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Is Neonatal Anemia a Risk Factor in Developing Retinopathy of Prematurity in Premature Babies: A Prospective Observational Study in Rural North India

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Abstract: ***Background: Retinopathy of prematurity (ROP) is a vision-threatening vasoproliferative disorder that predominantly affects premature infants and is a leading cause of avoidable childhood blindness worldwide. While low gestational age and birth weight are established risk factors, recent evidence suggests that neonatal anemia may independently contribute to ROP development through exacerbation of retinal hypoxia and altered angiogenic signaling. Aim: To determine the incidence of ROP in premature infants admitted to a rural Sick Newborn Care Unit (SNCU) in North India and evaluate whether neonatal anemia acts as a significant risk factor for ROP. Materials and Methods: A prospective observational study was conducted over one year (November 2023–October 2024) including 120 preterm infants with gestational age <34 weeks or birth weight <2000 g. Detailed clinical records including anemia status, blood transfusion history, and neonatal comorbidities were collected. ROP screening was performed by indirect ophthalmoscopy and classified according to ICROP guidelines. Statistical analysis was done using Chi-square test, with $p < 0.05$ considered significant. Results: ROP occurred in 32 of 120 infants (26.7%), with Stage 2 being the most common presentation (43.7%). Of the 32 affected infants, 10 (31.3%) required treatment while 22 (68.7%) showed spontaneous regression. Anemia was present in 30 infants; 14 (46.7%) developed ROP compared with 18 of 90 (20.0%) non-anemic infants ($p = 0.004$). ROP occurred in 56.2% of transfused infants versus 22.1% in non-transfused infants ($p = 0.01$). Conclusion: Neonatal anemia significantly increases the risk of ROP, and blood transfusion further compounds disease severity. Early detection and correction of anemia, alongside restrictive transfusion practices and structured screening, may reduce severe ROP burden in rural preterm populations.***

Keywords: Retinopathy of prematurity, neonatal anemia, prematurity, blood transfusion, VEGF, blindness prevention.

1. Introduction

Retinopathy of prematurity (ROP) is a vision-threatening vaso proliferative disorder of incompletely vascularized retina in premature infants and is a major cause of preventable childhood blindness worldwide.[1,2] Pathogenesis involves a biphasic process beginning with retinal vascular interruption and hypoxia followed by pathological neovascularization driven by vascular endothelial growth factor (VEGF).[2,3] Prematurity and low birth weight are universally recognized risk factors for ROP.[4,5]

Recently, neonatal anemia has emerged as a potential independent risk contributor. [1,6,7] Anemia may exacerbate retinal ischemia by reducing oxygen-carrying capacity, thereby upregulating VEGF and promoting neovascularization.[8] Dhawan et al.[1] and earlier studies by Rekha et al. [5] and Liu et al. [6] demonstrated significantly higher ROP prevalence among anemic infants. Blood transfusion has also been associated with ROP due to replacement of fetal hemoglobin with adult hemoglobin, modifying oxygen affinity and tissue oxidative stress. [7, 9–11] Studies from Brazil, India, and Europe have reported transfusion as an independent risk factor. [7,9]

However, limited evidence exists from rural neonatal care settings, where anemia prevalence and transfusion thresholds may differ, and screening infrastructure is fragmented. [1,12,13] The present study aimed to determine the incidence of ROP in premature infants in a rural SNCU and evaluate whether neonatal anemia increases the risk of developing ROP.

2. Materials and Method

This prospective observational study was carried out in the Sick Newborn Care Unit (SNCU) of a rural tertiary care hospital in North India over a period of one year, from November 2023 to October 2024. The study was initiated following approval from the Institutional Ethics Committee, and written informed consent was obtained from the parents or legal guardians of all enrolled neonates prior to participation. The study population consisted of 120 preterm infants who met the eligibility criteria and were consecutively admitted to the SNCU during the study period.

Eligible infants included those with a gestational age of less than 34 weeks or birth weight below 2000 g, consistent with standard ROP screening guidelines practiced across India and globally. [1,3] Infants with major congenital anomalies, ocular malformations, or those who were discharged or expired before the first ophthalmological screening were excluded to ensure adequate follow-up and reliable outcome assessment.

