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Research Article

Evaluation of the Efficacy of Single Dose of Intravitreal Bevacizumab in the Management of Macular Edema due to Retinal Vein Occlusions

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Abstract

Aim: Evaluation of the efficacy of single-dose intravitreal Bevacizumab in the management of macular edema due to retinal vein occlusions.

Objectives:

1. To evaluate the efficacy of single-dose intravitreal bevacizumab in the management of macular edema due to retinal vein occlusions in terms of reduction in central macular thickness.
2. To evaluate the efficacy single dose of intravitreal bevacizumab in the management of macular edema due to retinal vein occlusions in terms of improvement in visual acuity.
3. To evaluate the change in the Intraocular pressure in the eyes receiving intravitreal Bevacizumab.

Methods: This study was an Institutional Review Board approved prospective interventional study done in a Retina clinic at a tertiary eye hospital, where 45 patients were enrolled. All patients clinically diagnosed to have retinal vein occlusions with macular edema with all risk factors were enrolled for the study. After informed consent, all participants were subjected to the following examinations, visual acuity was recorded on Snellen's vision chart, followed by anterior segment evaluation, intraocular pressure, gonioscopy, slit-lamp biomicroscopy with 90D lens and fundus finding were confirmed by indirect ophthalmoscopy. Optical coherence tomography was done in every patient. The diagnosis of macular edema was established by clinical examination and optical coherence tomography was done to quantify central macular thickness (CMT) at baseline, 4 weeks and 8 weeks after a single injection of 1.25 mg (0.05 ml) intravitreal Bevacizumab.

Results: The mean central macular thickness (CMT) at presentation was 482.88 µm ± 173.6 µm (SD). The mean CMT decreased from baseline to 314.3 µm ± 129.9 µm at one month. The mean CMT decreased to 237.1 µm ± 97.08 µm at the end of 2 months which was statistically significant ($p < 0.05$). The logarithm of minimal angle of resolution (logMAR) vision at presentation 1.043 ± 0.443 improved to 0.690 ± 0.424 and 0.529 ± 0.440 at 1 month and 2 months respectively ($p < 0.05$). There was no statistically insignificant change in IOP after a single injection of Bevacizumab.

Conclusion: Intravitreal Bevacizumab even in a single dose is effective in the treatment of all types of retinal vein occlusions. There was a statistically significant improvement in visual acuity, the decrease in the central macular thickness was also statistically significant and effects were maintained throughout the follow-up period without any changes in IOP.

Keywords: Retinal Vein Occlusions; Macular Edema; Intravitreal Bevacizumab; Optical Coherence Tomography; Center Macular Thickness; Visual Acuity; Intraocular Pressure

Abbreviations

CMT: Central Macular Thickness; OCT: Optical Coherence Tomography; logMAR: Logarithm of Minimal Angle of Resolution; SD: Standard Deviation; IOP: Intraocular Pressure; BCVA: Best Corrected Visual Acuity; BRVO: Branch Retinal Vein Occlusion; CRVO: Central Retinal Vein Occlusion

Introduction

In elderly patient Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy leading to vision loss. There are two different types, based on the site of occlusion. In branch retinal vein occlusion, the occlusion is typically at an arteriovenous intersection. In central retinal-vein occlusion, the block is at or proximal to the lamina cribrosa of the optic nerve, where the central retinal vein exits the eye [1].

The prevalence of Retinal vein occlusion in patients over 40 years of age is 1 - 2% and affects 16 million persons worldwide [2,3]. Branch retinal-vein occlusion is four times as common as central retinal vein occlusion [4]. 10-year incidence of retinal-vein occlusion was found to be 1.6% in a population-based cohort study [5]. Bilateral retinal-vein occlusion is uncommon (occurring in about 5% of cases), although, in 10% of patients with retinal-vein occlusion in one eye, occlusion develops in the other eye over time [6]. Both branch retinal-vein occlusion and central retinal vein occlusion are further divided into the categories of perfused (non-ischemic) and nonperfused (ischemic), each of which has implications for prognosis and treatment.

