Original Article

Perinatal Risk Factors for Retinopathy of Prematurity in Preterm and Low Birth Weight Neonates

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Abstract

Background: Retinopathy of prematurity (ROP) is emerging as a leading cause of childhood blindness. The incidence of ROP is likely to increase after improvement in neonatal care unit in premature neonates. This study is conducted to determine the perinatal risk factors for ROP in preterm and low birth weight neonates.

Methods: This is a prospective, descriptive and clinical; hospital based study. A total of 92 preterm neonates with gestational age of 36 weeks or less and birth weight of 2000 grams or less admitted in Neonatal Intensive Care Unit (NICU) were screened. Detailed antenatal, perinatal and neonatal history; birth asphyxia and subsequent oxygen support records were noted. All the neonates underwent detailed anterior and posterior segment eye examination with indirect binocular ophthalmoscope after pupil dilatation within 4 weeks of life. Retinal vascular changes were classified according to the International Classification of Retinopathy of Prematurity. The Chi-square test with odds ratio was performed to derive the association between ROP and antenatal, perinatal and neonatal factors. A p-value was considered significant at 0.05.

Result: Out of 92 neonates, 21(22.8%) developed ROP. Twelve neonates (13%) had stage-1 ROP, 6(6.5%) had stage-2 and 3(3.3%) had stage-3 ROP. Birth weight (OR=2.9; p=0.04; 95% CI=1.0-8.3), gestational age (OR=3.9; p=0.01; 95% CI=1.3-11.8) and time span of oxygen exposure (OR=2.9; p=0.05; 95% CI=1.0-8.4) had a strong association with ROP.

Conclusion: The incidence of ROP is significantly high among preterm low birth weight neonates. The risk of developing ROP becomes even greater with lower gestational age and more duration of oxygen exposure.

Key words: Birth weight, Gestational age, Neonates, Preterm, Retinopathy of prematurity.

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative developmental abnormality of the retina of premature neonates (Wheatley CM et al, 2002). The spectrum of outcome findings in ROP extends from the most

minimal sequelae without affecting vision in the mild cases to bilateral, irreversible, and total blindness in more advanced cases (Flynn JT et al, 1987). It occurs in two overlapping phases: an acute phase in which vasculogenesis is interrupted and a response to injury is observable in the retina and a chronic or late proliferation of membranes into the vitreous (Foos R, 1985). ROP is a leading cause of childhood blindness (Steinkuller PG et al, 1993) and accounts for up to 10% of childhood blindness in developed countries (Fleck BW et al, 1994). However, ROP is emerging as an important cause of blindness in children even in middle-income countries as those in Asia, Latin America, and Eastern Europe (Gilbert C et al, 1997). ROP afflicts over 300,000 neonates worldwide (Wheatley CM et al, 2002, International Committee 1984 and Retinopathy of prematurity, 2006). The incidence of ROP is likely to increase after improvement in neonatal care unit in premature neonates (Shrestha JB et al, 2010). In a study done by Shrestha et al (2010), ROP was reported in 29.5% neonates. However, only three neonates (3.8%) with a gestational age of less than 32 weeks and birth weight less than 1500 grams showed threshold disease requiring laser treatment as per early treatment of ROP criteria (Shrestha JB et al, 2010). Previously high concentration of oxygen therapy was the major contributory factor in the development of ROP (Saugstad OD et al, 2001). However, a report has found ROP in cases without oxygen therapy (Lucey JF et al, 1984). Even after oxygen therapy, not all premature neonates develop ROP (Palmer EA et al, 1991). These studies suggest that factors other than oxygen play an important role in the development of ROP. In our context, there are few literatures that support oxygen to be the primary risk factor for ROP.

The increased survival rate of smaller and sicker neonates has resulted in an increased proportion of neonates needing retinal surgery (Globe RR et al, 1997). So, the present study has been conducted to determine the perinatal risk factors for retinopathy of prematurity in preterm and low birth weight neonates.

