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Efficacy of Anti-VEGF in Treatment of ROP

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that affects premature infants. Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of ROP. Anti-VEGF agents can potentially inhibit abnormal vessel growth in ROP. This study aimed to evaluate the efficacy of anti-VEGF (bevacizumab) in treatment of ROP. A prospective study was conducted on 75 patients including 70 adults and 5 ROP babies who received intravitreal injection of bevacizumab (Avastin). Distant visual acuity, slit lamp examination, indirect ophthalmoscopy and optical coherence tomography (OCT) were assessed at baseline, immediate, 1 week and 4 weeks post injection. Statistically significant improvement was observed in distant visual acuity and reduction in macular thickness after Avastin injection. At 4 weeks, best corrected visual acuity of 6/6 was attained by 15 adults and 3 ROP babies. OCT revealed decreased macular edema with mean reduction of 115.29µm. ROP subjects showed greater visual gain (mean acuity improvement - 2.4 lines) as compared to adults (mean acuity improvement - 1.52 lines). Significant correlation was found between better visual acuity and macular thickness less than 300µm. Intravitreal Avastin resulted in rapid regression of neovascularization in ROP. No ocular or systemic complications were observed. Single injection controlled disease progression in majority of cases. Anti-VEGF agents can be considered as primary modality for treating type 1 ROP due to their safety, efficacy and long-term benefits. Larger studies are required to establish optimal dosage and long-term effects.

Keywords: Retinopathy of prematurity; anti-VEGF; bevacizumab; Avastin; OCT.

1. Introduction

Retinopathy of prematurity (ROP) is a bilateral, vasoproliferative disease of the retina that affects premature infants with low birth weight and gestational age [1]. Advances in neonatal care have enhanced survival for extremely preterm infants, contributing to increased incidence of ROP which varies between 20-60% in infants with birth weight <2000g [2]. If untreated, some cases progress to retinal detachment which remains an important cause of childhood blindness worldwide [3].

Pathogenesis of ROP involves two phases. Phase I starts with delayed retinal vascularization after premature birth. Hypoxia induces upregulated secretion of vascular endothelial growth factor (VEGF), resulting in vasoproliferation in phase II. Abnormal angiogenesis leads to extraretinal fibrovascular proliferation at the interface of vascularized and avascular peripheral retina (Stage 3 ROP) which can progress to retinal detachment [4].

VEGF has been identified as a key factor involved in angiogenesis. Increased expression of VEGF in retina and vitreous correlates with severity of ROP [5,6]. Anti-VEGF agents can potentially inhibit VEGF action and control progression of neovascularization. Intravitreal anti-VEGF like bevacizumab, ranibizumab and aflibercept have shown promising results in treatment of ROP.

Bevacizumab (Avastin, Genentech) is a recombinant humanized monoclonal antibody that inhibits VEGF-A. It is approved for intravenous use in cancer therapy. Several studies have demonstrated that intravitreal injection of bevacizumab (IVB) induces rapid regression of ROP with few short-term adverse effects [7-10]. We aimed to evaluate efficacy of IVB for treatment of ROP.

2. Materials and Methods

In this study, a total of 79 eyes, including bilateral cases, were examined. Adult patients received a dose of 1.25mg in 0.05 ml solution of bevacizumab, administered one month apart. Postoperative vision was evaluated, and Optical Coherence Tomography (OCT) was conducted immediately after the procedure, as well as during follow-ups at one week and four weeks post-operation.[11-13]
Additionally, in 5 infants, bilateral intravitreal injections of AVASTIN were administered in 10 eyes with a dose of 0.625mg/0.025 ml of solution. These patients were monitored during the first, second, and third weeks post-injection for fundus examination using indirect ophthalmoscopy.[14]

Study Design: This study was conducted as a prospective investigation.

Study Place: The study took place at the Department of Ophthalmology in a tertiary care hospital.

Study Population: Participants were drawn from patients attending the Ophthalmology Outpatient Department (OPD) and undergoing treatment.

Study Period: The study spanned from November 2020 to May 2022, totaling 18 months.

Sample Size: The study included 75 patients with posterior segment vasculopathies who met the inclusion and exclusion criteria.

Rationale Of Sample Size: Based on statistical analysis, considering a prevalence rate of 24% for posterior segment vasculopathies in the adult population and an incidence of proliferative diabetic retinopathy at 3%, the sample size was determined using the formula n= z^2pq/L^2, resulting in N=70 (excluding infants).

