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Original Research Article

Does addition of intravitreal bevacizumab confer additional benefit in management of proliferative diabetic retinopathy?

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ABSTRACT

Introduction: To evaluate visual outcome and complications of PDR after treatment with Intravitreal Bevacizumab followed by Pan Retinal Photocoagulation

Materials and Methods: A hospital based retrospective study was done in the Department of Ophthalmology, to evaluate visual outcome and complications of PDR after treatment with intravitreal Bevacizumab followed by Pan Retinal Photocoagulation. Visual Acuity, Dilated fundus examination, OCT macula were done on subsequent follow ups

Results: 135 eyes of 133 patients were included in the study. The mean pre procedure visual acuity is 0.639±0.5327 which improved to 0.451±0.4089 post procedure. P value is <0.001 which is statistically significant.i.e, 94 (69.62%) eyes had improved vision, 21(15.55%) had stable vision and 20(14.81%) eyes had decreased vision. After injection followed by PRP out of 135 eyes,4(2.96%) eyes developed vitreous hemorrhage which resolved with repeat intravitreal anti-VEGF injection, 6(4.44%) eyes developed diabetic macular edema,3(2.2%) eyes developed Neovascularisation of iris and 4(2.96%)eyes developed vitreous hemorrhage with traction retinal detachment.

Conclusion: From our study it appears that addition of intravitreal anti VEGF to Pan Retinal Photocoagulation for PDR confers the additional benefit of less incidence of vitreous hemorrhage and less incidence of traction retinal detachment requiring surgery in the 1^{st} one year of follow up. This amounts to more compliance by the patient for taking the treatment as well as better visual outcome

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1. Introduction

Diabetic retinopathy is the most common cause of vision loss in working-aged individuals in developed nations.[1] Retinal neovascularization (NV) represents an important risk factor for severe vision loss in patients with diabetes mellitus.[2] About 60% of patients with proliferative diabetic retinopathy (PDR) respond to pan retinal photocoagulation (PRP) with regression of NV within 3 months.[3] However, many patients require additional laser treatment, and 4.5% ultimately undergo pars plana vitrectomy despite PRP.[4]

Although severe central vision loss because of PDR can be prevented with PRP in most cases, this destructive, often painful, laser procedure may be associated with decreased peripheral vision and an increased risk of macular oedema.[5]

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of human eye diseases characterized by,[6–9] and blockage of VEGF has been associated with inhibition of iris NV and suppression of retinal NV in primates.[10–13] and in humans.

Regression of optic disk NV was demonstrated after intravitreal injection of the antiangiogenic agent bevacizumab (Avastin®; Genentech, Inc.; South San Francisco, CA, USA) in the setting of diabetic

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retinopathy.[14,15] Nevertheless, this effect seems to be transient as retinal NV tended to recur by 12 weeks after a single intravitreal injection of bevacizumab.[16]

In 2007,[17] reported a synergistic effect of PRP and intravitreal bevacizumab for the treatment of patients with high-risk PDR. The objective of the current study is to investigate whether there are similar effects using IVR in conjunction with PRP in eyes with high-risk PDR.

Although Protocol S showed us that multiple intravitreal injections can be used as a treatment of PDR without laser photocoagulation, in our population to do the same, because of financial implication will be difficult. We have tried to combine a single injection of Anti VEGF along with PRP to reduce the incidence of post-operative VH and TRD requiring surgery. Studies in this direction have been less and that is the reason why we have done this study

To evaluate visual outcome and complications of PDR after treatment with Intravitreal bevacizumab followed by pan retinal photocoagulation.

2. Materials and Methods

A hospital based retrospective study was done in the Department of Ophthalmology, Amrita Institute of Medical Science to evaluate visual outcome and complications of PDR after treatment with intravitreal bevacizumab followed by pan retinal photocoagulation. The study took place from January 2015 to December 2020.

2.1. Study duration

1. 5 years

2.2. Study population

135 eyes of 133 patients who met in the inclusion criteria were included in the study population.

2.3. Inclusion criteria

1. All patients who underwent a single Intravitreal Anti VEGF injection followed by PRP for Proliferative Diabetic Retinopathy

2.4. Exclusion criteria

1. Patients who needed more than one intravitreal injection for reasons like CSME along with PDR.
2. Patients who were already planned for vitrectomy for traction retinal detachment.
3. Patients who had pre-existing traction retinal detachment.

