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Predictors of Retinopathy of Prematurity Reactivation in Pakistani Preterm Neonates After Anti-VEGF Therapy

Asadullah Jatoi[1*], Mariya Nazish Memon[1], Mona Liza Mahesar[1], Imtiaz Gilal[1], Shazia Memon[2], Ashok Kumar Narsani[1] and Muhammad Maisam[3]

[1]Department of Ophthalmology, Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[2]Department of Pediatrics, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[3]Department of Biomedical Sciences, China Medical University, Taiwan

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

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ABSTRACT

Retinopathy of prematurity (ROP) is a significant cause of preventable childhood blindness, particularly in low- and middle-income countries like Pakistan, where preterm survival rates are increasing. However, the risk of disease reactivation after initial regression remains a concern, particularly in settings with limited follow-up infrastructure. **Objectives:** To determine the incidence and identify clinical predictors of ROP reactivation among Pakistani preterm neonates treated with intravitreal anti-VEGF therapy. **Methods:** This observational study was conducted at the Neonatal Nursery of the Pediatric Ward, Liaquat University of Medical and Health Sciences, Jamshoro. A total of 47 preterm neonates (≤34 weeks' gestational age and/or ≤2000 grams' birth weight) who received anti-VEGF injections for treatment-requiring ROP were consecutively enrolled. Data on ROP zone, stage, gestational age, birth weight, and anti-VEGF agent were collected. Follow-up was performed to assess reactivation, defined as recurrence of plus disease or disease progression necessitating retreatment. Statistical analysis was performed using SPSS 25.0. **Results:** The mean gestational age and birth weight were 29.5 ± 1.5 weeks and 1250 ± 200 grams, respectively. ROP reactivation occurred in 8 of 47 neonates (17.0%). Zone I disease was significantly associated with higher reactivation risk (p=0.029). No significant associations were found with ROP stage, anti-VEGF type, or gestational age. **Conclusions:** ROP reactivation following anti-VEGF treatment occurred in 17% of cases. Zone I involvement was the only significant predictor, highlighting the need for vigilant long-term follow-up in these patients.

INTRODUCTION

Retinopathy of prematurity (ROP) remains a leading cause of preventable childhood blindness worldwide, particularly in low- and middle-income countries experiencing rising survival rates of preterm neonates without parallel improvements in neonatal intensive care [1]. ROP is a vaso-proliferative disorder of the immature retina, with its progression driven by fluctuations in oxygen exposure and subsequent neovascular responses [2]. In Pakistan, the increasing burden of preterm births, estimated at over 750,000 annually [3], has intensified the risk of ROP among neonates, especially in settings lacking standardized screening programs and advanced neonatal care infrastructure [3]. The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents such as Bevacizumab and Ranibizumab has transformed ROP management, offering targeted inhibition of pathological angiogenesis and favorable anatomical outcomes in posterior or aggressive ROP [4]. Compared to laser photocoagulation, anti-VEGF agents preserve peripheral retinal structures and are less likely to cause myopia,

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making them attractive in Zone I or aggressive posterior ROP cases [5]. However, one major concern surrounding anti-VEGF therapy is the risk of ROP reactivation, defined as recurrence of active disease requiring retreatment, occurring weeks or even months after initial regression [6]. Studies report that reactivation rates vary widely, ranging from 10% to 25% [7] depending on factors such as the type of anti-VEGF used, ROP zone and stage, gestational age, and duration of post-treatment follow-up [7]. In a multicenter cohort in Egypt, reactivation was more frequent with Bevacizumab compared to Ranibizumab, potentially due to its longer systemic half-life and more prolonged VEGF suppression [8]. Neonates with Zone I or Stage 3 ROP and those born with extremely low birth weights are considered to be at heightened risk of recurrence. The timing and predictors of reactivation, however, remain poorly characterized in resource-limited settings such as Pakistan, where follow-up continuity is often compromised and clinical protocols are inconsistently implemented [9]. Despite increasing utilization of anti-VEGF therapy in Pakistan due to its cost-effectiveness and logistical ease, there is limited local data on the actual burden and clinical predictors of ROP reactivation. This knowledge gap hampers the formulation of evidence-based follow-up guidelines, posing a risk of missed diagnoses and irreversible visual loss.

Despite the growing use of anti-VEGF therapy for retinopathy of prematurity (ROP), there remains limited evidence from low- and middle-income settings like Pakistan regarding post-treatment reactivation patterns and their predictors. Existing literature shows variable reactivation rates and inconsistent identification of risk factors, particularly regarding the role of ROP zone, stage, and anti-VEGF agent type. This lack of localized and stratified evidence creates uncertainty in follow-up protocols and risk prediction. Therefore, this study aimed to determine the incidence of ROP reactivation after anti-VEGF therapy and identify its clinical predictors among Pakistani preterm neonates.

