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Original Research Article

Clinical profile and risk factors of retinopathy of prematurity (ROP) in central Indian population

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Abstract:
Background: Retinopathy of prematurity (ROP) is a potentially blinding disorder of the neonates seen mostly in preterm neonates.
Objective: To study the incidence, risk factors, clinical profile and immediate outcome of neonates with ROP after screening.
Method: A prospective observational study was carried out among 336 neonates at Gandhi Medical College, Bhopal from January 2018 to June 2019. After recording detailed history of mother and neonate, eye examination and screening were performed. Prevalence, epidemiology, clinical profile, risk factors and outcomes of ROP were assessed.

Results: The incidence of ROP in the present study was 19.94%, 31.3% babies developed stage 1 ROP, 26.8% developed stage 2 ROP, 23.3% had stage 3 ROP, 13.4% had stage 4 ROP and 5.97% had stage 5 ROP. Of the 67 babies who developed ROP 35.82% babies had spontaneous regression of ROP and developed mature retina whereas 64.18% babies required treatment of ROP.
Conclusion: Our study concludes that low birth weight, gestational age, oxygen administration, duration of oxygen exposure, mechanical ventilation, respiratory distress syndrome, surfactant use, sepsis, blood transfusion, bronchopulmonary dysplasia, and apnoea are the risk factors which play a significant role in development of ROP.

Keywords: Retinopathy of prematurity, preterm, risk factors, incidence, low birth weight

1. INTRODUCTION

Retinopathy of Prematurity (ROP) is a retinal disorder mainly affecting low birth weight and premature infants. The stimulus for the abnormal growth of blood vessels comes from the peripheral immature retina. It presents either as mild disease with no visual defects or aggressive disease with new vessel formation with subsequent retinal detachment and blindness. In developing countries, with developments in neonatal care increases the survival of very low birth

infants which invariably increases the incidence of ROP. The incidence of ROP in India is between 20 to 30% [1, 2].
Neonatal screening shows that nearly one third to half of neonates show some degree of ROP, however in majority of infants ROP regresses on its own, while in some cases it can progress to the stage of retinal detachment and blindness [1]. Although dramatic vision loss may be prevented by appropriate treatment such as Laser photocoagulation or cryotherapy of the avascular retina which stops the progression of ROP to some extent, effective screening strategy still remains the mainstay of ROP management program. Major improvements in the screening methods of susceptible infants play an important role in saving vision in premature infants in India. Hence, the present study was designed to examine the incidence and risk factors of ROP and to study the clinical profile and immediate outcome of neonates with ROP after screening in new-born babies admitted in a tertiary hospital of tier two city, in central part of Madhya Pradesh which caters to the people in the district of Bhopal as well as nearby districts and is equipped with a good neonatal care.

2. MATERIAL AND METHODS:

A prospective observational study of 18 month duration was carried out among 336 neonates admitted in the SNCU, Department of Paediatrics in conjunction with Department of Ophthalmology, Gandhi Medical College Bhopal from January 2018 to June 2019. Prior to the study, an approval of ethical committee and an informed written consent from the parents of all neonates was obtained.

Following RBSK guidelines of June 2017, infants with birth weight less than 2000gm, gestational age less than 34 weeks and infants of gestational age between 34 to 36 weeks with risk factors such as, cardio-respiratory support, prolonged oxygen therapy, respiratory distress syndrome, chronic lung disease, foetal haemorrhage, blood transfusion, neonatal sepsis, exchange transfusion, intraventricular haemorrhage and apnoea and infants with unstable clinical course were included and screened in the study. Infants with lethal congenital malformation, infants with birth weight more than 2 kg and gestational age more than 34 weeks with stable clinical course and those who died before screening could be done were excluded.
A team consisting of Ophthalmologist, Paediatrician/Neonatologist and a trained nurse from SNCU carried out the first screening of the infants between 21st and 28th postnatal day. Infants with less than 28 weeks of gestation or with birth weight less than 1200 grams were first screened at 2-3 weeks after delivery. A detailed history of mother's antenatal visits, last menstrual period, perinatal period, maternal disease and the course of infant's admission in the hospital were recorded in a preset proforma. After stabilization of the infant, blood samples were drawn for complete blood counts, differential counts, CRP, blood culture and sensitivity, blood urea, creatinine and electrolytes**.** Eye examination and screening was performed by an Ophthalmologist using indirect ophthalmoscope and was repeated every two weeks until vascularization of the retina reached normal completion or until the regression of ROP or development of ROP requiring treatment.
Prevalence, epidemiology, clinical profile, risk factors and outcomes of ROP were assessed by data analysis using IBM SPSS ver. 20 software. Quantitative data was expressed as mean and

