Original Article

Determinants of retinopathy of prematurity: A prospective observational study from Tertiary Care Teaching Hospital from North India

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Abstract

Objective: This prospective observational study was designed to evaluate the point prevalence as well as various risk factors associated with retinopathy of prematurity (ROP) in preterm/low birth weight (LBW) babies <32 weeks of gestation and or birth weight ≤1500 g on both inborn and outborn babies. **Materials and Methods:** Binocular opthalmological examination was performed 4-6 weeks postnataly under local eye anesthesia in 200 newborns who qualified the above criteria. If ROP was detected, the 2nd evaluation was done after 1 week, 3rd evaluation after 2 weeks and 4th after 4 weeks. The examination was carried out by the same ophthalmologist. **Results:** 25 (12.5%) out of 200 babies developed ROP. 23 were in Stage 1 and 2 in Stage 2 at first evaluation. All showed regression, i.e., they had completed temporal vascularization on repeat follow-up evaluations. No baby showed progression to threshold stage at any time of follow-up examinations. On multiple logistic regression analysis, factors having significant association with development of ROP were birth weight (p = 0.0028), oxygen therapy (p = 0.0059), septicemia (p = 0.0062), and blood transfusion (p = 0.0013). **Conclusion:** In our study, point prevalence of ROP was 12.5 % (25/200) which is substantially high among preterm/LBW babies. Thus, evaluation for ROP should be done mandatorily in all preterm/LBW babies, particularly with gestation <32 weeks and or weight ≤1500 g and when risk factors are present, so as to prevent the long-term morbidity which ranges from mild myopia to blindness.

Key words: *Retinopathy, Prematurity, Low birth weight*

Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative retinal disorder that increases in the incidence with decreasing gestational age/birth weight and duration of ventilation [1-3]. ROP is the main cause of visual impairment in premature infants [4]. Advances in neonatology and improvements in the quality care have resulted in increasing number of premature and extremely low birth weight (ELBW) babies surviving the neonatal period leading to an increase in the population at risk for developing ROP [5,6]. 90% of infants with birth weight <750 g and 47% between 1000 and 1250 g develop ROP. Approximately, 80% of infants born at <28 weeks versus 30% born after 28 weeks are at risk for developing ROP [7].

Other factors implicated in the pathogenesis include vitamin E deficiency, multiple red blood transfusions, intra-ventricular hemorrhage, bronchopulmonary dysplasia, oxygen exposure, fluctuations in blood gas tensions, and sepsis [3]. In the majority of the infants, ROP is a mild disease and undergoes spontaneous regression with no significant visual sequelae. However, in a significant number of cases progression to advanced ROP occurs resulting in severe visual impairment. Long-term morbidity of ROP has a spectrum ranging from mild myopia to blindness. It therefore, continues to be important cause of childhood blindness [2].

Ours is a tertiary care teaching hospital, where many high-risk deliveries are conducted every day of which a large number are pre-terms/LBW babies and almost equal number of out born preterm/LBW babies are admitted daily being a referral hospital. Due to advances made in the neonatal care at our center (level III neonatal intensive care unit [NICU] without ventilators) and better survival in our center, there may be increasing number of preterm/LBW babies who are at risk of developing ROP. Previously no such study had been done in our hospital/state, thus this study was designed to evaluate incidence as well as various risk factors associated with ROP in preterm infant ≤1500 g and or <32 weeks of gestation.

MATERIALS AND METHODS

The present prospective observational study was conducted in the Postgraduate Department of Pediatrics and Ophthalmology of a Tertiary Care Teaching Hospital from north India over a period of 1 year from September 2008 to August 2009. Institutional Ethics Committee approval was obtained before starting the study. Preterm/LBW babies who were admitted in NICU, both inborn and outborn babies were recruited in the study after taking written consent from the parents.

All preterm/LBW with gestational age <32 weeks and/or birth weight ≤1500 g were included in the study. Gestational age was calculated according to new Ballard scoring system [8], last menstrual period, and antenatal ultrasonography. Investigations like sepsis screen, arterial blood gas analysis, echocardiography or any other investigations were done as and when required.

Following definitions were used for the study purposes [9].

Preterm baby: Baby with gestation of <37 completed weeks.

LBW baby: Baby with birth weight <2500 g (up to and including 2499 g), irrespective of the period of gestation.

Very LBW baby: Baby with weight <1500 g (up to and including 1499 g).

ELBW: Baby with birth weight <1000 g (up to and including 999 g).

Hypothermia: Hypothermia in a newborn baby was defined as skin temperature of 35.5°C or less or core temperature of 36.0°C or less.

