European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Comparison of Panretinal Photocoagulation Alone versus Panretinal Photocoagulation with Adjunctive Intravitreal Bevacizumab for Proliferative Diabetic Retinopathy with Diabetic Macular Edema

Article History:

Received: 08-10-2025
Revised: 19-11-2025
Accepted: 06-12-2025
Published: 24-12-2025

Name of Author:
[1]Dr. Raeesa Abdul Wahid, [2]Dr. Jawad bin Yamin Butt, [3]Dr. Ushna Sultan, [4]Dr. Kashif Hanif, [5]Dr. Ahmad Ilyas, [6]Dr. Abdul Basit

Affiliation: *[1,2,3,4,5]Layton Rahmatulla Benevolent Trust Free Eye, Township, Lahore*
[6]Shalamar Medical and Dental College

Corresponding Author:
Dr. Raeesa Abdul Wahid

Abstract: ***Objective:*** To compare the functional and anatomical outcomes of panretinal photocoagulation (PRP) alone with those of PRP combined with intravitreal bevacizumab (IVB) in eyes with proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). ***Methods:*** A randomized controlled trial was performed at LRBT Eye Hospital, Lahore, enrolling 180 eyes of 180 patients with PDR and DME. Participants were randomly assigned to PRP alone (Group A) or PRP plus IVB (Group B). PRP was delivered in three weekly sessions; Group B received 1.25 mg/0.05 mL IVB one week before the first and one week after the last PRP session. Central macular thickness (CMT, µm) and best-corrected visual acuity (BCVA, LogMAR) were measured by spectral-domain OCT and standardized LogMAR charts at baseline, 4, 12, and 24 weeks. Secondary outcomes included regression of neovascularization (NV), need for additional treatment, and safety. Data were analyzed using SPSS v26, with $p \leq 0.05$ considered significant. ***Results:*** One hundred sixty-eight eyes (84 per group) completed 24-week follow-up. Baseline characteristics were comparable. Mean CMT decreased from 465.8 ± 90.4 to 355.5 ± 70.8 µm in Group A and from 468.9 ± 88.7 to 290.3 ± 65.4 µm in Group B ($p < 0.001$). Mean BCVA improved from 0.69 ± 0.14 to 0.56 ± 0.11 in Group A and from 0.68 ± 0.15 to 0.45 ± 0.10 in Group B ($p < 0.001$). NV regression was achieved in 94% of combination-treated eyes versus 80% with PRP alone ($p = 0.012$). No cases of endophthalmitis, tractional retinal detachment, or sustained intraocular pressure (IOP) rise occurred. Subgroup analysis showed a larger benefit of combination therapy in patients with baseline CMT > 450 µm and diabetes duration > 10 years. ***Conclusion:*** Adjunctive IVB with PRP resulted in superior visual and anatomical outcomes without added risk. This limited-injection protocol may offer an effective, cost-efficient strategy for PDR with DME in resource-limited settings.

Keywords: Proliferative diabetic retinopathy; diabetic macular edema; panretinal photocoagulation; bevacizumab; optical coherence tomography; anti-VEGF.

INTRODUCTION

Diabetic retinopathy (DR) is a condition which is ranked as one of the most common microvascular complications of diabetes mellitus and is the number one cause of preventable blindness in adults of working age throughout the globe. Almost 80 percent of patients with long-term diabetes acquire some form of retinopathy in 20 years [2]. The two most vision threatening manifestations are proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) [3]. The two conditions are both caused

by retinal ischemia, which leads to the up-regulation of the vascular endothelial growth factor (VEGF), triggering pathological angiogenesis and elevated vascular permeability [4].

The main approach to the PDR management has been panretinal photocoagulation (PRP) since Diabetic Retinopathy Study (DRS) showed that it was able to

decrease the threat of a severe impairment of eyesight by over 50% [5]. It is a mechanism, which is used to ablate ischemic peripheral retina to decrease VEGF production and metabolic demand. Nevertheless, PRP is associated with such commonly known limitations: pain during the procedure, release of inflammatory cytokines, aggravation of macular edema, and permanent loss of peripheral visual field and night vision [6]. The inflammatory cascade activated by heat may worsen macular thickening in the eyes that have DME concurrently [7].

