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Research Article

Oxygen Therapy

Retinopathy of Prematurity and Its Association with Oxygen Therapy in Preterm Low Birth Weight Babies

Mandal AA[1*], Nahar K[2], Hosneara[3], Mazid AHMR[4], Yesmin N[5]

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[1*] Abul Azad Mandal, Senior Consultant (Pediatrics), General Hospital, Gaibandha, Bangladesh.
[2] Khairun Nahar, Junior Consultant (Pediatrics), General Hospital, Gaibandha, Bangladesh.
[3] Hosneara, Junior Consultant (Pediatrics), Aminbazar 20 Bed Hospital, Savar, Dhaka, Bangladesh.
[4] Abu Haider Md Raziul Mazid, Medical Officer (Pediatrics Haemato-Oncology), General Hospital, Gaibandha, Bangladesh.
[5] Nafisa Yesmin, Assistant Professor (Pediatrics Haemato-Oncology), Rangpur Medical College, Rangpur, Bangladesh.

Background: Retinopathy of prematurity (ROP) is a preventable cause of blindness in premature, low birth weight (LBW) infants, driven by abnormal retinal vascular development. Oxygen therapy, though life-saving, is a key modifiable risk factor when unmonitored, leading to retinal damage through disrupted angiogenesis. ROP follows a two-phase pathogenesis involving initial vessel growth suppression due to hyperoxia, followed by hypoxia-induced neovascularization. In countries like Bangladesh, rising preterm survival without adequate neonatal care infrastructure has increased ROP incidence.

Methods: This cross-sectional observational study was conducted in the NICU of Pediatrics Dept., General Hospital, Gaibandha in Bangladesh to assess the prevalence of ROP and its association with oxygen therapy among 50 preterm, low-birth-weight infants. Eligible neonates (<37 weeks, <2500g, oxygen-exposed, and screened for ROP) were enrolled over a defined study period of January to June 2023. Data were collected using structured forms covering clinical, demographic, and treatment details. ROP screening followed standard protocols using indirect ophthalmoscopy. Oxygen therapy mode and duration were recorded. Statistical analysis was performed using SPSS v26.0, applying descriptive statistics and chi-square/Fisher's exact tests, with significance set at $p < 0.05$.

Results: Among 50 preterm low birth weight infants, 36% developed retinopathy of prematurity (ROP). Most were male (56%), born at 28–31 weeks (48%), and weighed 1000–1499 g (64%). CPAP was the most common oxygen modality (48%), with a mean oxygen duration of 5.8±2.3 days. ROP primarily involved Zone II (61.1%) and Stages 1–2. Bilateral ROP occurred in 61.1%, and 50% of cases required treatment. A significant association was found between oxygen therapy and ROP (p=0.04), especially with prolonged exposure (≥5 days; p=0.02) and mechanical ventilation (p=0.03), highlighting oxygen therapy as a key risk factor for ROP development.

Conclusion: This study highlights a significant association between unregulated oxygen therapy and ROP in preterm, low-birth-weight infants. Improved oxygen monitoring, adherence to saturation targets, and early ROP screening are essential to prevent vision loss. Strengthening neonatal care protocols can reduce the burden of this preventable cause of childhood blindness.

Keywords: Retinopathy of Prematurity, Oxygen Therapy, Preterm Infants, ROP Screening and Premature Birth

Corresponding Author

Abul Azad Mandal, Senior Consultant (Pediatrics), , General Hospital, Gaibandha, , Bangladesh.
Email: hasanjaman567@gmail.com

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Introduction

Retinopathy of prematurity (ROP) is a potentially blinding eye disorder that primarily affects premature infants with low birth weight (LBW). First described in the 1940s as "retrolental fibroplasia," ROP has since become a significant cause of childhood blindness worldwide, particularly in countries with improving neonatal survival rates but limited access to comprehensive neonatal care [1], [2]. The disease is characterized by abnormal development of retinal blood vessels, often triggered by a range of perinatal factors, including oxygen therapy, sepsis, respiratory distress syndrome, and fluctuating blood oxygen levels [3].ROP predominantly affects infants born before 32 weeks of gestation or weighing less than 1500 grams at birth [4].

