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Original Article

To study the incidence of retinopathy of prematurity in high-risk neonates and the risk factors associated with the disease

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature infant. The challenge in India is that a large number of neonatal intensive care units (NICUs) don't have an effective ROP screening strategy. **Objective:** To measure the incidence of ROP in neonates with gestational age (≤32 weeks) or weighing <2000 g with risk factors and evaluation of risk factor associated with ROP. **Materials and Methods:** This prospective study was conducted in the Department of Pediatrics and Ophthalmology from January to July 2016. Neonates with gestational age ≤32 weeks, birth weight (BW) ≤1500 g, and selected preterm infants with a BW between 1501 and 2000 g with risk factors admitted in NICU/special newborn care unit were included in the study and screened for ROP by trained ophthalmologist under supervision of the pediatrician. All data were analyzed using SPSS or MedCalc. Univariate and multivariate logistic regression was done to determine the risk factors for the development of any ROP. **Result:** The incidence of ROP in our study was 19%. 4% of the neonates have severe (early treatment for ROP [ETROP] Type 1) ROP while 15% have non-severe (ETROP Type 2) ROP. 8 neonates developed Stage 1 ROP (42.11%), 7 developed Stage 2 (36.84%), and 4 neonates developed Stage 3 ROP (21.05%). **Conclusion:** The current study revealed that the incidence of ROP in sick neonates was 19%. Significant risk factors were found to be low BW, low gestational age, supplemental oxygen, and mechanical ventilation, culture proven sepsis, anemia, apnea, and respiratory distress syndrome (RDS).

Key words: *Early Treatment for Retinopathy of Prematurity, Low birth weight, Prematurity, Retinopathy of prematurity*

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature infants. ROP continues to be an important cause of potentially preventable blindness worldwide. It is believed to account for 6-18% of the childhood blindness in developed countries [1]. Neonates born before 32 weeks of gestation are at risk of developing ROP. However, preterm infants born at 32 weeks or later can develop severe ROP if they have been sick or they require oxygen therapy. Recent advances in neonatal care in the last decade, have improved the survival rates for premature infants.

In India 28 million children are born, out of which 3.5 million are preterm and lot of them would not survive but now they are surviving [2]. Earlier Indian studies have shown that the incidence of ROP varies from 38 to 51.9% among low birth weight (LBW) babies [3-5]. However, more recent studies have shown a lower rate of ROP ranging from 13 to 30% [6-10]. The challenge in India is that a large number of neonatal intensive care units (NICUs) don't have an effective ROP screening strategy and there is a need for an effective screening strategy for every NICU and Special Newborn Care Unit (SNCU).

Government of India under its National Health Mission and the Rashtriya Bal Swasthya Karyakram (RBSK) has set up a task force to set up the program for ROP screening across the whole country. Under RBSK scheme, ROP is included in the list of congenital defects for which a newborn will be screened. The Union Government under its RBSK is working toward establishing 634 SNCUs that are expected to provide ROP screening as a part of the essential newborn care for preterms. There is scarce data available for ROP in Rajasthan. Therefore, the current study has been conducted to bring out the incidence of ROP in high-risk neonates admitted in Jawaharlal Nehru Hospital, Ajmer, and the risk factors associated with the disease.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Pediatrics and Ophthalmology, between January 2016 and July 2016. First, 100 neonates who are born of gestational age <32 weeks and weighing <1500 g or selected preterm neonates with a BW between 1501 and 2000 g with risk factors were included in the study. The risk factors included were need of cardiorespiratory support, need of supplemental oxygen (>21% oxygen concentration), need for surfactant therapy, apnea of prematurity, anemia (asymptomatic neonates with hematocrit

Table 1: Incidence of ROP according to birth weight and gestational age

Parameter	Total cases	Number (%)		p value
		Cases with ROP	Cases without ROP	
Birth weight (g)				
<1000	6	4 (66.67)	2 (33.33)	0.0005
1000-1500	64	12 (18.75)	52 (81.25)	
1501-2000	30	3 (10.00)	27 (90.00)	
Gestational age in weeks				
<28	4	4 (100.0)	0 (0.00)	0.0001
28-32	69	12 (17.39)	57 (82.60)	
>32	27	3 (11.11)	24 (88.88)	

ROP: Retinopathy of prematurity

<21% or hematocrit <36% and requiring >35% oxygen concentration), intraventricular hemorrhage, respiratory distress, and culture proven neonatal sepsis. Clinically unstable newborn and neonates whose parents did not give consent for screening were excluded from the study. The plan for this study was approved by the Institutional Ethical Committee.

