ORIGINAL RESEARCH PAPER

Opthalmology

TO STUDY RISK FACTORS ASSOCIATED WITH ZONE- I RETINOPATHY OF PREMATURITY AND CORRELATE THE RISK FACTORS WITH CLINICAL OUTCOMES IN A TERTIARY CARE INSTITUTE

KEY WORDS: Retinopathy of Prematurity, Retina, Type 1 ROP, mechanical ventilation

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ABSTRACT

Introduction: Around 1 million children die each year because of complications of preterm birth and the preterm who survive face a lifetime disability, including learning disability, hearing impairment, and visual impairment. Retinopathy of prematurity (ROP) is a disorder of the development of retinal blood vessels in premature infants. Normally retinal vascularization starts from the optic disc to the Ora Serrata. Present study was conducted in a tertiary care centre to evaluate risk factors associated with Zone- I retinopathy of prematurity and correlate the risk factors with clinical outcomes. **Method:** Present study was a prospective observational study conducted at Department of Ophthalmology, Gandhi Medical College, and Hamidia Hospital, Bhopal. All the neonates having zone-I ROP at presentation according to ICROP classification were included in the study after obtaining permission from institutional ethics committee and consent from parents. **Results:** In present study, it was found that among the Type 1 ROP group baby Born with IVF was the most common maternal risk factor, followed by Twin pregnancy. And among the Type 2 ROP group twin pregnancy was the most common risk factor followed by PROM. When neonatal risk factors were studied, it was found that type 1 ROP was statistically significantly associated with gestational age < 28 weeks and with low birth weight< 1500 grams. History of NICU hospitalization, oxygen supplementation and mechanical ventilation history was statistically significant for type 1 ROP. **Conclusion:** Current study showed among the type 1 ROP group baby born with IVF was the most common maternal risk factor, followed by twin pregnancy. In our study duration of NICU admission and history of oxygen supplementation was found to be significant, which was longer in cases of type 1 ROP as compared to type 2 ROP.

INTRODUCTION

According to the world health organization (WHO), every year about 15 million babies are born prematurely around the world, which is more than one in ten babies(1). It is estimated that 15.22 million infants were born preterm in 2019, which is rising yearly(2). The preterm birth rate is 10.6% worldwide ranging from 8.7 to 13.4 % of infants born across regions(2). Around 1 million children die each year because of complications of preterm birth and the preterm who survive face a lifetime disability, including learning disability, hearing impairment, and visual impairment(1,2). Retinopathy of prematurity (ROP) is one of the important causes of preventable blindness in children globally(3). Developing countries are experiencing epidemic levels of retinopathy of prematurity (ROP), because of improved neonatal intensive care units with greater accessibility to NICU and improvement in survival rates of premature infants——(24). Retinopathy of prematurity (ROP) is a disorder of the development of retinal blood vessels in premature infants. Normally retinal vascularization starts from the optic disc to the Ora Serrata. Vascularization up to nasal Ora Serrata was completed by 8 months of gestation and temporal Ora by 10 months of gestation. This is why a peripheral avascular retina exists in a premature infant'——(57). Several studies have reported risk factors for the development of a severe form of retinopathy of prematurity (ROP) like gestational age (GA), low birth weight, Supplemental oxygen, prolonged mechanical ventilation, pulmonary complication, anemia, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), sepsis in Which Prematurity, low birth weight, septicemia, and raised bilirubin are seen with zone I ROP——(812). Present study was conducted in a tertiary care centre to evaluate risk factors associated with Zone- I retinopathy of prematurity and correlate the risk factors with clinical outcomes.

METHODS

Present study was a prospective observational study conducted at Department of Ophthalmology, Gandhi Medical College, and Hamidia Hospital, Bhopal. All the neonates having zone-I ROP at presentation according to ICROP classification were included in the study after obtaining permission from institutional ethics committee and consent from parents. Demographic data of all the infants were recorded in a preformed proforma. Data regarding neonatal risk factors such as gestational age, birth weight, duration of NICU admission, surfactant given, hyperbilirubinemia and phototherapy were noted at the start of study from their birth cards and medical cards they carried with them. Maternal risk factors such as pregnancy induced hypertension, preeclampsia, eclampsia, PROM, singleton or multiple pregnancy, cervical incompetence, UTI and assisted reproduction were noted. Significant post-natal problems such as apnoea, asphyxia, RDS, septicaemia and intraventricular haemorrhages, late postnatal steroid injection was also noted. History regarding need for mechanical ventilation, oxygen support and blood transfusion had also been taken into consideration. These risk factors were then correlated with the clinical outcomes.

