Original article

Comparison of intravitreal bevacizumab and panretinal photocoagulation for treatment of proliferative diabetic retinopathy without macular edema

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ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) is complication seen in patients with uncontrolled diabetes, resulting in visual loss in working-age individuals both in the developed and the developing nations. Left untreated it leads to blindness. Objective of this study was to compare short term efficacy of panretinal photocoagulation and intra-vitreal Bevacizumab in terms of visual acuity (better or worse) and neo-vascular regression in patients with proliferative diabetic retinopathy without macular edema.

Patients and methods: Prospective, randomized, interventional case series. Forty eyes of 20 PDR patients diagnosed clinically and further confirmed by fundus fluorescein angiography, unless contraindicated, and ocular coherence tomography for ruling out macula edema, were included in study. Patients were divided in 2 groups; Group A, panretinal photocoagulation (PRP) and Group B, intravitreal injection of anti-vascular endothelial growth factor (antiVEGF) Bevacizumab 1.25mg/0.05ml. PRP session (two weeks apart) for group A and injection Bevacizumab, monthly for three months for group B were planned. Baseline best-corrected visual acuity (BCVA), anterior segment and fundus examination and intraocular pressure (IOP) were recorded. Patients were examined one and six months from baseline. Main outcomes were BCVA, regression/ progression of neovascularization and vitreous hemorrhage at end of 6 months.

Results: Retinal neo-vascular regression observed after first follow-up with 70% clinical regression in Group A (PRP) and 15% in Group B (Bevacizumab). BCVA at baseline was similar in both groups 0.80±0.24 and 0.88±0.24 respectively. At 6 months, BCVA improved more in group A 0.60±0.20 than group B 0.92±0.13. Visual reduction was noted in group B due to progression of PDR with vitreous hemorrhage (VH) in 15% of group A and 30% of group B. Pars plana vitrectomy for persistent VH planned in 5% of Group A and 15% of group B eyes.

Conclusion: Short term follow up reveal anatomical and functional improvement in both groups with more so in PRP than Bevacizumab group in terms of BCVA, neo-vascular regression and VH. Further studies are required to assess the long term efficacy, compliance and safety of both treatment regimens

Keywords:
Proliferative diabetic retinopathy, visual acuity, neovascularization, panretinal photocoagulation, intra-vitreal Bevacizumab, Pars plana vitrectomy, vitreous hemorrhage

INTRODUCTION

Proliferative diabetic retinopathy (PDR) is complication seen in patients with uncontrolled diabetes, resulting in visual loss in working-age individuals.[1] When left untreated, it ultimately leads to blindness. Liverpool study reported the prevalence of DR and PDR as 46% and 4% in type 1 and 25% and 0.5% in type 2 diabetes respectively with prevalence varying according to duration of disease.[2] Pan retinal photocoagulation (PRP) is the gold standard treatment for PDR.[3] It aims at preserving central vision and neovessel regression. Documented side effects are visual field defects with difficulty in night driving, retinal fibrosis and epiretinal membrane formation. Recently intra-vitreal anti-vascular endothelial growth factors (antiVEGF) became available for management of diabetic macular edema. They play a role in neo-vessel regression. However, they need regular monthly injections based on the standard treatment protocol. So far no local study in the published indexed literature has been reported from Pakistan whereby PDR patients without macular edema are compared for the two treatment options. This randomized trial was designed to compare efficacy of PRP and anti-VEGF Bevacizumab in terms of BCVA and neovascularization (progression/regression) in patients with PDR without macular edema.

PATIENTS AND METHODS

The study was conducted in Eye department of Sir Ganga Ram hospital, Lahore from October 2015 till December