Ophthalmological Examination

Neonates admitted in NICU were screened by trained ophthalmologist in the neonatal unit itself under the supervision of attending pediatrician. Discomfort to the baby was minimized by pre-treatment of the eyes with a topical proparacaine screening of ROP involves indirect ophthalmoscopy using 20D or 28/30D lens by an experienced ophthalmologist.

Demographic profile and risk factors of the patient were recorded in a structured pro forma. Ophthalmological notes were made after each ROP examination, detailing zone, stage, and extent in terms of clock hours of any ROP and the presence of any preplus or plus disease. These notes also included the recommendation for the timing of the next examination and were kept with the baby's medical record.

The stage of ROP was assessed as per the international classification of ROP which describes the location (Zone), extent (Clock hours), and severity (Stage) of the disease [11]. The severity of ROP was classified on the basis of early treatment for ROP (ETROP) study into severe or Type 1 ROP (which require intervention) and nonsevere or Type 2 ROP (lesser stages of ROP which require follow-up) [12]. Type 1 ROP and Type 2 ROP according to ETROP study are:

- Type 1 ROP
  - Zone 1, any stage ROP with plus disease
  - Zone 1, Stage 3 ROP without plus disease
  - Zone 2, Stage 2, 3 ROP with plus disease
- Type 2 ROP
  - Zone 1, Stage 1 or 2 ROP without plus disease
  - Zone 2, Stage 3 ROP without plus disease

A first screening examination was carried out at 32 weeks of gestation or 4 weeks of age, whichever was later. Follow-up examinations were recommended by the examining ophthalmologist on the basis of retinal findings: The neonates whose ROP requiring peripheral retinal ablation were referred expeditiously to higher center as the procedure needs to be conducted within 72 h to improve structural outcome.

All data were entered into a spreadsheet and analyzed using SPSS or MedCalc. Univariate and multivariate logistic regression was done to determine the risk factors for the development of any ROP. p=0.05 or less was considered statistically significant. Relative risk and 95% confidence intervals were calculated for determining the independent risk factors.

RESULTS

The current study revealed that the incidence of ROP in out of 100 high-risk neonates was 19%. In this study, there were a total of 51 male infants (51%) and 49 female infants (49%) out of which 12 male (63.15%) and 7 female (36.84%) infants developed ROP. The incidence of ROP was 66.67% in babies <1000 g, 18.75% in babies between 1000 and 1500 g, and 10% in babies between 1501 and 2000 g. The mean weight of babies having ROP was 1231.05±282.4 g while the mean weight of babies without ROP was 1452.47±277.54 g. The incidence of ROP was 100% in babies <28 weeks, 17.39% in babies between 28 and 32 weeks, and 11.11% in babies >32 weeks gestational age (Table 1). Neonate <32 weeks gestational age developed severe ROP. 4% of the neonates had severe ROP while 15% had non-severe ROP as per ETROP classification. 8 neonates developed Stage 1 ROP (42.11%), 7 developed Stage 2 (36.84%), and 4 neonates developed Stage 3 ROP (21.05%) in which 1 neonate was Stage 3 ROP with plus disease (5.25%) (Table 2).

