Retinopathy of Prematurity in Bundelkhand: A Risk Factor Analysis

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Original Research Article

ABSTRACT

Retinopathy of prematurity(ROP) is a vasoproliferative disorder of the retina. It may progress to stage of retinal detachment and blindness. The purpose of this study was to assess the incidence and to identify the risk factors for retinopathy of prematurity (ROP) in bundelkhand region. One Hundred preterm neonates were screened in a tertiary care centre. Proper history, clinical examination and fundus examination of all patients was done and findings were noted. Out of the 50 neonates included in this study, 8 (16%) cases developed ROP in one or both eyes which was further classified as: 5 (62.5%) cases stage 1, 2 (25%) cases stage 2, and 1 (12.5%) case stage 3 with plus disease. None of the studied neonates presented ROP at stages 4 or 5. The incidence of ROP in this study was 16%. On univariate analysis gestational age was an independent risk factor while birth weight and duration of oxygen therapy found to be a relative risk factors. All high risk infants should be screened for ROP.

KEY WORDS: birth weight, gestational age, retinopathy of prematurity (ROP), risk factors

INTRODUCTION:

Retinopathy of prematurity is a vasoproliferative disorder of retina which affects premature low birth weight infants. It is characterized by abnormal neovascular development in the retina of premature infants. These abnormal blood vessels are fragile and can leak or bleed. This causes a tractional retinal detachment, which is the main cause of visual impairment and blindness in ROP[1].

Studies from India reporting incidence of ROP provide interesting insights. Although screening criteria differ across different units and time periods, overall incidence of ROP varies from 20% to 52%. Recent studies have reported lower rates of ROP ranging from 20% to 30%[2,3]. Recent advances in neonatal care in the last decade has improved survival rate for premature infants[4]. Consequently, the incidence of ROP has increased in parallel. ROP is under constant epidemological study around the world[5]. An early identification of risk factors and institution of appropriate treatment prevents blindness and offers child a better development.

There are several risk factors which are considered important for the development of ROP but three factors have shown consistent and significant association with ROP: low gestational age, low birth weight and prolonged exposure to supplementary oxygen following delivery[6]. Others are mechanical ventilation,[7] sepsis,[8] intraventricular hemorrhage,[6] surfactant therapy,[9] anemia,[10] frequent blood transfusions,[10] and aponea[7]. The precise roles of these factors individually in the progression of the disease have not yet been determined[11].

Incidence of ROP has now increased with better screening protocols, availability of assisted ventilation services and survival of sicker, smaller neonates. Prematurity is the single most important risk factor responsible for retinopathy of prematurity. Incidence of ROP increases with decreasing gestation and birth weight. However, not all preterm neonates develop ROP. Nevertheless, a very preterm extremely low birth weight neonate can develop ROP even without exposure to oxygen or presence of these risk factors. In general more than 50% of preterm infants weighing less than 1250 g at birth show evidence of

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ROP and about 10% of the infants develop severe ROP.

However, retinal detachment occurs and leads to visual loss in only a few percent of infants with severe ROP, and in most cases, ROP regresses spontaneously. The most conspicuous question is why ROP in some premature infants progresses despite rigorous and timely intervention while in other cases with similar clinical characteristics it regresses. Evidence has suggested that African-American infants are less prone to severe outcome ROP than white infants and Alaskan natives develop threshold ROP earlier than non-natives. This racial variation suggests that genetic, socioeconomic, or dietary factors may be involved[30]. Poor early weight gain in postnatal period has been observed to be a risk factor for development of severe ROP[31,32].

Hence, the aim of this prospective study was to estimate the incidence and to identify risk factors of ROP in preterm infants at the Neonatal Intensive Care Unit (NICU) at our Hospital.

