ORIGINAL ARTICLE

Panretinal Photocoagulation Plus Intravitreal Bevacizumab *Versus* Panretinal Photocoagulation Alone for Proliferative Diabetic Retinopathy

Warda Ali[1], Kanwal Zareen Abbasi[2] and Ali Raza[3]

ABSTRACT

Objective: To compare panretinal photocoagulation (PRP) plus intravitreal bevacizumab (IVB) against PRP alone in the treatment of proliferative diabetic retinopathy (PDR) in terms of mean change in best corrected visual acuity (BCVA), neovessels on disc (NVD) and neovessels elsewhere (NVE).

Study Design: Experimental study.

Place and Duration of Study: Department of Ophthalmology, Benazir Bhutto Hospital, Rawalpindi, from December 2014 to July 2015.

Methodology: Sixty eyes were randomized into two groups with 30 eyes in each. In group A, IVB was given 15 days prior to PRP but in group B only PRP was given. In both groups, BCVA and neovessels status at disc and elsewhere was assessed before and at day 30. NVDs were judged as per percentage of NVD occupying surface of the disc (DD%). NVE were also judged as per reference to diameter of disc surface.

Results: The mean age of the study patients was 52.27 ±6.7 years. Mean BCVA (logMAR) in the PRP plus IVB group improved considerably from mean 0.64 ±0.17 to mean 0.49 ±0.21 at 30th day. However, in PRP group, there was no significant change in BCVA 0.64 ±0.16 at baseline to 0.63 ±0.18 at day 30. There were extremely significant changes between the two groups at 4th week ($p<0.001$). Mean NVE at baseline in PRP plus group was 3.30 ±0.95% at baseline that changes to 1.50 ±1.06% at day 30. While in only PRP group, mean NVE was 3.33 ±0.7% at baseline and 3.17 ±0.7% at one month of follow-up. In PRP plus group, NVD changes from mean 31.27 ±9.8% at baseline to 11.40 ±5.5% at one month of follow-up. In only PRP group, NVD changes from mean 31.13 ±10.23% at baseline to 29.53 ±11.04% at 1 month of follow-up. There were extremely significant changes between two groups at day 30 ($p<0.001$).

Conclusion: Intravitreal bevacizumab in short duration is effective as adjunctive treatment to PRP with early and greater rate of regression of retinal neovessel than PRP alone in PDR patients.

Key Words: *Panretinal photocoagulation (PRP), Proliferative diabetic retinopathy (PDR), Intravitreal bevacizumab (IVB), Slit lamp biomicroscopy, Fundoscopy.*

INTRODUCTION

Diabetes is a major systemic disease and the seventh largest disease of Pakistan.[1] Out of the ocular complications, the most blinding is proliferative diabetic retinopathy (PDR) which has a prevalence of 5.90%.[2] Today timely detection and appropriate intervention can prevent blindness by PDR.[3] For nearly three decades, laser treatment (PRP) has been standard for PDR, but now adjunctive treatment with anti-VEGF agents have shown superior outcomes.[2,4] Anti-VEGF agents available are ranibizumab, bevacizumab and pegaptanib and VEGF Trap-Eye.[5] Recently, intravitreal bevacizumab (IVB) is gaining popularity because, injections are cost-effective, and easier to perform.[2] It provides stability and improvement in BCVA and central macular thickness in DME.[6]

Laser treatment reduces moderate visual loss having limited effects on improving BCVA; and intravitreal triamcinolone gives short term improvement in BCVA and causes cataract and glaucoma.[5] Although ranibizumab is licensed for the treatment of DME, but it is costly. Bevacizumab is not FDA approved for this indication but still practised because of cost-effectiveness and approval as anti-neoplastic agent.[7] IVB as adjuvant to PRP have shown to reduce deterioration in visual acuity and regression of retinal new vessels.[2,8] Sight threatening diabetic retinopathy (PDR, diabetic maculopathy) has significant impact on ophthalmic services, but through well-implemented programme timely treatment can be given, reducing the need for vitrectomy and blindness.[9,10]

The rationale of this study was to determine which technique among PRP plus IVB *versus* PRP alone is better in patients with PDR, regarding improvement in

[1] *Department of Eye, Shifa College of Medicine / Shifa Tameer-e-Millat University, Islamabad, Pakistan*