Inclusion Criteria:

- Patients with Retinal vasculopathies
- Patients with Choroidal vasculopathies
- Patients with Neovascular Glaucoma

Exclusion Criteria:

- Patients who had previously undergone intravitreal and retinal interventions medically or surgically
- Patients with central corneal opacities
- Unconscious or comatose patients
- Patients unwilling to participate

Parameters:
- Distant vision
- Near vision
- OCT for central macular thickness

Methods of Examination:
- Comprehensive medical history and general examination
- Ocular examination including visual acuity, slit lamp examination (Anterior segment, 90D), and fundus examination by indirect slit-lamp bio-microscopy using High Plus Condensing handheld lenses
- Intraocular pressure measurement (Non-Contact Tonometer)
- Fundoscopy (Direct and Indirect)

General Examination:
- Temperature
- Pulse Rate
- Blood Pressure
- Respiratory Rate

Investigations:
- Blood Sugar Level (BSL) - Fasting, Postprandial
- HIV, HbsAg, HCV screening

Additional Investigations:
- Fundus Photography: Utilizing a specialized fundus camera to capture magnified photographs of the optic disc and macula, aiding in documenting fundus abnormalities.
- Optical Coherence Tomography (OCT): A non-invasive diagnostic technique employing infrared light to analyze the retina, useful for detecting macular edema in Diabetic Macular Edema (DMO) characterized by hypo-reflective spaces within the retina, macular thickening, and loss of foveal depression.

Fundus fluorescein angiography (IN SELECTED CASES)

Fluorescein angiography is the technique of injecting a yellowish dye into a patient's antecubital vein, then photographically stimulating this dye with a blue green light at certain wavelengths to induce fluorescence, in the retinal vascular system of the human eye, and recording this fluorescence on photographic film using a fundus camera. [15]

Fig 1 Avastin Vial given in dose of 1.25 mg/0.05ml

Statistical Analysis

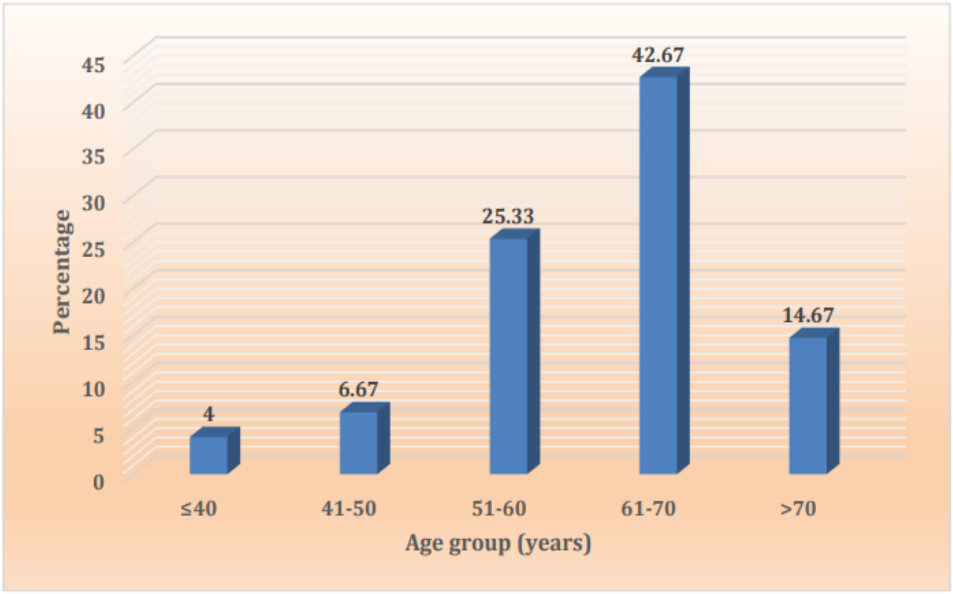
Data entry was performed using Microsoft Excel 2016, and analysis was conducted using SPSS version 22. The data were summarized using frequency tables, pie charts, and histograms. Categorical variables were presented as proportions, while continuous data were described as means with standard deviations, depending on the data distribution.[16]

4. Observations and Results

Table 1: Distribution according to age:

Age group (years)	No. of Patients	Percentage
Adults		
≤40	03	04.00
41-50	05	06.67
51-60	19	25.33
61-70	32	42.67
>70	11	14.67
Babies <32 weeks	05	06.67
Total	75	100

The table presents the age distribution of the study participants. Among the 75 patients, the majority belonged to the age group of 61-70 years (42.67%), followed by the age group of 51-60 years (25.33%). There were also 5 ROP (Retinopathy of Prematurity) babies, accounting for 6.67% of the total sample size.



