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Incidence and risk factors of Retinopathy of Prematurity – a prospective observational study

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Abstract

Objective: Retinopathy of Prematurity (ROP) is a vasoproliferative retinopathy that affects the developing retinal vessels of premature infants. Identification of risk factors is essential for its early detection and intervention. The study was aimed to assess the incidence of ROP and to determine the risk factors associated with ROP.

Methods: It was a prospective observational study which included preterm neonates admitted in neonatal intensive care unit of a tertiary care hospital in Chennai,Tamil nadu,India from December 2020 to September 2021. Screening for ROP was performed for all neonates below 34 weeks gestation and between 34 to 36 weeks with risk factors for ROP. Association between risk factors and ROP was determined using chi square test for categorical variables and students t test for continuous variables. A p value less than 0.05 was considered significant.

Results: Of the 140 neonates screened, 45(32.1%) neonates were diagnosed to have ROP. Among the neonates detected to have ROP there were 24(53.3%) male. 34(75.6%) neonates had a birth weight less than 1.75 kg, 27(60%) neonates had a gestational age less than 34 weeks,22 (48.9%)neonates were born to primi mothers, 25(55.6%) neonates were delivered by normal vaginal delivery. Among the neonatal risk factors studied, sepsis was found to have a significant association with ROP (p=0.02).). Risk factors like apnoea, respiratory distress syndrome, intraventricular hemorrhage, oxygen therapy and blood transfusion did not have a significant association with ROP.

Conclusion: The present study revealed an incidence of ROP of 32% and there was significant association with sepsis.

Keywords: Retinopathy of prematurity,gestational age,birth weight,sepsis

Introduction

Retinopathy of Prematurity (ROP) is a common blinding disease which is increasingly prevalent in the developing world.[1] It is a vasoproliferative retinopathy that affects the developing retinal vessels of premature infants. [2] In spite of being a treatable disorder with complete resolution in the early stages, in its more severe forms, it can lead to traction retinal detachment and blindness. Neonates from developing countries are at risk of more severe disease as they are exposed to a number of risk factors which are largely under control in industrialized countries.[3]

In India, incidence of ROP is around 38-52% among preterm low birth weight babies.[4] Annually around 2 million neonates are born in India with birth weight less than 2000 grams making them vulnerable to develop ROP.[5] ROP is seen in 80 to 90 % of low birth weight neonates who require oxygen supplementation. The incidence and severity of ROP both rise with the level of immaturity. The prevalence of ROP was 48.0% in neonates weighing less than 1000 g at birth, while in the very low birth weight group it was 6.98% and none of the neonates weighing more than 1500 grams had ROP.[6]

Although the exact etiology of ROP remains unclear the factors that have shown a significant association include low gestational age, low birth weight and prolonged supplementary oxygen exposure. Relative hyperoxia of the extra uterine environment exaggerated by supplemental oxygen and loss of maternally derived factors that contribute to normal vessel formation leads to cessation

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of vessel growth and constriction of already formed vessels.[7] Preterm neonates are susceptible to the effects of oxygen toxicity due to developmental deficits in the ability to mount rapid antioxidant responses to hyperoxia.[8] ROP is caused by disorganized blood vessel growth. The incompletely vascularized areas of the retina stimulate new vessel growth in response to hypoxia. Aberrant neovascularization or the fibrous/cicatricial changes in the retina result in macular dragging or retinal detachment and potential blindness.[7]

Retinopathy of Prematurity is a preventable cause of childhood blindness and identification of risk factors is essential for its early detection and intervention. As survival of preterm neonates has increased, the incidence of ROP is on the rise. As the risk of blindness is mainly in unrecognized and untreated ROP,timely screening and treatment of ROP is essential. The study was aimed to assess the incidence of ROP and to identify factors that increase the risk of ROP to formulate measures to reduce the incidence of this dreaded disease.

Methods

It was a prospective observational study which included preterm neonates admitted in neonatal intensive care unit of a tertiary care hospital in Chennai, Tamil nadu, India during the study period from December 2020 to September 2021. Neonates with congenital cataract and corneal opacity and neonates of parents who did not give consent were excluded.

