ORIGINAL ARTICLE

Comparison of Panretinal Photocoagulation alone With Panretinal Photocoagulation plus Intravitreal Bevacizumab in Treatment of High Risk Proliferative Diabetic Retinopathy

BUSHRA AKBAR[1], RANA INTISAR UL HAQ, AHSAN MUKHTAR, MAZHAR ISHAQ, MUHAMMAD SAIM KHAN

[1]Department of Ophthalmology, Armed Forces Institute of Ophthalmology, Rawalpindi

Correspondence to: Dr. Bushra Akbar, Post-Graduate Resident, Department of Ophthalmology, Armed Forces Institute of Ophthalmology, Rawalpindi. Email: dr.bushra.akbar@gmail.com

ABSTRACT

Objective: To compare the panretinal photocoagulation (PRP) with PRP plus intravitreal Bevacizumab in treatment of high risk proliferative diabetic retinopathy in terms of mean change of neovascularization on disc (NVD).

Design: It was a randomized controlled trial.

Place and Duration of Study: This study was conducted at the Department of Ophthalmology, Armed Forces institute of Ophthalmology, Rawalpindi over 6 months period from November 2014 through April 2015.

Patients and Methods: This study involved 60 consecutive patients of both genders aged between 20-65 years known to be diabetic for at least 10 years with HbA1C ≤7% presenting at Ophthalmology outdoor having high risk PDR. These patients were randomly allocated into two treatment groups. Patients allocated to Group-A received panretinal photocoagulation (PRP) in two sessions 2 weeks apart while patients in Group-B received single injection of intravitreal Bevacizumab (IVB) prior to 2 sessions of PRP as in Group-A. Outcome variable was mean clinical change of NVD described as percentage area of disc diameter affected by neovascularization on disc (NVD) regressed at 6 weeks follow-up.

Results: Both the study groups were comparable in terms of mean age (p=0.568), mean duration of diabetes (p=0.763), mean BMI (p=0.395), mean HbA1C levels (p=0.289) and frequency of various age (p=0.795), genders (p=0.796), duration of diabetes (p=0.774), BMI (p=0.559) and HbA1C groups (p=1.000). The mean NVD at baseline was 44.87±4.18% in Group-A and 44.67±4.91% in Group-B without any statistically significant difference between the two groups (p=0.866). The mean NVD at follow-up was significantly lower in both the groups as compared to base line; Group-A (43.28±4.26% vs. 44.87±4.18%; p=0.000) and Group-B (38.47±4.74% vs. 44.67±4.91%; p=0.000). However, the mean post-treatment NVD was significantly lower in Group-B as compared to Group-A (38.47±4.74% vs. 43.28±4.26%; p=0.000) across all age, gender, duration of diabetes, BMI and HbA1C groups. The mean decrease in NVD was significantly higher in Group-B (6.20±1.13% vs. 1.58±0.74%; p=0.000) as compared to Group-A and this difference was significant across all age, gender, duration of diabetes, BMI and HbA1C groups.

Conclusion: Combination therapy in the form of panretinal photocoagulation plus intravitreal Bevacizumab was found to be better with significantly lower mean NVD (38.47±4.74 vs. 43.28±4.26%; p=0.000) at follow-up as compared to panretinal photocoagulation alone. The mean decrease in NVD upon follow-up was significantly higher with combination therapy (6.20±1.13% vs. 1.58±0.74%; p=0.000) as compared to panretinal photocoagulation monotherapy.

Keywords: High Risk Proliferative Diabetic Retinopathy, Panretinal Photocoagulation, Intravitreal Bevacizumab, Neovascularization

INTRODUCTION

Proliferative diabetic retinopathy (PDR) a grave complication of diabetes is leading cause of preventable blindness with a reported incidence of 95% in 30 to 50% of diabetic population after 20 to 30 years of Type-I diabetes mellitus[1]. Long standing diabetes, poor glycemic control and hypertension have been identified as risk factors for the development of PDR[1,2]. PDR is associated with severe vision threatening complications like pre-retinal, vitreous hemorrhage, rhegmatogenous and tractional detachment owing to

neovascularization[1]. Retinal ischemia in these patients correlates with increased concentration of multiple angiogenic growth factors primarily the vascular endothelial growth factor (VEGF) in aqueous and vitreous cavity which provokes neovascularization[1,3].