Statistical Analysis

Data was collected and entered simultaneously in statistical package for social sciences (SPSS) version 23 and coded appropriately. The data was analysed keeping in view the aims and objectives of the study. Descriptive statistics were calculated to summarize the sample characteristics in terms of frequency and percentage. Graphs and Charts were made. Analytical and inferential analysis was applied between dependent variable and other independent variables. Significance was set at standard 0.05.

RESULTS

In the present study, 526 neonates were screened and Retinopathy of prematurity was detected in 131 neonates with an incidence of 24.90%. Out of those 131, Zone 1 ROP was detected in 50 neonates, giving an incidence of 9.50%. According to staging in the zone I ROP at first presentation, it was found that 52 (53.60%) eyes had stage 1, 21 (21.64%) eyes had stage 2, 16 (16.49%) eyes had stage 3 and 8 (8.24 %) eyes of 4 patients had bilateral APROP/AROP. The majority of patients had stage 1 disease. Also, 59 (60.82%) eyes had no plus or pre-plus disease, 20 (20.61%) eyes had plus disease and 18 (18.55%) eyes had the pre-plus disease.

When demographic characteristics were studied, it was found that in Type 1 ROP 20 were males and 12 were females and in Type 2 ROP,9 were males and 9 Were females. In patients with type 1 ROP, 11 patients were born before 28 weeks of gestation, and none of the patients were born after 35 weeks of gestation. The mean gestational age in type 1 ROP was 30.94weeks. In patients with type2 ROP, only one patient was born after 35 weeks of gestation, and no patients were born below 28 weeks of gestation. The mean gestational age in type 2ROP was 29.88 weeks. In the patients with type 1 ROP, 7 patients were < 1 kg which is extremely low birthweight and 23 patients were very low birth weight. The mean birth weight of type 1 ROP was 1247.60 grams. In the patient with type 2 ROP, only 2 patients were extremely low birthweight and 8 were very low birth weight. The mean birth weight of type 2 ROP was 1355.80 grams.

In present study, it was found that among the Type 1 ROP group baby Born with IVF was the most common maternal risk factor, followed by Twin pregnancy. And among the Type 2 ROP group twin pregnancy was the most common risk factor followed by PROM. No statistically significant association was found between any of the risk factors. When correlated with outcome, it was found that among infants with non-favourable outcome PIH and Eclampsia were the most common risk factor.

When neonatal risk factors were studied, it was found that type 1 ROP was statistically significantly associated with gestational age < 28 weeks and with low birth weight< 1500 grams. History of NICU hospitalization, oxygen supplementation and mechanical ventilation history was statistically significant for type 1 ROP. Rest all risk factors such as RDS, Surfactant, Asphyxia, blood transfusion, sepsis, PDA, Hyperbilirubinemia and Phototherapy were more common with the Type 1 ROP but had no significant association. When correlated with outcomes, it was found that all risk factors such as gender, gestational age, Birth weight, NICU admission, asphyxia, blood transfusion, sepsis, PDA, Hyperbilirubinemia and Phototherapy had no significant association with the outcome.

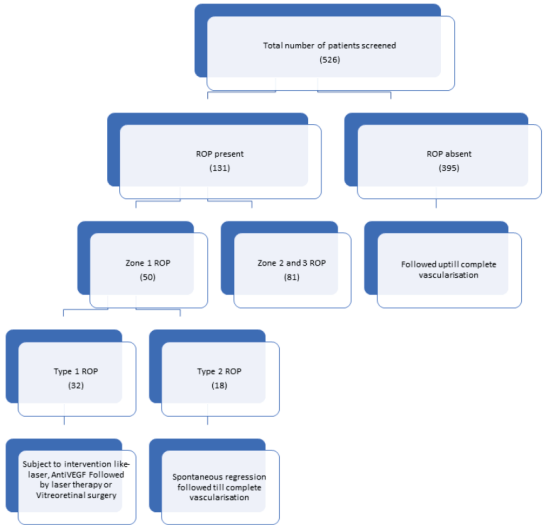

Table 1: Institutional Incidence Of Zone 1 ROP

Number of neonates	Frequency	Percentage
Total neonates screened	526	100
ROP detected	131	24.90%
Zone I ROP	50	09.50%
No ROP detected	395	75.09%

