

VISUAL OUTCOME AFTER INTRAVITREAL BEVACIZUMAB (AVASTIN) IN THE TREATMENT OF BRANCH RETINAL VEIN OCCLUSION

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ABSTRACT

Objective: To evaluate the visual outcome after intravitreal injection of bevacizumab (Avastin) in patients with branch retinal vein occlusion.

Study Design: Prospective study.

Place and Duration of Study: Combined Military Hospital (CMH) Kharian, from Mar 2016 to Nov 2017.

Material and Methods: Patients of branch retinal vein occlusion (BRVO), were injected with minimum of one intravitreal bevacizumab 1.25 mg in 0.05 ml. Patients were examined using Snellen visual acuity testing, Fundus Fluorescein Angiography (FFA) and Optical Coherence Tomography (OCT). Detailed eye examination was done before the procedure and follow-up visit on monthly basis was done for six months.

Results: Twenty eight eyes of 28 patients were included, with a mean age of 63 years (SD 16.1). The patients received a mean of 3 (SD 1.30) injections of bevacizumab per eye. No adverse events were seen. At the baseline the mean central macular thickness was 559 microns which improved to 380 micron at 3rd month ($p<0.001$) and 300 microns after six months. The mean baseline acuity was log MAR = 0.70 (SD 0.19) and at three month log MAR=0.40 (SD 0.20); the difference was significant ($p=0.001$). At last follow-up of 6 months, the mean visual acuity was log MAR = 0.30 (SD 0.21), which was better than baseline ($p<0.001$). Twenty seven eyes showed improvement in visual acuity.

Conclusion: Intravitreal bevacizumab caused substantial reduction in macular edema and enhancement in visual acuity. In this study the number of patients was limited and the follow-up was too short to makes recommendations of any specific treatment guidelines. Further studies are needed with long followup for treatment recommendations.

Keywords: Avastin, Bevacizumab, Branch retinal vein occlusion, Intravitreal injections, Vascular endothelial growth factor.

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INTRODUCTION

Among the vascular diseases of eye, Diabetes Mellitus ranks as number one where as venous occlusive disorders ranks at number two¹. There are many postulations regarding the cause of Retinal Vein occlusion (RVO), but exact nature of the disease causation is still not clear. Diabetes, hypertension and vessel wall changes secondary to these systemic conditions can lead to venous occlusion, both Branch and Central. Primary Open Angle Glaucoma is also postulated as a factor contributing to pressure on vein at the A-V crossing at or near to the optic disc². Retinal hypoxia secondary to low blood circulation may

cause sudden loss of vision. The vision may get worse than the initial loss of vision. Thus this reduction in oedema is the primary goal in the treatment of this condition. Studies done in the past have shown that after Branch Retinal Vein Occlusion (BRVO) there is increase in the levels of Vascular Endothelial Growth Factor (VEGF)³. After hypoxia of retina, VEGF is produced. This VEGF is a cytokine which stimulates the hypertrophy of endothelial cells, which causes reduction in the lumen of the capillaries. This further reduces the circulation and causes more ischaemia leading to more oedema. Thus treatment with Anti-VEGF could help break this vicious cycle and help in the resolution of macular oedema. Thus treatment options for managing macular oedema with BRVO include

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Received: 01 Apr 2018; revised received: 15 Aug 2018; accepted: 10 Sep 2018

both macular grid laser photo coagulation and intravitreal injections⁴⁻⁸.

We conducted a prospective clinical trial in Eye Department Combined Military Hospital Kharian to calculate the visual acuity (VA) outcome of Intravitreal bevacizumab after patients were diagnosed with BRVO, and were injected intravitreally with bevacizumab. All consecutive patients were enrolled and a protocol was set to treat and follow these selected patients over a period of six months. Follow-up of all these patients were done for a minimum of three months.

PATIENTS AND METHODS

All patients with BRVO were seen and enrolled in Eye Department of Combined Military Hospital (CMH) Kharian from March 2016 to Nov 2017. This clinical trial included 28 eyes of 28 patients who were diagnosed with BRVO and affected vision was low secondary to macular oedema only. Detailed eye examination was carried out.