Vision loss from retinal vein occlusion is mainly due to macular ischemia, macular edema, or complications of the neovascular disease. Visual acuity depends on the extent of macular involvement from 6/6 to counting fingers [7]. Many patients with branch retinal vein occlusion have a good prognosis, with one study showing that half had a return to 20/40 vision or better within 6 months, without treatment [8].

Fluorescein angiography has been critical for differentiating between the ischemic and nonischemic type of vein occlusion and detecting macular edema by identifying the characteristic stellar pattern of cystoid macular edema. By correlating results from fluorescein angiography and optical coherence tomography (OCT), fluid accumulation within and under the sensory retina can be confirmed and localised [9].

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. Recently, intraocular injections of anti-VEGF such as Bevacizumab, ranibizumab, and pegaptanib have shown to reduce vascular leakage resulting in improvement in macular edema and accelerate resorption of retinal hemorrhages and prevent worsening of capillary nonperfusion. The ideal regimen has not been defined, but it appears that monthly injections early in the course control edema and may help to limit disease severity in a large percentage of patients [10].

Treatment modalities include grid pattern laser photocoagulation, intravitreal bevacizumab, and intravitreal triamcinolone acetonide injection. Laser treatment of cases with media opacity, such as retinal hemorrhage and cataract, is challenging, and laser treatment is only effective for non-ischemic type macular edema. However, intravitreal triamcinolone acetonide injections are also associated with complications such as the formation of cataracts and an increase in intraocular pressure [11]. Intravitreal bevacizumab appears to be an effective treatment for macular edema secondary to retinal vein occlusion. Eyes treated with intravitreal bevacizumab showed a significant reduction in central foveal thickness and improvement in visual acuity [12].

So, our study is to evaluate the efficacy of a single injection of intravitreal bevacizumab in the treatment of macular edema due to retinal vein occlusions using optical coherence tomography and visual acuity.

Materials and Methods

This was a Prospective, clinical interventional study. All patients attending Retina Clinic in a tertiary eye hospital, which are diagnosed cases of Retinal vein occlusion and fulfilled the inclusion criteria, were included. Clearance from the hospital ethical committee and the scientific committee was obtained to conduct the study. Before the patients were enrolled in the study, written informed consent was taken from all. Patients included for the study were a total of 45 eyes of 45 patients of clinically diagnosed cases of Retinal vein occlusion with macular edema confirmed with Optical coherence tomography (Stratus OCT™, Carl Zeiss Meditec Inc., USA).

Patients with any media opacities preventing adequate visualization of the fundus, patients with a history of macular edema due to diabetic retinopathy, vitreous hemorrhage, neovascular glauco-

ma, optic atrophy, macular degeneration, and patients with a history of laser or intravitreal injection in the past in the affected eye were excluded from the study. In the case of uncontrolled systemic diseases like hypertension, diabetes mellitus, hyperlipidemia, systemic evaluation and treatment collaborated with general physician and fitness was obtained for the procedure for all patients.

At baseline, visual acuity was recorded on Snellen's vision chart and converted to log MAR (logarithm of the minimal angle of resolution) for statistical analysis, followed by anterior segment evaluation, intraocular pressure was recorded by Goldmann Applanation tonometry, gonioscopy was done using Sussman 4 mirror goniolens, Fundus finding was confirmed by, indirect ophthalmoscopy, and slit-lamp biomicroscopy with 90D lens. Optical coherence tomography was done in every patient. The diagnosis of macular edema was established by clinical examination and optical coherence tomography was done to quantify central macular thickness (CMT). These details were entered in a pre-structured proforma.

Written informed consent was taken from the patient after informing them about the documented adverse effects of the drug as well as the off label status of usage of drug. The patients enrolled for the study were administered a single dose of Intravitreal Bevacizumab 1.25 mg (0.05 ml) under strict aseptic conditions in Operation theatre. Post injection patients were started on topical antibiotics.

