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Correlation Between Macular Thickness and visual Acuity in Patients of Retinal Venous Occlusion Before and After Intravitreal Antivegf Injections, in South Rajasthan, India

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ABSTRACT
Retinal vein occlusion (RVO) is the second most common cause of retinal vascular disease after Diabetic Retinopathy. Visual impairment secondary to central or branch retinal vein occlusion (CRVO, BRVO) is mostly caused by macular oedema. Thus, the current study was planned with a purpose to study the correlation between visual outcome and the macular oedema after Anti-VEGF injections in eyes with macular oedema associated with a RVO. To accomplish this, we used OCT to follow up and determine the macular oedema in eyes before and after anti-VEGF injections. The current study is a hospital based Prospective Interventional cohort study. The central macular thickness was evaluated prior to the intervention with the help of OCT. Before treatment mean macular thickness was 536.12 um which was reduced to 250.28um after treatment with Antivegf injections. There was 53.3% improvement which was found to be statistically significant. Mean LogMAR visual acuity was 0.93(Pre) which was significantly improved to 0.35(Post) in BRVO. (P value 0.001).

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common cause of retinal vascular disease after Diabetic Retinopathy. Visual impairment secondary to central or branch retinal vein occlusion (CRVO, BRVO) is mostly caused by macular oedema[1]. Macular oedema is one of the most common causes of sudden visual loss in RVO. Branch retinal vein occlusion (BRVO) involving only a single retinal vein is the most common, while CRVO is less common[2] but is more serious and carries a high risk of complications and vision loss. RVO is more prevalent in men than women and is more frequent in older age (over 65 years). Its pathogenesis is still not completely understood. The condition may be due to a combination of three systemic changes known as Virchow's triad:-hemodynamic changes (venous stasis), degenerative changes of the vessel wall and blood hypercoagulopathy. The most recognized risk factors for RVO are age and systemic vascular disorders. In over half of the cases, the age of onset is over 65 years. However, patients under 45 can also develop an RVO[3]. Systemic risk factors are hypertension, diabetes mellitus, hyperlipidemia, atherosclerotic associated diseases: ischemic heart disease, obesity (high body mass index) and cigarette smoking. Systemic vasculitis includes systemic lupus erythematosus, sarcoidosis and syphilis. Hematological neoplasia's includes polycythaemia vera, multiple myeloma and leukaemia. Hypercoagulation diseases consists of antiphospholipid syndrome and protein S deficiency. Drug therapy includes oral contraceptives, diuretics and hypotensive drugs. Vascular endothelial growth factor (VEGF) is a hypoxia-inducible angiogenic peptide., a potent growth factor for vascular endothelial cells, which promotes neovascularization and increases vascular permeability iients with ischemic retinal diseases[4]. Anti-VEGF therapy at an early stage of retinal disease has been shown to be beneficial for visual recovery. Retinal ischemia and vascular damage in RVO eyes result in a breakdown of the inner blood-retinal barrier and disruption of this barrier is associated with complex cellular processes that lead to the release of angiogenic and inflammatory cytokines[5]. These cytokines have been found to be overexpressed in the aqueous humor or vitreous fluid of RVO eyes[6]. Both anti-VEGF-therapy and treatment with intravitreal corticosteroid-based agents have been found to be effective in reducing the intraocular level of cytokines and in the reduction of macular oedema due to RVO[7]. Studies in this field have been conducted using different anti-VEGF agents such as pegaptanib sodium, bevacizumab, ranibizumab and aflibercept[8]. Significant improvements in visual acuity (VA) and macular oedema (MO) among patients with RVO receiving VEGF inhibitors have been demonstrated in randomized clinical studies including Copernicus, Bravo, Cruise and Vibrant[9-11].The slow-release intravitreal dexamethasone implant (0.7 mg) has proved very effective in improving visual acuity and reducing macular thickness in patients with CRVO-related MO[12,13]. There is very limited data available on long-term outcomes of RVO treated with VEGF inhibitors and the number of injections required for these outcomes. Thus, the purpose of this study was to determine the correlation between visual outcome (Best corrected visual acuity) and the macular oedema after Anti-VEGF injections in eyes with macular oedema associated with a RVO. To accomplish this, we used OCT to follow up and determine the macular oedema in eyes before and after anti-VEGF injections.

