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INTRAVITREAL BEVACIZUMAB (AVASTIN) FOR MACULAR EDEMA SECONDARY TO RETINAL VEIN OCCLUSION.

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ABSTRACT **Aim:** The purpose of this study is to evaluate the efficacy and safety profile of intravitreal injection of bevacizumab for macular edema secondary to retinal vein occlusion. **Methods:** A prospective analysis was conducted on patients with macular edema because of retinal vein occlusion, who had been administered three doses of intravitreal injections of bevacizumab at four weeks interval and further retreatment was based on optical coherence tomography (OCT) findings. The changes in the retinal thickness and visual acuity were evaluated to judge the efficacy, and adverse events were noted for the safety profile over a period of 6 months. **Results:** A total of 37 eyes of thirty seven patients were included in the study. The mean age of the patients was 59 ± 14 years. The mean pre-injection best corrected visual acuity (BCVA) was 1.14± 0.48 log minimum angle of resolution (logMAR) and central foveal thickness (CFT)of 449.8 ± 115.22µm, and the post-injection BCVA at 6 months was 0.51 ± 0.36 logMAR with a CFT of259.9 ± 87.08µm, this change was statistically significant ($P < 0.05$). During the follow-up period after injection, no patient had inflammation, endophthalmitis, an increase in intra-ocular pressure, or systemic side effects. **Conclusion:** Intravitreal bevacizumab appears to be a safe and effective treatment in patients with macular edema secondary to retinal vein occlusion.

KEYWORDS : Central Retinal Vein Occlusion, Branch Retinal Vein Occlusion, Bevacizumab, Macular Edema.

INTRODUCTION

Retinal vein occlusion (RVO) is a common retinal vascular problem that is second in incidence only to diabetic retinopathy. Many risk factors have been associated with RVO, including age, hypertension, diabetes mellitus, atherosclerotic retinal vascular change, open angle glaucoma, hyperhomocysteinaemia and hypermetropia.[1–3] Retinal vein occlusion (RVO) encompasses two conditions: central RVO, in which the major outflow vessel of the retina is obstructed, and branch RVO, in which a proximal branch of the central retinal vein is obstructed. In both conditions, there is increased intraluminal and interstitial pressure throughout the retina drained by the obstructed vessels, resulting in reduced arterial perfusion, which is exacerbated by pre existent arterial insufficiency, and in variable amounts of retinal ischemia. Retinal ischemia causes increased production of vascular endothelial growth factor (VEGF), which causes vascular leakage and macular edema. High levels of VEGF also promote retinal hemorrhages and exacerbate capillary nonperfusion.

Macular grid laser is a proven treatment modality for reducing ME related to BRVO, but the Branch Vein Occlusion Study has shown a significant visual benefit only in persons with visual acuity of 20/40 or less, compared with the untreated control group.[4] Several studies have shown positive results with intravitreal steroids in reducing ME and improving vision in patients with BRVO, but its use has been limited due to side effects, such as cataract formation and increased intraocular pressure.[5,6]

Intraocular injections of a VEGF-binding protein reduce vascular leakage, resulting in improvement in macular edema, accelerate resorption of retinal hemorrhages, and prevent worsening of capillary nonperfusion. Bevacizumab (Avastin ®, Genentech, San Francisco, USA / Hoffmann La Roche, Basel, Switzerland), a recombinant monoclonal antibody binding all isoforms of VEGF, is approved for cancer therapy and available for off-label use in ophthalmology. Several retrospective case series and short term prospective studies have analyzed the effect of intravitreal bevacizumab for BRVO and CRVO, showing promising functional and anatomic results.[7] This prospective study evaluates the effect of intravitreal bevacizumab on macular edema secondary to retinal vein occlusion.

MATERIALS AND METHODS

In this prospective clinical study, 37 eyes of 37 patients with macular edema due to RVO were included. Patients with a history of treatment with laser therapy or intravitreal injections, age-related macular degeneration, diabetic retinopathy, macular scar, pre-existing glaucoma, or neovascular glaucoma secondary to RVO were excluded from the study. Patients with history of myocardial infarction, or cerebrovascular accident within three months of presentation also were excluded. Informed consent was obtained from all the patients, and the possible risks and benefits of intravitreal bevacizumab were explained to them. Ethical approval was obtained and the study was conducted according to the tenets of the Declaration of Helsinki.

