

Frequency and risk factors of retinopathy of prematurity in preterm babies at a tertiary care hospital in Lahore

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a serious but preventable morbidity, leading to childhood blindness. The aim of this study was to analyze the incidence and risk factors of ROP in preterm babies.

Subjects and methods: A prospective cohort study was conducted at Neonatology Unit, Hameed Latif Hospital, Lahore, from July 2017 to February 2019. All preterm babies born at Hameed Latif Hospital at ≤ 34 weeks of gestation, birth weight of <1.5 kg, born at 34-37 weeks of gestation with birth weight of 1.5- 2.5 kg having a significant course of illness, were included in the study. Their maternal history was obtained for gestational age, and maternal risk factors. Neonates were monitored and evaluated for clinical course, morbidity and mortality, during their stay at the hospital. These preterm neonates were screened for ROP by ophthalmological examination at 4-5 weeks of age. Data was analyzed to see the incidence of ROP and univariate and logistic regression analyses were applied to determine association of risk factors with ROP.

Results: Twenty eight percent ($n=21$) of the total screened ($n=75$) preterm neonates, had developed ROP. Logistic regression analysis showed that anemia (with Hb <10 g/dl or HCT $<30\%$) ($p=0.011$), fraction of inspired oxygen ($FiO_2>40\%$) ($p=0.018$) and birth weight <1.5 kg ($p=0.048$) were the risk factors associated with development of ROP.

Conclusion: Development of protocols and their implementation in neonatal units to save newborns from the identified associated risk factors can help prevent development of ROP leading to childhood blindness.

Keywords:

Preterm infants; Morbidity; Retinopathy of prematurity

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retinal blood vessels in preterm infants, which may lead to poor visual acuity or blindness.¹ Outcomes of ROP can be prevented by early diagnosis and treated by administration of intra vitreal anti vascular endothelial growth factor (Anti VEGF) and retinal ablation with laser therapy.² The incidence of ROP has increased with improvements in neonatal care and the development of neonatal intensive care units (NICUs), leading to improved survival rate of preterm neonates.³ The incidence in Pakistan is reported to be 10.5%.⁴ A number of risk factors have been reported to be associated with development of ROP worldwide. The commonly known risk factors that lead to development of ROP are, early gestational age, low birth weight and prolonged oxygen therapy.⁵

Other presumed risk factors include preeclampsia, mechanical ventilation, duration of oxygenation >7 days, respiratory distress syndrome, blood transfusions, apnea, phototherapy, intraventricular hemorrhage, sepsis, anemia and low APGAR score.⁵⁻⁹ Further studies are being carried out at different centers of the world to identify the association of various maternal and neonatal risk factors with ROP. Pakistan ranks 4th amongst the countries with highest number of preterm births.¹⁰ Preterm survival rate is low in rural areas of Pakistan due to non-availability of specialized healthcare facilities. However, during the last few decades the survival rate of preterm babies has improved in urban areas of Pakistan due to development of NICUs and provision of better medical facilities with a consequent increase in ROP as a cause of childhood blindness. Very few studies have been carried out in Pakistan to identify the incidence and risk factors of ROP among premature babies who survive. This study aimed to find out the incidence of ROP and risk factors associated with it in the local population represented at a tertiary care hospital of Lahore.

Conflict of Interest: The authors declared no conflict of interest exist.

Citation: Riaz M, Rafique S, Hina A, Bashir M, Majeed MT, Maqbool S. Frequency and risk factors of Retinopathy of prematurity in preterm babies at a tertiary care hospital in Lahore. *J Fatima Jinnah Medical Univ.* 2019; 13(3): 110-115.

