DOI: https://doi.org/10.54393/pjhs.v6i7.3255

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 07 (July 2025)

Original Article

OPEN ACCESS

Time to Complete Retinal Vascularization After Anti-VEGF Among Preterm Neonates in Pakistan

Mariya Nazish Memon[1], Asadullah Jatoi[1*], Mona Liza Mahesar[1], Imtiaz Gilal[1], Saroop Chand[2] and Ashok Kumar Narsani[1]

[1]Department of Ophthalmology, Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[2]Department of Neonatology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

ARTICLE INFO

Keywords:
Retinopathy of Prematurity, Anti-VEGF, Vascularization, Bevacizumab, Ranibizumab, Preterm Neonates

How to Cite:
Jatoi, A., Memon, M. N., Mahesar, M. L., Gilal, I., Chand, S., & Kumar Narsani, A. (2025). Time to Complete Retinal Vascularization After Anti-VEGF Among Preterm Neonates in Pakistan: Complete Retinal Vascularization After Anti-VEGF Among Preterm Neonates . Pakistan Journal of Health Sciences, 6(7), 241-245. https://doi.org/10.54393/pjhs.v6i7.3255

***Corresponding Author:**
Asadullah Jatoi
Department of Ophthalmology, Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
drasadullahjatoi@gmail.com

Received Date: 11th June, 2025
Revised Date: 19th July, 2025
Acceptance Date: 28th July, 2025
Published Date: 31st July, 2025

ABSTRACT

Retinopathy of prematurity (ROP) is a leading cause of preventable blindness in children. Anti-VEGF agents are widely used for treatment, but they pose concerns regarding delayed or incomplete retinal vascularization. There is limited local data on the vascularization timeline in Pakistani preterm neonates following anti-VEGF therapy. **Objectives:** To determine the time required to achieve complete retinal vascularization after intravitreal anti-VEGF injection in preterm neonates with ROP and to identify clinical predictors influencing this timeline. **Methods:** This prospective cohort study was conducted over 1.5 years from December 2023 to May 2025 at the neonatal nursery of the Pediatric Ward, Liaquat University of Medical and Health Sciences, Jamshoro. A total of 63 preterm neonates with treatment-requiring ROP received either Bevacizumab or Ranibizumab. Demographic, clinical, and treatment-related data were collected. Time to complete vascularization and postmenstrual age (PMA) at vascularization were recorded. ANOVA was used to assess statistical differences between subgroups. **Results:** The mean time to complete vascularization was 10.5 ± 2.0 weeks' post-treatment, with a PMA of 44.5 ± 2.1 weeks. Delayed vascularization (>50 weeks) occurred in 8.5% and reactivation in 6.4% of neonates. Stage 3 ROP, Zone I disease, and Bevacizumab were associated with slightly longer vascularization times, but none of these comparisons were statistically significant (p>0.05). **Conclusions:** Retinal vascularization typically completes within 10–12 weeks after anti-VEGF therapy. Although not statistically significant, trends suggest extended follow-up is advisable in neonates with more severe disease or ZONE I ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disorder that occurs almost exclusively in premature infants due to incomplete vascular development of the retina. With improvements in neonatal care and survival of very low birth weight infants, ROP has emerged as a major cause of avoidable childhood blindness globally, particularly in low- and middle-income countries (LMICs) like Pakistan [1]. According to the World Health Organization, over 15 million babies are born prematurely every year, and approximately 32% of surviving infants weighing less than 1500 grams may develop ROP [2]. In Pakistan, neonatal mortality remains high, and the burden of prematurity-related complications, including ROP, is increasing steadily [3, 4]. Traditionally, laser photocoagulation has been the gold standard for treating threshold or type 1 ROP. However, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents such as Bevacizumab and Ranibizumab have gained popularity due to their efficacy in posterior ROP, ability to preserve peripheral retina, and favorable anatomical outcomes [5]. Anti-VEGF therapy is especially effective in Zone I or aggressive posterior ROP (APROP), where laser treatment