Objective: To study the efficacy of Intravitreal Antivegf injections in patients of Retinal vein occlusion by assessing the visual outcome (best corrected visual acuity) and Central Macular Thickness.

MATERIALS AND METHODS

Study Site: This study was conducted at Dr Kothari's Eye Hospital Patel circle, Udaipur (Raj).

Study Design: This is a hospital based Prospective Interventional cohort study.

Study Durations: This study was conducted for 12 months from January 2019 to December 2019.

Method and Data Collection: This is a prospective hospital-based study of 25 patients diagnosed to have Retinal vein occlusions with macular oedema. After assessing the visual acuity and the central retinal thickness, an intravitreal injection of Antivegf like bevacizumab (1.25mg) will be given after ruling out all contraindications under aseptic conditions. Minimum 2 injections will be given to all the patients on monthly basis. All the patients will be followed up monthly & an OCT scan will be passed on each visit. Furthermore, injections will be given to those patients with Residual oedema present even after two injections. Final macular thickness will be measured via OCT after entire oedma has resolved.

Inclusion Criteria:

- All the patients of retinal venous occlusion with macular oedema were included aged 25 and above.
- Patients and/or his/her legally acceptable representative willing to provide their voluntary written informed consent for participation in the study.

Exclusion Criteria:

- Patients with any other pre-existing macular pathology.

- Patients with pathology leading to media opacity.
- Active intra ocular inflammation.
- Non cooperative patients.

Each patient underwent complete ophthalmic examination including best corrected visual acuity (BCVA) using snellen chart, Slit lamp Biomicroscopy, intraocular pressure measurement (IOP), Fundus Examination and Central foveal thickness (CFT) measurement on OCT. Intravitreal Antivegf injection was given under topical anaesthesia. Final Primary outcome measures were BCVA and CFT values on optical coherence tomography (OCT) before and after Intravitreal Antivegf Injections. All OCT scans were performed and Central macular thickness measured by embedded software in OCT machine. Internal fixation was used for all scans. After treatment OCT scans were repeated and Macular thickness noted.

Sample Size: Formula used for comparing Pre and post $N>=[(\text{standard deviation})^2 * (Za+Z\beta)]/(\text{mean difference})^2$ Where Za is value of Z at two-sided alpha error of 5% and Zß is value of Z at power of 80% and mean difference is difference in mean values of pre and post

Statistical Analysis: The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The Wilcoxon sign rank test (for quantitative data to compare before and after observations) was used for quantitative data comparison of all clinical indicators. Level of significance was set at P=0.05.

RESULTS AND DISCUSSIONS

In our study, majority of the patients were in the average age group of 50-60 years (36%), followed by 24% patients from the age group of 60-70 years, 16% patients from>70 years group and rest 12% patients belonged to 30-40 and 40-50 years each. In a study conducted by Thapa[14] concluded that Age group ranged from 60-95 years with a mean of 69.64±7.31 years in his study. Algvere[15] studied case material of the age group of 34-79 years with mean age of 56.5 years. The Age group profile of our study was found to be consistent with other studies. In our study out of 25 patients 13 (52%) were female and 12 (48%) were male. In a study group of 23 patients Quereshi[16] reported Fourteen patients (60.86%) to be male and nine (39.13%) to be female. Studies conducted by Hayreh[17] and Rath[18] have shown that males were more commonly affected than that of females. Gender based distribution was found to be similar to our study. Our study had 19 (76%) patients diagnosed with BRVO and 6 (24%) patients had CRVO. In an another multi center retrospective study by Jumper[19] showed medical records of 165 patients (95 branch RVO, 70 central RVO) treated with at least three anti-vegf injections in the study eye. Our study showed similarity with Qureshi[16] in which nine patients had CRVO and fourteen patients had BRVO.