After the injection, patients were followed up at regular intervals, on 3rd day, 1 week, 1 month, and 2 months. At 1 month and 2 months after the initial injection, all the baseline investigations and tests were repeated and data was recorded. Data were entered in Excel and Data analysis was done with the help of SPSS 20.0 statistical software. A paired t-test was used to compare the mean CMT, BCVA and IOP values between time points before and after intravitreal Bevacizumab. We tested the statistical significance (at the confidence interval of 95%) of differences for each of these parameters between the initial values and the values at various time points of 1 month and 2 months after injection.

Results and Discussion

In this study majority of the patients (73.4%) were in the age group of 51-70 years, establishing the fact that retinal vein occlusion is more common in the 5th and 6th decade of life. The male to female ratio was found to be 1.14:1; there was no significant sexual predilection for retinal vein occlusion seen in our study. In our study right eye was affected in 60% and left eye in 40% of patients (Table 1).

Age Group	Frequency	Percent
31 - 40 Years	2	4.4
41 - 50 Years	6	13.3
51 - 60 Years	17	37.8
61 - 70 Years	16	35.6
71 - 80 Years	4	8.9
Sex	**Frequency**	**Percent**
Male	24	53.3
Female	21	46.7
Laterality	**Frequency**	**Percent**
Right	27	60.0
Left	18	40.0
Total	45	100.0

Table 1: Demographics data.

In our study, CRVO was found in 42.2% patients, BRVO in 48.9% patients, hemicentral retinal vein occlusion in 6.7% patients, and Tributary retinal vein occlusion (TRVO) in 2.2%. In patients with BRVO, the majority of patients 59.1% (13 out of 22) had superotemporal quadrant BRVO, and 40.9% (9 out of 22) had inferotemporal quadrant BRVO, none of the patients had nasal quadrant BRVO (Figure 1).

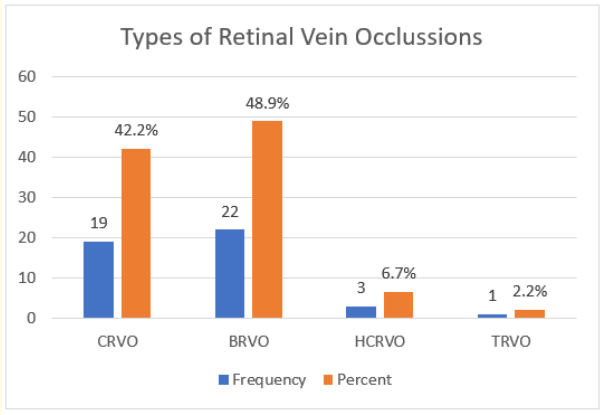

Figure 1: Types of retinal vein occlusion in the study.

The mean central macular thickness (CMT) at presentation was 482.88 µm ± 173.6 µm (SD). The mean CMT decreased from baseline to 314.3 µm +129.9 µm at 1 month. The mean CMT decreased to 237.1 µm ± 97.08 µm at the end of 2 months. The difference in the central macular thickness was statistically significant ($p < 0.05$) at 1 month and 2 months from the baseline (Figure 2).

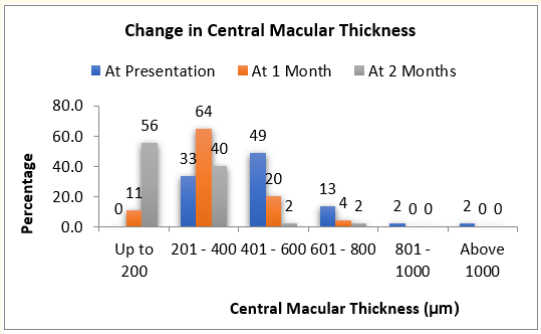

Figure 2: Distribution of central macular thickness after injection at subsequent visits.

The logarithm of minimal angle of resolution (logMAR) vision at presentation 1.043 ± 0.443 improved to 0.690 ± 0.424 and 0.529 ± 0.440 at 1 month and 2 months respectively. The improvement in the visual acuity was found to be statistically significant ($p < 0.05$) at 1 month and 2 months and was maintained (Table 2).

