

A STUDY ON THE RISK FACTORS OF RETINOPATHY OF PREMATURITY

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Abstract

Background: Retinopathy of prematurity (ROP) is a devastating disease that can cause permanent visual loss. Thus, we have assessed the risk factors which predispose to ROP. The aim is to identify the major risk factors which predispose to ROP in preterm infants, with birthweight up to 2000gm and /or gestational age ≤ 34 weeks. **Materials and Methods:** In this prospective study we examined 115 premature babies with a gestational age ≤ 34 weeks and/or birth weight ≤ 2000 g. Babies born between the gestational age of 34 to 36 weeks who are at high risk of developing ROP were also included. **Results:** Out of 115 babies, 27 infants developed ROP. Among the 27 babies with ROP 6 of them had stage I, 15 had stage II, 3 had stage III, and another 3 had stage IV disease. About 54.8% of babies were females and 45.2% of babies were males. The mean birth weight of neonates developing ROP was $1.4 \text{ kg} \pm 0.3$ and the mean weight of neonates not developing ROP was $1.6 \text{ kg} \pm 0.2$. The mean gestational age for the development of ROP was $31 \text{ weeks} \pm 2.5$ and the mean gestational age in babies without ROP was $33 \text{ weeks} \pm 1.7$. Our study showed a significant relationship between ROP and gestational age, birth weight, oxygen therapy, blood transfusion, RDS, and Apnea of prematurity. The association between the development of ROP and maternal PIH, Anemia, phototherapy, and hypotension was not significant. Our study showed that low birth weight, AOP, infants with respiratory distress, oxygen disorder, and blood transfusions are risk factors for the development of ROP. **Conclusion:** Low birth weight, oxygen therapy, blood transfusion, and apnea of prematurity are significantly associated with ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is characterized by abnormal vascular development of the retina in premature infants.^[1] Retinopathy of prematurity is a biphasic disease. The pathogenesis of ROP has two distinct phases. In the human fetus, Retinal vascularization starts from the center of the retina and proceeds in a centripetal fashion outward, This process starts during the fourth month of gestation and is completed just before birth. Therefore, the retinas of infants born prematurely are incompletely vascularized, leaving behind a peripheral avascular zone. In the first phase of ROP, the normal retinal vascular growth ceases after birth, and partial regression of developed vessels occurs. With maturation of the infant, the resulting non-

vascularized retina becomes increasingly metabolically active and increasingly hypoxic which triggers vaso-proliferative phase. Formation of new abnormal vessels is the second phase of ROP. Second phase is hypoxia induced pathological vessel growth and occurs at about 34 weeks post-menstrual age. Therefore, in infants born prematurely, the vascularization is incomplete, The gestational age at birth correlates to the area of avascular zone.^[2,3] ROP severity is directly proportional to degree of prematurity. Prematurity is the most prominent threat factor for ROP. Recent advances in neonatology have led to an increase in the survival of very young premature infants and subjected them to the risk of developing ROP. ROP emerges as one of the main sources of preventable childhood visual deficiency in India.^[1-]

⁴⁾As ours is a Government Medical College hospital, Previously a District Headquarters hospital, we have an increased number of preterm cases delivered in and referred to our hospital. Therefore, to prevent visual impairment and possible blindness; timely testing, recognition, and treatment of ROP are important.

AIM

To identify the major risk factors which predispose to ROP in preterm infants, with up to 2000gm weight and /or gestational age ≤ 34 weeks.

MATERIALS AND METHODS

It was a prospective longitudinal study conducted on 115 preterm neonates from October 2019 to December 2020. The inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Premature infants born < 34 weeks and/or birth weight <2000gms
- Babies born between 34 - 36 weeks of gestation who are at high risk of developing ROP like sepsis, blood transfusions, respiratory distress syndrome (RDS), Apnea of prematurity

Exclusion criteria

- Infants who died before a sufficient number of eye examinations
- Infants with major congenital malformations
- Infants who were lost to follow up

Consent and Ethical clearance

There were no major ethical issues involved in the study. Ethical approval was obtained from the Institutional Ethical Committee before the commencement of the data collection. Only clinical detailed history, retinal examination, and clinical outcomes were used for analysis. Prior written and informed consent was taken from the parents of the neonate after assuring that their identity will be kept anonymous.

