
Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr


Comparison of Effectiveness of Bevacizumab Combined with Panretinal Photocoagulation versus Panretinal Photocoagulation Alone in Patients with Proliferative Diabetic Retinopathy and Diabetic Macular Edema

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ABSTRACT

Background: In recent years, the introduction of anti-VEGF (vascular endothelial growth factor) has greatly transformed the way diabetic retinopathy is being approached. Bevacizumab is a humanized monoclonal antibody that targets VEGF-A. Recent studies have shown significant regression in retinal neo-vascularization after intravitreal anti-VEGF injection in patients with proliferative diabetic retinopathy.


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Objective: To compare the mean change in central macular thickness using pan-retinal photocoagulation alone versus pan-retinal photocoagulation combined with intravitreal bevacizumab in patients with proliferative diabetic retinopathy and diabetic macular oedema.

Method: This Randomized controlled trial was carried out at Mughal Eye Hospital Trust, Johar Town, Lahore, Pakistan from August 2024 to January 2025. 170 eyes of 85 patients included in the study who had proliferative diabetic retinopathy along with diabetic macular oedema. Patients were divided into two groups (A and B) who were treated with pan-retinal photocoagulation(PRP) alone and PRP combined with Intravitreal bevacizumab(IVB) respectively. Optical coherence tomography(OCT) was carried out pre-procedure and 12 weeks post-procedure to compare the mean change in central macular thickness between the two groups.

Results: The majority of the patients, 79 out of 170 (46.47%) were between 50 to 59 years of age, 75(44.12%) were male and 95(55.88%) were females. Moreover, the change in central macular thickness with PRP alone versus PRP combined with IVB was 82.78 ± 5.57 and 117.76 ± 7.94 µm respectively.

Conclusion: This study concluded that the pan-retinal photocoagulation combined with intravitreal bevacizumab is better as compared to PRP alone in terms of mean change in central macular thickness in patients with PDR and DME.

Keywords: Diabetic Macular Edema, Pan Retinal Photocoagulation, Intravitreal Bevacizumab, Proliferative Diabetic Retinopathy.

INTRODUCTION

Diabetes mellitus (DM) has an estimated worldwide prevalence of 8.3% and a predicted 205 million addition to the count by 2035[1] with Diabetic retinopathy (DR) being one of its most common complications.[2] The global prevalence of DR has been estimated to be 34.6%, with 6.96% having proliferative diabetic retinopathy (PDR) and 6.81% having

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diabetic macular oedema (DME) both of which are primarily responsible for vision loss in diabetic eye disease.[3,4] Patients with diabetes require regular follow up with primary care physicians to optimize their glycemic, blood pressure and lipid control in order to prevent development and progression of DR and other diabetes related complications.[5]

Diabetic macular edema is the main cause of visual impairment in diabetic retinopathy. Macular edema can be divided into focal diabetic macular edema which is caused by the accumulation of fluid from leaking microaneurysms and diffuse macular edema caused by leakage without any clear source[3]. Pan retinal photocoagulation (PRP) is the standard of care for prevention of vision loss in PDR.[6] This treatment ablates the peripheral retina which decrease the metabolic demand of oxygen and facilitates oxygen and nutrient supply to the inner retina, alleviating the ischemia that drives neovascularization in PDR.[6] However, PRP can damage the retina, resulting in peripheral vision loss or worsening DME.[7] This PRP-induced macular edema may cause temporary or permanent vision loss.[6]

The introduction of anti-VEGF (vascular endothelial growth factor) has greatly transformed the treatment method of diabetic patients. Bevacizumab is a humanized monoclonal antibody that targets VEGF-A.[8] Recent studies have shown significant regression in retinal neo-vascularization in patients with PDR and prior PRP.[9] Ophthalmic uses of bevacizumab are not FDA approved; however, its safety and efficacy have been shown in multiple neovascular age-related macular degeneration and DME trials.[10,11] IVB (intravitreal bevacizumab) as an adjuvant to PRP have shown to reduce deterioration in visual acuity and regression of retinal new vessels and is gaining popularity due to its cost-effectiveness and ease of use.[11]

Studies have shown argon diode laser PRP combined with IVB has superior visual and anatomical outcome than PRP alone in patients with combined presentation of PDR and DME.[12,13,14] Therefore, this study was carried out to compare the effectiveness of PRP


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alone versus combined with IVB in patients with PDR and DME.

