

A study of the risk factors associated with retinopathy of prematurity at tertiary health care centre

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Abstract

Background: ROP (Retinopathy of prematurity) is emerging as one of the leading causes of preventable childhood blindness in India. Infants with significant ROP have increased risk of high myopia, refractive errors, strabismus, amblyopia, astigmatism, retinal detachment and glaucoma. **Aim and objective:** To study the incidence and risk factors associated with retinopathy of prematurity in preterm infants with less than 34 weeks of gestational age or less than 1750 gm birth weight **Methodology:** Eighteen month hospital based prospective study to know the incidence of ROP, and to establish risk factors for development of ROP was conducted at NICU attached to a tertiary health care center. Two hundred babies satisfied the enrollment criteria. Data collected with pre tested questionnaire which included sociodemographic data, maternal risk factors, treatment given to neonates and findings of ophthalmoscopic examination. Data analysed with appropriate statistical tests. **Results:** The incidence of ROP was 19.3%. The birth weight of the ROP babies ranged from 900gm-1700 gm (mean 1340± 220 gm). Incidence of ROP was inversely proportional to birth weight and gestational age which is statistically significant. On univariate analysis, the duration of oxygen administration, mean of maximum and minimum SpO₂, need for oxygen supplementation, clinical sepsis, RDS, mean APGAR at first and fifth minute of life, acute kidney injury, convulsions, administration of blood and its products and hypotension are significantly associated with development of ROP. On multivariate analysis by application of multiple logistic regression models, GA, duration of hospital stay and day of establishment of feeds were independent risk factors.

Key Word: retinopathy, prematurity.

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INTRODUCTION

Retinopathy of prematurity (ROP) which was previously called as retrolental fibroplasia is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age (GA).¹ The

possible mechanism of injury suggested is vasoconstriction, increase in level of vasogenic factors like vasoendothelial growth factor and compensatory neo-vascularization leading to severe extra retinal fibro vascular proliferation and retinal detachment.¹ ROP is mostly limited to preterm babies with birth weight (BW) of less than 1500 gm or GA of less than 32 weeks, with an incidence varying between 35 to 60%.² Many risk factors are associated with ROP like low GA, low birth weight, prolonged oxygen exposure, severity of neonatal illnesses, severe respiratory distress requiring mechanical ventilation, shock, sepsis, hypoxia, prolonged ventilator support, need for blood transfusion, intraventricular hemorrhage, acidosis, anemia, high ambient light, vitamin E deficiency whereas breast feeding and history of maternal preeclampsia are protective.^{1,2,3} The most widely used classification for ROP is the International

Classification of Retinopathy of Prematurity (ICROP) which classifies ROP into stage 1 to 5, along with disease, extend, threshold and pre-threshold disease.⁶ Hardly any case of ROP is detected before 32 weeks of GA and the median age for detection of stage 1 ROP is 34 weeks, pre-threshold ROP is 36 weeks and threshold disease is 37 weeks. Retinal vascularization is complete by 40 weeks of GA. So the crucial period for detection of ROP is from 32-40 weeks. The critical phase is from 34-38 week's age when disease progression takes place and treatment may have to be instituted.⁴ Presence of ROP on the first examination, posterior location, increasing severity of stage, circumferential involvement, plus disease and rapid progression are the risk factors which necessitates treatment.¹ The percentage of pediatric blindness contributed by ROP ranges from 3% to 11% in high developed countries and as high as 60% in middle developed countries.^{5,6,7} Currently no definitive methods are available for the prevention of ROP. Since most of the risk factors associated with ROP mentioned above arise in the neonatal intensive care unit (NICU) itself and most of them are avoidable, cautious monitoring of the risk factors, early screening, follow up and surgical intervention have been shown to reduce the incidence and improve the outcome of ROP.² In view of paucity of Indian studies on the incidence and risk factors of ROP from tertiary care centres especially from the southern parts of India, the present study is undertaken. To study the risk factors associated with retinopathy of prematurity.

