Retinopathy of Prematurity: Incidence and Risk Factors

Research Article

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Abstract

Background: With improved neonatal care services across India, even the tiniest and sickest babies are surviving. However, they carry a high chance of developing retinopathy of prematurity (ROP). Therefore, pediatricians and ophthalmologists must be aware of the risk factors of ROP to detect and treat the disease at the earliest.
Aims: To study the incidence and risk factors that predispose to ROP.
Design: Observational study.
Methods: Preterm and low birth weight infants, born between the years 2012 and 2014, and admitted in the neonatal intensive care unit of Sri Aurobindo Medical College and PG Institute, Indore were screened for ROP. Neonates with gestational age ≤ 34 weeks and birth weight < 1500 grams were examined within 4 weeks of birth.
Results: The incidence of ROP was 23.4 % in 308 infants who were screened. Birth weight was significantly lower in infants with ROP than without ROP. Risk factors predisposing to ROP were septicemia (P=0.001), apnea (P<0.0001), oxygen therapy (P=0.003) and mechanical ventilation (P=0.004). However, only septicemia and apnea were found to be independent risk factors for development of ROP on multivariate analysis.
Conclusion: The incidence of ROP was 23.4 % and the risk factors predisposing to the disease were septicemia and apnea besides low birth weight and prematurity.

Keywords: Low-Birth Weight; Preterm; Blindness; Apnea; Septicemia.

Introduction

Retinopathy of prematurity (ROP) is a disease of premature and low-birth-weight infants. The immature incompletely vascularized retina of these babies develops abnormal blood vessels in the retina in response to ischemia. It is a heterogeneous disorder ranging from mild transient changes in the retina with visual deterioration to severe progressive scarring, detachment of retina and irreversible blindness [1]. If identified early, this ischemic retinopathy can be treated successfully.

Lesser the birth weight more the chances of ROP. Approximately 50% of neonates with birth weight less than 1000 grams develop some degree of ROP. Besides prematurity and low birth weight, various other factors are known to be associated with ROP such as administration of oxygen, ventilation support, sepsis, hypoglycemia, blood transfusions, and bronchopulmonary dysplasia [2,3]. With advances in neonatology and improved survival of low birth weight infants, the incidence of ROP has been increasing.

The aim of this study was to find out the incidence and risk factors of ROP in a tertiary care center of central India.

Materials and Methods

All premature neonates (≤34 weeks of gestational age) or babies with a birth weight of <1500 grams admitted to the neonatal intensive care unit (NICU) were screened for ROP between the years 2012-2014. The first screening was carried out at 4 weeks

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after birth or 31 to 33 weeks postmenstrual age (gestational age at birth plus postnatal age), whichever was later as suggested by National Neonatology Forum of India guidelines [4]. All the infants were screened by the same ophthalmologist. A prior informed and written consent of the parents was obtained.

Screening was also done for those neonates who had an unstable course with risk factors like ventilation, oxygen requirement, use of surfactant, septicemia, hyperbilirubinemia, congenital heart disease and apnea. A detailed history including birth weight, gestational age at birth, weight for gestation and, problems during NICU stay and its management were recorded.

The screening was done in the NICU in the presence of a pediatrician. Prior to screening the babies were fed in order to avoid hypoglycemia. The pupils were dilated using 0.50 % cyclopentolate and 2.5 % phenylephrine eye drop (Auropent plus) meant for premature babies. The eye drop was instilled 2 to 3 times at a gap of 10 to 15 minutes apart and excess of eye drop was wiped from the cheeks. The examination was done with a binocular indirect ophthalmoscope using 20 D and 28 D lenses (especially for poorly dilating pupils) and a pediatric scleral depressor. The eyelids were separated using a pediatric eye speculum after anesthetizing the ocular surface with 0.50 % proparacaine eye drop.

The stage or severity of the disease, as shown in Table 1, was recorded during the screening according to International Classification of Retinopathy of Prematurity (ICROP) [5].

The findings were recorded in the form of fundus drawings. The children who needed treatment were advised accordingly and those who required follow-up were given the dates for the next visit.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0. Univariate analysis was conducted using Chi square test. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables as those variables which were significant in the univariate analysis.