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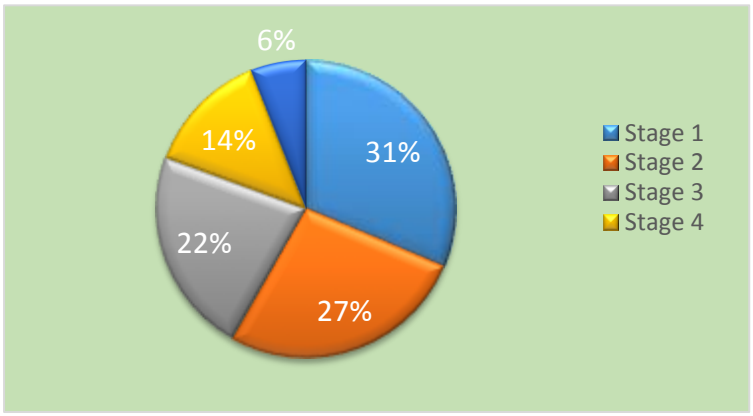
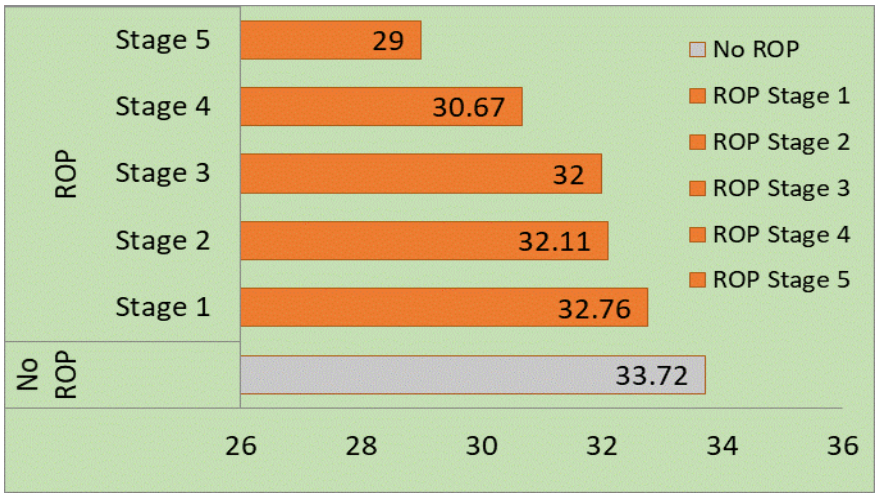
standard deviation. Categorical data was expressed as percentage. One-way ANOVA and student t test were used to compare the mean. Chi Square test was used to compare the percentage. Odds ratio was obtained using multivariate and binomial regression. Relative risk was obtained using chi square risk estimation. P value of <0.05 was considered as significant.