Methodology

All neonates born at Government Medical College Hospital (previously District Head Quarters Hospital), Namakkal, and those that are referred from Private Nursing Homes to the NICU of Government Medical College Hospital (previously District Head Quarters Hospital), Namakkal, who were eligible under the inclusion criteria were included in the present study. All eligible babies were screened at Neonatal Intensive Care Unit.

Preparation of the child

The pupils were dilated with a mixture of Phenylephrine 2.5% and Tropicamide 0.5% instilled 3 times at 10 minutes intervals about 1 hour before the scheduled examination. Resistance to dilation was noted. The examination was performed using a Pediatric wire speculum and Ret camera.

Follow-up protocol

If no ROP was detected at the initial examination, the infants were re-evaluated once every two weeks

until vascularisation was complete. If ROP was detected, examinations were performed weekly for stages 1-2 disease and more frequently for stage 3 disease, till the disease started resolving or progressed to the threshold stage. Babies showing evidence of regression were followed up till vascularisation was complete. Babies progressing to the threshold stage were referred.

Statistical Analysis

Data were analysed using SPSS Version 23.0. Continuous variables were expressed as mean and SD while categorical variables were expressed in frequency and percentage. To find the significant difference between the bivariate samples in independent groups the Unpaired sample t-test was used and in the Multivariate analysis, the Kruskal Wallis test was used. Categorical data were compared using the Chi-Square test was used. P value <0.05 is considered statistically significant.

RESULTS

Out of 115 neonates, 27 neonates (23.5%) were found to have ROP and 88 (76.5%) did not have ROP.

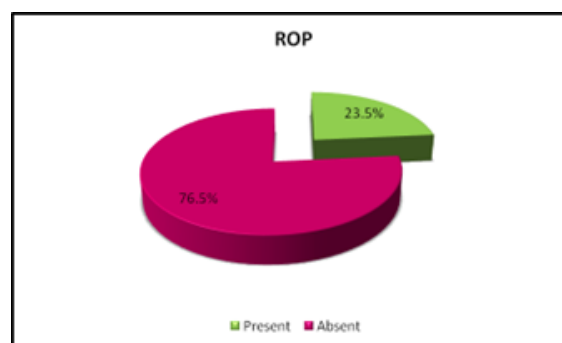


Figure 1: Distribution of ROP among the study population

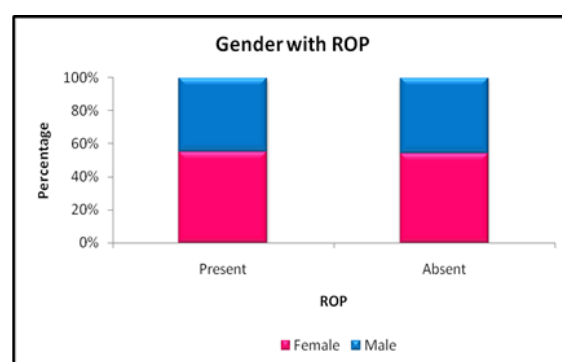


Figure 2: Distribution of sex among the study population

[Table 1] shows the ROP stages distribution where 22.2% is Stage I, 55.6% is Stage II, 11.1% is Stage III, and 11.1% is Stage IV.

[Figure 2] shows the comparison between Gender with ROP. Out of 115 neonates screened, 52 were male and 63 were female. Among the neonates who

developed ROP, 12 were male and 15 were female. There was no statistically significant difference. Table 2 shows a comparison of gestational age with ROP. The mean gestational age for the development of ROP was 31 ± 2.5 weeks compared with not developing ROP at a mean gestational age of 33 ± 1.7 weeks. The p-value was <0.01 showing a statistically significant difference.

Further, [Figure 3] shows the comparison of gestational age with stages of ROP. The development of the various stages of ROP was also significantly dependent on the gestational age (p-value: 0.0005), with the mean age of development of ROP inversely related to the severity of the disease (Stage I – mean GA = 33.3, SD = 1.5; Stage II – mean GA = 30.1, SD = 2.3; Stage III – mean GA = 29.3, SD 0.6; Stage IV – mean GA = 28.3; SD= 1.7).

