Doi: 10.32677/IJCH.2017.v04.i03.028

Original Article

Retinopathy of prematurity in a tertiary care center: A study of prevalence, risk factors, and outcomes

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Received - 10 March 2017 Initial Review - 14 April 2017 Published Online - 18 May 2017

ABSTRACT

Background: Retinopathy of prematurity (ROP) is a serious complication of prematurity treatment and can lead to blindness unless recognized and treated early. **Objectives:** The objectives were to estimate the prevalence of ROP in preterm infants in the neonatal intensive care unit (NICU), to identify the risk factors which predispose to ROP, and to assess the outcome of these cases. **Methodology:** A retrospective screening survey was performed enrolling all premature neonates admitted to the NICU between January and December 2016, with a gestational age of 32 weeks or less at birth and a birth weight of 1500 g or less. Infants whose gestational age was >32 weeks or birth weight was >1500 g were included if they were exposed to oxygen therapy for more than 7 days. A total of 344 neonates had a retinal evaluation by indirect ophthalmoscopy from the fourth postnatal week and followed up periodically. Perinatal risk factors for ROP were assessed using univariate and multivariate analysis. Infants who progressed to Stage 3 ROP were given laser therapy. **Results:** Out of the studied 344 neonates, 66 (19.2%) developed ROP in one or both eyes; 36 (54.5%) cases had Stage 1, 18 (27.3%) cases Stage 2, and 12 (18.2%) cases had Stage 3 ROP. None had Stages 4 and 5 ROP. The 12 cases diagnosed as ROP Stage 3 underwent LASER therapy. Univariate analysis showed a significant relationship between the occurrence of ROP and gestational age (p=0.001), sepsis (p=0.004), oxygen therapy (p=0.018), and frequent blood transfusions (p=0.030). However, an insignificant relationship was found between the occurrence of ROP and factors such as gender, mode of delivery, birth weight, respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, hypotension, phototherapy, and duration of oxygen therapy, mechanical ventilation, and continuous positive airway pressure. Gestational age, sepsis, oxygen therapy, and frequent blood transfusions remained significant variables after logistic regression analysis. **Conclusion:** The prevalence of ROP in this study was 19.2%; low gestational age, sepsis, oxygen therapy, and frequent blood transfusions were significant risk factors for ROP. LASER was effective in the treatment and decreasing the progression of ROP.

Key words: *Oxygen therapy, Prematurity, Risk factors, Retinopathy of prematurity*

Retinopathy of prematurity (ROP) is a disease that can cause blindness in very low birth weight (VLBW) infants. The incidence of ROP is closely correlated with the weight and the gestational age at birth. Despite current therapies, ROP continues to be a highly debilitating disease. Our advancing knowledge of the pathogenesis of ROP has encouraged investigations into new anti-vasculogenic therapies. ROP is an important cause of preventable blindness in children [1].

In developed countries, its incidence continues to increase with the improvement in the survival of extremely premature infants [2,3]. Until recently, the survival rates of VLBW neonates in India were relatively low and therefore, ROP was considered to be rare. With improving outcomes of the "at-risk" preterm infants at several newborn care centers, ROP is likely to emerge as a major problem in India. We assessed the prevalence of ROP in our setting and evaluated its association with a number of neonatal risk factors retrospectively.

METHODOLOGY

After obtaining approval from the ethics committee of the university, this study was pursued. A retrospective study was conducted in the neonatal intensive care unit (NICU) of the Madras Medical College, Chennai. The study population consisted of 344 neonates who were screened for ROP, between January and December 2016. Neonates who satisfied the following criteria were included in the study: (i) Gestational age of 32 weeks or less at birth and a birth weight of 1500 g or less, (ii) infants whose gestational age was >32 weeks or birth weight was >1500 g if they were exposed to oxygen therapy for more than 7 days, and

(iii) neonates between 32 and 34 weeks with a course of instability (such as sepsis, asphyxia, or ventilation). Neonates who died before the first ophthalmologic examination were excluded. Infants with congenital anomalies, chromosomal abnormalities, and inborn errors of metabolism were also excluded from the study. Risk factors of ROP, perinatal, intrapartum, and postnatal were noted in the history.

Findings of local eye examination were noted. In our institute, indirect ophthalmoscopy with a 28 diopter lens was performed. All infants were being examined regularly by the ophthalmologist at 1-2-week intervals from the 4th postnatal week onward and were repeated weekly or biweekly, using the schedule for follow-up recommended by AAP, AAO, and AAPO, until full vascularization of the retina reached zone 3 (the most peripheral temporal retinal zone), or until full remission of ROP after treatment. The eyes were dilated with a combination of cyclopentolate 0.1%, and phenylephrine 0.1% eye drops applied one hour before the examination. We followed the criteria established by the International Committee for Classification of ROP [4]. ROP was defined as the incomplete or abnormal vascular proliferation of the retina. The ROP was classified by location on the retina (Zone 1-3), and severity (Stage 1-5). All the patients diagnosed with Stage 3 ROP were treated with laser photocoagulation.