A detailed history was taken including chief complaints and presence of systemic diseases, such as hypertension, diabetes mellitus, cardiac diseases, and hyperlipidemia. Ocular evaluation included best-corrected visual acuity (BCVA) on a Snellen chart and anterior and posterior segment examinations using a slit-lamp and 90 D lens. Central foveal thickness (CFT) was assessed with optical coherence tomography (Stratus OCT; Carl Zeiss Meditec, Dublin, CA) at baseline and at every follow-up visit, at 4-6 weeks intervals, until the ME subsided, and then at 6 months of follow-up. Intraocular pressure was taken by Goldman applanation tonometry.

Systemic blood pressure was measured at baseline and at each follow-up visit. Fasting and postprandial blood sugar and lipid profile and serum homocysteine levels were recorded. All patients received 3 consecutive initial injections at monthly interval. Two eyes (5.40%) required continuous treatment up to 6 months.

The intravitreal bevacizumab was injected in a dose of 1.25 mg/0.05 mL through the pars plana with a 30 G needle. The intravitreal injections were administered aseptically in the operation theater. Afterwards, patients used a topical antibiotic four times a day for a week. Detailed ophthalmic evaluation was performed at each follow-up including visual acuity, anterior and posterior segment evaluation, and assessment of macular edema. Visual acuity was converted to LogMAR for visual outcome analysis. The data was analyzed in SPSS software (version 11.5; SPSS Inc, Chicago, IL). Paired *t*-tests were used for statistical analysis. *P* values less than 0.05 were considered statistically significant in this study.

RESULTS

A total of 37 eyes of thirty seven patients were included in the study, of them twenty four were males (65%) and thirteen were females(35%). The mean age of the patients was 59 ± 14 years. Fourteen eyes presented with CRVO, twenty two eyes with BRVO and one eye with hemiretinal vein occlusion. Systemic hypertension was found in 15 cases (40.5%), diabetes mellitus in four (10.8%), hyperlipidemia in three (8%) and hyperhomocysteinemia in two patients(5.4%).

The mean pre-injection best corrected visual acuity (BCVA) at baseline was 1.14± 0.48 log minimum angle of resolution (logMAR). After intravitreal bevacizumab, the mean BCVA was 0.84 ± 0.42 at 6 weeks, 0.57 ± 0.28 at 3 months, 0.51 ± 0.36 at 6 months. The improvement in BCVA was statistically significant at each follow-up (*P* <0.001) compared to baseline values.

The mean CFT at baseline was 449.8 ± 115.2 µm. The mean CFT was 299.8 ± 82.8 µm at 6 weeks, 254.1 ± 47.9 µm at 3 months, 259.9 ± 87.0 µm at 6 months follow-up. A statistically significant reduction in CFT was observed at each follow-up visit (*P*<0.001) relative to baseline values. The mean pre injection IOP was 16.08 ±1.69 mm of Hg and the mean post injection IOP was found to be 16.29±1.55 mm of Hg.

There was no reported major ocular or systemic problems after intravitreal bevacizumab, such as endophthalmitis, cataract, glaucoma, retinal detachment, or thromboembolic events in our study.

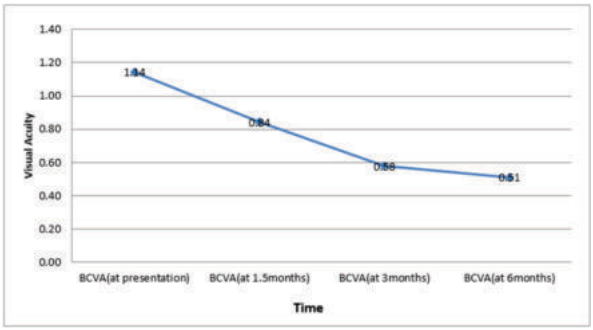

Figure 1: Status of best corrected visual acquity after intravitreal bevacizumab.

