

Intravitreal Bevacizumab (IVB) for Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO)

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ABSTRACT

Objective: To evaluate the effectiveness of intravitreal Bevacizumab in decreasing central macular thickness in branch retinal vein occlusion (BRVO) related macular edema.

Study Design: Quasi experimental study.

Place and Duration of Study: Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi, Pakistan, from March to August 2017.

Methodology: Intravitreal Bevacizumab (1.25 mg/0.05 ml) was given in inferotemporal quadrant under aseptic conditions on monthly basis for consecutive three months. Post-injection, all the patients were followed up on monthly basis for consecutive three months. CMT (in μm) was measured by using OCT at baseline and after intravitreal Bevacizumab injections at one month, two months, and finally at three months.

Results: Forty eyes of forty patients were included in the study. There were 25 (62.5%) male patients and 15 (37.5%) female patients. Baseline mean CMT \pm SD was $358 \pm 36 \mu\text{m}$ before IVB injection. Mean CMT was $252 \pm 12 \mu\text{m}$ at 3 months (after three IVB injections). At three months, mean percentage decrease in CMT was 29.60%.

Conclusion: Intravitreal Bevacizumab is effective and results in decrease in central macular thickness to normal or near-normal levels in branch retinal vein occlusion (BRVO) related macular edema.

Key Words: Branch retinal vein occlusion (BRVO), Central macular thickness (CMT), Ocular coherence tomography (OCT), Intravitreal Bevacizumab (IVB), Fluorescein angiography (FA), Intraocular pressure (IOP).

INTRODUCTION

Branch retinal vein occlusion (BRVO) is frequent, and remains the second most common sight-threatening retinal vascular disorder with prevalence of 4.42 per 1000 adults.^{1,2} In addition to age, systemic hypertension and the retinal arteriolar changes are associated with it, including arteriovenous nicking and retinal arteriolar narrowing, are well-established risk factors for BRVO. Other cardiovascular risk factors, such as diabetes, smoking, hyperlipidemia, atrial fibrillation, renal dysfunction, and atherosclerosis have also been associated with an increased risk of BRVO.³ The pathologic interruption of venous flow in these eyes almost always occurs at a retinal arteriovenous intersection, where a retinal artery crosses over a retinal vein. BRVO subtyped as a major BRVO where one of the four major branch retinal veins is affected or macular BRVO where only a smaller, macular vein is occluded. The most common location for BRVOs is in the superotemporal quadrant, which is due to larger number of arteriovenous crossings in the superotemporal quadrant.⁴ The common vision-limiting complications of

BRVO are macular edema, macular ischemia and sequelae of neovascularisation.⁵ Macular edema is the main cause of decreased visual acuity in BRVO.^{5,2} Retinal ischemia after vascular occlusion can cause vascular endothelial growth factor (VEGF) elevation and increased VEGF results in higher vascular permeability & associated macular edema in patients with BRVO.^{6,7} Bevacizumab, a full-length recombinant monoclonal antibody against human VEGF, is used off-label and can effectively lower intraocular level of VEGF and reduce vascular permeability in BRVO-related macular edema.⁷⁻⁹

Optical coherence tomography (OCT) is the most important imaging modality in the treatment of patients with BRVO and macular edema. OCT offers a noninvasive and rapid method of quantitatively measuring macular edema and its response to treatment.¹⁰ The characteristic findings on OCT scans are cystic spaces representing macular edema, hyperreflectivity from haemorrhages or exudates, shadowing from haemorrhages, and in chronic cases, photoreceptor ellipsoid zone and external limiting membrane abnormalities from longstanding macular ischemia, and macula edema may also be seen.¹¹

The objective of this study was to determine the anatomic outcomes following intravitreal Bevacizumab for macular edema due to BRVO.

METHODOLOGY

This quasi experimental study was conducted at Vitreoretina Department of Armed Forces Institute of

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Ophthalmology (AFIO), Rawalpindi for the duration of 6 months from March 01, 2017 to August 31, 2017. Non-probability consecutive sampling was used. Forty eyes of forty patients were included in the study. Patients of both genders, 50 to 70 years of age, pseudophakic and phakic, having visual acuity equal or less than 6/18 measured by Snellen's acuity chart were included. Exclusion criteria were any retinal pathology other than macular edema secondary to BRVO, previously treated patients for BRVO related macular edema, any significant media opacity, history of ocular trauma, patients unable to come for follow-up, patients with ocular inflammation, patients allergic to fluorescein and a history of vitrectomy.