This ophthalmic examination involved 1. Visual acuity assessment with Snellen chart and then conversion to Log Mar values. 2. Detailed examination of anterior segment with slitlamp. 3. Optical Coherence Tomography (OCT) done for macula using Optopol Tech Machine (Poland), for the measurement of central retinal thickness (CRT). 4. Fundus Fluorescein Angiography (FFA). To facilitate statistical analysis, BCVA was transformed into logMAR values. OCT done for the central macular cube was done using the software provided by the Optopol machine. These measurements (in μm) were recorded for CRT and printouts taken for future references. Informed consent for use of Bevacizumab as off-label drug was obtained from all patients prior to this prospective clinical trial. Ophthalmic history was taken to rule out any previous treatment taken. Systemic history was also taken to rule out any co-morbidities such as hypertension, diabetes mellitus and cardiac disease.

Patients with BRVO, having clear media, not having laser photocoagulation, and without any neovascularization were included in the study.

Patients having glaucoma, uveitis, vitreous hemorrhage, proliferative vitreoretinopathy, retinal detachment were excluded from this study. Presence of any advance renal disease, disproteinemia, or accelerated hypertension were also excluded from this study. Patients taking vasoactive drugs were also excluded from this study.

In this study all patients had macular oedema. FFA of these patients showed hyperfluorescence in the macular area. All patients were fully informed about the treatment and informed consent was obtained from each patient. Snellen chart was used for checking best corrected visual acuity (BCVA), at 6 meters. The average VA was calculated and transformed to the LogMAR equivalent, and then taking the average of these Log MAR values. Log Mar values calculated from conversion of BCVA were used in the statistical calculations.

Ophthalmic examination was done for first week and then monthly check up was done afterwards. Treatment results were assessed by results of improvement in visual acuity and reduction in CRT on OCT. Any side effects of intravitreal injection were recorded. In case of relapse, reinjections were given to the patients. Relapse was observed in those patients who developed decrease in vision and associated with macular oedema secondary to increase in intra retinal fluid accumulation. This was then detected on either OCT or FFA.

Three injections of Intravitreal bevacizumab (Avastin® Genentech) were given intravitreally to all patients in this study group, with a dose was 1.25 mg (0.05 ml). All intravitreal injections were performed under topical anesthesia with all aseptic precautions in the operating room.

Diluted 5% providineiodine was instilled in the conjunctival sac prior to the injection. Skin of the lids and face was prepared with 10% providineiodine and patient was injected in the

sterile environment of the operating room. Bevacizumab was prepared in complete sterile conditions from the Vial, using insulin syringes.

Injection of Bevacizumab was given 4mm behind the limbus in the temporal quadrant in the phakic patients and 3.5mm in the patients having pseudophakia. The aim of the injection was to deposit the medicine in the mid-vitreous cavity. After withdrawal of needle, cotton tip applicator was applied to the site to prevent reflux of medicine, which could lead to post-injection discomfort to the patient and loss of volume of the medicine. Topical moxifloxacin drops (Megamox, Sante) were given to be instilled 6 hourly for 10 days. Three injections were initially given to the patients at monthly intervals. These injections were repeated at monthly interval if there was a recurrence, as

Results of Visual Acuity and CRT

During the follow-up of our patients, the vision improved and the best corrected visual acuity (BCVA) at the end of three months was 80 EDTRS letters (corresponding to a vision of 20/50 on Snellen chart).