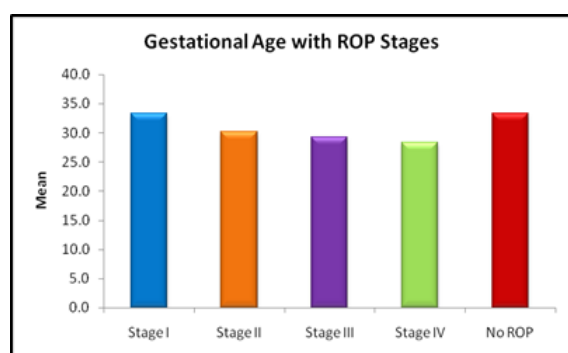


Figure 3: Comparison of Gestational Age with ROP Stages.

[Table 3] shows a comparison of birth weight with ROP. The mean birth weight of neonates developing ROP was 1.4 compared to the mean weight of neonates not developing ROP was 1.6 (p-value= 0.0003) which shows a highly statistically significant difference between birth weight and ROP.

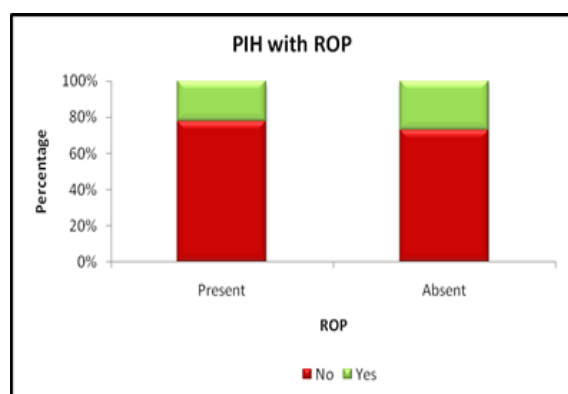


Figure 4: Comparison between maternal PIH with ROP

[Table 4] shows a comparison of birth weight with stages of ROP. The stages of ROP were also highly significant to the birth weight of the neonates developing ROP with lower birth weight neonates developing more severe stages of the disease than their heavier counterparts.

[Figure 4] shows a correlation between maternal PIH and with development of ROP. PIH is present in 22.2% of neonates with ROP and 27.3% of neonates without ROP (p-value=0.601) which shows no statistically significant association between PIH and ROP.

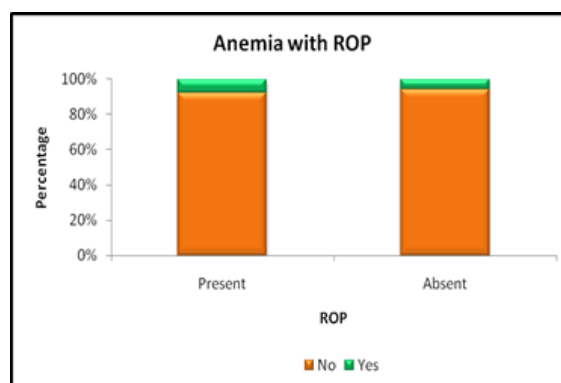


Figure 5: Comparison between Anemia with ROP

[Figure 5] shows a comparison between Anemia and the development of ROP. Anemia was present in 7.4% of the neonates with ROP and 6.1% of neonates without ROP; (p-value = 0.666), which shows no statistically significant association between Anemia and ROP.

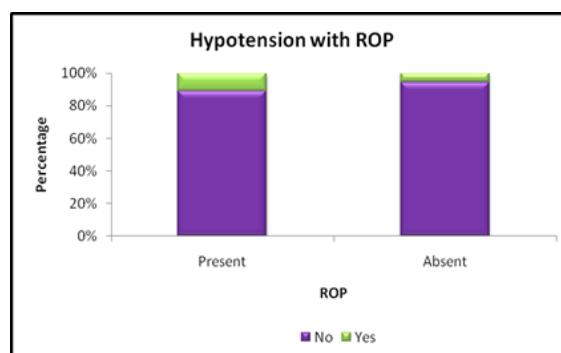


Figure 6: Comparison between Hypotension with ROP

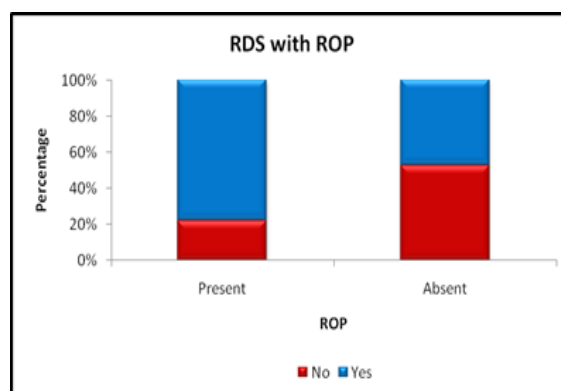


Figure 7: Comparison between RDS with ROP

[Figure 6] shows a comparison between Hypotension with ROP. Hypotension is present in 11.1% of neonates with ROP and 5.7% of neonates without ROP. But there was no significant association between Hypotension and ROP.

