

Visual Outcome after Intravitreal Bevacizumab Injection in Macular Edema Secondary to Central Retinal Vein Occlusion

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Objective: To evaluate visual outcome after intra-vitreous Bevacizumab in macular edema secondary to central retinal vein occlusion.

Materials and Methods: This prospective study was performed at Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Malir, Karachi. Patients with macular edema secondary to central retinal vein occlusion, ischemic and non-ischemic were selected from 1st February 2009 to 31st July 2009, by using non-probability purposive sampling technique.

Informed written consent was taken from the patients. Best-corrected visual acuity was checked before giving the intra-vitreous Bevacizumab injection and after 1st, 4th and 12th week.

Results: Out of 41 patients included in the study 32 patients (78 %) showed visual improvement of at least one line on Snellen visual acuity chart (P value of <0.05), while rest of the 9 patients (22 %) did not show visual improvement.

Conclusion: Intra-vitreous Bevacizumab injection results in modest visual improvement in patients with macular edema due to central retinal vein occlusion.

Central retinal vein occlusion (CRVO) is a relatively common cause of visual loss and after diabetic retinopathy; it is the most frequent vascular accident. The prevalence and five year incidence of CRVO were estimated to be 0.1-0.4% and 0.2%¹. Histopathologic studies have implicated thrombosis in the central retinal vein at the level of the lamina cribrosa or the retrolaminar optic nerve as the cause of CRVO. There are two types of CRVO - ischemic and non-ischemic.

The main cause of visual loss in patients with CRVO is macular edema¹. Vascular endothelial growth factor (VEGF) has been implicated in the pathophysiology of CRVO³. VEGF causes conformational changes of tight junctions of retinal vascular endothelial cells leading to increased vascular permeability.

There is still no safe treatment that promotes the return of lost vision. Treatments that target the secondary effects of venous occlusion, such as grid laser photocoagulation for macular edema and prophylactic pan retinal laser photocoagulation for nonperfused CRVO, were shown to be ineffective in improving visual acuity in the Central Vein Occlusion Study (CVOS)⁴.

At present there is considerable interest in intra-vitreous Bevacizumab (Avastin, Genentech), which is a humanized monoclonal antibody that inhibits all active isoforms of VEGF. Intra-vitreous Bevacizumab is a new treatment modality which is currently being tried out for use in macular edema following central retinal vein occlusion (CRVO). In one study use of intra vitreous bevacizumab resulted in visual improvement from 20/600 to 20/138 at 3 months⁵.

This study was conducted to evaluate the role of intra vitreal bevacizumab in treatment of macular oedema secondary to CRVO issue in our local environment.

MATERIALS AND METHODS

The study is an experimental study conducted at Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Malir, Karachi, from 1st February 2009 to 30th July 2009. 41(n=41, P=88%, D=10%, C-I=95%) patients were included in the study by non-probability purposive sampling.

Patients with macular edema secondary to central retinal vein occlusion that had persisted for more than three months were included in the study⁶. Macular edema was identified clinically on the basis of slit lamp bio-microscopy. Central retinal vein occlusion was clinically identified by multiple flame shaped hemorrhages all over the fundus and dilated retinal veins seen with a 90 D lens.

Patients with other visually significant ocular complications of central retinal vein occlusion, tractional retinal detachment, vitreous hemorrhage and glaucoma (Primary open angle and neo-vascular glaucoma) were excluded from the study.

Patients were selected from General Outdoor Patient Department of Al-Ibrahim Eye Hospital, according to inclusion criteria. Informed written consent was taken. Best corrected visual acuity (BCVA) was checked using Snellen acuity chart by the refractionist. This was taken as baseline BCVA for the study. Injection of 1.25 mg / 0.05 ml of Bevacizumab was given by an Ophthalmologist under topical anaesthesia in aseptic conditions in the operating theatre.

Patients were followed at 1, 4 and 12 weeks after the injection. Visual findings of last follow-up (12 weeks) were considered as final outcome. At each follow-up, best corrected visual acuity (BCVA) was checked by the refractionist using Snellen acuity chart. Difference between the best corrected visual acuity at baseline (before injection) and at final follow up visit (12 weeks) was evaluated and if at least single line improvement was seen at the final follow up (12 weeks), visual improvement was considered to be significant by the researcher.

Statistical analysis was done by SPSS version 13.0. Frequencies and percentages were calculated for gender, age groups (which were divided into age

groups of less than 20 years, 21 to 40 years, 41 to 60 and more than 61 years of age) and visual acuity. Marginal homogeneity test was used to compare the proportions of visual acuity before injection and after 12 weeks at 5% level of significance. Mean \pm Standard deviation was calculated for qualitative variables like age visual acuity and duration of CRVO.