The average decrease of CRT at the end of three months was 380um, a decrease of 179um ($p<0.001$)

At the end of six months of our study, the average vision of our patients had improved to 85 ETDRS letters (corresponding to a vision of 20/40 on Snellen chart). The average CRT had also reduced to an average of 300um, a decrease of 259um from the baseline ($p<0.001$)

Patients were followed for 6 months to document any side effects of intravitreal Bevacizumab. No patient in our study developed

Table: Mean LogMAR Value of patient before and after injection of Bevacizumab and their vision and CRT.

logMAR	value	CRT
Pre inj	0.70 ± 0.19	559um
3 months	0.40 ± 0.20	380um
6 months	0.30 ± 0.21	300um

evidenced on OCT (an increase in 1-mm CRT) or a reduction in visual acuity vision (loss of at least five ETDRS letters). For statistical analysis t-test was used to see changes in the recorded visual acuity. It was statistically significant if the value was less than 0.05. No patient in this study required grid or focal Argon laser treatment.

RESULTS

Out of 28 eyes booked for the study, 13 were females and 14 were males. The average age of the patients booked for this study was 63 years, ranging from 40 to 79 years. One patient was removed from the study after initial three injections, as he could not follow-up due to financial reasons.

The average vision at the start of the study was 20/79 (65 EDTRS letters or 6/24), and it had a range from 6/200 (24 ETDRS letters) to 20/25 (95 ETDRS letters). OCT done for average central retinal thickness (CRT) at baseline was 559um, ranging from 350um to 900um.

any side effects either ocular or systemic. Patients were monitored for development of any intra-ocular infection, cataract formation or any tear formation in the retina. No formation of neovascularization was seen in any of our booked patients. Systemically they were observed for any cardiovascular or renal pathology, none had any such side effects.

Inflammatory reaction was seen, but mild, in 4 patients (14.28%). Topical steroids were given in these patients for one week for the resolution. No other complication was noted either related to the injection procedure or injected drug. Table-I shows the average CRT and visual acuity. It shows the values before the injection and sequentially at 3 and 6 month. This table highlights that there was significant change statistically of visual acuity and CRT before and after treatment with intravitreal Bevacizumab ($p<0.001$). Vision improved in 27 out of 28 eyes (96.43%), three months after the patients were

seen in our clinic, and remained unchanged in one eye (3.54%).

This study shows marked decrease in CRT and vision improvement in patients treated with intravitreal Bevacizumab having BRVO and associated macular oedema. Similar results were shown in previous studies with intravitreal administration of triamcinolone⁸. No ocular side effects such as rise in IOP or cataract formation were observed with intravitreal Bevacizumab, in contrast to intravitreal triamcinolone.

DISCUSSION

In the past, patients having macular oedema with BRVO were only treated with Grid Argon laser photocoagulation. This was based on the Branch Vein Occlusion Study which determined that patients having a vision of 20/40 or less will have any improvement of vision after laser therapy, as compared to the control group⁴. Intravitreal triamcinolone (IVT) has been studied in the treatment of macular oedema secondary to BRVO (SCORE trial)⁸, but it exhibited only maintenance or a reasonable enhancement in visual acuity. IVT has many side effects which limit its routine use and these include a rise in intraocular pressure and formation of cataract in phakic eyes⁹. A sustained delivery, biodegradable dexamethasone intravitreal implant (OZURDEX, Allergan, Inc. Irvine, CA, USA) has been approved by united states Food and Drug Administration. Its main advantage is that there is a continuous release of drug for at least 06 months, thus leading to fewer injections and low risk for increase in IOP. There is also a role of autologous plasmin enzyme in patients with BRVO. This is a serine protease causing proteolysis of laminin, fibrin and fibronectin, which are the essential components of internal limiting membrane (ILM), responsible for adhesion of ILM to posterior vitreous cortex. Plasmin relieves traction by producing posterior vitreous detachment (PVD). A study was done which showed improvement in BCVA and reduction in foveal thickening following injection 0.2ml of plasmin, which lasted for 06 months.

Thus its proved that plasmin induced posterior vitreous detachment and vitreolysis has as good an effect as induced by pars planavitrectomy, with no surgical complications¹⁰.