2.5. Method of examination

A detailed ophthalmic evaluation was carried out for all the patients included in the study. The data collected included age, sex, visual acuity, anterior segment examination and fundus examination findings, final clinical diagnosis and the treatment planned. After dilation of pupil, fundus examination was carried out by Indirect ophthalmoscope and documented Optical Coherence Tomography (OCT) was done to assess the central macular thickness. Fundus Fluorescein Angiography (FFA) was done to evaluate the vascularity and stage the Diabetic retinopathy. Diagnosed cases of PDR with no significant retinal traction were treated with a single injection of Intravitreal Bevacizumab and full PRP.PRP was delivered through a slit lamp after anaesthetising the patient's eye using topical anaesthesia by a single surgeon,

2.6. Statistical analysis

Statistical analysis was done using IBM SPSS 20.0 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are given in Mean ± SD, and for categorical variables as percentage. To test the statistically significant mean comparison of numerical variables between groups, independent sample 't' test was applied. To test the statistically significant association of categorical variables, chi square with Fisher's exact test was applied. A p-value < 0.05 was considered as statistically significant.

3. Results

A total of 135 eyes of 133 patients were included in the study out of which 37 (28%) were females and 96 (72%) were males.(Figure 1)

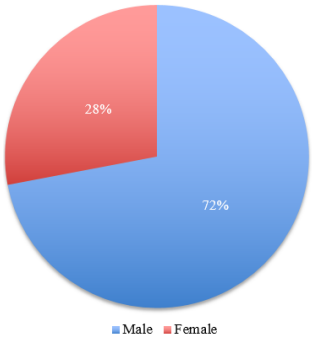

Figure 1: Gender distribution of study population

Patients included in the study were in the age group of 38 to 86 with mean age of 62.3+/-1.389 years

The mean pre procedure visual acuity with S.D is 0.639±0.5327 which improved to 0.451±0.4089 post procedure. (Table 1) P value is <0.001 which is statistically significant i.e., 94(69.70%) eyes had increased vision, 21(16.30%) had stable vision and 20(14%) eyes had decreased vision. (Table 2)

After injection followed by PRP out of 135 eyes, 17 eyes(12.59%) developed complications . 4(2.96%)

Table 1: Comparison of pre and post visual outcome at 1 year

Vision	Mean ± SD	P
Pre	0.639±0.5327	<0.001
Post	0.451±0.4089	

Table 2: Visual outcome post procedure

Visual outcome	No. of eyes	Percentage
Improved	94	69.62%
Stable	21	15.55%
Decreased	20	14.81%

eyes developed Vitreous Haemorrhage which resolved with repeat intravitreal anti VEGF injection and did not need vitrectomy, 4(2.96%) developed Vitreous hemorrhage along with tractional retinal detachment and underwent Vitrectomy. 6(4.4%) eyes developed clinically significant macular edema, 3(2.2%) eyes developed Neovascularization of Iris.(Figure 1)

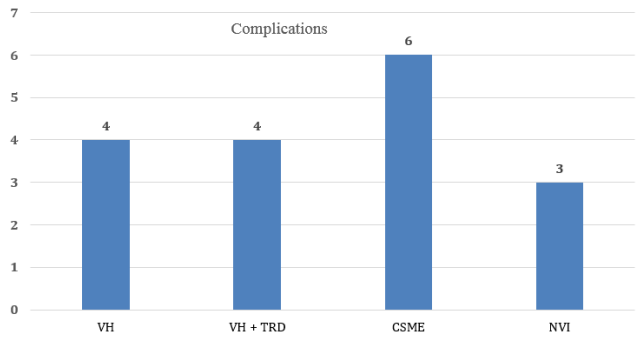

Figure 2: Complications noted during the study period

We found out that patients having decreased vision (20 eyes), the most common cause noted for decreased vision was DME (4.44%) other causes included VH accounting for 2.96%, and VH + TRD accounting for 2.96 % . Other causes include cataract 2.96%.

Since cataract was common in this age group, we found that 51 eyes had cataract out of 135 eyes out of which 23 eyes (45%) underwent cataract surgery.

Four eyes (2,96%) required vitrectomy surgery during follow-up. The mean of pre vitrectomy visual acuity with S.D is 1.318±.39003 and post vitrectomy visual acuity is 0.8405±. 38852. P value is <0.001 which is statistically significant. The mean time interval from intravitreal Avastin to vitrectomy was 8.1 weeks. (Table 3)

Table 3: Comparison of pre-vitrectomy and post- vitrectomy vision with mean logmar value

Vision	Mean ± SD	P
Pre OP	1.318±.39003	<0.001
Post OP	0.8405±.38852	

4. Discussion

Increased VEGF, triggered by hypoxia, is a key mediator of retinal NV and macular edema.[7,8,18] Previous study has also demonstrated that the VEGF concentration declined after successful laser PRP.[8] Furthermore, injection of VEGF in primates can produce an ischemic retinopathy like diabetic retinopathy and even produce iris NV.[19] Therefore, inhibition of VEGF by intravitreal bevacizumab could theoretically provide a potential therapeutic advantage for retinal NV in PDR.

