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Original Research Article

Maternal and Neonatal risk factors in retinopathy of prematurity: A study from coastal city in south India

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ABSTRACT

Introduction: Preterm babies often suffer from various systemic illnesses and struggle for survival in the neonatal intensive care unit (NICU). These preterm babies are at risk of developing ROP which is a potentially blinding condition. The presence of predisposing maternal and neonatal factors contributes for the development of ROP. Determining the association of risk factors with the development of ROP is essential in improving the screening and management of ROP.
Aim: To determine maternal, neonatal risk factors and influence of retinal immaturity at first screening for development of ROP.
Settings and design: Prospective, observational study conducted at a level of 3 PICU & department of ophthalmology.
Methods and Materials: All the preterm infants with gestational age ≤ 37 weeks admitted in NICU were first screened by 2 to 3 weeks of chronological age and followed up till the completion of retinal vascularization and regression of ROP following treatment. The zone of retinal vascularization at first screening and various maternal and neonatal risk factors were noted.
Results: Out of 166 babies screened, 18.67% progressed to ROP. Of the 36 babies with immature retina 58% developed ROP, while 7.7% neonates with mature retina developed ROP. Gestational age, birth weight, retina immaturity, respiratory distress syndrome and anaemia of prematurity were statistically significant for ROP.
Statistical analysis: Descriptive statistics was used to identify the association of risk factors with the development of ROP. Each risk factor was analyzed by univariate & multivariate logistic regression.
Conclusions: Low birth weight, low gestational age, immature retina and neonatal risk factors have a significant influence on the development of ROP.
Key Messages: Low birth weight, low gestational age and retinal immaturity are important risk factors for Retinopathy of prematurity.

1. Introduction

Preterm birth is associated with neonatal mortality and morbidity and is a significant public health problem. According to The World Health organization, in India3.5 million babies are born premature every year.[1] The incidence of Retinopathy of prematurity (ROP) in preterm births, in India ranges from 11.9-52%.[2] Preterm birth may be spontaneous or related to maternal co-morbidity. Preterm babies often suffer from various systemic illnesses and struggle for survival in the neonatal intensive care unit (NICU). The preterm babies could either have mature or immature retina at birth. These preterm babies are at risk of developing ROP which is a potentially blinding condition.

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Studies have attempted to identify the neonatal and maternal factors which increase the risk of developing ROP in infants.

1.1. Purpose

This study was planned to analyze the risk factors associated with ROP in the coastal Indian population. It also aimed to study the influence of retinal immaturity on the development of ROP and the influence of the risk factors on immature and mature retina for the development of ROP.

1.2. Study design

Cross Sectional Observational Study design

2. Materials and Methods

This prospective, non-interventional study was approved by the institutional ethics committee bearing protocol number YEC-1/2017/017, the patients were enrolled and followed up for a period of 2 years. It was conducted in accordance with ICMR ethical guidelines for biomedical research on human participants. The cohort consisted of preterm infants born between February 2017 and April 2019. This study was conducted in a medical college tertiary care hospital, having well equipped delivery facilities and state of art, level 3 NICU. The preterm infants were eligible for enrolment into the study, if the gestational age (GA) was ≤37 weeks and/or birth weight (BW) ≤2000 grams. The first screening for ROP was performed by 2 to 3 weeks of postnatal age, as per the National Neonatal forum of India guidelines.[3]

A written informed consent was obtained from the parent or legal guardian to include the child for the study. Census method of sampling was used and all of the parents approached to enroll in the study, consented to participate.

ROP screening was performed by a retina consultant designated for the study (Author 1). The pupillary dilatation was achieved with diluted tropicamide (0.5%) and phenylephrine (2.5%) eye drops. The examination was then performed with indirect ophthalmoscope using pediatric eye speculum and indenter, under topical anesthetic eye drop, 0.5% proparacaine hydrochloride ophthalmic solution. Zone and stage of the disease were noted as per the International Classification of Retinopathy of Prematurity (ICROP).[4] Follow up evaluation was done as per screening examination protocol.[5]

In the study, immature retina is defined as retinal vascularisation up to zone I and II, while mature retina refers to vascularisation up to zone III.[4,6] The demographic data, maternal & obstetric history, neonatal status, gestational age & birth weight were obtained at the time of first screening from the medical records. The final visit for the study purpose was till the retina completely vascularised or ROP regressed in babies following treatment. Retinal findings were documented during each screening. Neonatal history was again noted at the time discharge.

Babies with complete retinal vascularisation during first ROP screening and who failed to come for follow up till the final ROP screening were excluded from the study. For the purpose of this study, complete (full) retinal vascularization is in close proximity of retinal vessels to the ora serrata for 360°.[7] The data was entered in Microsoft excel. Chi square test was applied to compare significance of risk factors in babies with and without ROP. To identify the association of risk factors with the development of ROP, each risk factor was analyzed by univariate and multivariate logistic regression. The odds ratio and 95% confidence interval associated with each predictor were calculated from the logistic regression models. A p value < 0.05 was considered statistically significant. All analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL).