DOI: <https://doi.org/10.37018/jfjmu.v13i3.607>

PATIENTS AND METHODS

A prospective cohort study was conducted in the Neonatology Department of Hameed Latif Hospital, Lahore from July 2017 to Feb 2019. The hospital is a tertiary care teaching hospital in private setup providing 25 bedded NICU facilities. The Gynaecology and Obstetrics department of the hospital provides routine and assisted pregnancy facilities and receives patients mainly from central and South Punjab. The neonates were enrolled after approval from the ethical committee (reference number PED/H LH/042/17) and informed consent of the parents. Antenatal data of the enrolled cases was obtained from maternal records whereas the data pertaining to the course of illness was obtained from NICU and hospital records. All preterm infants born at <37 weeks of gestation at Gynaecology and Obstetrics department of Hameed Latif hospital were evaluated for inclusion in the study. Inclusion criteria comprised; preterm infants born at ≤ 34 weeks of gestation, preterm infants born with birth weight of <1.5 kg, born at 34-37 weeks of gestation with birth weight of 1.5- 2.5 kg having a significant course of illness in NICU. All preterm infant who were born with congenital anomalies or who expired before the age of ROP screening were excluded. Gestational age was assessed by antenatal ultrasounds and new Ballard score.¹¹ Weight was assessed by infant weighing scale and <1.5 kg was taken as low birth weight. Maternal record was probed for presence or absence of pregnancy-induced-hypertension (PIH). Respiratory distress syndrome (RDS) was diagnosed on clinical and radiological findings. Anemia was defined as Hb<10 g/dl or HCT<30%. Sepsis was considered by clinical suspicion, and confirmed by diagnostic tests and culture and sensitivity testing.⁵ Necrotizing enterocolitis (NEC) was diagnosed according to clinical, radiological and laboratory findings using Bell’s criteria.¹² Hypocalcemia was taken as total serum calcium level <8mg/dl. Oxygen therapy, considered as $FiO_2 >40\%$ (given for >24hrs), was calculated by Finers formula¹³ for those on low flow oxygen therapy and by the ventilator for ventilated neonates. Prolonged parenteral nutrition (PPN), duration of oxygenation and ventilation were defined as duration of >7 days. Eye examination of the preterm neonates, meeting the above mentioned criteria, was carried out at 4-5 weeks of age by the same Ophthalmologist. Tropicamide (1%) and phenylephrine (2.5%) eye drops were instilled in eyes, thrice, at 15 minutes interval and indirect ophthalmoscopy was performed. Stages of ROP were

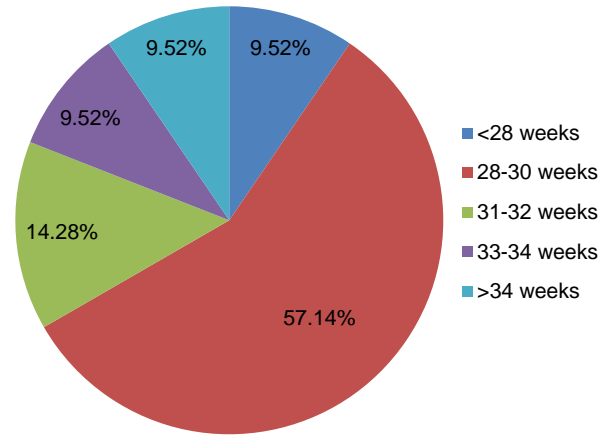


Figure 1. Distribution of patients with ROP according to gestational age

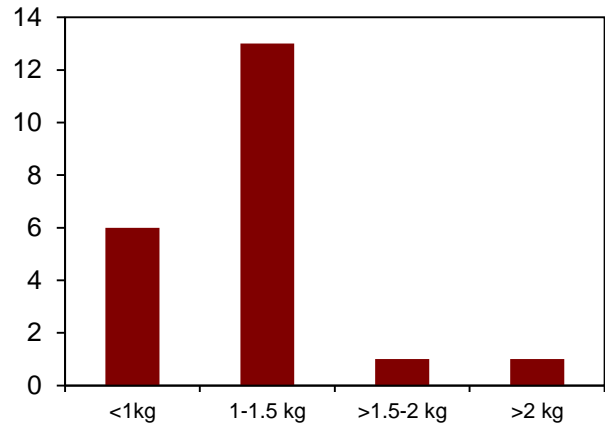


Figure 2. Frequency of patients with ROP according to birth weight

defined according to International Classification of Retinopathy (ICROP).¹⁴ Thereafter the infants were called for fortnightly follow up visits for eye examination till the age of 8 weeks if they were not diagnosed with ROP. Treatment of neonates with ROP was done according to Early Treatment of ROP (ETROP) guidelines.¹⁵

Data was analyzed by Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive statistical analyses were performed to see the incidence of ROP. Univariate analysis of maternal and neonatal risk factors was carried out using Chi-square test. The variables found to be significant ($p \leq 0.05$) in univariate analysis were further analyzed by logistic regression model to find out the factors associated with ROP. Adjusted odds ratio was recorded by 95% confidence interval and p-value of ≤ 0.05 was taken as significant.