RESULTS

Forty one eyes of 41 patients that fulfilled the inclusion and exclusion criteria were recruited in the study.

Out of 41 patients 24 (58.5%) were males and 17 (41.5%) were females. All patients were between 43-76 years of age. Mean ages of the patients were 55.6 years with standard deviation of 7.51. Most of the patients 25 (61%) belonged to the age group of 50-59 years, 7 patients (17%) belonged to the age group between 60-69 years, while 6 (15%) patients belonged to the age group of less than 50 years. Only 3 (7%) patients were older than 69 years.

Age distribution according to genders is as follows, Mean \pm SD = 7.58 with age range of 43-76 (mean=55.96) years for males and Mean \pm SD 7.58 with age range of 44 - 74 (mean=55.12) years for females.

The mean duration of central retinal vein occlusion before the intra-vitreous injection of Bevacizumab was 5 months with standard deviation of 2.25 the duration with the range of 4 months to 12 months.

Visual acuities before giving intra-vitreous injection of Bevacizumab are shown in Table 1.

Visual acuities on final follow up that are 12th week after intra-vitreous bevacizumab injection are shown in Table 2.

Out of 41 patients included in the study 32 patients (78%) showed visual improvement of at least one line on Snellen visual acuity chart (P value of <0.05), while rest of the 9 patients (22 %) did not show visual improvement, (Fig. 1).

DISCUSSION

The principal cause of decrease in vision, in patients with non-ischemic CRVO, is macular oedema. The central retinal vein occlusion study showed negative results of laser treatment (showed no benefit over the control group), which led to its abandonment⁴. This provoked.

Table 1: Visual acuity before intravitreal bevacizumab injection (baseline)

	Frequency n (%)
6/18	2 (4.9)
6/24	12 (29.3)
6/36	8 (19.5)
6/60	8 (19.5)
Counting fingers	3 (7.3)
Hand movement	6 (14.6)
Perception of light	2 (4.9)
Total	41 (100)

Table 2: Visual acuity after intravitreal injection of Bevacizumab (12th postoperative week)

	Frequency n (%)
6/6	8 (19.5)
6/9	14 (34.1)
6/12	4 (9.8)
6/18	3 (7.3)
6/24	1 (2.1)
6/36	1 (2.1)
6/60	2 (4.9)
Counting finger	2 (4.9)
Hand movement	3 (7.3)
Perception of light	3(7.3)
Total	41 (100)

Researchers and clinicians to evaluate other medical and surgical interventions in CRVO. Currently, there is interest in a new drug called Bevacizumab (Avastin, Genentech), an antibody against vascular endothelial growth factor (VEGF). Bevacizumab can lead to rapid reduction of macular edema which leads to improvement of vision as early as at the end of 1st week⁷. Many other reports have found visual improvement from 20/600 to 20/138 at 3 months (average 2.8 injections), however it has few

short-term safety issues⁵. These results suggest that Bevacizumab can be used in the treatment of macular edema, especially, because of lack of intraocular pressure (IOP) rise and absence of cataract formation. However, the effect does not appear to be persistent, and multiple intra-vitreous injections may be needed. It stabilizes the blood-retinal barrier in patients with CRVO and inhibits VEGF expression, thus reducing the retinal capillary permeability.