In our study screening for ROP was performed for all preterm neonates who were less than 34 weeks gestation and / or less than 1750 grams birth weight. Preterm neonates between 34 to 36 weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP such as respiratory distress syndrome (RDS), oxygen therapy, sepsis, apnoea, blood transfusion and intraventricular haemorrhage (IVH) were also screened.

Maternal risk factors evaluated were gestational diabetes (GDM), gestational hypertension (GHT), antepartum hemorrhage (APH) and multiple gestation. Screening was done at 4 weeks after birth in those born after 28 weeks of gestation and at 3 weeks in those born less than 28 weeks of gestation.

For fundus examination, pupils were dilated using half strength tropicamide 0.8% with phenylephrine 5% eye drops. Fundus examination was done using indirect ophthalmoscope by paediatric ophthalmologist. Redcam was used to facilitate the screening on the days the ophthalmologist was not able to make a visit to the NICU and to make interpretation uniform and without inter observer variability. Neonates diagnosed with ROP were identified and their risk factors for development of ROP was recorded. High risk neonates and neonates with features of ROP were screened at weekly intervals. Neonates with zone I ROP and posterior zone II vascularising and low risk pre threshold ROP were followed up at weekly intervals. Neonates with anterior zone II vascularising and zone III vascularising were followed up every 2 weeks. All the eligible neonates were screened until retinal vascularisation was complete or until ROP regressed. Ablative laser therapy was done for neonates who had Zone I stage 1 to 3 ROP with plus disease, Zone I stage 3 ROP without plus disease, Zone II stage 2 or 3 ROP with plus disease. Among the neonates with ROP in the study, 12 neonates were treated with laser. All neonates were followed up till one year of age.

Ethical approval was obtained from the Institutional ethics committee (ID No 426/2020), meeting held on 3-12-2020. Neonates fulfilling inclusion criteria were recruited after obtaining written informed consent from parents. Data was analysed using SPSS 24.0. Incidence of ROP was expressed as proportion. Univariate analysis was done to find out the association between neonatal and maternal risk factors and ROP. Neonatal variables like apnoea, sepsis, RDS, oxygen therapy, intaventricular hemorrhage and blood transfusion and maternal variables like gestational diabetes, gestational hypertension, antepartum hemorrhage and multiple gestation were analyzed by chi square test. Maternal age was analysed by students t test. A p value less than 0.05 was considered significant.

Results

During the study period there were 2221 neonates admitted to the Neonatal intensive care unit. Of these 547 were preterm neonates. In this study 140 neonates were eligible for ROP screening. Of these there were 75(53.6 %)male neonates. 75(53.6%)neonates were born to primi mothers. 78 neonates (55.7%) were delivered by normal vaginal delivery and 62(42.3%) by caesarean section. 90(64.3%) neonates had birth weight less than 1.75 kg and 69(49.3%) neonates were less than 34 weeks gestational age. The risk factors of birth weight and gestational age were considered as independent risk factors. Neonates who had both risk factors (less than 34 weeks and with birth weight less than 1750 gm)were not analysed as a separate group (Table 1).

Table 1: Baseline demographic features of the study population.

Factor	Number	Percentage
Gestational age		
<34 weeks	69	49
>34 weeks	71	51
Gender		
Male	75	53.6
Female	65	46.4
Birth Weight		
<1.75 kg	90	64.3
>1.75 kg	50	35.7

Of the 140 neonates screened, 45(32%) neonates were diagnosed to have ROP. Out of the 45 neonates with ROP 24(53.3%) were found to be males compared to 51(53.7%) males among the neonates without ROP and this was comparable among the groups (p 0.96). Among the neonates with ROP, 34(75.6%) neonates had birth weight of less than 1.75kg which was higher when compared to 56(58.9%) neonates with birth weight less than 1.75Kg who did not develop ROP (p =0.05). Out of the 45 neonates with ROP, 22(48.9%) neonates were born to primi mothers as compared to 53(55.8 %) among neonates without ROP (p 0.44). 25(55.6%) neonates who developed ROP were delivered by normal vaginal delivery as compared to 53(55.8%) among neonates without ROP (p 0.97). 27(60%) neonates who developed ROP had gestational age less than 34 weeks as compared to 42(44.2%) neonates among those who did not develop ROP (p 0.08). However though not statistically significant it was observed that even among neonates with the risk of ROP as per the gestational age criteria, 44.2% did not develop ROP stressing the role of other risk factors. The mean (SD) gestational age of the study population was 31.88(2.23). None of the demographic factors studied, like gender, order of birth, mode of delivery, gestational age and birth weight had a significant association with ROP (Table 2).

