EFFECTIVENESS OF INTRAVITREAL BEVACIZUMAB (AVASTIN) IN THE TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT

Objective: To assess the effectiveness of intravitreal injection of bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy.

Study Design: Quasi experimental study.

Place and Duration of Study: This study was conducted at the department of ophthalmology, Jinnah post graduate medical centre, Karachi from 26th January 2011 to 26th January 2012.

Material and Methods: The study group comprised of 55 eyes of proliferative diabetic retinopathy (PDR). Pre procedure fundus fluorescein angiography (FFA) was done in all patients. Intravitreal injection of 1.25 mg of bevacizumab (avastin) was injected 3.5 mm from the limbus under topical anesthetic drops. Post procedure follow up was scheduled on 1st post procedure day, two weeks and after one month. Post procedure FFA was performed on all patients at 1st month after 1st injection. Results were entered and analyzed using SPSS Version 17.

Results: Out of the 55 eyes of 41 patients who were given the intravitreal injection of avastin (bevacizumab), 42 eyes (72.17%) showed complete regression of neovascularisation, 12 eyes (21.8%) had partial regression and 3 eyes (5.5%) revealed no response.

Conclusion: Intravitreal injection of bevacizumab (avastin) is effective in regressing the retinal neovascularisation in controlled and uncontrolled diabetics of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients.

Keywords: Bevacizumab, Diabetic Retinopathy, Neovascularisation, Proliferative, Vascular Endothelial Growth Factor.

INTRODUCTION

Diabetic Retinopathy is a sight threatening disease[1]. Studies show that the presence of diabetic retinopathy in insulin dependent diabetics is 40% and in cases of non insulin dependent diabetics it is 20%[2]. Initially panretinal photocoagulation (PRP) has been considered as the treatment for proliferative diabetic retinopathy[3]. It is useful but can result in problems involving visual fields and difficulty in visualizing things at night[4,5]. In cases of vitreous hemorrhage obscuring the visualization of retina it becomes difficult for the surgeon to do pan retinal photocoagulation[6]. Vascular Endothelial Growth Factor (VEGF) plays an important role in the development of retinal neovascularization and was discovered about two and a half decades ago[7,8]. According to some studies VEGF levels proportionately increase as the proliferative diabetic retinopathy (PDR) worsens[9]. Bevacizumab (Avastin) is one of the anti VEGF[10] which works by binding to all subtypes of vascular endothelial growth factor[11]. Therefore, anti vascular endothelial growth factor treatment has been considered as an alternative or adjunctive treatment for proliferative diabetic retinopathy[1].

The rationale of this study was to find out the effect of intravitreal bevcizumab (Avastin) in the treatment of proliferative diabetic retinopathy patients. By identifying its effects in controlled and uncontrolled diabetics it could be used more purposefully in these categories.

MATERIAL AND METHODS

This quasi-experimental study was conducted at the department of Ophthalmology Jinnah Post Graduate Medical Centre, Karachi. It was carried out from 26th January 2011 to 26th January 2012. With the

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permission of the Hospital Ethical Committee, and informed consent patients of all ages, either gender with any type (IDDM or NIDDM), duration and severity of diabetes (controlled diabetes or uncontrolled controlled diabetes) having proliferative diabetic retinopathy were included. However patients having bleeding disorder, prior history of any ocular surgery in the last six months, active ocular infection, previous history of intravitreal bevacizumab (Avastin), recent myocardialm infarction, uncontrolled hypertension, pregnancy, obesity and smoking were excluded. Baseline ocular examination along with fundus fluorescein angiography was performed. Injection of 1.25 mg of bevacizumab (Avastin) was injected 3.5 mm from the limbus into the vitreous under topical anesthetic drops. Post procedure follow up was scheduled on 1st post procedure day, two weeks and after one month. Post procedure fundus fluorescein angiography (FFA) was performed on all patients at 1st month after 1st injection, this was when final outcome was determined on the basis of leakage of dye on FFA. Effectiveness of intravitreal injection of bevacizumab (Avastin) was assessed in proliferative diabetic retinopathy by analyzing response of neovascularisation on comparison of pre and post intravitreal bevacizumab (Avastin) fluorescein angiographies. Response of leakage of the dye after intravitreal bevacizumab (Avastin) was graded as under:

- Complete Regression of neo-vascularisation if no leakage or only minimal staining of dye was present.
- Partial Regression of neovascularisation if definite reduction in intensity of leakage of dye was present.
- No Response: if change in there was no intensity of leakage.

Partial regression or complete regression of neovascularisation constituted effectiveness of intravitreal injection of bevacizumab (Avastin).

Diabetes mellitus was labeled as controlled even if on medications random blood sugar was less than 14 mmol/l and uncontrolled if on medications random blood sugar is greater than 14 mmol/l[10].

Statistical software SPSS 17 was used for data analysis. Quantitatine variables were described using mean and standard deviation (SD) while quantitative variables were described through frequency and percentages. Independent sample t-test was applied for the comparison of quantitative variables. Chi-square test was used for comparison of response between controlled and uncontrolled DM. A *p*-value <0.05 was considered significant.

