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ORIGINAL ARTICLE

Incidence and Risk Factors of Retinopathy of Prematurity in Multicenter Neonatal Intensive Care Unit Patients

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Abstract

Background: Retinopathy of prematurity (ROP) poses a significant risk in the management of premature infants, potentially resulting in blindness if not promptly identified and addressed.

Objective: To determine the incidence of retinopathy of prematurity among newborns in multiple neonatal intensive care units (NICUs), pinpoint the associated risk factors, and evaluate the outcomes of such cases.

Material and Methods: A prospective observational study was done at the neonatal ICUs of Akbar Niazi Teaching Hospital, Islamabad, Pakistan Atomic Energy Commission (PAEC) Hospital, Islamabad and Holy Family Hospital, Rawalpindi between April 2022 to December 2023. A birth occurring at gestational age ≤ 32 weeks and birth weight ≤ 1500 g. Infants with gestational age exceeding 32 weeks or birth weight surpassing 1500 g were considered eligible for inclusion if oxygen therapy exceeding 7 days. Total350 infants underwent retinal examination through indirect ophthalmoscope from fourth week after birth, with subsequent follow-ups.

Results: Among 350 infants; 5.1% (n=18) were diagnosed with ROP in either one or both eyes. The classification revealed55.6% (n=10) at stage 1, 27.8% (n=5) at stage 2, and 16.7% (n=3) at stage-3. There was no reported case Winthrop at stage-4 or 5.Laser ablative therapy was administered to three cases with stage-3 ROP. In univariate analysis notable relation was observed between the incidence of ROP and factors such as gestational age (p = 0.0001), sepsis (p = 0.002), oxygen therapy (p = 0.0001), and blood transfusion rate (p = 0.002).Following logistic regression, gestational age, sepsis, oxygen therapy, and blood transfusion rate continued to be significant.

Conclusion: The ROP incidence was low, with low gestational age, sepsis, oxygen therapy, and reduced blood transfusion rate identified as significant risk factors.

Keywords: Eye; Retinopathy of prematurity; Risk factors; Intensive care units, Neonatal

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Introduction

Retinopathy of prematurity (ROP) is a disease marked by formation of unusual retina vessels. This occurs because the retinal tissue is not fully vascular zed, a result of hyperoxia causing a decrease in vascular endothelial growth factor (VEGF) and the demise of endothelial cells.1The process implies that VEGF plays a crucial role in supporting the endothelium. After cessation of vessel growth, the developing retina tissue experiences ischemia and hypoxia.2This sequence of events induces an increase in VEGF expression,

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resulting in the development of new blood vessels (revascularization).[3] The condition has garnered significant global research attention, primarily because of higher rate of survive found in very low birth weight newborn 1500 g or less, who face highest susceptibility to developing ROP.4The rise in these figures can be linked to advancements in perinatal care. The elevated rate contributes to a notable increase in the incidence of other comorbidities associated with newborn birth, carrying significant social implications, such as blindness resulting from ROP.[5]Globally, approximately 10% of all births occur prematurely, occurring before 37 weeks of gestation.[6]The risk factors linked to ROP were identified to differ based on geographical area. These discrepancies may be linked to diversity of population and disparities in neonate care.[7]

ROP is a disease influenced by multiple factors.2Numerous studies highlight various risk factors linked to this condition, with some capable of inducing severe ROP. These factors include birth weight, gestational age, APGAR score, supplemental oxygen, anemia, prolonged mechanical ventilation, intraventricular hemorrhage (IVH),pulmonary complications, sepsis, and necrotizing enterocolitis.[8,9]Identifying risk factors that influence the advancement of ROP, along with understanding its causes, can assist ophthalmologists and neonatologists in conducting meticulous screening, making precise diagnoses, and preventing the onset of the disease.[10]The study objective was to determine the ROP incidence and evaluate correlation between ROP and possible risk factors in infants admitted to multicenter neonatal intensive care units (ICUs).