Table 1. Univariate analysis showing significant risk factors of ROP development

Source	Type III Sum of Squares	Degree of freedom	Mean Square	F	p-value
Corrected model	10.421 ^a	13	0.802	10.406	0.000
Intercept	2.126	1	2.126	27.598	0.000
Gestational age	0.043	1	0.043	0.565	0.455
Birth weight (kg)	0.527	1	0.527	6.845	0.011
Pregnancy induced hypertension	0.046	1	0.046	0.591	0.445
Respiratory distress syndrome	0.006	1	0.006	0.077	0.783
Duration of oxygenation	0.073	1	0.073	0.948	0.334
FiO ₂	1.188	1	1.188	15.424	0.000
Duration of ventilation	0.098	1	0.098	1.278	0.263
Anemia	0.790	1	0.790	10.249	0.002
Multiple blood transfusions	0.017	1	0.017	0.218	0.642
Prolonged parenteral nutrition	0.013	1	0.013	0.168	0.683
Sepsis	0.151	1	0.151	1.955	0.167
Necrotizing enterocolitis	0.119	1	0.119	1.543	0.219
Hypocalcemia	0.433	1	0.433	5.623	0.021
Error	4.699	61	0.077		
Total	21.000	75			
Corrected total	15.120	74			

a. R Squared = 0.689 (Adjusted R Squared = 0.623)

Table 2. Binary logistic regression model showing risk factors associated with ROP

Variables	Regression coefficient	Standard error	Wald	Degree of freedom	Significance	Odds ratio	95% confidence Interval	
							Lower	Upper
Birth weight (kg)	-2.019	1.020	3.919	1	0.048	0.133	0.018	0.980
FiO ₂	2.343	0.995	5.550	1	0.018	10.417	1.483	73.192
Anemia	2.485	0.981	6.421	1	0.011	12.004	1.756	82.057
Hypocalcemia	20.259	14307.167	0.000	1	0.999	628467976.868	0.000	.
Constant	-3.060	0.997	9.424	1	0.002	0.047		

RESULTS

Total of 794 preterm infants were born at Hameed Latif Hospital, out of which 213 (26.8%) infants were included in the study. Seventy five (35.2%) of the included infants turned up for follow up ROP screening. Follow up examination revealed that 21 (28%) of the total 75 screened developed ROP. There were 13 male and 8 female infants with male to female ratio of 1.6:1. Majority of infants (12; 57.14%) were born at 28-30 weeks of gestation followed by those with 31-32 weeks of gestation (3; 14.28%) (Figure 1). Weight distribution showed that 13 (61.9%) infants had birth weight between 1-1.5 kg while 6 (28.5%) weighed <1 kg (Figure 2). Results of univariate comparison of various risk factors are shown in Table 1. The risk factors found to be statistically significant by univariate analysis were FiO₂ (p=0.000) followed by anemia (p=0.002), low birth weight (p=0.011) and hypocalcemia (p=0.021). Other risk factors including gestational age, pregnancy induced hypertension, respiratory distress syndrome, duration of oxygenation, duration of ventilation, multiple blood transfusions, prolonged parenteral nutrition, sepsis and necrotizing enterocolitis were found to be statistically insignificant (p-value >0.05) (Table 1).

Logistic regression analysis of significant risk factors revealed anemia (p=0.011) to be the most significant associated risk factor followed by FiO₂>40% (p=0.018) and low birth weight (p=0.048). However, no significant association of hypocalcemia (p=0.999) with ROP could be found (Table 2). Ten infants (47.61%) belonged to the ROP type responsive to anti-VEGF treatment while 11 (52.38%) responded to laser treatment. Frequency of the risk factors among these two types of ROP patients is shown in Table 3. The risk factors were analysed to compare their association with either of the ROP types. Results showed no statistically significant difference in association of any of the risk factors amongst these two groups of patients (Table 3). None of the identified risk factors showed statistically significant difference for association with either of the types of ROP (Table 3).

DISCUSSION

This study showed that incidence of ROP in premature infants was 28% which lies within the range (12.8%-59%) seen in studies in other parts of the world.^{8,16-19} In Pakistan, the incidence of retinopathy has been reported as 24.6%-32.4%.^{4,20} According to some studies, the incidence of ROP in developing countries, varies

Table 3. Frequency distribution and association of risk factors among two types of ROP