3. Results

The study cohort, which underwent ROP screening for the first time, consisted of 200 babies born during the 26 months period. A total of 166 premature neonates completed the follow up and were included for analysis. Figure 1 depicts the flowchart representing the process from enrollment to final follow up. Babies were divided into groups, babies with immature retina in group 1 and mature retina in group 2.

Total of 166 babies were screened for ROP, of which 31(18.7%) progressed to ROP and 7(4.2%) babies required treatment for threshold ROP. GA of babies without ROP was 33.42 ± 2.65 weeks and with ROP was 29.849 ± 2.88 weeks ($p<0.001$) and BW of babies without ROP was 1781.15 ± 516.61gms and with ROP was 1206.29 ± 421.16gms ($p<0.001$) Table 1 depicts univariate and multivariate analysis of neonatal risk factors in neonates with ROP. Among the neonatal risk factors, respiratory distress syndrome (RDS) and anaemia of prematurity were statistically significant. The neonates also presented with patent ductus arteriosus, atrial septal defect and ventricular septal defect – documented collectively as congenital heart disease (CHD). Central nervous system (CNS) related conditions like apnoea of prematurity and intra ventricular haemorrhage were also noted in the babies. The neonates also had associated sepsis and necrotising enterocolitis none of the CHD, CNS disorders or other risk factors showed any statistical significance. The association of maternal risk factors like gestational diabetes mellitus, pregnancy induced hypertension, anaemia and uteroplacental factors with ROP was also not statistically significant.

Table 2 shows neonatal risk factors in Group1 and Group 2 babies with ROP. GA ($p=0.032$ in group 1 and 0.034 in group 2) and BW ($p=0.06$ in group 1 and 0.02 in group 2) were statistically significant for the development of ROP in both the groups. None of the maternal or neonatal risk factors showed any significance. However, higher percentage of babies in group 2 (with ROP) had

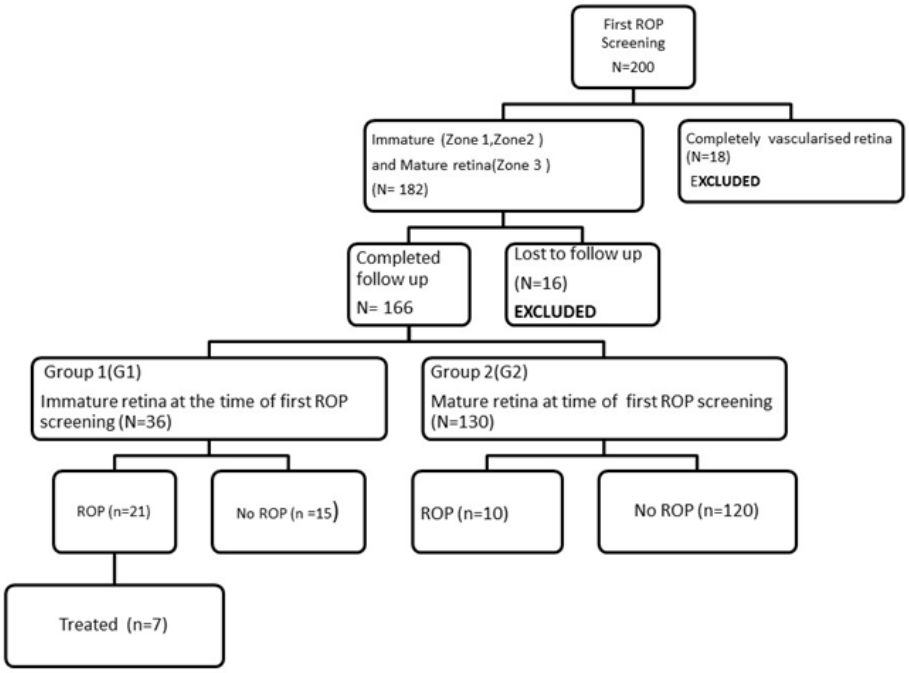

Fig. 1:

Table 1:

	N	Neonates with ROP N (%)	p-value	Univariate OR (95% CI)	Multivariate OR (95% CI)
Respiratory Distress Syndrome	88	23(26.13)	0.01	3.096 (1.294-7.408)	0.416 (0.161-1.072)
Sepsis	70	18(25.7)	(0.068)	2.210 (1.000-4.885)	0.882 (0.343-2.269)
Congenital heart disease	24	8(33.3)	0.08	2.587 (0.992-6.749)	0.550 (0.190-1.591)
Anaemia of prematurity	10	5(50)	0.02	5.000 (1.350-8.515)	0.369 (0.087-1.570)
Necrotising Enterocolitis	10	4(40)	0.09	3.185 (0.841-2.060)	0.442 (0.103-1.901)
Central Nervous system involvement	8	2(25)	0.64	1.483(0.285-7.722)	0.985 (0.160-6.050)
Gestational Diabetes Mellitus	16	3(18.8)	1.000	1.005 (0.268-3.767)	1.114 (0.293-4.242)
Pregnancy induced Hypertension	25	6(24)	0.419	1.465 (0.531-4.041)	0.679 (0.242-1.907)
Maternal anaemia	3	0(0)	1.000	-	-
Uteroplacental factors	31	5(16.1)	0.802	0.806 (0.283-2.30)	2.953 (0.415-1.012)

