

## Efficacy of Intravitreal Bevacizumab in Treatment of Macular Edema Secondary to Retinal Vein Occlusion

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### Abstract

**Purpose:** To study the effect of intravitreal injection of bevacizumab on central macular thickness in retinal vein occlusion patients at a tertiary care centre of North India. **Material and methods:** A retrospective, data based study was carried out on 89 patients of acute retinal vein occlusion, including 35 cases of CRVO and 54 cases of BRVO, presented to our OPD over a period of 10 years. All cases included in this study received intravitreal injection of bevacizumab (2.5mg/0.1ml) at presentation and were followed up every month post-injection to record any change in BCVA and CMT. **Results:** The mean age of patients in BRVO and CRVO group was 56.81±7.02 and 57.02±7.8 years. Mean CMT at baseline was 449.16±121.28 µm in BRVO group which significantly reduced to 304.84±78.14 µm at 1 month post-injection follow up visit. In CRVO group, mean CMT at baseline was 680.17±175.12 µm which significantly reduced to 399.97±88.43 µm at 1 month post injection. Mean BCVA in BRVO group at baseline was 0.96±0.36 LogMAR which got significantly improved to 0.65±0.24 LogMAR at 1<sup>st</sup> month post-injection while in CRVO group, mean BCVA at baseline was 1.59±0.48 LogMAR which got significantly improved to 1.02±0.34 LogMAR at 1<sup>st</sup> month post-injection. **Conclusion:** Intravitreal bevacizumab is beneficial in the improvement of BCVA and treatment of macular edema due to venous occlusion. However, any beneficial effect on visual acuity and reduction of macular edema on OCT seen initially starts weaning off after 2 months and gradually reaching to baseline value at 6 months.

**Keywords:** Bevacizumab, Retinal vein occlusion, Macular edema, VEGF, Intravitreal injection.

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## INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder, after diabetic retinopathy and leads to sudden painless loss of vision. Branch retinal vein occlusion (BRVO) is the most common among all retinal vein occlusions and is three times more common than Central Retinal Vein Occlusion (CRVO) [1]. BRVO involving a single vein is the most common type having a prevalence of 0.6-1.1%, while CRVO has a prevalence of 0.1-0.4% [2, 3].

RVO can be classified as central, hemi and branch RVO depending on the site of occlusion. Central RVO is an obstruction that occurs within the central retinal vein, which is the sole venous drainage source of the retina. Hemi RVO involves the anterior trunk of central retinal vein and BRVO is a venous occlusion that occurs at any of the branches of the central retinal vein [1].

Advancing age is an important risk factor for RVO. Various ocular, cardiovascular, coagulation disorders including thrombophilia and systemic conditions are known to predispose to the development of RVO. Raised intraocular pressure (IOP) and associated glaucoma may predispose to CRVO because of the increased ocular pressure leading to venous stasis in blood flow but are not considered as important risk factors for BRVO [1]. Major risk factors for RVO include hypertension (HTN), diabetes mellitus (DM), hyperlipidaemias, pregnancy, oral contraceptives and inherited thrombophilia [4-7].

Cystoid macular edema is a common sight-threatening complication of retinal venous occlusion. The pathogenesis of macular edema is complex and there are multiple factors contributing to it which include increased hydrostatic venous pressure, endothelial dysfunction, inflammation and increase in

vascular permeability growth factors like VEGF (Vascular endothelial growth factor).

Different pharmacological regimes have been introduced for the treatment of ME found in association with RVO which include intravitreal injection of VEGF inhibitors such as ranibizumab, bevacizumab or aflibercept and corticosteroids including dexamethasone [13, 14]. There is increasing evidence that intravitreal injection of bevacizumab can lead to significant reduction of ME. Bevacizumab (Avastin, Genentech; Roche, Basel, Switzerland) is a full-length, humanized, recombinant antibody that binds all isoforms of VEGF-A and has been used extensively off-label to treat macular edema associated with BRVO and CRVO. Several studies have shown that intravitreal bevacizumab injection improves visual acuity and reduces macular thickness in macular edema associated with BRVO and CRVO [8-10]. However, treatment success is often temporary, and in some patient's bevacizumab therapy is not effective, despite multiple intravitreal injections. It is still unclear whether there are any prognostic factors that can predict the success of bevacizumab therapy in venous occlusion patients.