DOI: https://doi.org/10.54393/pjhs.v6i7.3255

is often technically challenging and less effective [6]. Despite its therapeutic benefits, anti-VEGF use poses a unique challenge, the delayed or incomplete retinal vascularization that may extend for months' post-treatment, thereby necessitating prolonged and careful follow-up to monitor for disease recurrence or persistent avascular retina [7]. The timing of complete retinal vascularization following anti-VEGF therapy is a critical clinical endpoint, as it has implications for scheduling follow-ups, evaluating reactivation risk, and planning additional interventions. Several international studies have reported wide variability in the time to full vascularization, with some cases completing by 48–52 weeks postmenstrual age (PMA), while others may take significantly longer or fail to vascularize completely [8]. Factors influencing vascular maturation post-treatment include gestational age at birth, birth weight, zone and stage of ROP, and type of anti-VEGF agent used [9]. Ranibizumab, owing to its shorter systemic half-life, has been associated with relatively earlier revascularization compared to Bevacizumab [10]. In Pakistan, there is a significant gap in locally generated data regarding the time course of retinal vascularization following anti-VEGF therapy. Most neonatal units do not have standardized ROP treatment protocols or long-term follow-up systems, increasing the risk of undetected persistent avascular retina or late recurrence. The scarcity of evidence makes it difficult for ophthalmologists and neonatologists to counsel families regarding the expected duration of follow-up or predict the timeline of retinal maturation.

This study aimed to evaluate the time to complete retinal vascularization following anti-VEGF therapy in Pakistani preterm neonates and to identify potential clinical variables that may influence this timeline.

METHODS

This prospective cohort study was conducted over a duration of 1.5 years at the Neonatal Nursery of Pediatric Ward, Liaquat University of Medical and Health Sciences, Jamshoro. Ethical approval was obtained from the institutional review board before the commencement of the study by the ethical review committee of the Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, vide letter No. LUMHS/Dir/Ophth/-24. All neonates diagnosed with treatment-requiring ROP from December 2023 to May 2025 were assessed for eligibility and recruited consecutively following parental consent. The sample size was calculated via the Open Epi sample size calculator by taking the prevalence of ROP in Preterm neonates as 15.8% [11] with a 10% margin of error and a 97% confidence interval. Inclusion criteria comprised preterm neonates born at ≤34 weeks of gestation and/or with a birth weight ≤2000 grams, who received either Bevacizumab (0.625 mg) or Ranibizumab (0.25 mg) intravitreal injections as the primary treatment for ROP. Infants with congenital ocular anomalies, previous laser photocoagulation, or incomplete follow-up data were excluded. Baseline data were collected from hospital records and verified by the study team at enrollment. ROP zone, stage, and laterality were determined through dilated retinal examination by a pediatric ophthalmologist using indirect ophthalmoscopy (Keeler Vantage Plus), following the International Classification of ROP (ICROP, 3rd edition). Zone I includes the central posterior retina, Zone II extends to the nasal ora serrata, and Zone III comprises the peripheral temporal retina. Staging was based on disease severity: Stage 1 (demarcation line), Stage 2 (ridge), and Stage 3 (extraretinal proliferation). Systemic risk factors such as sepsis, oxygen therapy, mechanical ventilation, intraventricular hemorrhage, and necrotizing enterocolitis were identified from documented neonatal diagnoses. Each patient was followed at 1, 3, and 6 months' post-treatment, based on international guidelines and adapted for local feasibility, considering compliance challenges and follow-up limitations in the Pakistani healthcare setting. At every follow-up, indirect ophthalmoscopy was performed by a qualified ophthalmologist to assess retinal vascular progression, disease regression, or recurrence. Indirect ophthalmoscopy was performed using a Keeler Vantage Plus headset with a 20D condensing lens under topical anesthesia. The primary outcome variable was the time (in weeks) from anti-VEGF administration to the point of complete retinal vascularization, defined as full extension of retinal vessels to zone III without any active neovascularization or plus disease. Secondary outcomes included postmenstrual age (PMA) at completion of vascularization, presence of persistent avascular retina, reactivation of ROP, and any injection-related complications. Data were entered and analyzed using SPSS version 25.0. Descriptive statistics were used to summarize patient characteristics. Data were normally distributed, and the Normality of data distribution was measured via the Shapiro-Wilk test. Comparative analyses of time to complete vascularization across clinical subgroups (ROP stage, ROP zone, anti-VEGF type) were conducted using one-way ANOVA. A p-value of <0.05 was considered statistically significant.