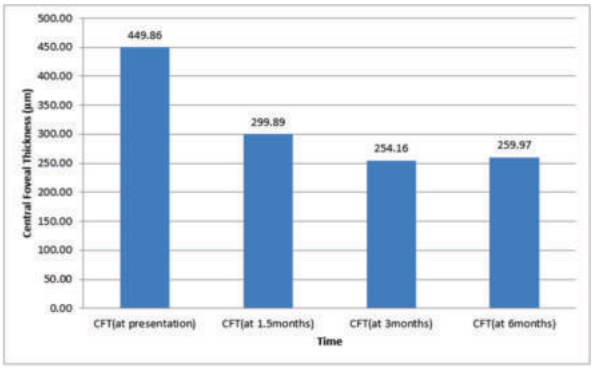

Figure 2: Status of central foveal thickness after intravitreal bevacizumab.

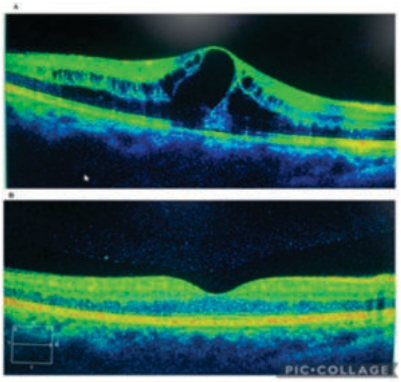

Figure 3: Pre Injection (A) and Post Injection (B) OCT- Macula of a patient with cystoid macular edema secondary to BRVO.

DISCUSSION

The use of intravitreal bevacizumab therapy shows promising results for treatment of macular edema in retinal vein occlusions (RVO). This prospective study demonstrated significant improvement in best corrected visual acquity and central foveal thickness over the period of 6 months without any major ocular and systemic side effects. The mean age of the patients was 59 ± 14 years. The prevalence of RVO is strongly associated with increasing age. Systemic hypertension was found in 40.5% patients, diabetes mellitus in 10.8%, hyperlipidemia in 8% and hyperhomocysteinemia in 5.4% patients. Hypertension, diabetes, hyperlipidemia and, and hyperhomocysteinemia were significantly higher in RVO cases as reported by previous studies.[1-3]

The prevalence of BRVO found to be much more than CRVO (59.4% vs. 37.8%) in our study, coinciding with previous study done by Song et al.[7] The average number of intravitreal bevacizumab in our study was 3.1, similar to the average number of injection needed in the study done by Thapa et al.[8]

The central foveal thickness improved significantly each follow-up visit compared to baseline values. Our findings were consistent with other reported studies.[8-11] None of the patient shown any severe drug related ocular side effects like uveitis, endophthalmitis, cataract or retinal detachment. There is no reported serious systemic side effect due to the drug like thromboembolic event or nephrotoxicity.

There is significant improvement in visual acquity form the baseline (p<0.001). None of the patients developed neovascularization. Poorer baseline vision and younger age were associated with more significant improvement in vision.

After 6 months 67.5% patients achieved a vision of 20/60 or better. The mean BCVA had increased significantly from 30 letters (20/250) to 60 letters (20/63). 73% of BRVO and 50% of CRVO eyes achieved a vision of 20/60 or better, similar to the 80% of BRVO and 28% of CRVO eyes seen in the RETAIN study.[12]The improvement of vision correlated significantly with the decrease of CFT.

However limitations of our study is that, this study include small sample size, shorter duration of follow up, fundus FA was not performed and therefore ischemic conversion might have remained undiagnosed clinically. In addition we have not taken in account the duration of the disease, as shorter disease duration was positively correlated with more vision improvement Patients with a long lasting pathology frequently showed good anatomical results, but did not gain vision; in contrast, patients who received treatment soon after the onset of the edema, presented with good anatomic and vision outcomes. These associations suggest that a long lasting pathology has led to irreversible retinal damage which cannot be restored merely by resolution of retinal edema.[13]

Future studies with a more significant number of patients will be required to strengthen the statistical power allowing for subgroup analyses. The main drawback of this treatment modality seems to be the short durability of the therapeutic effect with the need for frequent retreatments. Large randomised controlled clinical trials should be conducted to evaluate the long-term efficacy and safety after repeated bevacizumab treatment in patients with CMO secondary to RVO according to their ischaemic status.

CONCLUSION

The present study shows that initial treatment with three consecutive intravitreal injections of bevacizumab given at monthly interval improve vision and reduce ME significantly. These results justify its use in patients with ME secondary to RVO. Preoperative presence of macular ischemia can be useful in predicting the outcome of visual acuity. Anti VEGF therapy seems to be a novel, innovative approach, which should be further evaluated in large, prospective, controlled clinical studies.

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