METHODS

This observational study was conducted from December 2023 to November 2024, at the Neonatal Nursery of Pediatric Ward, Liaquat University of Medical and Health Sciences, Jamshoro. During the study period, all preterm neonates who met the eligibility criteria and underwent anti-VEGF treatment for ROP were consecutively enrolled after obtaining informed consent from their parents or legal guardians. Eligible participants included preterm neonates born at a gestational age of ≤34 weeks and/or with a birth weight of ≤2000 grams who were diagnosed with treatment-requiring ROP (Stage 2 or 3, with plus disease) and all neonates received same dose of intravitreal anti-VEGF therapy, either Bevacizumab 0.625 mg/0.025 mL and Ranibizumab 0.25 mg/0.025 mL, as reported in the BEAT-ROP and RAINBOW trials, respectively [10, 11]. The choice between Bevacizumab and Ranibizumab was based on the treating ophthalmologist's preference, drug availability, and caregiver consent. Group assignment was therefore non-random and followed a non-probability consecutive sampling approach. Neonates with congenital ocular anomalies, prior retinal surgery, or those who received initial laser therapy before anti-VEGF injection were excluded from the study. The study was approved by the ethical review committee of the Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, vide letter No. LUMHS/Dir/Ophth/-24. Data collection was carried out using a structured proforma that included demographic details (gestational age, birth weight, gender), clinical features (stage and zone of ROP, laterality), type of anti-VEGF agent administered, and the postmenstrual age at which the injection was given. Follow-up evaluations (via standardized follow-up protocol) were conducted weekly for the first month and biweekly thereafter until complete retinal vascularization or disease reactivation was observed. Compliance was ensured through caregiver counselling, appointment reminders and coordination with routine pediatric visits. ROP reactivation was defined as recurrence of plus disease, progression to a more advanced stage, or new extraretinal fibrovascular proliferation requiring retreatment. Each eye was evaluated independently by a trained ophthalmologist using indirect ophthalmoscopy with scleral depression, and findings were documented per the International Classification of ROP (ICROP-3). Indirect ophthalmoscopy was performed using a Keeler Vantage Plus headset with a 20D condensing lens under topical anesthesia. Data were analyzed using SPSS version 25.0. Descriptive statistics were applied to summarize demographic and clinical variables. The incidence of ROP reactivation was expressed as a percentage of total treated neonates. Inferential statistics, including the chi-square test, were applied to determine the association between reactivation and potential predictors such as gestational age group, birth weight category, ROP zone, ROP stage, and anti-VEGF agent used. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean gestational age was 29.5 ± 1.5 weeks, and the mean birth weight was 1250 grams, aligning with typical ROP risk profiles. Most infants had Stage 2 ROP (66%) and Zone II involvement (70.2%). Bevacizumab was the more commonly used anti-VEGF agent (70.2%) compared to Ranibizumab (29.8%) (Table 1).

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Table 1: Baseline features of Preterm Neonates (n=47)

Variables	Mean ± SD / Frequency (%)
Gestational Age (weeks)	29.5 ± 1.5
Birth Weight (grams)	1250 ± 200
ROP Stage	
Stage 2	31 (66.0%)
Stage 3	16 (34.0%)
ROP Zone	
Zone I	14 (29.8%)
Zone II	33 (70.2%)
Anti-VEGF Type	
Bevacizumab	33 (70.2%)
Ranibizumab	14 (29.8%)

The study highlights the overall incidence of ROP reactivation following anti-VEGF therapy. Reactivation was observed in 8 out of 47 neonates, yielding an incidence rate of 17.0% (Table 2).

Table 2: Frequency of Hypertension and Gender Distribution (n=182)

Reactivation Status	Frequency (%)
Yes	8 (17%)
No	39 (83%)
Total	47

ROP reactivation was slightly higher in Stage 3 (18.8%) than in Stage 2 (16.1%), with Zone I cases showing higher reactivation (21.4%) compared to Zone II (15.2%). Reactivation rates were similar between Bevacizumab (18.2%) and Ranibizumab (14.3%), with no significant difference (p=1.24). Gestational age groups also showed no significant variation in reactivation (p=0.34). Only the ROP zone was a significant predictor of recurrence (Table 3).