Material and Method:

Study design: Prospective observational study, Settings and duration: Neonatal ICUs of Akbar Niazi Teaching Hospital, Islamabad, PAEC General Hospital, Islamabad and Holy Family Hospital, Rawalpindi between April 2022 to December 2023.The study focused on newborn infants admitted to neonatal ICUs of the mentioned hospitals, and ethical approval was obtained from the respective committees of each hospital. Sample size and inclusion criteria: Total 350 infants were included with gestational age (GA) ≤ 32 weeks and birth weight (BW) ≤ 1500 g. Sample was determined by WHO calculator, whereas the parameters were as follows; the incidence of ROP was 33.9%,[2] confidence level 95%, and error of alpha was 5%.Exclusion criteria: Patients who either died priortothe full ROP resolution or failed to attend scheduled follow-ups examinations at OPD,infants having congenital glaucoma or cataract were excluded.

The study encompassed newborn infants who met any criteria:(1) GA≤32 weeks or BW≤1500g; (2) GA 32-37weeks or BW≥ 1500 g and one of the following risks: respiratory distress syndrome (RDS), blood transfusion, sepsis, intraventricular hemorrhage (IVH), and multiple pregnancies.

The comprehensive record of infants' history included an examination of perinatal factors, such as the identification of risk elements like prematurity, sepsis (involving amniotic fluid, premature tear of membranes exceeding 18 hrs, maternal UTI, and intrapartum fever surpassing 38°C), and perinatal asphyxia. The current medical history encompassed the prevalent indicators of RDS necessitating O2, congenital heart disease, sepsis, blood transfusion, and the need for phototherapy. A clinical assessment was conducted, encompassing examinations of weight, length, skull circumference, determination of GA (applying the modified Ballard score), assessment of vital signs, observation of neonate reflexes, and evaluation of circulatory, respiratory, and neurological manifestations. The ophthalmologist conducted regular examinations of all infants at intervals of 1-2 weeks starting from the fourth week after birth. Before one hour examination, eye dilation was achieved by administering a combine eye drops of cyclopentolate 0.1% and phenylephrine 0.1%.Examination with indirect ophthalmoscopy, utilizing a 28-diopter lens along with a speculum and scleral depression, was conducted. When necessary, the ophthalmologist conducted retinal examinations, including retinal drawing and fundus imaging using indirect ophthalmoscope.ROP was characterized by partial or abnormal vascular growth in retina. The ROP was categorized based on its retinal location (zones 1-3) and its severity (stages 1-5), following the outlined by International Committee for Classification (ICC).[11]Patients identified with ROP stage 3underwent laser photocoagulation as part of the treatment protocol.

Ophthalmology assessment commenced at fourth week of life and continued on a weekly or biweekly basis, adhering to follow-ups scheduled suggest by the American Academy of Pediatrics (AAP), American Academy of Ophthalmology (AAO), and American Association for Pediatric Ophthalmology (AAPO).12These assessments persisted until complete vascularization of retina extended to zone 3 (outermost temporal retina zone) or complete ROP reduction following treatment. The study investigated a range of various risk factors of prenatal and postnatal for ROP in

order to find independent factors linked to the occurrence of both mild and severe disease in NICU.Prenatal factors considered included GA, BW, gender, and delivery mode. The postnatal factors examined included RDS, oxygen (O2) therapy, phototherapy for jaundice, blood transfusion rate, sepsis (diagnosed clinically, with criteria including C-reactive protein ≥ 6.0 mg/dl or positive blood cultures), hypotension (determined by age and weight mean values), IVH detected by cranial ultrasound, and patent ductus arteriosus (PDA, identified by ECG).

Statistical analysis: The data were subjected to analysis using SPSS version 25. Descriptive statistics encompassed the mean ±SD for numerical variables, while categorical variables were presented as percentages across different categories. ROP incidence was expressed as a simple proportion. Association analysis for categorical variables was conducted using the chi-square test. Logistic regression test was executed, and adjusted odds ratio (95% CI) was calculated for risk factors that demonstrated significance in univariate analysis. The significant-value was set at ≤ 0.05.

