ORIGINAL ARTICLE

EVALUATING TREATMENT OUTCOMES OF INTRAVITREAL AFLIBERCEPT IN RETINOPATHY OF PREMATURITY

Muhammad Usama Idrees[1], Saima Amin[2], Zeeshan Kamil[3], Amna Ali[4], Muhammad Tanweer Hassan Khan[5], Sabrina Mehmood[6]

[1]Consultant Ophthalmologist, [2]Senior Consultant Ophthalmologist, Department of Pediatric Ophthalmology, [3]Senior Consultant Ophthalmologist, Department of Ophthalmology & Oculoplasty, [4] Senior Consultant Ophthalmologist, Department of Pediatric Ophthalmology, [5] Senior Consultant Ophthalmologist, Department of Ophthalmology & Vitreoretina, [6] Ophthalmologist Department of Ophthalmology, LRBT Tertiary Teaching Eye Hospital, Karachi, Pakistan.

ABSTRACT

Objective: To evaluate the anatomical treatment outcomes of intravitreal aflibercept in infants with severe Stage 3 retinopathy of prematurity (ROP).

Study Design: Prospective cohort study.

Place and Duration of Study: LRBT Tertiary Teaching Eye hospital, Karachi, 06 months (August 2025 to January 2026).

Methodology: This prospective cohort study was conducted at a tertiary care eye hospital. Sixteen infants (32 eyes) with gestational age <34 weeks and birth weight <2000 g, who had treatment-requiring Stage 3 ROP received intravitreal aflibercept (0.4 mg/0.01 mL). Outcomes were assessed at 1–2 weeks, 4–6 weeks, and 3 months. Continuous variables were summarized as mean ± SD and categorical variables as frequencies and percentages. Descriptive statistics were used. Because of the small sample size and the low number of unfavorable outcomes, any univariate analyses were considered exploratory.

Results: At 3 months, complete regression was achieved in 26 eyes (81.3%), partial regression in 4 eyes (12.5%), and no change in 2 eyes (6.2%). No eye showed disease progression or recurrence during follow-up. Two eyes (6.2%) belonging to one infant required rescue laser photocoagulation. Mild subconjunctival hemorrhage occurred in 4 eyes (12.5%); no major ocular or systemic adverse events were observed. Exploratory analysis shows that lower gestational age, lower birth weight, Zone I disease, and aggressive ROP were more in infants with unfavorable outcomes.

Conclusion: Intravitreal aflibercept appears to be a safe and effective option for the initial management of severe Stage 3 ROP, with high anatomical regression and few short-term complications. Larger studies with longer follow-up are needed to confirm long-term ocular and systemic safety.

Key words: *Aflibercept; Infant; Intravitreal injections; Retinopathy of prematurity; Treatment outcomes*

How to cite this article: *Idrees MU, Amin S, Kamil Z, Ali A, Khan MTH, Mehmood S. Evaluating Treatment Outcomes of Intravitreal Aflibercept in Retinopathy of Prematurity. HMDJ. 2026 June; 06(01): 13-17. https://doi.org/10.69884/hmdj.6.1.6853.*

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative retinal disorder that affects premature and low-birth-weight infants. Abnormal retinal vascular development after premature birth may lead to ischemia, pathological neovascularization, retinal detachment, and permanent visual impairment [1-3].

Correspondence to: Dr. Muhammad Usama Idrees, LRBT Tertiary Teaching Eye Hospital, Karachi.