Competing interest: The authors have declared no competing interests exist.
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2016 after approval from ethical review committee. After explaining treatment regime and follow-up period, voluntary consent was taken from every study patient. Patients with non-proliferative diabetic retinopathy, macular edema, previous treatment for DR, vitreous hemorrhage and those with cataract, uveitis or glaucoma were excluded. A total of 40 eyes diagnosed with high risk proliferative diabetic retinopathy (according to ETDRS criteria) without macular edema documented on clinical examination and diagnostic confirmation from Ocular coherence tomography (OCT) and fundus fluorescein angiography (FFA), where possible, were inducted. Patients were randomly allocated in two groups, A (PRP) and B (antiVEGF). Patients with proliferative diabetic retinopathy without macular edema and no previous treatment were included. Both groups included 20 eyes each with PDR without macular edema. Baseline examination included, BCVA (Snellen's chart), clinical examination (slit-lamp bio microscopy) for PDR assessment (neovasularisation at disc or elsewhere) and absence of macular edema, colored fundus photograph to clinical asses/measure NV size. Intraocular pressure and presence/ absence of cataract. Diagnostic assessment included FFA (unless contraindicated by nephrologist due to creatinine values) for neovascularization size, location, leakage. OCT was done to rule out macular edema. Cardiac and nephrology assessment obtained as baseline to rule out any contraindication to either anti-VEGF or FFA. Group A received pan retinal photocoagulation (2000 shots 1-2 sessions within 4 weeks) while Group B underwent a treatment plan of monthly intra-vitreal Bevacizumab 1.25mg/0.05ml for 3 months. In group A, 2 sessions of PRP was carried out in two weeks (maximum of 2000 shots), 200-300 microns spot size, one spot apart from extra macular zone to Ora serrate. In group B, monthly injection of intra-vitreal Bevacizumab 1.25mg/0.05mi injected in operation theatre using microscope under aseptic condition, choosing supero-temporal (9-10 o clock position for right eye and 2-3 o clock hour for left eye) quadrant. Post injection topical antibiotic was prescribed for 3 days to group B as prophylaxis intra-ocular infection control. Both treatment regimens were carried out by 2-3 experienced fellows. Treated patients were followed at one month (post PRP laser and intravitreal anti VEGF) and 6 months post therapy. First follow-up was done one month after PRP and intravitreal anti-VEGF injection and last follow-up at 6 months from baseline. More weightage was given to clinical assessment for comparison with baseline in the follow-up evaluation. Sign of neo-vascularization, regression, persistence or enhancement was the key follow-up indicator. Criteria set for the clinical assessment of neo-vessels was its size (increase, decrease or absence) which guided whether treatment maintained, improved or worsened PDR. If macular edema was noted on OCT during the follow-up, the patient was excluded from study. On each follow-up, BCVA, slit-lamp fundus examination using 90 D super-field, coloured fundus photograph documenting neo-vessel size and OCT. Results tabulated. Main outcomes measured were: change in BCVA (better or worse), neo-vessels change (progression, regression or persistence), macular thickness (DME development), and any other change in the level of PDR (vitreous hemorrhage requiring surgical intervention). Data was analyzed using SPSS 20.0. BCVA analyzed in both groups using LogMAR at each follow-up, tabulated with P-value. State of PDR (progression, regression or persistence of neo-vessels) and advancement (VH) requiring surgical intervention (PPV) in either group tabulated and described using frequency and percentages.

RESULTS

Forty eyes of 20 patients were enrolled in both groups. Twelve (60%) were females and 8 (40%) were males. Mean age was 55.81 ± 7.99 years. Both groups baseline clinical and FFA showed neo-vessels. OCT showed normal macular thickness (200-250 microns). In group A (PRP), baseline visual acuity ranged between counting finger to 6/12 (Snellen's chart) with LogMAR range of 0.80± 0.24 and in group B 0.88± 0.24. IOP was within normal range in either group. Group A (PRP) was lasered using diode laser with 200-micron spot size. A total of 2000 shots were applied. In Group B, 1.25mg/0.05ml intravitreal Bevacizumab was injected in affected eye under aseptic conditions. One month follow-up visual acuity, clinical fundus examination and OCT were documented in both study groups. Second and third injection of Bevacizumab in Group B was applied one month apart. At first month follow up for Group A visual acuity of 20 eyes; one eye with baseline hand movements remained the same, of 9 eyes with

Table 1. Comparison of Visual acuity and regression of neo-vessels in Group A and B