The immature retinal vasculature in these infants is highly susceptible to external influences, especially oxygen supplementation, which can disturb normal angiogenesis. During normal gestation, retinal vascularization is completed near term; however, preterm birth interrupts this process, making the retina vulnerable to pathological neovascularization in response to external stimuli like high oxygen concentrations [5].

Hence, while oxygen therapy is life-saving for preterm infants, it also poses a serious risk of developing ROP when not adequately monitored and regulated. The pathogenesis of ROP is understood to occur in two distinct phases. In the first phase, hyperoxia, often due to excessive supplemental oxygen, suppresses vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), halting normal vessel development. In the second phase, once oxygen levels normalize or drop, the retina becomes hypoxic, leading to a compensatory overproduction of VEGF, which stimulates disorganized and leaky neovascularization [6].

These pathological vessels can bleed, form fibrous scar tissue, and eventually cause retinal detachment and vision loss if not identified and managed early. Oxygen therapy has been consistently identified as one of ROP development's most significant modifiable risk factors. Multiple studies have demonstrated a strong association between unregulated oxygen administration and increased incidence and severity of ROP [7].

The landmark Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and Early Treatment for Retinopathy of Prematurity (ETROP) trials underscored importance of early detection and treatment but also highlighted role of careful oxygen titration in preventing disease progression [8],[9]. Recent efforts, such as SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) study, have attempted to refine optimal oxygen saturation targets to balance risks of ROP against those of other morbidities such as bronchopulmonary dysplasia and death [10].In resource-limited settings such as Bangladesh, burden of ROP is increasingly becoming apparent due to improved neonatal care and increased survival of preterm infants, but often without parallel implementation of screening and prevention protocols [11]. Many neonatal intensive care units (NICUs) lack stringent oxygen monitoring systems, exposing preterm infants to uncontrolled hyperoxia. This situation is exacerbated by inadequate training among healthcare providers and absence of national guidelines on oxygen therapy or ROP screening [12]. As a result, preventable cases of blindness due to ROP continue to rise. The global pattern of ROP is now described as occurring in three epidemic waves. The first was seen in 1940s and 1950s in high-income countries and was related to using unmonitored oxygen. The second occurred in 1970s and 1980s with improved neonatal survival. The third epidemic is currently unfolding in low- and middle-income countries, driven by increased access to neonatal care without proportional development of monitoring and screening infrastructure [13]. Given complex interplay between prematurity, low birth weight, and oxygen therapy in pathogenesis of ROP, this study aims to investigate association between oxygen therapy and development of ROP in preterm, low-birth-weight infants.

Methodology and Materials

This study employed a cross-sectional observational design conducted in the Neonatal Intensive Care Unit (NICU) of Pediatrics Dept., General Hospital, Gaibandha in Bangladesh. It aimed to determine the prevalence of retinopathy of prematurity (ROP) and evaluate its association with oxygen therapy among preterm low birth weight (LBW) infants. The study was conducted over 6 months, from January to June 2023. During the study period, 50 neonates were enrolled and analyzed in this study.

Inclusion Criteria:

- Preterm neonates (<37 weeks of gestational age)
- Birth weight less than 2500 grams
- Admitted within 24 hours of birth
- Received oxygen therapy during NICU stay
- Underwent ophthalmologic screening for ROP

Exclusion Criteria:

- Neonates with significant congenital anomalies
- Neonates who died before ROP screening
- Incomplete medical records
- Parental refusal of participation

Data Collection Tools and Techniques:

Data were collected using a structured data collection sheet, which included the following variables:

- Sociodemographic details: sex, gestational age, birth weight, mode of delivery
- Clinical interventions: type and duration of oxygen therapy, pulse oximeter monitoring, surfactant therapy, presence of sepsis, and need for blood transfusion.
- ROP-related findings: presence or absence of ROP, zone and stage classification, presence of plus disease, laterality, and treatment received

Gestational age was assessed using obstetric records and confirmed by clinical assessment (New Ballard Score when necessary). Birth weight was recorded using a calibrated digital scale within the first hour. Oxygen therapy details were recorded from NICU charts, including mode (nasal cannula, CPAP, mechanical ventilation) and duration (in days). Monitoring practices, sepsis diagnosis, and other interventions were extracted from patient records.