RESULTS

The majority were male (61.9%), delivered via cesarean section (57.1%), and born as singletons (74.6%). The mean gestational age was 29.5 ± 1.5 weeks, and the mean birth weight was 1250 ± 200 grams, aligning with known risk parameters for ROP in premature infants, Table 1.

DOI: https://doi.org/10.54393/pjhs.v6i7.3255

Table 1: Demographic Characteristics(n=63)

Variables	Frequency (%)
Gender	
Male	39(61.9%)
Female	24(38.1%)
Mode of Delivery	
Cesarean Section	36(57.1%)
Normal Vaginal	27(42.9%)
Birth Type	
Singleton	47(74.6%)
Multiple	16(25.4%)
Mean Gestational Age	29.5 ± 1.5 Weeks
Mean Birth Weight	1250 ± 200 Grams

Results outline the clinical characteristics. Most neonates had Stage 2 ROP(68.3%)followed by Stage 3(28.6%). Zone II was the most common site of disease(61.9%), with bilateral involvement seen in 90.5% of cases. Common systemic risk factors included sepsis (20.6%), oxygen therapy (19.0%), and ventilation(17.5%), indicating a high burden of neonatal complications contributing to ROP progression, Table 2.

Table 2: Clinical Characteristics

Variables	Frequency (%)
GendeROP Stage	
Stage 1	02(3.2%)
Stage 2	43(68.3%)
Stage 3	18(28.6%)
ROP Zone	
Zone I	19(30.2%)
Zone II	39(61.9%)
Zone III	05(7.9%)
Laterality	
Bilateral	57(90.5%)
Unilateral	6(9.5%)
Systemic Risk Factorsr	
Sepsis	13(20.6%)
02 Therapy	12(19.0%)
Ventilation	11(17.5%)
IVH	9(14.3%)
NEC	8(12.7%)
None	10(15.9%)

Findings describe the distribution of time to complete retinal vascularization. The mean time to complete vascularization post anti-VEGF treatment was 10.5 ± 2.0 weeks, with a median of 10 weeks and a range of 6–16 weeks. Delayed vascularization beyond 24 weeks was observed in 8.5% of cases, and ROP reactivation occurred in 6.4% of neonates, Table 3.

Table 3: Distribution of Time to Complete Retinal Vascularization

Variables	Value
Mean Time (Weeks Post Anti-VEGF)	10.5 ± 2.0 Weeks
Median Time	10 Weeks
Range	6 – 16 Weeks
Delayed Vascularization (>24 Weeks PMA)	4(8.5%)
ROP Reactivation After Regression	3(6.4%)

This study compares vascularization timing by clinical predictors. Stage 3 ROP, Zone I involvement, and Bevacizumab treatment were associated with numerically longer times to complete vascularization. However, ANOVA p-values showed no statistically significant differences among ROP stage (p=0.369), zone (p=0.197), or anti-VEGF type(p=0.980), Table 4.

