Original Article

Efficacy Of Intravitreal Bevacizumab in the Treatment of Vitreous Hemorrhage Secondary to Proliferative Diabetic Retinopathy

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ABSTRACT

Objective: To determine the efficacy of intravitreal bevacizumab in the treatment of vitreous hemorrhage secondary to proliferative diabetic retinopathy.

Study Design: Quasi-experimental study.

Place and Duration of Study: The study was conducted at PNS Shifa Hospital, Karachi Pakistan, from Sep 2018 to Feb 2019.

Methodology: The study included 131 patients with proliferative diabetic retinopathy who presented with vitreous hemorrhage. Vitreous hemorrhage was graded into mild-moderate or severe. Patients were randomized into two groups: the bevacizumab group was treated with three intravitreal injections of bevacizumab given on monthly intervals and the control group which was observed. Vitrectomy was performed if the patient had non resolving hemorrhage by four months or developed tractional retinal detachment during study period.

Results: Mean age of patients was 51.8±7.4 and 52.6±6.7 in treatment and control group respectively. Percentage of patients with vision of less than 6/60 in treatment group reduced from (58.7%) at baseline to (33%) at 4 months. Patients with mild to moderate VH who were subjected to intravitreal bevacizumab had significantly less chance of undergoing PPV at 4 months (4.76%) as compared with control group (20%). Improvement in visual acuity was also statistically significant at 4 months (p<0.05).

Conclusion: Intravitreal bevacizumab can be effective in diabetic retinopathy related mild to moderate vitreous hemorrhage in terms of improving the vision, reducing the rate of requirement for vitrectomy and completing panretinal laser photocoagulation.

Keywords: Diabetes, Ranibizumab, Retinopathy, Vitreous hemorrhage.

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INTRODUCTION

The world is changing at a fast pace. Life style changes have increased prevalence of diabetes mellitus. Number of years of life with diabetes mellitus has increased due to awareness of disease, better drugs and monitoring protocols, management of associated renal disease and control of end organ damage. This in turn has increased the probability of developing diabetic retinopathy and complications associated with it. In Pakistan, second national survey on prevalence of blindness in 2004 found that 8.6% of all diabetics were having diabetic retinopathy and blindness associated with it was <0.5%.[1] Shaw *et al* have shown that diabetes mellitus is going to double between 2000 and 2030 in developing countries.[2]

Among diabetic patients, diabetic macular edema is seen more commonly in clinical practice but vitreous hemorrhage and advanced diabetic eye disease frequently end up in severe visual impairment.[3] Panretinal photocoagulation has remained gold standard treatment for many decades. Adverse effects include nyctalopia and loss of peripheral vision which makes it a difficult treatment option in working age group.[4] New treatment protocols were adapted with the advent of anti-vascular endothelial growth factors. Diabetic Retinopathy Clinical Research (DRCR) Network compared PRP with ranibizumab and it found that visual acuity outcomes were not inferior in ranibizumab group compared to PRP at two year follow up.[5] Bivacizumab is a humanized monoclonal antibody against all isoforms of VEGF A. It is approved for treatment of colorectal carcinoma and ophthalmic use is off label. Cost effectiveness is the major advantage compared to other anti VEGF. At present it is commonly used to treat PDR but data on use in vitreous hemorrhage is limited.[3]

This study will assess the effectiveness of intravitreal bevacizumab in vitreous hemorrhage in our local population.

METHODOLOGY

The quasi-experimental study was conducted at

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the PNS Shifa Hospital Karachi between September 2018 and February 2019. The study was approved by the Review Board Committee of the Hospital(ERC/2020/OPH/07)Ethical standards of the Declaration of Helsinki were adhered to. Written informed consent was taken from all the patients before they were included in this study.

Inclusion Criteria: Patients with diabetic proliferative retinopathy who presented with fresh Vitreous Hemorrhage were included.

Exclusion Criteria: Patients with signs of advance diabetic eye disease including Neovessels on iris, neovascular glaucoma, tractional membranes or detachment were excluded. Cases with doubtful etiology of vitreous hemorrhage or cause other than diabetes millitis were excluded.

For the study purpose Vitreous hemorrhage was graded into severe, in which no fundus detail was visible and mild –moderate in which disc and vessels were visible.Follow-up duration of each patient was of 4 months. Baseline vision, intraocular pressure, slit lamp examination and dilated fundus examination was performed at baseline for all the patients. Ultrasound B-scan was performed in all to rule out tractional membranes and detachments. Patients were then randomly divided into two groups. Treatment group (Group-I) was treated with injection bevacizumab 1.25 mg under sterile conditions after proper topical anesthesia.Patients were examined next day and after 1 week for any possible injection related complication. Injectionwas repeated every month for a period of three months and were examined monthly and 1 month after the 3rd injection for final vision and fundoscopy. Observation group (Group-II) was observed closely for spontaneous absorption of vitreous hemorrhage.

