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RISK FACTORS FOR PREVALENCE OF RETINOPATHY OF PREMATURITY IN A TERTIARY CARE CENTRE OF NORTH INDIA

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ABSTRACT
Background: The goal of the current study was to shed light on the risk factors responsible for the prevalence of ROP in infants born before 34 weeks of gestation or in infants born with birth weights under 2000 g admitted in NICU at a tertiary care hospital. **Methods**: This study was a hospital based prospective observational study conducted on 160 neonates after ethical clearance within a period of four months. The study population comprised of neonates less than 34 week of gestational age and with birth weight less than 2000 gm and gestational age between 34-36 weeks. All statistical analysis was done using appropriate statistical software like SPSS (Statistical Sciences Package for Social). Categorical / Nominal variables were indicated as number and percentage and were surveyed using Chi square test or Fischer exact test. Continuous variables were expressed as mean and standard deviation. **Results**: Among the 160 neonates screened, 30 neonates were found to have Retinopathy of prematurity, giving a rate of 18.8% for ROP. Among the 30 neonates with ROP, 10 (33.3%) delivered at gestational age <32 weeks, 12 (40%) had respiratory distress syndrome, 19 (63.3%) had sepsis, 23 (76.7%) required oxygen therapy, 5 (16.7%) received mechanical ventilation, 18 (60%) received blood transfusion, 17 (56.7%) had hypoglycemia. Other risk factors have been discussed in detail in the article. **Conclusion:** Prematurity, low birth weight, inadvertent use of oxygen therapy blood transfusion, sepsis and hypoglycemia were found to be significant risk factor for ROP.

INTRODUCTION

Retinopathy of prematurity is a vaso-proliferative condition frequently affecting premature infants (ROP). In developing nations, the incidence of ROP blindness has been on the rise during the past ten years. According to studies, ROP—also known as the "third epidemic"—is the main cause of blindness

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in China, Southeast Asia, South and Latin America, and Eastern Europe, particularly in the cities of recently industrialized nations [1]. 500 children in India are thought to go blind from ROP each year [2]. Even though premature infant survival increased in the ensuing decades and monitoring techniques for oxygen supplementation were improved, ROP appeared with a rising incidence (second epidemic) [2].

Due to better survival rates among very low birth weight preterm neonates, especially birth weights ≤ 1500 g, who are most at risk for developing ROP, the condition has received considerable research on a global scale. The better prenatal care may be responsible for these higher numbers. The elevated rates are causing other preterm birth-related comorbidities, such as blindness secondary to ROP, to arise more frequently and with substantial social repercussions. Worldwide, nearly 10% of all births are premature (before 37 weeks' gestation) [3]. ROP is a multifactorial disease [4]. The condition is brought on by aberrant vascular proliferation in the developing retina, which results from insufficient vascularization of the retinal tissue brought on by hyperoxia, which kills endothelial cells and inhibits VEGF. The developing retinal tissue becomes ischemic and hypoxic as a result of the closure of emerging capillaries. Neovascularization results from this process' upregulation of VEGF [5-7]. ROP can proceed to severe ROP, which is linked to a higher risk of retinal detachment-related blindness. Macular folds, refractive amblyopia and strabismic amblyopia are possible further problems [8-12]. According to numerous studies, there are a number of risk factors for this condition, some of which can result in severe ROP (BW, GA, supplemental oxygen, prolonged mechanical ventilation, Apgar score, pulmonary complications, anaemia, intraventricular haemorrhage (IVH), necrotizing enterocolitis, sepsis). Other risk factors for ROP include apnea, different maternal conditions (such as diabetes, preeclampsia, and maternal smoking), heart illness, increased blood carbon dioxide intake, decreased blood O2, bradycardia, and transfusion [13-15]. Early detection of severe ROP and evaluation of risk factors enable the implementation of particular treatment interventions, minimizing the severity of ROP sequelae and adverse outcomes [16].

Stages of ROP

It denotes the degree of vascular changes. There are five stages.

Stage 1 A demarcation line between vascular & avascular retina

Stage 2 The demarcation line grows to form a ridge

Stage 3 Ridge with extra retinal fibrovascular proliferation

Stage 4 Subtotal retinal detachment

Stage 5 Total retinal detachment

Plus disease:

It is an indicator of severity of the disease and is defined as venous dilation and arterial tortuosity of the posterior pole vessels.

