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A Study on Effectiveness of Intravit Real Ranibizumab for Management of Different Retinal Vascular Disorders

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Abstract:-

- ***Introduction:***

Angiogenesis is a physiological process in which pre existing vessels develop into new ones. The earliest type of angiogenesis to be discovered was sprouting angiogenesis. It goes through a number of distinct stages. First, endothelial cells in veins that already exist have their receptors activated by angiogenic growth factors. Then the release of proteases enzymes is initiated by activated endothelial cells, to break down the basement membrane, enabling the endothelial cells to move away from the original vessel walls. Thereafter, the endothelial cells multiply inside surrounding matrix and create sturdy shoots that join nearby vessels. Using Adhesion molecules called integrins, endothelial cells migrate in synchrony with sprouts as they extend toward source of angiogenic stimulus. As cells move to the site of angiogenesis, these sprouts eventually develop into loops that eventually produce a fully developed vessel lumen. Sprouting allows new vessels to develop over gaps in vasculature and happens at a rate of several millimeters each day. But unlike splitting angiogenesis, it generates whole new vessels instead of splitting old ones, which makes a significant difference. VEGF, also known as Vascular Endothelial Growth Factor, has been proven to play significant role in angiogenesis. Elevated levels of VEGF-A are found in vitreous fluid of patients with diabetic retinopathy, wet age related macular degeneration, macular edema due to venous occlusions.

- ***Aim of the Study:***

To assess the safety and effectiveness of intra vitreal Ranibizumab in treating different retinal vascular disorders.

- ***Patients and Methodology:***

This is prospective study, done at Department of Ophthalmology, Katuri Medical College and Hospital from September 2022 to August 2023, spanning a period of 1 year. This study included patients with proliferative diabetic retinopathy, central retinal vein occlusion, branch retinal vein occlusion, Wet age related macular degeneration. This study excluded existence of any retinal disorders that could impact visual acuity and the development of significant cataracts. Comprehensive medical and ocular history was obtained on the initial visit. All patients received comprehensive ophthalmic examinations. 1. Best corrected visual acuity for distance and near vision. 2. Intraocular pressure measurement. 3. Ophthalmic examination with a slit lamp 4. Fundoscopy 5. Fundus photography 6. Fundus fluorescein angiography 7. Macular thickness assessment using Optical Coherence Tomography.50 eyes from 50 patients were examined. Follow-up was conducted at 3 days, 2 weeks, 1 month, and then monthly for 6 months.

- ***Results:***

The majority of patients are within age range of 51-60 years. Among 50 responders, 29 were female and 21 were male. 50 patients have received an injection ranibizumab in one eye. There were 33 cases of diabetic retinopathy, 3 cases of branch retinal vein occlusion, 3 cases of central retinal vein occlusion, and 11 cases of age-related macular degeneration.50 eyes were administered 0.5mg of Ranibizumab (Lucentis) in 0.05ml. Visual acuity improved in 40 eyes (80%) and remained unchanged in 10 eyes (20%).Visual acuity significantly improved one month after injection and continued to improve in all subsequent follow-up visits.A statistically significant association was found between periodic injections and increase in visual acuity.

Thirty-three patients exhibited PDR. 27 eyes showed improvement, while 6 eyes remained unchanged.

BRVO was observed in three cases. Two eyes showed improvement, while one eye remained unchanged.

CRVO was observed in three cases. Two eyes showed improvement, while one eye remained unchanged.

Age-related macular degeneration (ARMD) was observed in 11 cases. 9 eyes showed improvement while 2 eyes remained unchanged.

- ***Conclusion:***

Ranibizumab shows efficacy in treating several retinal vascular disorders. Best corrected visual acuity improvement was statistically significant. Ranibizumab's impact seems to be temporary, requiring further injections if recurrences occur.

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Complications from the procedure are quite uncommon. Ranibizumab appears to be a safe treatment choice for people who do not respond to traditional laser photocoagulation.

Keywords:- *Proliferative Diabetic Retinopathy(PDR), Age Related Macular Degeneration(ARMD),Branch Retinal Vein Occlusion(BRVO),Central Retinal Vein Occlusion(CRVO), Ranibizumab (Lucentis).*

I. INTRODUCTION

A. Angiogenesis

Angiogenesis is a natural process in which new blood vessels develop from old ones. Despite the existence of differing opinions on this matter, Vasculogenesis refers to the spontaneous creation of blood vessels, while intussusception describes the process of new blood vessel production by splitting off from pre-existing ones.

Angiogenesis is the formation of fragile structures lined with endothelial cells, sometimes with a smooth muscle layer and pericytes. This has essential role in maturity by acting as a "repair mechanism" for damaged tissues.

B. Vascular Endothelial Growth Factor (VEGF)

VEGF, or Vascular Endothelial Growth Factor, have crucial function in angiogenesis, the process of forming new capillaries within specific network. The early in vitro tests showed that bovine capillary endothelial cells display proliferation and development of tube-like structures when activated by VEGF and b FGF. The effects were more noticeable with VEGF. Research is being conducted to explore the possible therapeutic benefits of increased VEGF expression in promoting angiogenesis for treating vascular damage.

In vitro studies, clearly demonstrate that VEGF strongly promotes angiogenesis, since it causes endothelial cells to multiply and migrate, ultimately resulting in the formation of tube-like structures that resemble capillaries. VEGF triggers significant signaling cascade in endothelial cells.Activation of VEGF receptor -2 (VEGFR-2) initiates series of chemical reactions that activate a tyrosine kinase, leading to the production of factors that promote different effects on blood vessels. These effects include increased vessel permeability (through eNoS, which produces nitric oxide), cell growth and survival (through Bfgf), cell movement (through ICAMSNCAMs/MMPs), and ultimately the development of fully functional blood vessels.