Table 4: Comparative Analysis of Time to Complete Retinal Vascularization by Key Predictors(n=63)

Predictor Variables	Subgroup	Mean Time to Vascularization (Weeks)	95% CI (Time)	Delayed Vascularization (>50 Weeks)	p-value
ROP Stage	Stage 1	9.5 ± 1.5	8.43 – 10.57	1(10%)	0.369
	Stage 2	10.3 ± 1.6	9.73 – 10.87	1(6.1%)	
	Stage 3	11.3 ± 2.2	10.21 – 12.39	2(11.1%)	
ROP Zone	Zone I	11.2 ± 2.1	10.19 – 12.21	2(10.5%)	0.197
	Zone II	10.0 ± 1.8	9.42 – 10.58	2(6.3%)	
	Zone III	10.7 ± 2.0	8.73 – 12.67*	0(0.0%)	
Anti-VEGF Type	Bevacizumab	10.7 ± 2.0	10.08 – 11.32	3(6.8%)	0.980
	Ranibizumab	10.1 ± 2.1	9.16 – 11.04	1(5.3%)	

The results illustrate the cumulative outcomes of retinal vascularization, ROP reactivation, and delayed vascularization at 1, 3, and 6 months post-anti-VEGF treatment. It highlights a progressive increase in complete vascularization and a gradual emergence of complications requiring continued follow-up, Figure 1.

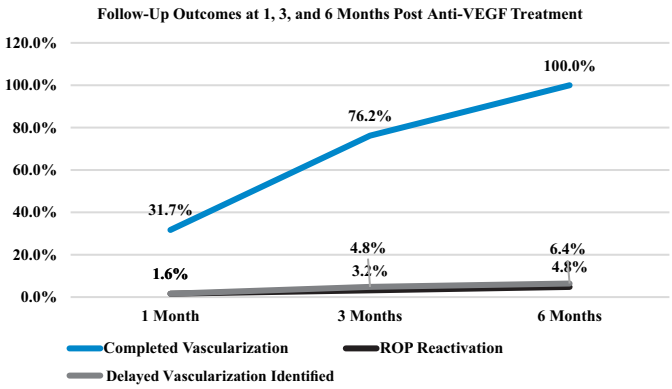

Figure 1: Follow-Up Outcomes at 1, 3, and 6 Months Post Anti-VEGF Treatment(n=63)

DISCUSSION

This study aims to evaluate the time to complete retinal vascularization after intravitreal anti-VEGF therapy in preterm neonates with ROP and to explore clinical factors influencing this timeline. The mean time to complete vascularization was found to be 10.5 ± 2.0 weeks, with a mean PMA at completion of 44.5 ± 2.1 weeks. These findings are consistent with previously published literature

DOI: https://doi.org/10.54393/pjhs.v6i7.3255

reporting vascularization completion within 10–12 weeks' post-treatment, typically around 44–46 weeks PMA [12]. In the present study, delayed vascularization beyond 50 weeks PMA was observed in 8.5% of cases. This rate is relatively low compared to international data, where delayed or incomplete vascularization has been reported in 10–20% of infants, depending on the anti-VEGF agent used and the severity of disease [13]. Kumawat *et al.* noted that delayed retinal maturation is more commonly associated with Zone I and Stage 3 ROP, similar to trends observed in current cohort [14]. Although not statistically significant, present findings indicated longer vascularization time in Stage 3 disease (11.3 ± 2.2 weeks) compared to Stage 1–2 (9.5–10.3 weeks), and in Zone I (11.2 ± 2.1 weeks) compared to Zone II–III (10.0–10.7 weeks). These observations are in line with a study by Dikopf et al. who found that posterior Retina of Prematurity and more advanced stages are associated with delayed vascularization and higher risk of persistent avascular retina [15]. The anti-VEGF agent used also influenced the outcome. Although the difference was not statistically significant (p=0.980), Bevacizumab-treated infants exhibited slightly longer times to vascularization compared to Ranibizumab (10.7 vs. 10.1 weeks). Similar findings were reported in the CARE-ROP study and other recent meta-analyses, which suggested that Ranibizumab, due to its shorter systemic half-life, may allow earlier revascularization than Bevacizumab [16, 17]. However, the clinical significance of this difference remains debated. Reactivation after initial regression was observed in 6.4% of cases, comparable to previously reported rates by Mintz-Hittner *et al.* in the BEAT-ROP trial (8%) [18]. The slightly lower reactivation rate in present cohort may be attributed to differences in follow-up duration, disease severity at baseline, or treatment protocols. This reinforces the need for structured and extended follow-up after anti-VEGF therapy, especially in Zone I and Stage 3 disease. Persistent avascular retina was observed in a minority (14.3%), a known risk factor for late-onset complications such as retinal tears or detachment [19]. Current study contributes local evidence that supports global trends and highlights the need for national ROP screening and monitoring guidelines. Globally, the debate continues regarding the superiority of anti-VEGF agents versus laser therapy. Although anti-VEGF allows continued peripheral retinal development and is more effective in posterior ROP, concerns remain regarding systemic VEGF suppression and unpredictable vascular outcomes [20].

