Original Article

Effect of Intravitreal Bevacizumab in Macular Edema Caused by Branch Retinal Vein Occlusion

Imran Ahmad, Mubashir Rehman, Mir Ali Shah, Irfan Aslam Khattak

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See end of article for authors affiliations

Correspondence to:
Mubashir Rehman
MBBS, FCPS, Assistant Professor, Department of Ophthalmology, Nowshera Medical College/Qazi Hussain Ahmad Medical Complex, Nowshera.
Email: drmubashirrehman78@gmail.com

Purpose: To evaluate the effect of intra-vitreal bevacizumab in macular edema caused by branch retinal vein occlusion.

Study Design: Interrupted time series study.

Place and Duration of Study: Department of Ophthalmology Hayatabad Medical Complex, Peshawar and department of Ophthalmology Lady Reading Hospital Peshawar from 1st July 2016 to 31st December 2016.

Material and Methods: There were 60 patients included in the study. All patients with macular edema due to BRVO visible clinically and evident on SD-OCT and visual acuity of less than 6/9 were included in the study. Patients who used other intra-vitreal drug for macular edema, those with surgery in the same eye and those with macular laser for macular edema were excluded from the study. All patients were given intra-vitreal 0.05 ml bevacizumab injection every month for 6 months. After 6 months OCT was repeated. At each monthly visit VA was measured and fundoscopy was done. Follow up of all patients was at six months.

Results: Our study included 60 patients with mean age of 54.42 ± 9.19 years. The mean baseline central macular thickness was 427.06 µ with SD ± 63.54 µ. After 6 months significant improvement in visual acuity was documented. Also marked reduction in central macular thickness was noted after six months with mean of 327.44 µ with SD ± 55.55 µ.

Conclusion: Intra-vitreal bevacizumab is an effective treatment for macular edema caused by BRVO in terms of both anatomic and visual improvement.

Key words: Branch retinal vein occlusion, bevacizumab, macular edema.

Branch retinal vein occlusion is not an uncommon condition that occurs in patients with underlying systemic illness like arteriosclerosis and hypertension. It is the second most common cause of macular edema after diabetes[1]. BRVO is caused by focal occlusion of a retinal vein usually at an arteriovenous crossing, where, mostly, the artery is passing superficial to the vein[2]. Narrowing of vascular lumen results in alteration in laminar blood flow and endothelial damage. The prevalence of BRVO is 4.42 per 1,000 and accounts for about 80% of retinal venous occlusions[3].

The main cause of visual impairment in BRVO is macular edema[4]. The exact pathogenesis of macular edema in patients with BRVO is not clearly understood, but multiple factors are supposed to be responsible for this, including increased hydrostatic venous pressure, abnormalities in endothelium tight junction, increased concentration of inflammatory cytokines, and vascular permeability factors[5]. Different studies have shown that in eyes with BRVO there is a significantly elevated level of vascular endothelial growth factor (VEGF) which is considered to be the major contributor to macular edema. The severity of macular edema in BRVO is directly related with an increase in VEGF levels[6]. On the basis of these findings, inhibition of VEGF is considered to be a more scientific approach in treating patients with macular edema due to BRVO.

Bevacizumab (Avastin, Genentech; Roche, Basil, Switzerland) is a full-length, humanized, recombinant antibody that binds to all isoforms of VEGF-A and has been used extensively off-label to treat macular edema associated with BRVO. Different studies have shown that intra-vitreal bevacizumab reduces macular thickness and improves visual acuity in BRVO[7,8].

Literature search has demonstrated the efficacy of ranibizumab on macular edema due to BRVO but very limited data is available for bevacizumab. Purpose of our study was to find out the efficacy of bevacizumab in the treatment of macular edema caused by BRVO.