Anti-VEGF therapy is an alternative treatment option for patients with macular oedema following BRVO. The treatment options include Bevacizumab, Ranibizumab and Aflibercept. A study conducted by Campochiaro *et al* demonstrated comparison of Ranibizumab and Bevacizumab on visual acuity and CRT in patients with BRVO^{11,12}. The results showed Ranibizumab has similar effects on visual acuity and CRT as Bevacizumab. MARVEL study evaluated the efficacy of Bevacizumab compared to Ranibizumab on a PRN basis for the management of BRVO with macular oedema. The study concluded that administration of either Bevacizumab or Ranibizumab was equally effective in reducing macular oedema with improvement in visual acuity with 2.53 letters difference between two drugs (Ranibizumab 18.08 letters, Bevacizumab 15.55 letters). Both treatments are equally effective in anatomical and functional restoration with PRN treatment with rescue laser therapy in 12/75 (16%) eyes⁶.

VIBRANT study was a double masked, multicenter trial which assessed the efficacy of Aflibercept in comparison with macular laser, in eyes with macular oedema secondary to BRVO. Rescue laser therapy was done after 12 weeks as required. After 6 months, the eyes treated with Aflibercept had better outcomes in terms of reduced oedema (Aflibercept 280.5u/Laser 128u) or visual recovery (Aflibercept 17 letters/ Laser 6.9 letters). Aflibercept injections at 8 weeks interval, after first 6 months, helped maintain vision and foveal thickness, in the Aflibercept arm of the study. At the end of 52 weeks, in laser arm of this study, rescue Aflibercept for the patients resulted in marked improvement in vision and foveal thickness. In Aflibercept arm, rescue laser was given at 36 weeks in 10.6% eyes, while in laser arm, Aflibercept injection was given between 24 and 48 weeks of the study in 80.7% eyes. This was the first study to directly

compare the efficacy of anti-VEGF agent to laser therapy. It showed that anti-VEGF was superior as compared to laser. However there was no statistically significant difference in the visual outcomes Ranibizumab and Aflibercept⁷.

Pars planavitrectomy with ILM peeling is an another treatment option for the management of macular oedema secondary to BRVO¹³. This treatment causes relief of traction, improved oxygenation of vitreous and retina. It also prevents loss of photoreceptor cells, remove inflammatory and permeability factors such as VEGF. The EVRS group found vitrectomy with ILM peeling as a good management option. Visual gains reported was almost twice as high as anti-VEGF agents at 24 months postoperatively¹⁴.

Bevacizumab is a full length, monoclonal antibody, that blocks all the active forms of VEGF, and approved by the Food and Drug Administration for the treatment of metastatic colorectal cancer¹⁵. It has shown favorable effects in many ocular diseases.

Bevacizumab was first used in 2005 in ophthalmic cases and showed a favorable response in the treated cases of BRVO. This encouraged many case series showing its advantages with improvement of vision and a decrease in CRT^{10,17}. The European vitreoretinal society (EVRS) also found that single treatment with anti-VEGF were greater to any form of combination therapy¹⁵.

Our study results have revealed that Intravitreal Bevacizumab is better in the primary management of oedema associated with BRVO. 96.43% patients in our study showed an improvement in vision with a reduction in CRT and associated decrease in leakage on FFA. Our study results endorse previous reports, showing the valuable effect of Intravitreal Bevacizumab in the treatment of BRVO. This success in our study may be the result of injecting Intravitreal Bevacizumab injection as the primary management of BRVO. This led to a decrease in the leakage, as seen on FFA in our cases, with a reduction in macular oedema, as seen by OCT.

No patient presented with any of severe drug-related systemic or ocular side effects for as long as 6 months. Although almost all patients exhibited a good initial response to Intravitreal bevacizumab treatment, macular oedema did not resolve totally in six patients even after four injections.