Table 4: Comparison of our study with other studies which used PRP alone as treatment for PDR

Study	Complications
Mohan et.al[20] 2005	• 31.7% VH
	• 23.8% Chronic macular edema
	• 9.5% preretinal hemorrhage in macula
	• 4.7% preretinal fibrosis in macula
Dogru et.al[21] 1999	• 50% (stage 5)-Macular traction +NVD
	• 40% (stage 4)-Recurrence of VH
	• 25% (stage 3)-VH
	• 7.7% (stage 2)-macular edema
Kaiser et.al[22] 1999	• 37% VH
	• 6% TRD
	• 6% CSME
	• 8%NVD
Our study (Intravitreal Anti-VEGF +PRP)	• 4.44% DME
	• 3.22% NVI
	• 2.96% VH
	• 2.96% VH +TRD

Table 5: Comparison of our study with similar study which used Intravitreal Anti-VEGF + PRP as treatment for PDR

Study	Complications
Yang et.al[23]	66.7% Dense VH
	33.3% Focal TRD
Our study (Intravitreal Anti-VEGF +PRP)	• 4.44% DME
	• 3.22% NVI
	• 2.96% VH
	• 2.96% VH +TRD

PRP currently is the mainstay and gold standard therapy for PDR since the Diabetic Retinopathy Study was published.[5] It is estimated that about 60% PDR patients respond to laser PRP with retinal NV regression within 3 months.[3] However, it is a destructive procedure, often painful, and may be associated with a decreased peripheral visual field and an increased risk of macular edema.[5] Many diabetic patients need additional laser therapy and

4.5% of them eventually require vitrectomy surgery despite laser PRP. Moreover, NV regression may take several weeks after completion of PRP, and NV continues to grow despite the first session of PRP in one-third of patients.[24] Therefore, VH may lead to visual loss and preclude complete laser PRP in these patients. The current study demonstrated the advantage of intravitreal bevacizumab on the management of patients with PDR and VH. It may play as a new therapeutic option or an adjuvant agent to PRP in some patients of PDR, such as when VH precludes the visualization of fundus and prevents adequate laser PRP. However, the possibility of worsening TRD is a major concern. The main shortcoming of bevacizumab is the short duration of its effect. Conversely, laser PRP has better durability. In the present study, intravitreal bevacizumab may also have synergistic effects, when used in combination with PRP for the treatment of high-risk PDR with severe NVD.

In a study done by Mohan Rema et al,36 to assess the visual outcome of one-year follow-up after pan retinal photo coagulation alone (PRP) in type 2 diabetes mellitus subjects with proliferative diabetic retinopathy (PDR) and associated risk factors, PRP was done in 413 eyes, of which 261 eyes of 160 subjects were eligible for their study. In these patients NVE was observed in 77.8% (203 eyes) and tractional retinal detachment was present in only 1.2(3 eyes). Vitreous haemorrhage and premacular haemorrhage was observed in 13.0% (21 eyes) and 13.8% (22 eyes) respectively. The causes of visual loss at one year after PRP was Vitreous haemorrhage, cataract, chronic macular oedema, pre-retinal haemorrhage in the macula, and pre-retinal fibrosis in the macula

In our study out of 135 eyes of 133 patients who underwent injection followed by PRP, 4(2.96%) eyes had VH which resolved with intravitreal injections 6(4.44%) eyes had DME, 3(2.2%) eyes had NVI and 4(2.96%)eyes had VH+TRD.

The study conducted by Chang-Sue Yang, Kuo-Che Hung et al,[23] was to assess Intravitreal Bevacizumab (Avastin) and Pan retinal Photocoagulation in the treatment of high-risk proliferative diabetic retinopathy. A total of 17 consecutive patients (20 eyes) with high-risk PDR, complicated by VH or NVD, were enrolled and investigated in this study. Out of 17 patients 10 were female and 7 were male. Mean logarithm of the visual acuity improved from 1.03 at baseline to 0.36 at 1 month, 0.38 at 3 months and 0.48 at 6 months (P is <0.01).Out of 20 eyes,3 eyes required vitrectomy surgery during follow up. The mean time interval from intravitreal Avastin to vitrectomy was 7.3 weeks. Among those 3 eyes, the indication for vitrectomy was dense, persistent VH in 2 eyes (66.7%), and development and progression of focal TRD in 1 eye (33.3%)

In our study, the visual acuity improved from 0.639 at baseline to 0.451 in one year (P is <0.001). Out of 135 eyes, 4 eyes required vitrectomy during follow up. The mean time interval from intravitreal Avastin to vitrectomy was 8.1 weeks. Among those 4 eyes, the indication for vitrectomy was Vitreous haemorrhage with tractional retinal detachment.

5. Conclusion

From our study it appears that addition of intravitreal anti VEGF to Pan Retinal Photocoagulation for PDR confers the additional benefit of less incidence of vitreous hemorrhage and less incidence of traction retinal detachment requiring surgery in the 1^{st} one year of follow up. This amounts to more compliance by the patient for taking the treatment as well as better visual outcome

6. Source of Funding

None.

7. Conflict of Interest

None.

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