Results

Three hundred and eight infants were screened for ROP in the NICU from year 2012-2014. Their birth weight ranged from 640 to 2000 grams with a mean of 1300 ± 242 grams. The gestational age ranged from 22 - 37 weeks with a mean of 29.1 ± 2.2 weeks. There were 188 males and 120 females. ROP was observed in 72 (23.4 %) infants; out of which 41 (57 %) were males and 31 (43 %) were females. Mean days of hospitalization was 24.8 ± 12.9 days.

The overall incidence of ROP was 23.4 %. In 69 (96 %) infants, both eyes were affected and in 3 (4 %) infants, only one eye was affected (Table 2). The mean birth weight of patients with ROP and without ROP was 1029 ± 152 grams and 1380 ± 202 grams, respectively. The difference in mean birth weight between two groups was statistically significant (P< 0.0001).

The risk factors identified were oxygen therapy, ventilation, congenital heart disease, septicemia, apnea, hyperbilirubinemia, phototherapy, hyaline membrane disease (HMD), necrotizing enterocolitis (NEC) and pneumonia. A univariate analysis was done taking each risk factor for ROP. Out of the ten risk factors that were studied, septicemia (P=0.001), apnea (P <0.0001), oxygen therapy (P=0.003) and ventilation (P=0.004) were found to be significantly associated with ROP (Table 3). On multiple logistic regression analysis, only septicemia and apnea were found to be independent risk factors for the development of retinopathy of prematurity, as shown in Table 4.

Discussion

The incidence of ROP in India is reported to be between 38 and 51.9 % in low birth weight infants [6-8]. With improved survival rates of sick neonates the incidence of ROP in India has increased. The nasal retina is vascularized at birth in a normal term newborn while temporal retina gets vascularized by 39 to 41 weeks postnatally. During intrauterine life, the avascular retina produces vascular endothelial growth factor (VEGF) that helps in vasculogenesis of developing retina. In premature and preterm infant there occurs down regulation of VEFG due to hyperoxia. However, due to increased oxygen demand of fast developing eye, VEGF is up regulated which results in ROP within 4 to 5

Table 1: ICROP staging.

Stage 1 : Demarcation line **Stage 2 :** Demarcation ridge **Stage 3 :** Extraretinal fibrovascular proliferation **Stage 4 :** Partial retinal detachment – **4a** is without foveal involvement and **4b** is with foveal involvement **Stage 5 :** Total retinal detachment

Table 2: Frequency distribution of stages of ROP.

Staging of ROP	Right Eye [n (%)]	Left Eye [n (%)]
I	28 (40.5)	30 (41.6)
II	23 (33.3)	23 (31.9)
III	13 (18.8)	14 (19.4)
IV	4 (5.8)	4 (5.5)
V	1 (1.4)	1 (1.3)
Total	69	72

Table 3 . Univariate determinants of ROP.

Risk Factors	ROP (+ve) n=72 (23.4%)	ROP (-ve) n=236 (76.6%)	Univariate analysis		P value
			Odd's Ratio	95% CI	
Oxygen therapy	43 (59.72%)	92 (38.9%)	2.32	1.35- 3.97	0.003*
Sepsis	19 (26.38%)	25 (10.59%)	3.02	1.55- 5.90	0.001*
Hyperbilirubinemia	40 (55.55%)	120 (50.84%)	1.2	0.71- 2.05	0.571
HMD	15 (20.83%)	56 (23.72%)	0.84	0.44- 1.60	0.725
Phototherapy	21 (29.16%)	42 (17.79%)	1.9	1.03- 3.49	0.054
Ventilation	31 (43.05%)	58 (24.57%)	2.32	1.33- 4.03	0.004*
NEC	17 (23.61%)	37 (15.67%)	1.66	0.87- 3.17	0.169
Apnea	28 (38.88%)	26 (11.01%)	5.14	2.75- 9.60	<0.001*
CHD	7 (9.72%)	11 (4.66%)	2.2	0.82- 5.91	0.188
Pneumonia	13 (18.05%)	43 (18.22%)	0.98	0.49- 1.96	0.97

ROP-Retinopathy of prematurity; HMD- Hyaline membrane disease; NEC-Necrotizing enterocolitis;
CHD- Congenital Heart Disease; * = statistically significant

Table 4. Multivariate analysis of ROP risk factors those were significant in univariate analysis.