[Figure 7] shows a comparison between RDS with ROP. Out of 115 babies screened, 63 had RDS, and 21 developed ROP ($p=0.006$) which shows a highly statistically significant association between RDS and ROP.

[Table 5] shows a comparison between sepsis with ROP. In our study, 50 babies had sepsis and 14 babies developed ROP compared to 36 babies who did not develop ROP. Sepsis was not found to be a significant risk factor for the development of ROP in this study ($p=0.316$).

[Table 6] shows the comparison between AOP with ROP. Out of 115 babies screened, 41 babies had AOP and 14 babies developed ROP compared to 27 babies who did not develop ROP. Apnea of prematurity was found to be a significant factor for the development of ROP in this study (p value=0.045).

[Table 7] shows the comparison between O₂ given with ROP. Out of 115 babies screened 75 babies were given oxygen and 25 babies developed ROP. Our study showed a highly significant correlation between the development of ROP and oxygen use (p -value < 0.01).

[Table 8] shows a correlation between blood transfusions and the development of ROP. ROP developed in 74.1% of neonates who received blood

transfusions compared to 25.9% of neonates who did not receive blood transfusions (p -value = 0.0005) which shows a statistically significant association.

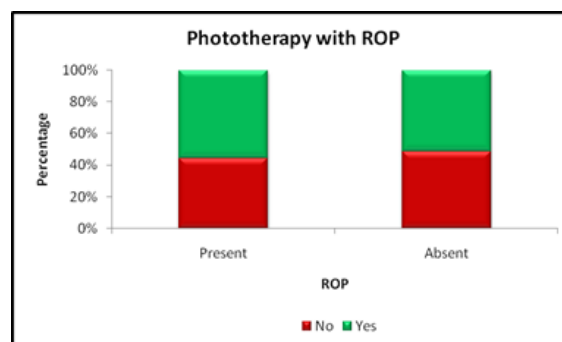


Figure 8: Comparison between Phototherapy with ROP

[Figure 8] shows a comparison between Phototherapy with ROP. 60 babies were given phototherapy and 15 developed ROP. Phototherapy was not a significant factor in the development of ROP ($p=0.688$).

Table 1: ROP Stages distribution.

ROP Stages	Frequency	Percent
Stage I	6	22.2
Stage II	15	55.6
Stage III	3	11.1
Stage IV	3	11.1
Total	27	100.0

Table 2: Comparison of Gestational Age with ROP

	ROP	N	Mean	SD	p-value
Gestational Age	Present	27	31	2.5	0.0005
	Absent	88	33	1.7	

Table 3: Comparison of Birth Weight with ROP

Variable	ROP	N	Mean	SD	p-value
Birth Weight	Present	27	1.4	0.3	0.0003
	Absent	88	1.6	0.2	

Table 4: Comparison of Birth Weight with ROP Stages

Birth Weight	N	Mean	SD	KW- χ^2 value	p-value
Stage I	6	1.5	0.2	14.290	0.006
Stage II	15	1.4	0.2		
Stage III	3	1.2	0.4		
Stage IV	3	1.2	0.2		
No ROP	88	1.6	0.2		

Table 5: Comparison between Sepsis with ROP

Sepsis	ROP		Total	χ^2 - value	p-value
	Present	Absent			
Yes	14(51.9%)	36(40.9%)	50(43.5%)	1.007	0.316
No	13(48.1%)	52(59.1%)	65(56.5%)		
Total	27(100.0%)	88(100.0%)	115(100.0%)		

Table 6: Comparison between AOP with ROP

AOP	ROP		Total	χ^2 - value	p-value
	Present	Absent			

Yes	14(51.9%)	27(30.7%)	41(35.7%)	4.036	0.045
No	13(48.1%)	61(69.3%)	74(64.3%)		
Total	27(100.0%)	88(100.0%)	115(100.0%)		