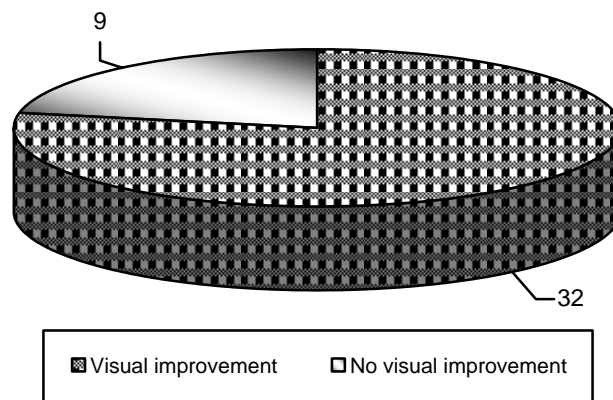


Fig. 1: Visual improvement n = 41

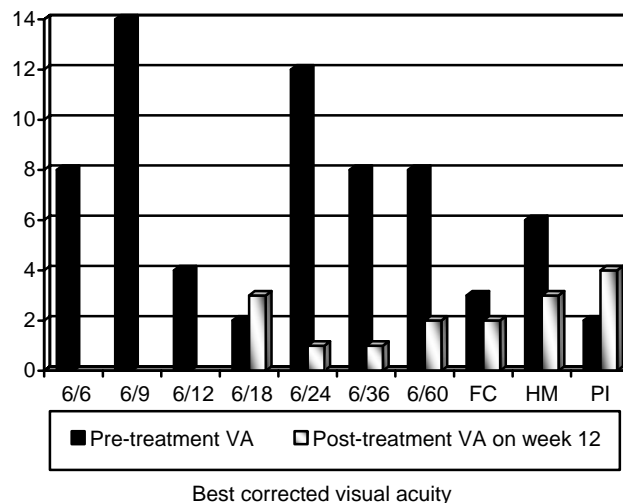


Fig. 2: Pre-treatment (baseline) and post-treatment (on week 12) visual acuity distribution n = 41
VA = Visual acuity, HM = hand movement
FC = Finger counting, PI = perception of light

Many treatments for CRVO have been developed but most have not stood the test of time. Intra-vitreous steroids may be beneficial in selected cases of macular edema but have many adverse side effects. Similarly,

anti-VEGF agents such as Bevacizumab appear to be promising, but their role still needs to be tested. Among interventions aimed at the underlying pathophysiology of CRVO, haemodilution seems to be useful but it also requires careful patient selection and more trials. The exact therapeutic advantage of treatments such as RON, fibrinolytic therapy, and CRVA is not known fully.

Our study demonstrated the early and clinically relevant benefits of Bevacizumab injection for macular edema due to Central Retinal Vein Occlusion. In our study, we found that intra-vitreous injections of Bevacizumab resulted in a significant improvement of visual acuity in patients with Central Retinal Vein Occlusion along with reduction in macular edema, which was noted on clinical examination. The useful effects of intra-vitreous Bevacizumab were observed as early as the first week and over a 3-month follow-up period.

Results of our study after 3 months showed that intra-vitreous Bevacizumab treatment in patients with macular edema secondary to CRVO was associated with a significant improvement in visual acuity ($p < 0.05$). During this study, no severe ocular adverse events, such as endophthalmitis, retinal detachment, traumatic cataract or uveitis, were detected, for as long as 6 months (including follow up time of 3 months). None of the patients showed any evidence of severe drug-related systemic adverse events (e.g. thromboembolic events, hypertensive crisis or kidney failure). Our study was too small to present solid data on safety, but several studies have showed comparable results regarding lack of severe adverse events^{8,9}.

The results in our study are comparable to the preliminary results of several recently published papers⁵. The most comprehensive data on the natural history of CRVO was provided by the Central Vein Occlusion Study Group¹⁰. It is widely thought that clinical outcomes of every new treatment option for CRVO must match with these data. According to the CVOSG, in the natural course of CRVO, only 19% of patients with initial visual acuity of less than 20/200 had a chance of visual acuity of better than 20/200.¹⁰ It reported that patients who presented with initial visual acuity between 20/200 and 20/50 had improved to better than 20/50 in 19% of cases, while in 44% of cases visual acuity remained between 20/200 and 20/50 and showed no improvement. On the other hand visual acuity of only 37% of patients became worse than 20/200. Compared with this data,

patients treated with intra-vitreous Bevacizumab have shown much better improvement in visual acuity. One study reported improvement in visual acuity from 20/250 at baseline to 20/80 at the 6-month follow-up ($p < 0.001$) in a group of 46 CRVO patients¹¹. Similarly, along with improvement in vision the mean central retinal thickness also decreased from 535 ± 48 microns at baseline to 323 ± 116 microns at the 6-month follow-up¹¹. In another series of 30 eyes of CRVO patients reported improvement in visual acuity from 20/394 at baseline to 20/313 at the 3-month follow-up, ($p < 0.05$)¹². Results of these studies indicate that Bevacizumab can be considered as an effective treatment option for CRVO and it may improve the long-term prognosis of CRVO.

Our study does have some limitations that must be recognized. There was no control group in our study and there was only a limited follow-up so we were unable to study the need of reinjection. Another very important limitation in our study was that we failed to compare the anatomical changes in macular edema due to the absence of optical coherence tomography testing facility in our setup, so we had to depend on clinical assessment to evaluate improvement in the macular edema.

CONCLUSION

Bevacizumab is an emerging treatment modality; the promising results reported here in our study indicate that intra-vitreous Bevacizumab injection can help treat macular edema secondary to central retinal vein occlusion with modest improvement in vision.

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