METHODS

This Randomized controlled trial was carried out at Mughal Eye Hopsital Trust, Johar Town, Lahore, Pakistan from August 2024 to January 2025.Sample size was calculated using Open EPI info calculator and came out to be 170 eyes(85 patients), where both eyes of a patient were considered separately. Patients were selected using non probability, consecutive sampling, all being newly diagnosed cases of PDR with DME without any prior therapy. The age range was adjusted from 30-70 years and the baseline central macular thickness was restricted between 250-450 um. In order to remove the influence of confounding factors, patients having significant cataract (hindering fundal view and OCT recording) and having any other ocular pathology such as age related macular degeneration, central serous chorio-retinopaty (CSCR) , central vein occlusion, cystoid macular edema (CMO) were excluded from the study.

DATA COLLECTION PROCEDURE:

A written informed consent was taken before collecting data and demographic details were noted in form of age, gender and contact details. Detailed ophthalmic clinical examination of all the patients was carried out. All cases were randomly divided into two groups i.e. group-A and group-B by using random allocation software 2.0 to obtain trial sequence which is sealed in the numbered opaque envelops generated by the researcher. Central macular thickness(CMT) was measured using Topcon 3D OCT-2000 prior to intervention in all cases. Patients in group A were treated with pan-retinal photocoagulation in a single session using Viridis laser machine with argon laser(532nm) and Mainster PRP 165 laser lens. In the PRP session, 1500-2000 burns were applied under topical anaesthesia (proparacaine hydrochloride 0.5%) with 200um spot size and power starting from 250 mW until a mild grey reaction was achieved. All patients were prescribed topical NSAIDS (nepafenac 0.1%) after the PRP session . Follow up was after 3 months of the PRP session

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where CMT was measured again. The two readings of CMT were subtracted to acquire change in CMT for patients in group A. In group B, PRP was applied in the same manner as that of group A and the first intravitreal injection of bevacizumab was given after 1 week of the PRP session. Injection was given via pars plana under aseptic conditions in the operation room and before injection, topical anaesthetic eye drops(proparacaine hydrochloride 0.5%) were instilled . The conjunctival sac and periocular area were rinsed with the povidone-iodine solution. After application of a sterile drape, a lid speculum was inserted. The dosage for intravitreal bevacizumab injections was 1.25 mg (0.05 mL), injected using a syringe with a 30G needle at a distance of 4.0 mm from the limbus in phakic eyes, and 3.5 mm in pseudophakic eyes. After the injection, antibiotic eye drops(ofloxacin) were prescribed, 4 times a day for 1 week. The second injection was given in the same manner after 1 month of the first injection and similarly the third injection was given one month after the second injection. The follow up was one month after the third injection where Topcon 3D OCT-2000 was used to measure the final CMT for patients in group B. This CMT reading was subtracted from the CMT measured prior to the intervention to get the induced change in the central macular thickness for patients in group B. All data was recorded on predefined proforma.

DATA ANALYSIS PROCEDURE:

All collected data was entered and analyzed using SPSS 24. Mean and S.D were calculated using quantitative variables like age (years) and change in CMT. Frequency (%) was used for gender and eye laterality. Independent sample t-test was applied to compare mean change in CMT in both groups. Data was stratified for age, gender and the eye laterality. Post stratified independent sample t-test was applied taking p-value ≤ 0.5 as significant.

RESULTS

Group A and Group B consisted of 85 patients each**.** Out of the 170 patients included

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in this study, 75 (44.12%) were male and 95 (55.88%) were females. In group A, there were 43(50.59%) males and 42(49.41%) females whereas in group B, there were 32 males (37.65%) and 53(62.35%) females**.** The mean age of patients in group A was 51.16 ± 8.21 whereas the mean age of patients in group B was 49.38 ± 6.44. **(Table I).** In group A(n=85), the mean pretreatment CMT was 323.56± 8.43 µm and the mean post-treatment CMT was 241.14 ± 7.22 µm.**(Table I).** The change in CMT in group A was 82.78 ± 5.57 µm(Table II).

In comparison , in group B(n=85), mean pretreatment CMT was 391.42± 9.55 µm and the mean post treatment CMT was 273.65± 5.52 µm(Table I) with change in CMT calculated to be 117.76 ± 7.94 µm(Table II)

TABLE I Mean Values of Various Variables

Variable	N	Group A	Group B
Age	85	51.16 ± 8.21	49.38 ± 6.44
Pre-treatment CMT(um)	85	323.56± 8.43	391.42± 9.55
Post-treatment CMT(um)	85	241.14 ± 7.22	273.65± 5.52

TABLE II Induced Change in Central Macular Thickness(CMT)

	Group A n=85	Group B n=85	
	Mean ± SD	Mean ± SD	P value
Change in CMT(um)	82.78 ± 5.57	117.76 ± 7.94	<0.001