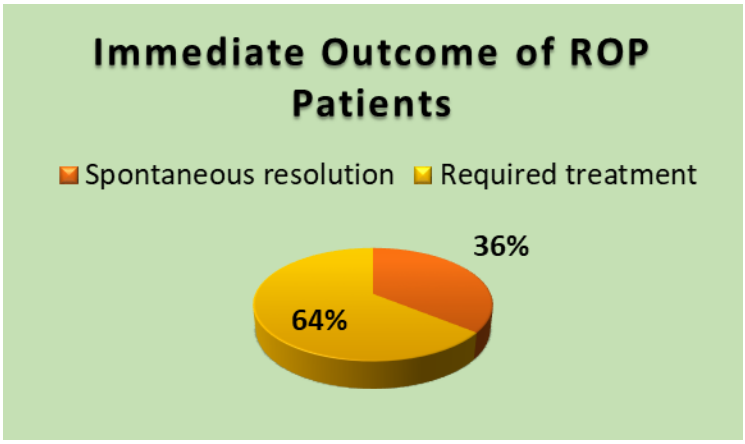
3. RESULTS:



Graph 1 Stage wise Frequency distribution of ROP patients



Graph 2 Stage wise mean Gestational Age of babies with ROP



Graph 3 Immediate outcome of patients with ROP

Table 1: Demographic characteristics of neonates and mother

General and neonatal factors		ROP	No ROP	Total	p value
Mode of Delivery	**NVD**	43 (12.8 %)	174 (51.79 %)	217 (64.58 %)	0.9384
	LSCS	24 (7.14 %)	95 (28.27 %)	119 (35.42 %)	
Multiple Births	**Present**	11 (3.27 %)	36 (10.71 %)	47 (13.99 %)	0.5216
	Absent	56 (16.67 %)	233 (69.35 %)	289 (86.01 %)	
Weight for Gestational Age	**AGA**	13 (3.87 %)	78 (23.21 %)	91 (27.08 %)	0.113
	SGA	54 (16.07 %)	191 (56.85 %)	245 (72.92 %)	
Gender	**Male**	30 (8.93 %)	129 (38.39 %)	**159 (47.32 %)**	0.641
	Female	37 (11.01 %)	140 (41.67 %)	**177 (52.28 %)**	
Gestational Age	**≤34 weeks**	65 (19.35 %)	119 (35.42 %)	184 (54.76 %)	**<0.0001**
	> 34 weeks	2 (0.6 %)	150 (44.64 %)	258 (47.02 %)	
Birth weight	**≤ 2 kg**	66 (19.64 %)	216 (64.29 %)	**282 (83.93 %)**	**<0.0001**
	> 2kg	1 (0.3 %)	53 (15.77 %)	**54 (16.07 %)**	
Maternal factors					
Age	**20-34 years**	28 (8.33 %)	118 (35.12 %)	146 (43.45 %)	0.9538
	<20 years	33 (9.82 %)	128 (38.1 %)	161 (47.92 %)	
	>34 years	6 (1.79 %)	23 (6.85 %)	29 (8.63 %)	
Obstetric History	**Nullipara**	27 (8.04 %)	113 (33.63 %)	140 (41.67 %)	0.7996
	Multipara	40 (11.9 %)	156 (46.43 %)	196 (58.33 %)	
Anemia	**Present**	25 (7.44 %)	115 (34.23 %)	140 (41.67 %)	0.4192
	Absent	42 (12.5 %)	154 (45.83 %)	196 (58.33 %)	
Infection	**Present**	13 (3.87 %)	57 (16.96 %)	70 (20.83 %)	0.7473

	Absent	54 (16.07 %)	212 (63.1 %)	266 (79.17 %)	
Complication	**Present**	23 (6.85 %)	73 (21.73 %)	96 (28.57 %)	0.2437
	Absent	44 (13.1 %)	196 (58.33 %)	240 (71.43 %)	
Antenatal steroids	**Given**	48 (14.29 %)	184 (54.76 %)	232 (69.05 %)	0.7473
	Not given	19 (5.65 %)	85 (25.3 %)	104 (30.95 %)	

