PANRETINAL PHOTOCOAGULATION VS. PANRETINAL PHOTOCOAGULATION PLUS INTRAVITREAL RANIBIZUMAB IN HIGH-RISK PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT

BACKGROUND

Diabetic retinopathy is most common ocular complication of diabetes mellitus. Retinal neovascularisation is important cause of vision loss in diabetic patients. Panretinal photocoagulation has been standard treatment for proliferative diabetic retinopathy for several decades. However, intravitreal anti-VEGF now becoming popular in treatment of proliferative diabetic retinopathy and macular oedema.

The aim of the study is to compare the effects of Panretinal Photocoagulation (PRP) with PRP plus intravitreal injection of ranibizumab in patients with high-risk Proliferative Diabetic Retinopathy (PDR).

MATERIALS AND METHODS

It is hospital-based prospective longitudinal interventional study included patients with high-risk PDR randomly assigned to receive PRP (PRP group) or PRP plus IVR (PRP plus group). Seventy eyes of 36 patients were part of this study. PRP was administered in two sessions (weeks 0 and 2) and panretinal photocoagulation done 7 days after intravitreal injection in PRP plus group. In follow up period, ophthalmic evaluations including Best-Corrected Visual Acuity (BCVA), fluorescein angiography to measure area of Fluorescein Leakage (FLA) and Optical Coherence Tomography (OCT) for the assessment of Central Subfield Macular Thickness (CSMT) were performed at baseline and at weeks 12, 16 and 24. Group analysis at baseline were performed with ANOVA and t-test, while effect of treatment compared by Wilcoxon rank sum test.

RESULTS

At baseline, there was no significant difference between two groups in BCVA, CSMT and FLA. Best-corrected visual acuity worsening was observed at all study visits after treatment in the PRP group ($p < 0.05$), while significant increase in BCVA changes were observed in the PRP plus group. A significant CSMT increase was observed in the PRP group at all study visits, while a significant decrease in CSMT was observed in the PRP plus group at weeks 12, 16 and 24.

CONCLUSION

Intravitreal ranibizumab with PRP was associated with greater improvement of visual acuity, larger reduction of fluorescence leakage and greater resolution of macular oedema when compared with PRP alone in eyes with high-risk PDR.

KEYWORDS

Angiogenesis - Diabetes - Laser Treatment - Vascular Endothelial Growth Factor.

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BACKGROUND

Diabetes mellitus is a major medical problem with long-term systemic diabetes affects nearly every part of the visual system, but most vision loss results from complications of Diabetic Retinopathy (DR). In diabetic patients, one of the important risk factor for severe visual loss is progressive retinal new vessels.[1,2]

Laser photocoagulation has been the standard treatment for Proliferative Diabetic Retinopathy (PDR) for several decades. Panretinal photocoagulation is hypothesised to exert its effect by improving oxygenation of the inner retina subsequently decreasing Vascular Endothelial Growth Factor (VEGF) production and inducing regression or stabilisation of neovascularisation. Laser therapy frequently delayed or prevented vision loss, but significant improvement in visual acuity was uncommon.[3]

While efficacious, PRP has a number of potential adverse effects including exacerbation of macular oedema, peripheral visual field defects and nyctalopia, decreased contrast sensitivity and its administration can be difficult in

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the presence of Vitreous Haemorrhage (VH), a complication of retinal neovascularisation. NV regression may take several weeks after completion of PRP and continues to grow despite the first session of PRP. Therefore, VH may lead to visual loss and preclude complete laser PRP in these patients.[4]

In the absence of oxygenation, tissues upregulate Vascular Endothelial Growth Factor (VEGF), a potent signalling molecule that plays an integral role in angiogenesis by inducing endothelial cell proliferation and migration.[5]

Samples from human eyes have established the importance of VEGF in PDR. Significantly elevated levels of VEGF were demonstrated in vitreous and ocular fluid samples collected at the time of intraocular surgery from patients with active PDR when compared to individuals with NPDR or non-diabetic patients.[6,7]

The discovery of Vascular Endothelial Growth Factor (VEGF) and the subsequent determination of its critical role in the development proliferative diabetic retinopathy and diabetic macular oedema has led to the development of VEGF inhibitory drugs.

Ranibizumab is recombinant humanised antibody fragment that binds Vascular Endothelial Growth Factor (VEGF). Ranibizumab inhibits the biologic activity of human Vascular Endothelial Growth Factor A (VEGF-A). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptor on the surface of endothelial cells, which reduces endothelial cell proliferation and new blood vessel formation. Ranibizumab was the first anti-VEGF drug approved for the treatment of both DME and diabetic retinopathy in eyes with diabetic macular oedema.

MATERIALS AND METHODS

This is hospital-based prospective longitudinal interventional study conducted in tertiary eye care center in central India during period from January 2016 to November 2017 approved by ethical committee. Written informed consent taken from all the patients before commencement of the study. Seventy eyes of 39 patients were part of this study.