Risk factors	ROP (+ve) n=72 (23.4%)	ROP (-ve) n=236 (76.6%)	Multivariate analysis		P value
			Odd's Ratio	95% C I	
Apnea	28 (38.88%)	26 (11.01%)	4.56	8.87 – 1038.23	0.000*
Sepsis	19(26.38%)	25 (10.59%)	2.47	0.010 – 0.725	0.024*
Oxygen therapy	43 (59.72%)	92 (38.9%)	0.56	0.812 – 3.78	0.153
Ventilation	31 (43.05%)	58 (24.57%)	1.32	0.69 – 1.029	0.055

ROP=Retinopathy of Prematurity; * = statistically significant

weeks after birth.
Screening for ROP is mandatory in order to detect and diagnose infants with early treatable form of the disease [9]. The treated eyes show a better visual outcome than untreated eyes [10-12]. Different countries follow different ROP screening guidelines [13-18]. American Academy of Pediatrics recommended to screen all neonates with a birth weight <1500 grams or gestational age ≤28 weeks, as well as selected children between 1500 and 2000 grams with an unstable course who are believed to be at high risks by their attending pediatrician [13]. According to the Joint Working Party of the Royal College of Ophthalmologists and the British Association of Perinatal Medicine infants with a birth weight of ≤1500 grams or a gestational age of ≤31 weeks should be screened for ROP [18].

National Neonatology Forum of India has recommended the guidelines for ROP screening of Indian babies [4]. According to it, all preterm neonates who are <34 weeks of gestation and/ or <1750 grams birth weight should be screened for ROP. Tiny infants who are <28 weeks or <1200 grams birth weight should be screened early at 2 to 3 weeks of post menstrual age (gestational age at birth plus postnatal age in weeks) because they may develop an aggressive form of ROP (aggressive posterior ROP, AP-ROP) [15, 19]. AP-ROP is reported to be common in Indian babies which has a worse visual prognosis as compared to classical ROP [20, 21]. The cessation of screening is recommended on full retinal vascularization or regression of retinal signs of ROP.

We screened all neonates admitted in NICU with birth weight <1500 grams and gestation ≤34 weeks as recommended by many authors [22-25]. Infants with birth weight ≥1500 grams

and gestation more than 34 weeks were also screened when the treating neonatologist felt the requirement for it. Tiny and younger infants were screened at 2 to 3 weeks of birth. The incidence of ROP in our study was 23.7 %. It was same as reported in other studies [26-28]. In a recent study done on Indian population, Chatopadhayay et al [29] found 44 % incidence of ROP which was almost similar to that noted by Gopal et al (38 %) [7].

Prematurity and low birth weight are recognized as major risk factors for ROP [30-32]. The lower the gestational age or birth weight, the higher the risk of developing severe ROP. The third factor besides the two major risk factors also plays a role in the pathogenesis of the disease. This includes prolonged unmonitored oxygen therapy, anemia, double volume exchange, packed cell volume transfusion, septicemia, apnea and ventilation [14, 26, 33, 34]. Many studies have found erythrocyte transfusion to be an independent risk factor for ROP due to the presence of non-protein bound iron load in the plasma, a potent catalyst of oxidative injury [35-37]. In our study, children having septicemia, apnea, prolonged oxygen therapy and mechanical ventilation showed high frequency of ROP. However, only septicemia and apnea were found to be independent significant risk factors for the development of ROP. Similar to our finding, other authors have also reported septicemia and apnea to be the risk factors for ROP [14, 26, 29].

Conclusion

Screening for ROP aids in diagnosing the disease early and helps in preventing childhood blindness. A carefully timed retinal examination by an ophthalmologist, of at risk infants determined

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by pediatrician, becomes extremely important in ROP as the disease in its initial stages remains asymptomatic.

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