Therefore, this retrospective study was conducted to determine the efficacy of intravitreal injection of bevacizumab in patients with BRVO and CRVO and study the improvement in BCVA and reduction in CMT in these patients after intravitreal injection of bevacizumab at monthly follow up visits till 6 months.

## MATERIAL & METHODS

A retrospective, data based study was carried out in 89 patients of RVO, comprising of 35 cases of CRVO and 54 cases of BRVO, presented to our OPD over a period of 10 years after taking clearance from Institutional Ethics Committee, RIO PGIMS Rohtak.

### Inclusion criteria

89 patients diagnosed with acute retinal vein occlusion of <12 week duration, were included in this study with best-corrected visual acuity in affected eye < 6/12 (0.3 logMAR) on Snellen's acuity chart and central macular sub-field thickness > 350  $\mu$ m on Spectral Domain Optical Coherence Tomography.

### Exclusion criteria

- Patients with coexisting diabetic retinopathy
- Patients with history of open angle glaucoma
- Patients with history of being a steroid responder in the past
- Patients with a history of an incisional glaucoma surgery
- Patients with poor optical media in whom good quality OCT images (Signal Strength Index, SSI  $\geq$  40) were not obtained

- Patients who had undergone cataract surgery in the last three months
- Patients with a history of complicated cataract surgery (posterior capsular rent)
- Patients who had undergone vitreoretinal surgery in the past
- Patients with active or healed uveitis
- Patients who underwent panretinal photocoagulation or macular laser photocoagulation were also excluded

Each patient's detailed history of onset, duration of symptoms and complete systemic medical history related to the disease was recorded. Ocular history including history of glaucoma, trauma, inflammation, any intraocular surgery including cataract surgery and intravitreal drug therapy in the past was recorded from the data available.

In every patient, unaided and BCVA using Snellen's chart had been recorded at every visit and a detailed anterior segment examination was carried out using slit lamp. IOP had been measured in both the eyes using Goldman applanation tonometer (GAT). After dilation of the pupil, the lens status was determined and a detailed fundus examination had been performed in every patient. SD-OCT scan had been performed to assess the macular thickness and to screen the patients for any pre-existing vitreoretinal interface abnormalities. OCT machine (RTVue, model- RT100 of OPTOVUE Inc. FREMONT, CALIFORNIA), software version 5.0 was used for imaging. The MM6 macular scan protocol, composing of six linear scans in a spoke pattern configuration, equally spaced 30 degrees apart, centred at fovea was used. Retinal thickness was measured using the location of the vitreo-retinal interface and retinal pigment epithelium defining the inner and outer boundaries of retina, respectively.

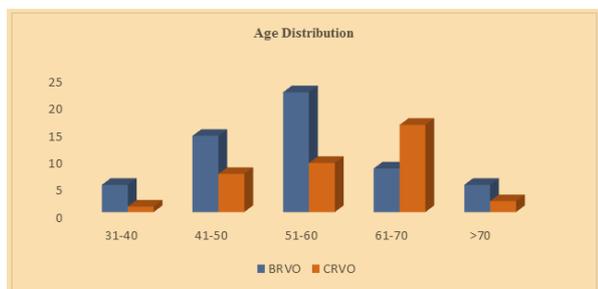
All cases included in the study received intravitreal injection of bevacizumab (2.5 mg/0.1ml) in an operation theatre under strict asepsis after taking informed written consent, with special note to its off-label use. All the patients had been followed up on the first day and after that every month for any evidence of intraocular inflammation and a change in BCVA, CMT and IOP. Any associated systemic co-morbidity had been managed with the help of a physician.