No.	Age	Sex	Visual acuity at baseline	Follow-up visual acuity PRP (Group A)			Follow-up visual acuity IVB (Group B)			Regression in size of neovessels (last follow-up)		VH	PPV
				1st	2nd	Last	1st	2nd	Last	PRP	IVB		
1	60	F	R. CF; L. CF	L 6/60	6/36	6/24↑	R. 6/36	6/60	6/60↔	+		-	-
2	55	M	R. CF; L. 6/36	L 6/36	6/36	6/24↑	R. 6/36	6/60	6/60↓	+		-	-
3	52	M	R. 6/12; L. 6/36	R. 6/18	6/18	6/12↑	L. 6/60	CF	CF↓	+		+ L.	+ L.
4	58	M	R. CF; L. 6/18	L. 6/24	6/18	6/12↑	R. 6/36	6/24	6/60↓	+		+ R.	+ R.
5	52	M	R. 6/36; L. CF	L. 6/36	6/36	6/18↑	R. 6/36	6/24	6/60↓	+		-	-

6	62	F	R. 6/60; L. CF	L. 6/60	6/36	6/18↑	R. 6/60	6/36	CF↓	+		+ R.	-
7	45	M	R. CF; L. CF	L. CF	6/60	6/36↑	R. 6/36	6/60	CF↓	+		-	-
8	65	F	R. 6/24; L. 6/24	L. 6/24	6/24	6/18↑	R. 6/24	6/18	6/36↓	+		-	-
9	62	F	R. 6/60; L. CF	R. 6/60	6/60	6/36↑	L. 6/60	6/60	6/60↔	+		-	-
10	58	F	R. 6/24; L. 6/24	L. 6/36	6/24	6/18↑	R. 6/24	6/18	6/36↓	+		-	-
11	59	M	R. 6/18; L. 6/18	R. 6/24	6/24	6/18↑	L. 6/12	6/24	6/24↓	same	same	-	-
12	61	F	R. 6/36; L. CF	R. 6/60	6/36	6/18↑	L. CF	6/36	6/60↔	same	same	-	-
13	62	F	R. CF; L. CF	6/60	6/24	6/24↑	R. 6/60	6/36	CF↓	+		+ R.	+ R.
14	42	F	R. CF; L. 6/36	R. CF	6/60	HM↓	L. 6/24	6/24	6/36↓		+	+ R.	+ R.
15	38	M	R. 6/60; L. 6/36	L. 6/60	6/60	6/24↑	R. 6/60	6/24	6/36↔	+		-	-
16	62	F	R. 6/60; L. HM	L. HM	CF	HM↓	R. 6/36	6/60	6/36↔		+	+ L.	-
17	58	M	R. 6/60; L. 6/60	L. 6/60	6/60	6/36↑	R. 6/60	6/60	6/60↔	same	same	-	-
18	62	F	R. CF; L. CF	L. CF	CF	6/36↑	R. CF	6/36	6/60↑	+		-	-
19	65	M	R. HM; L. CF	L. CF	6/60	6/60↑	6/60	6/60	CF↔	+		+ R.	-
20	57	M	R. CF; L. CF	L. CF	6/60	HM↓	CF	6/36	6/36↑		+	+ L.	+ L.

M: male; **F:** female; **L.** left eye; **R.:** right eye; **PRP:** panretinal photocoagulation; **IVB:** intravitreal bevacizumab; **HM:** hand movements; **VH:** vitreous hemorrhage; **PPV:** pars plana vitrectom

baseline VA of counting fingers, 2 improved to 6/60 and 1 to 6/36, whereas remaining 6 showed no improvement. Two eyes with VA of 6/60 remained unchanged. Of 3 eyes with baseline VA of 6/36, 1 eye remained static while 2 eyes worsened by one line (6/60). One eye with baseline 6/24 remained unchanged while second dropped to 6/36. Two eyes with 6/18 baseline worsened by one line, 6/24. One eye with baseline 6/12 reduced to 6/18. Clinical examination showed no regression in size of neo-vessels. OCT showed no macular edema. As for the 20 eyes in group B on first month follow up, 1 eye baseline hand movement showed good improvement to 6/60. Nine eyes baseline VA was counting fingers. Of these, 2 eyes improved to 6/60, 4 eyes to 6/36 and 3 remained static. Four eyes baseline VA was 6/60. 3 remained unchanged while one improved by one line (6/36). 3 eyes were 6/36. Of these, it remained unchanged in one eye, improved one line (6/24) in one and worsened by one line (6/60) in one eye. 2 eyes with baseline 6/24 and one with 6/12 remained unchanged. Clinical examination of fundus showed neo-vessels size remained unchanged. OCT showed stable macula.