The risk factors found to be associated with occurrence of ROP on univariate analysis were lower gestation (p=0.0001), birth weight (p<0.001), oxygen therapy (p<0.001), and mechanical ventilation (p<0.01), culture proven sepsis (p<0.05), anemia requiring packed cell transfusion (p<0.001), intraventricular hemorrhage (p<0.05), apnea (p<0.05), and respiratory distress syndrome (RDS) (p<0.0001) (Table 3)..The mean duration of supplemental oxygen therapy (FiO2 >21%) was 8.94±8.4 days in ROP cases whereas, in non-ROP cases, it was 3.09±3.78 days. The mean duration of ventilation was 3±3.22 days in ROP cases whereas, in non-ROP cases, it was 0.59±1.44 days. BW <1000 g (p<0.01) and gestational age <28 weeks (p<0.001) were found to be important risk factors for ROP. Mean BW associated with ROP was 1231 g (95% confidence interval [CI]: 666 – 1795 g) compared to 1452 g (95% CI: 897 – 2007 g) for those without ROP.

On multivariate analysis, factors independently found to be associated with ROP were LBW and low gestational age (Table 4). 4 (21.05%) neonates in this study developed severe ROP for which they were referred to the higher center for peripheral retinal ablation. Rest 15 (78.95%) neonates who developed ROP did not require intervention and were followed till ROP regression or vascularization of the peripheral retina.

Table 2: Distribution of cases according to severity of ROP according to ETROP study

Zone	Zone	Plus disease	Classification as per ETROP	Number	Severity of ROP	
					Non-severe	Severe
1	Stage 1	+	Type 1			
		-	Type 2	4	4	
	Stage 2	+	Type 1			
		-	Type 2	3	3	
	Stage 3	+	Type 1	1		1
		-	Type 1	3		3
2	Stage 1	+				
		-		2	2	
	Stage 2	+	Type 1			
		-		3	3	
	Stage 3	+	Type 1			
		-	Type 2			
3	Stage 1	+				
		-		2	2	
	Stage 2	+				
		-		1	1	
	Stage 3	+				
		-				
Total				19	15	4

ETROP: Early treatment for retinopathy of prematurity, ROP: Retinopathy of prematurity

Table 3: Association of ROP with risk factors

Risk factors	Total cases (n=100)	Number (%)		p value
		Cases with ROP (n=19)	Cases without ROP (n=81)	
Oxygen given	55	17 (89.47)	38 (46.91)	0.0007
Oxygen not given	45	2 (10.53)	43 (53.09)	
Ventilation done	25	10 (52.63)	15 (18.52)	0.0019
Ventilation not done	75	9 (47.37)	66 (81.48)	
Sepsis present	23	8 (42.10)	15 (18.52)	0.028
Sepsis absent	77	11 (57.89)	66 (81.48)	
RDS present	43	14 (73.68)	29 (35.80)	0.0009
RDS absent	67	5 (26.31)	62 (76.54)	
Apnea present	23	8 (42.10)	15 (18.51)	0.027
Apnea absent	77	11 (57.89)	66 (81.48)	
PCV given	21	10 (47.61)	11 (52.38)	0.0871
PCV not given	79	9 (11.37)	70 (88.60)	

ROP: Retinopathy of prematurity, RDS: Respiratory distress syndrome, PCV: Packed cell volume

DISCUSSION

ROP continues to be an important cause of potentially preventable blindness worldwide. Recent advances in neonatal care in the last decade, have improved the survival rates for premature infants. Consequently, the incidence of ROP has increased in parallel. ROP is under constant epidemiological study around the world. Early identification of retinal damage and the institution of appropriate treatment prevent blindness and offer child better overall development. We have done this study to know the incidence of ROP in our institute.

In our study, the incidence of ROP was 19% and Type 1 ROP was 4%. In an earlier study by Gopal et al. [3], the incidence of ROP was found to be 38%, and threshold ROP was 16%. Maheshwari et al. [4] found 20% incidence of ROP (threshold ROP 9.1%) while Rekha et al. [5] found 46% (threshold ROP 9%) and Chaudhari et al. [7] reported 22.3% incidence of ROP (threshold ROP 7.4%). However, Aggarwal et al. [9] and Prasad et al. [8] found incidence to be 32% (Type 1-2.6%) and 13% (Type 1-3%), respectively.