Physiologically, VEGF expression is enhanced through mechanical stimulation caused by muscle contractions, leading to augmented blood perfusion in the affected regions. The heightened flow additionally results in a substantial augmentation in the mRNA synthesis of VEGF receptors 1 and 2. The rise in receptor synthesis implies that muscle contractions could stimulate the upregulation of the signaling cascade associated with angiogenesis. NO is widely recognized as a crucial component to the angiogenic response in the angiogenic signaling cascade. Significantly reducing NO inhibits the impacts of angiogenic growth factors. Nevertheless, the suppression of nitric oxide (NO) during physical activity does not impede the process of angiogenesis, suggesting the presence of additional components contributing to the angiogenic response.

II. STUDY OBJECTIVES

To assess the safety and effectiveness of intravitreal Ranibizumab in treating different retinal vascular disorders.

III. PATIENTS AND METHODOLOGY

This prospective study was done at Department of Ophthalmology, Katuri Medical College and Hospital from June 2022 to May 2023,spanning a period of 1 year.

- *Conflict of Interest: NIL.*

- *Inclusion Criteria*

- Patients diagnosed with Proliferative Diabetic Retinopathy.
- Patients diagnosed with central and branch retinal vein occlusion.
- Patients diagnosed with wet Age related Macular Degeneration.

- *Exclusion Criteria*

- Presence of other retinal disorders impacting Visual Acuity.
- Presence of cataract.

Comprehensive medical and ocular history was obtained on initial visit. All patients received comprehensive ocular examinations.

- Best corrected visual acuity for distance and near vision
- Intraocular pressure measurement
- Ophthalmic Examination using a slit lamp
- Fundoscopy
- Fundus photography
- Fundus Fluorescein Angiography
- Macular thickness measured using Optical Coherence Tomography (OCT)

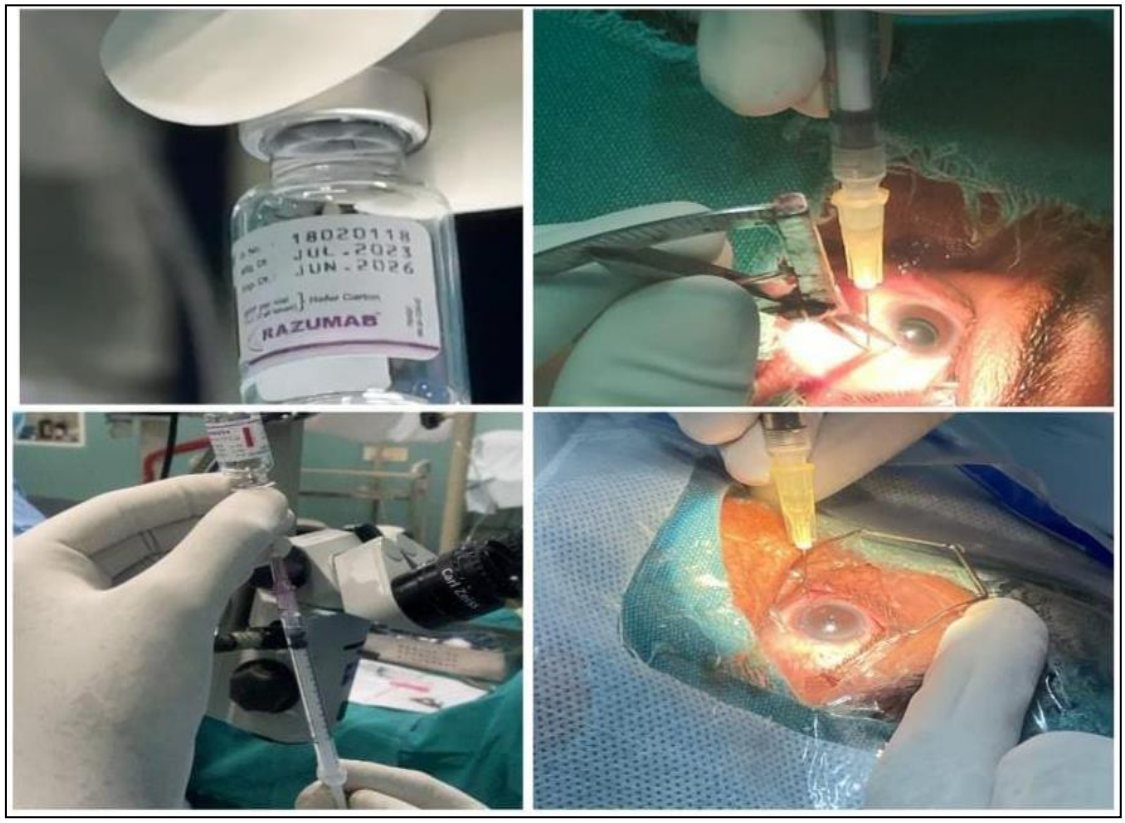

Fig. 1: Procedure of Intra vitreal Injection

IV. RESULT

During the study period from September 2022 to August 2023, 50 eyes of 50 patients got intra vitreal injection of 0.5mg in 0.05ml of Ranibizumab (Lucentis). This study involved individuals diagnosed with Diabetic Retinopathy, Branch Retinal Vein Occlusion, Central Retinal Vein Occlusion, and Age-related Macular Degeneration.