All the data was recorded, compiled and tabulated in Microsoft excel spread sheet. For statistical analysis, CRVO and BRVO were strictly separated. Statistical analysis of data was done with SPSS (Statistical Package for Social Sciences) version 21.0.

## RESULTS

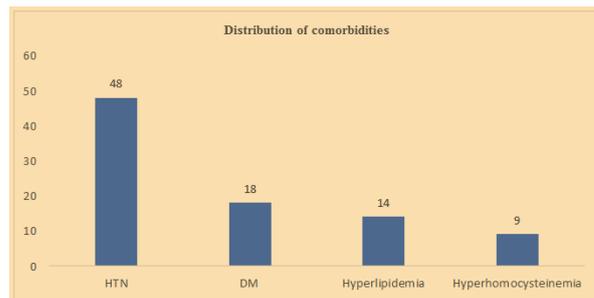
A retrospective study was carried out in 89 patients of RVO presenting to our OPD over a period of

five years. In this study, the mean age of patients in BRVO group was 56.81±7.02 years while in CRVO group; it was 57.02±7.8 years with M: F ratio of 1.7:1 and 1.5:1 in BRVO and CRVO group respectively. Maximum number of patients was of 51-60 age group in BRVO group while in CRVO group, majority of patients belonged to 61-70 years age group (Figure 1).



**Fig-1: Age distribution in BRVO & CRVO groups**

The most common co-morbidity in retinal venous occlusion patients was found to be hypertension in 53.93% patients while diabetes mellitus, hyperlipidaemia and hyperhomocysteinemia were present in 20.22%, 15.73% and 10.12% of the patients respectively (Fig. 2).