Fever: Fever was defined as core temperature of 38.0°C or more or skin temperature 37.5°C or more.

Sepsis: Sepsis was diagnosed clinically and supported by changes in leukocyte count (leukocyte count >20000/mm^3 or <5000/mm^3 or absolute neutropenia <1000/mm^3), the band cell count of >20% and band count to total neutrophil ratio of ≥0.2, C-reactive protein >8 mcg/ml and/or positive blood culture.

Birth asphyxia: Birth asphyxia was defined as gasping or no breathing at 1 min or Apgar score <4 at 1-min.

All the recruited babies were subjected to indirect binocular opthalmological examination between 4 and 6 weeks of postnatal age as recommended by the American Academy of Opthalmology for detection of retinopathy [10]. Pupillary dilatation was achieved by instillation of eyes drops containing tropicamide 0.5 % and phenylephrine 2% one drop every 10 min for 3 times 1 h prior to the examination. The examination was done under local anesthetic drops put into the eyes and using eyelid speculum after restraining the baby in the mother's lap.

If no ROP was detected in the initial examination, the infants were re-evaluated once every 2 weeks until they were discharged from the hospital. There after they were examined every 4 weeks until vascularization was complete. If ROP was detected, the 2nd re-evaluation was done after 1 week, 3nd after 2 weeks and 4th after 4 weeks for stage 1 and 2 and more frequently for stage 3 disease, till the disease started resolving or showed progression to the threshold stage. Babies showing evidence of regression were followed weekly till vascularization was complete. Because the procedure could be stressful, the babies examined were clinically stable at the time of examination. Parents were informed about the diagnosis when it was first made and given subsequent date with follow-up examination. All ophthalmological examinations were performed by the same ophthalmologist with no prior knowledge of the patient's medical history. Staging of ROP was done according to the International Classification of ROP [3,11,12].

Statistical Analysis

The data were analyzed with the help of SPSS Statistics for Windows, Version 12.0 (SPSS Inc., Chicago, USA). Qualitative variables reported as percentages, mean and standard deviation. Univariate analysis was conducted to assess the relationship of various variable with the outcome i.e., ROP. Chi-square test/ Chi-square for time trend was applied to develop statistical significance. The strength of association was reported as odd's ratio (OR) with its 95% confidence interval (CI). Multivariate analysis was implied to assess the independent effect of each variable in the development of ROP. The value of <0.05 was considered as statistically significant.

RESULTS

During the study period, 200 preterm/LBW babies with gestational age <32 weeks and/or birth weight of ≤1500 g were screened for development of ROP. 75% (3/4), 70% (14/20), and 3.4% (8/176) of newborn with birth weight up to 1000 g, 1001-1250 g and 1251-1500 g developed ROP, respectively. The overall risk of development of ROP in neonates with birth weight up to 1000 g was observed to be 63 (OR) with 95% CI of 4.86-1779 and in newborn with weight between 1001 and 1250 g, the overall risk was 49 with 95% CI (13.09-196.84). The observation was statistically highly significant ($p < 0.00001$). Same was the relationship of gestational age with ROP as of birth weight (Table 1). As regards sex the risk of development of ROP in male neonate was observed to be 1.50 (OR) with 95% CI (0.58-3.90). However, this observation is not statistically significant ($p < 0.48$).

Of 56 newborns who received oxygen therapy, 30.3% (17/56) developed ROP as compared to 4.8% (8/144) of newborn who did not. The oxygen therapy was given from centralized oxygen source, through headbox for duration from 1 h to 50 h (mean 6 h) at an ambient concentration raised to 40% or more depending upon the need. The aim was either relief of cyanosis or maintenance of arterial po2 between 50 and 80 mm Hg. No baby was put on continuous positive airway pressure or ventilator. The overall risk of development of ROP in newborn receiving oxygen therapy was 7.41 (OR) with 95% CI (2.75-20.44). This observation was statistically highly significant ($p < 0.000$).

Table 1: Relation of weight and gestational age with ROP

Weight (g)/gestational age (weeks)	No. (%)		Crude OR	(95% CI)
	ROP (*n*=25)	No ROP (*n*=175)		
Up to 1000/28 (*n*=4)	3 (75)	1 (25)	63	4.86-1779
1001-1250/29-30 (*n*=20)	14 (70)	6 (30)	49	13.09-196.84
1251-1500/31-32 (*n*=176)	8 (3.4)	168 (97.7)	(reference)	

χ^2 for time trend=77.2, p<0.0000, OR: Odd's ratio, CI: Confidence interval, ROP: Retinopathy of prematurity

The overall risk of ROP in babies having anemia was 12.96 (OR) with 95% CI (4.22-40.62) and 52.3% (11/21) of babies with anemia developed ROP against 7.8% (14/179) without anemia ($p < 0.0001$). Similarly, 52.3% (11/21) of babies who received blood transfusion developed ROP as compared to 7.8% (14/179) of babies who did not (OR: 12.96, 95% CI: 4.22-40.62).