Table 2: Univariate and multivariate analysis of the variables in the study

Variable	**ROP**	**No ROP**	**Univariate analysis**		**Multivariate analysis**	
			Odds (95% CI)	**p value**	**Odds (95% CI)**	**p value (Logistic Regression)**
Oxygen therapy	65	165	20.48 (5.537 to 86.53)	<**0.0001**	6.02 (1.63 to 25.45)	**0.003**
Ventilation	7	4	4.85 (2.475 to 8.742)	<**0.0001**	1.56 (0.8 to 2.82)	0.072
RDS	36	77	2.896 (1.677 to 5.08)	<**0.0001**	1.93 (0.54 to 2.64)	**0.0491**
Anemia	21	56	1.736 (0.9585 to 3.074)	0.0666	1.69 (0.38 to 3.23)	0.4528
BPD	6	2	13.13 (3.13 to 64.55)	<**0.0001**	4.38 (1.04 to 21.52)	0.0537
Sepsis	16	167	0.1916 (0.1036 to 0.3562)	<**0.0001**	1.08 (0.47 to 2.15)	**0.0023**
IVH	4	8	2.071 (0.6738 to 6.54)	0.237	1.59 (0.73 to 3.87)	0.633
Surfactant	2	1	8.246 (0.9393 to 119.8)	**0.0419**	2.5 (0.98 to 8.3)	0.0748
PDA	7	19	1.535 (0.5865 to 3.614)	0.3536	1.67 (0.26 to 4.57)	0.5716
HIE	58	222	1.364 (0.6279 to 2.969)	0.4273	1.57 (0.58 to 3.23)	0.8333
Birth weight <2 Kg	66	1	16.19 (2.827 to 166.6)	<**0.0001**	5.78 (1.01 to 59.5)	**0.001**
Gestational age <34	65	2	40.97 (11.09 to 172.5)	<**0.0001**	11.71 (3.17 to 49.29)	**0.0021**

The present study was conducted to study the incidence and risk factors of ROP in neonates. Mean gestational age and mean birth weight of newborns in our study was 33.25±2.05 and1.62±0.40 kg respectively. A total of 67 out of 336 babies were found to have ROP with the incidence of 19.94%. Stage wise distribution of the ROP patients is shown in graph 1. In ROP

group, 19.35% babies were of ≤ 34 weeks of gestational age, while only 0.6% were above 34 weeks. Newborn with ROP had mean gestational age of 31.91±1.411 weeks and that of without ROP is 33.71±2.027 weeks. Our study noticed a significant association between gestational age and development of ROP (P<0.0001). Stage wise distribution of mean age of neonates is described in graph 2 which shows decrease in mean age with increase in the stage of ROP. Most of neonates (19.64%) weighed less than 2000gm among which 14.58 % weighed between 100-1499 gms and only 1 child weighed more than 2000gm. Incidence of ROP decreased with increasing Birth weight. Low birth weight was found to be significant risk factor with (P<0.0001). Mean birth weight of neonates in with ROP was 1.35±0.27 kg while that of without ROP was 1.69±0.39, the comparison was statistically significant (p<0.0001). However, the mean birth weight in stage 1 of ROP was 1.48 ± 0.24 which was not statistically significant (p>0.05). The maternal and neonatal demographic characteristics are depicted in table 1.

Univariate and multivariate odds were calculated for important risk factors and significant correlations (odds) was seen with oxygen exposure, ventilation, Respiratory distress syndrome (RDS), Bronchopulmonary dysplasia (BPD), Sepsis, use of surfactant, intraventricular hemorrahage (IVH), anemia, Hypoxic Ischemic Encephalopathy (HIE), acute kidney injury (AKI), Shock requiring inotropes, PDA and jaundice requiring phototherapy (table 2).