Email: m.usamaidrees@gmail.com

Received: 31-03-2026
Revision: 07-06-2026
Accepted: 23-06-2026

ROP remains an important cause of childhood blindness, particularly in low- and middle-income countries where survival of preterm infants has improved but screening and treatment systems remain inconsistent[3,4]. On average, about 15 million preterm infants are born annually all around the world, and about 20,000 to 30,000 infants are born with severe ROP[5]. ROP differs a great deal regarding the gestational age, birth weight, and quality of the provided neonatal care. The incidence of ROP is increasing in South Asia and developing countries, as extremely premature neonates are surviving. The management of this condition requires early therapeutic interventions that are more effective and safer[6]. In Pakistan, reported rates of ROP among preterm infants vary across centres, reflecting differences in neonatal risk profiles, survival, and screening practices[7].

https://doi.org/10.69884/hmdj.6.1.6853

The pathogenesis of ROP is often described in two phases. Early exposure to supplemental oxygen suppresses vascular endothelial growth factor (VEGF) and interrupts normal retinal vascularization. Subsequent relative retinal hypoxia increases VEGF expression and drives pathologic neovascularization, so this biological mechanism provides the rationale for anti-VEGF treatment [8].

Laser photocoagulation has historically been the standard treatment for threshold and type 1 ROP, but it is associated with peripheral retinal ablation, visual field loss, high myopia, and the need for technically demanding procedures. Intravitreal anti-VEGF therapy offers a targeted alternative that may preserve more peripheral retina [8-12].

Aflibercept is a recombinant fusion protein that binds VEGF-A, VEGF-B, and placental growth factor. Its high binding affinity and relatively prolonged duration of action make it an attractive candidate for severe ROP [11]. Some clinical trials have documented good results with intravitreal aflibercept, such as regression of neovascularization and low rates of recurrence, though there are still some concerns that need to be addressed about systemic absorption, optimal dosage, long-term ocular development, and neurodevelopmental safety in premature babies[12,13]. However, data from low-resource settings remain limited, and real-world evidence on short-term outcomes is still evolving.

The objective of this study was to evaluate the anatomical treatment outcomes and short-term safety of intravitreal aflibercept in infants with severe Stage 3 ROP.

CAPSULE SUMMARY

Treatment outcomes of intravitreal aflibercept in infants with severe Stage 3 retinopathy of prematurity (ROP) were evaluated. It appeared to be a safe and effective option for initial management, with high anatomical regression and few short-term complications.

METHODOLOGY

This prospective cohort study was conducted at a Tertiary Care Teaching Eye Hospital (LRBT Tertiary Teaching Eye hospital, Karachi) from August 1, 2025, to January 31, 2026, after approval from the Ethical Review Committee. Written informed consent was obtained from parents or guardians of all enrolled infants.

The calculated sample size using OpenEpi version 3 was 45 infants, based on an expected favourable outcome proportion of 97%, a 95% confidence level, and 5% margin of error[14]. However, because treatment-requiring severe ROP was infrequent during the study period, only 16 infants (32 eyes) could be enrolled. Therefore, this study should be interpreted as an exploratory prospective cohort providing preliminary real-world evidence.

Non-probability consecutive sampling was used. Eligible participants were premature infants with gestational age <34 weeks, birth weight <2000 g, and treatment-requiring Stage 3 ROP who received intravitreal aflibercept and whose guardians provided consent. Infants with congenital ocular anomalies, prior laser photocoagulation, previous anti-VEGF therapy, systemic congenital syndromes affecting ocular development, or loss to follow-up were excluded.

Baseline demographic and clinical variables included gestational age, birth weight, sex, mode of delivery, oxygen exposure, neonatal intensive care stay, and systemic comorbidities. Ophthalmic assessment included ROP stage, retinal zone, and disease status using indirect ophthalmoscopy and wide-field retinal imaging when available. A trained pediatric ophthalmologist and a vitreoretinal specialist confirmed the findings.

Intravitreal aflibercept (0.4 mg/0.01 mL) was administered under strict aseptic conditions in the operating room by a trained pediatric ophthalmologist. Topical anaesthesia, povidone-iodine antisepsis, and a sterile eyelid speculum were used. Aflibercept was injected through the pars plicata using a 30-gauge needle at an age-appropriate distance from the limbus. Bilateral treatment was performed on the same day when indicated. Topical antibiotics were prescribed post-procedure, and infants were monitored for immediate ocular and systemic adverse events.