Detailed clinical information was collected for each participant from medical and electronic hospital records,

including sex, gestational age, birth weight, anemia status, presence of neonatal sepsis, duration of supplemental oxygen therapy, requirement of respiratory support such as CPAP or mechanical ventilation, and history of packed red cell transfusion. Neonatal anemia was defined as a haemoglobin concentration below 13 g/dL when assessed at 2–3 weeks of life.

Ophthalmologic examination was performed by a trained paediatric ophthalmologist using indirect ophthalmoscopy with a 20-diopter lens. Pupillary dilation was achieved using topical tropicamide 0.5% and phenylephrine 2.5% instilled at least three times at 10-minute intervals. Examinations were performed initially at 2–4 weeks of chronological age and were repeated every 1–3 weeks depending on disease severity until full retinal vascularization or until criteria for intervention were met. The diagnosis and classification of ROP, including zone, stage, and presence of plus disease, followed the International Classification of Retinopathy of Prematurity (ICROP) guidelines. Treatment decisions were based on Type-1 ROP thresholds requiring laser photocoagulation or anti-VEGF therapy according to established standards.

All collected data were entered into Microsoft Excel and subsequently analyzed using IBM SPSS Statistics software version 22. Descriptive statistics were generated to summarize demographic and clinical variables. Categorical variables were expressed as frequencies and percentages, and comparisons between groups such as anemic versus non-anemic infants, and transfused versus non-transfused infants, were evaluated using the Chi-square test. A p-value less than 0.05 was considered statistically significant for determining associations between clinical risk factors and occurrence of ROP.

3. Results

Baseline Characteristics

Table 1: Baseline demographic and clinical characteristics of the study population

Parameter	Value
Total babies screened	120
Male	65 (54.2%)
Female	55 (45.8%)
Gestational Age Range	27–34 weeks
Birth Weight Range	850–2000 g

A total of 120 preterm infants fulfilled the inclusion criteria and were recruited for the study. Of these, 65 (54.2%) were male and 55 (45.8%) were female. The infants had a mean gestational age of **31.2 ± 2.1 weeks** (range 27–34 weeks), and the mean birth weight was **1450 ± 350 g** (range 850–2000 g). These values indicate a moderately preterm population typical of a rural SNCU environment and inherently at increased risk for complications associated with prematurity.

Incidence and Severity of ROP

Table 2: Prevalence and Treatment Outcomes of Retinopathy of Prematurity (ROP) in the Study Cohort

Parameter	n	%
ROP Present	32	26.7%
ROP Absent	88	73.3%
Required Treatment		
(Laser/Anti-VEGF)	10	31.3%
Spontaneous Regression	22	68.7%