Risk factors	Type of ROP (n = 21)		p-value
	Anti-VEGF n (%)	Laser n (%)	
Gestational age			
<32 weeks	09 (90)	08 (72.73)	0.314
>32 weeks	01 (10)	03 (27.2)	
Birth weight			
<1.5 kg	09 (90)	10 (90.91)	0.943
>1.5 kg	01 (10)	01 (9.09)	
Pregnancy Induced hypertension			
No	06 (60)	07 (63.64)	0.864
Yes	04 (40)	04 (36.36)	
Respiratory distress syndrome			
No	05 (50)	04 (36.36)	0.528
Yes	05 (50)	07 (63.64)	
Duration of oxygenation			
<7 days	01 (10)	03 (27.27)	0.314
>7 days	09 (90)	08 (72.73)	
FiO₂			
<40%	01 (10)	01 (9.09)	0.943
>40%	09 (90)	10 (90.91)	
Duration of ventilation			
<7 days	06 (60)	08 (72.73)	0.537
>7 days	04 (40)	03 (27.27)	
Anemia			
No	02 (20)	01 (9.09)	0.476
Yes	08 (80)	10 (90.91)	
Multiple blood transfusions			
No	02 (20)	04 (36.36)	0.407
Yes	08 (80)	07 (63.64)	
Prolonged parenteral nutrition			
No	05 (50)	07 (63.64)	0.528
Yes	05 (50)	04 (36.36)	
Sepsis			
No	01 (10)	03 (27.27)	0.314
Yes	09 (90)	08 (72.73)	
Necrotizing enterocolitis			
No	08 (80)	11 (100)	0.119
Yes	02 (20)	0	
Hypocalcemia			
No	07 (70)	07 (63.64)	0.757
Yes	03 (30)	04 (36.36)	

from 12.8% to 59%, whereas in developed countries it ranges from 13.2 to 46%. which is comparable to 28% observed in this study.^{8,16-19} Male preterm infants in this study, had a higher incidence of ROP as agreed by other researchers.^{7,21} Three risk factors including anemia, FiO₂>40% and low birth weight are observed significantly associated with development of ROP. Association of these risk factors with ROP is reported in previous studies.^{5,22-24} Hypocalcemia was found to be significant on univariate analysis but was not associated with ROP on logistic regression analysis, in this study. This is in contrast with results of Samatha and coauthors, where, hypocalcemia was reported a risk factor for development of ROP.²⁵ Difference in sample size and number of diagnosed cases may be the reason of this disparity in results. Results of this study showed

that low gestational age was not associated with development of ROP, while this association has been well established in various studies conducted worldwide.⁴ Mortality rate in premature infants especially those with <32 weeks of gestation was high in developing resource-poor countries like Pakistan. In this study, a higher mortality rate of infants of <32 weeks of gestation who had fulfilled the criteria for screening, seems to be a plausible explanation of lack of significant association with gestational age. Prolonged oxygen supplementation, mechanical ventilation, multiple blood transfusions, and sepsis have been reported to be commonly associated with ROP by various authors.^{7,12,26,27} This study could not establish these factors with ROP. This may be due to the large number of preterm infants who after a prolonged

course of illness and exposure to oxygen, did not turn up for follow up screening. Necrotizing enterocolitis, peripheral parenteral nutrition, respiratory distress syndrome and pregnancy induced hypertension are other risk factors which have not been unequivocally associated with ROP. This study could not find a significant association of these factors with the disease despite a small sample size. These results are comparable to the results of various studies worldwide.^{2,16,17,28} While none of the evaluated risk factors showed significant relationship with severity of ROP in this study, Anuja and coworkers reported oxygen supplementation and RDS to be significant for developing severe form of ROP.⁷ Similarly, another study conducted by Celebi and colleagues reported low gestational age, low birth weight, sepsis and blood transfusions to be associated with severe form of ROP requiring laser treatment.²⁹ This discrepancy in results may be attributed to the small number of cases diagnosed with ROP in present study.

This study has the limitation of a large drop out in preterm infants called for ophthalmological examination. Therefore, it could not be determined whether they developed ROP or not. Keeping in view the identified risk factor information, some of these preterm babies could have developed retinopathy, leading to blindness. This emphasizes the need for more vigorous efforts to ensure proper communication regarding the importance of ROP, as well as a more robust follow up system to ensure better compliance. Only then can a significant impact be made on prevention of morbidity specially blindness in preterm infants with known risk factors.

CONCLUSION

With the advancement in neonatal care in urban cities and improvement in survival rate of preterm infants, the incidence of ROP is increasing. It is crucial, therefore, to implement proper screening criteria in NICUs, and mandatory for doctors to create awareness among parents of high risk preterm babies as well as to ensure a good follow up with the ophthalmologist. There is need for larger prospective studies to determine true incidence of ROP and its risk factors. Identification and appropriate management of risk factors can help prevent this condition and avoid the serious consequences of blindness.

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