Follow-up examinations were scheduled at 1–2 weeks, 4–6 weeks, and 3 months. Outcomes included regression of neovascularization, resolution of plus disease, disease progression or recurrence, and need for additional treatment. A favourable outcome was defined as complete regression without need for retreatment by 3 months. Unfavourable outcomes were considered as partial regression, no regression, recurrence, and requirement for additional treatment.

Data were analysed using SPSS version 26. Continuous variables were assessed for normality using the Shapiro–Wilk test. Continuous variables were summarized as mean ± standard deviation; categorical variables as frequency and percentage. Primary analysis was conducted at the eye level. An exploratory infant-level univariate analysis was performed to compare the characteristics of infants with favourable vs unfavourable outcomes. Continuous variables were compared using the Mann-Whitney U test. The Fisher's exact test was used to compare categorical variables. Given the small sample size and only three unfavourable outcomes, these univariate analyses were considered exploratory and interpreted cautiously. A p-value ≤0.05 was considered statistically significant.

RESULTS

Sixteen infants (32 eyes) were included. The cohort represented a high-risk neonatal population with low gestational age and low birth weight. Primary outcome analysis was done at eye level. All eyes had Stage 3 ROP. Zone II was the most commonly involved retinal zone, while more than one-third of eyes had

Table 1. Baseline demographic, clinical, and ophthalmic characteristics of infants with ROP [n=16 infants; 32 eyes]

Variable	Value
Male sex ; n(%)	9 (56.3)
Female sex ; n(%)	7 (43.7)
Gestational age (weeks) ; mean±SD	28.4 ± 2.1
Birth weight (g) ; mean±SD	1125 ± 285
ROP stage ; n(%)	Stage 3 in 32 eyes (100)
Zone I disease ; n(%)	12 eyes (37.5)
Zone II disease ; n(%)	18 eyes (56.3)
Zone III disease ; n(%)	2 eyes (6.2)
Plus disease present ; n(%)	20 eyes (62.5)
Aggressive ROP ; n(%)	14 eyes (43.8)

Table 2. Frequency of treatment characteristics of intravitreal aflibercept

Variable	Frequency (%)
Dose administered (0.4 mg/0.01 mL)	32 eyes (100)
Bilateral injections	16 infants (100)
Topical anesthesia used	16 infants (100)
Rescue laser photocoagulation	2 eyes (6.2)

Table 3. Frequency of follow-Up outcomes after intravitreal aflibercept (32 eyes)

Outcome	1–2 weeks Frequency(%)	4–6 weeks Frequency(%)	3 months Frequency(%)
Complete regression	14 (43.8)	22 (68.8)	26 (81.3)
Partial regression	12 (37.5)	8 (25.0)	4 (12.5)
No change	6 (18.7)	2 (6.2)	2 (6.2)
Progression	0 (0)	0 (0)	0 (0)
Additional treatment required	0 (0)	2 (6.2)	2 (6.2)

Zone I disease. Plus disease and aggressive ROP were also common at presentation. (Table 1)

All eyes received intravitreal aflibercept at the standard study dose. Bilateral injections were performed for all infants. Most procedures were completed under topical anaesthesia. Two eyes (6.2%), belonging to one infant, later required rescue laser photocoagulation. (Table 2)

Serial follow-up demonstrated progressive retinal vascularization and regression of neovascularization over 3 months. The proportion of eyes with complete regression increased across follow-up visits, whereas partial regression and no-change categories decreased. No eye showed progression during follow-up. (Table 3)

Table 4. Frequency of final treatment outcomes at 3 months (32 eyes)