Mean maternal age (SD) of neonates with ROP was 25.73 (3.91) as against 25.01(3.98) in neonates without ROP. However this comparison was statistically not significant (p=0.315) (Table 3).

Table 3: Comparison of Mean Maternal age among Neonates with and without ROP

Group	Number	Mean	SD	T	p value
With ROP	45	25.73	3.91	1.008	0.315
Without ROP	95	25.01	3.98		

Table 2: Comparison of demographic factors among infants with ROP against those without ROP

Factor		With ROP (%)	Without ROP(%)	p value
Gender	Male	24(53.3)	51(53.7)	
	Female	21(46.7)	44(46.3)	0.96
Order of birth	Primi	22(48.9)	53(55.8)	
	Multipara	23(51.1)	42(44.2)	0.44
Mode of delivery	Normal vaginal	25(55.6)	53(55.8)	
	LSCS	20(44.4)	42(44.2)	0.97
Birth weight	<1.75 kg	34(75.6)	56(58.9)	
	>1.75 kg	11(24.4)	39(41.1)	0.05
Gestational age	<34 weeks	27(60)	42(44.2)	
	>34 weeks	18(40)	53(55.8)	0.08

It was observed that among the neonates who developed ROP, 4(8.9%) neonates had apnoea as compared to 8(8.4%) neonates with apnoea among those who did not develop ROP (p 0.92). Of the neonates with ROP, 32(71.1%) had respiratory distress syndrome as compared to 55(57.9%) neonates with RDS among those without ROP (p 0.13). 26(57.8%) neonates had sepsis among those with ROP as compared to 36(37.9%) neonates with sepsis in the group without ROP (p 0.02). 44(97.8%) neonates with ROP were administered oxygen as compared to 85(89.5%) neonates who required oxygen therapy among those without ROP (p 0.08). Among the neonates with ROP, 16(35.6%) were given blood transfusion as compared to 21(22.1) neonates who received blood transfusion among the neonates without ROP (p 0.09). Details about the FiO2 and the duration of oxygen therapy was not studied. Also regarding blood transfusion the number of units transfused was not studied. (Table 4).

Among the neonates who had ROP 3(6.7%) were born to mothers with gestational diabetes as compared to 13(13.7%) neonates among those who did not develop ROP (p 0.22). 12(26.7%) neonates among those with ROP were born to mothers with gestational hypertension as compared to 19(20%) neonates among those without ROP (p 0.37). One (2.2%)neonate was born to mother with antepartum hemorrhage in the ROP group as compared to one (1.1%) neonate among those who did not develop ROP(p 0.58). 6(13.3%) neonates among those with ROP were born of multiple gestation as compared

to 18(18.9%) neonates among those who did not develop ROP (p 0.41) (Table 5).

Table 4: Comparison of Neonatal risk factors among infants with ROP against those without ROP

Factor		With ROP	Without ROP	p value
Apnoea	Yes	4(8.9)	8(8.4)	
	No	41(91.1)	87(91.6)	0.92
RDS	Yes	32(71.1)	55(57.9)	
	No	13(28.9)	40(42.1)	0.13
Sepsis	Yes	26(57.8)	36(37.9)	
	No	19(42.2)	59(62.1)	0.02
IVH	Yes	0(0)	2(2.1)	
	No	45(100)	93(97.9)	0.3
Oxygen therapy	Yes	44(97.8)	85(89.5)	
	No	1(2.2)	10(10.5)	0.08
Blood transfusion	Yes	16(35.6)	21(22.1)	
	No	29(64.4)	74(77.9)	0.09

Sepsis was found to have a significant association with ROP (p=0.02). The other risk factors like apnoea, RDS, intraventricular hemorrhage, oxygen therapy and blood transfusion did not have a significant association with ROP by univariate analysis. The maternal factors like gestational diabetes, gestational hypertension, antepartum hemorrhage and multiple gestation did not have a significant association with ROP.