The intraocular pressure recorded by Goldmann applanation tonometry was 16.73 mmHg ± 2.623 mmHg at baseline. The mean IOP at 1 month was 17.09 mmHg ± 2.592 mmHg. The mean IOP at 2months was 16.62 mmHg ± 2.534 mmHg. There was no statistically significant change in IOP noted (Figure 3).

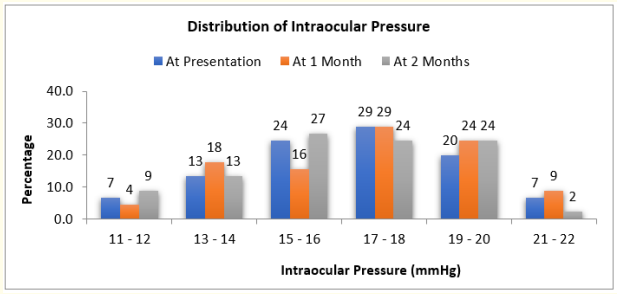

Figure 3: Comparison of the IOP at presentation, at 1 month and 2 months post injection.

No intraoperative complications were encountered. No other ocular complications such as retinal detachment, vitreous hemorrhage, or endophthalmitis were observed and no systemic complications such as myocardial infarction and cerebral infarction were observed during the course of the study.

Visual Acuity	At Presentation		At 1 Month		At 2 Months	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
1/60	6	13.3	2	4.4	1	2.2
2/60	6	13.3	1	2.2	1	2.2
3/60	2	4.4	1	2.2	1	2.2
4/60	0	0.0	1	2.2	2	4.4
5/60	7	15.6	3	6.7	1	2.2
6/60	9	20.0	6	13.3	4	8.9
6/36	4	8.9	6	13.3	5	11.1
6/24	3	6.7	7	15.6	3	6.7
6/18	6	13.3	7	15.6	5	11.1
6/12	1	2.2	4	8.9	6	13.3
6/9	1	2.2	5	11.1	11	24.4
6/6	0	0.0	2	4.4	5	11.1
Total	45	100.0	45	100.0	45	100.0

Table 2: Comparison of the best corrected visual acuity after injection at subsequent visits.

Discussion

Laser photocoagulation applied in a grid distribution was shown to improve macular edema in the Branch and Central Vein Occlusion Study, but there was no improvement in visual acuity [13,14]. Other treatments such as laser-induced chorioretinal anastomosis, intravitreal tissue plasminogen activator and radial optic neurotomy have failed to show favorable results consistently. Intravitreal VEGF inhibitors are recently evaluated and many retrospective case series and prospective trials have shown positive effects of anti VEGFs in reducing macular edema and improving visual acuity in the patients with retinal vein occlusion. Our study shows the efficacy of a single injection of intravitreal bevacizumab in the treatment of retinal vein occlusion.

In our study, the mean age was 59.3 years with a range of 32 to 80 years. The majority of the patients 73.4% (33 out of 45) were in 51 - 70 years age group. RVO was found to be more prevalent in the 5th and 6th decade of life. Kazuyuki., *et al*. reported the mean age of the patients was 66.1 ± 10.7 years with a range from 34 years to 91 years in their study [15]. Costa., *et al*. in his study reported that the median age of the patients was 65 years (range, 58 - 74 years) [16]. Our study results were also similar to these studies.

There was no significant sexual predilection for the development of retinal vein occlusion seen in our study. Klein., *et al*. in the Beaver Dam Eye Study, found that the incidence of retinal vein occlusion was similar in men and women, our study results are also similar [3]. Ehlers., *et al*. in their study, bevacizumab for macular edema secondary to branch retinal vein occlusion, reported 53% of male patients and 47% of female patients, this was similar to our study [12].

The incidence of retinal vein occlusion was found to be more in the right eye in our study. Ehlers., *et al*. Bevacizumab for macular edema secondary to branch retinal vein occlusion, found that the right eye was involved in 59% of subjects and left eye in 41% of subjects [12]. Klein., *et al*. in their study, found that the incidence was similar in right and left eye, it did not match our study and the possible reason could be the small sample size in our study [3].