Retinal vascular disease has been transformed through anti-VEGF therapy. Bevacizumab (Avastin®) is a full-length humanized monoclonal antibody that binds all forms of VEGF-A and blocks the actions of angiogenesis and vascular permeability [8]. Even though it is used off-label to treat DR, its efficacy and cost-effectiveness have been proven by numerous trials in clinical use of the treatment [9]. The DRCR.net Protocol S demonstrated that ranibizumab was not inferior to PRP at 2 years and less visual-field loss[10]. Likewise, the CLARITY study showed a better visual improvement when using aflibercept over PRP in one year of study[11]. Nevertheless, long term anti-VEGF treatment entails regular injections and close follow-ups, which are costly logistically and economically in developing nations. By administering PRP and a combination of few anti-VEGF injections, it may hence maximize short term and long term results.

A number of studies have been done on this integrated method. Figueira et al (PROTEUS study) found that neovascular regression with ranibizumab and PRP compared to PRP alone at 12 months was significantly better[12]. Zhang and colleagues' meta-analyses established that PRP with anti-VEGF yielded more significant central macular thickness and visual improvement with no extra safety issues [13]. However, the published data is mostly of high-income nations. In Pakistan, locally, there is limited research and the trend in treatment is in favour of laser monotherapy. Thus, the trial was made to compare the effectiveness of PRP used alone versus PRP used in combination with intravitreal bevacizumab in PDR patients with DME, visual and anatomical improvement, safety, and response predictors.

Material and Methods

It was a prospective, parallel, randomized controlled trial that was performed in the Department of Ophthalmology, LRBT Eye Hospital, Lahore. The institutional ethics committee approved the protocol and informed consent was obtained in writing before the participants were enrolled in the protocol. Participants who had type 1 or type 2 diabetes, were 18-60 yrs old, had PDR (new vessels on disc, or elsewhere) and center involving DME with central macular thickness of 350 u m on OCT were eligible. The exclusion criteria were previous PRP or macular laser, anti-VEGF or steroid injection within 6 months, ischemic maculopathy, HgA1c of 10 and above, blood pressure of 170/100mmHg or above, renal failure on dialysis, and other ocular comorbidities which would affect vision. The subjects were randomized (1:1) through sealed envelope lottery to Group A (PRP alone) or Group B (PRP + IVB). The two groups received three PRP sessions of 532 nm laser (spot size 200 µm, 20 ms of laser power adjusted to different levels of light gray burns, and a total of 2500 to 3000 burns). In group B, 1.25mg/0.05 mL bevacizumab was administered a week prior to the initial laser and one week post-last session. Baseline assessment was done with an examination of the eye, measurement of BCVA with LogMAR charts, fundus photography and spectral-domain OCT of macular thickness. Follow-up visit was done at week four, twelve and twenty four. Mean change in CMT and BCVA at baseline and 24 weeks were used as primary outcomes. NV regression (complete, partial, or none) and need rescue therapy, adverse events were the secondary outcomes. They were also measured on systemic parameters (HbA1c, blood pressure, renal functioning) to rule out systemic confounders. Continuous variables were given as mean standard deviation with the independent t-tests between group and paired t-test within group. The use of chi-square or Fisher exact test was used in categorical variables. Subgroup analyses investigated the treatment effects according to age (<50 vs ≥50 years), duration of diabetes (<10 vs ≥10 years) and baseline CMT (<450 vs ≥450 µm). The p-value was deemed as significant at 0.05.

RESULTS

The number of patients that were screened was 205; 180 of them fit the inclusion criteria and were randomized (90 per group). There were 168 eyes (84 per arm) for final analysis as 12 of the patients were lost to follow-up (6 per group). Figure 3 is a CONSORT diagram to show participant flow.

Baseline demographics and clinical characteristics are shown in Table 1. The average age was 53.1 Standard Deviation 7.2; 97 (57.7) patients were males. The average duration of diabetes was 11.0 + 3.3 years, and the average level of HbA1c was 8.4 + 1.3%. There was no significant difference at the baseline in groups ($p > 0.05$).