Pre-plus disease

It is defined as posterior pole vascular dilation and tortuosity which is more than normal but less than plus disease

Aggressive posterior ROP

This refers to a rare, fast progressing ROP variant once known as "rush sickness." Its posterior location, severe plus disease, and flat intraretinal neovascularization are distinguishing features. If not treated right away, it can develop into stage 5 ROP and blindness very quickly.

The goal of the current study was to shed light on the previous research on ROP in infants born before 34 weeks of gestation or in infants born with birth weights under 2000 g and gestational ages between 34 and 36 weeks with emphasis on their prevalence and incidence.

METHODS

This study was a hospital based prospective observational study conducted on 160 neonates after ethical clearance within a period of four months. The study population comprised of neonates less than 34 week of gestational age and those babies with birth weight less than 2000 gm and gestational age between 34-36 weeks with risk factors admitted to NICU during the study period and screened for retinopathy of prematurity.

Data was collected using a semi structured proforma. To obtain information from subjects, relevant history and written informed consent was taken from parents.

Inclusion criteria

1. All neonates of both sexes born less than 34 weeks of gestation
2. All neonates of both sexes born between 34-36 weeks of gestation and babies weighing less than 2000gm admitted in NICU with following risk factor
    - Hyerglycemia/hypoglycemia
    - Oxygen therapy given via mechanical ventilator/ CPAP/ HFNC/ NASAL PRONGES/ HOOD for any duration

- Multiple pregnancy
- Blood component transfusion
- Anemia in mother or baby
- Sepsis
- Apnea of prematurity
- Respiratory disstress syndrome
- Shock/use of inotropes
- Patent ductus artrieosus
- Neonatal jaundice

Exclusion criteria:

- Babies with ocular disorder which interfere with fundus examination.
- Babies who were not following up till complete vascularisation of retina.
- Babies with congenital retinal abnormalities.

A written informed consent was acquired from parent / guardian before inclusion into the study. All neonates included in the study were subjected to following:

1. Detailed maternal history, details of assessment of intrauterine fetal wellbeing, Gestational age at birth, sex and weight of baby, mode/ duration/fio2 given for oxygen therapy and other risk factor of the baby were recorded on the predesigned proforma.
2. Thorough clinical and neurological examination was done. The babies were then evaluated by an ophthalmologist for assessing presence of retinopathy of prematurity.
3. Investigation like Complete blood counts, blood culture, CRP, Peripheral smear were done in the central lab to establish the risk factors for ROP.
4. They were followed up till 40 weeks of post menstrual age or till retina maturation was completed, or treatment started.
5. First screening examination was done after 3 weeks in babies born before 28 weeks and after 4 weeks in babies born after 28 week of gestation and whichever earlier.

Procedure of ophthalmologic examination:

- Pupils were dilated with Phenylephrine 2.5% and Tropicamide 0.5%. One drop of Tropicamide was instilled every 10-15 minutes for 4 times starting 1 hour before the scheduled time for examination.

  This was followed by phenylephrine, one drop just before examination.
- Screening of ROP involved a wide angle digital pediatric retinal imaging system (RETCAM) by an experienced ophthalmologist.

STATISTICAL ANALYSIS

All data originating from this study were entered into performa and then into a MS Excel sheet, cleaned and verified.

- Categorical / Nominal variables were indicated as number and percentage and were studied using Chi square test or Fischer exact test as applicable. Fischer exact test was used when one of the cells in 2x2 contingency table has expected value <5.
- Continuous variables were expressed as mean and standard deviation and were analyzed using independent sample t test for comparison between the two groups.
- A p value <0.05 was taken as statistically significant.
- All statistical analysis was done using appropriate statistical software like SPSS (Statistical Sciences Package for Social).

RESULTS

Among the 160 neonates screened, 30 neonates were found to have Retinopathy of prematurity, giving a rate of 18.8% for ROP. Among the 30 neonates with ROP, 10 (33.3%) delivered at gestational age <32 weeks, 12 (40%) had respiratory distress syndrome, 19 (63.3%) had sepsis, only 1 (3.3%) had patent ductus arteriosus, 13 (43.3%) had shock requiring inotrop support, 26 (86.7%) received phototherapy, 23 (76.7%) required oxygen therapy, 5 (16.7%) received mechanical ventilation, 9 (30%) received CPAP, 7 (23.3%) received FiO_2<30%, 12 (40%) received FiO_2 30%-40% and 11 (36.7%) received FiO_2>40%. 18 (60%) received blood transfusion, 17 (56.7%) had hypoglycemia, 15 (50%) had anaemia, 5 (16.7%) had seizure, 5 (16.7%) had received surfactant and 7 (23.3%) had apnea.