About 45% (9/20) of babies who received phototherapy developed ROP as compared to 8.8% (1/180) of babies who did not receive phototherapy. The overall risk of ROP in these babies was 8.39 (OR) with 95% CI 2.70-26.18, ($p < 0.0000$). Similar trend in babies receiving exchange transfusion and 53.8% (7/13) of babies who underwent exchange transfusion developed ROP compared to 9.6% (18/187) who did not (OR: 10.95, 95% CI: 2.90-42.31, $p < 0.0000$).

Blood culture was positive in 30 babies out of 50 babies with sepsis. The overall risk of development of ROP in babies who had septicemia was 11.49 (OR) with 95% CI of 4.09-33.44. 36% (18/50) of babies who had septicemia developed ROP as compared to 4.6% babies (7/150) without septicemia ($p < 0.0000$). 31.3% (14/43) of babies with birth asphyxia developed ROP as compared to 7% (11/157) of non-asphyxiated babies (OR: 6.41, 95% CI: 2.44 -17.02, $p < 0.0002$). The overall risk of ROP in babies with congenital heart disease was 24.05 (OR) (95% CI: 5.85-106.83, $p < 0.0000$). As regards the relation of mode of delivery, the overall risk of ROP in newborns delivered per vaginally was 1.20 (OR) (95% CI: 1.45-3.09, $p < 0.68$). The risk of ROP in hospital born preterm versus home born was 1.48 (OR) with 95% CI: 1.59-3.78 ($p < 0.36$).

On multiple logistic regression analysis, factors having statistically significant association with development of ROP were birth weight ($p = 0.0028$), oxygen therapy ($p = 0.0059$), septicemia ($p = 0.0062$), and blood transfusion ($p = 0.0013$) as shown in Table 2.

Of 200 babies, 25 (12.5%) developed ROP and out of these 25 babies, 23 (92%) were in Stage 1 and 2 (8%) were in stage 2. After 2nd evaluation after 1 week, 16 (64%) were in Stage 1 and 2 (8%) were still in Stage 2, while in 3rd evaluation after 2 weeks only 9 (36%) were in Stage 1 and none of them was in Stage 2. After 4th evaluation done after 4 weeks, all the babies showed spontaneous resolution and none of the baby was in any stage of ROP (Table 3). No baby showed progression to threshold stage at any time of follow-up examination and all had completed temporal vascularization.

DISCUSSION

The point prevalence of ROP was 12.5% in this study. Various studies have reported higher incidence of ROP varying from 18% to 32.4% as shown in Table 4. The low incidence of ROP in the present study could p ossibly be due to non-availability of ventilatory support as not much of preterm/very ELBW babies survived till 4-6 weeks of post-conceptional age when first ROP examination was done. Previous studies have shown the association of duration of ventilation with increasing incidence of ROP besides decreasing gestational age/LBW [1,3]. In our study, birth weight, oxygen therapy, septicemia, and blood transfusion were the independent factors found to be associated with the development of ROP.

LBW and prematurity have been well-documented to be associated with the development of ROP in many studies [12-15]. In this study, birth weight of 1000 g and between 1001-1500 g had a significant association with risk of development of ROP (OR: 63; 95% CI: 4.86-17.79 and OR: 49; 95% CI: 13.09-196.84, respectively). These observations are comparable with the observations of Hussain et al. [6] and Bonotto et al. [16], who also observed significantly high risk of development of ROP in LBW babies. Similar are our observations, as regards gestational age and babies with gestational age of up to 28 weeks and those between 29 and 30 weeks had a higher chances of development of ROP (OR 63; 95% CI 4.86-17.79 and OR 49; 95% CI 13.09-196.84 respectively). Gupta et al. [15] also found that lower gestational significantly increased the incidence of ROP. In our study, gender had no significant association with ROP ($p < 0.48$) as seen by Gupta et al. [15] and Shah et al. [17].

Kinsey and Zacharias [18], Prendiville and Schulenburg [1] found significant association between oxygen therapy and ROP. In our study also, highly significant association ($p<0.000$) was seen between two as 30.3% preterm who were exposed to oxygen therapy developed ROP as compared to 4.8% who were not. Al-Essa et al. [19] found high concentration of oxygen therapy (OR 94; 95% CI 0.91-0.97; $p = 0.0001$) independently associated with the risk of development of ROP.

