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EVALUATE THE EFFICIENCY OF INTRAVITREAL BEVACIZUMAB INJECTIONS IN IMPROVING THE VISUAL ACUITY FOR DIABETIC RETINOPATHY TREATMENT

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Abstract:

Objective: *The purpose of study was to evaluate the efficiency of intravitreal bevacizumab injections in improving the visual acuity for diabetic retinopathy treatment.*

Study Design: *A prospective study.*

Place and Duration: *This study was conducted at District Headquarters Hospital Muzaffarabad for the duration of one year starting from September, 2019 to August, 2020.*

Methodology: *In our study we include 59 diabetic patients who were having diabetic macular edema and fresh vitreous hemorrhage. With a dose of 1.25mg in 0.05ml (at 0month, 1 month, 2 months) each of patients were given three intravitreal bevacizumab injections at the period of 3 months with final follow up. Stabilization was considered if the visual acuity was unchanged relative to the baseline while the criteria for improvement was a gain of at least one line on Snellen's visual acuity chart, compared to the baseline.*

Results: *In our present study 59 patients were included. According to gender distribution, intravitreal injection was given to 34 patients (50.84%) who were females and 25 patients (49.1%) who were male and their age range from 45-67 years. The patients with diabetic macular edema, 26 eyes (44.06%) show improvement while whereas visual acuity was found in 4 eyes (6.7%). Patients with vitreous hemorrhage, visual acuity stabilization were noticed in 2 eyes (3.3%) whereas 27 eyes (45.76%) show improvement. We don't notice any patient with falling of visual acuity.*

Conclusion: *At the end of our study, we conclude that the effective thing for the improvement of visual outcomes in diabetic patients who were having macular edema and vitreous hemorrhage is intravitreal bevacizumab injection.*

Key Words: *Intravitreal, Visual Outcome, Diabetic Retinopathy, Bevacizumab.*

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INTRODUCTION:

As the prevalence of diabetes is increasing in the world, Diabetic retinopathy (DR) is becoming a most important public health problem and threat to sight in the working-age population [1,2]. It is also a major cause of blindness in developing countries. According to the Diabetic Association of Pakistan – World Health Organization (DAP-WHO) survey (1994-1998), overall prevalence of diabetes in Pakistani population is 11.47% [3]. In diabetic retinopathy there are abnormal retinal blood vessels which can be either due to the proliferation of new vessels (proliferative retinopathy) or due to functionally incompetent and leaky vessels. The vascular endothelial growth factor (VEGF) has been suggested as a main factor, firstly in proliferation of new weak vessels which can rupture causing vitreous hemorrhage and resulting in decrease visual acuity, and secondly it causes the breakdown of the blood-retinal barrier causing increased vascular permeability which results in retinal edema by disturbing the endothelial tight junction proteins. This retinal edema in macular area is called diabetic macular edema and when it fulfills a certain-clinical criterion, it is known as clinically significant macular edema [4,5].

Most of the adults became blind due to proliferative diabetic retinopathy (PDR) and principally treated by pars plana vitrectomy and Argon laser but the bleeding from fibrovascular membrane (FVM) is still a risk to be considered. A humanized vascular endothelial growth factor (VEGF) antibody known as Bevacizumab (Avastin Genetech Inc, South San Francisco, California, USA) previously used for metastatic colorectal carcinoma but recent reports have showed its effectiveness in the treatment of neovascular disorder in the eye like proliferative diabetic retinopathy and in diabetic macular edema [6]. Though the normal human retina contains VEGF, its levels are considerably raised in eyes with diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). Therefore, intravitreal anti-VEGF treatments have been recommended as an adjunctive treatment for DME [7]. The drug acts by decreasing the size and number of new vessels and also helps in resolving the vitreous hemorrhage. Currently, some anti-VEGF drugs, including pegaptanib, ranibizumab, bevacizumab, and aflibercept, are available [8]. Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full-length humanized antibody, it binds to and competitively inhibits all isoforms of the VEGF-A family. While bevacizumab is presently FDA approved for the treatment of metastatic colorectal cancer, metastatic breast cancer, and non-small cell lung cancer, it is widely used off-label for treatment of ocular diseases like retinal vein occlusion, neovascular age-related macular degeneration, DME, proliferative diabetic retinopathy, rubeosis irides, and retinopathy of prematurity.