Table 2: Demographic Characteristics Of Study Population

Neonatal risk factors		Type 1 ROP (N=32)	Type 2 ROP (N = 18)	P value
Gender	Male	20 (62.5%)	9 (50.0%)	0.39
	Female	12 (37.5%)	9 (50.0%)	
Gestational age	< 28 weeks (Extremely preterm)	11 (34.4%)	0 (0.0%)	0.034
	28 – 30 weeks	6 (18.8%)	7 (38.9%)	
	31 – 32 weeks	7 (21.9%)	6 (33.3%)	
	33 – 34 weeks	8 (25.0%)	4 (22.2%)	
	35 – 36 weeks (Late preterm)	0 (0.0%)	1 (5.6%)	
	Mean SD	30.94 ± 1.59	29.88 ± 1.72	0.035
Birth weight	< 1 kg (Extremely low birthweight)	7 (21.9%)	2 (11.1%)	0.005
	1 – 1.5 kg (Very low birth weight)	23 (71.9%)	8 (44.4%)	
	1.6– 2 kg (Low birth weight)	2 (6.3%)	8 (44.4%)	
	Mean ± SD	1247.60 ± 254	1355.80 ± 290	.01

Table 3: Association Of Maternal Risk Factors For Type 1 And Type 2 In Zone 1 ROP

Maternal Risk Factors		Type 1 ROP (N = 32)	Type 2 ROP (N =18)	P value
PIH		3 (9.4%)	0 (0.0%)	0.18
Eclampsia/Preeclampsia		2 (6.3%)	0 (0.0%)	0.279
Premature rupture of membrane		0 (0.0%)	2 (11.1%)	0.054
Twin pregnancy		5 (15.6%)	3 (16.7%)	0.923
Born with IVF		6 (18.8%)	1 (5.6%)	0.197
Mode of delivery	Vaginal	24 (75.0%)	17 (94.4%)	0.086
	LSCS	8 (25.0%)	1 (5.6%)	

Table 4: Association Of Maternal Risk Factors For Favourable And Non Favourable Outcomes In Zone 1 ROP

Maternal Risk Factors		Favourable (N = 60)	Non favourable (N = 4)	P value
PIH		4	2	0.042
Eclampsia/Preeclampsia		2	2	0.008
Premature rupture of membrane		0	0	-
Twin pregnancy		10	0	0.530
Born with IVF		12	0	0.483
Mode of delivery	Vaginal	44	4	0.399
	LSCS	16	0	

Table 5: Association Of Neonatal Risk Factors For Type 1 Rop And Type 2 ROP In Zone 1 ROP

Neonatal risk factors		Type 1 ROP (N =32)	Type 2 ROP (N = 18)	P value
Duration of NICU hospitalization	< 1 week	4 (12.5%)	3 (16.7%)	0.684
	>1 week	28 (87.5%)	15 (83.3%)	
Mean duration of NICU (days)		21.32±12.185	16.12±7.656	.05
Oxygen supplementation	< 1 week	6 (18.75%)	6 (33.3%)	0.246
	>1 week	26 (81.25%))	12 (66.7%)	

Mean oxygen supplementation (days)		16.32±10.80	11.76±5.953	.04
Ventilator support	<1 week	8 (57.1%)	4 (66.7%)	0.69
	>1 week	6 (42.9%)	2 (33.3%)	
Mean ventilator history (days)		6.29±3.352	5.13±4.291	.03
RDS		30 (93.8%)	16 (88.9%)	0.543
Surfactant		27 (84.4%)	12 (66.7%)	0.417
Asphyxia		10 (31.3%)	5 (27.8%)	0.797
Sepsis		16 (50.0%)	8 (44.4%)	0.706
PDA		1 (3.1%)	0 (0.0%)	0.449
Blood transfusion		4 (12.5%)	5 (27.8%)	0.177
Hyperbilirubinemia		8 (25.0%)	1 (5.6%)	0.086
Phototherapy		6 (18.8%)	1 (5.6%)	0.197