Panretinal photocoagulation (PRP) causes relapse of neovascularization in about 60% patients within 3 months[2,3,4] considerably reducing visual loss and blindness from diabetic retinopathy by eliminating the source of hypoxic retina and subsequent reduction in the release of VEGF[1,5]. The anti-VEGF intravitreal Bevacizumab (IVB) causes neovascularization regression by blocking the effect of VEGF with lesser destructive effect than PRP[3]. Though the gold standard treatment of proliferative diabetic retinopathy (PDR) is panretinal photocoagulation, anti-VEGF utilization along with PRP has shown promising outcome in the management of PDR[3,6].

However, the available evidence on the use of this combination therapy in the management of PDR was limited. The purpose of the current study was to repeat this trial to further confirm the advantage of PRP plus IVB combination therapy over PRP monotherapy.

PATIENTS AND METHODS

This was a randomized controlled trial conducted at Armed forces institute of Ophthalmology, Rawalpindi over 6 months period from November 2014 through April 2015.

This study involved 60 consecutive patients of both genders aged between 20-65 years known to be diabetic for at least 10 years with HbA1C ≤7% presenting at Ophthalmology outdoor having high risk severe PDR. High risk sever PDR was labeled upon the presence of neovascularization at the disc (NVD) > 33% of the total disc area. Patients with high BMI (>28Kg/m^2), deranged renal profile (ser. Creatinine>1.2mg/dL), uncontrolled hypertension, persistent vitreous hemorrhage, neovascular glaucoma, tractional retinal detachment and those with history of prior laser treatment, intravitreal Bevacizumab, vitrectomy, thromboembolic phenomenon, or major surgery in the past 6 months period were excluded. A written informed consent was taken from every patient.

These patients were randomly allocated into two treatment groups. Patients allocated to Group-A received panretinal photocoagulation (PRP) with total of 1800 to 2000 moderate intensity laser burns (200 micron spot size, 0.2 to 0.5 seconds duration) in two sessions 2 weeks apart while patients in Group-B received single injection of intravitreal Bevacizumab (1.25mg/0.05ml) prior to 2 sessions of PRP as in Group-A. Outcome variable was mean clinical change of NVD described as as percentage area of disc diameter affected by neovascularization on disc (NVD) regressed at 6 weeks follow-up.

All the treatments and clinical examinations were performed by a single consultant ophthalmologist to eliminate bias.

RESULTS

The age of the patients ranged from 40 years to 65 years with a mean of 53.68±6.04 years. There were 31 (51.7%) male and 29 (48.3%) female patients in the study group. The mean duration of diabetes was 12.18±2.11 years while the mean BMI was 25.97±1.80 Kg/m^2. The HbA1C level ranged from 6.0-6.9% with a mean of 6.54±0.25%. Both the study groups were comparable in terms of mean age (p=0.568), mean duration of diabetes (p=0.763), mean BMI (p=0.395), mean HbA1C (p=0.289) levels and frequency of various age (p=0.795), gender (p=0.796), duration of diabetes (p=0.774), BMI (p=0.559) and HbA1C groups (p=1.000) as shown in Table 1.

The mean NVD at baseline was 44.87±4.18% in Group-A and 44.67±4.91% in Group-B without any statistically significant difference between the two groups (p=0.866). The mean NVD at follow-up was significantly lower in both the groups as compared to base line; Group-A (43.28±4.26% vs. 44.87±4.18%; p=0.000) and Group-B (38.47±4.74% vs. 44.67±4.91%; p=0.000). However, the mean post-treatment NVD was significantly lower in Group-B as compared to Group-A (38.47±4.74% vs. 43.28±4.26%; p=0.000). All these findings have been summarized in Table 2.