Although intravitreal use of bevacizumab is an off-label option, its use has increased exponentially in the past few years primarily due to its efficacy and cost effectiveness [5]. The purpose of this study was to evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual outcomes (best corrected visual acuity (BCVA)), as measured by Snellen's visual acuity charts, for diabetic retinopathy.

METHODOLOGY:

This prospective study was conducted at District Headquarters Hospital Muzaffarabad for the duration of one year starting from September, 2019 to August, 2020. A total number of 59 eyes of 59 patients were selected on the basis of non-probability, purposive sampling. Inclusion criteria was diabetic patients with vitreous hemorrhage (associated with proliferative diabetic retinopathy) with absence of tractional retinal detachment on B-scan ultrasonography, diabetic macular edema with any stage of non-proliferative diabetic retinopathy and diabetic macular edema with proliferative diabetic retinopathy but without vitreous hemorrhage. Diabetic patients who had received prior treatments with other modalities like laser photocoagulation, intravitreal Ranibizumab, intravitreal or posterior subtenon triamcinolone, patients with anterior segment diseases, diseases affecting the vision like corneal opacity, uveitis, glaucoma, visually significant cataract, etc. due to which exact role of bevacizumab, regarding visual outcome, cannot be assessed.

Patients with other associated posterior segment diseases affecting the vision like age related macular degeneration, central retinal vein occlusion, central retinal artery occlusion, retinal detachment (hematogenous, tractional, serous, all type of), optic nerve disease, etc. and patients who developed any complications of intravitreal Bevacizumab which can affect the visual acuity, were excluded. Pre-operatively visual acuity was measured using Snellen's acuity chart, complete anterior segment and posterior segment examination was done using slit lamp, +90D lens, indirect ophthalmoscopy. Intraocular pressure (IOP) was measured using Goldman applanation tonometer. Fundus Fluorescein Angiography and B-scan ultrasound examinations were done where necessary. The risks and benefits of

treatment were discussed and informed consent was taken.

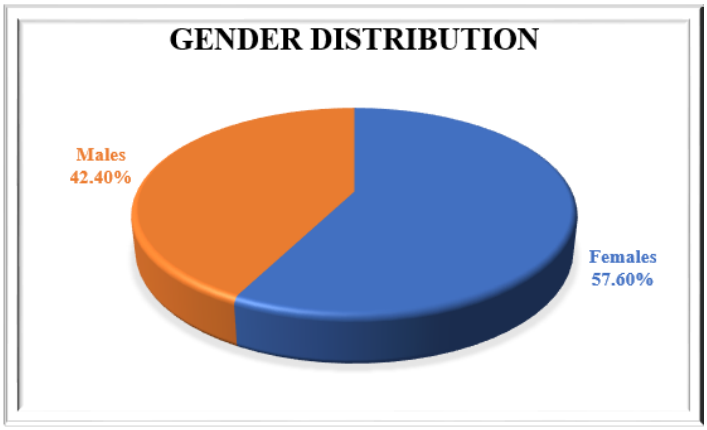
All the patients included in the study received intravitreal bevacizumab with a dose of 1.25mg in 0.05ml and given by the same surgeon. Topical anesthetic proparacaine was given before injection and repeated as necessary. All the injections were given with strict sterile technique (cleaning conjunctival sac with diluted povidone iodine) under full aseptic conditions in operation theatre. Injection was given 4mm, 3.5mm, 3mm posterior to the limbus in phakic, pseudophakia and aphakic eyes respectively through the infero-temporal pars plana with a 30-gauge needle. The injection site was compressed for several seconds to avoid reflux of Avastin when the needle was removed. Patients were advised to use antibiotic and steroid combination eye drops for 07 days after the intravitreal injection. Follow up was scheduled after 1 week, 4 weeks and every month till the end of follow up at 3 months. Follow up visits included checking visual acuity by Snellen's chart and complete ocular examination. At each visit complications like endophthalmitis, vitreous hemorrhage (not present pre-injection, in case of macular edema), traumatic cataract, uveitis, retinal detachment which can affect the visual acuity, were evaluated. The primary end point of the treatment was a change in best corrected visual acuity from baseline over 03 months. The maximum number of injections given was three for each eye and they were given four weeks a part. The criteria for improvement was a gain of at least one line on Snellen's visual acuity chart, compared to the baseline while stabilization was considered if the visual acuity on the Snellen's chart was unchanged relative to the baseline.