[2] *Department of Eye, Benazir Bhutto Hospital, Rawalpindi, Pakistan*

[3] *Department of Eye, RMC and Allied Hospitals Rawalpindi, Pakistan*

Correspondence: Dr. Warda Ali, Department of Eye, Shifa College of Medicine / Shifa Tameer-e-Millat University, Islamabad, Pakistan
E-mail: wardabinteali@gmail.com

Received: January 25, 2018; Accepted: July 19, 2018

vision and regression of neovessles. So far, to authors' information, very inadequate local data is present. The objective of this study was to compare the therapeutic efficacy of these two treatment protocols in terms of BCVA, NVD's and NVE's.

METHODOLOGY

It was an experimental study done in Department of Ophthalmology, Benazir Bhutto Hospital, Rawalpindi, from December 2014 to July 2015. After approval from the Ethical Review Committee, every patient was enrolled according to inclusion criteria, *i.e.* all patients of age 40-65 years, of both genders and patients with bilateral proliferative diabetic retinopathy with new vessels (NVD's or NVE's) associated with or without clinically significant macular edema (CSME), presenting with BCVA ≥6/60 or ≤6/12. Exclusion criteria were all patients with non-proliferative diabetic retinopathy (NPDR) and advanced diabetic eye disease (tractional retinal detachment), an increase in retinal thickness and new vessels found in other ocular disorders such as age-related macular degeneration, central serous chorio-retinopathy (CSCR) and retinal vein occlusion, patients diagnosed with significant cataract and glaucoma. The purpose, procedure, risks and benefits of injection and laser treatment were explained to the patient and informed consent was taken.

A total of 60 patients were enrolled in this study over a period of six months and randomized into two groups, *i.e.* group A and B each with 30 eyes. Baseline data involved patients' age, gender, and duration of diabetes mellitus, blood pressure, and intraocular pressure. Patients also underwent clinical examination including best-corrected visual acuity (BCVA) measured with log MAR chart, biomicroscopic non-contact fundus examination with a 78-diopter lens. Follow-up visit was scheduled at day 30. NVD was measured in percentage of disc surface diameter (DD%) while NVE was also measured as referred to disc surface diameter (DD). Clinical examination at baseline and at the follow-up visit was the same.

The main outcome measures were the alterations in NVD and NVE and BCVA. By simple lottery method, both eyes of the same patient were randomized into two groups. Single blind experienced surgeon performed the procedure.

Group A was given IVB 15 days prior to PRP session and group B was given only PRP. Laser treatment was administered in 1500-2000 shots (200-500 μm spots), 0.05-0.1 second duration, 0.1 interval, 300-500 W power per episode, under topical anesthesia. The eye undergoing treatment with injection was prepared by applying 5% povidone iodine, an eyelid speculum was placed so that eyelids become stable, and under topical anaesthesia the injection of 1.25 mg (0.05 ml) of bevacizumab was given through the infero-temporal pars plana with a 30-gauge needle, 3.5-4 mm posterior to the limbus. IOP and retinal artery perfusion were checked after the injection, and patients were commenced on topical antibiotics for 7 days. After treatment at day 30, the clinical status of the two eyes in terms of retinal vessels (NVD/NVE) status were compared and evaluated by using BCVA, slit lamp biomicroscopy and fundus photography.

At the time of discharge, a note was made of diabetic retinopathy status of the patients in terms of ETDRS. Statistical analysis of data was done using SPSS version 17. All the variables were identified. Descriptive statistics was used to calculate qualitative and quantitative variables. Qualitative variable like gender was measured in frequency and percentage. For quantitative variables like age, BCVA, NVD's, NVE's mean and standard deviation was calculated. Mean BCVA, NVD's and NVE's was compared between two groups by independent sample t-test. P-value ≤0.05 was considered significant. Data was stratified for age and gender to address the effect modifiers. Post-stratification t-test for quantitative variables was done.

RESULTS

Sixty eyes of 30 patients fulfilling the inclusion criteria were managed with IVB plus PRP in group A and only PRP in group B with 30 eyes in each group. Following are the findings obtained in this study.

Minimum and maximum age of presentation was 40 and 65 years, respectively. Both study groups comprised of same patients. The mean and standard deviation for age was 52.27 ±6.8 years.