The mean post-treatment NVD was significantly lower in Group-B as compared to Group-A across all age, gender, duration of diabetes, BMI and HbA1C groups as shown in Table 3.

The mean decrease in NVD was significantly higher in Group-B (6.20±1.13% vs. 1.58±0.74%; p=0.000) as compared to Group-A and this difference was significant across all age, gender, duration of diabetes, BMI and HbA1C groups as shown in Table 4.

Table 1: Baseline Characteristics of Study Population

Characteristics	Overall	Panretinal Photocoagulation alone (n=30)	Panretinal Photocoagulation + Intravitreal Bevacizumab (n=30)	P value
Age (years)	53.68±6.04	53.23±5.44	54.13±6.64	0.568
Age Groups				
• 40-52 years	27 (45.0%)	14 (46.7%)	13 (43.3%)	0.795
• 53-65 years	33 (55.0%)	16 (53.3%)	17 (56.7%)	
Gender				
• Male	31 (51.7%)	15 (50.0%)	16 (53.3%)	0.796
• Female	29 (48.3%)	15 (50.0%)	14 (46.7%)	
Duration of DM (years)	12.18±2.11	12.27±1.98	12.10±2.26	0.763
Duration of DM Groups				
• 10-13 years	43 (71.7%)	22 (73.3%)	21 (70.0%)	0.774
• 14-18 years	17 (28.3%)	8 (26.7%)	9 (30.0%)	
BMI	25.97±1.80	26.17±1.98	25.77±1.61	0.395
BMI Groups				
• 20-24 Kg/m^2	16 (26.7%)	7 (23.3%)	9 (30.0%)	0.559
• 25-28 Kg/m^2	44 (73.3%)	23 (76.7%)	21 (70.0%)	
HbA1C (%)	6.54±0.25	6.50±0.28	6.57±0.22	0.289
HbA1C Groups				
• 6.0-6.4 %	20 (33.3%)	10 (33.3%)	10 (33.3%)	1.000
• 6.5-6.9%	40 (66.7%)	20 (66.7%)	20 (66.7%)	

Independent sample t-test and chi-square test, observed difference was statistically insignificant

Table 2: Comparison of Mean NVD (%) at baseline and Follow-up

	NVD% (mean±sd)		P value b/w Groups
	Panretinal Photocoagulation alone (n=30)	Panretinal Photocoagulation + Intravitreal Bevacizumab (n=30)	
Baseline	44.87±4.18	44.67±4.91	0.866
Follow-up	43.28±4.26	38.47±4.74	0.000*
P value (before and after treatment)	0.000*	0.000*	

Independent sample t-test, * observed difference was statistically significant

Table 3: Comparison of Mean NVD (%) at Follow-up between the Study Groups

	NVD% (mean±sd)		P value
	Panretinal Photocoagulation alone (n=30)	Panretinal Photocoagulation + Intravitreal Bevacizumab (n=30)	
Overall	43.28±4.26	38.47±4.74	0.000*
Age Groups			
• 40-52 years	43.79±5.39	37.92±5.20	0.008*
• 53-65 years	42.84±3.08	38.88±4.47	0.006*
Gender			
• Male	43.07±3.75	38.88±4.17	0.007*
• Female	43.50±4.84	38.00±5.43	0.008*

Duration of DM Groups			
• 10-13 years	42.39±2.97	38.52±4.62	0.002*
• 14-18 years	45.75±6.27	38.33±5.29	0.018*
BMI Groups			
• 20-24 Kg/m^2	44.14±4.53	37.33±6.50	0.034*
• 25-28 Kg/m^2	43.02±4.25	38.95±3.85	0.002*
HbA1C Groups			
• 6.0-6.4 %	43.00±4.05	38.40±5.54	0.048*
• 6.5-6.9%	43.43±4.46	38.50±4.44	0.001*