CONCLUSION

Intravitreal bevacizumab caused substantial reduction in macular edema and enhancement in visual acuity. In this study the number of patients was limited and the follow-up was too short to makes recommendations of any specific treatment guidelines. Further studies are needed with long followup for treatment recommendations.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Lam FC, Chia SN, Lee RM. Macular grid laser photocoagulation for branch retinal vein occlusion. *Cochrane Database Syst Rev* 2015; 5: CD008732.
2. David R, Zangwill L, Badarna M, Yassur Y: Epidemiology of retinal vein occlusion and its association with glaucoma and increased intraocular pressure. *Ophthalmologica Journal international d'ophtalmologie Int J Ophthal* 1988; 197(2): 69-74.
3. Noma H, Funatsu H, Yamasaki M, Tsukamoto H, Mimura T, Sone T, Jian K, Sakamoto I, Nakano K, Yamashita H, et al: Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. *Am J Ophthalmol* 2005; 140(2): 256-61.
4. Argon laser photocoagulation for macular edema in branch vein occlusion. The branch vein occlusion study group. *Am J Ophthalmol* 1984; 98: 271-82.
5. Haller JA, Bandello F, Belfort R, Jr, Blumenkranz MS, Gillies M, Heier J, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010; 117: 1134-46.
6. Narayanan R, Panchal B, Das T, Chhablani J, Jalali S, Ali MH MARVEL study group. A randomised, double-masked, controlled study of the efficacy and safety of Intravitreal bevacizumab versus ranibizumab in the treatment of macular edema due to branch retinal vein occlusion: MARVEL Report No 1. *Br J Ophthalmol* 2015; 99: 954-9.
7. Campochiaro PA, Clark WL, Boyer DS, Heier JS, Brown DM, Vitti R, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: The 24-week results of the VIBRANT study. *Ophthalmol* 2015; 122: 538-44.
8. Scott IU, Ip MS, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: The Standard Care vs Corticosteroid for Retinal

- Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol* 2009; 127: 1115-28.
9. Ozkiris A, Erkilic K. Complications of intravitreal injection of triamcinolone acetonide. *Can J Ophthalmol* 2005; 40: 63-68.
 10. Rabena MD, Pieramici DJ, Castellarin AA, Nasir MA, Avery RL: Intravitreal Bevacizumab (Avastin) In The Treatment Of Macular Edema Secondary To Branch Retinal Vein Occlusion. *Retina* 2007; 27(4): 419-25.
 11. Udaondo P, Diaz-Llopis M, Garcia-Delpech S, Salom D, Romero FJ. Intravitreal plasmin without vitrectomy for macular edema secondary to branch retinal vein occlusion. *Arch Ophthalmol*. 2011; 129: 283-7.
 12. Campochiaro PA, Sophie R, Pearlman J, Brown DM, Boyer DS, Heier JS, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: The RETAIN study. *Ophthalmol* 2014; 121: 209-19.
 13. Campochiaro PA, Wykoff CC, Singer M, Johnson R, Marcus D, Yau L, et al. Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion: The SHORE study. *Ophthalmol* 2014; 121: 2432-42.
 14. Okunuki Y, Usui Y, Katai N, Kezuka T, Takeuchi M, Goto H, et al. Relation of intraocular concentrations of inflammatory factors and improvement of macular edema after vitrectomy in branch retinal vein occlusion. *Am J Ophthalmol* 2011; 151: 610-6.
 15. Adelman RA, Parnes AJ, Bopp S, Saad Othman I, Ducournau D. Strategy for the management of macular edema in retinal vein occlusion: The European VitreoRetinal Society macular edema study. *Biomed Res Int* 2015; 2015: 870987.
 16. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997; 57: 4593-99.
 17. Hikichi T, Higuchi M, Matsushita T, Kosaka S, Matsushita R, Takami K, et al. Two-year outcomes of Intravitreal bevacizumab therapy for macular oedema secondary to branch retinal vein occlusion. *Br J Ophthalmol* 2014; 98: 195-9.
 18. Kriechbaum K, Michels S, Prager F, Georgopoulos M, Funk M, Geitzenauer W, Schmidt-Erfurth U: Intravitreal avastin for macular edema secondary to retinal vein occlusion - a prospective study. *Br J Ophthalmol* 2008; 92 (4): 518-22.
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