ORIGINAL ARTICLE

Outcomes of Intravitreal Bevacizumab for Macular Edema Secondary to Branch Retinal Vein Occlusion

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ABSTRACT

Purpose: To determine the functional and anatomical outcome of intravitreal Bevacizumab in patients with macular edema secondary to branch retinal vein occlusion.

Study Design: Quasi Experimental study.

Place and Duration of Study: Institute of Ophthalmology, King Edward Medical University/Mayo hospital Lahore, from February 2016 to December 2018.

Material and Methods: Forty eyes of 40 patients with macular edema on OCT (macular thickness > 300 µm) secondary to BRVO were included in the study. All the patients suffering from other types of macular edema caused by diabetes, epi-retinal membrane (ERM), surgery involving posterior segment, vitreoretinal traction and history of intravitreal VEGF or steroids were excluded from the study. Intravitreal Bevacizumab was given when macular thickness was > 300 µm or Visual acuity was < 6/12. Follow-up was at 1st, 3rd, 6th and 12th month.

Results: The mean age of the patients was 52.12 ± 5.63 years. Male to female ratio was 1.5:1. Infero-temporal venous arcade was the most common site of BRVO (55%) followed by supero-temporal (35%) and macular BRVO (10%). Baseline visual acuity was 6/12 or better in 17.5% of the patients at presentation. This proportion increased to 27.5%, 40%, 52.5% and 67.5% at 1, 3, 6 and 12 months respectively. Macular thickness measured at presentation was 540 ± 120 µm. Macular thickness gradually reduced on follow-up. At one month mean macular thickness was 430 ± 90 µm. It was less than 300 µm after 6 months.

Conclusion: Intravitreal bevacizumab results in improved functional and anatomical outcomes in cases of macular edema secondary to BRVO.

Key Words: Bevacizumab, retinal vein occlusion, branch retinal vein occlusion, vascular endothelial growth factor, macular edema.

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INTRODUCTION

Among the vascular diseases of retina, branch retinal vein occlusion (BRVO) is the most common disease after diabetic retinopathy[1,2]. Several factors have been associated with pathogenesis of BRVO. These include hypertension, diabetes mellitus, age, open angle glaucoma, hyperlipidemia, alcohol and increased alpha2 globulin[3-5]. The possible mechanism of its progress is occlusion of vein leading to stasis of blood. This is turn leads to wide spread retinal hemorrhages along the distribution of involved branch retinal vein.

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Resulting hypoxia leads to production of vascular endothelial growth factor (VEGF). VEGF causes proliferation of abnormal new vessels, which are leaky and have increased permeability. This ultimately leads to swelling of the macula, termed as macular edema[6].

Macular edema (ME) occurs due to accumulation of extracellular fluid within the retina because of break down in blood retinal barrier[7]. Fluid accumulates primarily in the outer plexiform and inner nuclear layers[8,9].

There have been several therapeutic modalities for the treatment of macular edema secondary to BRVO, which include both interventional and pharmacological therapies. The earliest of all interventional procedures was laser photocoagulation[10-11]. Among pharmacological therapies, people have been using topical non-steroidal anti-inflammatory drugs, oral acetazolamide, corticosteroids, sub-tenon steroid and intravitreal injections to treat macular edema[12]. Intravitreal dexamethasone was initially used to reduce inflammatory cytokines in addition to stabilizing vascular membranes[13]. Later, intra-vitreal triamcinolone was used[14]. Latest modality is anti-VEGF treatment that inhibits growth of new vessels offering a better era of treatment of macular edema in BRVO[15]. These anti-VEGF includes Aflibercept, Ranibizumab[16], Bevacizumab[17] and Pegaptanib[18]. Bevacizumab is used off label but is the most commonly used due to its low cost[19].

The purpose of our study was to see the improvement in visual acuity (as per Snellen chart) and anatomy of macula (macular thickness on OCT) after the use of intravitreal anti- vascular endothelial growth factor (Anti-VEGF).

MATERIAL AND METHODS

Single arm, single centre, open-label, prospective Quasi-experimental study was conducted at the Institute of Ophthalmology, King Edward Medical University/Mayo hospital Lahore. Patients with macular edema secondary to BRVO were diagnosed on fundus examination and confirmed on OCT (macular thickness > 300 μm). Treatment regimen was on as needed basis. All the patients suffering from other diseases leading to macular edema like diabetic retinopathy, epi-retinal membrane (ERM), any history of surgery involving posterior segment, vitreoretinal traction and any history of intravitreal VEGF or steroids were excluded from the study.

Applying inclusion and exclusion criteria, 40 eyes of 40 patients with a diagnosis of macular edema due to BRVO were included. Participants of the study were informed about the details of study and an institutional permission of ethical board was taken. All the participants were examined by a single observer in order to reduce bias. Complete examination of anterior and posterior segment was done. Visual acuity was recorded using Snellen's visual acuity chart. OCT macula was done to measure macular thickness. Intravitreal injection of bevacizumab 1.25mg /0.05ml was given in operation theatre taking aseptic measures. Decision of second injection was based on macular thickness on OCT (> 300 μm) and visual acuity (< 6/12). Patients were followed up at 1 month, 3 months, 6 months and after 12 months. On each follow-up, visual acuity was measured with Snellen chart and OCT macula was done. Collected data was analyzed using SPSS 20.