The data was stratified for age, group 1 (40-52 years) and group 2 (53-65 years). Age was not an effect modifier in this study regarding BCVA. However, age was an effect modifier regarding NVE and NVD based on independent sample t-test (p<0.001, Table I).

Among 30 patients, the female patients were slightly more in number as compared to male patients, frequency and percentage of female patients was 19

Table I: Stratification of age.

Age	Group	BCVA			NVD			NVE		
		Mean	S.D	p-value	Mean	S.D	p-value	Mean	S.D	p-value
40-52	Group-A (PRP plus IVB)	0.462	±0.24	0.337	12.9	±5.02	<0.001	1.62	± 0.961	<0.001
	Group-B (PRP)	0.546	±0.18		28.69	±11.07		3.31	± 0.63	
53-65	Group-A (PRP plus IVB)	0.51	±0.18	0.005	10.24	±5.7	<0.001	1.41	±0.57	<0.001
	Group-B (PRP)	0.69	±0.15		30.18	±11.3		3.06	±0.89	

Table II: Stratification for gender.

Age	Group	BCVA			NVD			NVE		
		Mean	S.D	p-value	Mean	S.D	p-value	Mean	S.D	p-value
Male	Group-A (PRP plus IVB)	0.46	±0.21	0.069	11.36	±5.5	<0.001	1.36	±0.50	<0.001
	Group-B (PRP)	0.63	±0.20		28.73	±12.8		3.18	±0.98	
Female	Group-A (PRP plus IVB)	0.51	±0.21	0.076	11.4	±5.6	<0.001	1.58	±0.83	<0.001
	Group-B (PRP)	0.62	±0.17		30.0	±10.1		3.16	±0.68	

Table III: Mean and SD of BCVA, NVE and NVD at baseline and at day 30.

	At Baseline				AT DAY 30				
	Group A		Group B		Group A		Group B		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
BCVA	0.64	±0.17	0.6	±0.16	0.49	±0.21	0.6	±0.18	<0.001
NVE	3.30	0.95	3.33	±0.7	1.50	1.06	3.17	±0.7	<0.001
NVD	31.27	±9.8	31.13	±10.23	11.40	±5.5	29.53	±11.04	<0.001

(63.3%) while of male patients 11 (36.6%). Gender was not an effect modifier regarding BCVA, However, it was an effect modifier regarding NVE and NVD (Table II).

The mean duration of diabetes was 10 ±4.9 years. At baseline, systolic and diastolic blood pressure of all 30 patients was recorded and mean and standard deviation was 124 ±19.04 mmHg and 79.67 ±17.7 mmHg for systolic and diastolic blood pressure, respectively. HbA1c of all patients was done and mean and standard deviation was 7.6 ±2.2.

In 60 eyes, presence of CSME was also noted on fundoscopy and there were 36 (60%) eyes with presence of CSME and 24 (40%) eyes with absence of CSME in both groups. In all eyes, IOP was checked on applanation tonometer and recorded in mmHg. The mean IOP of IVB plus PRP group was 14 (±3.8) mmHg and of the patients, receiving only PRP was 12.87 (±3.1) mmHg. In all eyes BCVA, NVE and NVD at one month was compared amongst the study groups and independent sample t-test was applied (Table III). For BCVA, results were statistically significant with a p=0.010 and for NVE and NVD were highly statistically significant with a p<0.001.

DISCUSSION

This research intended to assess the effectiveness of IVB as adjunctive treatment option to PRP in term of regression of NVE's and NVD's, while improvement in BCVA in patients with PDR, and our results have revealed that IVB appears to be an encouraging adjunctive management to PRP in the cure of PDR. On follow-up visit, there was no significant change in BCVA, NVE and NVD in only PRP group; but significant change in PRP plus IVB group.

In eyes with PDR, we considered the change in regression of neovessels between IVB injection plus PRP *versus* PRP alone. It was found that IVB plus PRP group showed early regression of NV as compared to only PRP group. On day 30, the difference in NV regression in two groups was statistically significance (p<0.001).