ROP Screening and Diagnosis:

All enrolled infants underwent ROP screening as per the hospital's standard protocol:

- The first ophthalmologic examination was performed between 4 to 6 weeks or at 31 weeks postmenstrual age, whichever was later.
- Indirect ophthalmoscopy was performed by a trained pediatric ophthalmologist using a dilated pupil examination with a 20D lens.
- ROP was staged and zoned according to the International Classification of Retinopathy of Prematurity (ICROP).
- Follow-up examinations were conducted weekly or biweekly, depending on the stage and zone of disease.

Statistical Analysis:

Data were entered into Microsoft Excel and analyzed using SPSS version 26.0. Descriptive statistics such as frequencies, percentages, means, and standard deviations were used to summarize demographic and clinical variables. The chi-square or Fisher's exact test (as applicable) was used to assess associations between categorical variables. A p-value <0.05 was considered statistically significant.

Results

The present study evaluated 50 preterm low birth weight babies to assess the association between oxygen therapy and the development of retinopathy of prematurity (ROP). As shown in Table 1, the study population consisted of 56% males and 44% females, with most infants born between 28–31 weeks of gestation (48%) and weighing between 1000–1499 g (very low birth weight, 64%). Cesarean section was the predominant mode of delivery (66%). Regarding oxygen support (Table 2), CPAP was the most commonly used modality (48%), followed by mechanical ventilation (28%) and nasal cannula (24%), with a mean oxygen therapy duration of 5.8±2.3 days. Continuous pulse oximeter monitoring was used in only 36% of cases, and comorbid conditions such as sepsis (42%), surfactant therapy (30%), and blood transfusion (26%) were also documented. Figure 1 reveals that ROP was detected in 18 infants (36%), while the remaining 32 (64%) showed no signs of the disease. Among those with ROP (Table 3), Zone II involvement was the most common (61.1%), and the most frequent stages were Stage 1 (27.8%) and Stage 2 (38.9%). Plus, the disease was present in 33.3% of the ROP cases. Bilateral involvement occurred in 61.1% of affected infants, and 50% required treatment. Among those treated, 55.6% underwent laser therapy, and 44.4% received anti-VEGF injections. A significant association was found between oxygen therapy and the occurrence of ROP (p=0.04), as shown in Table 4, where 40.5% of infants who received oxygen developed ROP compared to 12.5% who did not.

Table 5 further indicates that more prolonged oxygen exposure (≥5 days) was significantly associated with ROP development (72.2% vs. 20.8%; p = 0.02). Mechanical ventilation was statistically associated with ROP (66.7% vs. 33%; p=0.03), while CPAP and nasal cannula did not demonstrate significant relationships (p=0.08 and 0.12, respectively).

Table 1: Sociodemographic and Perinatal Characteristics of Preterm Low Birth Weight Babies (n = 50)

Variable	Frequency (n)	Percentage (%)
Sex of Baby		
Male	28	56.00
Female	22	44.00
Gestational Age		
<28 weeks	6	12.00
28–31 weeks	24	48.00
32–36 weeks	20	40.00
Birth Weight		
<1000 g (ELBW)	5	10.00
1000–1499 g (VLBW)	32	64.00
1500–2500 g (LBW)	13	26.00
Mode of Delivery		
Normal Vaginal Delivery	17	34.00
Cesarean Section	33	66.00