In patients with BRVO, the majority of patients 59.1% (13 out of 22) had superotemporal quadrant BRVO and 40.9% (9 out of 22) had inferotemporal quadrant BRVO, none of the patients had nasal quadrant BRVO. Klein., *et al*. reported that of the eyes with retinal vein occlusion, the site of the branch vein occlusion involved the superotemporal quadrant in 58.1% of eyes (18/31), the inferotemporal quadrant in 29% of eyes (9/31), and outside the temporal quadrants in 12.9% of eyes (4/31) [3]. Our study also showed similar results with the superotemporal quadrant being the most common site.

There was a statistically significant decrease in the central macular thickness measured by OCT after injection of intravitreal Bevacizumab at 1 month and 2 months which was maintained over the follow-up period (Figure 4). Iturradle., *et al*. in his study, 16 eyes of 15 patients were treated, the mean central macular thickness was 887 µm and decreased to 372 µm at 1 month after injection. The mean follow-up was 3 months and the decrease in CMT was maintained in his study [17]. In a study by Figuerao., *et al*. in Spain, 18 eyes with CRVO, and 28 eyes with BRVO were treated. The mean central macular thickness decreased to 268.2 µm (SD 62.5 µm) at 6 months from 486.9 µm (SD 138.5 µm) at baseline in the BRVO group and to 326.17 µm (SD 96.70 µm) in CRVO group [18]. Epstein., *et al*. in his prospective clinical trial of 30 patients with CRVO, received bevacizumab and 30 control patients received a sham injection, at the end of 6 months, the mean decrease in CMT was significantly greater, 426 µm in the study group than in the control group (102 µm). No residual edema was found in 26 of 30 patients (86.7%) in the study group as compared with 6 of 30 patients (20%) in the control group [19]. Our study showed similar results to these studies.

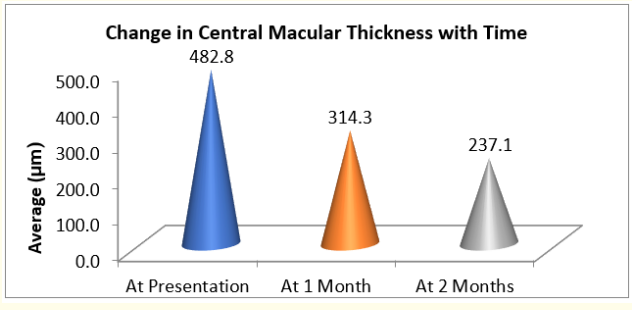

Figure 4: Comparision of reduction of central macular thickness ($p < 0.05$ statistically significant).

There was a significant change in the BCVA observed in the patients after the injection of bevacizumab and was maintained at the follow-up visit (Figure 5). Iturrdale., *et al*. in their study, treated 16 eyes of 15 patients. 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 the last follow-up, a mean of 3 months after the first injection, the mean visual acuity was 20/138 (logMAR = 0.84), which was significantly better than baseline (P < 0.001) [17]. Figuerao., *et al*. in their study found that in the BRVO group mean baseline logMAR visual acuity was 0.80 (SD 0.38) it improved to 0.44 (SD 0.34) at 6 months. In the

CRVO group, the baseline logMAR values were 1.13 (SD 0.21) and it improved significantly to 0.83 (SD 0.45) at 6 months [18]. Epstein., *et al*. in their trial, had 30 patients with CRVO who received bevacizumab and 30 control patients who received a sham injection. At the end of 6 months, 18 of 30 patients (60%) in the study group gained more than 15 letters compared with 6 of 30 patients in the control group (P = 0.003) [19]. Our study results were comparable to these studies.