MATERIALS AND METHODS:

This prospective cohort study was conducted in Neonatal Intensive Care Unit (NICU) of Maharani Laxmi Bai Medical College, Jhansi & associated Hospital (a tertiary referral hospital) in cooperation between the Departments of Neonatology and Ophthalmology. All preterm infants admitted to the NICU from March 2015 to February 2016, with a gestational age of 32 weeks or less at birth and a birth weight of 1500 g or less who fulfilled our inclusion criteria were enrolled in this study. Infants whom 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. Also infants who were born between 32 and 34 weeks gestational age were screened if they had a course of instability (like sepsis, asphyxia or ventilation). Neonates who died before the first ophthalmological examination were excluded (n=24). Infants with congenital anomalies, chromosomal abnormalities and inborn errors of metabolism were excluded from the study (n=26). While 50 preterm neonates continued the study, all neonates included in this study were subjected to the detailed perinatal history, clinical examinations for weight, length and other systemic illness. Then local eye examination with detailed fundus examination under direct and indirect ophthalmoscope was done. The eyes were dilated with a combination of cyclopentolate 0.2% and phenylephrine 1% eye drops applied 1 hour before the examination. ROP was classified by location on the retina (zone 1-3), and severity (stage 1-5), according to the International Committee for Classification of ROP (Table 6).

Suspected pre and postnatal risk factors for ROP were identified in NICU conditions.

The prenatal variables were gestational age, birth weight, gender and mode of delivery. The after-birth variables were respiratory distress syndrome, oxygen therapy (through nasal catheter, mask, CPAP, or mechanical ventilation), phototherapy for jaundice, frequency of blood transfusions and sepsis (by clinical diagnosis, with either C-reactive protein greater than 6.0 mg/dl, or blood culture positive cases).

Data collected was analyzed by the Statistical Package for the Social Sciences (SPSS for windows, version 16.0). The incidence rate of ROP was described in simple proportion. Group comparisons were done by the chi-square ($\chi 2$) test. A logistic regression model was performed and the adjusted OR (95% CI) was obtained for the risk factors which had been shown to be significant in the univariate analysis. A probability (P) of less than 0.05 was considered significant.

RESULTS:

The study population included 50 neonates; all preterms with a gestational age of 32 weeks or less at birth (table 2) and a birth weight of 1500 g or less and preterm infants whom gestational age was >32 weeks or birth weight was >1500 g with unstable condition, admitted in NICU during the duration from march 2015 to febuary 2016 .

Out of the 50 neonates; 15 (30%) were females. The mean gestational age was 30.4±1.65 weeks; 35 were <32 weeks and 15 were >32 weeks. The gestational age was found to be significant risk factor with p value 0.043. More severe ROP was found in >32 weeks cases (table 2). The birth weight ranged from 900 to 1650 g with a mean of 1352 ± 175 g. 23 cases (46%) were delivered vaginally and 27 (54%) cases were delivered by Cesarean section (Table 1).

Out of the 50 neonates; 8 (16%) cases developed ROP in one or both eyes classified as: 5 (62.5%) cases stage 1, 2 (25%) cases stage 2, and 1 (12.5%) case stage 3 with plus disease. None of the studied neonates presented ROP at stages 4 or 5 (Table 2).

Gestational age (Table 2), duration of oxygen therapy and birth weight (Table 3) were found to be significant risk factors for the development of ROP.

Duration of oxygen therapy was found to be significant risk factor as p value 0.014 and birth weight

Table 1: Demographic data of studied cases.

Data	N (%) or Mean± SD
Male	35
Female	15
Vaginal delivery	23
Cesarean section	27
Gestational age (weeks)	30.4 ±1.65
Birth weight (g)	1352 ±175

Table 2: Relation between Stages of ROP & gestational age.

	≤32 weeks with ROP (n=3)	>32 weeks with ROP (n=5)	p-value
Stage 1 ROP (n=5)	2	3	
Stage 2 ROP (n=2)	1	1	
Stage 3 ROP with plus dzs (n=1)		1	0.043

Table 3: Relationship of oxygen therapy and ROP.

	ROP not present	ROP present	p-value
Oxygen Therapy not given (24)	23	1	-
Oxygen Therapy given (26)	19	7	
Oxygen therapy not given at all or Oxygen therapy given more than a week (36)	30	6	0.604
Oxygen therapy given for less than a week (14)	12	2	
Oxygen therapy not given at all or Oxygen therapy given for less than a week (38)	35	3	0.014
Oxygen therapy given for more than a week (12)	7	5	

Oxygen therapy if given for less than a week is non significant risk factor for development of ROP; (p = 0.604) but if given for more than a week it is a significant risk factor (p = 0.014).

was found to be significant risk factor as p value was 0.041. While RDS (respiratory distress syndrome), sepsis, phototherapy, mechanichal ventilation, CPAP (continuous positive airway pressure) and blood transfusion were found to be non significant risk factors (Table 4).