Distribution according to age:

Table 2: Distribution according to Sex:

Sex	No. of Patients	Percentage
Adult		
Male	44	58.67
Female	26	34.67
Babies		
Male	03	04.00
Female	02	02.66
Total	75	100

The table illustrates the gender distribution among all study subjects. Among adults, 58.67% were male, while 34.67% were female. In the infant group, 4.00% were male, and 2.66% were female.

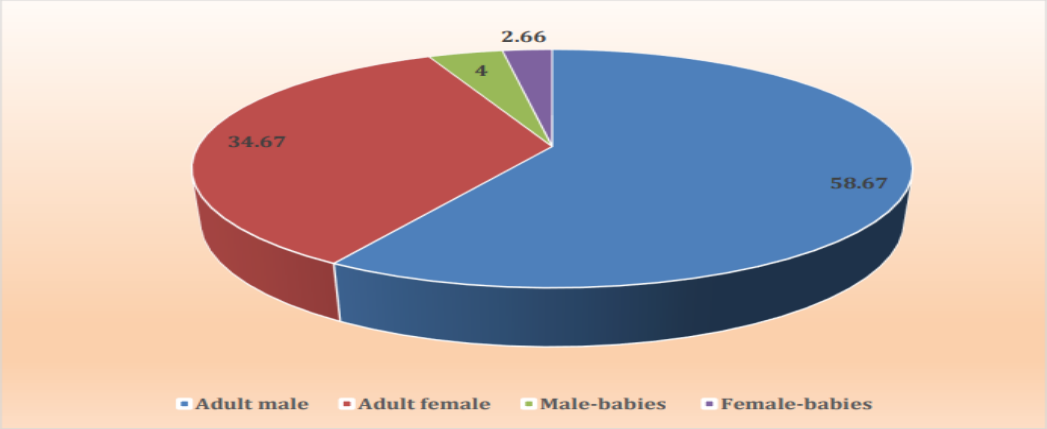


Table 3: Distribution according to posterior segment vasculopathy:

Etiology	No. of Patients	Percentage
PDR	21	28.00
CNVM	18	24.00
CRVO	09	12.00
BRVO	07	09.33
STBRVO	09	12.00
ITBRVO	04	05.33
ROP	05	06.67

NG	01	01.33
Wet ARMD	01	01.33
Total	75	100

The table displays the distribution of posterior segment vasculopathy among the study subjects. Out of 75 patients, the majority were diagnosed with PDR (28%), followed by BRVO (26%), CNVM (24%), CRVO (12%), ROP (6.67%), NG (1.33%), and Wet ARMD (1.33%).

Table 4: Distribution according to affected eyes in adults:

Side	**No. of Eyes**	**Percentage**
Adults		
Right	33	41.14
Left	28	40.00
Bilateral	09	12.86
Total	70	100

This table presents the distribution of affected eyes in adults with posterior segment vasculopathy. Out of 70 adult patients, the majority had the affected eye on the right side (41.14%), followed by the left eye (40.00%), and bilateral cases (12.86%).

Among the 9 bilateral cases, 5 cases belonged to PDR requiring intravitreal injection bilaterally, while 4 cases were bilateral active CNVM cases.

Table 5: Distribution according to affected eyes in babies:

Side	**No. of Eyes**	**Percentage**
Babies		
Right	05	50.00
Left	05	50.00
Total	10	100

This table illustrates the distribution of affected eyes with posterior segment vasculopathy among babies. Out of 5 babies, both eyes were equally affected.

Table 6: Distribution according to co-morbidities:

Co-morbidities	**No. of Patients (n=70)**	**Percentage**
Hypertension	29	41.42

Diabetes mellitus	29	41.42
H/O previous Cataract Surgery	05	07.14
Others (CKD/ trauma)	04	05.71

This table presents the distribution of co-morbidities among patients with posterior segment vasculopathy. Out of 70 patients, the majority had hypertension (41.42%) and diabetes mellitus (41.42%), followed by a history of previous cataract surgery (7.14%), and other conditions (5.71%).