A. Age Distribution

Table 1: Distribution of Patients by their Age

Age Group (Years)	No. of Patients	Percentage (%)
30-40	2	4
41-50	12	24
51-60	23	46
61-70	10	20
71-80	3	6
Total	50	100

As observed in age distribution (Table-1 & Figure-1) 4% of patients were aged 30-40, 24% were aged 41-50, 46% were aged 51-60, 20% were aged 61-70, and 6% were aged 71-80.46% of patients were in the age group of 51 – 60. The youngest patient was 39 years old, and oldest was 75 years old.

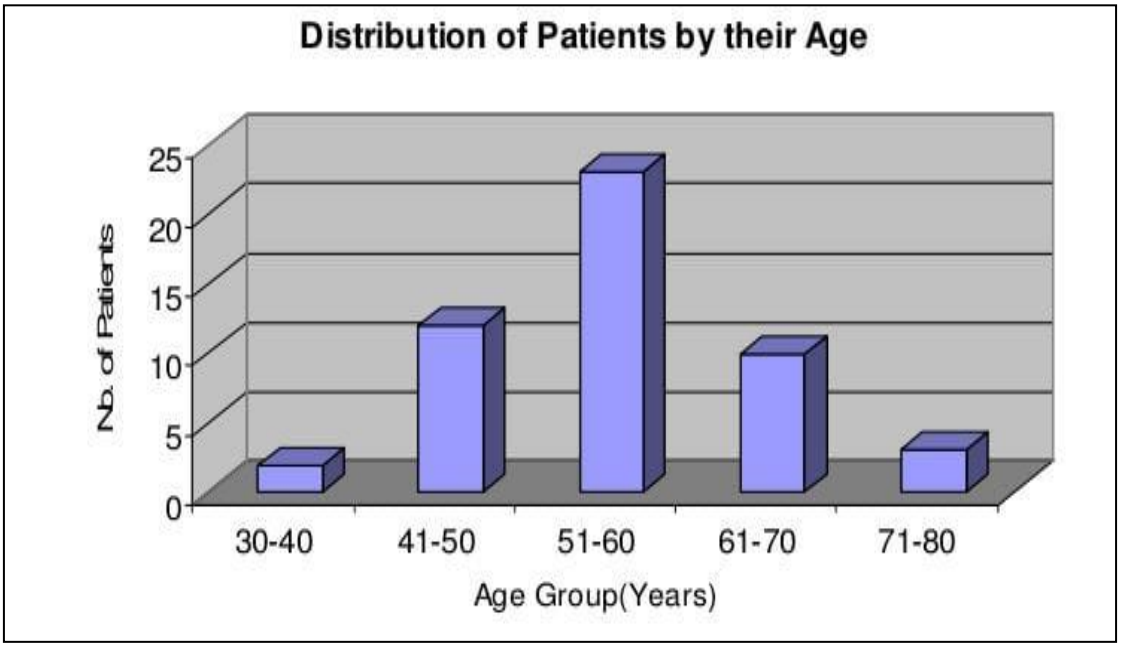

Fig. 1: Distribution of Patients by their Age

B. Gender Distribution

Table 2: Distribution of Patients by their Gender

Gender	No. of Patients	Percentage (%)
Male	21	42
Female	29	58
Total	50	100

In Gender distribution 42% of patients are males (21 out of 50) while the remaining 58% are females (29 out of 50) as shown in Table-2 and Figure-2.