MATERIAL AND METHODS

A total of sixty patients were included in our study. All the patients were screened following the inclusion criteria which included macular edema due to BRVO visible clinically through indirect ophthalmoscopy through slit lamp and 78 D lens, macular edema of more than 250 µ measured on Spectral domain optical coherence tomography and visual acuity of less than 6/9 on Snellen visual acuity chart. Patients who had previous history of other intra-vitreal drug injection for macular edema, those with history of surgery in the same eye, history of scatter or macular laser for edema and patients with other macular diseases like age related macular degeneration were excluded from the study. All the patients underwent detailed ocular examination including visual acuity, anterior segment examination, dilated fundus examination and measurement of intra ocular pressure. SD-OCT was performed at baseline to measure the amount of macular edema and fundus fluorescein angiography was performed to check the macular perfusion.

All the patients were given intravitreal 0.05 ml (1.25 mg) bevacizumab injection using 30 gauge needle in the operation theater under sterile conditions using topical anesthesia. Povidone-iodine 5% solution was used to clean the periocular region. Injections were given monthly for the first 6 months. After 6 months OCT was repeated to check for macular thickness, if macular thickness was more than 250 µ, the injections were continued. At each monthly visit VA was measured and fundoscopy was done. All

patients were followed for at least six months.

Effectiveness was determined in terms of improvement in visual acuity of at least two lines on Snellen visual acuity chart from baseline visual acuity and decrease in macular thickness on SD-OCT of 200 microns from baseline macular thickness after 6 months.

Data analysis was done using SPSS version 20.0. Quantitative variables include age, central macular thickness and visual acuity; and qualitative variables include gender. Mean ± standard deviation was calculated for quantitative variables; percentage and proportion was calculated for qualitative variables.

RESULTS

A total of sixty patients were included in our study with age ranges from 42 years to 78 years with mean age of 54.42 ± 9.19 years. Table 1 shows age distribution of patients.

Table 1: Age Distribution.

Age	Frequency	Percentage
41 – 50 Years	12	20.00%
51 – 60 Years	22	36.67%
61 – 70 Years	18	30.00%
71 – 80 Years	8	13.33%
Total	60	100%

Mean age was 54.42 years with SD ± 9.19

Gender distribution among patients was analyzed as 38 (63.33%) patients were male while 22 (36.67%) patients were female.

All the patients received intravitreal injections of 0.05ml (1.25 mg) of bevacizumab monthly injections. Table 2 and table 3 shows baseline visual acuity and central macular thickness respectively.

Table 2: Base Line VA (n = 60 eyes).

Base line VA	Frequency	Percentage
< 6/36	4	6.66
6/36 – 6/18	31	51.67%
6/24 – 6/12	13	21.67%
6/18 – 6/9	12	20.00%
Total	60	100%

Table 3: Base Line OCT (n = 60 eyes).

Base Line OCT	Frequency	Total
> 500 µ	6	10.00%
400 – 500 µ	32	53.34%
300 – 400 µ	18	30.00%
200 – 300 µ	4	6.66%
Total	60	100%

Mean baseline OCT was 427.06 µ with SD ± 63.54µ

After 6 months significant improvement in visual acuity was documented (table 4). Similarly central macular thickness also reduced (table 5).

Table 4: VA at 6 months (n = 60 eyes).

VA at 6 Months	Frequency	Total
< 6/36	2	3.34%
6/36 – 6/18	10	16.66%
6/18 – 6/12	16	26.66%
6/12 – 6/9	32	53.34%
Total	60	100%

Table 5: OCT at 6 Months (n = 60 eyes).

OCT at 6 Months	Frequency	Total
>500 µ	2	3.33%
400 – 500 µ	12	20.00%
300 – 400 µ	38	63.33%
200 – 300 µ	8	13.34%
Total	60	100%

Mean OCT 6 months was 327.44µ with SD ± 55.55µ

Efficacy of intra-vitreal bevacizumab in causing improvement in VA was analyzed as bevacizumab was effective in 49 (81.67%) patients and efficacy of intra-vitreal bevacizumab in causing reduction in macular thickness was analyzed as bevacizumab was effective in 42 (70.00%) patients (table 6 and table 7).

Table 6: Efficacy Regarding VA (n = 60 eyes).