RESULTS:

In our present study 59 patients were included. According to gender distribution, intravitreal injection was given to 34 patients (57.6%) who were females and 25 patients (42.4%) who were male and their age range from 45-67 years.

Table No 01: Gender Distribution

Gender	Qty	%age
Females	34	57.6%
Males	25	42.4%
Total	59	100%



The patients with diabetic macular edema, 26 eyes (44.06%) show improvement while whereas visual acuity was found in 4 eyes (6.7%). Patients with vitreous hemorrhage, visual acuity stabilization were noticed in 2 eyes (3.3%) whereas 27 eyes (45.76%) show improvement. We don't notice any patient with falling of visual acuity.

Table No 02: Frequency of DME and Vitreous Hemorrhage

Disease	Qty	%age
DME	30	50.85%
Vitreous Hemorrhage	29	49.15%
Total	59	100%

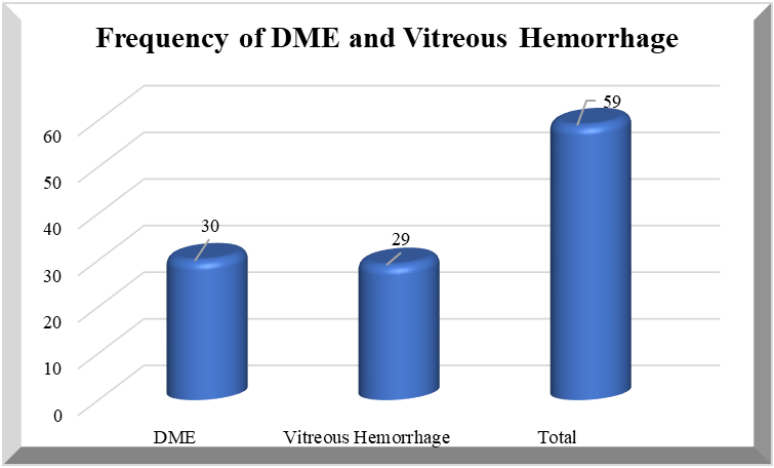


Table No 06: Wilcoxon test:

Mean Acuity Injection Visual Before	Mean Visual Acuity After Injection	P-value
0.921	0.562	0.001

DISCUSSION:

Common causes of visual loss in patients of diabetic retinopathy are macular edema, vitreous hemorrhage and tractional retinal detachment. To evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual acuity measured by Snellen's visual acuity charts for diabetic retinopathy. In patients of diabetic retinopathy, angiogenic mediators such as insulin like growth factor-1, erythropoietin, fibroblast growth factor and endothelial growth factor (VEGF) are released as a result of retinal ischemia and lead to the formation of new vessels in the retina. Vitreous hemorrhage occurs as a result of these neovascular growths and by precluding the retinal view, prevents pan retinal photocoagulation, the gold standard treatment in proliferative diabetic retinopathy. The clinical use of anti-angiogenic agents has developed new opportunities for the treatment of retinal vascular disorders. Considering the antiangiogenic therapy, it accelerates the resolution of hemorrhage and facilitates PRP. So, it's a good choice for patients with vitreous hemorrhage [9].