Independent sample t-test, * observed difference was statistically significant

Table 4: Comparison of Mean Decrease in NVD (%) at Follow-up between the Study Groups
Independent sample t-test, * observed difference was statistically significant

	Mean Decrease in NVD% (mean±sd)		**P value**
	Panretinal Photocoagulation alone (n=30)	**Panretinal Photocoagulation + Intravitreal Bevacizumab (n=30)**	
Overall	1.58±0.74	6.20±1.13	0.000*
Age Groups			
• 40-52 years	1.64±0.93	6.38±0.87	0.000*
• 53-65 years	1.53±0.56	6.06±1.30	0.000*
Gender			
• Male	1.47±0.83	6.44±1.09	0.000*
• Female	1.70±0.65	5.93±1.14	0.000*
Duration of DM Groups			
• 10-13 years	1.57±0.70	6.19±1.25	0.000*
• 14-18 years	1.63±0.92	6.22±0.83	0.000*
BMI Groups			
• 20-24 Kg/m^2	1.43±0.54	5.89±1.45	0.000*
• 25-28 Kg/m^2	1.63±0.80	6.33±0.97	0.000*
HbA1C Groups			
• 6.0-6.4 %	1.50±0.70	6.20±1.03	0.000*
• 6.5-6.9%	1.63±0.78	6.20±1.20	0.000*

DISCUSSION

Diabetic retinopathy is the most frequent microvascular complication of diabetes and remains one of the leading causes of blindness among adults aged 20-74 years across the world. The two most important visual complications of diabetic retinopathy are proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). The occurrence of retinal new vessels (NVs) represents an imperative preventable risk factor for severe vision loss in patients with diabetes mellitus. About 60% of patients with proliferative diabetic retinopathy (PDR) respond to pan retinal photocoagulation (PRP) with recession of neovascularization within 3 months[7]. However, many such patients need further laser treatment and 4.5% eventually entail pars plana vitrectomy despite PRP[8].

Although severe central vision loss resulting from PDR can be prohibited with PRP in most cases, this caustic, often painful, laser procedure may be accompanied by diminished peripheral vision and greater likelihood of macular edema[9].

Vascular endothelial growth factor (VEGF) has been associated in the pathogenesis of a number of human eye diseases characterized by neovascularization and blockage of VEGF has been associated with the recession of iris neovascularization and diminished retinal NV formation in primates and humans[10,11]. Several

studies demonstrated that intravitreal injection of bevacizumab (IVB) resulted in marked regression of retinal and iris neovascularization, and prompt resolution of vitreous hemorrhage in patients with PDR[12]. But this effect appears to be transient and reinjection is required after 12 weeks. In addition, IVB injection was revealed to be an effective adjunctive treatment to PRP in the treatment of PDR. Intravitreal bevacizumab injection before PRP was established to be beneficial in preventing PRP-induced visual disturbance and foveal stiffening and was linked to a greater reduction in the area of active leaking new vessels than PRP alone in patients with PDR[6,13].

Therefore, the present study was aimed at comparing the possible synergistic properties of intravitreal bevacizumab when used in combination with PRP to the effect of PRP alone in the treatment of high-risk proliferative diabetic retinopathy.

In the present study, the mean age of the patients was 53.68±6.04 years. A similar mean age has been reported previously by Tonello et al.[6] (54.06±11.74 years) and Lucena et al.[14] (51.1±11.3 years) in Brazil, Ahmad et al.[3] (51.0±6.0 years) in Pakistan, Yang et al.[15] (54.9±9.1 years) in China and Sinawat et al.[16] (47.7±12.69 years) in Thailand among diabetic patients with high risk PDR. Filho et al.[17] observed relatively higher mean age of 63.3±2.5 years in American such patients.

