Original Article



# A Prospective Study on Efficacy of Bevacizumab for Retinal Vein Occlusion

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## ABSTRACT

**Objective:** To evaluate the efficacy of intravitreal Bevacizumab for branch retinal vein occlusion and central retinal vein occlusion.

**Study Design:** A prospective, non-randomized interventional trial.

**Place and Duration of Study:** This study was conducted at the Eye Department, Multan Medical and Dental College in collaboration with Bodla Eye Care, Multan from June 2014 till May 2016.

**Materials and Methods:** This study was conducted on patients who presented with central or branch retinal vein occlusion. They had intravitreal bevacizumab in operating room settings.

**Results:** A total of 43 patients were recruited in the study starting from June 2014 till May 2016. 21 were diagnosed to have Branch Retinal Vein Occlusion BRVO and 22 had Central Retinal Vein Occlusion CRVO. Drop outs (lost to follow up) were excluded from the study. Patients were followed for twelve months. By the end BRVO patients improved a mean of 9.7 ($p<0.05$) ETDRS letters, while CRVO improved by a mean of 1.6 letters ($p=0.50$). The percentage of patients who lost >15 ETDRS letters were 45.4%. in CRVO group, while 9.5% in BRVO group, A reduction of mean central macular thickness was noted in both groups over a period of twelve months. In CRVO group mean reduction was 231 microns ($p<0.001$) in CRVO and 214 microns ($p<0.001$) in BRVO group. However it was noticed that anatomical reduction in foveal thickness did not translated into improvement in visual acuity.

**Conclusion:** Our study looked at the effect of Bevacizumab in clinical practice on retinal vein occlusion. There was significant improvement in BRVO group in terms of visual acuity as well as reduction in CMT central macular thickness. In CRVO group, however Bevacizumab failed to show any significant improvement in terms of improvement in visual acuity despite of clinically significant reduction in macular thickness.


**Key Words:** Central Retinal Vein Occlusion, Branch Retinal Vein Occlusion, Bevacizumab.

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## INTRODUCTION

Retinal vein occlusion, as the name applies results from occlusion of one of the main retinal vein tributaries resulting in central or branch retinal vein occlusion. [1,2] Changes in retinal blood flow leads to exudations resulting in macular oedema. [2,3] This can lead to a significant reduction in visual acuity, providing that macula gets involved. [4] Central retinal vein occlusion CRVO carries a relatively guarded prognosis. [2,5] It is not uncommon to develop further complications as rubeotic glaucoma from the primary pathology. [1,3] Visual acuity seldom improves following treatment in CRVO. Contrary to this, BRVO carries relatively promising prognosis with treatment. [5,6]There has been several case reports of spontaneous improvement of visual acuity in BRVO. [6]

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The primary challenge in the pathology is management of macular oedema. For a long time, macular grid laser was the main stay of treatment in BRVO while no options were there for CRVO. [7]Studies revealed that vascular endothelial growth factors were found to be markedly increased in patients who had retinal vein occlusion. [1,7]With the availability of commercially produced Anti vascular endothelial growth factor Anti-VEGF as Bevacizumab and Ranibizumab the scenario appears to have changed altogether with Anti-VEGF as the main stay for treatment. [2,6] There has been two large randomized, multicentre studies CRUISE and BRAVO carried out in last few years and have found Ranibizumab as beneficial for the treatment of retinal vein occlusions. [1,4,8] Since Ranibizumab cannot be the drug of choice in underprivileged, developed part of the world as South Punjab, authors decided to look into effects of Bevacizumab, Anti-VEGF on retinal vein occlusion. Bevacizumab is widely available at a fraction of cost in our part of the world. We designed a non randomized trial with prospective data collection looking into efficacy of Bevacizumab. Patients were recruited from two sites i.e. Multan Medical and Dental College and Bodla Eye Care, Multan, both tertiary eye care facilities in private sector.

## MATERIALS AND METHODS

Patients were recruited for a period of two years starting from June 2014 till May 2016. Patients who lost to follow up were excluded from the study data base. Exclusion criterias included diabetics with macular oedema, patients with apparent vitreomacular tractions, patients who had triamcinolone intravitreally or any who underwent cataract surgery during follow up. Patients had a detailed informed consent at the time of recruitment. They underwent a comprehensive ophthalmic assessment. Visual acuity was noted on ETDRS charts. Patients had a slit lamp assessment of anterior and posterior segment. Intraocular pressures were measured using Goldmann applanation tonometry. Patients underwent optical coherence tomography on Zeiss Stratus OCT machine. Hemiretinal vein occlusion was taken as a branch retinal vein occlusion.