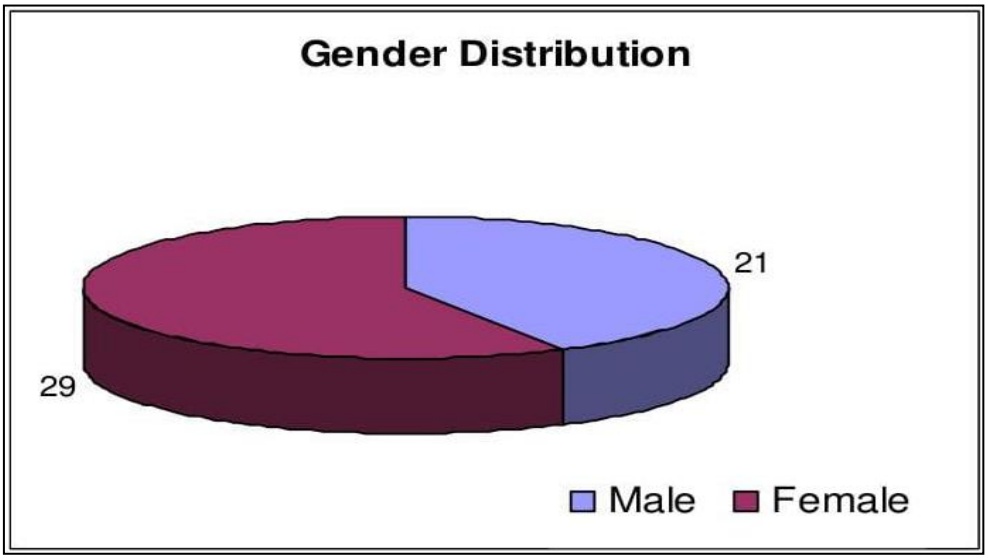

Fig. 2: Gender Distribution

C. Disease Distribution

Table 3: Distribution of Patients by their Disease

Disease	No. of Patients	Percentage (%)
PDR	33	66
BRVO	3	6
CRVO	3	6
ARMD	11	22

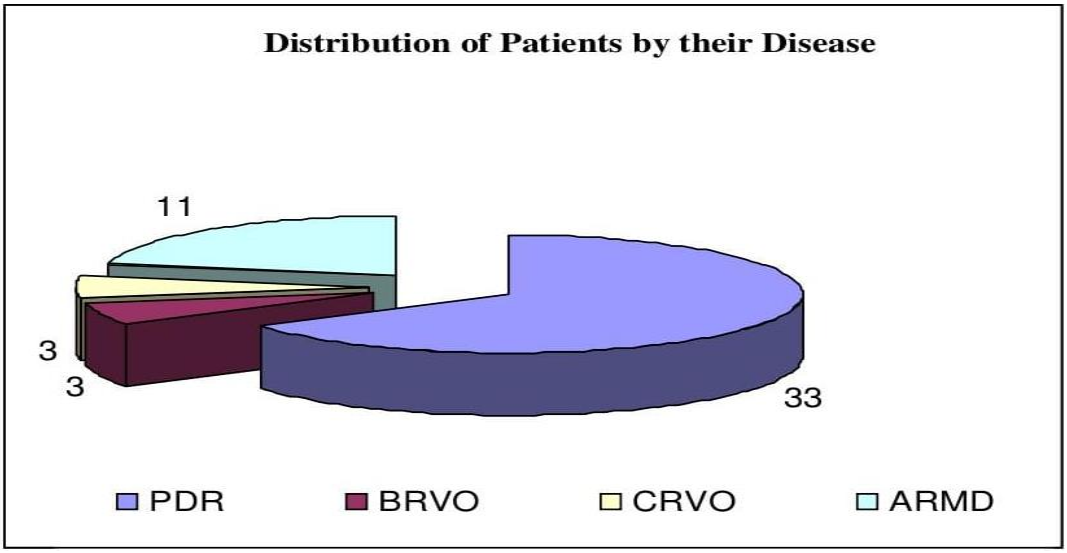

Fig. 3: Distribution of Patients by their Disease

An analysis of Disease Distribution by patient revealed that 66% had PDR (Diabetic Retinopathy), 6% had BRVO (Retinal Vein Occlusions), 6% had CRVO (Central Retinal Vein Occlusions), and 22% had ARMD (Age-related Macular Degeneration) as shown in Table-3 and Figure-3.

Table 4: Distribution of Patients by Pre Injection Best Visual Activity (BCVA)

Visual Acuity (in Decimal)	No. of Patients			
	PDR	BRVO	CRVO	ARMD
0.02	9	0	0	3
0.03	3	0	1	1
0.05	1	0	0	0
0.07	1	0	0	1
0.08	6	1	0	3
0.10	7	0	2	3
0.17	1	0	0	0
0.25	2	0	0	0
0.33	1	0	0	0
0.50	1	1	0	0
0.67	1	0	0	0
1.00	0	1	0	0

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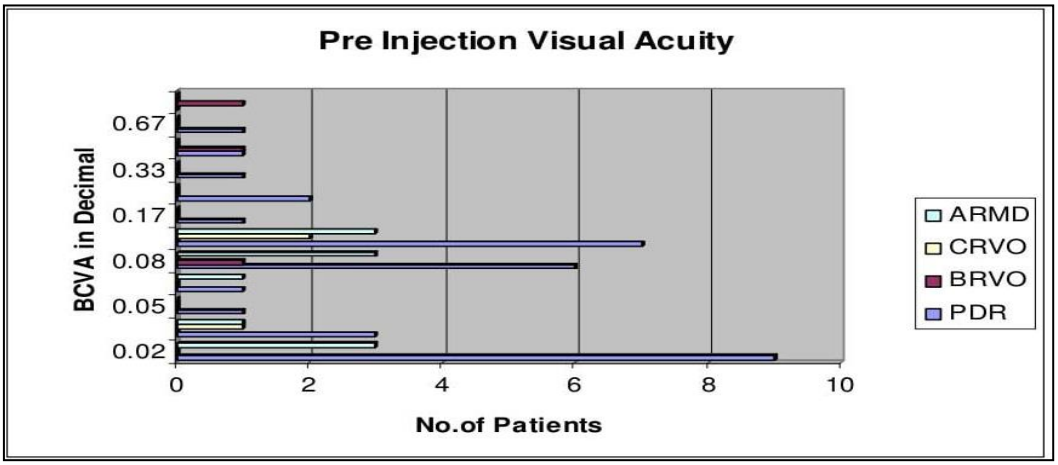

Fig. 4: Pre Injection Visual Activity

Analysis of pre-injection best corrected visual acuity distribution(Table-4 and Figure-4) revealed that 12 patients (PDR-9, BRVO-0, CRVO-0, ARMD-3) had visual acuity at 1/60, 5 patients (PDR-3, BRVO-0, CRVO-1, ARMD-1) had visual acuity at 2/60, 1 patient (PDR-1, BRVO-0, CRVO-0, ARMD-0) had visual acuity at 3/60, and 2 patients (PDR-1, BRVO-0, CRVO-0, ARMD-1) had visual acuity at 4/60. 10 patients had visual acuity at 5/60, 12 patients had visual acuity at 6/60 and 1 patient had visual acuity at 6/36.

Two patients(PDR-2) were impacted by visual acuity at 6/24, while one patient (PDR-1 and ARMD-1) was impacted by visual acuity at 6/18. Two patients(PDR-1 and BRVO-1) had visual acuity at 6/12, one patient with BRVO-1 had visual acuity at 6/9, and one patient with PDR-1 had visual acuity at 6/6.