Panretinal photocoagulation is the gold standard therapy for proliferative diabetic retinopathy after publication of diabetic retinopathy study (DRS).[2,13]

While PRP decreases the risk of severe loss of visual, it has various adverse effects, such as macular edema, visual field constriction, and vitreous hemorrhage. Moreover, further laser therapy or intravitreal injection was required after PRP. Recent studies have shown that VEGF plays a major role in ocular neovascularization, and that intravitreal anti-VEGF injection can cause regression of NV in neovascular age-related macular degeneration, central retinal vein obstruction, iris neovascularization and proliferative diabetic retinopathy.[2,11]

Combined treatment with anti-VEGF agents and PRP appear as an alternative or adjunctive therapeutic choice for PDR.[2,4,8,9,11-16]

Ahmed studied 54 eyes and randomized them into two groups (PRP and PRP plus), all of them completed 90 days of follow-up. Mean BCVA (logMAR) in the PRP group worsened considerably 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 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<0.001) and at week 12 (p<0.001). Mean NVE in the PRP group worsened from mean 2 ±0.75 to mean 2.25 ±0.75 at 30th day and mean 2 ±0.50 at day 90. However, in PRP-Plus group, NVE become better from 2±0.50 to 1 ±0.50 at week 4 and 0.75 ±0.25 at week 12. There were highly significant changes between the two groups at week 4 (p<0.001) and at week 12 (p<0.001). Mean NVD in the PRP group worsened significantly from mean 40 ±5 to mean 50 ±7 at 30th day and mean 40 ±6 at day 90. However, in PRP-Plus group, NVD become improved from 40 ±7 to 10 ±5 at week 4 and 11 ±3 at week 12. There were highly significant changes between the two groups at week 4 (p<0.001) and at week 12 (p<0.001).[2] In this study, 60 eyes were studied and follow-up was done at day 30.

Results showed no significant improvement in BCVA, NVE and NVD in only PRP group, but there were significant change in PRP plus group ($p \leq 0.05$). In Ahmed's study, CSME in PRP only group was 44.13% and in PRP plus group was 48.14%.[2] In the present study, CSME was 30% in both groups.

Yang studied safety and effectiveness of intravitreal bevacizumab (Avastin) injection with PRP in high-risk PDR, all patients had evident decrease in vascular leakage and regression of retinal neovascularization (NV) at the 1- and 3-month follow-up. The mean follow-up duration was 7.5 months. Mean visual acuity (logMar) improved from 1.03 at baseline to 0.36 at 1-month, 0.38 at 3-month, and 0.48 at the follow-up of 6-month ($p<0.001$). According to this study, bevacizumab acts as a new therapeutic option or an adjuvant agent to PRP in some patients of PDR, in presence of VH, which prevents the fundal view and precludes adequate laser PRP. However, the possibility of worsening TRD is a major concern. The main inadequacy of bevacizumab is the short duration of its effect. On the other hand, laser PRP has better durability. Intravitreal bevacizumab showed synergistic effects, when used in combination with PRP for the treatment of high-risk PDR patients with severe NVD. Consequently, to sustain a steady outcome in patients with high VEGF levels, a regular follow-up with repeated bevacizumab injections, followed by PRP, may be required.[8]

Jorge *et al*. reported maximal bevacizumab effect on retinal NV regression at week 6, with recurrent NV leakage seen in 93% of eyes at the 12th week. However, the area of leakage in recurrent NV at week 12 was considerably decreased as compared to the baseline area.[17] Matsumoto *et al*. also reported rebound macular edema after intravitreal bevacizumab in patients with chronic nature of retinal vein occlusion. According to them bevacizumab-induced upregulation of VEGF receptors may be more profound to the VEGF in the condition of ischemia.[13] Due to limited follow-up of 1-month, I was unable to see reperfusion of NV after intravitreal bevacizumab.

Cho *et al*. studied the advantage of IVB as an adjunctive treatment to PRP. Total 41 eyes of patients having high-risk PDR were included in his study and IVB was injected one week before commencing PRP. BCVA remain unchanged in the PRP 'Plus' group, while in the PRP group it worsened significantly at 3 months ($p=0.041$).[9] In the present study, BCVA remain unchanged in PRP only group but shows significant improvement in PRP plus group at day 30 ($p=0.01$).

