

ORIGINAL ARTICLE

COMPARISON BETWEEN PANRETINAL PHOTOCOAGULATION AND PANRETINAL PHOTOCOAGULATION PLUS INTRAVITREAL BEVACIZUMAB IN PROLIFERATIVE DIABETIC RETINOPATHY

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Background: Patients with diabetes often develop ocular complications. The most common and most blinding of these complications, however, is diabetic retinopathy. The objective of this study was to compare the retinal neovessels regression in Proliferative Diabetic Retinopathy (PDR) treated with Pan Retinal Photocoagulation (PRP) versus panretinal photocoagulation plus Intra Vitreal Bevacizumab (IVB). **Methods:** A comparative study was conducted at Khyber Institute of Ophthalmic Medical Sciences, Hayatabad Medical Complex, Peshawar from 1st October 2010 to 31st August 2011. A total of 54 eyes were randomised into two groups. Neovessels status was assessed before and at every follow up visit. Neo Vessels on the Disc (NVDs) were assessed as per percentage of NVD occupying the disc surface whereas Neo Vessels Elsewhere (NVE) were also assessed as per reference to disc surface diameter. **Results:** Neovascularization on the disc was 40±5% at presentation which increased to 50±7% on 30th day and stabilised to 40±6% on day 90 in PRP group. In PRP-plus group, 40±7% NVD regressed to 10±5% on 30th day and 11±3% on day 90. The NVE in PRP group was 2±0.75% at baseline, 2.25±0.75% on 30th day, and 2.00±0.50% on day 90. In PRP-plus group it was 2±0.50% at baseline, 1±0.5% on day 30, and 0.75±0.25% on day 90. On day 90 both the groups had highly significant different NVD ($p=0.00008$) and NVE ($p=0.0001$). **Conclusion:** Intra Vitreal Bevacizumab in short term is effective as adjunctive treatment to PRP with early and higher rate of retinal neovessels regression than PRP alone in PDR patients.

Keywords: Panretinal Photocoagulation, Diabetic Retinopathy, Intravitreal Bevacizumab

INTRODUCTION

Diabetes Mellitus (DM) is a major medical problem with long-term systemic complications and affects individuals in their most productive years of life. The disease has considerable socioeconomic impact on the affected individuals and the society.¹ Prevalence of diabetes is increasing day by day throughout the world.² Globally about 8000 eyes blind per year, 12% of these blindness is due to diabetic eye diseases.³ Patients with diabetes often develop diabetic retinopathy. Prevalence of non-proliferative diabetic retinopathy is 76.50%; maculopathy and proliferative diabetic retinopathy are 17.60%, and 5.90% respectively.⁵ In diabetic patients one of the important risk factor for severe visual loss is progressive Retinal Neovessels (RN). All those patients who had proliferative diabetic retinopathy (PDR) received treatment with photocoagulation severe visual loss (ETDRS) is reduced by 50% or more as compared to those patients who did not received the treatment.⁶ In high-risk PDR, even in some cases with non-high risk PDR and severe non-proliferative diabetic retinopathy (NPDR) with poor compliance, panretinal photocoagulation (PRP) is indicated.^{6,7} Recently the use of Bevacizumab is becoming popular to treat ocular neovascular disorder including proliferative diabetic retinopathy.⁸ Recently some authors reported the role of Intra Vitreal Bevacizumab (IVB) in preventing PRP induced visual dysfunction and foveal thickening in diabetic retinopathy.⁹ Bevacizumab also decreases more

quickly the area of active leaking of NV in PDR patients.¹⁰ This alternative therapy is welcomed for two reasons, IVB injections are certainly easier to perform and seem not to affect the vision negatively. IVB also treats the disease by (blocking the effect of vascular endothelial growth factor (VEGF) a different mechanism which has no destructive effect like PRP laser and increases the chances of achieving stability of retinopathy status. On the other hand, IVB does not change the relative ischemia in the retina. Although standard treatment of proliferative diabetic retinopathy is panretinal photocoagulation, anti-VEGF use has shown promising results in term of neovessels regression and also on decreased macular oedema if present.¹¹

So far, to our knowledge, no or very limited local data are available regarding this topic. This study was designed to compare both treatments in the same patient; intravitreal Bevacizumab plus panretinal photocoagulation in one eye, compared to panretinal photocoagulation alone in the contralateral eye.