Table 7: Distribution according to visual acuity PRE-INJECTION:

VISUAL ACUITY	Right Eye %	Left Eye %
6/6	04 (5.71)	08 (11.43)
6/9	04 (5.71)	02 (02.86)
6/12	03 (4.29)	03 (04.29)
6/18	03 (4.29)	09 (12.86)
6/24	04 (5.71)	01 (01.42)
6/36	09 (12.86)	05 (07.14)
6/60	02 (2.86)	06 (08.57)
<6/60	41 (58.57)	36 (51.43)

This table illustrates the visual acuity among study subjects pre-injection. It was observed that the majority of subjects had visual acuity less than 6/60 in both the right eye (58.57%) and left eye (51.43%).

Table 8: Distribution according to IOP PRE-INJECTION:

IOP	Right Eye %	Left Eye %
<10	02 (2.86)	03 (4.29)
10-21	68 (97.14)	65 (92.86)
>21	00	02 (2.85)
Total	70	70

This table displays the distribution of intraocular pressure (IOP) among study subjects before injection. The majority of subjects had IOP between 10-21 mmHg in both the right eye (97.14%) and left eye (92.86%).

Table 9: Comparison of Vision (D) after injection AVASTIN among patients' eyes: (POST-INJECTION)

Vision Pre-op	After injection Avastin	P value
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	02
6/18	05	07
6/24	04	11
6/36	11	10
6/60	12	13
<6/60	49	36
Total	79	79

This table compares the vision (D) after injection AVASTIN among study subjects' eyes post-injection. Gradual improvement in distant vision was observed over time, with statistical significance (P<0.05).

Table 10: Comparison of OCT (macular thickness) after injection AVASTIN among patients' Eyes (POST-INJECTION)

OCT Pre-op (n=79)	After injection Avastin (n=79)	P value
	Immediate	1 week later

This table compares the OCT (macular thickness) after injection AVASTIN among study eyes post-injection. Gradual decrease in macular thickness was observed over time, with statistical significance (P<0.05).

Table 12: Comparison of Vision (D) after injection AVASTIN among PDR eyes (POST-INJECTION)

Vision Pre-op	After injection Avastin	P value
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	01

6/18	01	01
6/24	02	02
6/36	03	04
6/60	02	03
<6/60	18	15
Total	26	26

It was observed that visual acuity of 6/12 was achieved by 4 eyes (15.38%) 4 weeks later.

Table 13: Comparison of Vision (D) after injection AVASTIN among CNVM eyes (POST-INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	01
6/18	01	01
6/24	02	02
6/36	02	03
6/60	02	03
<6/60	15	12
Total	22	22

It was observed that visual acuity of 6/6 was achieved by 5 eyes (22.72%) 4 weeks later.

Table 14: Comparison of Vision (D) after injection AVASTIN among CRVO eyes (POST-INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00
6/9	00	00

6/12	00	00
6/18	01	01
6/24	00	02
6/36	01	01
6/60	02	02
<6/60	05	03
Total	09	09

It was observed that visual acuity of 6/6 was achieved by 3 subjects (33.33%) 4 weeks later.

Table 15: Comparison of Vision (D) after injection AVASTIN among BRVO eyes (POST-INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	00
6/18	01	01
6/24	00	02
6/36	01	01
6/60	01	01
<6/60	04	02
Total	07	07

It was observed that visual acuity of 6/6 was gained by 3 subjects (42.85%) 4 weeks later.

Table 16: Comparison of Vision (D) after injection AVASTIN among STBRVO eyes: (POST – INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00

6/9	00	00
6/12	00	00
6/18	01	01
6/24	00	02
6/36	01	01
6/60	02	02
<6/60	05	03
Total	09	09

It was observed that visual acuity of 6/6 was achieved by 3 subjects (42.85%) 4 weeks later.

Table 17: Comparison of Vision (D) after injection AVASTIN among ITBRVO eyes: (POST-INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	02
6/24	00	00
6/36	01	00
6/60	01	01
<6/60	02	01
Total	04	04

It was observed that visual acuity of 6/6 was achieved by 1 subject (25%) 4 weeks later.

Table 18: Comparison of Vision (D) after injection AVASTIN among NG eyes: (POST – INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later

6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00
6/24	00	00
6/36	00	00
6/60	01	01
<6/60	00	00
Total	01	01

It was observed that the patient's vision remained at 6/36 post-injection after 4 weeks, and there was regression of neovascularization of the iris.

Table 19: Comparison of Vision (D) after injection AVASTIN among Wet AMD eyes: (POST – INJECTION)

Vision Pre-op	**After injection Avastin**	**P value**
	Immediate	1 week later
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00
6/24	00	01
6/36	00	00
6/60	01	00
<6/60	00	00
Total	01	01

It was observed that visual acuity of 6/9 was achieved after 4 weeks.

