the PRP group (15%), although this difference was not statistically significant (p > 0.05).

Table 4: Complication Rates

Complication	PRP Alone	PRP + Bevacizumab	p-Value
Exacerbation of DME (%)	20	5	0.01
Tractional Retinal Detachment (%)	0	0	-
Ocular Discomfort (%)	15	10	> 0.05

At baseline, BCVA, NVE, and NVD were comparable between the groups (p > 0.05). By day 30, BCVA improved more significantly in the combination group (0.32 ± 0.1 logMAR) than in the PRP group (0.36 ± 0.1 logMAR, p = 0.04). Similarly, the reduction in neovascularization elsewhere (NVE) and neovascularization at the disc (NVD) was greater in the PRP + Bevacizumab group, with NVE decreasing to 3.8 ± 0.9 mm² compared to 4.8 ± 1.1 mm² in the PRP group (p = 0.02) and NVD reducing to 0.9 ± 0.2 mm² compared to 1.1 ± 0.3 mm² in the PRP group (p = 0.03).

Table 5: Mean and SD of BCVA, NVE, and NVD at Baseline and Day 30

Parameter	PRP Alone (Mean ± SD)	PRP + Bevacizumab (Mean ± SD)	p-Value
BCVA (logMAR) - Baseline	0.4 ± 0.1	0.42 ± 0.1	> 0.05
BCVA (logMAR) - Day 30	0.36 ± 0.1	0.32 ± 0.1	0.04
NVE (area in mm²) - Baseline	5.2 ± 1.0	5.3 ± 1.1	> 0.05
NVE (area in mm²) - Day 30	4.8 ± 1.1	3.8 ± 0.9	0.02
NVD (area in mm²) - Baseline	1.3 ± 0.3	1.4 ± 0.2	> 0.05
NVD (area in mm²) - Day 30	1.1 ± 0.3	0.9 ± 0.2	0.03

Discussion

The management of proliferative diabetic retinopathy (PDR) has evolved significantly with the advent of anti-vascular endothelial growth factor (VEGF) therapies. The purpose of this work was to compare the outcomes and side effects of PRP in patients with PDR treated with PRP only or PRP together with intravitreal bevacizumab. From the results provided it was determined that the combination therapy provides enhanced neovascular regression, vision acuity enhancement and reduction in central macular thickness (CMT) (11). In the six-month follow-up assessment, contained complete neovascular regression has been marked significantly high in the group that was treated with PRP + Bevacizumab than that of the PRP group, 75%

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& 55% respectively. This supports current research that posits that the use of anti-VEGF in conjunction with PRP boosts outcomes of the treatment procedure in PDR (12). For example, a cross sectional study published in 2023 revealed that intravitreous injection of conbercept along with PRP effected a significant improvement in the diabetic retinopathy score and reduced the severity of vision threatening complication. We also documented a slightly better visual acuity on the combine treatment in our study (13). Statistically significant results in terms of number of lines gained were observed in the PRP + Bevacizumab group at six months compared to PRP group, both in terms of BCVA (0.32 ± 0.1 logMAR in the PRP + Bevacizumab group as compared to 0.36 ± 0.1 logMAR in the PRP group) (14). We concur with a 2024 cross-sectional cohort study that compared the effects of monotherapy with anti-VEGF and PRP and the results indicated that patients with PRP monotherapy had a significantly poorer visual outcome; the rate of vitreous hemorrhage as well as tractional RD was also significantly higher in the group that received PRP monotherapy (15). As far as CMT is concerned, our study reported lesser risk of PRP + Bevacizumab for sake of managing diabetic macular edema (DME). This is in concordance with a study done in 2023 showing that preoperative intravitreal bevacizumab reduced macular thickness prior to vitrectomy for PDR complications and aided reported surgery outcomes. Vitreous hemorrhages occurred in, combination therapy group 10% and the PRP group 30%. This is in accordance with a study conducted in 2024 showing that patients given anti-VEGF administered more commonly than PRP had a considerably less frequency of vitreous hemorrhage and also, the pars plana vitrectomy. Indeed, as illustrated in our study and in some recent literature, PRP should be used in conjunction with anti-VEGF therapy (16). However, questions regarding patient compliance and follow-up must also be taken into consideration. Anti-VEGF therapies involve multiple injections and that patients have to attend frequent follow up appointments. A paper in 2022 highlighted on the relation between LTFU and tractional RD in patients with PDR and hence the importance of constant patient contact (17). A limitation of this study is the small sample size which may pose a severe threat to external validity. Moreover, the follow-up time was only six months; hence, it is inadequate to describe long-term consequences such as repeated neovascularization or even proliferation of complications like tractional retinal detachment in patients. The present research failed to consider the effects of multiple dosing, as well as the general benefits that come with repeat injections of bevacizumab.

Conclusion

It is concluded that the combination of panretinal photocoagulation and intravitreal bevacizumab offers superior outcomes in managing proliferative diabetic retinopathy compared to PRP alone. This approach enhances neovascular regression, improves visual acuity, and reduces diabetic macular edema with fewer complications. Incorporating anti-VEGF therapy into treatment protocols can significantly improve patient outcomes when supported by consistent follow-up and adherence.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department Concerned. (IRBEC-TCHR-23)
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Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

SARA RIAZ (Associate Professor)
Final Approval of version
NADEEM AHMED (Assistant Professor)
Revisiting Critically
ADNAN KHAN (Assistant Professor)
Data Analysis
AAMNA JABRAN (Senior Registrar)
Drafting
IRUM RAZA (Consultant Ophthalmology)
Concept & Design of Study

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