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DISCUSSION

Diabetic retinopathy is a leading cause of blindness in advanced countries[14]. The Diabetic Retinopathy Study demonstrated that panretinal photocoagulation (PRP) laser reduces the risk of severe vision loss by 50% in patients with proliferative diabetic retinopathy (PDR) compared with patients without treatment.[14] However, PRP does not eliminate the possibility of vision loss in high-risk eyes, and the treatment itself may have potentially significant complications.[14] In addition to adverse effects such as nyctalopia, dyschromatopsia, peripheral visual field defects and decreased contrast sensitivity, PRP may also induce macular edema resulting in decreased visual acuity.[72-73] Early studies revealed that 25% to 43% of eyes with PDR treated with PRP developed macular edema and visual dysfunction.[14] The exact mechanism responsible for macular edema after PRP has not been determined, although some studies suggest that the laser induces release of inflammatory cell mediators such as interleukin-6 and interleukin-8 and the upregulation of vascular endothelial growth factor which play a role in the pathogenesis of the macular edema.[14]

PDR and DME are two manifestations of Diabetic eye disease that are responsible for visual loss in majority of the patients and they are treated primarily with panretinal photocoagulation and intravitreal anti VEGF respectively. However, recent use of anti VEGF agents in PDR has shown promising results not inferior to PRP.[14] Numerous recent studies have demonstrated the utility of intravitreal bevacizumab (IVB) in reducing macular thickening secondary to central retinal vein occlusion, neovascular age-related macular degeneration, and DME.[12] IVB(intravitreal bevacizumab) as an adjuvant to PRP has shown to reduce deterioration in visual acuity and regression of retinal new vessels and


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is gaining popularity due to its cost-effectiveness and ease of use.[11] The proposed mechanism of IVB in resolution of both DME and PDR is binding to all forms of endogenous VEGF which is responsible for pathogenesis of DME as well as PDR.[12]

This study aimed to evaluate the efficacy of IVB as an adjuvant to PRP by evaluating the change in central macular thickness in PRP alone and PRP combined with intravitreal bevacizumab using optical coherence tomography (OCT). In this study, the change in central macular thickness with pan-retinal photocoagulation alone versus pan-retinal photocoagulation combined with intravitreal bevacizumab was 82.78 ± 5.57 µm and 117.76 ± 7.94 µm respectively (p-value = 0.001). The results have shown that IVB seems to be a promising adjunctive treatment to PRP in the treatment of PDR and DME as there is a significant reduction in central macular thickness in the combined therapy as compared to PRP monotherapy.

Other studies have also shown argon diode laser PRP combined with IVB has a superior visual and anatomical outcome than PRP alone in patients with combined presentation of PDR and DME.[12] A local study reported that the mean induced change in central macular thickness (CMT) after treatment was 77.44 ± 92.30 um in PRP alone and 117.50 ± 93.82 um in PRP along with the intravitreal bevacizumab group.[12] Zhou AY, et al. reported an approximate 10% increase in CSMT(central subfield macular thickness in the PRP group ($P>0.05$) in comparison to a significant reduction in CSMT in the PRP-Plus group ($P<0.05$) at all study visits.[13] Moreover, another study by Mason JO ,et al. revealed a marked difference in the foveal thickness(FT) between the two groups ($P=0.001$) with FT showing a dramatic increase in control group versus significant reduction in study group in comparison to baseline FT.[14] Similar results were concluded in studies conducted by Rebecca et al[15] and Ahmed et al[16], further corroborating to the results of this study. Similar studies comparing the effectiveness of PRP alone versus PRP plus intravitreal Anti-VEGF other than bevacizumab have also been conducted and showed superior anatomical and


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visual outcomes in the combined group. [17,18,19]

LIMITATIONS

Even though the results of this study supported the proposed hypothesis but there were a few limitations that may have influenced the outcome. The main limitation of this study was the short follow-up time of 3 months. Longer follow-up studies are clearly needed to establish the benefit of combined therapy (PRP plus anti-VEGF injections) .There was only a limited sample size and the study was conducted in only one clinical setup .There was a lack of availability of abundant local data that would have corroborated the results of this study.The restriction on the eligibility criteria may have also reduced the actual representatives of the study population and the generalizability of the findings. This study did not take into consideration comordities such as hypertension, diabetic nephropathy and the duration of diabetes in each group.BCVA and rate of regression of neovascularization was not studied, which would have further supported the hypothesis of superiority of combined therapy in terms of both visual and anatomical outcome.

CONCLUSION

It is concluded that the pan-retinal photocoagulation combined with intravitreal bevacizumab is better as compared to pan-retinal photocoagulation alone in terms of mean change in central macular thickness in patients with proliferative diabetic retinopathy and diabetic macular oedema. However, it must be noted here that the sample size may not be the true representation of the entire population considering that it was chosen from a single tertiary clinical setup and the observations were made over a span of 6 months only. Therefore, in order to deduce more conclusive results further studies may need to be conducted for an irrefutable conclusion.

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