Inclusion criteria included patients with high-risk proliferative diabetic retinopathy, which was defined according to the guidelines set forth by the Early Treatment Diabetic Retinopathy Study as- (1) NVD that is approximately one-quarter to one-third disc area or more in size (i.e., greater than or equal to NVD in standard photograph 10A); (2) Any amount of NVD if fresh vitreous or preretinal haemorrhage is present; or (3) NVE greater than or equal to one-half disc area in size if fresh vitreous or preretinal haemorrhage is present. Exclusion criteria included history of prior laser treatment or vitrectomy in the study eye, PRP is impossible because of severe vitreous or preretinal haemorrhages, history of thromboembolic event including myocardial infarction or cerebrovascular accident.

Patients are divided into 2 groups. First group received panretinal photocoagulation (PRP group) and second group received panretinal photocoagulation and intravitreal ranibizumab (PRP plus group). Patient presenting with high-risk PDR were randomly assigned (1:1) receive Panretinal Photocoagulation (PRP) alone or PRP plus intravitreal ranibizumab. For patients presenting with high-risk proliferative diabetic retinopathy in both eyes, eyes randomly allotted in each group.

At baseline, each patient received a detailed ophthalmologic examination including measurement BCVA, dilated slit-lamp biomicroscopic examinations and indirect funduscopic examination, Optical Coherence Tomography (OCT) and digital red-free fundus photography fluorescein angiography were performed using fundus camera system.

All patients underwent PRP performed at two time-points (at weeks 1 and 3) according to ETDRS guidelines. Before PRP, topical anaesthesia using 0.5% Parcaine was dropped. Six hundred to eight hundred diode laser (532 nm) burns with a spot size of 500 µm were made each time (1600-1800 burns in total) using a fundus contact lens PRP was executed in the inferior, nasal, superior and temporal areas of eyes.

Ranibizumab was injected into the vitreous cavity via a 30-gauge needle inserted through the inferotemporal pars plana 3.0-3.5 mm posterior to the limbus for a pseudophakic or aphakic eye, 3.5-4 mm posterior to limbus in phakic eyes and using topical Parcaine drops under sterile conditions. Seven days after intravitreal injection PRP done in same eye in PRP plus group. Strict blood sugar is maintained during treatment and follow up period.

Patients were scheduled for follow-up examinations at weeks 12, 16 and 24. Exactly, the same procedures as performed at baseline were performed at each study visit. Systemic and local adverse events were monitored throughout the study, including changes in Intraocular Pressure (IOP).

Statistical Analysis- Group comparisons at baseline were performed with One-Way Analysis of Variance (ANOVA) and t-test, while the effect of treatment (PRP and PRP plus) was compared between (Wilcoxon rank sum test) groups for the intraindividual differences of FLA, BCVA and CSMT values found after treatment minus baseline. All analyses considered $p < 0.05$ as the level of significance.

RESULTS

The average age at treatment was 61 years in PRP group and 58 years in PRP plus group ranibizumab group. There were 21 males and 15 females. Out of 36 patients, 2 (5.5%) patients had unilateral presentation and 34 (94.5%) patients had bilateral disease. No drug-related adverse effects observed in all 35 eyes receiving ranibizumab injections.

Patients were scheduled for follow-up examinations at weeks 12, 16 and 24. Three outcomes measured the change in BCVA, the total area (measured in mm2) of fluorescein leakage from active NVs (NVDs and/or NVEs), Central Subfield Macular Thickness (CSMT) (µm) on OCT.

The mean of baseline BCVA was 0.38 ± 0.09 in PRP group and 0.39 ± 0.09 in PRP plus group (P=0.6161) that is not statistically significant. A BCVA decrease of 0.2 LogMAR compared with baseline observed at 12, 16 and 24 weeks

observed in PRP group (P <0.05), while increase of 0.1 compared with baseline was observed at weeks 16 and 24 in PRP plus group in BCVA was observed in PRP plus group (P <0.05). Between the group analysis showed better BCVA in PRP plus group as compared to PRP group at weeks 16 and 24 (P<0.05).

There was no significant difference in FLA at baseline between two groups. Mean ± SD FLA was 8.42 ± 0.51 in PRP group and 9.27 ± 0.52 in PRP plus group (p<0.0001, t test). Intragroup comparison shows significant FLA reduction compared with baseline was found at weeks 12, 16 and 24 in both groups (p<0.05). Intragroup comparison shows significant larger FLA reduction observed at weeks 12, 16 and 24 in PRP plus group as compared to PRP group.

At baseline, mean CSMT ± SD in PRP group was 248.34 ± 9.31 and in PRP plus group was 298.28 ± 21.75. Using paired t-test, p <0.0001 that is not statistically significant. Statistically significant increase in CSMT observed in PRP group by about 20% (p<0.05), while trend towards significant decrease in CSMT observed in PRP plus group (p<0.05) at all study visits.