Table 3: Predictors of ROP Reactivation by Risk Factors

Predictor Variables		Reactivation		p-value
		Yes	No	
ROP Stage	Stage 2	5 (16.1%)	26 (83.9%)	0.710
	Stage 3	3 (18.8%)	13 (81.2%)	
ROP Zone	Zone I	3 (21.4%)	11 (78.6%)	0.029
	Zone II	5 (15.2%)	28 (84.8%)	
Anti-VEGF Type	Bevacizumab	6 (18.2%)	27 (81.8%)	1.240
	Ranibizumab	2 (14.3%)	12 (85.7%)	
Gestational Age	<28 Weeks	2 (18.2%)	9 (81.8%)	0.340
	28-30 Weeks	4 (16.0%)	21 (84.0%)	
	>30 Weeks	2 (18.2%)	9 (81.8%)	

DISCUSSION

This study assessed the incidence and predictors of ROP reactivation among Pakistani preterm neonates following intravitreal anti-VEGF therapy. The incidence of ROP reactivation was found to be 17.0%, consistent with international estimates ranging from 10% to 25%, depending on population characteristics, ROP severity, and anti-VEGF agent used [12, 13]. The baseline characteristics of neonates in this cohort revealed a mean gestational age of 29.5 ± 1.5 weeks and a mean birth weight of 1250 ± 200 grams, aligning with known epidemiological profiles of ROP in South Asia [14]. A higher proportion of cases involved Zone II disease (70.2%) and Stage 2 ROP (66.0%). Bevacizumab was the more commonly used anti-VEGF agent (70.2%), reflecting its accessibility and lower cost compared to Ranibizumab in the Pakistani healthcare setting [15]. The reactivation rate of 17.0% observed in our study parallels findings by Huang *et al.* who reported recurrence in 16–22% of cases following Bevacizumab monotherapy in Taiwan [16]. Similarly, Wallace *et al.* observed a recurrence rate of 18% in the Bevacizumab trial [17], while Stahl *et al.* reported lower rates with Ranibizumab in the RAINBOW trial [11]. In our cohort, although Bevacizumab had a slightly higher reactivation rate (18.2%) than Ranibizumab (14.3%), the difference was not statistically significant (p=1.24), consistent with a recent Indian study that suggests minimal difference in recurrence between the two agents when follow-up protocols are rigorously followed [17]. Importantly, ROP zone emerged as the only statistically significant predictor of reactivation in our study (p=0.029). Neonates with Zone I disease had a reactivation rate of 21.4%, significantly higher than the 15.2% seen in Zone II cases. This aligns with findings of an Indian study indicating that posterior ROP (Zone I) is biologically more aggressive, has a longer avascular period, and is more likely to reactivate following VEGF suppression [18]. In contrast, the ROP stage did not show a statistically significant association with reactivation (p=0.71), though numerically higher recurrence was seen in Stage 3 (18.8%) versus Stage 2 (16.1%). These findings are consistent with the results from a large-scale study by Milani AE *et al.* which found the ROP zone to be a more reliable predictor of recurrence than stage alone [19]. Similarly, gestational age did not significantly affect reactivation rates in our cohort (p=0.34), despite some global studies linking lower gestational age with poor retinal vascularization and higher recurrence risk [20]. The absence of a significant association between anti-VEGF type and recurrence in our study may be partially due to the small sample size and the need for longer-term follow-up. However, international data remain divided on this issue. While Stahl *et al.* and others have shown lower systemic VEGF suppression with Ranibizumab and potentially earlier revascularization [11], studies such as the CARE-ROP trial have not found meaningful differences in long-term reactivation rates [21].

This study is limited by its relatively small sample size and single-center design, which may restrict generalizability to broader neonatal populations. The non-randomized assignment of anti-VEGF agents and short follow-up duration may also introduce selection bias and limit assessment of late reactivation. Additionally, potential confounders such as oxygen exposure variability and systemic neonatal factors were not fully controlled. Future

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multicenter studies with larger cohorts and longer follow-up periods are recommended to validate predictors of reactivation and develop standardized national guidelines for post-anti-VEGF surveillance in ROP

CONCLUSIONS

Our study supports international findings that ROP reactivation is a relevant concern after anti-VEGF therapy, with Zone I involvement as a significant predictor. These results advocate for intensified surveillance in Zone I disease, regardless of the anti-VEGF agent used. Future multicenter research in Pakistan is needed to validate these findings and guide national clinical guidelines.

Authors' Contribution

Conceptualization: AJ
Methodology: AJ, MNM, MLM, IG, AKN
Formal analysis: SM
Writing and Drafting: MNM, MLM, IG, MM
Review and Editing: MNM, MLM, IG, MM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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