Table 4:Some other risk factors and their relation with ROP.

Risk Factors	Cases without ROP	Cases with ROP	p-value
RDS (n=17)	13	04	0.258
SEPSIS (n=30)	25	05	0.599
Phototherapy (n=45)	38	07	0.599
Mechanical Ventilation (n=5)	03	02	0.176
CPAP(n=8)	06	02	0.378
Blood Transfusion - ONCE(n=7)	05	02	0.310
>ONCE(n=6)	05	01	0.670

Table 5: Univariate Regression Analysis.

Risk Factors	OR
Gestational age	>1
Birth weight	<1
Duration of oxygen therapy	<1

*Gestational age is independent risk factor for ROP while birth weight and duration of oxygen therapy were related risk factors for ROP.

DISCUSSION:

Retinopathy of prematurity is a disorder of retinal vascular development in preterm infants. It continues to be a significant complication in preterm neonates despite advances in neonatal care and remains a major cause of childhood blindness worldwide.[9] The incidence of ROP in this study was 16% which was lower than previously reported by other studies; 24% in India,[12] 29.2% in Singapore,[7] and 32.4% in Pakistan.[13] This can be explained by the fact that these studies involved only very low birth weight infants.

In our study we found a significant relationship (p=0.043) with gestational age and development of ROP. This study is consistent with Shah VA, Yeo CL, Ling YL, Ho LY.(2005)[7] which

also found in his study that the median age of onset of ROP was 35 weeks (range, 31 to 40 weeks) postmenstrual age and Karna P, Muttineni J, Angell L, Karmaus W(2005)[9] which stated that increased survival of extremely low birth infants due to advances in antenatal and neonatal care has resulted in a population of infants at high risk of developing retinopathy of prematurity. However, Burton J. Kushner, MD; David Essner; Ira J. Cohen; John T. Flynn, MD(1977)[14] observed that variability of the level of maturation of the retinal vasculature only roughly correlated with gestational age.

In our study we found a significant realationship with birth weight and development of ROP (p =0.041). Our study was consistent with Shah VA, Yeo CL, Ling YL, Ho LY.(2005)[7]. Fortes Filho JB, Eckert GU, Procianoy L, Barros CK, Procianoy RS(2009)[15] as their study showed reduced survival rates, high incidence of ROP, and a greater need of treatment in low birth weight infants. Our study was in disagreement with Arrøe M, Peitersen B(1994),[16] as according to their study ROP was related significantly to early intubation, hypotension, persistent ductus arteriosus and necrotizing enterocolitis.

We found non significant relationship with sepsis and development of ROP (p=0.599) and this is in consistent with Smith LE (2002)[17] which stated that IGF-1 is critical to normal vascular development. Low IGF-1 predicts ROP and restoration of IGF-1 to normal levels may prevent ROP. ROP and sepsis was not significantly correlated. Our study differed from Shah VA, Yeo CL, Ling YL, Ho LY.(2005)[7] and Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A.(2007)[18] according to which risk factors for threshold or worse disease were, 'outborn babies' (P = 0.007) and exchange transfusion (P = 0.003).

Our study observed non significant relationship with oxygen therapy and development of ROP (p=0.123) and this was in agreement with Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG, Krom CP, Tung B. Cryotherapy for Retinopathy of Prematurity Cooperative Group(2005)[19] which reported that oxygen therapy was a non significant factor for occurrence of ROP. They reported that ROP may develop in cases that did not receive oxygen therapy. Shah VA, Yeo CL, Ling YL, Ho LY.(2005),[7] Babu K, Murthy KR (2006)[20] observed that oxygen induces aberrant physiologic responses that can be damaging in premature infants. For example, vasoconstriction in the retina is an early response to oxygen that can lead to vaso-obliteration, neovascularization, and retinal traction (retinopathy of prematurity).