Results:

350 infants were enrolled in present study with gestational age (GA) mean was 30.13±2.63 weeks; there were 310infants ≤ 32 weeks, and 40infants >32 weeks. The birth weight (BW) ranges from 1000 to 1900g and mean was 1521.21±324g.Among 350 infants, 60% (n=210) were males and 40% (n=140) were females. 60% (n=210) cases were delivered aginally and 40% (n=140) cases were delivered by C-section. The demographics of all infants are summarized in Table 1.

Table 1. Demographics stats of all study infants(n=350)

Variables	n (%)
Gender	
Male	210(60)
Female	140(40)
Delivery mode	
Vaginal	210(60)
C-section	140(40)
Gestational age (weeks) (Mean ± SD)	30.13±2.63
Birth weight (g) (Mean ± SD)	1521.21±324

Among350infants; 5.1% (n=18) were diagnosed with ROP in either one or both eyes.The classification revealed55.6% (n=10) at stage 1, 27.8% (n=5) at stage 2, and 16.7% (n=3) at stage-3. There was no reported case with ROP at stage-4 or 5.Association between ROP and various risk factors is assessed (Table 2).

Table 2:Association between ROP and risk factors(n=350

Variables	**Infants with ROP, (n=18)**	**Infants without ROP, (n=332)**	**p**
Gender			
Male	10 (55.6%)	200 (60.2%)	0.257
Female	8 (44.4%)	132 (39.8%)	
Delivery mode			
Vaginal	12 (66.7%)	198 (59.6%)	0.314
C-section	6 (33.3%)	134 (40.4%)	
Gestational age (Weeks)			
≤ 32	14 (77.8%)	296 (89.2%)	0.0001
> 32	4 (22.2%)	36 (10.8%)	
Birth weight (Grams)			
≤ 1500	10 (55.6%)	200 (60.2%)	0.256
> 1500	8 (44.4%)	132 (39.8%)	
Blood transfusion rate			
Once	2 (11.1%)	60 (18.1%)	0.002
>Once	6 (33.3%)	36 (10.8%)	
Respiratory Distress Syndrome	8 (44.4%)	117 (35.2%)	0.147
Sepsis	16 (88.9%)	213 (64.2%)	0.002
Patent Ductus Arteriosus	1 (5.6%)	16 (4.8%)	0.114
Intra Ventricular Hemorrhage	3 (16.7%)	50 (15.1%)	0.546
Hypotension	5 (27.8%)	87 (26.2%)	0.482
Phototherapy	17 (94.4%)	313 (94.3%)	1.241
O2 Therapy	13 (72.2%)	150 (45.2%)	0.0001

A notable association was found between ROP incidence and GA (p = 0.0001), sepsis (p = 0.002), O2 therapy (p = 0.0001), and blood transfusion rate (p = 0.002).Nevertheless, non-significant association was observed between ROP incidence and factors i.e., gender, delivery mode, BW, RDS, PDA, IVH, hypotension, and phototherapy (p≥ 0.05).The association between gestational age (GA) and ROP stages is evaluated (Table 3).

Table 3: Association between GA and ROP stages (n=18)

Variables	**≤ 32 weeks, (n=14)**	**> 32 weeks, (n=4)**	***p***
Stage 1 (n=10)	8 (57.1%)	2 (50%)	.189
Stage 2 (n=5)	4 (28.6%)	1 (25%)	
Stage 3 (n=3)	2 (14.3%)	1 (25%)	

There was insignificant association observed between GA and ROP stages (p=0.189).Variables that showed statistical significance in univariate analysis were further examined applying logistic regression. GA,

Table 4:Logistic regression between GA, sepsis, O2 therapy, and blood transfusion,(n=350)			
Variables	OR	95% CI	p
GA	4.75	2.54-8.12	.0001
Sepsis	1.61	1.17-1.86	.0001
O2 therapy	1.11	0.99-1.20	.0001
Blood transfusion	3.37	1.07-4.11	.0001

sepsis, O2 therapy, and blood transfusion rate continued to be significant (Table 4).

ROP outcome in diagnosed cases was assessed (Table 5).