At 6 months follow up of 20 eyes for Group A, 1 patient with hand movements (HM) that had improved initially worsened again to HM. Counting finger (9 eyes) at baseline improved to 6/36 (in two eyes), 6/24 (in three eyes), 6/18 (in two eyes), and worsened to hand movements (in two eyes) at last follow-up. Two eyes with 6/60 remained static in first two follow-ups but at six month showed improvement to 6/36. Baseline VA of 6/36 (3 eyes) improved to 6/24 in 2 eyes and 6/18 in 1 eye. Two eyes with 6/24 improved to 6/18. Out of 2 eyes with 6/18, one improved to 6/12, while other one worsened in previous follow-ups and the improved again to baseline VA of 6/18 at last follow-up. Similar findings were noted in 1 eye with VA of 6/12 which worsened and then returned to baseline 6/12. Clinical Examination of fundus showed complete regression in 14 (70%) eyes. In 6 eyes (30%) neo-vascularization persisted. Of these 6 eyes, 3 (15%) had VH. 2 eyes (5%) were planned for PPV. No macular edema developed in any case.

At 6 months follow up of 20 eyes in Group B, 1 eye with hand movement at baseline improved to 6/60 and worsened to CF at 6 month follow-up. Out of 9 with CF at baseline, 7 improvement to 6/60 (3 eyes), 6/36 (3 eyes), 6/12 (1 eye) and 2 eyes worsened to counting finger. However greater improvement was seen in earlier follow up than at last one. Of 4 eyes with 6/60 baseline, 1 remained the same, 2 improved to 6/36 and 1 worsened to CF. Of 3 eyes with 6/36 baseline, all improved initially, then one eye worsened to CF, one to 6/60 and one to 6/36. Of 2 eyes with VA of 6/24improved, and then worsened to 6/36. 1 eye with

Table 2. Comparison of visual acuity in LogMAR in Group A and B

Visual acuity	Group A PRP	Group B IVB	p-value
Baseline	0.80 ± 0.24	0.88 ± 0.24	0.317
First follow-up (1st month)	0.85±0.19	0.80±0.19	0.455
Second follow-up (3rd month)	0.79±0.19	0.76±0.20	0.603
Third follow-up (6th month)	0.60±0.20	0.92±0.13	0
p-value change from baseline-3rd follow up in each group	0.001	0.144	

Table 3. Comparison of regression of neo-vessels in Group A and B

Regression of neo vessels (last follow up 6 months)	Group A PRP	Group B IVB	Total	p-value
Yes	14 (70%)	3 (15%)	17 (42.5%)	0.144
No	6 (30%)	17 (85%)	23 (57.5%)	

Table 4. Comparison of vitreous hemorrhage between two groups

Vitreous hemorrhage (last follow up)	Group A PRP	Group B IVB	Total	p-value

Yes	3 (15%)	6 (30%)	9 (22.50%)	
No	17 (85%)	14 (70%)	31 (77.5%)	0.144
Total	20 (100%)	20 (100%)	40 (100%)	

6/18 improved and then worsened to 6/18 at last follow-up. Clinical examination showed complete regression of neo-vessels size in 3 (15%) eyes. 85% persisted. Of these, 6 (30%) developed VH. PPV was planned for 3 (15%). Remaining observed for spontaneous clearance as VH was slight. Table 1 summarizes the comparison of VA and regression of neovessels in two groups. Table 2 shows the LogMAR comparison in both groups. Table 3 compares the regression of neovessels in 2 groups whereas Table 4 depicts the comparison of vitreous haemorrhage in both groups. No complications like lens changes and raised IOP was observed in either group.