CONCLUSIONS

Curent findings support a follow-up strategy stratified by disease severity and anti-VEGF type. While anti-VEGF therapy was generally effective in achieving retinal vascularization within 10–12 weeks, neonates with Zone I or Stage 3 ROP and those treated with Bevacizumab may require extended monitoring. Although subgroup differences were not statistically significant, clinical trends reinforce the need for individualized, risk-adapted protocols. This study adds valuable local data to the limited evidence base on post-anti-VEGF outcomes in Pakistani preterm neonates, supporting context-specific follow-up planning.

Authors Contribution

Conceptualization: MNM
Methodology: MNM, AJ, MLM, IG, AKN
Formal analysis: SC
Writing review and editing: AJ, MLM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Kaur K and Mikes BA. Retinopathy of Prematurity. [Updated 2025 Jun]. In: Stat Pearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.

[2] World Health Organization. Preterm birth. WHO Fact Sheets. 2023 May 10 [cited 2025 Jun 12].

[3] Soni M, Khatib MN, Balaraman AK, Roopashree R, Kaur M, Srivastava M *et al.* Mortality Projections, Regional Disparities in the Burden of Neonatal Disorders, and the Status of Achieving SDG Targets by 2030 in South Asia: Insights from the Global Burden of Disease Study 2021. Journal of Epidemiology and Global Health. 2025 Mar; 15(1): 43. doi: 10.1007/s44197-025-00359-0.

[4] Shahid N, Kazmi T, Farhat S, Naqvi SZ, Ahmed H. A Decade of Perinatal Mortality in Pakistan: Systematic Review of Patterns and Challenges (2013–2022). Journal of Taibah University Medical Sciences. 2025 Apr; 20(2): 139-50. doi: 10.1016/j.jtumed.2025.02.008.

[5] Roohipoor R, Torabi H, Karkhaneh R, Riazi-Eafahani M. Comparison of Intravitreal Bevacizumab Injection and Laser Photocoagulation for Type 1 Zone II Retinopathy of Prematurity. Journal of Current Ophthalmology.2019Mar;31(1):61-5.doi:10.1016/j.joco .2018.10.008.

[6] Nowroozzadeh MH, Sadeghi E, Shahriari-Garaee H, Badie MR, Banihashemi J, Garg SJ. An Update on Anti-Vascular Endothelial Growth Factor Treatment for Retinopathy of Prematurity.Journal of Current Ophthalmology.2023Apr;35(2):125-34.doi: 10.4103

DOI: https://doi.org/10.54393/pjhs.v6i7.3255

/joco.joco_38_23.

[7] Kang HG, Choi EY, Byeon SH, Kim SS, Koh HJ, Lee SC *et al*. Anti-Vascular Endothelial Growth Factor Treatment of Retinopathy of Prematurity: Efficacy, Safety, and Anatomical Outcomes. Korean Journal of Ophthalmology.2018Nov;32(6):451.doi:10.3341/kjo.2018.0011.

[8] Zhang X, Peng J, Yang Y, Liu Y, Zhang W, Gu VY *et al.* Vascular Development Analysis: A Study for Tertiary Anti-Vascular Endothelial Growth Factor Therapy After Second Reactivation of Retinopathy of Prematurity. Frontiers in Medicine.2024Jul;11:1421894. doi: 10.3389/fmed.2024.1421894.