Table 1. Baseline Characteristics (n = 168)

Parameter	PRP (n=84)	PRP + IVB (n=84)	p-value
Age (years), mean ± SD	53.3 ± 7.0	52.9 ± 7.3	0.74
Male sex, n (%)	52 (62%)	50 (60%)	0.78
Diabetes duration (years), mean ± SD	10.9 ± 3.5	11.1 ± 3.1	0.68
HbA1c (%), mean ± SD	8.4 ± 1.2	8.5 ± 1.3	0.81
Baseline CMT (µm), mean ± SD	465.8 ± 90.4	468.9 ± 88.7	0.82
Baseline BCVA (LogMAR), mean ± SD	0.69 ± 0.14	0.68 ± 0.15	0.81

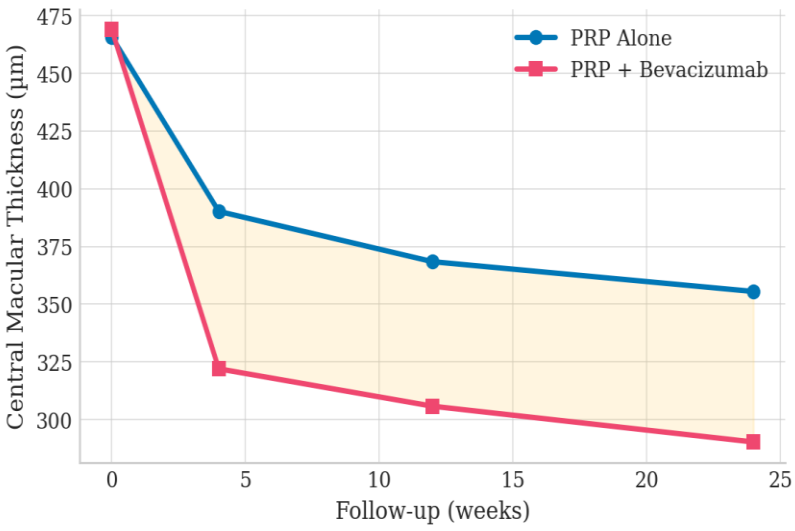
Table 2. Anatomical and Functional Outcomes

Parameter	Week 4	Week 12	Week 24	p-value (Week 24)
CMT (µm), PRP	390.2 ± 82.0	368.4 ± 78.5	355.5 ± 70.8	<0.001
CMT (µm), PRP + IVB	322.0 ± 75.1	305.8 ± 68.3	290.3 ± 65.4	<0.001
BCVA (LogMAR), PRP	0.63 ± 0.13	0.59 ± 0.12	0.56 ± 0.11	<0.001
BCVA (LogMAR), PRP + IVB	0.57 ± 0.12	0.50 ± 0.11	0.45 ± 0.10	<0.001
NV Regression (%)	74%	86%	94%	0.012

Central Macular Thickness

The baseline to 24-week differences in CMT were significant in both groups, although the degree of improvement was higher among PRP + IVB. In Group A, the mean CMT of 465.8 with 90.4 became 355.5 with 70.8 µm (-110.3 µm; p 0.001), and in Group B, 468.9 with 88.7 became 290.3 with 65.4 -178.6 -1. There was a significant between-group difference at week 4, 12 and 24 (all p < 0.001). Figure 1 shows the time trend of the CMT, which shows a steeper and continued decrease in the combination arm.

Figure 1. Central Macular Thickness Over 24 Weeks



Best-Corrected Visual Acuity.

There was progressive improvement in both groups but with PRP + IVB with a greater amount. The baseline BCVA in Group A and Group B was 0.69 and 0.68 (LogMAR) respectively. At week 24, the values were increased to 0.56±

0.11 and 0.45 ± 0.10 respectively (P < 0.001). The mean gain in BCVA was 0.13 in the PRP group and 0.23 in the combination group (p < 0.001). Figure 2 shows the improvement pattern, which indicates that the visual recovery is faster and the visual recovery is more in the adjunctive IVB.

Figure 2. Improvement in BCVA (LogMAR) Over 24 Weeks

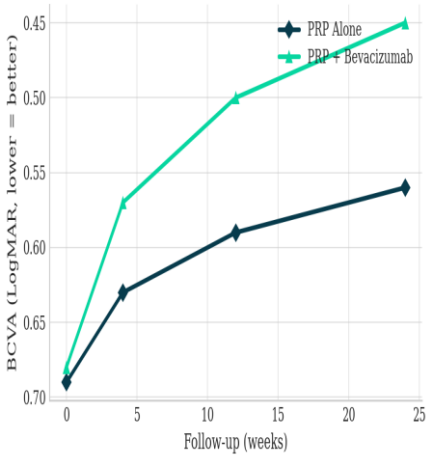
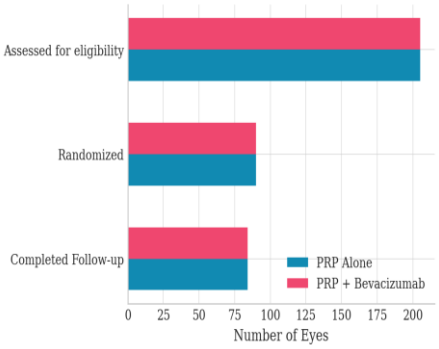


Figure 3. Study Flow and Follow-up Completion



Neovascular Rescue Therapy and Regression.