In our study, Out of 336 neonates 68.45% received oxygen therapy while 31.5% did not receive oxygen in any form. The mean oxygen exposure for No ROP Group 2.45± 3.56 days was significantly lower than that of ROP group. The mean oxygen exposure with increments in the stage of ROP gradually increased till stage 3 compared to No ROP group. RDS was seen in 33.63% neonates out of which 36 patients belonged to the ROP group and 77 belonged to no ROP group. Surfactant was administered in 3 patients in our study out of which 2 neonates developed ROP. Out of 67 babies with ROP 20.9% had episodes of Apnoea during their SNCU stay. During the study period, 8 (2.39%) neonates developed BPD out of which signs of ROP was present in 75% and 25% showed no signs of ROP. A total of 19.4% neonates showed culture proven sepsis while 56.71% neonates had probable sepsis. Total 19% neonates in our study received blood transfusion (packed RBC) out of which 29.7% showed signs of ROP.

IVH was seen in 6% and 3% neonates of ROP and no ROP group respectively. In ROP group 31.34% patients had anemia compared 20.8% in no ROP group. Out of 336, 16.67% patients had HIE, of which 16% had ROP. While the incidence of ROP was 20.71% in patients without HIE. In ROP group 6% patients had AKI compared to 5.6% no ROP group. A total of 11.31% patients developed shock that required inotropes and out of those 23.7% developed ROP. While 88.69% patients were without shock and among them 19.4 % patients developed ROP. Out 67 patients with ROP 10.44% were associated with PDA while in no ROP group PDA was present in 7% of patients.

In our study 24.4% neonates developed jaundice and were given phototherapy, among which 23.17% neonates developed. Among the rest of neonates (75.6%) who did not receive phototherapy, only 18.9% developed ROP. Among the 12 (3.57%) neonates who required DVET, 3 (25%) neonates developed ROP while 9 (75%) neonates did not show any sign of ROP. The chi-square analysis revealed oxygen exposure, RDS, BPD, proven and probable sepsis to be an important risk factor associated with the development of ROP with p<0.0001, apnea, blood transfusion with p<0.05. However no significant association was noted between IVH, anemia, HIE, AKI, shock requiring iontophoresis, jaundice requiring phototherapy, double volume

exchange transfusion (DVET) and ROP (p>0.05). Among the diagnosed 67 babies 21 babies had spontaneous regression of ROP and developed mature retina. 43 babies needed laser and/or vitreoretinal surgery. Out of 43 babies 16 underwent laser surgery in our own department and 27 babies were referred to higher centre due to lack of infrastructure and expert care for vitreoretinal surgery. Out 43 babies 7 babies needed second laser surgery and 16 babies died due to complications related to prematurity and VLBW (graph 3)

4. DISCUSSION

Screening for retinopathy of prematurity is essential in all high-risk babies, which is almost not possible in developing countries like India with poor resources. The present study was carried out to study the incidence and risk factors of ROP among neonates and we found the incidence of ROP to be 19.94% which is well within the national average of ROP that is 20-30% [1]. Although several studies [3-5] have shown similar incidences, few have reported higher and lower incidences [6-10] which could be because of different screening criteria and variable sample size of the study. ROP is a disease of immature retina, occurrence of which is inversely related to gestational age. More premature the infant, the more likely the disease is to develop [11]. Results of our study are in agreement to this fact. Mean gestational age of babies with ROP in our study was 31.91±1.411 weeks which is known to be an independent risk factor of ROP as described by Rao et al [12]. According to literature there exists a significant relationship between ROP and birth weight, among VLBW (<1500 gram) and ELBW (<1000 gram) babies [13-15]. We found low birth weight as significant risk factor for ROP with p value of < 0.001 which is in accordance with other studies [16, 17].

Several studies have provided evidence that oxygen use as well as fluctuations in oxygen concentration is now a recognized risk for ROP as supported by earlier basic research [18-24]. York and colleagues [23] believed that fluctuations in oxygen level increased the odds of a preterm infant developing severe ROP. These fluctuations in oxygen delivered to the retina in the preterm infant occurs due to apnoea and bradycardia, changes in foetal/adult haemoglobin, shunting of blood in the lungs, and changes in CO2 and temperature. Similarly in our study, Oxygen use and mechanical ventilation was found to be significant risk factor with p value of <0.001 which is in accordance with studies by Shah et al [16] and Taqui1 et al [25].