Table 5: Mean Pre Injection Visual Acuity (BCVA)

Disease	Visual Acuity Mean Value (in Decimal)
PDR	0.11
BRVO	0.53
CRVO	0.08
ARMD	0.06

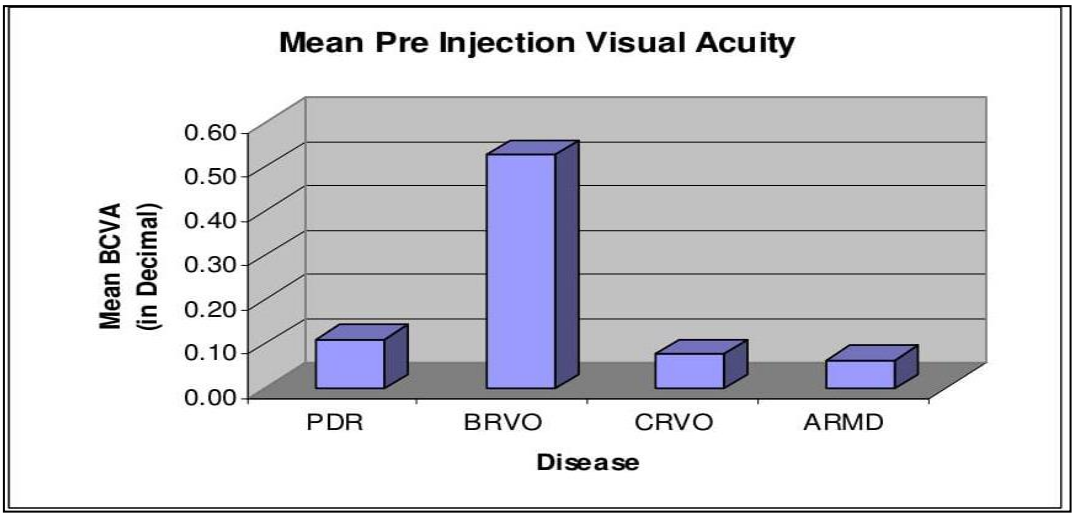

Fig. 5: Mean Pre Injection Visual Acuity

The Pre-injection Best Corrected Visual Acuity distribution by disease showed the following mean values: 0.11 for PDR, 0.53 for BRVO, 0.08 for CRVO, and 0.06 for ARMD as shown in Table-5 and Figure-5.

Table 6: Mean Post Injection Visual Acuity

Disease	Visual Acuity Mean Value (in Decimal)
PDR	0.28
BRVO	0.56
CRVO	0.06
ARMD	0.17

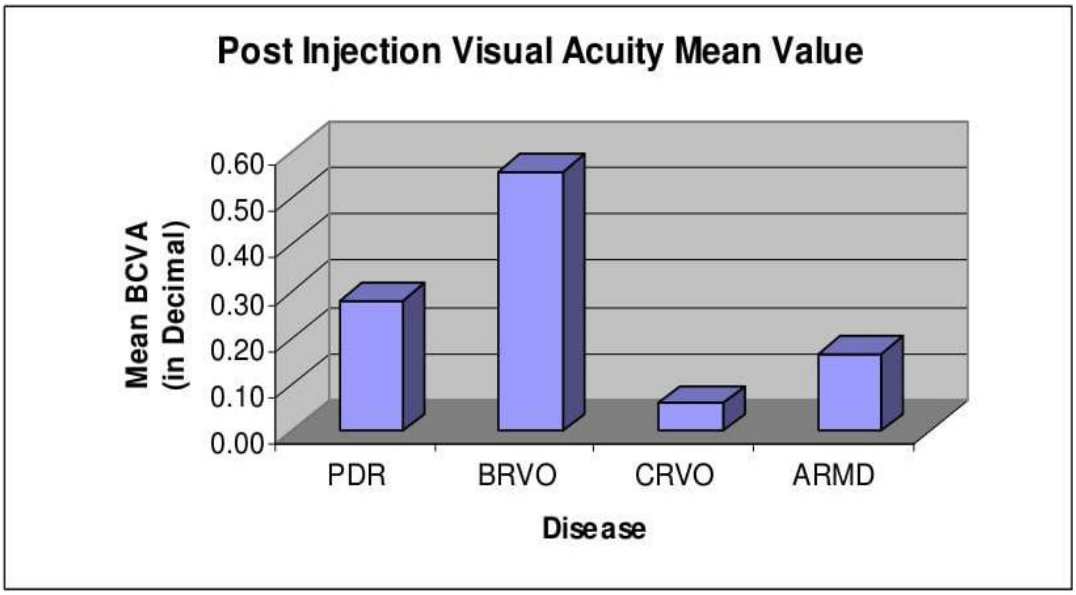

Fig. 6: Post Injection Visual Acuity Mean Value

The analysis of post-injection Visual Acuity distribution as shown in Table-6 and Figure-6 by patient revealed mean values of 0.28 for PDR, 0.56 for BRVO, 0.06 for CRVO, and 0.17 for ARMD. After two-week interval, all the mean values showed an improvement in vision. The maximum mean value for Best Corrected Visual Acuity in the right eye was 0.56 decimal.