As regard the effect of low gestational age on the occurrence of ROP, our study found that it is a significant risk factor in ROP on univariate regression. This was in agreement with the results of studies conducted by Shah et al. [13], Karna et al. [14], and Fortes et al. [15]. This study found a significant relationship between gestational age and the severity of ROP; this was in

Table 4: Multivariate logistic regression for various risk factors associate with occurrence of ROP

Risk factors	Cases with ROP (n=19)	Cases without ROP (n=81)	Total (n=100)	p value (multiple logistic regression)
Gender				
Male	12	39	49	0.9399
Female	7	42	51	
Birth weight is taken as a continuous variable				0.0042
Gestational age calculated by Ballard score as continuous variable				0.0098
Blood transfusion				
PCV given	10	11	21	0.0871
Not given	9	70	79	
Duration of supplemental oxygen taken as continuous variable in days				0.2697
Duration of ventilation taken as continuous variable in days				0.0867
Culture proven sepsis				
Present	8	15	23	0.1647
Absent	11	66	77	
Apnea				
Apnea present	8	15	23	0.4280
Apnea absent	11	66	77	
RDS				
RDS present	14	29	43	0.8856
RDS absent	5	62	67	

ROP: Retinopathy of prematurity, RDS: Respiratory distress syndrome, PCV: Packed cell volume

agreement with other studies showing that lower gestational age was significantly associated with severe ROP [13,15]. In our study using multivariate analysis, BW and gestational age emerged as independent risk factors. Similar results were found by Kim [16]. However, other studies have failed to find these as independent risk factors.

Our study revealed insignificant relationship between sex and occurrence of ROP, in contrast to Darlow et al. [17] and Aggarwal et al. [9] who found that male sex is a significant risk factor. Our study found a significant relationship between the occurrence of ROP and use of oxygen therapy on univariate analysis. The same result was drawn by Chaudhari et al. [7], Prasad et al. [8], and Gupta et al. [18]. On the other hand, Palmer [19] and Aggarwal et al. [9] reported that oxygen therapy was a non-significant factor for the occurrence of ROP. They reported that ROP may develop in cases that did not receive oxygen therapy. In our study, 2 out of 19 neonates developed ROP had not received supplemental oxygen. Our study found that mechanical ventilation was significant risk factors for ROP on univariate analysis and this agreed with Shah et al. [13] and Chaudhari et al. [7] and explained by the increased exposure to oxygen. However, Murthy and Nagendra [20] observed that ventilator support and continuous positive airway pressure were not significantly associated with the development of ROP.

Our study found that the packed cell transfusions are a significant risk factor for the development of ROP, and this agreed with Chaudhari et al. [7], Dutta et al. [21], and Rekha and Battu [5]. This can be explained by the fact that, adult red blood cells are rich in 2,3-diphosphoglycerate and adult hemoglobin which binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue. While Hirano et al. [22] stated that it is controversial and iron overload rather than number of transfusions may contribute to the development of ROP. However, our study did not find packed cell transfusion as an independent risk factor in contrast with Hakeem et al. [23] and Datta S. Our study found that sepsis was significantly associated with the development of ROP. This was in agreement with Shah et al. [13] and Vinekar et al. [10] which may be due to the effect of endotoxin on retinal blood vessels. On the other hand, this was in disagreement with the results of Chaudhari et al. [7].

Our study showed a significant relationship between apnea and occurrence of ROP. This was in agreement with Rekha and Battu [5], Aggarwal et al. [9], Gupta et al. [18], Chaudhari et al. [7], and Prasad et al. [8] and was attributed to hypoxia of retinal vasculature leading to stoppage of normal angiogenesis followed by neovascularization. However, Kim et al. found apnea as an independent risk factor for ROP which was not seen in this study. Our study showed a significant association between RDS and occurrence of ROP. Taqui et al. [24] observed a significant relation between RDS and the development of ROP and related this to the fact that systemic hypoxia results in retinal hypoxia and more need for oxygen therapy. The limitation of our study is a small sample size of 100 neonates while the study provided data for incidence of ROP in Rajasthan which is not readily available.

CONCLUSION

Our study revealed that the incidence of ROP in sick neonates was 19%. 4% of neonate has severe ROP while 15% have non-severe ROP. Significant risk factors were found to be LBW, low gestational age, supplemental oxygen, and mechanical ventilation, culture proven sepsis, anemia, apnea, and RDS.

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