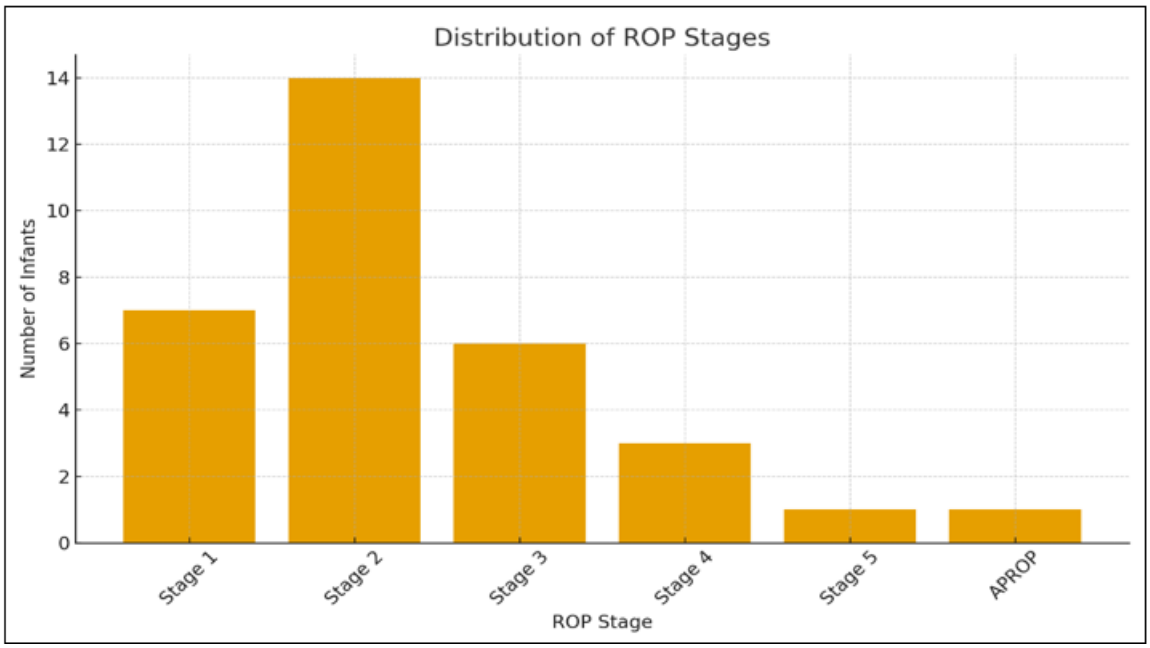

Figure 1: Distribution of ROP stages among affected preterm infants

Bar graph demonstrating the frequency of different stages of retinopathy of prematurity (ROP) in the study cohort (n = 32). Stage 2 was the most common presentation (43.7%), followed by Stage 1 (21.8%) and Stage 3 (18.7%). Severe forms including Stage 4, Stage 5, and APROP were less frequently observed.

Retinopathy of prematurity was diagnosed in **32 infants (26.7%)**, whereas **88 infants (73.3%)** demonstrated normal maturation of retinal vasculature throughout the screening period. Among those affected, **Stage 2 ROP was the most common presentation**, seen in 14 infants (43.7%), followed by Stage 1 in 7 infants (21.8%). More advanced disease forms were recorded less frequently: Stage 3 in 6 cases (18.7%), Stage 4 in 3 cases (9.3%), and Stage 5 in 1 case (3.1%). Additionally, one infant (3.1%) exhibited Aggressive Posterior ROP (APROP), representing the most rapidly progressive and severe subtype. Of the 32 infants diagnosed with ROP, **10 babies (31.3%) required active retinal intervention** (laser photocoagulation or anti-VEGF therapy), while **22 infants (68.7%) showed spontaneous regression**, indicating that the majority exhibited milder forms of the disease that resolved without treatment.

Association of Anemia with ROP

Anemia	ROP+	ROP-	Total
Present	14 (46.7%)	16 (53.3%)	30
Absent	18 (20%)	72 (80%)	90
Total	32	88	120
Chi-square = 8.21, p = 0.004 → Significant association			

Neonatal anemia was documented in 30 infants among the study group. Of these, **14 infants (46.7%) developed ROP**, compared with **18 of the 90 non-anemic infants (20.0%)**. The association between anemia and ROP was statistically significant (**p = 0.004**), implying that anemic infants were more than twice as likely to develop ROP. This relationship suggests that reduced oxygen-carrying capacity may contribute to retinal hypoxia and increase vulnerability to pathological neovascularization.

Blood Transfusion and ROP

Transfusion	ROP+	ROP-	Total
Given	9 (56.2%)	7 (43.8%)	16
Not Given	23 (22.8%)	78 (77.2%)	102
Chi-square = 6.14, p = 0.01 → Significant			

A total of 16 infants required packed red blood cell transfusion during their course of hospitalization. Among them, **9 infants (56.2%) developed ROP**, while only **23 of the 104 infants (22.1%)** who did not receive transfusion developed the disease. This association was statistically significant (**p = 0.01**), demonstrating that transfused infants had a markedly higher incidence of ROP. Severe disease stages (Stages 3–5 and APROP) and treatment-requiring ROP were more common among transfused infants, supporting previously described concerns regarding transfusion-related modulation of oxygenation dynamics and oxidative stress.