Table 7: Post Injection Visual Status, Disease Wise

Disease	Improvement in Eyes	Remained Same
PDR	27	6
BRVO	2	1
CRVO	2	1
ARMD	9	2

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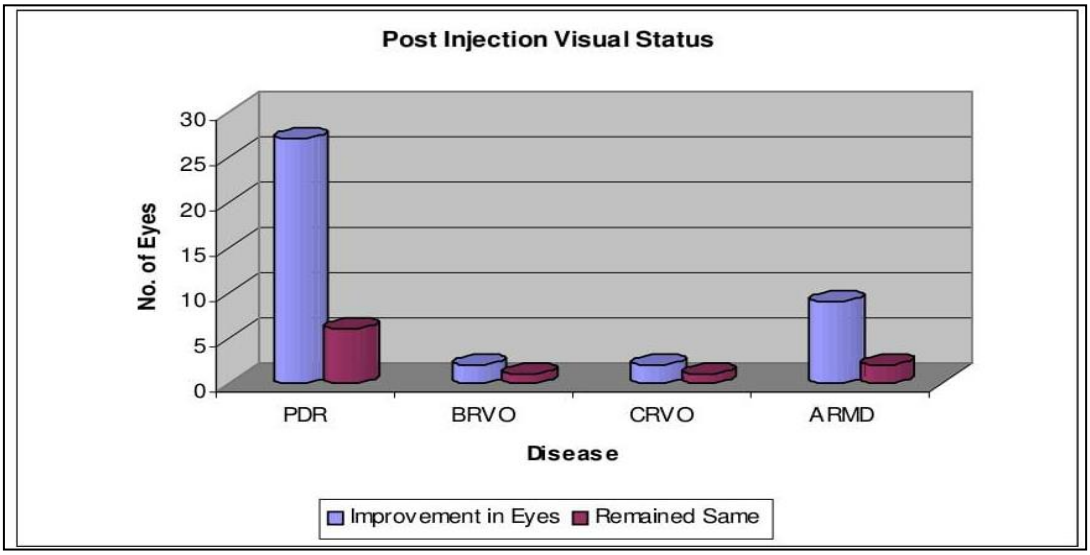

Fig. 7: Post Injection Visual Status

The disease wise analysis of post-injection visual acuity improvement (Table-7 and Figure-7) revealed that 27 eyes with PDR, 2 eyes with BRVO, 2 eyes with CRVO, and 9 eyes with ARMD showed improvement in visual status after the injection. There were of 6 eyes in PDR, 1 eye in BRVO, 1 eye in CRVO, and 2 patients which had no improvement.

Table 8: Post Injection Visual Status, Patient Wise

Visual Status	Improvement (No. of Patients)	Percentage (%)
Improvement	40	80
Remained Same	10	20

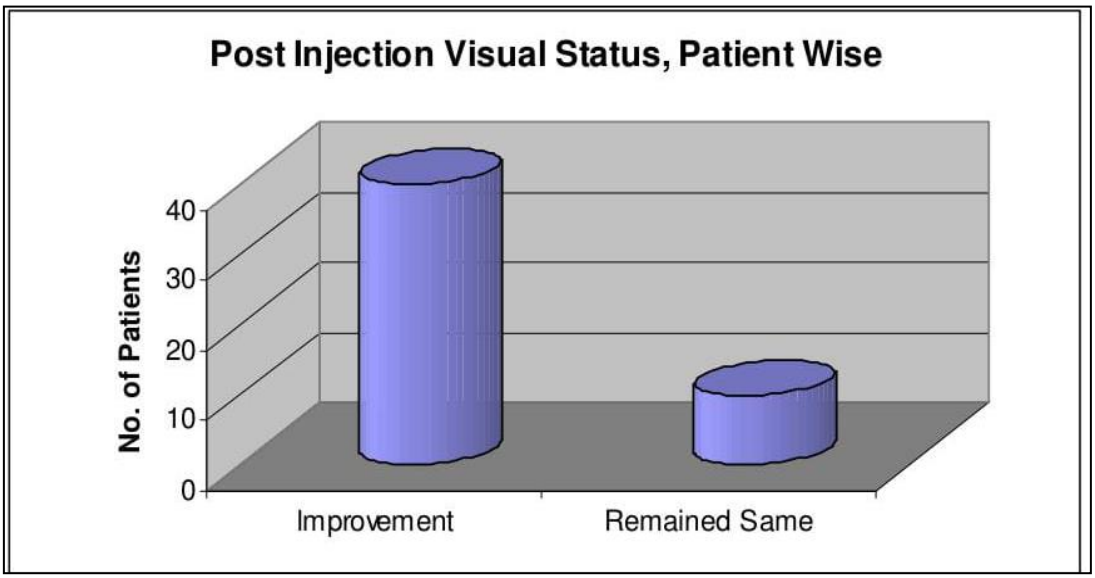

Fig. 8: Post Injection Visual Status, Patient Wise

An analysis of post-injection visual acuity status improvement distribution showed that 80% of patients experienced better visual outcome, while 20% remained unchanged as shown in Table-8 and Figure-8.

Table 9: Change in Best Corrected Visual Acuity (BCVA)

Period	Mean BCVA (in Decimal)	P value (T Test)
Pre injection	0.12	
Post injection	0.26	0.001

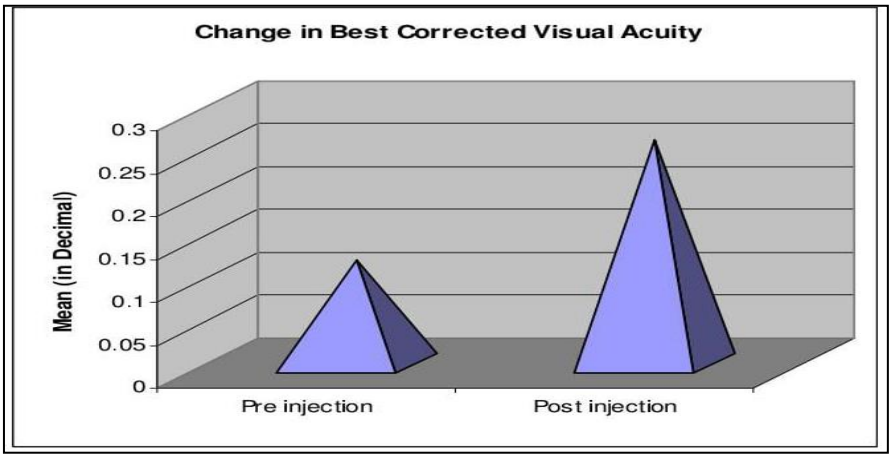

Fig. 9: Change in best Corrected Visual Acuity

As shown in Table-9 and Figure-9 analysis showed a statistically significant association between periodic injections and improvement in Best Visual Acuity. During the following appointments, the enhanced eyesight showed a statistically significant improvement (p=0.001).