Aim and objective:

To study the incidence and risk factors associated with retinopathy of prematurity in preterm infants with less than 34 weeks of gestational age or less than 1750 gm birth weight.

MATERIAL AND METHODS

Present study is a Prospective observational study carried out on 200 premature babies admitted in NICU of department of Pediatrics in a tertiary health care center. All the Premature babies admitted to NICU during 2016 to 2018 which fulfilled the inclusion criteria were examined regularly by ophthalmologist from 4th postnatal week and followed up regularly.

Inclusion criteria: All preterm babies less than 34 weeks of gestational age or less than 1750 grams of birth weight

Exclusion criteria:

1. All neonates more than or equal to 34 weeks of gestational age, or more than or equal to 1750 grams of birth weight.
2. Neonates with major congenital malformations
3. Neonates with suspected chromosomal anomalies.
4. Neonates with suspected inborn errors of metabolism

Study was approved by ethical committee. A valid written consent was taken from parents of neonates after explaining study to them. Data was collected with pretested questionnaire. Data included assessment of risk factors like Low Gestational Age, Low Birth Weight, Oxygen Exposure, Hypoxia and Hyperoxemia, Hyperglycemia, Thrombocytopenia, Severe respiratory illness requiring mechanical ventilation, Severity of illness, Septicemia, Anemia, Amount of blood transfusion and Duration of stay in the hospital. Neonates were examined by trained ophthalmologist between 3 and 4 weeks of age postnatally. Neonates were examined by dilating the pupils with a mixture of 1% tropicamide and 1% phenylephrine eye drops applied about 30 minutes prior to examination. Scleral depression was performed using infant scleral depressor. The depression was carried out transconjunctivally after topical anesthesia using 2% Lignocaine eye drops. They were examined either in the NICU if they were hospitalized for a prolonged period or at ophthalmic outpatient department. Eyes were examined by indirect ophthalmoscopy. Staging was performed using international classification. Neonates were referred up for ROP between 3rd and 4th postnatal week. Depending on the finding the patients were given further appointments e.g. schedule for screening was once in two weeks in stage 1 zone III disease, once a week stage 2 disease occur in posterior pole and once in 3 days if it is zone I with plus disease. Screening was continued till term gestation and subsequent follow up once in 3 to 6 months. For risk factor analysis all pertinent information, such as birth weight, gestational age (determined by Ballard's scoring), sex, details of respiratory support, blood transfusion, sepsis, surfactant administration, intraventricular hemorrhage, APGAR scores at 1st and 5th minute, multiple gestations, medications especially antenatal steroids, Indomethacin used for treatment of Patent ductus arteriosus, Aminophylline, parity, hyperbilirubinemia requiring of Phototherapy with duration, convulsions, maternal risk factors parity, type of delivery, maternal sepsis, premature rupture of membranes, maternal diabetes and pregnancy induced hypertension were recorded prospectively. To diagnose intraventricular hemorrhage, cranial ultrasound was done when suspected clinically. The clinical evidence of patent ductus arteriosus was confirmed by echocardiography. All infants receiving oxygen therapy had continuous monitoring by pulse oxymeter and arterial blood gas through umbilical or peripheral arterial sampling. Apnea was defined as a cessation of respiration for >20 seconds which required resuscitation with bag and mask and oxygen. Sepsis was diagnosed by clinical picture, changes in the leukocyte count, elevated C-reactive protein and positive bacterial culture. All the babies were managed as per the standard protocol with

regard to temperature management respiratory support, management of jaundice and feeding.