There is no incidence of complications such as increased IOP, cataract development or progression or increased rates of endophthalmitis after intravitreal injection.

Out of 36 patients, 14 patients have associated hypertension. We found in our study that patients without hypertension have better visual outcome than patients with hypertension in both PRP and PRP plus groups. However, detailed evaluation is not possible due to inadequate sample size. Further studies needed for this purpose.

Demographic Data-

	PRP	PRP Plus	P Value
Age	61	58	1.000, NS
Gender M/F	21/15	21/15	1.000, NS
Duration of diabetes	13.1 ± 2.3	14.1 ± 2.5	0.0817, NS
Hypertensive patients	14	14	1.000, NS
Patient with deranged kidney function test (serum creatinine >1 mg/dL)	8	8	1.000, NS

Outcome	Weeks	PRP	PRP Plus	P Value
V/A	12	-0.002 ± 0.016	0.034 ± 0.08	0.0159
	16	-0.13 ± 0.08	0.087 ± 0.08	<0.001
	24	-0.23 ± 0.10	0.085 ± 0.08	<0.001
FLA	12	2.29 ± 0.18	4.50 ± 0.29	<0.001, HS
	16	2.80 ± 0.18	5.56 ± 0.30	<0.001, HS
	24	3.17 ± 0.18	6.58 ± 0.33	<0.001, HS
CSMT	12	30.05 ± 4.91	-15.65 ± 4.02	<0.001, HS
	16	42.8 ± 8.46	-26.31 ± 16.66	<0.001, HS
	24	49.34 ± 8.16	-39.02 ± 17.67	<0.001, HS

DISCUSSION

In our study group, patients had a mean age of presentation in PRP group is 61 years in PRP group and 58 years in PRP plus group, which was comparable to the mean age in the study by Filho et al[8] (63.3 years in PRP group and 50.5 in PRP plus group), Panshi et al[9] (66.3 years), Josef et al[10] (65 years in PRP group and 64 years in PRP plus group), Fequira et al[11] (60 years in PRP group and 62 years in PRP plus group) and Daniel et al[12] (56 years in PRP group and 59 years in PRP plus group). Most of our patients were males (21, 58.33%), which is similar in other studies. We also had majority of patients have bilateral disease (34, 94.44%). We followed patients for 24 weeks.

Intragroup comparison showed a significantly larger reduction in FLA at week 24 in the PRP plus group compared with the PRP group, which is similar to previous studies. According to the ETDRS, approximately 60% of patients with PDR respond to PRP with regression of NV within 3 months (12 weeks) of treatment using ETDRS guidelines (ETDR Study Research Group 1987; Vander et al, 1991).

Macular oedema is the leading cause of visual loss in diabetic retinopathy patients.[13] The intravitreal anti-VEGF injection can reduce macular interstitial fluid or oedema that, even when subclinical might cause retinal functional impairment.[14]

In our study, no difference in average CSMT emerged between the groups throughout the 24-week follow-up period. A trend towards CSMT decrease was observed in the PRP plus group, while a CSMT increase was observed in eyes treated with PRP alone. This result is similar to other studies.

There are also more comfort and less retinal functional loss for PRP plus intravitreal anti-VEGF injection in comparison to PRP alone for high-risk PDR treatment.[15,16]

A BCVA decrease compared with baseline observed in PRP group, while increase of BCVA compared with baseline was observed in PRP plus group. A study done by Filho et al[8] shows a LogMAR BCVA decrease of compared with baseline was observed after treatment in the PRP group, while no statistically significant change in BCVA was observed in the PRP plus group.

The results of the current study are consistent with data from other studies[8-12] regarding the absence of any apparent association between intravitreal ranibizumab injection and increased IOP, cataract development or progression or increased rates of endophthalmitis related to the study drug.

Out of 36 patients, 14 patients have associated hypertension and 8 patients have deranged kidney function tests (serum creatinine level >1 mg/dL). We found in our study that patients without hypertension and normal kidney function test have better visual outcome than patients with hypertension and deranged kidney function test in both PRP and PRP plus groups. However, detailed evaluation is not possible due to inadequate sample size, further studies needed for this purpose.

Due to our study design and limited follow up, we were unable to determine in the long-term whether IVR plus PRP inhibits the recurrence of NV or maintains a remission state beyond 6 months.

CONCLUSION

PRP plus intravitreal ranibizumab associated with greater visual acuity improvement as compared to PRP group.

PRP plus intravitreal ranibizumab associated with greater and early resolution of macular oedema associated with proliferative diabetic retinopathy than PRP only group.

A higher and early rate of regression of active neovascularisation in PRP plus group than PRP alone in patients with PDR.

Short duration and limited follow up is limitation of our study, so long-term effects of IVR plus PRP on neovascularisation cannot be determined. We can conclude that ranibizumab can be considered as effective adjuvant to panretinal photocoagulation in short term for treatment of proliferative diabetic retinopathy.

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