Efficacy	Frequency	Percentage
Yes	49	81.67%
No	11	18.33%
Total	60	100%

The mean number of intra-vitreal injections required per 6 months were 3.87 ± 0.54 whereas the re-

treatment rate of intravitreal bevacizumab after first 3 injections was 24.6%.

Table 7: Efficacy Regarding OCT (n = 60 eyes).

Efficacy	Frequency	Percentage
Yes	42	70.00%
No	18	30.00%
Total	60	100%

DISCUSSION

Different studies have reported that repeated intra-vitreal anti-vascular endothelial growth factor treatments are associated with significant improvements at six months, and no significant safety concerns relating to the drug were identified in this time. Our study also showed that the first intra-vitreal injection of bevacizumab was associated with significant improvement visually and anatomically. The mean improvement was 0.24 after first injection with a further improvement of 0.30 after 6 months. In the Branch retinal vein occlusion (BRVO) study, six monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab provided rapid anatomic and visual improvements in patients with BRVO[9,10]. Ranibizumab or bevacizumab for macular edema secondary to BRVO may have similar efficacy for improving the VA.

Branch retinal vein occlusion is associated with decreased perfusion of retinal cells resulting in hypoxia. This hypoxia causes increased release of VEGF, which increases vascular permeability resulting in vascular leakage. Intra-vitreal bevacizumab is a vascular endothelial growth factor inhibitor which causes a rapid improvement in macular edema but repeated injections are usually required to maintain this effect[11,12]. The transient nature of the effect of bevacizumab may be explained by the short intra-vitreal half-life of 1.25 mg (approximately 3 days), resulting in a rapid reduction in the intra-ocular concentration of the drug[11]. Several studies have suggested that in ischemic BRVO the amount of non-perfused areas are associated with the severity of macular edema. Noma et al. reported in their study that there is a positive correlation between the amount of macular edema measured on OCT and non-perfused area size[13,14]. Significant improvements in macular edema secondary to BRVO have been reported after intra-vitreal bevacizumab injections[15]. Bevacizumab may not require monthly injections to gain an optimal therapeutic response. An early report of intra-vitreal anti-VEGF agents in animal models suggested that bevacizumab has a longer intra-vitreal half-life than ranibizumab. In rabbits, the vitreous half-life of ranibizumab is 2.88 days while it is 4.32 days for bevacizumab[16,17]. Although there is no clinical evidence that patients receiving bevacizumab for retinal disease require less frequent injections than patients receiving ranibizumab, Epstein and coworkers[23] achieved the same visual improvement in response to intra-vitreal bevacizumab injections administered every 6 weeks for central retinal vein occlusion as that obtained after ranibizumab administered every 4 weeks in the treatment of macular edema after central retinal vein occlusion[18-20].

CONCLUSION

Intra-vitreal bevacizumab is an effective treatment for macular edema caused by BRVO in terms of both anatomic and visual improvement.

Author's Affiliations

Dr. Imran Ahmad
MBBS, FICO, FCPS,
Assistant Professor, Department of Ophthalmology, Gajju Khan Medical College/Bacha Khan Medical Complex, Swabi.

Dr. Mubashir Rehman
MBBS, FCPS.
Assistant Professor, department of Ophthalmology, Nowshera Medical College/Qazi Hussain Ahmad Medical Complex, Nowshera.

Prof. Mir Ali Shah
MBBS, FCPS.
Associate Professor, department of Ophthalmology, Postgraduate Medical Institute, Lady Reading Hospital Peshawar.

Dr. Irfan Aslam Khattak
MBBS, FCPS.
Vitreo-retina Trainee, Department of Ophthalmology, Hayat Abad Medical Complex, Peshawar.

Author's contribution

Dr. Imran Ahmad
Patient's selection, Data collection, results and discussion

Dr. Mubashir Rehman
Patient's selection, Data collection, results and discussion

Prof.Mir Ali Shah
Patient's selection, Data collection, results and discussion

Dr. Irfan Aslam Khattak
Literature search

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