Table 5 Comparison of Maternal risk factors among infants with ROP against those without ROP

Factor		With ROP	Without ROP	p value
GDM	Yes	3(6.7)	13(13.7)	0.22
	No	42(93.3)	82(86.3)	
GHT	Yes	12(26.7)	19(20)	0.37
	No	33(73.3)	76(80)	
APH	Yes	1(2.2)	1(1.1)	0.58
	No	44(97.8)	94(98.9)	
Multiple gestation	Yes	6(13.3)	18(18.9)	0.41
	No	39(86.7)	77(81.1)	

Discussion

In the present study among the preterm neonates screened 32% were detected to have retinopathy of prematurity. Similar incidence was reported by a previous study. [9] Previous studies have reported a wide variation in the incidence of ROP ranging from as low as 11.44% to as high as 56%. [10-18]. The incidence of ROP varies in different populations, races, and neonatal units. The variation in ROP incidence may be attributed to the difference in neonatal practice, studied subjects, as well as genetic and racial background. Lower rates were observed by centers where the enrolled neonates were of higher gestational age [19]. There was no significant association between gender and ROP. Similar observations were made by other studies. [10, 12, 14] However another study found a higher incidence (52%) among female neonates. [9] The variation in the association between gender and ROP in different studies may be due to the coexisting variation in the other risk factors like birth weight and gestational age among the screened neonates.

Majority of the neonates who were identified to have ROP had a birth weight less than 1.75 kg and gestational age less than 34 weeks. However there was no significant association between birth weight and gestational age and ROP. There have been varying findings in previous

studies with significant association being found between gestational age and ROP in some, [9,12,14,20,21]between birth weight and ROP in others ,[17] and in some studies association has been found between both gestational age and birth weight and ROP. [16, 19, 22] However no association was found between birth weight and ROP in one study.[14] The association between birth weight and gestational age and the occurrence of ROP was variable in different studies. The association may have been modified by the distribution of neonates of extreme prematurity and extremely low birth weight among the screened neonates. In the present study though the neonates less than 34 weeks were eligible, majority of the survivors who were screened were above 30 weeks of gestation and only 4 neonates were below 30 weeks. Similarly extremely low birth weight neonates (birth weight less than 1000 gm) were only 4 . The lack of survivors of significant numbers of extreme prematurity and extremely low birth weight may have modified the association.

Review of the distribution pattern of the gestational age and birth weight of the screened neonates in the previous studies have found that majority of the studies had included neonates with lower birth weight and gestational age compared to our study. Only 36.8% of neonates were above 33 weeks while 63.2 % of neonates were less than 33 weeks. [9]

About 70% of neonates were between 28 and 32 weeks and 30% were less than 28 weeks [12]. 13.9% of neonates were less than 32 weeks and 3 neonates were less than 1000 gm. [14] Other studies have included only neonates who were less than 1500 gm and less than 32 weeks gestation [16,20,21].

The most significant independent risk factor for the development of ROP was gestational age at birth.[18] Low gestational age with immaturity of the nervous and vascular systems of preterm neonates increases the risk of ROP.[23] Another study has observed that preterm neonates more than 30 weeks gestation did not develop severe ROP.[24] A higher incidence of ROP of 27% was observed among very low birth weight babies as against 20% among all preterm in a previous study.[13] A prospective cohort study in Michigan observed an increased odds ratio of 8.49 and 3.19 for development of severe ROP in neonates $\leq$ 28 weeks and 29 weeks respectively.[25] A multicentric study (CRYO ROP) observed that lower birth weight and younger gestational age were associated with "threshold" ROP.[26]

It was observed that multiple births did not significantly increase the risk of ROP. However contrary findings were observed by a previous study which found that multiple birth predisposed to ROP.[10] Multiple births were observed to be a non significant variable in ROP development and progression.[27] No significant difference was observed between multiple-birth neonates and matched singletons in terms of frequency and severity of ROP. Any apparent higher rate may be due to independent risk factors such as low birth weight and gestational age rather than multiple pregnancies per se[28]. In the present study it was observed that ROP was more common among neonates delivered by caesarean section but it was not statistically significant. Similar observations have been made by a previous study. [14] Contrary findings have been observed by other studies. A study on extremely low birth weight (ELBW) preterm neonates revealed that the vaginal delivery was an independent predictor of threshold ROP. [29] A previous study revealed that ROP tended to decrease with caesarean section deliveries. [30]

In this study maternal age of neonates with and without ROP was comparable. Low maternal age was a significant factor in ROP development and progression among preterm neonates less than 33 weeks.[27] Similar observations were made in a previous study where ROP was significantly associated with younger maternal age.[19] None of the maternal risk factors were significantly associated with ROP.