RESULTS

Mean age of the patients was 52.12 ± 5.63 years. Hypertension was found in 60% (24 patients) patients, Ischemic heart disease in 10% (4 patients), Diabetes in 15% (6 patients), Cerebrovascular accidents were found to be in 2.5% of the patients, while hematological disorders were present in 7.5% (3 patients). All these factors were compared with outcome using chi-square test. It was found that none of them was associated with outcome *(p-value was more than 0.05)*. This showed that outcome of macular edema was independent of these factors.

At presentation VA of 6/9 to 6/12 was found in 7 patients, 6/18 – 6/24 in 12 patients, 6/36 – 6/60 in 14 patients and Counting finger or worse in 7 patients. Number of patients presenting with supero-temporal

Table1: *Number of injections per patient.*

No. of Patients	No of Injections Given	Percentage
2	1	5%
5	2	12.5%
6	3	15%
12	4	30%
15	5 – 7	37.5%
40		100%

BRVO were 14. Twenty-four patients had infero-temporal BRVO while 4 had macular BRVO. Visual acuity improved to 6/6 in 60% cases, 6/9 – 6/12 in 7.5% cases, 6/18 – 6/24 in 20% cases and 6/36 – 6/60 in 12.8% cases in 12 months. Further details of improvement in visual acuity are shown in table 2. Efficacy of this treatment was found significant functionally by applying paired sample t-test. P-value was less than 0.005. This proves the functional outcome of intravitreal bevacizumab (Table 3). The mean central retinal thickness at presentation was 540 ± 120 that reduced to 430 ± 90 at 1 month, 360 ± 110 at 3 months, 270 ± 60 at 6 months and 210 ± 40 at 1 year. (Table 4, Figure 1).

Table 2: *Functional Improvement after injection.*

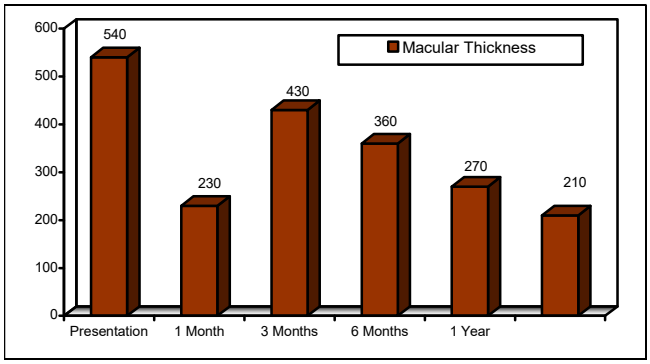
Visual Acuity	No of Patients Improved after Therapy			
	After 1 Month	After 3 Months	After 6 Months	After 12 Months
6/6	0	1	6	24
6/9 to 6/12	11	16	21	3
6/18 to 6/24	16	14	9	8
6/36 to 6/60	13	9	4	5

Table 3: *Statistical significance of visual improvement.*

Variables	p-value
VA at Presentation and VA at 12 months	0.000
VA at presentation & VA at 1 month	0.000
VA at 3 Months & VA at 6 months	0.000
VA at 6 Months & VA at 12 months	0.000

Table 4: *Anatomical improvement after injection.*

Duration (Follow-up)	Central Macular Thickness (µm)
Basal thickness at presentation	540 ± 120
1 Month	430 ± 90
3 Month	360 ± 110
6 Month	270 ± 60
12 Month	210 ± 40



Graph 1: Macular thickness at different times after injection.

DISCUSSION

Our study demonstrates the safety and beneficial outcomes of bevacizumab in terms of improvement in visual acuity (VA) and decrease in macular thickness, in patients with macular edema secondary to BRVO. In this prospective study baseline visual acuity was 6/12 or better in 17.5% of the patients. After 1 month, 27.5% of the patients had VA of 6/12 or better. Trend towards further improvement in VA was seen on successive follow-ups. The BERVOLT study showed significant improvement in visual acuity and decrease in Central Macular Thickness with no adverse events with intravitreal Bevacizumab in macular edema due to BRVO[20]. In a local, single center study done by Azhar et al, baseline macular thickness was 358 ± 36 µm. At one month, 2 months and 3 months macular thickness reduced to 326 ± 34 µm, 295 ± 34 µm and 252 ± 12 µm respectively. The macular thickness was below 300 µm, as early as 2 months after intravitreal bevacizumab. In this study regimen was three consecutive injection of bevacizumab at one monthly interval[21]. In our study higher baseline macular thickness was noted and macular thickness was below 300 µm after approximately 6 month follow up. This is in accordance with a study done by Kondo M., et al[22]. They showed that macular thickness decreased significantly from 523 to 305 µm during the 12-month follow-up period. Maximum number of intravitreal bevacizumab injections given to a single patient were 07[24]. In our study 95% of the patients required more than one injection of bevacizumab.

This study is limited to single center. Prospective multi center trials are needed to highlight the safety and effectiveness of this treatment modality.

CONCLUSION

Intravitreal bevacizumab is a safe treatment modality. It can be used for treatment of macular edema secondary to BRVO. It results in improvement in visual acuity and also helps in the return of macular thickness over time to normal.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board.

Conflict of Interest

Authors declared no conflict of interest.

Authors' Designation and Contribution

Nasir Ahmad Chaudhry; Professor: *Supervisor of this project, study design, final manuscript review.*

Sarmad Zahoor; Medical Officer: *Data Collection and analysis, Statistical work.*

Usama Iqbal; Post Graduate Resident: *Manuscript writing and final review*

Muhammad Owais Sharif; Senior Registrar: *Data Collection, Article review.*

Muhammad Sharjeel; Assistant Professor: D*ata collection and compiling, final review, Discussion writing.*

Asima Rafique; Post Graduate Resident: *Data Collection, Manuscript writing, final review*

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