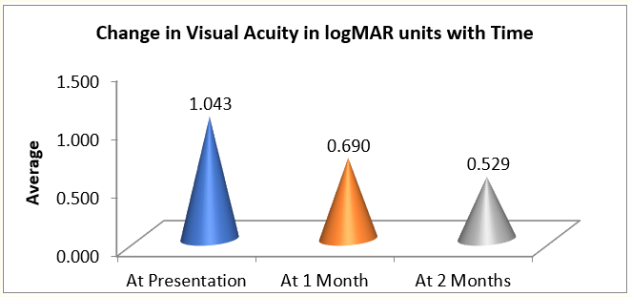

Figure 5: Change in visual acuity in logMAR units with time (p < 0.05 statistically significant).

There was no significant change in IOP noted after the injection, the p-value at 1 month was (p = 0.207) and at 2 months (p = 0.708), the p-value was greater than 0.05 which implies there was no statistically significant difference (Figure 6). Algevre PV., *et al*. intravitreal bevacizumab in CRVO, 18-months results of a prospective clinical trial, reported no increase in IOP at baseline it was 15.2 mmHg and 15.8 mmHg at the end of their study [20]. Ali RI., *et al*. in their study found that the mean IOP was 21 mmHg at 1 month and 15 mmHg at the end of 3 months [21]. There was no raised IOP noted in the above studies and our results also match these studies.

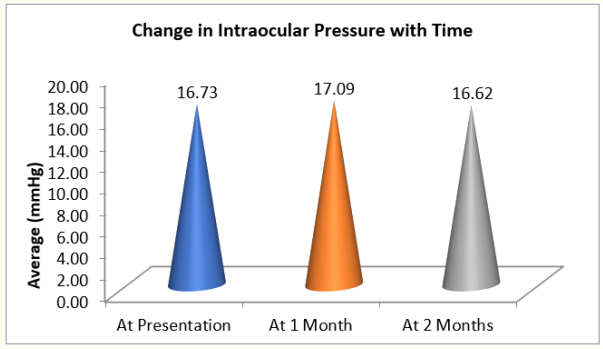

Figure 6: Change in intraocular pressure after injection (p > 0.05 statistically insignificant).

Pai, Sivakami A., *et al*. clinical, anatomic, and electrophysiologic evaluation following intravitreal bevacizumab for macular edema in retinal vein occlusion, concluded that no ocular toxicity or adverse effects were noted with the use of intravitreal bevacizumab in their study [22]. During our study period, we did not find any case of angle or iris neovascularization or adverse drug reaction. Our study showed similar results when compared with other published studies for treatment of macular edema due of Retinal vein occlusion with intravitreal bevacizumab (Table 3).

Similar Studies	Number of patients	Baseline CMT (µm)	Baseline BCVA	CMT at the end of study	BCVA at the end of study
Iturrdale., *et al*. [17]	16	887	20/600	372	20/138
Figuerao., *et al*. [18]	46	486	logMAR 0.80	268	logMAR 0.44
Kazuyuki., *et al*. [15]	41	554	logMAR 0.52	350	logMAR 0.31
Jason HS., *et al*. [23]	29	418	20/200	285	20/80
Rabena., *et al*. [24]	27	478	20/200^{-}	332	20/100
This study	45	482	logMAR 1.043	237	logMAR 0.529

Table 3: Comparisons of outcomes of other published studies with our study.

Limitations of the Study

The study did not take into consideration if the retinal vein occlusion was ischemic or nonischemic. FFA was not done for all the patients routinely. The study did not take into consideration the time from onset of symptoms and presentation to the hospital. The patients requiring repeat injection after the completion of the study are not discussed here. Short follow up period, small sample size, and absence of a control group are limitations to conclusively demonstrate the advantages of the intravitreal bevacizumab.

Conclusion

Intravitreous bevacizumab has the advantages of simplicity, relative safety, and is cost-effective when compared to the other treatments. Thus, we conclude that intravitreal bevacizumab even in a single dose is effective in the treatment of all types of retinal vein occlusions. The effects were maintained throughout the follow-up period and there was a statistically significant improvement in visual acuity and decrease in the central macular thickness.

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Conflict of Interest

The study was funded by Arasan Eye Hospital Research Committee, Erode, Tami Nadu, India. The author(s) declare(s) that there is no conflict of interest.

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