Table 20: Comparison of Vision (D) and Macular thickness among PDR:

Vision	Macular thickness	P value
	At 4 weeks	
	<300	301-400
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00
6/24	01	02
6/36	01	02
6/60	00	02
<6/60	00	02
Total	02	08

It was observed that 4 eyes (33.33%) achieved 6/9 vision 4 weeks later at macular thickness <300 microns, and 4 (33.33%) subjects achieved 6/12 vision after 4 weeks at macular thickness <300 microns.

Table 21: Comparison of Vision (D) and Macular thickness among CNVM:

Vision	Macular thickness	P value
	At 4 weeks	
	<300	301-400
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00
6/24	01	02
6/36	01	02
6/60	00	02
<6/60	00	02

Total	02	06

It was observed that 4 eyes (33.33%) achieved 6/6 vision after 4 weeks with macular thickness <300 microns after the 2nd dose of injection, and 1 subject achieved it after the 1st dose itself at macular thickness <300 microns.

Table 22: Comparison of Vision (D) and Macular thickness among CRVO:

Vision	**Macular thickness**	**P value**
	At 4 weeks	
	<300	301-400
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00
6/24	00	01
6/36	01	01
6/60	00	01
<6/60	00	00
Total	01	03

It was observed that 3 subjects (50%) achieved 6/6 vision at 4 weeks. Out of 3 subjects, 2 (33.33%) subjects achieved 6/6 vision after the 2nd dose of injection at 4 weeks with macular thickness <300 microns.

Table 23: Comparison of Vision (D) and Macular thickness among BRVO:

Vision	**Macular thickness**	**P value**
	At 4 weeks	
	<300	301-400
6/6	00	00
6/9	00	00
6/12	00	00
6/18	00	00

6/24	00	01
6/36	01	01
6/60	00	00
<6/60	00	00
Total	01	01

It was observed that 3 (60%) subjects gained 6/6 vision at 4 weeks. Out of which 2 (20%) subjects achieved it at the 1st dose itself, and 1 (40%) subject achieved it after the 2nd dose of injection after 4 weeks at macular thickness <300 microns.