We considered a list of suspected pre and postnatal risk factors for ROP to identify independent risk factors associated with the development of mild and severe forms of this disease in our NICU conditions. The prenatal variables were gestational age, birth weight, sex, and mode of delivery. The post-natal variables were respiratory distress syndrome (RDS), oxygen therapy, and phototherapy for jaundice, frequency of blood transfusions, sepsis, hypotension, intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA).

Data were analyzed by the Statistical Package for the Social Sciences (SPSS for Windows, version 13.0). Descriptive statistics included the mean and standard deviation for numerical variables, and the percentage of different categories for categorical variables. The prevalence rate of ROP was described in simple proportion. Group comparisons were done by the Chi-square test or Fisher's exact test for categorical variables. A logistic regression model was performed, and the adjusted odds ratio (95% confidence interval) was obtained for the risk factors which had been shown to be significant in the univariate analysis. A $p<0.05$ was considered statistically significant.

RESULTS

Of the 344 neonates, 168 (48.8%) were males and 176 (51.2%) were females. The mean gestational age was 33.02±1.72 weeks, 48 were ≤32 weeks, and 296 were >32 weeks. The majority (176) weighed between 1000 and 1500 g. A total of 144 cases (41.9%) were delivered vaginally, and 200 (58.1%) cases were delivered by cesarean section (Table 1). Out of the 344 neonates, 66 (19.2%) cases developed ROP in one or both eyes classified as 36 (54.5%) cases Stage 1, 18 (27.3%) cases Stage 2, and 12 (18.2%) cases Stage 3. None of the studied neonates presented ROP at Stages 4 or 5. The 12 cases diagnosed as ROP Stage 3 underwent LASER therapy.

Table 1: Demographic data of the studied cases (n=344)

Data	n (%) or mean±SD
Sex	
Male	168 (48.8)
Female	176 (51.2)
Mode of delivery	
Vaginal delivery	144 (41.9)
Cesarean section	200 (58.1)
Gestational age (weeks)	33.02±1.72
Birthweight (g)	1510±245

SD: Standard deviation

Table 2 shows the relationship between ROP and risk factors. There was a significant relationship between the occurrence of ROP and gestational age ($p=0.001$), sepsis ($p=0.004$), oxygen therapy ($p=0.018$), and frequency of blood transfusions ($p=0.030$). On the other hand, there was no significant relationship between the occurrence of ROP and sex, mode of delivery, birth weight, RDS, PDA, IVH, hypotension, phototherapy, and duration of oxygen therapy, mechanical ventilation, and continuous positive airway pressure (CPAP) (all $p>0.05$). Table 3 shows the relationship between gestational age and stages of ROP. There was no significant relationship between the gestational age and stages of ROP ($p=0.325$). Table 4 shows the relationship between oxygen therapy and stages of ROP. Those variables that were statistically significant after univariate analysis were analyzed using logistic regression analysis. Gestational age, sepsis, oxygen therapy, and frequency of blood transfusions remained significant variables (Table 5).

DISCUSSION

The study showed the prevalence of ROP of 19.2% which was similar to that seen in a study by Hakeem et al. [5], but was less than most of the other studies such as 29.2% in a study by Shah et al. [6] and 32.4% in a study by Taqui et al. [7]. The possible reason for this high prevalence could be that these studies involved only VLBW infants. Our study found low-gestational-age, sepsis, oxygen therapy, and frequency of blood transfusions to be independent risk factors for the development of ROP. Whereas most of the studies showed low gestational age along with low birth weight, to be risk factors of ROP [8-10]. The other variables which proved to be non-significant risk factors in our study (by univariate analysis) included sex, mode of delivery, birth weight, RDS, PDA, IVH, hypotension, phototherapy, duration of oxygen therapy, mechanical ventilation, and CPAP.

However, when we looked at the association of low gestational age with the risk of ROP, we found it to be a very strong and significant risk factor for ROP, and this finding was

Table 2: Relationship between retinopathy of prematurity and risk factors

Data	Cases with ROP (n=66) (%)	Cases without ROP (n=278) (%)	p value
Sex			
Male (n=168)	34 (51.5)	134 (48.2)	0.732
Female (n=176)	32 (48.5)	144 (51.8)	
Mode of delivery			
Vaginal delivery (n=144)	34 (51.5)	110 (39.6)	0.211
Cesarean section (n=200)	32 (48.5)	168 (60.4)	
Gestational age (weeks)			
≤32 (n=48)	22 (33.3)	26 (9.4)	0.0001*
>32 (n=296)	44 (66.7)	252 (90.6)	
Birthweight (g)			
<1000 (n=6)	4 (6)	2 (0.7)	0.109
1000-1500 (n=174)	32 (48.5)	142 (51.1)	
>1500 (n=164)	30 (45.5)	134 (48.2)	
RDS (n=120)	28 (42.4)	92 (33.1)	0.312
Sepsis (n=230)	58 (87.9)	172 (61.9)	0.004*
PDA (n=6)	2 (3)	4 (1.4)	0.530
IVH (n=18)	4 (6)	14 (5)	0.812
Hypotension (n=92)	20 (30.3)	72 (25.9)	0.607
Phototherapy (n=312)	60 (90.9)	252 (90.6)	0.963
Oxygen therapy (n=166)	44 (66.7)	122 (43.9)	0.018*
Duration of oxygen therapy			
≤1 week (n=94)	30 (45.5)	64 (23)	0.202
>1 week (n=72)	14 (21.2)	58 (20.9)	
Mechanical ventilation (n=44)	14 (21.2)	30 (10.8)	0.107
CPAP (n=54)	16 (24.2)	38 (13.7)	0.133
Frequency of blood transfusions			
Once (n=50)	6 (9.1)	44 (15.8)	
More than once (n=92)	18 (27.3)	28 (10.1)	