Data analysis

A prospective analysis was done on the data available from the cohorts to identified risk factors associated with ROP and non-ROP infants. The associations between potential related risk factors with ROP were studied initially through a univariate analysis. The categorical variables were assessed using Pearson chi-square. To estimate the independent effect of the factors that were significantly associated with grading (marks scored) the confounding effect they may have on each other, logistic regression analysis was done. The variables were included if their respective univariate analysis yielded $p < 0.10$. A backward stepwise elimination procedure based on the likelihood statistics (using removal probability of 0.10 and considering the change in classification accuracy) was also performed to identify the best subset of variables. The potential risk factor variables considered were neonatal and maternal risk factors mentioned in material and method section, statistical tests were carried out at 5% level of significance.

RESULTS

A total of 596 admissions were made in neonatal intensive care unit during the study period among them 256 neonates were preterm with gestational age lesser than 37 weeks. 200 fulfilling the inclusion and exclusion criteria were included in the study. The incidence of ROP in the present study is 19.3%. In our study we found that majority of the neonates were with birth weight of 1501-1750 grams. (46%) followed by 1251-1500 grams (44.5%). Among the ROP cases majority cases were with birth weight of 1251-1500 grams (36.8%) followed by 1001-1250 (28.9%). Table 2 shows distribution of neonates according to gestational age. Majority of the patients were with the gestational age of 33-34 weeks (46.5%) followed by 31-32 weeks (40%) among all screened babies. In ROP cases majority cases were with gestational age 29-30 weeks (34.2%) followed by 31-32 weeks (31.5%). In our study we found male preponderance (57.8%) in ROP cases as compared to female (42.2%). In our study we found that majority of the neonates were delivered by vaginal

delivery in both all screened (94.5%) and neonates with ROP (92.2%). Delivery by caesarean section was observed in 5.2% neonates with ROP. Instrumental delivery was seen in 2.6% neonates. From table 4 it was observed that APGAR SCORE at one minute was maximum in screened patients at score of 6 and 7. In case of ROP patients score of 6 was seen in 17 patients and score of 7 was seen in 4 patients only. Difference in the APGAR score in screened (controls) was significantly higher than ROP cases ($p=0.0001$). Similarly APGAR score at end of 5 minutes was significantly lower in ROP cases than screened controls. ($p=0.0001$) Mean APGAR score at 1 minute in screened patients was 6.02 ± 0.95 and in ROP cases was 5.47 ± 0.97 . APGAR score at 5 minutes in screened patients was 8.46 ± 0.87 and in ROP cases was 7.76 ± 0.74 . after applying t test we found that APGAR score in ROP cases was significantly lower in ROP cases ($p=0.0001$) In our study we found that mean birth weight in screened patients was 1462.64 ± 187.45 grams while birth weight in ROP cases was 1326.97 ± 234.53 grams. It was observed that mean birth weight of neonates in ROP cases was significantly lower than screened neonates. ($p=0.0001$) Table 7 shows O2 duration in hours and SPO2 in screened neonates and ROP neonates. Mean o2 duration in hours in screened (control) and ROP neonates were 24.69 ± 19.42 and 68.33 ± 52.26 hours. It was significantly higher in ROP neonates ($p=0.0001$) Maximum SPO2 in ROP cases was 98.23 ± 1.22 and in controls was 99.12 ± 1.64 . this difference was statistically significant. Minimum SPO2 was 80.62 ± 5.58 in ROP neonates while it was 88.26 ± 3.35 in controls. This difference was statistically significant. Table 8 shows maternal risk factors determined to be associated with preterm babies. There was a difference between risk factors in ROP cases and controls, but none was statistically significant. Table 9 shows complications associated with preterm babies. Respiratory distress syndrome, sepsis, convulsions, hypotension and acute renal damage shows significant difference in screened neonates and ROP neonates. ($p < 0.05$) other complications did not show any significant difference in both the groups. Maximum neonates with ROP were from stage 1 of ROP (21). Stage 2 ROP was seen in 12 patients and stage 3 was observed in 5 neonates.