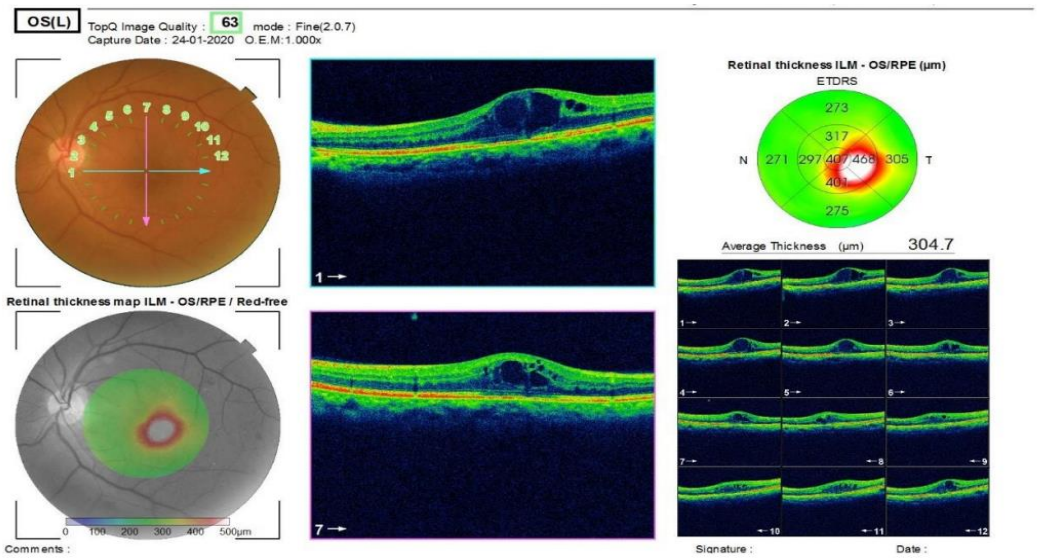


Fig 2 PDR Pre injection macular thickness

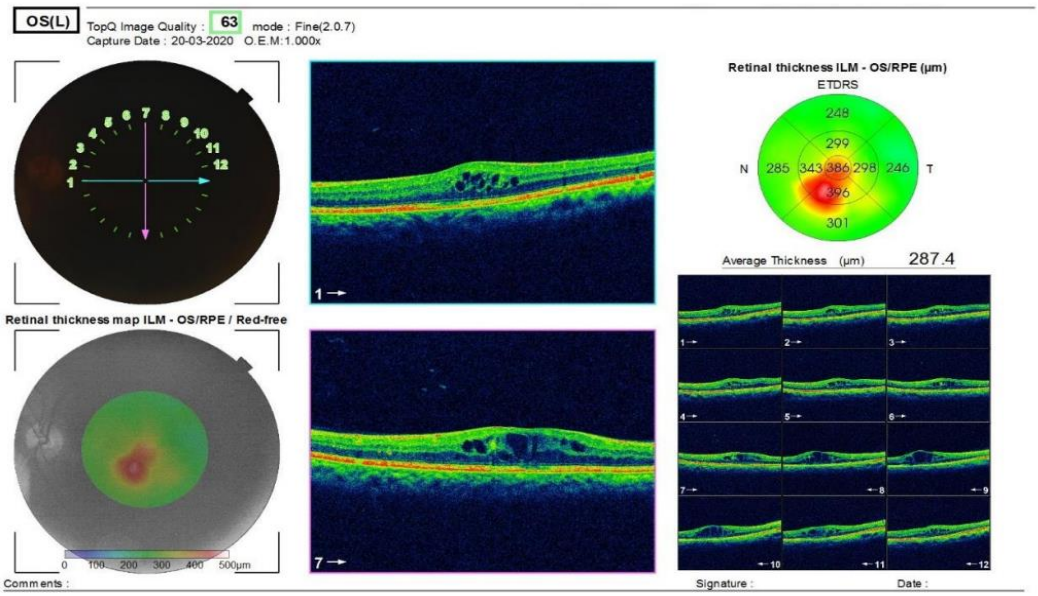


Fig 3 PDR Macular thickness after 1 week follow up

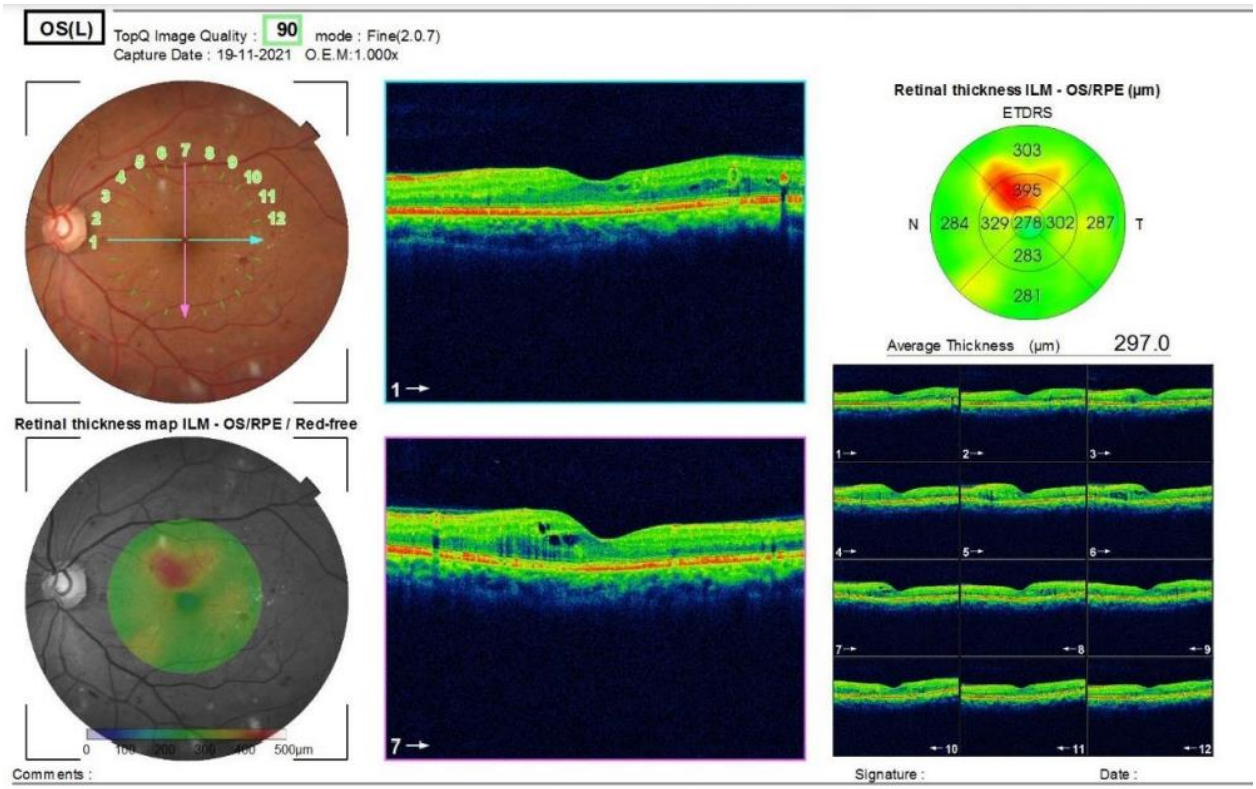


Fig 4 PDR Macular thickness after 4 week follow up

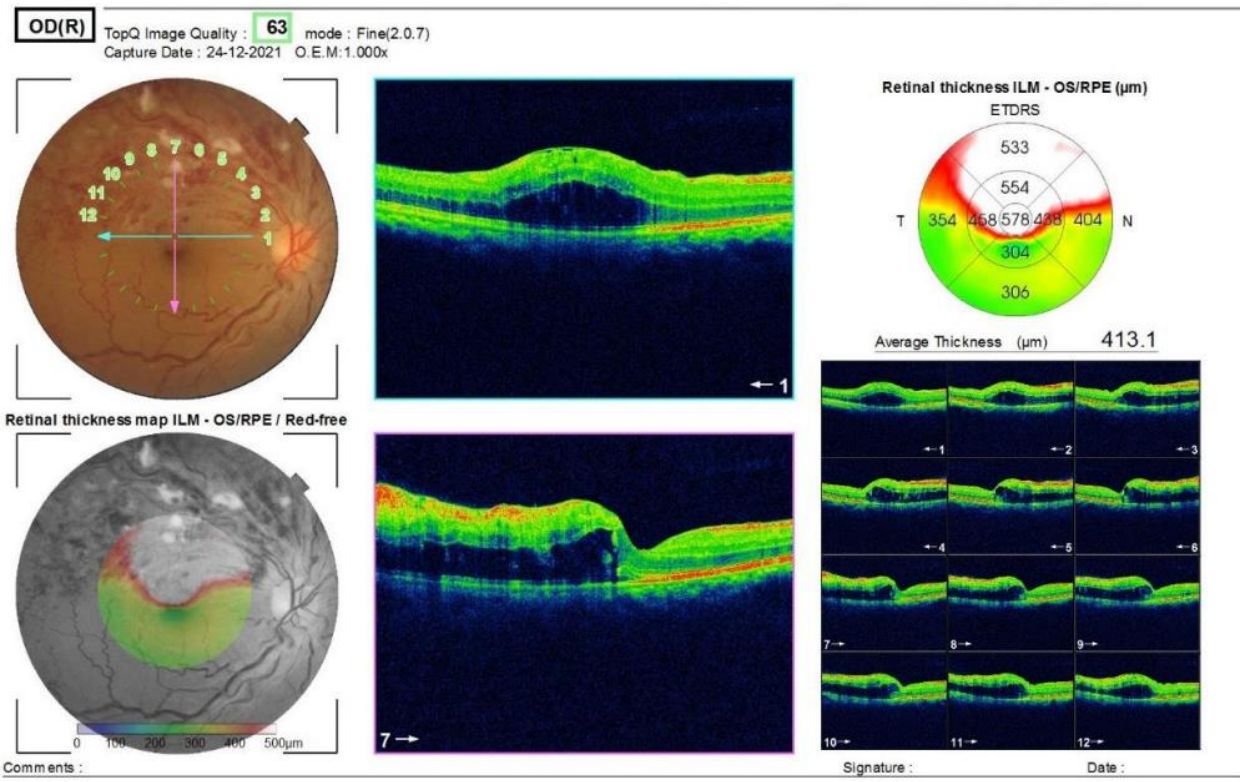


Fig 5 BRVO Pre injection macular thickness

The present study aimed to investigate the effects of intravitreal anti-VEGF injection Avastin in posterior segment vasculopathies. Conducted at a tertiary care hospital from November 2020 to May 2022, the study included patients with various posterior segment vasculopathies.

Demographics:

- Majority of the patients were in the age group of 61-70 years (42.67%), with a mean age of 58.13 years.
- Male subjects comprised 58.67% of the study population, while females comprised 34.67%.
- The distribution of posterior segment vasculopathies among the study subjects was as follows: PDR (28%), BRVO (26%), CNVM (24%), CRVO (12%), ROP (6.67%), NG (1.33%), and wet ARMD (1.33%).