Significant association of ROP was found between gestational age, birth weight, sepsis, oxygen therapy, duration of oxygen support, higher FiO2, CPAP, neonates with shock requiring inotropic support, blood transfusion, hypoglycemia and anemia (Table 1,2). However, presence of RDS, PDA, delivery of phototherapy, mechanical ventilation, use of surfactant, seizure disorder and apnoea/birth asphyxia were not found to be significantly associated with the development of ROP (Table 3). Among these birth weight and gestational age are the primary risk factors affecting the occurrence of ROP (Figure 1,2).

Table 1: ROP in relation to presence of sepsis, inotropic support, oxygen therapy, CPAP, blood transfusion, hypoglycemia & anemia among study subjects

		ROP		No ROP		Total	
		N	%	N	%	N	%
SEPSIS (Chi-square = 9.749 with 1 degree of freedom; P = 0.002 (S)	**YES**	19	63.3	40	30.8	59	36.9
	NO	11	36.7	90	69.2	101	63.1
SHOCK REQUIRING INOTROPIC SUPPORT (Chi-square = 9.986 with 1 degree of freedom; P = 0.002 (S))	**YES**	13	43.3	20	15.4	33	20.6
	NO	17	56.7	110	84.6	127	79.4
OXYGEN THERAPY (Chi-square = 10.183 with 1 degree of freedom; P = 0.001 (S)	**YES**	23	76.7	55	42.3	78	48.8
	NO	7	23.3	75	57.7	82	51.2
CPAP (Chi-square = 4.523 with 1 degree of freedom; P = 0.033 (S))	**YES**	9	30	16	12.3	25	25.6
	NO	21	70	114	87.7	135	84.4
BLOOD TRANSFUSION (Chi-square = 19.632 with 1 degree of freedom; P < 0.001 (S))	**YES**	18	60.0	24	18.5	42	26.2
	NO	12	40.0	106	81.5	118	73.8
HYPOGLYCEMIA (Chi-square = 9.093 with 1 degree of freedom; P = 0.003 (S))	**YES**	17	56.7	34	26.2	51	31.9
	NO	13	43.3	96	73.8	109	68.1
ANAEMIA (Chi-square = 9.301 with 1 degree of freedom; P = 0.002 (S))	**YES**	15	50.0	27	20.8	42	26.2
	NO	15	50.0	103	79.2	118	73.8