Patients in both groups were examined every month for a period of 4 months. At every visit slit lamp examination, tonometery and dilated fundoscopy was performed. Ultrasound B scan was done whenever hazy fundus view made visualizing tractional membranes and detachment difficult.

Patients in both the groups underwent pan retinal photocoagulation (PRP)whenever fundus view was adequate enough for it to be performed.

Pars plana vitrectomy (PPV) was done in patients of both groups whenever there was aggravation of disease condition to advance diabetic eye disease evidence by presence of tractional complexes or detachments either visible on fundoscopy or B-scan ultrasound. Patients with non-resolving vitreous hemorrhageafter 4 months also underwent PPV.

The prime parameters for study were final visual acuity, requirement of PPV, rate of recurrent vitreoushemorrhage during the treatment/study period and rate of completion of 360 degree PRP.Statistical analysis was performed using the Statistical Program for Social Sciences version 22.0software. A student t-test andchi-square were used for statistical analysis. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

One hundred and thirtyone patients were included in this study using consecutive sampling technique. Sixty three patients were randomly assigned to bevacizumab group (treatment group) and sixty eight to observation group (control group) with mean age of 51.8±7.4 yearsand 52.6±6.7 years respectively.There was no statistically significant difference between ages of both the groups. The study outcomes for the two groups are summarized in Table.

Table: Study outcomes in Treatment and Control Groups (n=131)

	Bevacizumab group	Control group	*p*-value
Age	51.8±7.4	52.6±6.7	>0.05
Mild-mod VH	26(41.3%)	33(48.5%)	>0.05
Severe VH	37(58.7%)	35(51.5%)	>0.05
Baseline vision worse than 6/60	37(58.7%)	44(64.7%)	>0.05
Final VA worse than 6/60	21(33%)	40(58.8%)	<0.05
Overall rate of PPV at 3 months	15(23.8%)	25(36.8%)	>0.05
Rate of PPV in mild–mod VH	3(4.76%)	14(20%)	<0.05
Rate of PPV in severe VH	12(19%)	11(16.17%)	>0.05
Recurrence of hemorrhage	20(31.7%)	31(45.6%)	>0.05
Complete PRP	48(76.2%)	40(58.8%)	<0.05

In patients that presented with mild-moderate vitreous hemorrhage at baseline and treated with injection bevacizumab required statistically less pars plana vitrectomy in the follow-up period as compared with the group that was observed ($p<0.05$). However, no such difference was observed between the two groups (treatment vs control) with initially severe vitreous hemorrhage or when all patients of vitreous hemorrhage were considered as a whole ($p>0.05$).

During the 3 months of follow-up, recurrence of vitreous hemorrhage occurred in 20 patients in the bevacizumab group (31.7%) versus 31 patients in the control group 45.6% (p>0.05).

Improvement in visual acuity in treatment group was significant. (58.7%) patients in bevacizumab group had a baseline vision of worse than 6/60 which reduced to (33%) at 3 months. It was as compared to (64.7%) reducing to 58.8% in control group at 3 months (p<0.05).

Patients with vitreous hemorrhage were subject to Pan retinal photocoagulation irrespective of the study group whenever the fundus view allowed this. Bevacizumab injection allowed completion of PRP in statistically significant percentage of patients as compared with observation group. At the end of the follow-up period 48 patients in the ranibizumab group (76.2%) while 40patients in the control group (58.8%) with a (p<0.05) had a complete PRP (Figure).

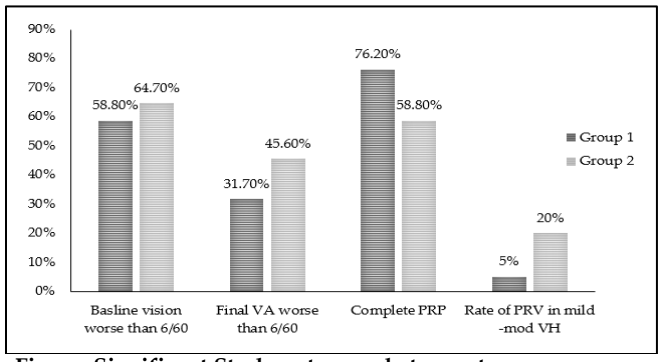

Figure: Significant Study outcomes between two groups(n=131)

DISCUSSION

Vitreous hemorrhage is a common cause of sudden visual loss in patients with diabetic retinopathy. Often a time it's the first presenting symptom. Role of observation, laser photocoagulation and anti VEGF have been studied by many authors. If not treated timely and effectively the affected eye can land up in tractional retinal detachment and advance diabetic eye disease.