Outcome	Frequency (%)
Complete regression of ROP	26 (81.3)
Partial regression	4 (12.5)
No change	2 (6.2)
Recurrence of ROP	0 (0)
Need for repeat aflibercept injection	0 (0)
Need for rescue laser photo-coagulation	2 (6.2)
Overall favorable outcome	26 (81.3)

Table 5. Frequency of ocular and systemic complications

Complication	Frequency (%)
Subconjunctival hemorrhage	4 eyes (12.5)
No ocular complications	28 eyes (87.5)
Systemic complications	0 (0)

By 3 months, 26 eyes (81.3%) had complete regression, 4 eyes (12.5%) had partial regression, and 2 eyes (6.2%) showed no change. No recurrence was documented within the follow-up period, and no repeat aflibercept injection was required. (Table 4)

Treatment was generally well tolerated. Mild subconjunctival haemorrhage occurred in 4 eyes (12.5%) and resolved without intervention. No retinal detachment, endophthalmitis, cataract, vitreous haemorrhage, or systemic adverse events were documented. (Table 5)

Table 6. Exploratory comparison of characteristics of infants with Favourable versus Unfavourable Outcomes

Variable	Favorable outcome (n=13 infants)	Unfavorable outcome (n=3 infants)	p-value
Gestational age (weeks) ; mean±SD	29.1 ± 1.9	26.4 ± 1.6	0.02
Birth weight (g) ; mean±SD	1210 ± 260	890 ± 190	0.03
Zone I disease ;n(%)	4 (30.8)	2 (66.7)	0.04
Plus disease ;n(%)	7 (53.8)	3 (100)	0.08
Aggressive ROP;n(%)	4 (30.8)	2 (66.7)	0.04
Need for laser therapy ;n(%)	0 (0)	1 (33.3)	0.01
Subconjunctival hemorrhage ;n(%)	2 (15.4)	2 (66.7)	0.09

Exploratory risk factor analysis was performed at the infant level. On exploratory analyses, lower gestational age, lower birth weight, Zone I disease, aggressive ROP, and need for rescue laser were more common in infants with unfavourable outcomes. (Table 6)

DISCUSSION

This prospective cohort suggests that intravitreal aflibercept may provide favourable short-term anatomical outcomes in severe Stage 3 ROP. More than four-fifths of treated eyes achieved complete regression by 3 months, and no recurrence was observed during the follow-up period. The low complication rate further supports its short-term tolerability in this cohort.

Our findings are broadly consistent with published studies reporting good anatomical regression after aflibercept in treatment-requiring ROP. The presence of Zone I disease, aggressive posterior features, and greater prematurity in infants with less favourable outcomes also aligns with the established understanding that both systemic immaturity and posterior disease severity influence prognosis [15,16]. The low complication rate further supports its short-term tolerability in this cohort [17].

Only two eyes required rescue laser photocoagulation, suggesting that aflibercept was adequate as primary therapy for most eyes in this series. However, infants with severe posterior disease may still need adjunctive treatment, emphasizing the need for close follow-up after anti-VEGF therapy [18,19,20,21]. The FIREFLEYE next study at longer-term follow-up confirmed that sustained disease control with aflibercept could be maintained to at least two years of age with minimal reactivation and reduced late adverse effects, consistent with the durability of anti-VEGF therapy in the present study's short-term, three-month follow-up[20].

The safety profile in this study was reassuring, with only minor subconjunctival haemorrhage and no observed major ocular or systemic complications. Nevertheless, the follow-up duration was short, and this study was not powered to evaluate uncommon adverse events or long-term visual and neurodevelopmental outcomes.

Limitations: The sample size was smaller than originally calculated, limiting statistical power and generalizability. The single-centre design and 3-month follow-up reduce the ability to assess late recurrence, peripheral vascularization, refractive outcomes, and systemic safety. In addition, because of the low number of unfavourable events, multivariable regression analysis was not performed, and exploratory univariate analysis should be interpreted with caution.

Despite these limitations, this study provides useful preliminary real-world evidence from a resource-constrained setting and supports further larger prospective studies evaluating aflibercept in ROP.