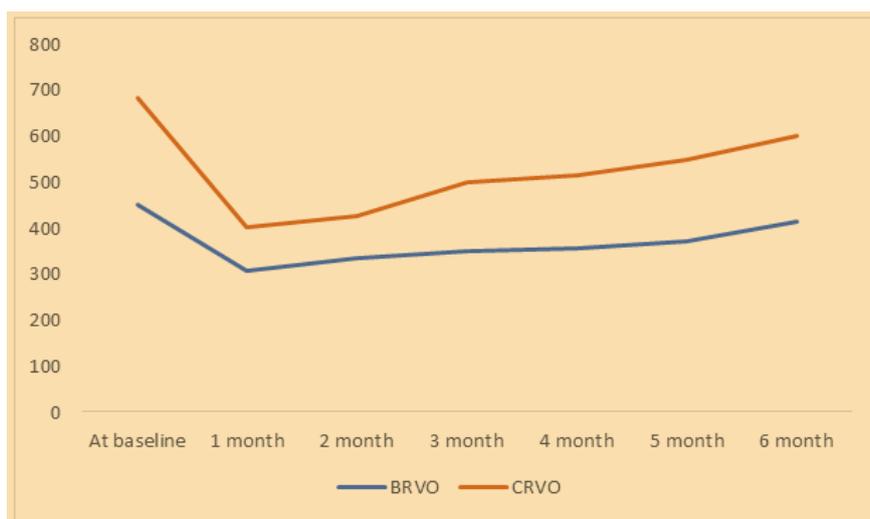


**Fig-2: Distribution of comorbidities in RVO patients**

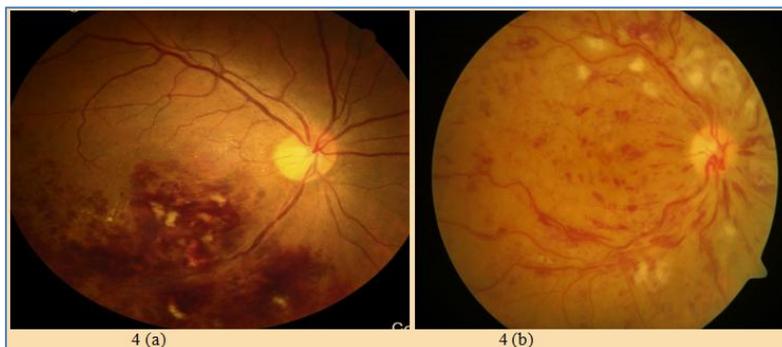
Mean CMT at baseline was 449.16±121.28 μm in BRVO group which significantly reduced to 304.84±78.14 μm at 1 month post-injection follow up visit. On monthly follow up visit, CMT gradually increased and reaching to near baseline value on 6 month follow up visit. In CRVO group, mean CMT at baseline was 680.17±175.12 μm which was significantly higher than BRVO group and it got significantly reduced to 399.97±88.43 μm at 1 month post injection. Similar to BRVO group patients, CMT gradually increased on monthly follow up visits and reaching to near baseline value on 6 month follow up visit.

**Table-1: Mean CMT of study groups at different post injection follow up visits**

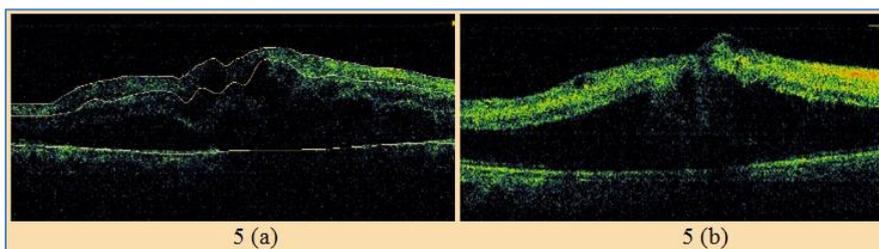
|                      | BRVO           | CRVO          |
|----------------------|----------------|---------------|
| Mean CMT at baseline | 449.16±121.28  | 680.17±175.12 |
| Mean CMT at 1 month  | 304.84±78.14   | 399.97±88.43  |
| Mean CMT at 2 month  | 333.03±80.28   | 424.54±111.78 |
| Mean CMT at 3 month  | 349.01±91.36   | 498.97±145.21 |
| Mean CMT at 4 month  | 356.924±101.38 | 514.88±160.68 |
| Mean CMT at 5 month  | 371.62±111.17  | 546.67±160.28 |
| Mean CMT at 6 month  | 413.07±119.42  | 598.24±174.11 |



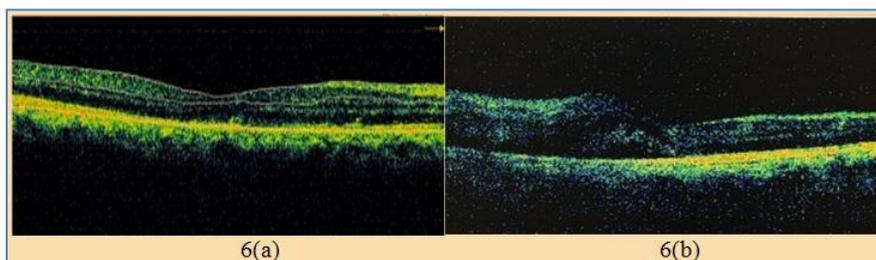
**Fig-3: Mean CMT at monthly follow up visits in BRVO and CRVO group**



**Fig-4: (a) R/E fundus photo showing IT-BRVO with macular edema. (b) R/E fundus photo showing ischemic CRVO with macular edema**



**Fig-5: (a) OCT R/E showing spongiform macular edema with CMT 380 micron at resensation in IT-BRVO case (b) OCT R/E showing cystoid macular edema with CMT 503 micron at presentation in CRVO case**



**Fig-6: (a)OCT R/E post intravitreal injection avastin at 1 month follow up visit showing significant reduction in macular edema with CMT 256 micron in IT-BRVO case (b): OCT R/E post intravitreal injection avastin at 1 month follow up visit showing reduction in macular edema with NSD with CMT 340 micron in CRVO case**

Mean BCVA in BRVO group at baseline was 0.96+0.36 LogMAR which got significantly improved to 0.65 +0.24 LogMAR at 1<sup>st</sup> month post-injection while in CRVO group, mean BCVA at baseline was 1.59+0.48 LogMAR which got significantly improved to 1.02+0.34 LogMAR at 1<sup>st</sup> month post-injection. However, this effect gradually vanished in both study groups on monthly follow up visits and reached to near baseline value on 6 month post injection follow up visit.