DISCUSSION

Pan-retinal photocoagulation has been the gold standard in treatment of proliferative diabetic retinopathy since 1981 documented by diabetic retinopathy study.[3] A survey reported in 2014 showed 98% of retina specialists perform PRP for initial PDR management in the absence of diabetic macular edema (DME).[4] However, PRP results in ocular side effects like permanent peripheral visual field loss, decreased night vision, exacerbation of diabetic macular edema and worsening of PDR (5%).[5] Many PDR patients require additional laser and despite all, 4.5% still end in getting Pars plana vitrectomy.[6] Reports show VEGF play a vital role in NV formation. Intravitreal anti VEGF can lead to regression in PDR and other conditions.[7] Ophthalmologists worldwide are more inclined to inject them for macular edema (wet AMD and diabetic macular edema) and regression of neo-vascularisation. Ocular side effects like endophthalmitis, lens changes, lens touch, raised IOP are documented. Main shortcoming of drug is short duration of its effect. Research documents average time to recurrence of neovascularization following anti-VEGF treatment ranged from 2 weeks to 3 months.[8] Proposed monthly injections protocol is the key to this treatment therapy. This study focused on these two treatment regimens for new cases of PDR without macular edema documented on initial clinical fundus examination, diagnostic FFA (unless contraindicated) and OCT. Due to this restriction criteria of no macular edema and previous treatment for PDR, study number was limited to 20 eyes each with total of 40 eyes with a study period of 6 months (last follow-up). Zhou and coauthors from China reported their findings in 36 eyes of 36 consecutive patients with follow-up period of 48 weeks while our study cut off period was 24 weeks from baseline treatment.[9] Their study treatment regimen was PRP alone and PRP plus Bevacizumab 1.25mg in respective groups while our study noted the effect of PRP and Bevacizumab respectively in two groups. The main outcome was vitreous clear up time and neo-vessel regression. The author reported mean interval time from treatment to complete NVD regression on FA examination as 15.2±3.5 weeks in PRP group and 12.5±3.1 week in PRP Plus group representing superiority of NV clearance in Plus group. Current study showed clinical examination outcome of neo-vessel regression in 24 weeks follow-up period to be 70% (14 eyes) in PRP group and 15% (3 eyes) in Bevacizumab group. Both studies showed NV regression rate but it was better in PRP plus IVB group for the Chinese study. Ours on other hand did not combine the two treatment regimen and PRP alone showed promising NV regression by last follow up. In present study, baseline visual acuity was not statistically different between the two groups with 0.80±0.24 in PRP alone group and 0.88±0.24 in IVB alone group (p=0.317). No significant difference seen in either group on first follow-up. The last (6 month) follow up showed better VA in PRP group (0.60±0.20) as compared to IVB group (0.92±0.13). The difference may be explained by lesser neo-vessel regression with formation of VH (30%) in group B as compared to (15%) in Group A. In a recent study, the IVB resulted in early visual gains but did not maintain it 5 years post treatment.[10] In present study the central macular thickness was within normal range as documented with OCT on baseline and follow ups. The PRP did not add to the macular thickness on any follow up. Likewise, Zhou and colleagues included PDR without CSME.[9] However, they documented a CSME increase in their PRP alone treated patients. PPV was planned in 2 eyes of PRP group and 3 of PRP group for non-clearing VH. Beaulieu and coauthors in 2016 reported a superior result of anti VEGF than PRP in their study group with follow up of 2 years.[11] However, it included PDR eyes with or without macular edema, and intra vitreal Ranibizumab. VA change was studied only. Their 5-year result concludes that both Ranibizumab and PRP show similar VA results at 5 year follow-up with 50% vitreous hemorrhage in either group. Mean injections (19) vs mean 5 PRP sessions in 5 years.[11,12] Present study with short 6 month follow up in comparison was based on results of Bevacizumab on PDR without macular edema showing greater neovascular regression, better BCVA with less VH in PRP group. No complications like lens changes and raised IOP was observed in either group in this study. This is consistent with data from other studies showing no apparent association of IVB and IOP rise, cataract formation or endophthalmitis.[13] Limitations of present study include a short follow-up and only three monthly IVB. Limitation of use of IVB monthly for three months restricts the results in terms of efficacy and maintenance of neo vessel regression phase. Other anti-VEGF like Ranibizumab and Aflibercept were not compared. Long term prospective study is needed to endorse the

maintenance of beneficial effects, ocular and systemic side effects and cost effectiveness.

CONCLUSION

Short term follow up reveal anatomical and functional improvement in both groups with more so in PRP than Bevacizumab group in terms of BCVA, neo-vascular regression and VH. Further studies are recommended to assess the long term efficacy, compliance and safety of both treatment regimens.

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