Table 7: Comparison between O2 given with ROP

O2 given	ROP		□ 2 -value	p-value
	Present	Absent		
Yes	25(92.6%)	50(56.8%)	11.656	0.0004
No	2(7.4%)	38(43.2%)		
Total	27(100.0%)	88(100.0%)		

Table 8: Comparison between Blood Transfusion with ROP

Blood Transfusion	ROP		□ 2 – value	p-value
	Present	Absent		
Yes	20(74.1%)	25(28.4%)	18.088	0.0005
No	7(25.9%)	63(71.6%)		
Total	27(100.0%)	88(100.0%)		

DISCUSSION

In our study, among the 115 neonates examined for ROP, 27 neonates were found to have ROP (23.5%) and 88 did not have ROP. The incidence of ROP was 23.5%. This finding was in accordance with most of the Indian studies published on ROP (Maheshwari – 20%, Agarwal – 20%, Gupta – 21.7%, Nair – 25.4%) and a few international studies (Hussain – 21.3%, Shah – 29.2%).^[5-10] Among the 27 neonates with ROP, 22.2% of them had a stage I disease, 55.6% had stage II disease, 11.1% had stage III disease, and another 11.1% had a stage IV disease. Stage II ROP contributed to more than half the number of cases of ROP in our study. The sex of the neonate did not have a statistically significant difference in the development of ROP. The risk of severe retinopathy of prematurity is higher in females >25 weeks of gestation,^[11] which however was not the case in our study.

Gestational age is an already accepted risk factor for developing ROP and in our study also we have seen a significant difference. Furthermore, the development of the various stages of ROP was also significantly dependent on the gestational age, with the mean age of development of ROP being inversely related to the severity of the disease.^[11] Birth weight is another universally recognized risk factor for the development of ROP. Our data showed a statistical significance for low birth weight as a risk factor for developing ROP. The stages of ROP were also highly significant to the birth weight of the neonates developing ROP with lower birth weight neonates developing more severe stages of the disease than their heavier counterparts.

Moving on to the other proposed risk factors, maternal PIH did not seem to play a role in the development of ROP. Anaemia has been proposed as a probable risk factor for the development of ROP. There are however conflicting studies on this topic and our study did not find a significant association between anaemia and the development of ROP. Hypotension was also not found to have a

significant association with the development of ROP.^[12-14]

Neonates with respiratory distress syndrome had a statistically significant risk of developing ROP. This can be indirectly hypothesized to the conclusions drawn by Reka,^[12] who showed that the widespread use of prophylactic surfactant therapy will increase the absolute number of affected patients because of a decrease in the mortality of extremely low birth weight infants. Hence the number of at-risk infants for the development of ROP is increased. Furthermore, neonates with RDS received oxygen more than their counterparts.

Various studies showed sepsis to be an independent risk factor for the development of ROP. Agarwal et al^[6] reported positive blood cultures in 67% of infants who later developed ROP and in only 31% of infants with normal eyes. Liu et al,^[15] in their study found sepsis as the most significant factor contributing to ROP. In our study, sepsis has shown no association with the development of ROP.

Apnoea of prematurity is an independent risk factor for the development of ROP. The frequency of apnoeic episodes increased the progression of ROP to severe stages. In concordance with the previous findings, we found that the development of ROP in infants with apnoea of prematurity was significantly increased.

Hyperoxia is the single most important risk factor for the development of ROP. Our study showed a highly significant correlation between the development of ROP and oxygen use. Blood transfusions have been implicated by many authors as potential risk factors for the development of ROP. Our study also found a statistically significant difference between blood transfusions and the development of ROP.^[16-19]

CONCLUSION

ROP is recognized as the leading cause of preventable blindness and visual impairment in the Pediatric population. The ROP incidence has risen over the years and is probably related to advanced management at NICU, thereby improving the

survival rates of premature infants who have never survived before. In developing countries like India, the introduction of Retcam-assisted testing allows for screening and follow-up of the rural population where an experienced ophthalmologist is not always available. Careful control of oxygen saturation, judicious use of oxygen in the delivery room and the NICU, and reduction in blood transfusion in the NICU could promote adequate postnatal growth and improve neural and vascular development of the retina.

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