[9] Blazon MN, Rezar-Dreindl S, Wassermann L, Neumayer T, Berger A, Stifter E. Retinopathy of Prematurity: Incidence, Risk Factors, and Treatment Outcomes in A Tertiary Care Center.Journal of Clinical Medicine.2024Nov;13(22):6926.doi:10.3390/jcm13226926.

[10] Bakbak B, Ozturk BT, Gonul S, Gedik S. The Effect of Intravitreal Bevacizumab and Ranibizumab on Macular Edema of the Contralateral Eye: A Comparative Study of Two Anti-VEGFs.Oman Journal of Ophthalmology.2016Jan;9(1):44-8.doi:10.4103/0974-620X.176100.

[11] Gul N, Sethi S, Ahmad I, Mansoor A, Nadeem ZA, Najeeb W *et al.* Exploring Retinopathy of Prematurity: Insights from the First USAID-Funded Screening Program in KPK, Pakistan. Pakistan Journal of Medical Sciences.2025Jul;41(7):2073-9.doi: 10.12669/pjms.41.7.11021.

[12] Alzuabi AK, Alshammari OM, Almousa AN, Abouammoh MA. Anti-Vascular Endothelial Growth Factor Therapy in Retinopathy of Prematurity: An Updated Literature Review. Saudi Journal of Ophthalmology.2022Jul;36(3):260-9.doi:10.4103/sjopt.sjopt_12_22.

[13] Dogra MR and Vinekar A. Role of Anti-Vascular Endothelial Growth Factor (Anti-VEGF) in the Treatment of Retinopathy of Prematurity: A Narrative Review in the Context of Middle-Income Countries. Pediatric Health, Medicine and Therapeutics.2023Dec:59-69. doi: 10.2147/PHMT.S391591.

[14] Kumawat D, Sachan A, Shah P, Chawla R, Chandra P. Aggressive Posterior Retinopathy of Prematurity: A Review on Current Understanding. Eye.2021Apr;35(4):1140-58. doi: 10.1038/s41433-021-01392-6.

[15] Dikopf MS, Machen LA, Hallak JA, Chau FY, Kassem IS. Zone of Retinal Vascularization and Refractive Error in Premature Eyes with and without Spontaneously Regressed Retinopathy of Prematurity. Journal of American Association for Pediatric Ophthalmology and Strabismus.2019Aug;23(4):211-e1.doi:10.1016/j.jaapos.2019.03.006.

[16] Stahl A, Bründer MC, Lagrèze WA, Molnár FE, Barth T, Eter N *et al.* Ranibizumab in Retinopathy of Prematurity–One-Year Follow-Up of Ophthalmic Outcomes and Two-Year Follow-Up of Neurodevelopmental Outcomes from the CARE-ROP Study. Acta Ophthalmologica.2022Feb;100(1):e91-9.doi:10.1111/aos.14852.

[17] Wang AT, Gupta I, Dai S. A Review of Refractive Errors Post Anti-Vascular Endothelial Growth Factor Injection and Laser Photocoagulation Treatment for Retinopathy of Prematurity. Journal of Clinical Medicine.2025 Jan; 14(3): 810. doi: 10.3390/jcm14 030 810.

[18] Mintz-Hittner HMD, The University of Texas Health Science Center, Houston. Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP). ClinicalTrials.Gov Identifier:NCT00622726June. 2017; 6.

[19] Lee CC, Chiang MC, Chu SM, Wu WC, Ho MM, Lien R. Clinical Risk Factors for Retinopathy of Prematurity Reactivation After Intravitreal Antivascular Endothelial Growth Factor Injection. The Journal of Pediatrics.2024 Oct; 273: 113913. doi: 10.1016/j.jpeds.2024.113913

[20] Wang SD and Zhang GM, Shenzhen Screening for Retinopathy of Prematurity Cooperative Group. Laser Therapy Versus Intravitreal Injection of Anti-VEGF Agents in Monotherapy of ROP: A Meta-Analysis. International Journal of Ophthalmology. 2020 May; 13(5): 806. doi: 10.18240/ijo.2020.05.17.