**Table-2: Mean VA (LogMAR) of study groups at different post injection follow up visits**

|                     | BRVO | CRVO |
|---------------------|------|------|
| Mean VA at baseline | 0.96 | 1.59 |
| Mean VA at 1 month  | 0.65 | 1.02 |
| Mean VA at 2 month  | 0.67 | 1.10 |
| Mean VA at 3 month  | 0.70 | 1.14 |
| Mean VA at 4 month  | 0.76 | 1.19 |
| Mean VA at 5 month  | 0.80 | 1.40 |
| Mean VA at 6 month  | 0.88 | 1.48 |



**Fig-7: Mean VA (LogMAR) in BRVO and CRVO patients at monthly post injection follow ups**

No intraocular or systemic adverse effects were reported in our study during 6 months of follow-up such as increased intraocular pressure (IOP), retinal tear, retinal detachment, induced cataract formation, inflammation, infection, and systemic hypertension or thromboembolic events and hence IVA seems to be safe and effective in treatment of RVOs.

## DISCUSSION

In this study, the mean age of patients in BRVO group was 56.81±7.02 years while in CRVO group, it was 57.02±7.8 years. M:F ratio was 1.7:1 in BRVO group while 1.5:1 in CRVO group. Maximum number of patients was of 51-60 age group in BRVO group while in CRVO group, majority of patients belonged to 61-70 years age groups, which was similar to the results of the study conducted by Baptiste *et al.* [8] and Kuppermann *et al.* [9].

In our study, the most common co-morbidity in retinal venous occlusion patients was found to be hypertension in 53.93% patients while diabetes mellitus, hyperlipidaemia and hyperhomocysteinemia were present in 20.22%, 15.73% and 10.12% of the patients respectively. This was similar to the results of Moisseiev *et al.* [10] and Baptiste *et al.* [8] where hypertension was found in 64.7% and 55.4% patients respectively.

In our study, mean CMT at baseline was 449.16±121.28 µm in BRVO group which significantly reduced to 304.84±78.14 µm at 1 month post-injection follow up visit. In CRVO group, mean CMT at baseline was 680.17± 175.12 µm which was significantly higher than BRVO group and it got significantly reduced to 399.97±88.43 µm at 1 month post injection. On monthly follow up visit, CMT gradually increased and reaching to near baseline value on 6 month follow up visit. Mean BCVA in BRVO group at baseline was 0.96±0.36 LogMAR which got significantly improved to 0.65 ±0.24 LogMAR at 1<sup>st</sup> month post-injection while in CRVO group, mean BCVA at baseline was 1.59±0.48 LogMAR which got significantly improved to 1.02±0.34 LogMAR at 1<sup>st</sup> month post-injection.

These results are in accordance with the results of study conducted by Shaaban *et al.* in 30 eyes of 30 patients with recent retinal venous occlusion of less than 3 months duration. 12 eyes (40%) of patients with central retinal vein occlusion (CRVO) and 18 eyes (60%) with branch retinal vein occlusion (BRVO) were injected with intravitreal bevacizumab 1.25 mg (0.05 ml) of commercially available bevacizumab [Avastin; Genentech, Inc., San Francisco, CA] at a concentration of 25 mg/ml as a primary treatment. The mean baseline CRT was 455 µm ± 126 (range, 386–510), decreased to 356 µm ± 118 (range, 296–416) after 1 month with statistically significance difference change ( $P < 0.02$ ) and to 402 µm ± 170 (range, 338–468) after 6 months ( $P < 0.067$ ). However this effect starts weaning off after 6 weeks and require repeat intravitreal injection [11]. Similar results were produced by Pikkil J *et al.* in their retrospective study of 68 patients treated by intravitreal bevacizumab (Avastin) injections for macular edema due to CRVO. Mean visual acuity improved more for patients treated by a

protocol of 3 prescheduled injections than for those treated with one primary injection. Improvement in mean visual acuity was greater for patients who received their first injection within the first month than those treated after 3 months [12]. Similar results were produced by Kornhauser T *et al.* [13], Jaissle B *et al.* [14] and Mehany S *et al.* [15] in their respective studies.