CONCLUSION

Intravitreal aflibercept appears to be a safe and effective short-term treatment option for severe Stage 3 ROP. High complete regression rates and low complication rates were observed. Lower gestational age, lower birth weight, Zone I disease, and aggressive ROP were common in infants with less favourable outcomes. Larger multicentre studies with longer follow-up are needed to establish long-term ocular and systemic safety and to evaluate the long-term efficacy of intravitreal aflibercept in ROP.

ETHICAL APPROVAL: *Approval No: LRBT/TTEH/ERC/4597/39, 30th July 2025.*

CONSENT FOR PUBLICATION: *Written, informed consent was obtained from the study participants.*

AVAILABILITY OF DATA: *Data is available from the corresponding author on a justified request.*

FINANCIAL DISCLOSURE/ FUNDING: *None*

ARTIFICIAL INTELLIGENCE TOOLS DISCLOSURE: *None*

CONFLICT OF INTEREST: *None*

ACKNOWLEDGEMENT: *None*

AUTHORS' CONTRIBUTION

- ***Muhammad Usama Idrees:*** *Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision*
- ***Saima Amin:*** *Conception and design, Acquisition of data, Critical revision*
- ***Zeeshan Kamil:*** *Acquisition of data, Analysis and interpretation of data, Drafting the article*
- ***Amna Ali:*** *Drafting the article, Critical revision*
- ***Muhammad Tanweer Hassan Khan:*** *Conception and design, Acquisition of data, Analysis and interpretation of data*
- ***Sabrina Mehmood:*** *Analysis and interpretation of data, Critical revision*

REFERENCES

1. Sabri K, Ells AL, Lee EY, Dutta S, Vinekar A. Retinopathy of prematurity: a global perspective and recent developments. Pediatrics. 2022;150(3):e2021053924. doi:10.1542/peds.2021-053924.
2. Yucel OE, Eraydin B, Niyaz L, Terzi O. Incidence and risk factors for retinopathy of prematurity in premature, extremely low birth weight and extremely low gestational age infants. BMC Ophthalmol. 2022;22(1):367. doi:10.1186/s12886-022-02591-9.
3. Zhang RH, Liu YM, Dong L, Li HY, Li YF, Zhou WD, et al. Prevalence, years lived with disability, and time trends for 16 causes of blindness and vision impairment: findings highlight retinopathy of prematurity. Front Pediatr. 2022;10:735335. doi:10.3389/fped.2022.735335.
4. Wang EY, Kong X, Wolle M, Gasquet N, Ssekasanvu J, Mariotti SP, et al. Global trends in blindness and vision impairment resulting from corneal opacity 1984-2020: a meta-analysis. Ophthalmol. 2023;130(8):863-871. doi:10.1016/j.ophtha.2023.03.012.
5. Wang J, Ma Q, Du F. Predictive value of postnatal weight gain rate for severe retinopathy of prematurity in preterm infants: a retrospective analysis. J Multidiscip Healthc. 2025;18:5381-5391. doi:10.2147/JMDH.

S528155.