Week 12 showed partial or complete NV regression in 74 percent of the PRP-alone eyes and 89 percent of the combination ones (p = 0.018). By week 24 full regression was observed in 94 percent of Group B and 80 percent of Group A (p = 0.012). The PRP group (17 percent) needed rescue bevacizumab on 14 eyes because of continuing DME and the combination group (3.6 percent) needed 3 (p = 0.002).

Subgroup Analysis

The advantage of combination therapy was greatest in patients where the baseline CMT was 450 µm and longer than 10 years, indicating an increased pathophysiology mediated by VEGF. The visual gain (0.26 vs 0.21 LogMAR) was also slightly higher in the younger patients (less than 50 years) compared to the older ones although the interaction did not reach statistical significance (p = 0.08).

Adverse Events

There were no endophthalmitis, retinal detachment, or long term increase of IOP. Acute surges of IOP resolved under topical treatment. Mild cases of vitreous hemorrhage (PRP and PRP + IVB) were observed in 3 and 2 eyes respectively, and they healed by themselves in 2-3 weeks. None of the systemic thromboembolic events were present.

Table 3. Adverse Events

Event	PRP	PRP + IVB
Transient IOP rise	3 (3.6%)	2 (2.4%)
Vitreous hemorrhage	3 (3.6%)	2 (2.4%)
Endophthalmitis	0	0
Systemic event	0	0

DISCUSSION

The current research indicates that adjunctive intravitreal bevacizumab can be of great help in improving not only anatomic but also functional outcome in cases of the proliferative diabetic retinopathy and complementary diabetic macular edema, as opposed to using the panretinal photocoagulation alone. The extent of benefit in this case (reduction of CMT, increase in BCVA, and regression of NV) is in line with that available worldwide in favor of the supplementary effect of anti-VEGF therapy in concert with laser photocoagulation.

Our findings are consistent with those of Sameen et al. who observed high-quality reduction in macular thickness and visual acuity after combined therapy as opposed to PRP alone among a Pakistani cohort14. With combination treatment, Ahmad and Jan also reported better short-term results with combination therapy15. A PROTEUS study was conducted internationally and showed that ranibizumab combined with PRP had greater neovascular regression (92) compared to PRP alone at 12 months (70)12. The DRCR.net Protocol S trial demonstrated that anti-VEGF therapy was able to replace PRP in PDR with similar or better results at five years10. The findings of ours fill these gaps, demonstrating that a short, timely anti-VEGF treatment can almost equally benefit when applied in combination with PRP.

PRP decreases ischemic motivation by ablating the peripheral retina that is oxygen-deprived, thus suppressing VEGF synthesis in weeks. On the other hand, bevacizumab has a rapid anti-permeability effect that occurs within days, which reduces the macular edema and induces the regression of the new vessels16. It inhibits transient VEGF bursts caused by laser-induced inflammation when administered prior to PRP, avoiding the worsening of macular edema17. Post-laser injection also helps stabilize vascular integrity that results in lasting anatomical enhancement. This combination therefore integrates the long-term advantages of PRP and the VEGF-inhibitory effect of bevacizumab which is fast acting.

PRP to be used in combination with two timely injections of bevacizumab is a practical trade off in low- and middle-income nations, where monthly anti-VEGF treatment is frequently impractical. The current one, pre-laser and post-laser dosing, was effective in reducing CMT by almost 180 µm and vision improvement by 0.23 LogMAR which was better than PRP alone with minimum injection burden and cost. These practices have the potential to increase access to care that saves vision without affecting its effectiveness.