All patients with macular oedema and reduced visual acuity had intravitreal bevacizumab. Bevacizumab was initiated as three serial injection four to five weeks apart. Patients had a detailed ophthalmic assessment with repeat OCT, four weeks following their third injection. Decision of further injections were made if macular oedema was still present in the form of cysts, intraretinal fluid. Reasons for discontinuation were unchanged or worsening of visual acuity as well as refractory macular oedema as confirmed on OCT scan. Panretinal photocoagulation was reserved only for those patients who had confirmed development of neovascularization.

All patients had the standard dose of bevacizumab (1.25 mg/0.05 mL) provided by a single local supplier. Source of injections were certified compounding pharmacies based in Lahore. All injections were administered under the sterile conditions in operating theatre. Surgeon used mask, sterile gloves ,theatre gowns and had surgical scrub prior to the procedure. Patients had topical anaesthetic drops (Alcaine manufactured by Alcon) preoperatively for local anaesthesia. Injections were administered using standard prefilled insulin syringes with 30 gauge needles on them. Prefilled syringes however, as provided by the local supplier were non sterile as is the common practice in our country. All patients had a thorough cleaning of periocular tissue and lids using 5-10% povidone iodine. Same drops were instilled in the eyes to be operated for two to three minutes in order to achieve the maximum possible sterility.Patients had a self-adhesive surgical drape covering periocular tissue, nose and part of face prior to the procedure. Patients had a sterile speculum inserted followed by the intravitreal injection. Injections were performed in the inferotemporalquadrant . Needle was inserted 3.5mm from the limbus for phakic and 3.5mm for pseudophakic and aphakic patients. Following the procedure, speculum was removed and patients had a single drop of ofloxacin eye drops combined with a single drop of povidone iodine solution. All patients had a sterile eye pad and were instructed to remove it 2-3 hours post procedure. No topical antibiotics were used preoperatively. All patients were prescribed with topical ofloxacin eye drops. Clear written instructions in native language were provided to them for the use of topical antibiotic drops to be used four times a day for five days in the operated eye, starting on the same day following eye pad removal.

A paired students t-test was used to analyze the data collected. Best corrected visual acuity and central retinal thickness was analyzed from day of presentation till end of study. A p value of less than 0.005 was considered to be significant.

## RESULTS

A total of 43 patients were included in the study since they met all the inclusion criterias. Nine patients were excluded with diabetic macular oedema as the primary reason. Two patients had vitreomacular traction and one had intravitreal triamcinolone. All patients included in the study were followed for a period of one year. Mean age (years) in the BRVO group was 66 and in CRVO group was 72. 20 were male while 23 patients were females. Mean duration of symptoms were 2 months for BRVO and 3 months for CRVO group. Mean intraocular pressure at the time of recruitment was 15 mm of Hg for BRVO and 19mm of Hg for CRVO group. Coming to best corrected visual acuity mean number of ETDRS letters for BRVO group was 54.1 and 46.7 for the CRVO group.Mean central macular thickness for BRVO group was 521 um and 529 um for CRVO group.

Analysis of treatment outcome revealed BRVO patients improved a mean of 9.1 letters at four and 9.7 ($p<0.05$) ETDRS letters at twelve months, while CRVO improved by a mean of 1.1 letters at four and 1.6 letters ($p=0.50$) by twelve months. Ten out of twenty two , 45.5% patients in CRVO group lost their vision from baseline. Such a percentage was not observed in the BRVO group i.e. 9.5%.

Evaluation of central macular thickness revealed a reduction of mean central macular thickness in both groups over a period of twelve months. In CRVO group mean reduction was 211 um at four months and 231 microns ($p<0.001$) in twelve months. In BRVO central macular thickness reduced by 196 um in four and upto 214 microns ($p<0.001$) in twelve months. Comparing the anatomical success with functional improvement it was obvious the functionality in terms of best corrected visual acuity BCVA did not get translated nor was proportional to reduction in central macular thickness.