There were 31 (51.7%) male and 29 (48.3%) female patients in the study group. A similar male predominance has also been reported by Ahmad et al.[3] (59.25% vs. 40.75%) in Pakistan, Lucena et al.[14] (58.82% vs. 41.18%) and Tonello et al.[6] (73.3% vs. 26.7%) in Brazil and Filho et al.[17] (60% vs. 40%) in USA. Sinawat et al.[16] however reported equal gender distribution among diabetic patients with high risk PDR in Thailand. Khalid et al.[18] on the other hand observed female predominance (72.3% vs. 21.7%) in Pakistani such patients.

The mean duration of diabetes was 12.18±2.11 years in the present study. Ahmad et al.[3] (12±5 years), Lucena et al.[14] (12.9±8.8 years), Aziz et al.[19] (13±7.94 years), Hussain et al.[20] (9.66±1.31 years) and Sinawat et al.[16] (9.7±7.7 years) observed similar mean duration of diabetes in patients presenting with high risk PDR. Filho et al.[17] (17.0±2.5 years) and Tonello et al.[6] (17.3±7.26 years) however observed much higher mean duration of diabetes among such patients. The HbA1C level ranged from 6.0-6.9% with a mean of 6.54±0.25%. Ahmad et al.[3] reported similar mean HbA1c level of 7.3±1.4% among such patients.

Both the study groups were comparable in terms of mean age (p=0.568), mean duration of diabetes (p=0.763), mean BMI (p=0.395), mean HbA1C (p=0.289) levels and frequency of various age (p=0.795), gender (p=0.796), duration of diabetes (p=0.774), BMI (p=0.559) and HbA1C groups (p=1.000). Thus there was no inherent bias among the study groups.

The mean NVD at baseline was 44.87±4.18% in Group-A and 44.67±4.91% in Group-B without any statistically significant difference between the two groups (p=0.866). The mean NVD at follow-up was significantly lower in both the groups as compared to base line; Group-A (43.28±4.26% vs. 44.87±4.18%; p=0.000) and Group-B (38.47±4.74% vs. 44.67±4.91%; p=0.000). Thus both the treatments were effective and significantly reduced mean NVD (%). However, the mean post-treatment NVD was significantly lower in Group-B as compared to Group-A (38.47±4.74% vs. 43.28±4.26%; p=0.000) suggesting combination therapy to be significantly more effective as compared to PRP alone. Our results are in line with the previously published results by Ahmad et al.[3] who observed significant decrease in post-treatment NVD compared to the baseline with combination therapy (11±3% vs. 40±7%; p=.00008). They also reported significantly lower post-treatment NVD (11±3% vs. 40±6; p=0.000) compared to the PRP monotherapy. The mean decrease in NVD was significantly higher in Group-B (6.20±1.13% vs. 1.58±0.74%; p=0.000) as compared to Group-A and this difference was significant across all age, gender, duration of diabetes, BMI and HbA1C groups again confirming the advantage of combination therapy in the form of significantly greater decrease in NVD%. Ergür et al.[21] in a similar study also observed that IVB considerably amplified the response to PRP and caused accelerated regression of retinal neovascularization but they did not observe difference in visual acuity results.

The present study adds to the limited existing evidence on this topic and confirms the supremacy of PRP plus IVB in the treatment of high risk PDR. Though there are lot of studies on this topic but the outcome variable in these studies is the improvement in visual acuity. The present study has focused on the actual pathological change in

retina responsible for loss of vision and its response to treatment. In the light of the results of the present study it can be advocated that future patients with high risk PDR should receive single injection of intravitreal Bevacizumab (1.25mg/0.05ml) prior to 2 sessions of PRP. A very strong limitation to the present study is that side effects[22] of this new combination therapy were not considered which are however important and should be considered in future studies before adopting it in routine practice.

CONCLUSION

Combination therapy in the form of panretinal photocoagulation plus intravitreal Bevacizumab was found to be better with significantly lower mean NVD (38.47±4.74 vs. 43.28±4.26%; p=0.000) at follow-up as compared to panretinal photocoagulation alone. The mean decrease in NVD upon follow-up was significantly higher with combination therapy (6.20±1.13% vs. 1.58±0.74%; p=0.000) as compared to panretinal photocoagulation monotherapy.