Table 2:

Risk Factors	Group 1 (Immature Retina) with ROP (N-21)	Group2 (Mature retina) with ROP (N-10)
Gestational Age (weeks)	29.29±2.493	31±3.399
Birth weight (grams)	1085.71±398.012	1459.50±366.155
Respiratory distress syndrome	15(71%)	8(80%)
Sepsis	11(52.3%)	7(70%)
Congenital heart disease	6(28%)	2(20%)
Anaemia of prematurity	3(14.2%)	2(20%)
Necrotizing enterocolitis	1(4.76%)	3(30%)
Central nervous system disorder	2(9.5%)	0(0)
Neonatal Hyperbilirubinemia	9(42%)	6(60%)

neonatal risk factors.

4. Discussion

This prospective, follow up study was designed to identify the influence of retinal immaturity, maternal and neonatal risk factors towards the development of ROP.

Maternal health, uterine and placental function is vital for the normal foetal growth and development. Maternal factors primarily increase the risk of ROP by precipitating premature labour.[8] Among the maternal risk factors none in the present study showed statistical significance for the development of ROP (Table 1). Population-based studies have observed that in low birth weight babies, maternal pre-eclampsia was not linked to the development of ROP.[9] However, some studies have mentioned eclampsia and pre-eclampsia having a protective role in ROP.[10] In the present study utero placental factors, collectively accounted for 16.1% of babies with ROP, which was statistically insignificant. In an experimental rat model study, it was concluded that combination of maternal uteroplacental insufficiency and oxygen fluctuation led to reduced severity of ROP.[11] Maternal risk factors like abruptio placenta, placenta previa were also not significant in the development of ROP in a study done by Gupta et al.[12] In a study done in south India, pregnancy induced hypertension, gestational diabetes mellitus, oligohydramnios, and premature rupture of membrane were found to be associated with ROP.[13] A study done by Gebesce, did not show influence of maternal risk factors on ROP which is similar to our observation.[8]

The ROP screening guidelines are purely based on well recognized neonatal risk factors- BW and GA. In the present study the mean GA and BW of babies with ROP was statistically significant. In a study done in southern India the mean GA of babies with ROP was lower than 29.71 weeks which matches our finding.[14] Low birth weight and low gestational age are prominent independent risk factors for ROP.[14–16] The neonatal risk factors for the development of ROP, identified in the present study, are RDS, sepsis, CHD, anaemia of prematurity, Necrotizing enterocolitis (NEC) and CNS disorders. In our study RDS was a significant risk factor for ROP. RDS is also highlighted as a significant risk factor for ROP.[17] Al-Essa reported that the incidence of ROP in preterm infants with sepsis was 3.5 times higher than in those without sepsis.[18] In our study 25.7% with sepsis developed ROP and the difference was not statistically significant (0.068). Four babies (33.3%) with CHD had ROP and the P value was 0.084. The risk of ROP increases with increasing severity of anaemia.[19] Similarly, the presence of NEC further enhances the severity of ROP in a baby with other pre-existing risk factors.[20] In our study 40% of babies with NEC developed ROP but it was not statistically significant. In the present series 25% of babies with CNS involvement developed ROP, which was not statistically significant, however, in a study done in Turkey, showed a correlation between development of ROP with apnoea& intra ventricular haemorrhage (CNS disorders).[21]

A retrospective study on Asian preterm infants concluded that more severe immature retina, at first screening, is more likely to develop ROP and 46.5% of immature retina developed ROP as compared to 15 % of mature retina.[22] In another study, 62.5% infants with immature retina developed ROP and none of the infants with mature retina developed ROP.[23] In our study 58.3%babies with an immature retina developed ROP and 7.7% babies with mature retina developed ROP, indicating that immature retina is a sensitive factor for the development of ROP.

Koerner F et al mentioned that the influence of neonatal risk factors is greater on immature retina.[24] A hospital-based Brazilian study concluded that babies with gestational age less than 32 weeks developed ROP, primarily due to retinal immaturity, whereas in the bigger babies, with gestational age more than or equal to 32 weeks, the associated comorbidities, played a significant role in precipitating ROP.[15]

In our study higher percentage of babies with mature retina who developed ROP had neonatal risk factors when compared to babies with immature retina. We observed that neonatal risk factors had greater influence for the development of ROP as compared to maternal risk factors. Retinal immaturity had a greater effect on development of ROP. Higher percentages of babies with mature retina were influenced by risk factors.

Study Limitations: The larger sample size would have helped in generalizing the results. Some of the neonatal parameters were not included in the study. In future, study evaluating role of neonatal factors like oxygen saturation and role of blood transfusion can be planned.

5. Conclusion

Low birth weight and low gestational age are the risk factors for ROP. The retinal immaturity, at first screening, itself is one of the risk factors for development of ROP. Neonatal risk factors in general have influence on the development of ROP as compared to maternal risk factors. Influence of neonatal risk factors for development of ROP is higher in mature retina.

6. Acknowledgement

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7. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

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None.

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