Mirshahi *et al*. studied patients with high-risk PDR, with the bevacizumab as adjunctive to laser photocoagulation. With combination therapy, a very effective response was attained in NV regression at six weeks of follow-up. However, the results were same in both the groups for complete regression, because at 16th week of follow-up, there was recurrence of PDR seen in the bevacizumab-injected eyes. After treatment, BCVA was unchanged in both the groups.[14] Due to the limited duration of follow-up, the present authors were unable to conclude for the long-term whether IVB plus PRP prevents the NV recurrence or maintains remission.

A similar study by Tonello *et al*. revealed no significant improvement in BCVA, but in high risk PDR patients, the area of leaking NVs was extensively decreased in the PRP plus IVB group as compared with the PRP group with follow-up at weeks 4, 9, and 16 ($p<0.001$). In this study, the bevacizumab injection was given at the end of the second laser session.[15] In the present study, IVB was given 2 weeks before the laser session and only one laser session was done, with follow-up at day 30. It was noted that the IVB with PRP give rise to prompt neovessels regression and decreased the possibility of complications like vitreous haemorrhage and fibro-vascular proliferation.

A prospective study was done by Filho *et al*. on PRP alone compared with PRP plus ranibizumab in high-risk PDR. In one group, PRP treatment was done in two sessions; whereas, in the second group intravitreal ranibizumab was given at the end of the first laser session. It was found that intravitreal ranibizumab after PRP showed that there was a greater reduction in total area (mm2) of fluorescein leakage at week 48, as compared with only PRP.[16] This study also prove that combine treatment of anti VEGF agent and PRP has profound effect on regression of new vessels as compared to only PRP, similar to this study. In this study, only one laser session was done in both groups and IVB was given 2 weeks before laser in group A.

The ideal dose of intravitreal bevacizumab in treating PDR is still undecided. In the literature, doses of bevacizumab used have ranged from 1.25 to 2.5 mg.[8] Arevalo *et al*. stated a dose-dependent response that 2.5 mg dosage appeared to be more effective as compared to 1.25 mg to achieve complete dis-appearance of NV.[17] However, according to one study, a possible therapeutic effect in the fellow eye raises fear that systemic side effects are possible in patients taking intravitreal bevacizumab (6.2 μg-1.25 mg) treatment, and a lower dose regimen may achieve a therapeutic result with less risk of systemic side effects.[18]

Furthermore, Arevalo *et al*. reported the development of TRD in 5.2% patients with severe PDR after intravitreal bevacizumab.[19] Careful examination should be done *via* intravitreal bevacizumab to exclude the patients with broad vitreoretinal adhesion. Thereafter, careful eye examinations and echographic evidence of VRT should be checked carefully at the follow-up visit after intravitreal bevacizumab therapy.[8]

In 1970s, primary therapy for DR was PRP and it was considered to decrease the risk of severe loss of vision by 50%. VEGF plays a fundamental role in neovascu-

larisation of eye. PRP causes NV regression of through inhibition of VEGF production. However, destruction does not occur without use of anti-VEGF agents, including pegaptanib, bevacizumab, and ranibizumab. In the recent years, intravitreal injection of anti-VEGF agents has appeared as the most innovative treatment of the distressing complications in diabetes. The function of these agents is direct neutralisation of the function of VEGF. Current studies have shown that patients can get advantage more from anti-VEGF therapy than panretinal photocogulation, like less intervention in patients with opacified media and subsequent development of macular edema. In addition, preoperative IVB injections in PDR may reduce the bleeding during an operation and decrease the complications.[20]

Avery *et al*. reported a rapid regression of retinal (73%) and iris (82%) neovascularisation secondary to PDR after a single intravitreal bevacizumab.[18] Arevalo *et al*. reported that, after treatment with IVB, 61.4% patients showed total involution of retinal neovessels (RNV), 34.1% patients showed incomplete regression, and ETDRS BCVA testing and OCT confirmed noteworthy improvement after an average follow-up of 28.4 weeks (range, 24-40 weeks).[19]

However, the exact mechanism of IVB on PDR is uncertain. Han XX observed that IVB pretreatment predominantly decreases amounts of vascular endothelial cells in NVM. VEGF and HIF-1α levels were considerably lower in neovascular membranes (NVMs) as compared to the non-IVB group. HIF-1 and VEGF were involved in new vessels formation of PDR membranes since HIF-1 facilitates the angiogenesis after low oxygen by upregulating the expression of numerous angiogenic cytokines and VEGF stimulates proliferation, migration, and tube formation of vascular endothelial cells.[20]

CONCLUSION

Intravitreal bevacizumab in short duration is effective as adjunctive treatment to PRP with early and greater rate of retinal neovessel regression than PRP alone in patients of PDR.