Evaluation of the neonatal risk factors revealed that oxygen administration, respiratory distress syndrome, sepsis and blood transfusion were commonly observed among the neonates who were detected to have ROP.

There was no significant association between oxygen therapy and ROP. However previous studies have observed that supplementary oxygen use was associated with ROP. [11, 14, 16] Duration of oxygen therapy was associated with development of ROP in a few studies. [9, 17, 19] Our observation may have been due to the fact that the screened neonates were of higher gestational age and had strict oxygen saturation monitoring in the NICU.

We observed that there was no significant association between RDS and ROP and similar findings were reported earlier.[14] However in a previous study RDS was found to predispose to ROP.[10] Respiratory distress syndrome was significantly associated with ROP which was due to use of supplemental oxygen in neonates with RDS which can cause hyperoxemia and arrest of retinal blood vessel growth. [31] Our observation may be due to inclusion of neonates of higher gestational age who may not have had severe RDS and also due to stringent saturation monitoring done in neonates on oxygen therapy. In the present study we ob-

served that sepsis was significantly associated with ROP (p=0.02). Among the factors studied it was observed that sepsis predisposed to development of ROP.[10,11,14] A retrospective study observed that late onset sepsis and gram negative sepsis were associated with ROP[19] [32] while clinical sepsis was also found to increase the risk of ROP [13]. Sepsis is a strong stimulator of neonatal systemic inflammatory response which can increase the risk of ROP. [33]

We observed that there was no significant association between blood transfusion and ROP. Our study did not analyze blood transfusion in terms of number of units or volume of blood received. Few studies have found an association between blood transfusion and ROP. [13, 14,19] Multiple blood transfusions have been found to predispose to ROP [10] and blood transfusion has been identified as an independent risk factor for ROP requiring treatment. [34] Analysis of risk factors for ROP revealed that blood transfusion had an impact on progression of ROP [31]. Blood transfusion increases adult hemoglobin and iron load in preterm neonates and results in increased oxygen delivery to the developing retina and iron load results in free radical formation [35]. Blood transfusions, recombinant erythropoietin therapy and anemia are risk factors for ROP. Iron load from transfusions catalyze the formation of reactive oxygen species, and accelerate oxidative damage, predisposing to ROP. [36] Blood transfusion was recognized as an independent risk factor for ROP that required therapy. [34]

It was observed that intraventricular hemorrhage did not significantly increase the risk of ROP. It was observed earlier that there was no significant relationship between the occurrence of ROP and intraventricular hemorrhage. [14] A strong evidence (p = 0.023) of an association between the presence of IVH and treatment of threshold ROP was observed. [37] IVH occurs due to the young vasculature of the germinal matrix and variations in cerebral blood flow, which is comparable to ROP in that both disorders are linked with immature vasculature and an unstable O2 supply [38]. Our observation of non significant relationship may be due to lesser number of neonates with intraventricular hemorrhage included in the study.

The limitations of the study include that it was done in a single center with limited sample size. The sample of screened neonates did not include significant number of neonates who were less than 28 weeks and less than 1000 gm as the mortality in this group was high and the small number of neonates who survived were not brought for follow up examination after discharge. The risk factors like duration of oxygen therapy and the FiO2 administered were not analysed. Also the number of units of blood transfused was also not analyzed.

Conclusion

The present study evaluated the incidence and risk factors influencing ROP and observed an incidence of ROP of 32% and there was significant association with sepsis. None of the maternal risk factors were significantly associated with ROP. Incorporating risk factors into ROP screening may help in early identification of ROP.

Conflicts of Interest: No conflicts declared.

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