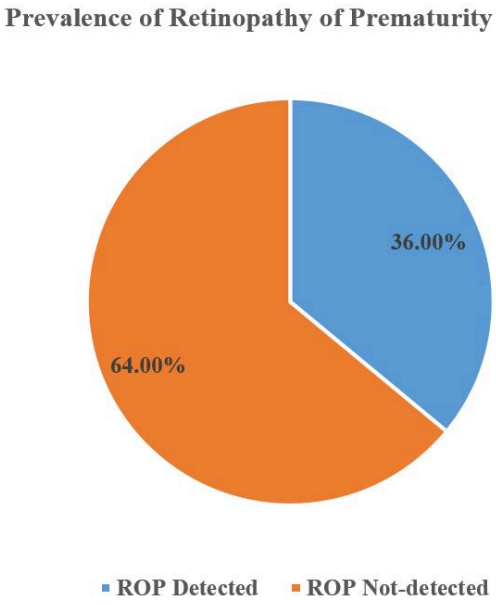

Figure 1: Prevalence of Retinopathy of Prematurity (ROP) Among Study Population (n = 50)

Table 2: Clinical and Supportive Care Interventions among Study Participants (n = 50)

Variable	Frequency (n)	Percentage (%)
Type of Oxygen Support		
Nasal Cannula	12	24.00
CPAP	24	48.00
Mechanical Ventilation	14	28.00
Duration of Oxygen Therapy (Mean±SD)	5.8 ± 2.3 days	
Pulse Oximeter Monitoring		
Continuous	18	36.00
Intermittent	20	40.00
Not Used	12	24.00
Surfactant Therapy	15	30.00
Sepsis	21	42.00
Blood Transfusion	13	26.00

Table 3: Distribution of ROP Characteristics, Laterality, and Management in Affected Infants (n = 18)

Variable	Frequency (n)	Percentage (%)
Zone of ROP		
Zone I	3	16.70
Zone II	11	61.10
Zone III	4	22.20
Stage of ROP		
Stage 1	5	27.80
Stage 2	7	38.90
Stage 3	4	22.20
Stage 4	2	11.10
Stage 5	0	0.00
Plus Disease	6	33.3
Laterality		
Unilateral	7	38.90
Bilateral	11	61.10
Treatment Required		
Yes	9	50.00
No	9	50.00
Treatment Given		
Laser Therapy	5	55.60
Anti-VEGF	4	44.40
Surgery	0	0.00

Table 4: Association between Oxygen Therapy and Occurrence of ROP (n = 50)

Oxygen Therapy Given	ROP Present		ROP Absent		p-value
	n	%	n	%	
Yes (n = 42)	17	40.5	25	59.5	0.04*
No (n = 8)	1	12.5	7	87.5	

Table 5: Association of Oxygen Duration & Mode of Delivery with Presence of ROP (n = 50)

Variable	ROP Present		ROP Absent		p-value
	n	%	n	%	
Oxygen Duration ≥5 days	13	72.20	9	27.80	0.02*
Oxygen Duration <5 days	5	20.80	19	79.20	
CPAP (n = 20)	6	30.00	14	70.00	0.08
Mechanical Ventilation	8	66.70	4	33.00	0.03*
Nasal Cannula	3	30.00	7	70.00	0.12

Discussion

Retinopathy of prematurity (ROP) remains a significant cause of preventable childhood blindness, particularly in developing countries where advancements in neonatal care have improved survival of premature infants, but not always with adequate monitoring protocols for ROP prevention. In this study, ROP was detected in 36% of 50 preterm LBW infants, aligning with prior findings in similar settings. Study in India reported an ROP prevalence of 30% among infants with comparable gestational ages and birth weights [14]. In contrast, higher-income countries report lower incidences, typically due to more stringent oxygen monitoring protocols and early screening practices [15]. This underscores importance of context-specific interventions in low-resource settings to mitigate preventable visual impairment. Our results demonstrate statistically significant association between oxygen therapy & ROP development. Among infants who received oxygen therapy (n=42), 40.5% developed ROP, whereas only 12.5% of those who did not receive oxygen showed signs of ROP (p=0.04). This finding is consistent with established understanding that unregulated oxygen supplementation is major modifiable risk factor for ROP. High oxygen concentrations can disrupt retinal vascularization, causing vaso-obliteration followed by abnormal neovascularizationa hallmark of ROP pathogenesis [16,17]. WHO & American Academy of Pediatrics recommend maintaining oxygen saturation between 90-95% to balance risks of hypoxia & hyperoxia [18].