The data of our study supported the positive safety profile of intravitreal bevacizumab. There were no cases of endophthalmitis, retinal detachments, or systemic thromboembolic events, which is consistent with extensive safety surveys by Falavarjani and Nguyen18. The self-limiting and transient elevations in IOP were mild. The off-label administration of Bevacizumab remains reasonable in the conditions when the ranibizumab or aflibercept are prohibitively expensive.

Those with a thicker base maculae with a longer period of diabetes received more benefit with adjunctive IVB implying that chronic ischemic retina produces more VEGF and hence more receptive to anti-VEGF blockade. Functional recovery was somewhat improved in younger patients, which could be because of less irreversible ischemic damage. Nevertheless, such results should be confirmed by bigger studies.

The major weakness of this research is the comparatively short 24 weeks follow up. Although this is adequate to identify anatomical and early functional changes, the long-term data will be required to determine permanency and the repeat of the neovascularization. Second, bevacizumab is not pharmacologically similar to ranibizumab and aflibercept, and so, may not be generalizable to all anti-VEGF agents. Lastly, there was no repeat of fluorescein angiography in every visit, which did not allow the analysis of the microvasculature in detail.

Future research needs to investigate how many and when to inject the maximum synergy with PRP, cost-effectiveness studies in various healthcare facilities, and individualized therapy using biomarkers. Optical coherence tomography angiography (OCTA) has the potential to become an effective method of monitoring microvascular healing after PRP + IVB. Also, further

follow-up could be useful to determine whether combination therapy prevents recurrence and prolongs fibrovascular growth over PRP.

CONCLUSION

The PRP plus intravitreal bevacizumab regression of neovascularization, better reduction of macular thickness and visual outcomes are greater in eyes with concomitant diabetic retinopathy and diabetic macular edema than with PRP. The therapy is safe and economically viable and logistically viable in resource-restrained tertiary centers. Limited anti-VEGF regimen together with conventional PRP must be a best-practice approach to saving the sight of diabetic populations.

References

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–564.
2. Klein R, Klein BE, Moss SE. The Wisconsin epidemiologic study of diabetic retinopathy. Arch Ophthalmol. 1984;102:520–526.
3. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376:124–136.
4. Aiello LP, Avery RL, Arrigg PG, et al. VEGF in ocular fluid of diabetic retinopathy. N Engl J Med. 1994;331:1480–1487.
5. Diabetic Retinopathy Study Research Group. Preliminary report on PRP in proliferative diabetic retinopathy. Am J Ophthalmol. 1976;81:383–396.
6. Early Treatment Diabetic Retinopathy Study (ETDRS) Group. Photocoagulation for diabetic macular edema. Arch Ophthalmol. 1985;103:1796–1806.
7. Stefánsson E. The therapeutic effects of retinal laser treatment and vitrectomy. Prog Retin Eye Res. 2001;20:141–168.
8. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab. Nat Rev Drug Discov. 2004;3:391–400.
9. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema (RISE/RIDE). Ophthalmology. 2012;119:789–801.
10. Gross JG, Glassman AR, Liu D, et al. Panretinal photocoagulation vs intravitreal ranibizumab for PDR. N Engl J Med. 2015;372(12):1190–1200.
11. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. CLARITY: aflibercept vs PRP for PDR at 52 weeks. Lancet. 2017;389:2193–2203.
12. Figueira J, Fletcher E, Massin P, et al. Ranibizumab plus PRP versus PRP alone (PROTEUS). Ophthalmology. 2018;125:691–700.
13. Zhang W, Sang A, Sun L, et al. PRP plus anti-VEGF vs PRP alone: meta-analysis. Front Endocrinol. 2022;13:807687.
14. Sameen M, Khan MS, Mukhtar A, et al. Efficacy of intravitreal bevacizumab combined with PRP vs PRP alone. Pak J Med Sci. 2017;33(1):142–146.
15. Ahmad M, Jan S. PRP vs PRP + bevacizumab in proliferative diabetic retinopathy. J Ayub Med Coll Abbottabad. 2012;24(3-4):10–13.
16. Funatsu H, Yamashita H, Yamauchi M, et al. Angiogenic factors in diabetic macular edema before and after laser. Invest Ophthalmol Vis Sci. 2002;43(3):907–916.
17. Stewart MW. Anti-VEGF therapy for diabetic retinopathy: 2022 update. Retina Today. 2022;1:47–54.
18. Falavarjani KG, Nguyen QD. Adverse events associated with intravitreal anti-VEGF. Eye. 2013;27:787–794.