Table 2: Results of multiple logistic regression analysis in ROP

Variable	β	SE	Significance	R	Inference
Gestational age	−0.0388	0.3990	0.9226	0.0000	NS
Birth weight	−13.5861	4.5481	0.0028	−0.4330	S
Oxygen	3.8578	1.4008	0.0059	0.3889	S
Septicemia	4.0296	1.4711	0.0062	0.3860	S
Phototherapy	3.0856	1.7919	0.0851	0.1617	NS
Blood transfusion	4.6394	1.4380	0.0013	0.4771	S
Exchange transfusion	1.9272	1.4513	0.1842	0.0000	NS
Gender	1.5545	1.851	0.1896	0.0000	NS
Constant	12.2999	9.5926	0.1998	-	NS

S: Significant, NS: Non significant, ROP: Retinopathy of prematurity

Table 3: Stage of ROP in 25 babies at first screening and subsequent follow-up

Timing of examination (in weeks)	Stage 1	Stage 2	Stage 3	Stage 4
1st evaluation (4-6 weeks of PCA)	23 (92)	2 (8)	-	-
2nd evaluation (after 1 week)	16	2	-	-
3rd evaluation (after 2 week)	9	0	-	-
4th evaluation (after 4 week)	0	0	-	-

Figures in parenthesis are percentages, ROP: Retinopathy of prematurity

Table 4: Incidence of ROP reported in various studies

Study group	Year	Incidence (%)
Darwan et al. [29]	1996	21
Patil et al. [13]	1997	18
Varughese et al. [30]	2001	21
Yang et al. [28]	2001	25
Nair et al. [14]	2003	25.4
Gupta et al. [15]	2004	21
Taqui et al. [18]	2008	32.4
Present study	2009	12.5

In this study, association between ROP and phototherapy was highly significant ($p < 0.0000$). Nair et al. [14] also found phototherapy as a risk factor for development of ROP. Yeo et al. [20] reported that phototherapy by reducing bilirubin which is an endogenous antioxidant may promote free radical mediated injury and thus increase risk of diseases such as ROP. Exchange transfusion was also observed to be associated with ROP ($p < 0.0000$) as reported by other researchers also [21-23].

We found that blood transfusion was an independent risk factor for the development of ROP (OR: 12.96; 95% CI: 4.22-40.62). Previously conducted studies by Nair et al. [14], Ballard et al. [8], and Bonotto et al. [16] also showed similar association. It has been shown that adult hemoglobin, being more capable of releasing oxygen to tissues, causes tissue level hyperoxia and thus leads to development of ROP [24-26]. In the present study, 52.3% of anemic preterm developed ROP as compared to 7.8% without anemia ($p<0.0001$). Swarna and Battu [12] and Dutta et al. [23] also found anemia as a significant risk factor for development of ROP.

In our study, 36% of preterm babies with septicemia developed ROP as compared to 4.6% without septicemia ($p < 0.0000$). Various studies also found septicemia as independent risk factor for ROP [12,14,15,20,21,27]. It has been observed that sepsis may act through cytokines and endotoxins or by oxidative burst in the neutrophils consequent to infection leading to ROP [15,21]. We found significant association between history of delayed cry/hypoxic ischemic encephalopathy as a risk factor for ROP was ($p < 0.0002$). Shah et al. also showed that infants with threshold ROP had lower 1 min Apgar score as compared to infants without ROP [17]. We also found association between history of congenital heart disease requiring ionotropes and development of ROP which is in collaboration with results of studies conducted by Nair et al. [14] and Yang et al. [28].

In our study, 25 babies developed ROP at first evaluation out of 200 babies screened. Of these 25 babies, 23 (92%) were in Stage 1 ROP and 2 (8%) in Stage 2. After repeated evaluations done after 1, 2, and 4 weeks, all of these showed evidence of regression i.e., they had completed temporal vascularization. No baby showed progression to threshold stage at any time of follow-up examination.

Few limitations of our study include small sample size, short follow-up period, and less number of high risk babies due to less ELBW babies and inclusion of only nonventilated babies due to non-availability of the ventilator in our setup.

CONCLUSION

Retinopathy is substantially high among preterm/LBW babies. Therefore, all preterm/LBW babies, particularly neonates with

gestation <32 weeks and/or weight ≤1500 g and when risk factors are present, should be screened for ROP so that timely treatment can be instituted in babies who have progressed to threshold stage disease so as to prevent long-term morbidity of ROP.

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