Diabetic macular edema is the main cause of decreased central vision in patients with diabetic retinopathy. It can be diffuse or localized. Clinically significant macular edema includes retinal thickening within 500 µm of the center of the fovea, hard exudates within 500 µm of the center with associated retinal thickening (which may be outside the 500 µm) and at least one-disc diameter of retinal thickening, any part of which is within one-disc diameter of the center of the fovea [10]. Diagnosis of macular edema is clinical but we also confirmed our diagnosis by fundus fluorescein angiography, the available investigation in our department. Anti-angiogenic agents have been proved to be effective in resolving this macular edema. The agent which we used was Bevacizumab. Bevacizumab was first approved by the US Food and Drug Administration (FDA), for the treatment of carcinomas [11]. Bevacizumab is used as an off-label treatment intravitreally for ocular diseases with high levels of VEGF, such as choroidal neovascularization (CNV), proliferative diabetic retinopathy, diabetic maculopathy and retinal vein occlusion.

VEGF, was first documented in 2013 by Napoleon Ferrara [8]. VEGF inhibition induces several effects

on endothelial cells including inhibition of proliferation. Bevacizumab has been used on "off-label" basis since 2015. It is used as first line treatment in macular degeneration because of its cost effectiveness as compared to other drugs like Lucentis and Macugen (FDA approved anti VEGF) [12,13]. The most common indications of Bevacizumab shown in one paper by Lihteh Wu et al were diabetic retinopathy and CNV of several etiologies [14]. Similarly, in our study, the main indications were diabetic retinopathy, with diabetic macular edema (50.84%) and PDR with vitreous hemorrhage (49.1%). In diseases like diabetic retinopathy, diabetic maculopathy, and retinal vein occlusions, increased levels of VEGF were found in vitreous. Regardless of a large antibody, bevacizumab confirmed full penetration of retina [15]. No evidence of a noxious effect was observed in patients treated with 1.25mg of bevacizumab measured by full field and multifocal ERG [16].

In a prospective study of patients with proliferative diabetic retinopathy treated with intravitreal injections of bevacizumab, a rapid regression of actively leaking neovascularization, as well as significant improvement in mean visual acuity from 20/160 to 20/125 at three months follow up, was found [17]. In our prospective study, out of 59 patients with diabetic macular edema and PDR, 53 patients showed significant improvement (89.8%), however, 6 patients (10.2%), shows no change in BCVA, and there was no patient with worsening of visual acuity. It is comparable to a local study by Jahangir T, et al which also showed significant improvement in visual acuity in patients with diabetic macular edema after intravitreal Avastin [15/18].

In a study by Tareen IFH, the mean BCVA at base line was 0.42±0.14 Log Mar units [16]. This improved to 0.34±0.13, 0.25±0.12, 0.17±0.12 and 0.16±0.14 Log Mar units at 1 month after 1st, 2nd 3rd injections and at final visit at 6 months respectively, a difference that was statistically significant (P>0.0001) from base line. The mean 1mm central macular thickness measurement was 452.9 ± 143.1 µm at base line, improving to 279.8 ± 65.2 µm (P<0.0001) on final visit. In a study of Bahoo MLA, Overall improvement rate was 11 (15.7%) with significant improvement from 1.028 log MAR at baseline to 0.99 at 12 weeks. In a study of Bokhari SA, mean central macular thickness (CMT) reduced from 502µm to 384µm. 18In a study of Shaikh FF, mean central macular thickness was 520.40±139.1 µm at baseline, which decreased to 385.90±98.30 µm (p<0.0001) at one month and to 427.40±112.6 µm (p=<0.0001) at three months [19].

CONCLUSION:

At the end of our study, we conclude that the effective thing for the improvement of visual outcomes in diabetic patients who were having macular edema and vitreous hemorrhage is intravitreal bevacizumab injection.