Unfortunately, only 36% of infants in this study had continuous pulse oximeter monitoring, highlighting a significant gap in care that may contribute to overexposure. The duration of oxygen therapy was also significantly associated with ROP. Infants receiving oxygen for ≥5 days had a markedly higher incidence of ROP (72.2%) compared to those receiving it for <5 days (20.8%), with a p-value of 0.02. These findings are corroborated by studies such as Dutta et al. [19], who reported a similar trend, emphasizing need to restrict duration of oxygen administration to only as long as clinically indicated. Notably, mechanical ventilation, a more invasive form of oxygen support, was associated with a significantly higher risk of ROP (66.7%) than those not ventilated (p=0.03). In contrast, CPAP and nasal cannula use did not show statistically significant associations, which may reflect differences in oxygen concentration and exposure intensity delivered by these modalities. Birth weight and gestational age were also critical in ROP risk stratification. The majority of infants with ROP were within very low birth weight category (1000–1499 g) and born between 28–31 weeks of gestation. This corresponds with existing literature, where immaturity of retina in lower gestational age infants predisposes them to vascular anomalies characteristic of ROP [20,21]. However, ROP was not exclusive to extremely low birth weight (ELBW) infants, suggesting that even moderately preterm infants are at risk when exposed to unregulated oxygen therapy. This finding reinforces need for universal screening guidelines tailored to local realities. The staging and classification of ROP in this study revealed that most cases were in Stage 1 (27.8%) and Stage 2 (38.9%), consistent with natural progression of disease in early detection settings. However, more severe stages like Stage 3 (22.2%) and Stage 4 (11.1%) were also observed, raising concern about delayed screening or rapid progression in some cases. Most ROP cases involved Zone II (61.1%), followed by Zone III and Zone I. These patterns align with Early Treatment for ROP (ETROP) study findings, which identified Zone I and posterior Zone II involvement as high-risk features [9]. The presence of plus disease in 33.3% of affected infants further underscores severity in a subset of cases. Treatment interventions were necessary for 50% of ROP-diagnosed infants, with laser therapy being predominant method (55.6%), followed by anti-VEGF therapy (44.4%).

These treatment modalities reflect global trends in ROP management, where anti-VEGF is increasingly used, especially in posterior ROP or when laser therapy is not feasible due to media opacity or systemic instability [22]. The absence of cases requiring surgery in this cohort suggests timely detection and management may have prevented progression to retinal detachment stages (Stage 5). Additionally, clinical comorbidities such as sepsis (42%), blood transfusions (26%), and the need for surfactant therapy (30%) were prevalent among the cohort, reflecting the multifactorial risk profile of these neonates. Prior studies have shown that systemic inflammation, oxidative stress, and transfusions contribute to the pathogenesis of ROP [23,24]. These associations further stress the importance of comprehensive neonatal care, including infection control, judicious transfusion practices, and regulated respiratory support.

Conclusion and Recommendations

In conclusion, the findings of this study reaffirm the strong link between unregulated oxygen therapy, exceptionally prolonged and high-concentration delivery, and the development of ROP in preterm, low-birth-weight infants. The results advocate for improved monitoring practices, including widespread use of continuous pulse oximetry and adherence to oxygen saturation guidelines, to prevent this avoidable cause of childhood blindness. Moreover, early screening and timely intervention remain critical components in managing ROP. Given the observed prevalence and treatment burden, this study highlights the urgent need to integrate ROP screening and oxygen regulation protocols into standard neonatal care practices in tertiary hospitals across Bangladesh.

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