## DISCUSSION

CRUISE and BRAVO studies were the bench mark in designing and conducting this particular study. [1,4] As

mentioned authors were interested in looking at the effect of Bevacizumab as compared to Ranibizumab on retinal vein occlusion for specific reasons. Ranibizumab simply cannot be the drug of choice in our part of the world due to financial constrains. Our results from BRVO group were in comparison to BRAVO study, while CRVO group performed below expectations in comparison with CRUISE study. This can be argued upon since we used Bevacizumab instead of Ranibizumab, however Brynskov et al have reported findings similar to us in their study on retinal vein occlusion. Reduction in central macular thickness CMT was significant in both groups with use of Bevacizumab but the improvement in macular thickness was not in proportion to improvement in visual acuity.

We believe there can be more than one reason in having results contrary to CRUISE study. We used Bevacizumab instead of Ranibizumab. Their inclusion criteria did not included patients with BCVA above 70 ETDRS letters, apparently a group with lesser potential to improve. [9,10]Moreover patients with visual acuity worse tan 6/60 were also excluded from the study and these carry a limited chance to improve by 15 ETDRS letters due to intensified pathology. [11] Moreover our exclusion criteria did not included the pupillary response as is the case in the study performed by Brynskov et al. Patients with relative afferent papillary defect are likely to have ischemic central retinal vein occlusion and carry minimal chance to improve. [12,13] Since the criteria were not in place, and it is not possible to quantify the response, our study had different results. In our study flourescien angiography was not the part of necessary assessments; hence it was not possible to quantify the level of ischemia. [15] Being a rural community with majority of patients presenting late, it can be hypothesized that severity of disease in our cohort was worse than what clinicians commonly come across in the west. The other main difference lied in the intervention. We went for a series of three injections followed by a minimal period of eight weeks without any intervention, again model followed by Brynskov et al. Contrary to this in CRUISE and BRAVO, six consecutive injections were administered a month apart followed by further intervention on as required bases. [16,17] Since we administered three injections only, this could have led to recurrence of macular oedema. Authors believe that above mentioned differences satisfy the contrary results we had from CRUISE study. [18] Authors are of the view that inclusion and exclusion criteria's were designed keeping in view the local pathology and logistics of the management patterns in rural Punjab.

Our results failed to show any significant improvement in terms of BCVA in our CRVO group. This is disappointing but characterizes the severity of disease in our cohort. Our patients in this group had a mean age above seventy years. Moreover visual acuity at time of presentation was lower than the BRVO group. This also signifies the possibility of co morbidities as hypertension, hypercholesterolemia and diabetes in our cohort. [19,20]

In the BRVO group how ever there was a significant improvement in best corrected visual acuity following bevacizumab injections. [4,6] These patients presented with a better BBCVA and a 15 letter or more improvement was identified on ETDRS scale. These findings correlate to what was found in the BRAVO study. [21]

Our patients had a mean 6.7 injections during the twelve months study. This number is less than documented in other trials. [22] Authors subjective assessment could have influenced the results especially in CRVO group.

Looking at the complications, none of our patients encountered endophthalmitis, vitreous haemorrhage or retinal detatchment. Two patients developed uveitis following the injections and were treated with topical steroids and cycloplegics. None of the patients developed any thromboembolic episode during the study. [23] Our safety levels were found to be at par with the west.

Main limitation of the study is sample size. Moreover fundus flourescien angiography which was omitted due to lack of resources and logistics would had provided a detailed assessment of level of retinal ischemia. This could have made easier differentiating ischemic from non ischemic retinal vein occlusion. [24] This study confirms the efficacy of Bevacizumab for use in retinal vein occlusion in our rural South Punjab settings. Authors believe that Bevacizumab is a safe and effective substitute for Ranibizumab to be used in economically deprived parts of the world as ours. Authors recommend further studies on the pattern of BRAVO and CRUISE trial using Bevacizumab to further confirm its efficacy.

# CONCLUSION

Our study looked at the effect of Bevacizumab in clinical practice on retinal vein occlusion. There was significant improvement in BRVO group in terms of visual acuity as well as reduction in CMT central macular thickness. In CRVO group, however Bevacizumab failed to show any significant improvement in terms of improvement in visual acuity despite of clinically significant reduction in macular thickness.

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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