Table 7: Association Of Neonatal Risk Factors For Favourable And Non-favourable Outcome ROP In Zone 1 ROP

Neonatal risk factors		Favourable (N = 60)	Non favourable (N = 4)	P value
Gender	Male	36	4	0.25
	Female	24	0	
Gestational age	< 28 weeks	20	2	0.60
	28 – 30 weeks	12	0	
	31 – 32 weeks	12	2	
	33 – 34 weeks	16	0	
	35 – 36 weeks	0	0	
Birth weight	< 1 kg	14	0	0.65
	1 – 1.5 kg	42	4	
	1.6– 2 kg	4	0	
Duration of NICU hospitalization	< 1 week	8	0	0.58
	>1 week	52	4	
Mean duration of NICU (days)		21 ± 12	28 ± 1	0.49
Oxygen supplementation	< 1 week	10	2	0.24
	>1 week	50	2	
Mean oxygen supplementation (days)		16 ± 10	13 ± 10	0.72
Ventilator support	<1 week	16	0	-
	>1 week	12	0	
Mean ventilator history (days)		6 ± 3		
RDS		58	2	0.00
Surfactant		54	0	0.00
Asphyxia		20	0	0.32
Sepsis		30	2	1
PDA		2	0	0.79
Blood transfusion		6	2	.09
Hyperbilirubinemia		14	2	0.39
Phototherapy		10	2	0.24

DISCUSSION

In the present study, 526 infants were screened and showed an institutional incidence of ROP of 24.9% (131 out of 526 infants) and zone I ROP of 9.5% (50 infants).