Methods

Subjects and sample size: This is a prospective, descriptive and clinical; hospital based study. A total of 92 preterm neonates with gestational age of 36 weeks or less and birth weight of 2000 grams or less admitted in Neonatal Intensive Care Unit (NICU) from January 1, 2012 to June 31, 2014 were included. Informed consent was received from parents of the neonates.

Assessment: Detailed antenatal history, perinatal history including multiple births and mode of delivery, neonate's birth history, resuscitation at birth, age of gestation, gender and birth weight in grams were recorded. Gestational age was calculated by Modified Ballard's Technique (Ballard JL et al, 1991). The concentration as well as duration of oxygen supply from birth to weaning was recorded. Oxygen concentration was measured by reading fractional index of oxygen (FiO2) from the display of the ventilator machine whereas in those neonates getting oxygen supply by a head box or a mask, it was measured by pulse oxymetry. In children kept in mechanical ventilation, arterial blood gas values and acid base level reports were also recorded. All the neonates underwent detailed eye examination within 4 weeks of life (Shrestha JB et al, 2010). Clinical examination of the anterior segment was performed using a portable slit lamp biomicroscope (Haag Streit, BA 904, USA) to detect other anterior segment anomalies.

Pupillary dilatation was carried out using a combination of tropicamide 1% and phenylephrine 2.5% drops by instilling two drops at an interval of 15 minutes in both eyes. Posterior segment examination was scheduled one hour after the instillation of the first drop. Infant wire eye speculum was

used for eyelid retraction. Fundus evaluation was performed by using a binocular indirect ophthalmoscope (Heine Sigma 250) along with +20D aspheric lens (Volk, USA). A scleral depressor was used for indentation to view the peripheral retina. Repeated fundus evaluation was also performed when it was indicated. Retinal vascular changes were classified and recorded according to the stage of ROP using the International Classification of Retinopathy of Prematurity (ICROP) (The International Classification of Retinopathy of Prematurity Revisited, 2005).

Data Analysis: Data was entered in a computer database for statistical analysis. The Statistical Package for the Social Sciences version 22 (SPSS, Inc., Chicago, IL) and Microsoft Excel (Microsoft Corporation, Redmond, WA) software were used for this purpose. Descriptive data was presented in frequency and percentage. The association between Retinopathy of Prematurity (ROP) with birth weight, age of gestation, oxygen saturation concentration, duration of oxygen supply, neonatal factors and sex distribution was presented by Chi- square test with odds ratio for 95% confidence interval (95% CI) having p-value significant at 0.05.

Results

Among 92 neonates, all the neonates comprised of gestation age between 29 weeks to 36 weeks and birth weight ≤ 2000 gms (Table 1).

Regarding gravida, 50 (54.3%) mothers was primigravida and 42 (45.7%) were multigravida. Among these, 50 (54.3%) mothers delivered neonates through Lower Segment Caesarean Section (LSCS), 40 (43.5%) mothers had normal vaginal delivery (NVD) at hospital and two (2.2%) mothers had normal vaginal delivery at home. Twenty nine (31.5%) neonates were resuscitated with oxygen support at birth. Majority of neonates (75%) were kept in oxygen support for less than fourteen days.

Fifty three mothers (57.6%) had uneventful antenatal conditions. The most common antenatal conditions were premature rupture of membrane (PROM) in 27 mothers (50.9%) followed by oligohydramnios in 12 mothers (22.6%) and pregnancy induced hypertension (PIH) in 10 mothers (18.9%).

Systemic diagnosis was present in 77 neonates (83.7%). Majority of neonates (71.4%) were admitted for Respiratory Distress Syndrome (RDS), followed by neonatal sepsis (61.0%) and neonatal jaundice (40.3**).**

Birth weight, age of gestation and duration of oxygen support presented a strong association with ROP. The birth weight ≤ 1500gms had relative risk of developing ROP by factor 2.9 (p=0.04; CI=1.0-8.3); similarly, age of gestation below 32 weeks had odds ratio of 3.9 (p=0.01; CI=1.3-11.8) and duration of oxygen support greater than or equal to 14 days had odds ratio of 2.9 (p=0.05; CI=1.0).