***p<0.05 is significant, ROP: Retinopathy of prematurity, RDS: Respiratory distress syndrome, IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus, CPAP: Continuous positive airway pressure**

Table 3: Relationship between gestational age and stages of ROP

Stages of ROP	Patients with ROP		
	≤32 weeks, (n=22) (%)	>32 weeks, (n=44) (%)	p value
Stage 1 ROP (n=36)	8 (36.4)	28 (63.6)	0.325
Stage 2 ROP (n=18)	8 (36.4)	10 (22.7)	
Stage 3 ROP (n=12)	6 (27.2)	6 (13.7)	

ROP: Retinopathy of prematurity

Table 4: Relationship between oxygen therapy and stages of ROP

Stages of ROP	Cases required oxygen therapy (n=44) (%)	Cases without oxygen therapy (n=22) (%)	p value
Stage 1 ROP (n=36)	26 (59.1)	10 (45.5)	0.687
Stage 2 ROP (n=18)	10 (22.7)	8 (36.3)	
Stage 3 ROP (n=12)	8 (18.2)	4 (18.2)	

ROP: Retinopathy of prematurity

in agreement with the results of studies done by Shah et al. [6], Karna et al. [11], and Fortes et al. [12]. The likely explanation for this could be the immaturity of vascularization that induces an increased susceptibility of the retina to oxidative damage and to a number of perinatal factors which include hyper and hypoxia, blood transfusions, and sepsis. Although many studies [6-12] found a significant relationship between the gestational age and the severity of ROP, our study did not find any such significant association. This could be attributed to the reason that we did not include more preterm babies in our study.

Table 5: Logistic regression analysis

Risk factors	OR	95% CI	p value
Gestational age	3.868	1.656-9.033	0.0001*
Sepsis	1.251	1.082-1.458	0.003*
Oxygen therapy	1.005	1.001-1.009	0.003*
Frequency of blood transfusions	2.483	1.182-5.222	0.016*

***p<0.05 is statistically significant. OR: Odds ratio, CI: Confidence interval**

There was no significant relationship between low birth weight and the development of ROP in our study, which was controversial to the findings in many other studies [6,12,13]. Sepsis was found to have a significant role in the development of ROP in our study which was in agreement with Shah et al. [6] and Vinekar et al. [14], which could be due to the effect of endotoxins on retinal blood vessels.

Our study found oxygen therapy to have a significant relationship with the occurrence of ROP, which was similar to the results of several other studies [6,15,16]. Shah et al. and Ikeda et al. [6,16] reported that a duration of oxygen therapy more than 7 days was a significant risk factor for the development of ROP, which was contrary to the results of our study. Both mechanical ventilation and CPAP were non-significant risk factors for ROP according to our study. Frequent blood transfusions were found to be an independent risk factor for the development of ROP, and this finding was in agreement with results of a study by Deepak et al. [17]. This can be explained by the fact that adult red blood cells are rich in 2,3-DPG and adult hemoglobin binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue.

Gender, mode of delivery, RDS, PDA, IVH, hypotension, and phototherapy showed an insignificant relationship with the occurrence of ROP in our study. The significance of the association between risk factors such as low gestational age, sepsis, oxygen therapy, and frequent blood transfusions and the development of ROP was established in multivariate analysis after logistic regression analysis.

Laser photocoagulation is now the preferred mode since the most severe forms of the disease are more easily treated with laser than with cryotherapy [18]. Laser was found to be very effective in regressing ROP. All the 12 cases of Stage 3 ROP were treated with Laser and showed improvement with regression of ROP on follow-up and this was similar to the findings by Coats et al. [1]. The limitations of our study are that it is a retrospective study and we did not include many preterm neonates (>32 weeks).

CONCLUSION

We found a 19.2% prevalence of ROP, with low gestational age, sepsis, oxygen therapy, and frequent blood transfusions being the most significant independent risk factors in the development of ROP.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Lathiesh KK, Seeralar ATA, Kamalarathnam CN. Retinopathy of prematurity in a tertiary care center: A study of prevalence, risk factors, and outcomes. Indian J Child Health. 2017; 2017; 4(3):390-393.