Laterality and Visual Acuity:

- The majority of affected eyes were on the right side (41.14%), followed closely by the left eye (40%), with bilateral involvement in 12.86% of cases.
- The study observed a significant improvement in visual acuity from <6/60 to 6/6 four weeks after injection Avastin across different etiologies of posterior segment vasculopathies.

Previous Studies and Comparisons:

- Previous studies by Gulsah Gumus et al. and N.N.Kabedi et al. observed similar mean ages among patients receiving intravitreal bevacizumab injections.
- Distribution of posterior segment vasculopathies in this study aligned with findings from other studies, albeit with different percentages.[18]
- The improvement in visual acuity observed in this study after Avastin injections is consistent with findings from studies evaluating the efficacy of bevacizumab in various eye conditions, such as diabetic macular edema (DME) and neovascular age-related macular degeneration (AMD). [19]
- Decrease in central macular thickness after Avastin injections was observed, consistent with findings from other studies evaluating the effectiveness of bevacizumab in reducing macular edema associated with DME.

4. Conclusion

The present study demonstrates the effectiveness of intravitreal Avastin injections in improving visual acuity and reducing macular thickness in patients with posterior segment vasculopathies. These findings support the use of anti-VEGF therapy as a viable treatment option for various retinal diseases, offering significant improvements in visual outcomes and macular morphology.

References

1. Bastawrous A. Posterior segment eye diseases: A growing problem. British Journal of Ophthalmology. 2012.
2. Verma R, Khanna P, Prinja S, Rajput M, Arora V. The national programme for control of blindness in India. Australasian Medical Journal. 2011;4(1):01-03.
3. Zhao YX, Chen XW. Diabetes and risk of glaucoma: Systematic review and a Meta-analysis of prospective cohort studies. International Journal of Ophthalmology. 2017;10(9):1430-35.
4. Grzybowski A, Told R, Sacu S, Bandello F, Moisseiev E, Loewenstein A, Schmidt-Erfurth U. 2018 update on intravitreal injections: Euretina expert consensus recommendations. Ophthalmologica. 2018;239(4):181-93.

5. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. New England Journal of Medicine. 1994; 331:1480–7.
6. Adamis AP, Miller JW, Bernal MT, D′Amico DJ, Folkman J, Yeo TK, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. American Journal of Ophthalmology. 1994; 118:445–50.
7. Cohen MH, Gootenberg J, Keegan P, Pazdur R. "FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer". The Oncologist. 2007; 12 (3): 356–61.
8. Kaplan HJ. Anatomy and function of the eye. Immune Response and the Eye. 2007;92:4-10.
9. Kolb H, Fernandez E, Nelson R, eds. The organization of the retina and visual system. Salt Lake City, UT: University of Utah Health Sciences Center; 1995.
10. Palmer AM, Stephenson FA, Williams RJ. "Society for Medicines Research: 40th anniversary symposium". Drug News & Perspectives. 2007; 20 (3): 191–6.
11. Ribatti D. "Napoleone Ferrara and the saga of vascular endothelial growth factor". Endothelium. 2008; 15 (1): 1–8.
12. World Health Organization. WHO model list of essential medicines: 22nd list. Geneva: World Health Organization. 2021.
13. Lucentis (ranibizumab) FDA Approval History - Drugs.com. (n.d.). 2016. https://www.drugs.com/history/lucentis.html
14. LUCENTIS ranibizumab injection full U.S. prescribing information. 2015.
15. Nguyen, Q. D., Brown, D. M., Marcus, D. M., Boyer, D. S., & Patel, S. Ranibizumab for Diabetic Macular Edema. 2012.
16. Rosenfeld, P., Brown, D., & Heier, J. Ranibizumab for Neovascular Age-Related Macular Degeneration. 2006.
17. Alon, T., Hemo, I., Itin, A., Pe'er, J., Stone, J., & Keshet, E. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nature Medicine. 1995; 1(10), 1024-1028.
18. Steinbrook, R. The Price of Sight — Ranibizumab, Bevacizumab, and the Treatment of Macular Degeneration. New England Journal of Medicine. 2006; 355(14), 1409-1412.
19. Klettner, A., & Roider, J. Comparison of Bevacizumab, Ranibizumab, and Pegaptanib In Vitro: Efficiency and Possible Additional Pathways. Investigative Ophthalmology & Visual Science. 2008; 49(10), 4523.