4. Discussion

In the present study, the incidence of retinopathy of prematurity was found to be **26.7%**, which is consistent with the range reported in similar Indian secondary-level neonatal units. Dhawan et al. reported an incidence of 24% in a rural central Indian SNCU, closely aligning with our findings, likely due to similar patient profiles and clinical settings.[1] Higher rates have been reported in tertiary-level NICUs caring for more critically ill neonates, such as the 38% incidence observed by Gopal et al.[4] and the 46% reported by Rekha and Battu.[5] This variation emphasizes the influence of care level, illness severity, and survival of extremely premature infants in ROP prevalence trends.

The current study demonstrated a statistically significant association between **neonatal anemia and development of ROP**, with 46.7% of anemic infants affected compared with only 20% of non-anemic infants (p = 0.004). This is consistent with the findings of Dhawan et al., who also noted anemia as a significant independent risk factor.[1] Rekha et al.[5] and Liu et al.[6] similarly identified anemia as a key predictor for ROP progression. A plausible pathophysiological explanation is that reduced hemoglobin impairs oxygen transport, leading to retinal hypoxia, which in turn upregulates VEGF and accelerates abnormal neovascularization.[8] Tang et al. further reinforced the association between hematological instability and ROP, suggesting that altered RBC indices, platelet dysfunction, and inflammatory markers contribute to disease severity.[8]

A significant relationship was also observed between **packed RBC transfusion and ROP**, where transfused infants exhibited nearly a threefold increased risk (56.2% vs 22.1%, p = 0.01). Similar findings have been reported by Maheshwari et al. [7] and Pinheiro et al. [9], who identified transfusion as an independent risk factor for severe ROP. The mechanism behind this association may involve replacement of fetal hemoglobin (HbF), which has higher oxygen affinity, with adult hemoglobin (HbA), which releases oxygen more readily to tissues, leading paradoxically to hyperoxia–hypoxia fluctuations and oxidative injury to retinal vasculature.[10,11] Hellgren et al. and Cakir et al. also identified transfusion-associated thrombocytopenia and VEGF-mediated vascular fragility as contributors to aggressive disease phenotypes.[12,11] In our study, a majority of treatment-requiring ROP cases were from the transfused subgroup, supporting this mechanistic hypothesis.

The observed higher frequency of moderate ROP (Stages 1–2) with spontaneous regression and smaller proportion of severe or APROP cases reflects effective early screening and timely intervention strategies recommended by the ICROP guidelines.[3] However, the presence of severe cases underscores the critical importance of standardized protocols for follow-up, especially in rural environments where delayed screening continues to be a primary risk factor for blindness. [12–14]

The strengths of this study include its prospective design, uniform ophthalmic evaluation by a trained specialist, and focus on a rural region where data are scarce. However, limitations include a single-center sample, absence of multivariable regression to adjust for confounders such as oxygen therapy, sepsis, and ventilation days, and the relatively small cohort size. Future research should incorporate multicenter enrollment and longitudinal monitoring to better evaluate causal pathways and preventive strategies.

Overall, the findings reinforce that neonatal anemia represents a potentially modifiable risk factor for ROP and, when combined with restrictive transfusion protocols, enhanced nutrition, and optimized oxygen delivery, may

improve outcomes and reduce preventable blindness in premature infants. The study further highlights the need for strengthening screening networks and neonatal monitoring systems across resource-limited rural India.

5. Conclusion

Retinopathy of prematurity remains a major preventable cause of childhood blindness, especially in resource-limited rural settings. In this study, the incidence of ROP was 26.7%, with Stage 2 being the most common presentation. Neonatal anemia showed a strong and statistically significant association with the development of ROP, and blood transfusion further increased disease severity. These findings indicate that anemia is an important modifiable risk factor that warrants early identification and management. Strengthening neonatal screening, adopting restrictive transfusion practices, and ensuring timely ophthalmic evaluation can reduce progression to severe ROP and improve long-term visual outcomes in premature infants.

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