Table 1: Distribution of patients according to birth weight

Birth weight (grams)	Number screened	ROP cases
<1000	5(2.5%)	4(10.5%)
1001-1250	14(7%)	11(28.9%)
1251-1500	89(44.5%)	14(36.8%)
1501-1750	92(46%)	9(23.6%)
	200	38

Table 2: Distribution of patients according to gestational age

Gestational age (weeks)	No: screened	ROP cases
<28	6 (3%)	5(13.5%)
29-30	21(10.5%)	13(34.2%)
31-32	80(40%)	12(31.5%)
33-34	93(46.5%)	8(21%)
	200	38

Table 3: Distribution of patients according to type of delivery

Gender	Number screened	ROP cases
Vaginal delivery	189(94.5%)	35(92.2%)
LSCS	7(3.5%)	2(5.2%)
Vaginal delivery with assistance (instruments)	4(2%)	1(2.6%)
Total	200	38

Table 4: Comparison of APGAR Score in screened and ROP cases

Time	Apgar Score	Number screened	ROP cases	
1 st minute	3	4	2	p=0.0001
	4	10	3	
	5	29	12	
	6	94	17	
	7	63	4	
5 minute	6	12	2	p=0.0001
	7	16	10	
	8	45	21	
	9	127	5	

Table 5: Comparison of APGAR score in screened and ROP neonates

Apgar score	Number of cases screened (Mean $\pm$ SD)	ROP cases (Mean $\pm$ SD)	
1 st minute	6.02 $\pm$ 0.95	5.47 $\pm$ 0.97	t=3.26 (p=0.0001)
5 minute	8.46 $\pm$ 0.87	7.76 $\pm$ 0.74	t=4.664(p=0.0001)

Table 6: comparison of mean birth weight in screened and ROP neonates

	Number of cases screened (Mean $\pm$ SD)	ROP cases (Mean $\pm$ SD)	
Birth weight	1462.64 $\pm$ 187.45	1326.97 $\pm$ 234.53	t=3.89 (p=0.0001)

Table 7: Comparison of SPO2 in screened and ROP neonates

	ROP cases n=38	Controls n=136	
O2 Duration in hours	68.33 $\pm$ 52.26	24.69 $\pm$ 19.42	t=8.0(p=0.0001)
Mean $\pm$ SD			
SpO ₂ maximum	98.23 $\pm$ 1.22	99.12 $\pm$ 1.64	t=3.12(p=0.002)
Mean $\pm$ SD			
SpO ₂ minimum	80.62 $\pm$ 5.58	88.26 $\pm$ 3.35	t=9.25(p=0.0001)
Mean $\pm$ SD			

Table 8: Maternal risk factors determined to be associated with preterm babies

Risk factor	ROP cases		Total screened		P value
	Present	Absent	Present	Absent	
Pregnancy induced hypertension in mothers	9	29	32	178	NS
Gestational diabetes in mothers	17	21	46	154	NS
Oligohydramnios	6	32	18	182	NS
Premature rupture of membrane (PROM)	21	17	47	153	NS
Ante partum hemorrhage	3	35	9	191	NS
Meconium stained aspiration	10	28	25	175	NS

Table 9: Neonatal complications association with preterm babies

Neonatal complication	ROP cases		Total screened		P value
	Present	Absent	Present	Absent	
Respiratory distress syndrome	24	14	31	169	S
Sepsis	18	20	24	176	S
Convulsions	6	32	10	190	S
Hypotension	9	29	11	189	S
Blood transfusion	14	24	35	165	NS
Acute renal damage	11	27	17	183	S
Hypothermia	6	32	34	166	NS
Anemia	12	26	29	171	NS
Patent ductus arteriosus	3	35	9	191	NS
Intra ventricular hemorrhage	5	33	10	190	NS
Surfactant administration	7	31	30	170	NS
Neonatal hyperbilirubinemia	34	4	129	71	NS
Hemorrhagic diseases of new born	2	36	16	184	NS