Table 1: IOP Wise Distribution of the Study

	Mean	Std. Deviation	P-value
Pre-treatment	15.56	5.78	0.02 (S)
Post-treatment	16.92	4.61	

Mean IOP was 15.9 mmhg before treatment and 17.02 mmhg after treatment showing that no significant rise in IOP was seen after Antivegf injections (Table 1). Algvere[15] showed similarity stating mean IOP of 15.2 mm hg at baseline and IOP of 17.3mm hg at 6 months after intravitreal bevacizumab injections. Fung[20] in a worldwide assessment of safety of intravitreal bevacizumab using the internet, assessed the response by various ophthalmologists across the world who had used the drug intraviterally for various indications, showed that it did not cause any significant sustained elevation of IOP that required IOP lowering agents. So, in our small sample size we could not found significant difference in IOP pre and post Injections. It showed similarity with above mention studies.

Table 2: Descriptive Statistics of the Study

	Minimum	Maximum	Mean	Std. Dev.
Intravitreal Antivegf Injections	2.00	4.00	2.68	0.74
Follow-up Visits	2.00	6.00	3.72	0.93

Mean Intravitreal Anti VEGF injections given were 2.68 and mean follow up visit was 3.72. (Table 2).

Table 3: Intravitreal Antivegf Injections and RVO

Number	Mean	Injections	Std. Dev.	P-value
BRVO	19	2.68	0.74	0.98
CRVO	6	2.66	0.81	

Mean 2.68 Intravitreal Antivegf Injections were given in BRVO group and Mean 2.66 Intravitreal Antivegf Injections were given in CRVO group. (Table 3). Pre-existing Systemic Disease like Hypertension was found in 17 (68%) patients and diabetes in 9 (36%) patients. One patient (4%) also had pre-existing hypercholesteremia in our study group. Both Hypertension and diabetes mellitus was found in 5 patients. Ehlers[21] noted Pre-existing conditions included hypertension in 42 (79%) and diabetes in 18 (34%) in his study. The eye disease case control study found that an increased risk occurred in any type of Venous occlusive disease in those patients with systemic hypertension and DM. Several authors Dodson[22], Hayreh[23], Johnson[24] have reported the incidence of diabetes in patients with CRVO to found to vary from 13-34%. Association of hyperlipidemia with central retinal vein occlusion has been reported. The incidence of hyperlipidemia has been found to be low as reported by Walters[25] and Frucht[26]. Because of

small group of patients, we could not appreciate hyperlidemia and other pre-existing systemic disease association in our study group. Required Laser treatment was given to 20% of the patient due to significant hypoxic retina secondary to RVO where Pan retinal photocoagulation was done in 20% patients and sectoral laser treatment offered in 4% of patients in present study. Out of 25 patients 6 patients required Laser treatment. In this PRP was done to 5 CRVO cases and Sectoral Laser done in 1 BRVO case. Similarly, Jumper[19] reported that panretinal photocoagulation done in 5.5% patients and sectoral laser in 0.6% patients. Shah N and Shah[27] were to evaluate the effect of single-dose intravitreal bevacizumab followed by panretinal and macular grid laser, early in the course of CRVO and showed rapid improvement in the form of rapid clearance of retinal hemorrhages, decreased optic disc swelling, venous dilation and tortuosity.