RESULT

Intravitreal injection of bevacizumab was given in 55 eyes of 41 patients. Out of them, male patients were 28 (68.3%) and females were 13 (31.7%), thus male to female ratio was 2.15: 1. Their ages ranged from 50 to 74 years. Thirty three (60%) eyes were of patients who had good control of diabetes mellitus (controlled group) and 22 (40%) eyes were of patients who had poor control of diabetes mellitus (uncontrolled group). Mean age of controlled group was 61.0 ± 1.10 years however mean age of uncontrolled group was 64.0 ± 1.18 years. Mean duration of diabetes in uncontrolled group was significantly higher than the controlled group ($p < 0.01$). Thirty (91%) eyes were of IDDM and 3(9%) eyes were of NIDDM patients in controlled group however 18 (82%) eyes were of IDDM and 4(18%) eyes were of NIDDM patients in uncontrolled group. (table-1). Total regression of neovascularization was found in 40 eyes (72.7%), 12 eyes (21.8%) had partial regression whereas 3 eyes (5.5%) were having no response to the treatment. Out of the 33 eyes of controlled diabetic patients, better results were observed in the treated eyes with 32 eyes having total regression (97%) and 1 eye (3%) having partial regression. In contrast, out of the 22 (40%) eyes of uncontrolled diabetic patients, 8 eyes (36.36%) had total regression, 11 eyes (50%) had partial regression and 3 eyes (13.64%) revealed no response. Effect of treatment at post procedure follow up of one day, two weeks and four weeks are shown in Table 2. Recurrence of fluorescein leakage varied. No recurrent leakage was noted at a follow up of four weeks.

DISCUSSION

Patients with PDR may present with cataract and vitreous hemorrhage denser enough making it difficult for the doctor to do complete pan retinal photocoagulation. In addition PDR patients can have iris neovascularization and raised intraocular pressures resulting in corneal haze. In these patients full pan retinal photocoagulation can't be done. In some cases even full PRP fails to completely regress neovascularization. However, intravitreal bevacizumab has shown dramatic and rapid response and is found to be effective in most cases of proliferative diabetic retinopathy[6]. In addition bevacizumab is a useful tool in decreasing m a c u l a r edema due to diabetic retinopathy, venous occlusive diseases and choroidal neovascularizations[12-14].

The ratio of male as compared to female (2.15:1) in our study was probably due to the greater number of consultations by male as compared to females. As such no specific causes could be found to have attributed towards more consultations by males.

Patient's ages ranged from 50 to 74 years. Mean age of patients who had good control of DM was 61.0 ± 1.10 years however mean age of the patients who had poor control of DM was 64.0 ± 1.18 years. The maximum numbers of patients were in their sixth decade. The attributing factor towards this age group could be longer duration of diabetes and related complications. JF Arevalo et al in a study reported mean age of 57.2 years (range from 23 to 82 years) out of 33 consecutive patients (44 eyes)[15]. The studies on diabetic retinopathy patients showed variation in the age groups affected in different geographical settings. However proliferative diabetic retinopathy has been found in later stages of age due to more duration of diabetes mellitus.The mean duration of diabetes in control group was 10.8 ± 3.98 years and in uncontrolled group was 15.4 ± 4.36 years. In a study conducted by Mason et al the mean duration of diabetes in 30 patients was 18.4 years with a range of 3 years to 27 years[15].

In our study, out of the 55 eyes of 41 patients, 48 eyes (87.3%) were of insulin dependent diabetic (IDDM) patients whereas 7 eyes (12.7%) were of non insulin dependent diabetic (NIDDM) patients. Greater number of

Table-1: General characteristics of controlled and uncontrolled diabetes (n=55).

Variable	Controlled diabetes (n=33)	Uncontrolled diabetes (n=22)	*p*-value
Age in years			
(Mean ± S.D)	61.0 ± 1.10	64.0 ± 1.18	0.058
Duration of diabetes mellitus (DM) in years			
Mean ± S.D	10.8 ± 3.98	15.4 ± 4.36	0.001*
Type of diabetes mellitus (DM)	n (%)	n (%)	
IDDM	30 (91)	18 (82)	0.322
NIDDM	3 (9)	4(18)	

*Statistically significant $p<0.05$

Table- 2: Effects of treatment after post procedure follow-up (n=55).

Follow-Up	Controlled diabetes (n=33)			Uncontrolled diabetes n=22			*p*-value
	Total regression n (%)	Partial regression	No response n (%)	Total regression n (%)	Partial regression n (%)	No response n (%)	
1st PPD*	-	-	33 (100)	-		22 (100)	1.000
2nd week	32 (97)	1 (3)	-	8 (36)	11 (50)	3 (14)	0.001**
4th week	32 (97)	1 (3)		8 (36)	11 (50)	3 (14)	0.001**

*Post procedure day

** Statistically significant $p<0.05$

IDDM patients was probably because of poor control of diabetes on oral hypoglycemic agents and some patients even on Insulin were not able to control their diabetes. Arevalo et al conducted a study in which 23 patients (69.7%) out of 33 patients had IDDM whereas 10 patients (31.3%) had NIDDM[16].

Out of the 55 eyes treated for this study, 33 eyes (60%) were of patients whose diabetes was controlled on medicines whereas 22 eyes (40%) were of patients whose diabetes was uncontrolled through medicines.

Similar study compiled by Minnella et al included patients having PDR in 15 eyes, severe PDR in 13 eyes and repeated vitreous hemorrhage in two eyes. They observed regression of neovessels in all eyes by one month. These effects remained for a period 3 months[17]. In comparison to this our study showed regression of neovessels as early as two weeks and no recurrent leakage was observed within a span of one month.

Intravitreal bevacizumab proved to be effective in the treatment of proliferative diabetic retinopathy in this study. Neither systemic nor any sort of ocular complications of intravitreal bevacizumab were observed in our study. The main limitation of this study was small follow up period and limited number of patients.

CONCLUSION

Intravitreal bevacizumab is a promising treatment adjunct for PDR. Our study demonstrated that bevacizumab was effective in at least short term regression of neovascularization which was observed in both controlled and uncontrolled diabetics. Better results were observed in controlled diabetics as compared to uncontrolled group. NIDDM patients of controlled and uncontrolled groups showed better results as compared to IDDM patients in these categories.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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