6. Darlow BA. Primary prevention of retinopathy of prematurity: more can be done in all settings. Expert Rev Ophthalmol. 2023;18(3):177-191. doi: 10.1080/17469899.2023.2245143.
7. Zeeshan M, Ali A, Qadir W, Rafique A, Rafiq A, Younas I. Frequency and risk factors associated with retinopathy of prematurity: a single centre study. Pak J Health Sci. 2024;5(10):19-23. doi:10.54393/pjhs.v5i10.2147.
8. Ahmad A, Nawaz MI. Molecular mechanism of VEGF and its role in pathological angiogenesis. J Cell Biochem. 2022;123(12):1938-1965. doi:10.1002/jcb.30344.
9. Cao JK, Han T, Tang HY, Zhang S, Wang ZH, Feng ZC, et al. Comparison of post-treatment recurrence between ranibizumab injection and laser photocoagulation for type 1 retinopathy of prematurity. BMC Ophthalmol. 2023;23(1):137. doi:10.1186/s12886-023-02886-5.
10. Oba S, Kiriishi T, Omi M, Hattori Y, Mori H, Ohnaka M, et al. Short-term efficacy of two-step treatment of retinopathy of prematurity in a Japanese cohort: anti-VEGF therapy followed by routine laser photocoagulation. J Clin Med. 2025;14(19):7094. doi:10.3390/jcm14197094
11. Liberski S, Wichrowska M, Kocięcki J. Aflibercept versus faricimab in the treatment of neovascular age-related macular degeneration and diabetic macular edema: a review. Int J Mol Sci. 2022;23(16):9424. doi:10.3390/ijms23169424.
12. Beccasio A, Mignini C, Caricato A, Iaccheri B, Di Cara G, Verrotti A, et al. New trends in intravitreal anti-VEGF therapy for ROP. Eur J Ophthalmol. 2022;32(3):1340-1351. doi:10.1177/11206721211073405.
13. Chatziralli I. Ranibizumab for the treatment of diabetic retinopathy. Expert Opin Biol Ther. 2021;21(8):991-997. doi:10.1080/14712598.2021.1928629.
14. Chen PJ, Rossin EJ, Vavvas DG. Aflibercept for retinopathy of prematurity: a systematic review and meta-analysis. Ophthalmic Surg Lasers Imaging Retina. 2021;52(12):673-681. doi:10.3928/23258160-20211124-01.
15. Huang C, Zou W, Ma W, Li J, Bai Y, Wu R, et al. Effect and factors associated with reactivation after intravitreal conbercept or aflibercept in retinopathy of prematurity. Eur J Med Res. 2025;30(1):55. doi:10.1186/s40001-024-02206-7.
16. Zhang X, Wan C, Zhang CR, Liu XL. Incidence and treatment outcomes of retinopathy of prematurity in preterm infants assessed through wide-field fundus imaging: a retrospective cohort study. Transl Pediatr. 2025;14(9):2158-2166. doi:10.21037/tp-2025-224.
17. Yang T, Zhang J, Hao Q, Ma S, Cheng X. Efficacy and safety of aflibercept and ranibizumab in the treatment of retinopathy of prematurity. Clin Ther. 2024;46(10):773-777. doi:10.1016/j.clinthera.2024.08.011.
18. Zhang W, Ma H, Wang J, Chen Z, Zhang X, Xiao H, et al. Comparison of clinical and angiographic outcomes of ranibizumab and aflibercept in type 1 and aggressive retinopathy of prematurity. Clin Exp Ophthalmol. 2025;53(8):956-966. doi:10.1111/ceo.14575.
19. Stahl A, Sukgen EA, Wu WC, Lepore D, Nakanishi H, Mazela J, et al. Effect of intravitreal aflibercept vs laser photocoagulation on treatment success of retinopathy of prematurity: the FIREFLEYE randomized clinical trial. JAMA. 2022;328(4):348-359. doi:10.1001/jama.2022.10564.
20. Stahl A, Nakanishi H, Lepore D, Wu WC, Azuma N, Jacas C, et al. Intravitreal aflibercept vs laser therapy for retinopathy of prematurity: two-year efficacy and safety outcomes in the nonrandomized controlled trial FIREFLEYE next. JAMA Netw Open. 2024;7(4):e248383. doi:10.1001/jamanetworkopen.2024.8383.
21. Riazi-Esfahani H, Mahmoudi A, Sanatkar M, Farahani AD, Bazvand F. Comparison of aflibercept and bevacizumab in the treatment of type 1 retinopathy of prematurity. Int J Retina Vitreous. 2021;7(1):60. doi:10.1186/s40942-021-00334-4.