Table 1: Characteristics of Preterm and Low Birth Weight infants (gestational age of ≤ 36 weeks and birth weight of ≤ 2000gm)

Characteristics		**No (%)**
Sex	Male	52 (56.5)
	Female	40 (43.5)
Gestation age in weeks	29-32	48 (52.2)
	33-36	44 (47.8)
Birth weight in grams	≤1000	3 (3.3)
	1001-1500	45 (48.9)
	1501-2000	44 (47.8)

Birth asphyxia and resuscitation at	No	63 (68.5)
birth with oxygen support	Yes	29 (31.5)
Duration of supplemental oxygen in days	<14	69 (75.0)
	14- 28	18 (19.5)
	>28	2 (2.2)
	None	3 (3.3)

Table 2: Antenatal conditions in preterm and low birth weight babies

Antenatal risk factors	**Frequency**	**Percent**
PROM	27	29.34
Oligohydramnios	12	13.0
PIH	10	10.86
ABO setting	4	4.34
APH	4	4.34
Twin	2	2.17
Eclampsia	2	2.17
Pre-eclampsia	3	3.26
GDM	2	2.17
Rh negative	1	1.08

Table 3: Systemic diagnosis of babies admitted in NICU

Systemic diagnosis of babies	**Frequency**	**Percent**
RDS	55	59.7
Neonatal sepsis	47	51.08
Neonatal jaundice	31	33.69
IUGR	3	3.26
NEC	4	4.34
Hypoglycemia	1	1.08
PDA	2	2.17
ASD	2	2.17
Meningitis	3	3.26
Septic shock	5	5.43
Pneumonia	2	2.17
None	15	16.3
Total	**170**	**184.65**

Table 4: Association of Retinopathy of prematurity with birth weight, age of gestation, oxygen saturation concentration, duration of oxygen supply, neonatal factors and sex distribution

Conditions		**Retinopathy of prematurity**		**p-value**	**OR (95% CI)**
		Yes	**No**		
		No (%)	**No (%)**		
Birth weight in grams	≤1500	15 (31.3)	33 (68.7)	0.04	2.9 (1.0-8.3)
	≥1500	6 (13.6)	38 (86.4)		

Age of gestation in weeks	29-32	16 (33.3)	32 (66.7)	0.01	3.9 (1.3-11.8)
	33-36	5 (11.4)	39 (88.6)		
Oxygen saturation concentration (n=89)	High (98-100%)	19 (28.4)	48 (81.6)	0.06	3.9 (0.8-18.6)
	Low (90-96%)	2 (9.1)	20 (90.9)		
Duration of Oxygen Support in days (n=89)	≥14	8 (40.0)	12 (60.0)	0.05	2.9 (1.0-8.4)
	<14	13 (18.8)	56 (81.2)		

Discussion

A total of 92 preterm neonates of gestational age ≤ 36 weeks and birth weight ≤ 2000gms admitted to Neonatal Intensive Care Unit were included in the study. In this study, incidence of ROP is 22.8% (n=21) which is slightly lesser than the study done by Shrestha JB et al (2010) 29.5% (n=23). Hussain et al (1999) reported ROP in 21.3% infants in the multicenter retrospective study, which is comparable to our study. Adhikari S et al (2008) has reported 25.55% develop ROP in neonates with gestational age of 34 weeks or less and, or birth weight of 1700 gm or less in another study from eastern region of Nepal (Adhikari S et al, 2008). Regarding the eye examination time, we performed the initial eye examination within four weeks of life as in the Shrestha at al study in order to take a caution that no neonate babies would miss the eye examination before they were discharged or shifted from NICU to other departments as the awareness level of ROP screening in our country has been observed very low. In our study preterm neonates with gestational age ≤ 36 weeks and birth weight ≤ 2000 gms were enrolled.