Table 4: Macular Thickness Wise Distribution of the Study

	Mean	Std. Dev.	Mean Diff.	Improvement	P value
Pre-treatment	536.12	253.62	285.84	53.3%	0.001 (S)
Post-treatment	250.28	76.38			

The central macular thickness was evaluated prior to the intervention with the help of OCT. Before treatment mean macular thickness was 536.12 um which was reduced to 250.28 um after treatment with Antivegf injections. There was 53.3% improvement which was found to be statistically significant. Similarly Qureshi[16] indicted mean CRT of 527µm at baseline that decreased to 274µm after 12 weeks of IVB treatment. In another Study by Algvere[15] also showed strong similarity in patients receiving intravitreal Antivegf injections of bevacizumab diagnosed with CRVO demonstrating average foveal thickness of 596 um at baseline and improved to 288um at 6 months (p<0.005) Foveal thickness showed a substantial decline at 6 weeks after one single IVB, on an average reduction to half of the baseline value. Iturralde and associates[28] described that the mean central macular thickness at baseline was 887 micron and decreased to a mean of 372 micron at 1 month (P<0.001). In Our study, Pre-treatment Mean CRT was 531.78µm which was significantly reduced to mean CRT of 235.1 µm in BRVO patients whereas mean CRT of 625.33µm which was significantly reduced to mean CRT of 270.16 µm was seen in CRVO patients. Group based similarity also showed by Qureshi[16] where mean CRT was reduced significantly from 468.7µm to 257.36µm in BRVO group while in in CRVO group, it was significantly reduced from 617.8µm-310.5µm. Present study showed consistancy with other studies.(Table 4). Mean Macular thickness was 531.78 micron which was significantly reduced to 235.1 micron in BRVO patients after Antivegf injections. (P value 0.001). Mean Macular thickness was 625.33 micron which was significantly reduced to 270.16 micron in CRVO patients after Antivegf injections. (P value 0.001) .

Table 5 : Visual Acuity (BCVA) Wise Distribution of the Study

	Mean	Std. Dev.	V/A	P-value
Pre-treatment	0.987	0.495	6/48	0.001 (S)
Post-treatment	0.386	0.192	6/12	

In our study, baseline visual acuity was 0.98 log MAR (6/48) which improved to 0.38 log MAR (6/12). The improvement was statistically significant (p value 0.001). Haritoglou[29] recorded a baseline visual acuity of 0.86 log MAR of Snellens letters which improved to 0.75. Qureshi[16] also showed that at base line mean visual acuity was Log MAR 0.73 and showed improvement to mean Log MAR 0.39 at 12 weeks after intravitreal Bevacizumab (IVB) injection. They also showed that in CRVO group, the mean LogMAR VA 0.91 was improved significantly (p<0.022) to 0.49 and in BRVO group mean LogMAR VA of 0.62 was significantly improved (p<0.003) to 0.36. In present study, Mean LogMAR VA was significantly improved in both BRVO (0.97-0.31) and CRVO (0.98-0.28) after treatment with injections. Results of Hkassan[31] showed that intra-vitreal Bevacizumab treatment in patients with macular edema secondary to RVO was associated with a significant improvement in visual acuity (p<0.05) after 3 months follow up. Prospective study by Algvere[15] demonstrated significant improvement at 6 months the mean increase in BCVA was 24 ETDRS letters (LogMAR 0.48) from 0.13 (LogMar 0.86) at baseline to 0.4 (LogMar 0.38). Increase in BCVA from baseline was statistically significant (p<0.005) at each point. In a study with short term follow up by Iturralde and associates (2006)29 16 eyes of RVO were treated with macular oedema with intravitreal bevacizumab in which intravitreal corticosteroid therapy had failed, nearly every patient showed anatomical and visual improvement. The mean baseline acuity was 20/600 (logMAR=1.48) and the mean acuity at month 1 was 20/200 (logMAR=1.05), a difference that was highly significant (P = 0.001). At last follow-up, a mean of 3 months after the first injection was calculated and the mean visual acuity was 20/138 (logMAR = 0.84), which was significantly better than baseline (P<0.001). The results of the present study were found to be consistant with other studies. (Table 5).