S: Statistically significant NS: Not Significant

Table 10: Distribution of cases depending on severity of ROP

Stage of ROP	No. of cases
Stage 1 of ROP	21
Stage 2 of ROP	12
Stage 3 of ROP	5

DISCUSSION

The incidence of ROP in the present study is 19.3%. Various studies have shown that about 9.4%-25.4% of babies with gestational age 32wk or less develop some degree of ROP. Studies in the literature usually use a cut-off point of a BW of 1,250gm or 1,500gm or 1,750gm, a GA of 28wk or 32 wks, or both. Using a BW of 1750gm or less, a GA of 34 wk or less, or both as criteria for inclusion in this study explains the similar incidence of ROP when compared to other Indian studies. Maheshwari⁸ *et al.* in 1996 reported overall incidence as 20% and severe ROP as 7%. Patil⁹ *et al.* reported the overall incidence of ROP as 17.5% and there was no case of severe ROP. They studied 40 babies with <32wk or < 1250gm. They studied 66 babies with <35wk or <1500gm. Gupta *et al.*¹⁰ in 2003 reported overall incidence as 21.7% and severe ROP as 5%. They studied 60 babies with ≤ 35 wk or ≤ 1500 gm. However, the inclusion criteria are different in every study, it is not possible to compare studies. The incidence of ROP in our study would have increased if the screening was done only in babies weighing <1300gm or in babies <32wk of GA at birth. Screening of babies with a GA of <34wk and/or <1750gm BW in this study have made the incidence of ROP comparable to other Indian studies. The inclusion criteria of ROP Screening if changed to lower limit of GA or BW (≤ 30 wk and ≤ 1250 gm) that would make screening more cost effective and detect the more severe stages of ROP easily enough to permit treatment, reduce unnecessary examinations and avoid wastage of time and manpower.^{11,12} With the screening and early treatment there are no chances of missing ROP cases and its

sequelae. In the present study all the babies who were ≤ 28 wk of GA developed ROP. All the babies who had a BW ≤ 1250 gm developed stage 1 ROP which was the maximum stage of ROP in this study.

Most of the studies consider stage 3 and above as severe ROP. The percentage of severe ROP among various stages of ROP is depicted in the box below.

Study	Maheshwari ⁸ 1996	Rekha ¹³ 1996	Patil ⁹ 1997	Gupta ¹⁰ 2004	Austeng ¹⁴ 2009
Severe ROP(%)	7	8	0	5	34.8

In our study there were stages of ROP above stage 2, which was similar to study conducted by Maheshwari *et al.*⁸

SIGNIFICANT RISK FACTORS IN VARIOUS STUDIES

The main contributing etiological factors in the pathophysiology of ROP are immaturity of retina and a period of hyperoxia. In our study, the incidence of ROP was significantly inversely proportional to both birth weight and gestational age.

On univariate analysis, the duration of oxygen administration, mean of maximum and minimum SpO₂, need for oxygen supplementation, clinical sepsis, RDS, mean APGAR at first and fifth minute of life, acute kidney injury, convulsions, administration of blood and its products and hypotension are significantly associated with development of ROP.

LOW BIRTH WEIGHT AND PREMATURITY

The prevalence of ROP was more among VLBW neonates and the risk is inversely proportional to BW and GA in

studies conducted by Maheshwari *et al.*⁸ The mean gestational age of the cases was 29.93wk $\pm$ 2.18wk and the controls were 32.42wk $\pm$ 0.89wk. The range of gestational age was 27 wks – 34wks among cases and 29wk-34wk among controls. Mean birth weight of the ROP cases were 1340gms and non ROP babies was 1480gms. Incidence and severity of ROP increased as the birth weight decreased.