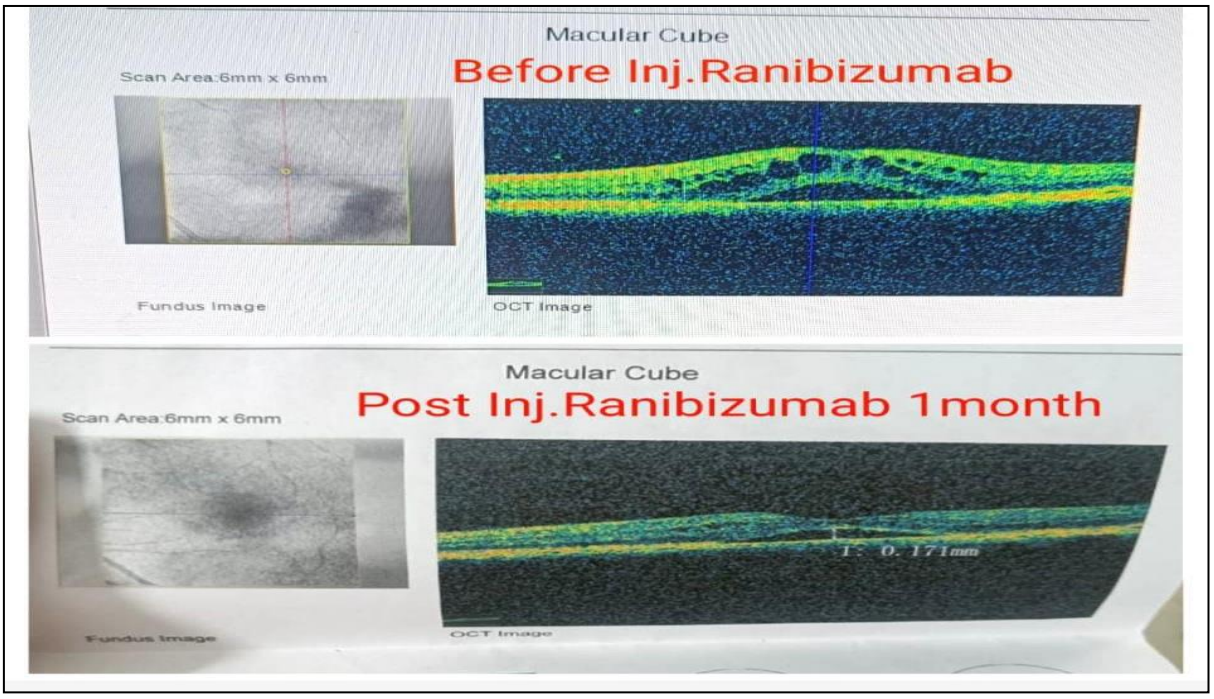

Fig. 10: Before and Post Mascular Cube

There is Decrease in Central Macular Thickness Measured with OCT after Post Injection Ranibizumab after 1 Month as Shown in Figure-10.

V. DISCUSSION

A. Proliferative Diabetic Retinopathy

Haritoglou C and colleagues evaluated effectiveness of ranibizumab in treating diabetic macular edema in a group of 51 subjects with diffuse diabetic macular edema, with an average age of 64 years. Each patient had received prior treatments, including focal laser therapy (33%), full-scatter pan retinal laser therapy (35%), vitrectomy (10%), and intravitreal injection of triamcinolone (22%). There were no notable changes in ETDRS letters during the course of the follow-up period. The mean retinal thickness decreased to 425 +/- 180 µm at 2 weeks (P = 0.002), 416 +/- 180 µm at 6 weeks (P = 0.001), and 377 +/- 117 µm at 12 weeks (P = 0.001).

The correlation between changes in retinal thickness and visual acuity was found to be modest, with a correlation coefficient (r) of -0.480 and a significance level (P) of 0.03 after 6 weeks. Similarly, at 12 weeks, the correlation coefficient was -0.462 with a significance level of 0.07. The enhancement in visual outcome after 6 weeks, evaluated with ETDRS charts, was best forecasted by the initial visual acuity level. No other characteristics, including age, thickness evaluated by optical coherence tomography, or previous treatments, were indicative of the increase in visual acuity. In cases of diffuse diabetic macular edema that did not improve with previous treatments like photocoagulation, intravitreal triamcinolone injection, or vitrectomy, administering intravitreal ranibizumab injection has been found to improve visual acuity and reduce retinal thickness. Due to its brevity, this study does not offer detailed treatment recommendations. However, the first findings suggest the need for future prospective research involving diverse treatment modality groups and longer follow-up periods.

The current investigation demonstrated the presence of Diabetic Retinopathy in 50 eyes.The average pre-injection visual acuity was 0.11. The average value in PDR is statistically significant in almost all visits, with a mean post-injection visual acuity of 0.27. The ongoing study showed improved visual sharpness in 27 eyes. No change in visual acuity was seen in six eyes after the injection.