Table 6 : RVO and Visual Acuity (VA) LogMar

		Mean	Std. Dev.	V/A	P-value
BRVO	Pre	0.93	0.48	6/48	0.001 (S)
	Post	0.35	0.15	6/12	
CRVO	Pre	1.32	0.57	6/120	0.005 (S)
	Post	0.506	0.25	6/19	

Mean LogMAR visual acuity was 0.93 which was significantly improved to 0.35 in BRVO. (P value 0.001).Mean LogMAR visual acuity was 1.32 which was significantly reduced to 0.50 in CRVO. (P value 0.001) (Table 6). RVO cause visual loss due to initial hypoxia and delayed macular oedema. The oedema may cause an additional reduction in visual acuity that often exceeds the primary ischaemic damage[32]. The central retinal vein occlusion study showed negative results of

laser treatment (showed no benefit over the control group), which lead to its abandonment[33]. The optimal treatment protocol for IVB is still unknown. A study[34] by Wu L (2008) *et al* had examined the differences in clinical response between 1.25mg of Intravitreal Bevacizumab (IVB) and 2.5mg of IVB and found no significant difference in functional and anatomical outcomes. Regarding duration of injection intervals, many clinicians give a series of injections followed by an assessment of clinical response. With monthly injections for 6 months, the BRAVO study showed impressive visual acuity results[35]. However, IVB may not require monthly dosing to get an optimal therapeutic response. An optical coherence tomography-guided treatment protocol with IVB resulted in a significant improvement in ME and visual acuity with a mean of 2.9 injections over 59 weeks[36]. Based on recommendations from the Branch Vein Occlusion Study[37], the traditional approach to Macular oedema (MO) has been to wait for 3 months before initiating treatment. However, evidence is accumulating that earlier treatment may improve outcome in eyes with BRVO. The study proved to the existing evidence that earlier intervention with anti-VEGF therapy may result in improved functional outcome. The 12-month results from the Phase III BRAVO study demonstrated that earlier treatment with intravitreal ranibizumab resulted in greater improvement in visual acuity. The sham group showed improvement once anti-VEGF therapy was initiated at 6 months., however, the gain in visual acuity did not reach the level achieved in the groups treated earlier in the disease course. Thus, the purpose of this study was to determine the visual outcome (Best corrected visual acuity) and the macular thickness after anti-VEGF injections in eyes with macular edema associated with RVO. In the present study, Minimum 2 injections and Maximum 4 injections were given to patients of RVO and on an average 2.68 injections in BRVO patients and 2.66 injections were required in CRVO patients. Many other reports including Iturralde and associates[29] showed that average 2.8 intravitreal Anti-vegf injections were given for macular edema secondary to CRVO. In a study using health insurance claims from a database covering 64 million individuals in the USA from 2008 to 2011, almost all anti- VEGF injections administered for treatment of RVO were bevacizumab and for patients who began treatment with bevacizumab in 2010, the mean annual number of injections was only 3.3 for patients with BRVO and 3.5 for patients with CRVO[30]. In present study of 25 people showed comparable data regarding average number of injections received.

CONCLUSION

Optical coherence tomography is a very essential and important diagnostic and prognostic tool for assessment and management of macular oedema seconday to venous occlusions. Macular oedema showed considerable reduction in macular thickness with visual improvement after intravitreal Antivegf Injections. The current study concludes that Antivegf administered intravitreally improved visual acuity by decreasing macular oedema significantly caused by retinal vein occlusion. This study provided additional evidence that the use of intravitreal Antivegf injection give viable option for treating macular oedema secondary to RVO and further supports the notion that earlier intervention with anti-VEGF therapy results in better visual prognosis.

Limitation: The number of patients in the study were small also and 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. Recurrent Macular Oedema and refractory cases can only be identified by the help of long-term follow up in RVO patients. Long term study is needed to determine the differential effectiveness of Intravitreal Bevacizumab compared with Ranibizumab and to identify long term potential side effects of Antivegf injections, the optimal timing of treatment initiation, and appropriate dosing intervals.

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