REFERENCES

1. Qidwai W, Ashfaq T. Imminent epidemic of diabetes mellitis in Pakistan: Issues and challenges for health care providers. *J Liaquat Univ Med Health Sci* 2010; **9**:112-3.
2. Ahmad M, Jan S. Comparison between panretinal photocoagulation and panretinal photocoagulation plus intravitreal bevacizumab in proliferative diabetic retinopathy. *J Ayub Med Coll Abbottabad* 2012; **24**:10-3.
3. Romero-Aroca P. Current status in diabetic macular edema treatments. *World J Diabetes* 2013; **4**:165-9.
4. Mitchell P, Wong TY. Diabetic macular edema treatment guideline working group. Management paradigms for diabetic macular edema. *Am J Ophthalmol* 2014; **157**:505-13.
5. Abu El-Asrar AM. Evolving strategies in the management of diabetic retinopathy. *Middle East Afr J Ophthalmol* 2013; **20**: 273-82.
6. Tareen IU, Rahman A, Mahar PS, Memon MS. Primary effects of intravitreal bevacizumab in patients with diabetic macular edema. *Pak J Med Sci* 2013; **29**:1018-22.
7. Al Rashaed S, Arevalo JF. Combined therapy for diabetic macular edema Middle East. *Afr J Ophthalmol* 2013; **20**:315-20.
8. Yang CS, Hung KC, Huang YM, Hsu WM. Intravitreal bevacizumab (Avastin) and panretinal photocoagulation in the treatment of high-risk proliferative diabetic retinopathy. *J Ocul Pharmacol Ther* 2013; **29**:550-5.
9. Cho WB, Oh SB, Moon JW, Kim HC. Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy. *Retina* 2009; **29**:516-22.
10. Papavasileiou E, Dereklis D, Oikonomidis P, Grixti A, Vineeth Kumar B, Prasad S. An effective programme to systematic diabetic retinopathy screening in order to reduce diabetic retinopathy blindness. *Hell J Nucl Med* 2014; **17**(Suppl 1):30-4.
11. Shin YW, Lee YJ, MD, Lee BR, Cho HY. Effects of an intravitreal bevacizumab injection combined with panretinal photocoagulation on high-risk proliferative diabetic retinopathy. *Korean J Ophthalmol* 2009; **23**:266-72.
12. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study). *Retina* 2006; **26**:1006-13.
13. Matsumoto Y, Freund KB, Peiretti E, Cooney MJ, Ferrara DC, Yannuzzi LA. Rebound macular edema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. *Retina* 2007; **27**:426-31.
14. Mirshahi A, Roohipoor R, Lashay A, Mohammadi SF, Abdoallahi A, Faghihi H. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: a randomized double-masked clinical trial. *Eur J Ophthalmol* 2008; **18**:263-9.
15. Tonello M, Costa RA, Almeida FP, Barbosa JC, Scott IU, Jorge R. Panretinal photocoagulation versus PRP plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy (IBeHi study). *Acta Ophthalmol* 2008; **86**:385-9.
16. Filho JA, Messias A, Almeida FP, Ribeiro JA, Costa RA, Scott IU, Jorge R. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. *Acta Ophthalmol* 2011; **89**:e567-72.
17. Arevalo JF, Wu L, Sanchez JG, Maia M, Saravia MJ, Fernandez CF *et al*. Intravitreal bevacizumab (Avastin) for proliferative diabetic retinopathy: 6-months follow-up. *Eye (Lond)* 2009; **23**:117-23.
18. Avery RL, Pearlsman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA *et al*. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006; **113**:1695.e1-15.
19. Arevalo JF, Maia M, Flynn HW Jr, Saravia M, Avery RL, Wu L, *et al*. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; **92**:213-6.
20. Han XX, Guo CM, Li Y and Hui YN. Effects of bevacizumab on the neovascular membrane of proliferative diabetic retinopathy: Reduction of endothelial cells and expressions of VEGF and HIF-1α. *Mol Vis* 2012; **18**:1-9.