In our study, according to staging in zone I at first presentation 52 (53.60%), 21 (21.64%), 16 (16.49%), and 8 (8.24%) eyes had stage 1, stage 2, stage 3, and APROP/AROP respectively. Out of these 3 neonates have unilateral involvement with stage 1 others had bilateral involvement. 4 infants had bilateral APROP/AROP. Of these 20.61% of neonates had the plus disease at presentation. The current study showed among the type 1 ROP group baby born with IVF was 18.8% as compared to 5.6% in type 2 ROP was the most common maternal risk factor. Friling R et al(13) (2007) found that assisted conception is not a risk factor for ROP. Blumenfeld et al–(14) (1998) found no association between multiple gestation and ROP. The lack of association of many of the maternal risk factors with ROP in the present study that are ideally expected to have an association could be due to inadequate documentation of maternal condition and lack of awareness among people regarding various conditions. Where we found that extreme prematurity and very low birth weight was to be a significant risk factor for the development of zone I type 1 ROP. In our study NICU hospitalization duration was evaluated in zone I and we found that type 1 ROP group was significantly higher mean duration of NICU hospitalization of 21.32 ± 12.185 days as compared to 16.12 ± 7.656 days in type 2 ROP group. This difference was found statistically significant with the development of type 1 ROP in zone I. Ali AA, Gomaa NAS, Awadein AR, et al(15) (2017) found that a longer duration of hospitalization is responsible for the development and progression of ROP which are similar to our study. We evaluated mean oxygen supplementation duration in zone I and we found that in type 1 ROP mean oxygen supplementation duration was significantly higher 16.32 ± 10.80 days as compared to 11.76 ± 5.953 days in type 2 ROP. This difference was found statistically significant with the development of type 1 ROP in zone I. According to an Indian study by Nikhil R et al(16) (2016) screened 78 babies out of them 51 were given oxygen therapy and 15 (29.41%) of them developed ROP. Anudeep K et al(17) (2019) found the mean duration of oxygen therapy in babies with ROP was 11 days, and in babies without ROP was 3.37 days. In our study, on evaluating the mean ventilation history we found that type 1 ROP has significantly higher mean ventilation history of 6.29 ± 3.352 days as compared to 5.13 ± 4.291 days in type 2 ROP. This difference was found statistically significant with the development of type 1 ROP in zone I (P-value <0.05). In our study, respiratory distress syndrome (93.8%) and asphyxia (31.3%) were more common among newborns with type 1 ROP as compared to type 2 ROP in zone I but no statistical significance was seen. In an Indian study, Thakre et al(18) (2013) found out of 33 neonates detected with ROP, 26 has RDS (78.7%), and 10 required mechanical ventilation (30.3%) with a p-value of both being <0.001%. According to Rachel et al—(19), (2020), cases with type 1 ROP had more prolonged days of invasive ventilation and higher fractional oxygenation requirements. Cases were intubated for significantly longer periods (median 20 days for cases vs 5 days for controls, p-value of 0.002) and on oxygen therapy for a significantly longer period (median 35.5 days for cases vs 6 days for controls, p-value of 0.006). In our study sepsis was also significantly more in neonates with type 1 (50%) as compared to those with type 2 (44.4%) in zone I but no statistical significance is seen. According to Hakeem et al(20) (2012), reported that sepsis was significantly associated with the development of ROP. According to Sen et al(21) (2019) study, infants with zone I ROP found septicaemia in 23.07%. In our study, 12.5% of infants with type 1 ROP had blood transfusions as compared to 27.8% with type 2 ROP. Blood transfusion is a risk factor for the development of ROP but is not significantly associated with type 1 ROP in zone I. Unlike our study Yau GS et al(22) (2016) found anaemia to be associated with the development of both ROP and type 1 ROP. In our study 25% of infants with type 1 ROP had raised bilirubin as compared to 5.6% in type 2 ROP in zone I and 18.8% received phototherapy in type 1 ROP as compared to 5.6% in type 2 ROP. In accordance with our study Hosono S et al(23) (2002) also found no protective effect of bilirubin on the development of severe ROP. According to Indian studies by Gupta A K et al(24) (2009) phototherapy is statistically significant for the development of ROP. In our study, we found that for infants with unfavourable anatomical outcomes all of them had a vaginal delivery, the infant's mother had pregnancy-induced hypertension and eclampsia, both infants were male, one of them was extremely preterm and both of them was very low birth weight. The mean duration of NICU hospitalization is higher (28 ± 1 vs 21 ± 12) with infants with unfavourable outcomes. Infants who had RDS and received surfactants had a favourable outcome as compared to those who did not received surfactant due to delayed presentation. According to Parchand et al(25) (2021), the study observed that babies with unfavourable anatomical

outcomes, were extremely low birth weight, preterm had anaemia, had repeated blood transfusions, and required oxygen supplementation ventilator support, and NICU admission.

CONCLUSION

Current study showed among the type 1 ROP group baby born with IVF was the most common maternal risk factor, followed by twin pregnancy. In our study duration of NICU admission and history of oxygen supplementation was found to be significant, which was longer in cases of type 1 ROP as compared to type 2 ROP. Rest of the risk factors such as RDS, surfactant, Asphyxia, and blood transfusion were more common with type 1 ROP. A favourable outcome is seen in 93.75% and a non-favourable outcome is seen in 6.25% after treatment. Among babies with unfavourable outcomes PIH and eclampsia were the most common risk factors. Non favourable outcome infants were extreme preterm and BW was less than 1500 grams. The mean duration of NICU hospitalization is higher with infants with unfavourable outcomes. Infants who had RDS and received surfactants had a favourable outcome.

As ROP is a sight-threatening condition especially in zone I and if not treated promptly it is important to be very cautious while screening in each follow up visit so that none of the findings are missed

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Limitations and Scope: Major limitation of this study is sample size, as zone I retinopathy is seen mostly in extreme preterm babies which are mostly having other comorbidities and screening is delayed. Also, oxygen exposure was measured in terms of duration of oxygenation. However, quantification with respect to oxygen concentration and oxygen saturation (SpO2) was not done. More maternal factors like anaemia during pregnancy, gestational diabetes mellitus and chorioamnionitis could not be included in the study due to lack of documentation.

Conflicts of Interest: No potential conflict of interest relevant to this article was reported

Ethical Approval: Approved

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