REFERENCES:

1. Tareen I, Aziz-ur-Rahman, Mahar PS, Memon MS. Primary Effects of Intravitreal Bevacizumab in patients with diabetic macular edema. Pak J Med Sci. 2013; 29(4): 1018–22.
2. Bahoo MLA, Karamat B, Mirza KA, Frooq MU. Effect of intravitreal bevacizumab injection on visual acuity in patients with diabetic retinopathy. Pak J Med Sci 2011;27(5):1063-66.
3. Bokhari SA, Kamil Z, Rizwi F. To compare the effect of intravitreal bevacizumab on the resolution of macular edema secondary to diabetic retinopathy and branch retinal vein occlusion. Pak J Ophthalmol 2012; 28 (2): 117-20
4. Khaled AG, Shala BY. Ocular Complications after intravitreal Bevacizumab (Avastin) in Patients with diabetic retinopathy. Journal of American Science 2012;8(12):111014.
5. Shima C, Sakaguchi H, Gomi F, Kamei M, Ikuno Y. complications in patients after intravitreal injection of bevacizumab. Acta Ophthalmol 2018;86(4):372-76.
6. Sigfourd DK, Reddy S, Mollineaux C, Schaal S. Global reported endophthalmitis risk following intravitreal injections of anti-VEGF: a literature review and analysis. Clin Ophthalmol.2015; 9: 773–81.
7. Khan A, Mahar PS, Hanfi AN, Qidwai U. Ocular complications after intravitreal Bevacizumab injection in eyes with choroidal and retinal neovascularization. Pak J Ophthalmol 2010;26(4): 291-95
8. Falavarjani KG, Nguyen Q D. Adverse events and complications associated with intravitreal injection of anti VEGF agents: a review of literature. Eye 2013; 27(7): 787– 94.
9. Alagoz C, Yildirim Y, Kocamaz M, Baz O, Cicek U. The efficacy of intravitreal Bevacizumab in vitreous hemorrhage of diabetic subjects. Turk J Ophthalmol. 2016; 46(5):221 25.
10. Chun D W, Heier JS, Topping TM. A pilot study of multiple intravitreal injections of Ranibizumab in patients with center involving clinically significant macular edema. Ophthalmology 2006; 113:1706-12.
11. Afaq A, Shahid E, Sharif-ul-Hassan K. Effectiveness of intravitreal Bevacizumab in

various ocular diseases. Pak J Ophthalmol 2013;29(2):578-81
12. Ferrara N, Hillan KJ, Gerber HP, Novothy W. Discovery and development of Bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Disc. 2014; 3: 391-400.
13. Lihteh Wu, María A, Castellanos M, Quiroz-Mercado H. 12-month safety of intravitreal injection of bevacizumab, results of Pan-American Collaborative Retina Study Group (PA CORES). Graefes Arch lin Exp Ophthalmol 2018; 246: 81-87
14. Hames D. Assessing tumor angiogenesis using macromolecular MR imaging contrast media. J Magn Reson Imaging. 2015; 7; 68-74.
15. Shahar J, Avery R L, hell well G. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). Retina 2016; 26: 262-69.
16. Maturi R K, Bleau IA, Wilson DL. Electro physiologic findings after intravitreal bevacizumab (Avastin) treatment. Retina 2016; 26: 270-74.
17. Jorge R, Costa RA, Callucci D. Intravitreal bevacizumab for persistent new vessels in diabetic retinopathy (IBEPPE study). Retina 2016; 26; 1006-13.
18. Jahangir T, Jahangir S, Tayyab H, Hamza U. Visual Outcome after Intravitreal Avastin (Bevacizumab) for Persistent Diabetic Macular Edema. Pak J Ophthalmol 2011; 27; 4;187-90
19. Shaikh FF, Arain A. Effect of intravitreal bevacizumab in diabetic macular edema. Pak J Med Sci 2011; 27(3): 1018-22