Similarly we also noted RDS and administration of surfactant to be a significant risk factors in development of ROP (p<0.001**).** There is mixed opinion about the relationship between RDS and surfactant with development of ROP in literature. Parekh et al [26] and Parmar et al [6] found significant association, while Kumar et al [10] and Shahidullah et al [27] did not find any correlation between RDS and surfactant use in the development of ROP. Although administration of surfactant was a significant risk factor in our study, as only 3 neonates were given surfactant the outcome of which cannot be extrapolated in a large cohort. More studies are required with this perspective. We found sepsis to be another important risk factor in development of ROP which is in accordance with studies by Aggarwal et al [28] and Taqui1 et al [25]. However, Shahidullah et al [27] and Kumar et al [10] in their respective studies did not find a significant relationship between sepsis and ROP. ROP and BPD are multifactorial diseases mainly occurring in premature infants. It is believed that some factors found in babies with BPD affect both the initiation and severity of ROP [29]. We found BPD to be yet another important risk factor for the development of ROP with p value <0.001 which is in accordance with study

results by Sabzehei et al [4] and Shah et al [16].

Apnoea causes an increase in oxygen use as well as fluctuations in oxygen delivered to the retina in an infant, is recognised as an important risk factor for development of ROP. Along with the results of Aggarwal et al [28] and Dutta et al [30] results of our study are in agreement to this fact, however Parmar et al [6] in his study did not find apnoea to be an important risk factor. In our study, both Hyperbilirubineamia requiring phototherapy and Hyperbilirubineamia requiring DVET had no significant association with ROP which is similar to results reported by Hakeem et al [5] and Wani et al [31]. Whereas, VA Shah et al [16] found both these factors to be significant for the development of ROP. Although, anemia and packed red cell blood transfusion are found to be one amongst the many risk factors for ROP [2], similar to reports by Parekh et al [26] and Dutta et al [30] we did not find a significant relationship between them. Similarly, other risk factors such as IVH, HIE, AKI, Shock and PDA were also studied in our study and they were found to be not significant in the development of ROP. While, Hakeem et al [5] and Raj et al [8] reported similar findings in their studies, Shah et al [16], Taqui1 et al [25] and Sabzehei et al [4] reported IVH, PDA and shock requiring inotropes to be a significant risk factor for ROP.
Several maternal factors were considered as risk factors of ROP such as age, parity, maternal anemaia, maternal infection, complication related to pregnancy such as Antepartum haemorrhage, Pre-eclampsia and eclampsia, multiple births and use of antenatal steroids. However we did not find a significant association between maternal factors and development of ROP. Similar results were reported by Ahuja et al [7], Yau et al [32] and Huang et al [33]. Increasing maternal age has recently been reported as a risk factor for the development of ROP in Taiwan by Wu et al [34] and in another study by Shah et al [16] preeclampsia and prenatal betamethasone exposure were found to be associated with ROP; however, we did not observe this trend in the present study.
Despite including most of the risk factors in our study, since it was a single centred study, the results does not echo the actual epidemiology. Short duration of the study limited the follow up of ophthalmic morbidities, Fio2 could not be measured in a resource limited setting. Since limited neonates received surfactant therapy, its correlation of ROP could not be assessed properly. Further studies are advised to find out association of risk factors and co morbidities implicated in the development of ROP.

5. CONCLUSION

ROP is emerging as one of the complications of prematurity and important causes of preventable childhood blindness in India. Timely retinal screening with indirect ophthalmoscopy is the key for early detection, so that timely intervention could be done to halt its progression and prevent morbidities. Hence it is of utmost importance to increase the awareness of the disease and to make sure that these babies should be screened timely, so that appropriate measures could be taken.

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