Table 5: ROP outcome in diagnosed cases (n=18)		
Variables	n (%)	Outcome
Stage 1	10 (55.6%)	Regressed spontaneously at follow up
Stage 2	5 (27.8%)	Regressed spontaneously at follow up
Stage 3	3 (16.7%)	Needed laser and improved

Three cases with stage 3 required interventions through laser therapy, and patients demonstrated improvement during subsequent follow-ups. The remaining 15 cases exhibited regressed spontaneously without requiring any intervention.

Discussion:

Retinopathy of prematurity refers to a condition marked by the atypical growth of blood vessels in the retina of newborn infants. The advancements in care of neonates, ROP is a notable complication in preterm neonates and continues to be a significant contributor to childhood blindness globally.[13]In this study, the ROP incidence was 5.1%, a rate lower than that reported in several other studies, such as 18.5% in India, 16.1% in Malaysia, and 15% in Pakistan.[14-16]Nevertheless, our study's incidence rate of 5.1% is higher than that reported in a study conducted in Islamabad, Pakistan. It's worth noting that the Islamabad study involved infants with higher GA and BW, specifically up to 32 weeks GA, and reported an incidence of 3.2%.[17]

ROP is a complex condition influenced by various factors. LowGA, BW, sepsis, O2therapy,RDS, and blood transfusion rate have all been considered potential contributors to ROPincidence.[18]Numerous studies consistently demonstrate that the primary risk factors associated with the onset of ROP are low GA and BW.[8,10] In this study, low GA, sepsis, O2therapy, and rate of blood transfusionas independent risk factors for ROP incidence. However, factors such as gender, delivery mode, BW, RDS, PDA, IVH, hypotension, and phototherapy were deemed insignificant as risk factors based on univariate analysis.

Regarding the impact of low GA on the incidence of ROP, our findings highlight it as the most crucial risk factor for ROP development. These observations align with findings of study conducted by Boo et al.[15]The phenomenon was attributed to the underdeveloped vascularization, making the retina more susceptible to oxidative damage. Perinatal factors such as blood transfusion, hypoxia, and sepsis were identified as contributing factors. In our study, in significant association between GA and ROP severity. However, these findings contrast with some other study findings that have demonstrated a significant association, indicating that lower GA is linked to more severe cases of ROP.[19, 20]

Afzal et al findingswerenonsignificant association between ROP and PDA, IVH. However, they noted significant association between RDS and onset of ROP. This was linked with the concept that systemic hypoxia results in retinal hypoxia, necessitating increased O2 therapy and potentially contributing to ROP development.21Contrastingly, Ng et al noted an association between onset of ROP and PDA, IVH, and hypotension.19Hakeem et al note non significant effects of phototherapy on the onset of ROP.[18]

Following multivariate analysis, it was showed that low GA, sepsis, O2 therapy, and blood transfusion rate continued to be notable risk factors for ROP incidence. Laser photocoagulation was identified as highly effective in causing regression of ROP. Consistent findings of Kulkarni etal,[22]our study revealed that three cases necessitating laser intervention demonstrated improvement, and regressed ROP during follow-ups. Laser therapy is currently ideal mode of treatment, as it is more effective in addressing the severity of ROP compared to cryotherapy.[22]

Clinicians should remain vigilant regarding the other risk factors when monitoring the infants in NICU. Analyzing the risk factors for onset of ROP contributes to a better understanding and prediction of the condition in vulnerable infants. Conducting timely retinal screenings for high-risk infants is crucial in preventing the progression to advanced stages of ROP. Given that ROP can lead to severe consequences, including complete blindness, it is imperative to make every effort to prevent the progression to advanced stages. This involves strategies such as reducing preterm births, enhancing neonatal care practices, and improving the detection of early markers indicating the threat of ROP.

Conclusion:

The ROP incidence was low, with low gestational age, sepsis, oxygen therapy, and reduced blood transfusion rate identified as significant risk factors. Laser therapy demonstrated effectiveness in both treating the condition and reducing the progression of the disease. Infants diagnosed with ROP experienced positive outcomes when timely treatment was administered for this serious condition.

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