MATERIAL AND METHODS

This was a comparative study performed in the Department of Vitreoretinal Surgery, Khyber Institute of Ophthalmic Medical Sciences, Hayatabad Medical Complex, Peshawar from 1st October 2010 to 31st August 2011. The study protocol was approved by the local institutional ethical review board. The off-label use of the drug and its potential risks and benefits were

discussed extensively and written informed consent was taken from all patients.

Sample size was calculated alpha risk of 5% and power of the study 80%, the required sample size was 23 eyes in each group. We added 4 eyes in each group to cover follow-up losses. Total of 54 eyes were studied. Both eyes of each patient were randomly selected by simple lottery method for PRP group (only laser therapy) and PRP plus group (laser plus intravitreal bevacizumab injection). The physician did not know which eye has been injected.

All patients aged ≥ 18 year who presented with first-time PDR with almost same changes in both eyes with no prior retinal laser besides macular laser treatment were included in the study. High-risk PDR and non-high risk PDR were defined according to the guidelines set forth by the ETDRS.⁶ Exclusion criteria included, history of prior PRP or vitrectomy. Pre-treatment baseline data included age, sex, type, and duration of diabetes mellitus. Patients also underwent clinical examination including Best-Corrected Visual Acuity (BCVA) measured with Snellen's chart converted to log MAR for data analysis, bio-microscopic non-contact fundus examination with a 78-diopter lens. Neo Vessels on the Disc (NVD) were taken in percentage of disc surface diameter while NVE was also measured as referred to disc surface diameter. Follow-up visits were scheduled after initial intervention (PRP and PRP plus IVB) at 30th day and day 90. Exactly the same clinical examination was performed at baseline and at each study visit. The primary outcome measures were the changes in NVD and NVE. All patients underwent PRP in two sessions performed at day 1 and day 15 as per ETDRS guidelines in both eyes and only one injection of IVB to eyes in PRP plus group just 3 hours after PRP session. Treatment was administered in 800–1000 (300 μ m spots) per episode, at the discretion of the treating ophthalmologist. The eyes with clinically significant macular oedema received macular laser treatment as per ETDRS protocol before or at the time of initiating PRP.⁶ After completion of PRP session, one eye (treatment group) was prepared in a standard manner using 5% povidone/iodine, an eyelid speculum was used to stabilise the eyelids, and the injection of 1.25 mg (0.05 ml) of bevacizumab was given 3.5–4 mm posterior to the limbus through the infero-temporal pars plana with a 30-gauge needle under topical anaesthesia. After the injection IOP and retinal artery perfusion were checked and patients were instructed to administer topical antibiotics for 7 days. The clinical status of the two sets of eyes at day 30 and day 90 after treatment in terms of retinal vessels (NVD/NVE) status were compared and analysed using BCVA, slitlamp biomicroscopy and fundus photography by single blind experienced retinal surgeon. SPSS-12 was used for data analysis.

RESULTS

Total of 54 eyes were randomised in two groups all of them completed the 90 days follow-up. Baseline characteristics of both groups are shown in Table-1. Mean NVD and NVE status of both the groups at baseline, day 30, and day 90 are shown in Table-2.

Argon laser power was used mean 300 ± 51 mW in PRP group and 300 ± 42 mW in PRP-plus group. Total number of burns applied at PRP and PRP-plus group were 1850 ± 96 and 1820 ± 90 respectively in two sessions.

Mean BCVA (logMAR) in the PRP group worsened significantly from mean 0.30 ± 0.07 to mean 0.40 ± 0.04 at 30th day and mean 0.40 ± 0.04 at day 90. However, in PRP-Plus group, BCVA become improved from 0.30 ± 0.05 to 0.1 ± 0.03 at week 4 and 0.1 ± 0.02 at week 12. There were highly significant changes between the two groups at week 4 ($p=0.00004$) and at week 12 ($p=0.00002$) (Table-2).

Table-1: Baseline characteristics of patients (n=54)

Baseline characteristics	PRP group n=27 (Mean \pm SD)	PRP-Plus group n=27 (Mean \pm SD)
Age (years)	50.8 \pm 6.8	51.0 \pm 6.0
Male (%)	59.25	62.96
Female (%)	40.75	37.04
Duration of DM (years)	12 \pm 5	13 \pm 4.5
HbA1c (%)	7.9 \pm 1.5	7.3 \pm 1.4
Systolic BP (mm Hg)	140 \pm 21	143 \pm 15
Diastolic BP (mm Hg)	98 \pm 15	96 \pm 14
BCVA (logMAR)	0.34 \pm 0.60	33 \pm 0.6
Eyes with CSME (%)	44.13	48.14
IOP (mm Hg)	16 \pm 5	15 \pm 5