The duration of oxygen therapy more than 7 days was a significant risk factor for development of ROP(p=0.014) in the present study which was in agreement with Shah VA, Yeo CL, Ling YL, Ho LY.(2005)[7] and Ikeda H, Kuriyama S.(2004)[21] while it was different from observations of Dutta S, Narang S, Narang A, Dogra M, Gupta A(2004)[22] who demonstrated that administration of blood products increases the risk of developing Threshold-ROP among patients who have ROP.

We found that mechanical ventilation (p=0.176) and CPAP (p=0.378) were non significant risk factors for ROP and this agreed with Murthy et al.[20] However it is contradictory with Shah VA, Yeo CL, Ling YL, Ho LY.(2005)[7] who found that risk factors predisposing to ROP were septicemia (P<0.001), aponea (p=0.0001) and oxygen therapy (P=0.031). The frequency of blood transfusion is not significant risk factor for development of ROP (p=0.670) herein which was similar to study done by Hirano et al.(2001),[23] who stated that it is controversial and iron overload rather than number of transfusions may contribute to the development of ROP. But it was in disagreement with Chawla et al (2012).[24] This was explained by the fact that, adult RBCs are rich in 2,3 DPG and adult hemoglobin which binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue.

Our study revealed non significant relationship between sex and occurrence of ROP (P=0.451), in contrast to Darlow et al[25] who found that male gender was also a significant risk factor (odds ratio: 1.73; 95% confidence interval: 1.25-2.40). Seiberth and Lindarkomp, (2000)[26] found non significant relationship between the mode of delivery and occurrence of ROP (p=0.552) similar to our study, whereas Shah et al[7] observed that cesarean section delivery was significantly associated with occurrence of ROP.

Other risk factors including respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, hypotension, and phototherapy showed non significant relationship with the occurrence of ROP. Similarly Taqui et al.(2008)[13] reported non significant relation between ROP and patent ductus arteriosus and intraventricular hemorrhage, but observed a significant relation between respiratory distress syndrome and the development of ROP and related this to the fact that systemic hypoxia results in retinal hypoxia and more

Table 6: classification of ROP[33]

Location	Zone I	Circle with optic nerve at centre and a radius of twice the distance from optic nerve to macula
	Zone II	From edge of Zone I to the nasal oral serrata nasally and equator temporally
	Zone III	Lateral most crescent shaped area from Zone II to ora-serrata temporally
Severity	Stage 1	Presence of thin white demarcation line separating the vascular from avascular retina
	Stage 2	The line becomes prominent because of lifting of retina to form a ridge having height and width
	Stage 3	Presence of extra retinal fibro-vascular proliferation with abnormal vessels and fibrous tissue arising from ridge and extending into vitreous
	Stage 4	Partial retinal detachment; not involving macula (4A) or involving macula (4B)
	Stage 5	Complete retinal detachment
Pulse disease		Presence of dilatation and tortousity of posterior retinal vessels. Associated with vitreous haze, papillary rigidity
Extent		Extent of involvement of the retina as expressed as clock hours (30 degree sectors)
Pre-plus disease		Vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal .

need for oxygen therapy. On the other hand, Shah et al.(2005)[7] reported a significant relation between ROP development and patent ductus arteriosus, intraventricular hemorrhage and hypotension. Chaudhari et al (2009)[2] observed non significant effect of phototherapy on ROP.

Logistic regression analysis, confirmed that low gestational age was found to be independent risk factor while low birth weight and duration of oxygen therapy were related risk factors for development of ROP (Table 5).

CONCLUSION:

The incidence of ROP in this study was 16%, most having >1500 gm birth weight. Our these receiving oxygen therapy more than one week. It is inferred that low gestational age, low birth weight, and duration of oxygen therapy are significant risk factors in the development of ROP. Hence, clinicians should be aware of the presence of the additional risk factors when monitoring preterm infants. The analysis of herein identified risk factors for ROP development will help to understand and predict it in preterm infants. The timely retinal screening of high-risk preterm infants is important to prevent the development of advanced ROP. Since ROP may produce serious sequelae up to complete blindness, all efforts must be made to prevent the development of advanced ROP by minimizing preterm births, improving neonatal care and improvement ROP markers.

A collaborative effort involving neonatologists, ophthalmologists, and the nursing staff has contributed greatly to reduce the incidence of ROP.

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