REFERENCES

1. Singh R, Ramasamy K, Abraham C, Gupta V, Gupta A. Diabetic retinopathy: An update. Indian J Ophthalmol 2008;56(3):179-88.
2. Muqit MM, Marcellino GR, Henson DB, Young LB, Turner GS, Stanga PE. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study Report 4. Eye (Lond) 2011;25(11):1447-56.
3. Ahmad M, Jan S. Comparison between Panretinal Photocoagulation and Panretinal Photocoagulation plus Intravitreal Bevacizumab in Proliferative Diabetic Retinopathy. J Ayub Med Coll Abbott 2012;24(3):10-3.
4. Muraly P, Limbad P, Srinivasan K, Ramasamy K. Single session of Pascal versus multiple sessions of conventional laser for panretinal photocoagulation in proliferative diabetic retinopathy: a comparitive study. Retina 2011;31(7):1359-65.
5. Chappelow AV, Tan K, Waheed NK, Kaiser PK. Panretinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. Am J Ophthalmol 2012;153(1):137-42.
6. Tonello M1, 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(4):385-9.
7. Diabetic retinopathy study. Report Number 6. Design, methods, and baseline results. Report Number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the Diabetic Retinopathy. Invest Ophthalmol Vis Sci 1981;21(1):1-226.
8. Flynn HW Jr, Chew EY, Simons BD, Barton FB, Remaley NA, Ferris FL 3rd. Pars plana vitrectomy in the Early Treatment Diabetic Retinopathy Study. ETDRS report number 17. The Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1992;99(9):1351-7.
9. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98(Suppl-5):766-85.
10. Avery RL1, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006;113(10):1695.
11. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. Retina 2006;26(3):275-8.
12. Arevalo JF, Garcia-Amaris RA. Intravitreal bevacizumab for diabetic retinopathy. Curr Diabetes Rev 2009;5(1):39-46.
13. Cho WB, Oh SB, Moon JW, Kim HC. Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy. Retina 2009;29(4):516-22.
14. Lucena CR, Ramos Filho JA, Messias AM, Silva JA, Almeida FP, Scott IU, et al. Panretinal photocoagulation versus intravitreal injection retreatment pain in high-risk proliferative diabetic retinopathy. Arq Bras Oftalmol 2013;76(1):18-20.
15. 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(6):550-5.
16. Sinawat S, Rattanapakorn T, Sanguansak T, Yospaiboon Y, Sinawat S. Intravitreal bevacizumab for proliferative diabetic

retinopathy with new dense vitreous hemorrhage after full panretinal photocoagulation. Eye (Lond) 2013;27(12):1391-6.
17. Filho JA, Messias A, Almeida FP, Ribeiro JA, Costa RA, Scott IU, et al. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. Acta Ophthalmol 2011;89(7):e567-72.
18. Khalid S, Moin M, Khan MH. Screening of diabetic retinopathy in a diabetic medical center. Pak J Ophthalmol 2015;31(3):140-5.
19. Azia KMA. Association between high risk foot, retinopathy and HbA1c in Saudi diabetic population. Pak J Physiol 2010;6(2):22-8.
20. Hussain F, Arif M, Ahmad M. The prevalence of diabetic retinopathy in Faisalabad, Pakistan: a population-based study. Turk J Med Sci 2011;41(4):735-42.
21. Ergür O, Bayhan HA, Takmaz T, Gurdal C, Can I. [Comparison of panretinal photocoagulation (prp) with prp plus intravitreal bevacizumab in the treatment of proliferative diabetic retinopathy]. Ret-Vit 2009;17:273-7.
22. Oh J, Kim S, Kim K. Panretinal photocoagulation(PRP) versus Intravitreal bevacizumab plus PRP for diabetic retinopathy. Invest Ophthalmol Visual Sci 2014;55:3900.