OXYGEN ADMINISTRATION

The independent risk factor for development of ROP is the duration of oxygen administered. 66.6% of babies who received oxygen therapy developed ROP in the present study and nearly 50 %of the babies on oxygen therapy developed the disease in other studies.^{10,15} Though cases were exposed to hyperoxia and hypoxia more than the controls, it was not found to be a significant factor in causing ROP. This can be explained due to the close monitoring of babies on oxygen therapy by pulse oximetry and arterial blood gas analysis in our unit. By controlled trials and clinical studies the causal link between ROP and supplemental oxygen has been confirmed.^{15,16} However, a safe level of oxygen usage has not been defined. Preliminary work has suggested the incidence of ROP can be reduced by continuous oxygen monitoring. In present study oxygen administration is a significant risk factor for development of ROP but not an independent risk factor on multivariate analysis.

LOW APGAR SCORE

Preterm babies who had a lower APGAR at 1 minute had a higher risk of having ROP in the study conducted by Shah *et al.*¹⁷ In our study APGAR at 1 minute and APGAR at 5 minutes were both lower among cases compared to controls, but was not an independent predictor of ROP on multivariate analysis.

RDS

RDS is significant risk factor in the present study but not an independent risk factor on multivariate analysis. Gupta *et al.*¹⁰ and associates reported ROP in 33.3% of babies with RDS. In our study, 63% of babies among cases had RDS, which is almost comparable to the other studies mentioned.

SURFACTANT ADMINISTRATION

To reduce the risk of ROP surfactant was used to treat hyaline membrane disease but it did not significantly reduced the incidence of ROP in the present study. It may be due to the fact that very few cases among babies having RDS had surfactant therapy.

BLOOD TRANSFUSION AND EXCHANGE TRANSFUSION

Studies have shown that the adult hemoglobin, being more capable of releasing oxygen to tissues, causes tissue-level hyperoxia and cause ROP.¹⁸ Rekha *et al.* and Maheshwari *et al.* have identified exchange transfusion as a risk factor

for the development of ROP.^{13,8} The hyperoxia in the tissues causes release of free oxygen radical and reflex vasoconstriction leading on to the familiar cascade of events that causes ROP.^{19,20} In our study blood transfusion was found to be a risk factor for development of ROP on univariate analysis, but not so on multivariate analysis.

SEPSIS

Clinical Sepsis is an independent risk factor for ROP in the present study and corroborates with findings of other studies.^{10,15,21} Gupta *et al.* in his study reported 52% sepsis among babies with ROP.¹⁰ In the present study clinical sepsis was a risk factor on univariate analysis and 47% of the cases had clinical sepsis, but it was not an independent risk factor on multivariate analysis. Its prevention and early treatment may reduce the incidence of ROP. The risk of ROP was independently proportional to the presence of bacterial and fungal sepsis only in ELBW babies and those with threshold ROP in the study conducted by Vikek and associates.²² But in our study, culture proven sepsis was not an independent risk factor of ROP.

MULTIVARIATE ANALYSIS OF THE RISK FACTORS

In study conducted by Chaudhari²³ *et al.* septicemia, apnea and oxygen therapy were independent risk factors. In our study on multivariate analysis, GA, duration of hospital stay, day of establishment of feeds and duration of oxygen administration were found to be independently significant risk factors.

EVALUATION OF NEED FOR TREATMENT AMONG CASES

In study by Austeng,¹⁴ 33.3% required treatment. In our study, only 5 babies (13.15%) had stage 2 plus disease and required laser treatment. This may be due to the fact that our study had wide screening criteria compared to the other study and also there was strict monitoring for the avoidable risk factors and appropriate and timely screening as per the AAP guidelines.

CONCLUSION

On multivariate analysis by application of multiple logistic regression models, GA, duration of hospital stay, day of establishment of feeds and duration of oxygen administration were found to be independent risk factors. Meticulous fundus examination with indirect ophthalmoscopy should be done in all preterm babies as per the guidelines and screening should be intensified in the presence of factors like oxygen administration, clinical sepsis, RDS, low APGAR, acute kidney injury, convulsions, clinical sepsis, administration of blood and its products and hypotension.

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