After taking written informed consent and approval from hospital Ethical Committee, a predesigned proforma was used for documentation of data containing information like name, age, gender and study variable central macular thickness (CMT; in μm).

Slitlamp with superfield lens, fluorescein angiography (FA) and OCT were used to diagnose BRVO related macular edema. After explaining injection related risks and benefits to the patients; eye was draped, a sterile eyelid speculum was applied and conjunctival sac was instilled with 5% povidone iodine after topical anaesthesia. Intravitreal Bevacizumab (1.25 mg/0.05 ml) was given through pars plana in the inferotemporal quadrant; 3.5 mm from limbus in pseudophakic and 4.0 mm from limbus in phakic patients under aseptic conditions in the operation theater under operating microscope; a sterile cotton bud was placed at injection site for conjunctival displacement and to prevent reflux of drug or vitreous. After the injection, patients were instructed to take ciprofloxacin 500 mg BD PO for 3 days and ciprofloxacin 0.3% eye drops QID for five days. Intravitreal Bevacizumab (IVB) was given on monthly basis for consecutive three months. Post-injection, all the patients were followed up on monthly basis for consecutive three months. CMT (in μm) was measured by using OCT at baseline and after injecting intravitreal Bevacizumab at one month, two months and finally at three months.

Data analysed by SPSS version 20. Quantitative data presented in the form of mean \pm SD like CMT (in μm). The qualitative variables were presented as frequencies along with percentages. The formula " $X1 - X2 / X1 \times 100$ " was used to calculate mean percentage decrease in central macular thickness, where X1 is mean central macular thickness at baseline, X2 is mean central macular thickness at 3 months.

RESULTS

There were 25 (62.5%) male patients and 15 (37.5%) female patients. In age distribution, age ranges from 50 - 70 years.

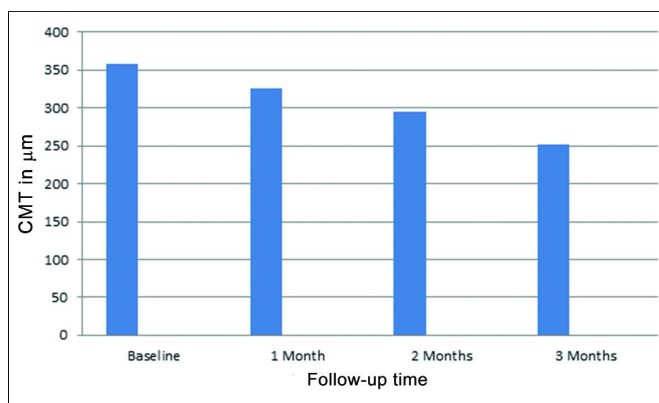


Figure 1: Mean CMT in μm measured by OCT.

Table I: Mean percentage decrease in CMT at 3 months.

Mean CMT (μm)	Mean percentage decrease in CMT $X1-X2/X1 \times 100$
Baseline (X1) 358	358-252/358 \times 100 = 29.60%
At 3 months (X2) 252	

CMT: central macular thickness, μm : micron meter.

Baseline mean CMT \pm SD was 358 \pm 36 μm (before IVB injection). At one month mean CMT \pm SD was 326 \pm 34 μm (after one IVB injection). Mean CMT \pm SD was 295 \pm 34 μm at 2 months (after two IVB injections). Mean CMT \pm SD was 252 \pm 12 μm at 3 months (after three IVB injections), (Figure 1).

At three months Mean percentage decrease in CMT was calculated, i.e 29.60% (Table I). Out of 40, two eyes (5%) had increased IOP which were controlled by topical IOP lowering medications, three eyes (7.5%) had sub-conj haemorrhage and no case of endophthalmitis was reported.

In this study all patients received three injections of intravitreal Bevacizumab (IVB), each injection 1 month apart and all the patients were followed up on monthly basis for 3 months. Mean CMT \pm SD decreased from 358 \pm 36 μm at baseline to 252 \pm 12 μm at 3 months. Mean percentage decrease in CMT was 29.60% at 3 months (after three IVB injections).