In a study done by Stahl *et al.*, mean VA from all 21 patients increased by more than 2 lines (2.4±0.4 lines;  $p < 0.01$  compared to baseline). The improvement of VA after bevacizumab injection was concordant with a decrease in central retinal thickness. Peak VA was reached between 3 and 6 weeks after injection. Between week 6 and 9 a decrease in VA was observed. This VA decrease was precipitated by an increase in CME between week 3 and 6. In subgroup analyses, patients receiving bevacizumab injection within the first 3 months after RVO showed an average VA gain of 4 lines (range 2–7 lines) compared to an average gain of 1.8 (range 1–3) and 2.5 (range 1–7) in patients receiving bevacizumab between 4–6 months and after more than 6 months, respectively [16].

A study done on persistent ME due to RVO on sixty-one patients with a minimum follow-up of 25 weeks were included in this analysis and mean follow-up was 60 ± 29 wks. In CRVO patients, central retinal thickness (CRT) decreased from 748 ± 265 µm to 372 ± 224 µm ( $p < 0.001$ ) and visual acuity (VA) improved by 1.9 +/- 3.2 lines. In BRVO patients, mean CRT decreased from 601 ± 206 µm to 386 ± 178 µm ( $p < 0.001$ ) and VA improved by 1.8 ± 2.6 lines. Thirty-three percent of CRVO and 15% of BRVO patients did not show a ME recurrence for > or =25 wks at last visit. Thirty-seven percent of CRVO and 50% of BRVO patients suffered recurrences of ME within the last 25 wks, whereas 30% of CRVO and 35% of BRVO patients did not achieve a complete resolution of ME at any follow-up visit after receiving a minimum of three injections. CRVO patients with dry interval of > or =25 weeks at last visit were significantly younger, had a thinner CRT at baseline and more often had a complete resolution of ME after the first injection. In CRVO and BRVO, final VA was correlated significantly with initial VA, patients' age and final CRT. Change of VA was correlated with change of CRT in BRVO [17].

In a study done on 25 eyes with macular oedema caused by non-ischaemic central retinal vein occlusion, Mean visual acuity improved significantly from 0.97 +/- 0.40 logMAR at baseline to 0.70 ± 0.42 logMAR ( $P = 0.007$ ) at 1 month after intravitreal bevacizumab, 0.69 ± 0.46 ( $p = 0.006$ ) 3 months and 0.69 ± 0.52 ( $p = 0.015$ ) 6 months after the first injection. Mean central retinal thickness decreased significantly from 530 ± 152 µm at baseline to 347 ± 127 µm ( $p < 0.001$ ) at 1 month, 370 ± 165 µm ( $p < 0.001$ ) 3 months and 346 ± 129 µm ( $P < 0.001$ ) 6 months ( $P < 0.001$ )

after the first injection. The increase in visual acuity correlated significantly ( $P < 0.01$ ) with the decrease in macular thickness [18].

## CONCLUSION

Intravitreal injection bevacizumab is an effective, safe and despicable option in treatment of macular edema secondary to retinal venous occlusion and especially in a developing country like India where affordability is a major concern; it should be given as an alternate option in such cases.

### Limitations of the study

Patients may not be able to seek medical attention due to limited access to the health care. Therefore, it was possible that a selection bias existed among patients who were included in the study. Centration of macular scans of fovea involving pathology in patients with poor vision was difficult. Other limitations are relatively short-term follow-up, small sample size, and lack of a control group.

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