PRP=Panretinal photocoagulation, BCVA=best corrected visual acuity, CSME=clinically significant macular oedema, DM=diabetic mellitus, HbA1c=glycosylated haemoglobin, IOP=intraocular pressure, IVB=intravitreal bevacizumab, logMAR=logarithm of minimum angle of resolution

Table-2: NVD, NVE, and BCVA status at presentation and follow up (n=54)

	PRP-Group n=27 (Mean \pm SD)	PRP Plus-Group n=27 (Mean \pm SD)	P
NVD (DD\pmSD)			
Baseline	40 \pm 5	40 \pm 7	-
Day 30	50 \pm 7	10 \pm 5	0.00004
Day 90	40 \pm 6	11 \pm 3	0.00008
NVE (DD\pmSD)			
Baseline	2 \pm 0.75	2 \pm 0.50	-
Day 30	2.25 \pm 0.75	1 \pm 0.5	0.0001
Day 90	2.00 \pm 0.50	0.75 \pm 0.25	0.0001
BCVA (log MAR)			
Baseline	0.30 \pm 0.07	0.30 \pm 0.05	-
Day 30	0.40 \pm 0.05	0.1 \pm 0.03	0.00004
Day 90	0.40 \pm 0.04	0.1 \pm 0.02	0.00002

PRP=panretinal photocoagulation, PRP-plus=panretinal photocoagulation plus intravitreal injection of 1.25 mg of bevacizumab, NVD=Neovessels on the disc, NVE=new vessels elsewhere, DD=Disc diameter, BCVA=best corrected visual acuity, logMAR=logarithm of minimum angle of resolution

DISCUSSION

The two study groups were well balanced overall for demographic and baseline ocular characteristics. Standard therapy for PDR is still PRP and severe visual loss reduces with PRP, but it has some side effects such as macular oedema and constricted visual field.^{12,13} The use of anti-VEGF compounds for RN in diabetic retinopathy have been reported in several studies.¹⁴ Some case reports demonstrated RN regression with intravitreal use of bevacizumab in PDR patients.¹⁵⁻¹⁷ One of the recent study demonstrated that IVB appears to stabilise or improve PDR in conjunction with PRP, at least in the short term.¹⁸ We aimed to evaluate the efficacy of IVB as adjunctive treatments to PRP in term of regression of new vessels in PDR, and our results have shown that IVB seems to be a promising adjunctive treatment to PRP in the treatment of PDR. During the follow-up period, there was significantly higher proportion of eyes with visual deteriorations and increase in severe NVD and NVE in PRP group than in the PRP Plus groups. Current study shows the role of intravitreal anti-VEGF in regression of retinal neovessels in PDR and some other conditions like central retinal vein obstruction, neovascular age-related macular degeneration, iris neovascularization etc.¹⁹ Another study reported rapid regressions in retinal and iris neovessels after intravitreal bevacizumab injection.²⁰

We studied the difference in regression of neovessels between PRP combined with a single IVB injection versus PRP alone in eyes with PDR. It was noted that IVB adjuvant group had early regression of NV as compared to PRP only group. The difference in NV regression in two groups on day 90 was statistically significance ($p < 0.0001$). Mirshahi, *et al* evaluated high-risk PDR patients with the bevacizumab-augmented retinal laser photocoagulation. A very effective response was achieved with combination therapy for regression of NV at 6 weeks of follow-up. However, both the groups had similar results for complete regression, as PDR recurred at 16th week of follow-up in the bevacizumab-injected eyes.²¹

Due to our study design and limited follow-up we were unable to determine in the long-term whether IVB plus PRP inhibits the recurrence of NV or maintains a remission state. Tonello, *et al* had reported combined effect of IVB plus PRP and noted that combined effect are much better and had greater area of reduction of active leaking NV than PRP only in patients with high risk PDR.⁹ We noted that the IVB with PRP resulted in rapid regression of neovascularization and decreased the risk for development of vitreous haemorrhage and fibrovascular proliferation.

LIMITATIONS OF THE STUDY

Ideally blocked randomization should have been done and the present process of randomization may be a limitation of the study.

CONCLUSION

IVB is a safe and effective adjunctive treatment to PRP in the short term. PRP plus IVB is associated with a higher and early rate of regression of active NVs than PRP alone in patients with PDR. PRP plus IVB treated eyes also showed better visual outcome compared to PRP only eyes in PDR. Further studies will be needed to determine whether IVB plus PRP is a satisfactory treatment for the prevention of vision-threatening complications such as vitreous haemorrhage and tractional retinal detachment.

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