DISCUSSION

BRVO is a common cause of retinal vascular disease in the elderly; and occurs most frequently between the ages of 60 to 70 years.¹² Pathologic interruption of venous flow in these eyes almost always occurs at a retinal arteriovenous intersection, where a retinal artery crosses over a retinal vein. The lumen of the vein may be compressed up to 33% at a normal arteriovenous crossing site, and this may be further exacerbated by increased rigidity and thickening of the arterial wall due to arteriosclerosis. The location of the venous blockage determines the distribution of the intraretinal haemorrhage; venous blockage can be at the optic nerve head or peripheral to the disc.^{12,13} Macular grid

laser photocoagulation was the standard of care for macular edema in perfused BRVO, according to results of the Branch Vein Occlusion Study. However, the visual improvement following macular laser was limited. In patients with BRVO, retinal ischemia related complications are retinal and iris neovascularisation, vitreous haemorrhage, traction retinal detachment, and neovascular glaucoma.¹⁴

Anti-VEGF intraocular injection has been shown to be a new promising treatment modality, which results in noticeable functional and anatomical improvement. Intravitreal Bevacizumab is employed to lower the intraocular VEGF level, which resulted in effectively reducing BRVO-related macular edema.^{15,16}

The BERVOLT study showed significant improvement in visual acuity and decrease in CMT with no adverse events with intravitreal Bevacizumab (IVB) in macular edema due to BRVO.¹⁷ The Pan-American Collaborative Retina Study Group treated 63 BRVO related macular edema patients with intravitreal Bevacizumab in PRN regimen. The 2-year results demonstrated that Bevacizumab 1.25 mg injection resulted in a gain of 3.8 lines. Decreased macular thickness was found, without accompanying serious ocular and systemic adverse events.¹⁸ Ahn *et al.* treated 69 eyes with three loading injections on monthly interval and then PRN for 3 months with IVB injections; and 26 eyes with three monthly PRN injections. The 6-month results revealed functional and anatomical improvement in both groups, and there was no significant difference between two groups in CMT and final visual acuity. Injection number was far less in PRN only regimen (mean 1.8) than in three-loading and PRN group (mean 3.4).¹⁹ Pai *et al.* treated 12 patients of BRVO related macular edema. All patients were followed for duration of three months after only one IVB injection (1.25 mg). In his study, CMT decreased to 320 μm at last visit from baseline 647 μm .²⁰

In current study, intravitreal Bevacizumab was injected as primary treatment for macular edema secondary to BRVO for consecutive three months, on the basis of monthly interval and showed reduction in CMT. The response for improvement and recurrence depends on degree of macular ischemia, amount of retinal haemorrhages, extend of irreversible photoreceptor damage, and progression over time from perfused to nonperfused BRVO. Previously reported studies showed that IVB injection was safe and well tolerated.^{21,22} No endophthalmitis, retinal detachment, significant worsening of cataract, were noted in any of our 120 injections. The most common adverse effect was local hyperemia or subconjunctival haemorrhage at the site of injection. No systemic adverse events were noted. Limitations of this study are relatively short-term follow-up, small sample size, and lack of a control group.

In this study, mean baseline CMT was 358 \pm 36 μm , which decreased to 252 \pm 12 μm after three IVB injections at 3 months, that is comparable with results obtained by Noritatsu *et al.*²¹ in which they studied intravitreal Bevacizumab injection in 20 eyes of 20 patients with retinal vein occlusions and found CMT decreased after repeated injections from mean of 560 \pm 125 μm at baseline to 391 \pm 145 μm at 6 months.

The present results showed that intravitreal Bevacizumab is effective in decreasing BRVO-related macular edema and resulted in reduction in CMT. In this study, all patients received three IVB injections on the basis of monthly interval, and results showed that mean percentage decrease in CMT was 29.60% at 3 months, that is comparable to mean percentage decrease in CMT, *i.e.* 30.17% in older studies.^{21,22}

CONCLUSION

Intravitreal Bevacizumab is effective and results in decrease in central macular thickness to normal or near-normal levels in BRVO-related macular edema.

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