B. Central Retinal Vein Occlusion

Costa RA and colleagues conducted an assessment to determine the safety, changes in visual acuity, and morphological consequences of intravitreal Ranibizumab injections are used to treat macular edema resulting from ischemic central retinal vein occlusion (CRVO). This study involved 7 individuals with macular edema caused by ischemic central or hemicentral retinal vein occlusion (RVO). These patients received intravitreal injections of 0.5 mg in 0.05 mL of ranibizumab every 12 weeks. The median age of the 7 patients was 65 years, with a range of 58 to 74 years. The median length of symptoms before injection was 7 months, with a range of 2.5 to 16 months. Initially, the average best-corrected visual acuity (BCVA) of the affected eye was 1.21, which is similar to around 20/320 on the Snellen chart. The average initial central macular thickness (CMT) was 730.1 micrometers, whereas the total macular volume (TMV) was 17.1 cubic millimeters. Fluorescein leakage was seen in macula and affected retinal quadrants in all seven eyes. At the 25-week point, six patients had a follow-up evaluation and were given reinjections at weeks 12 and 24.Conjunctival hyperemia and subconjunctival bleeding at the injection site were the most frequently seen negative effects. During the most recent evaluation, the average best-corrected visual acuity (BCVA) in the eye that was impacted was measured to be 0.68, which is equivalent to 20/100(+1) on the Snellen chart. There was no observed decline in BCVA among any of the patients. The average central macular thickness (CMT) and total macular volume (TMV) at the 25-week follow-up were measured to be 260.3 microns and 9.0 mm(3), respectively. The patients exhibited a significant decrease in fluorescein leakage compared to the initial measurements.

When combined with fluorescein angiographic findings, OCT data indicate pattern of macular edema reoccurrence occurring between 6 weeks and 12 weeks following injection.

Therefore administration of intravitreal ranibizumab injections, with a dosage of 0.5 mg given every 12 weeks, was well tolerated by all patients with ischemic retinal vein occlusion (RVO) and macular edema. These injections resulted in either the stabilization or improvement of short-term best-corrected visual acuity (BCVA) and favorable alterations in the macula.

The present investigation revealed the occurrence of Central Retinal vein occlusions in a total of 50 eyes. Prior to the injection, the visual acuity was measured to be 0.08.The mean value of post-injection visual acuity in CRVO is statistically significant in almost all visits, with a mean value of 0.06. The ongoing investigation showed an enhancement in visual acuity in two eyes. The visual acuity in one eye remained unchanged after the injection.

C. Age Related Macular Degeneration

Goff MJ and colleagues conducted a research on the optical coherence tomography (OCT) results and visual outcomes in individuals who were treated with intravitreal ranibizumab for choroidal neovascularization (CNV) linked to age-related macular degeneration (ARMD). The study aimed to describe whether there is a difference in treatment response between patients who had been previously treated and those who were receiving treatment for the first time. A retrospective analysis was conducted on patients who received intravitreal ranibizumab for choroidal neovascularization (CNV) caused by age-related macular degeneration (ARMD) and had a visual acuity of 20/320 or higher. We identified fifty-four eyes of fifty-one patients who received intravitreal ranibizumab treatment for choroidal neovascularization (CNV) caused by age-related macular degeneration (ARMD). A grand number of 178 injections were executed. The average duration of follow-up was 138 days, with 91% of patients having a minimum of 90 days of follow-up. 70% of patients have received prior treatment for CNV. The average number of intravitreal

ranibizumab injections per eye was 3.3. At the initial intravitreal injection, 20% of subjects received a combined treatment involving photodynamic therapy. The OCT data revealed an average thickness of 362 micrometers initially, decreasing to 278 microns after 1 week, 235 microns after 1 month, 238 microns after 3 months, and 244 microns at the end of the follow-up period. Most instances demonstrated the disappearance of cystic retinal edema, subretinal fluid, and pigment epithelial detachment. Pigment epithelial detachment may required an extended period to resolve. The average visual acuity at the beginning was 20/125 (logMAR 0.8), and at the end, it was 20/100 (logMAR 0.7) with a statistical significance of P = 0.03. There were no significant discrepancies in OCT or visual acuity outcomes between individuals who had received previous treatment and those who had not.

There were no significant differences in OCT or visual acuity results between patients who received combination therapy and those who got monotherapy with intravitreal ranibizumab. No adverse effects, either systemic or ocular, were documented. Therefore Administering intravitreal ranibizumab to treat choroidal neovascularization (CNV) caused by age-related macular degeneration (ARMD) leads to a fast reduction in retinal thickness as evaluated by optical coherence tomography (OCT) in most instances. Visual acuity demonstrated improvement in this series, indicating a potential concurrent visual advantage. This series indicates that individuals who have received previous treatment and those who have not have same outcomes.

The research revealed the existence of Age-Related Macular Degeneration (AMD) in 50 eyes. The visual acuity before the injection was assessed at 0.06 in decimal form. The average age in age-related macular degeneration (ARMD) shows statistical significance in almost all visits and visual acuity after post-injection.

The average visual acuity value was 0.25. The current investigation demonstrated enhanced visual acuity in a total of 9 eyes. Visual acuity in 2 eyes remained unchanged after the injection.

VI. CONCLUSION

- Ranibizumab demonstrates efficacy in treating a range of retinal vascular disorders.
- The enhancement in the visual acuity after correction was statistically significant.
- The impact of Ranibizumab seems to be temporary, requiring further injections if recurrences occur.
- Complications arising from the surgery, like endophthalmitis and vitreous hemorrhage, are quite uncommon.
- Ranibizumab appears to be a safe treatment choice for people who do not respond to traditional laser photocoagulation.

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