PRP is considered the gold standard in cases of PDR and after Effective PRP severe visual loss is encountered in only (40-50%).[6] Intravitreal antiVEGF agents like bevacizumab, ranibizumab, aflibercept have been studied for Diabetic retinopathy in terms of efficacy and cost effectiveness.[7-9] Reviews prove the cost effectiveness of bevacizumab as compared with laser in DME but limited studies are available regarding the comparison of bevacizumab in VH.[10]

After an injection of anti VEGF, leakage from the neovessels stop within 24 hours but Time for neovessels to regress completely following PRP may vary from weeks to months depending upon the severity, duration and efficacy of laser treatment.[11] Anti VEGF followed by prompt or deferred laser has been studied by many authors as well. Presence of VH can prevent the visibility of retina and thus effective laser therapy. Intravitreal anti VEGF after ruling out active traction with the help of ultrasound B scan is the possible treatment in such cases.

Intravitreal bevacizumab in specific and other anti VEGF in general induce neovascular endothelial cell death thereby causing their regression.However mature neovessels may not regress completely or canalize againas anti VEGF effect weins off. Anti VEGF also stabilize the vessels and reduce leakage by induction of pericytes.[12]

On the other hand if these neovessels are not controlled or managed they lead to formation of fibrovascular tractional complexes which pull the retinal leading to traction retinal detachment in (2.2-5.26%) cases as reported in various studies.[13,14] Anti VEGF is contraindicated in present of active fibro vascular traction. Thus an ultrasound B scan is a prerequisite in cases where fundus view is compromised by dense vitreous hemorrhage. Pre op laser PRP may stabilize the retina and is thus helpful in cases of fibrovascular traction needing PPV.[15] Similarly the role of anti VEGF as a pre-op modality few days before PPV may help reduce the vascular component of fibrovascular membranes thus reducing per op bleeding.

Various authors studied various treatment modalities either in isolation or in combination.Abdhish *et al* found that there was short term benefit of anti VEGF interms of visual improvement, completion of PRP and reduced recurrence of vitreous hemorrhage,[16] however long term benefit of anti VEGF on these variables and on lowering the need for vitrectomy cannot be determined.

Various studies showed that anti VEGF injections reduced the rate of vitrectomy required in cases of VH/PDR, however the findings are variable. Jampol *et al.* found that rate of vitrectomy after anti VEGF in patients of VH/PDR was (27.9%) which was quite high as compared to other similar studies.[17] DRCR prptocol S reported this rate to be (4%) while Arevalo *et al.* reported (3.6%).[18] Result of our study is consistent with

these later studies as we report a rate of (4.76%) in mild to moderate VH.

Jaafar *et al* found that PRP is the mainstay of treatment if retinal view allows.[19] In our study we also did laser PRP as soon as retinal view allowed. The anti VEGF injections helped in completion of 360 degree PRP in statistically significant percentage as compared with observation group. Generally laser photocoagulationis possible in superior peripheral retina initially followed by more inferior areas in successive sessions as vitreous hemorrhage resolves and retinal view clears inferiorly. PRP not only converts the ischemic retina into dead retina thereby reducing the VEGF drive for neovascsulization but also helps reduce the number of anti VEGF injections required.[20] However we didn't included this parameter in our study. A complete and effective PRP and absence of neovessels is also a good prognostic factor for good visual recovery aftervitrectomyif required in cases of VH/PDR.[21]

Some authorssuggested the role of combined antivegf and PRP in early resolution of vitreous hemorrhage in patietns of PDR.[22]

We in our study found that the patients with mild to moderate VH required less vitrectomy after anti VEGF injections as compared to observation. There was statistically significant improvement in vision after treatment with a anti VEGF however the reduction of recurrent vitreous hemorrhage was not significant in our study. Anti VEGFalso helped in completion of pan retinal photocoagulation.

CONCLUSION

Intravitreal antivegf injection is an effective treatment modality in cases of VH secondary to PDR not only in achieving good final visual acuity but also in completion of laser PRP and thus reducing the requirement of vitrectomy.

Conflict of interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

OF & BJ: Supervision, Conception, Study design, analysis and Interperitation of data, Critically reviewed manuscript & approval for the final version to be published.

AH & UY: Co-supervision, Data entry, analysis and interpretation, manuscript writing & approval for the final version to be published.

NA & FY: Critically reviewed, Drafted manuscript & approval for the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investi-gated and resolved.

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