Similarly in a study done by Jalali S et al (2003) have recommended screening babies born at ≤ 37 weeks and /or birth weight 2000 gms. In the present study, ROP developed in 76.2% among neonates in the gestational age of 29 to 32 weeks compared to neonates in the gestational age of 33-36 weeks (23.8%). This difference might be due to the racial variation and in the management (such as duration of NICU stay, oxygen and other treatment) protocol applied by the neonatal unit of population studied. However, The Cryo-ROP multicenter study reported no ROP in infants born at more than 32 weeks, and no severe ROP in infants at more than 28 weeks of gestational age (Palmer EA et al, 1990). In a study by Shrestha et al, (2010), thirteen infants (56.6%) had stage-1 ROP and 5 each (21.7%) were found to have stage-2 and stage-3 ROP (Shrestha JB et al 2010). Out of 21 neonates, we found stage-1 ROP in 12 neonates (57.1%) followed by stage-2 ROP in six (28.6%) and stage-3 ROP in three neonates (14.3%) respectively. Among the three cases that had stage-3 ROP, one had stage 3 with pre-threshold ROP and another had stage-3 with threshold plus disease. Advanced ROP stages (4 and 5) were not seen. In one study it was found; Stage-1 ROP in 37.1% neonates, stage-2 in 42.85%, stage-3 in 21.42% (Adhikari S et al, 2008). Literature also suggests the incidence of ROP increase with decreasing birth weight and gestational age (Shrestha JB et al, 2010; Adhikari S et al, 2008). In our study the findings regarding association between duration of oxygen supply and development of ROP were similar to the study done by Murthy et al (2006). However, Flynn et al, (1987) study reported ROP correlated with the birth weight of the infants and did not correlate with the duration of oxygen supply among infants weighing less than or equal to 1300gms. In our study, 19 (29.2%) neonates had ROP who received high (98-100%) Sp02, and 2 (8.3%) neonates had ROP who were in the low (90-96%) Sp02. The relation between oxygen saturation concentration (Sp02) and development of ROP is statistically insignificant. Wallace et al also

supported our findings the relation between oxygen saturation concentration (Sp02) and development of ROP was not significant (Wallace DK et al, 2007). In the early 1950's with the role of oxygen in the development of ROP becoming apparent there was a dramatic decline. ROP has also been reported in premature infants that have not received oxygen and babies with cyanotic heart disease (Flynn JT et al 1979). It was also reported that there was no reduction in the incidence of ROP in spite of continuous oxygen monitoring (range 50-70mm of Hg) suggesting that other factors might also play a role in the development of ROP (Flynn JT et al 1987). Regarding neonatal factors such as the cases of respiratory distress syndrome, neonatal sepsis, premature rupture of membrane and other systemic diseases, there was no significant association with ROP. Bassiouny et al (1996) reported that trans-parenteral nutrition, intra-ventricular hemorrhage, sepsis, lower birth weight, gestational age, apnea, blood transfusion, mechanical ventilation and metabolic acidosis were associated with development of ROP. Taqui AM et al (2008) reported that low gestational age, sepsis and respiratory distress syndrome were independent predictors for the development of ROP. Murthy KR et al (2006) reported that sepsis, low birth weight, mechanical ventilation, twin pregnancies and maternal risk factors had no influence on the incidence of ROP. In the Abrahamson Pediatric Eye Institute, Cincinnati, Ohio study, the CRIB score was a predictor of neonatal mortality rate but race and gender did not prognosticate the CRIB (Clinical Risk Index for babies) score or neonatal mortality rate (Yang MB et al, 2006). The CRIB score estimates illness severity using data collected in the first 12 hours after birth (Mcleod DS et al, 1996). The CRIB score is highly predictive of in-hospital mortality for premature infants and has also been useful in predicting certain neonatal morbidities (Eriksson M et al, 2002). The study on CRIB score has shown whether illness severity is a predictive factor for threshold or severe pre-threshold ROP warranting surgery (Yang MB et al, 2006). The finding of risks factors including race, gender and CRIB were similar to a study done by Yang MB et al (2006).

Conclusion

It is recommended that preterm neonates weighing ≤ 2000 gms and gestational age of ≤ 36 weeks should be screened at 4- 6 weeks postnatally for early detection and treatment to prevent irreversible and total blindness.

Limitations: Association between maternal risk factors like twin pregnancy, eclampsia, preeclampsia, oligohydramnios and antepartum haemorrhage with ROP could not be established owing to the small sample size.

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