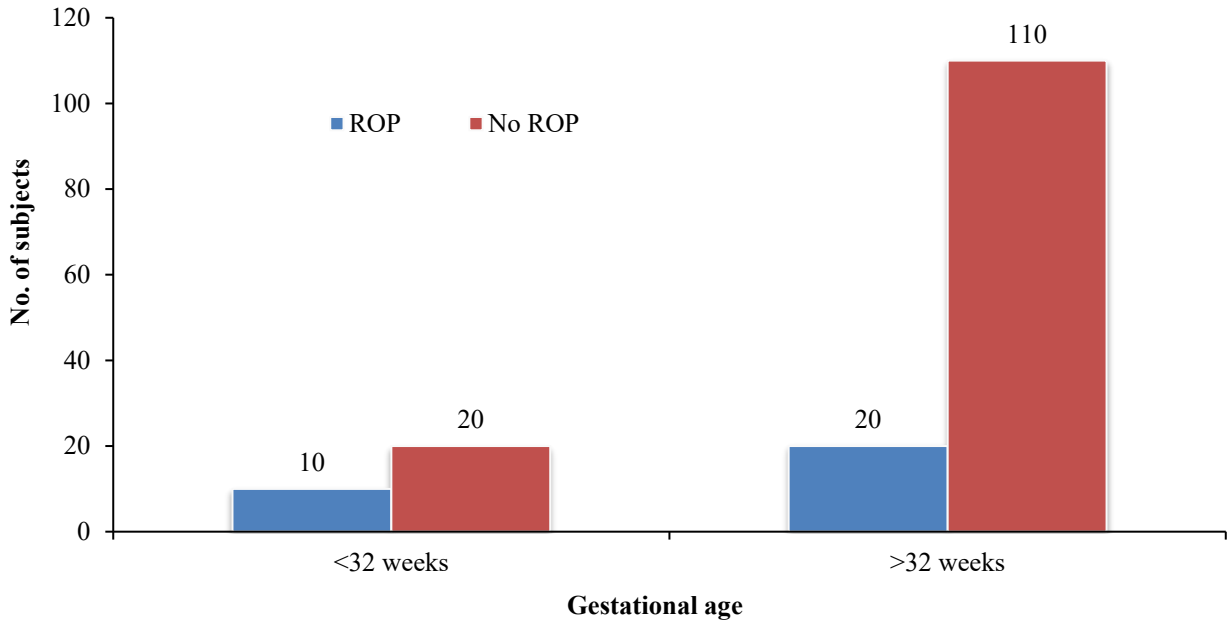

Figure 1: ROP in relation to gestational age of study subjects

Table 2: ROP in relation to Duration of oxygen

Duration of oxygen	ROP		No ROP		Total	
	N	%	N	%	N	%
<6 days	3	10.0	48	36.9	51	31.9
6-10 days	9	30.0	41	31.5	50	31.2
11-15 days	4	13.3	22	16.9	26	16.3
16-20 days	7	23.3	14	10.8	21	13.1
21-25 days	7	23.3	5	3.8	12	7.5
Total	**30**	**100**	**130**	**100**	**160**	**100**
Chi-square = 21.028 with 4 degrees of freedom; P < 0.001 (S)						

Table 3: ROP in relation to RDS, PDA, Phototherapy, Mechanical ventilation, Seizure, Surfactant, Apnoea.

		ROP		No ROP		Total	
		N	%	N	%	N	%
RDS (Chi-square = 0.709 with 1 degree of freedom; P = 0.400)	**YES**	12	40.0	39	30.0	51	31.9
	NO	18	60.0	91	70.0	109	68.1
PDA (Chi-square = 0.009 with 1 degree of freedom; P = 0.926)	**YES**	1	3.3	2	1.5	3	1.9
	NO	29	96.7	128	98.5	157	98.1
PHOTOTHERAPY (Chi-square = 0.114 with 1 degree of freedom; P = 0.736)	**YES**	26	86.7	118	90.8	144	90.0
	NO	4	13.3	12	9.2	16	10.0
MECHANICAL VENTILATION (Chi-square = 0.345 with 1 degree of freedom; P = 0.557)	**YES**	5	16.7	14	10.8	19	11.9
	NO	25	83.3	116	89.2	141	88.1
SEIZURE (Chi-square = with 1 degree of freedom; P = 0.126)	**YES**	5	16.7	8	6.2	13	8.1
	NO	25	83.3	122	93.8	147	91.9
SURFACTANT (Chi-square = 0.114 with 1 degree of freedom; P = 0.736)	**YES**	4	13.3	12	9.2	16	10.0
	NO	26	86.7	118	90.8	144	90.0
APNOEA (Chi-square = 0.004 with 1 degree of freedom; P = 0.951)	**YES**	7	23.3	27	20.8	34	21.2
	NO	23	76.7	103	79.2	126	78.8

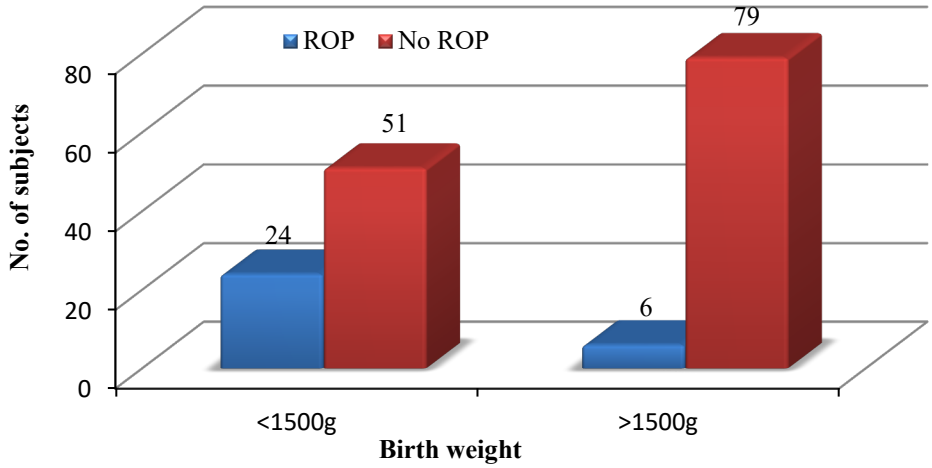

Figure 2: ROP in relation to birth weight of study subjects

DISCUSSION

Among the 30 neonates with ROP, 10 (33.3%) delivered at gestational age <32 weeks and 20 (66.7%) delivered at gestational age >32 weeks (Fig. 1). While, among the 130 neonates without ROP, only 20 (15.4%) delivered at gestational age <32 weeks and most (84.6%) delivered by at gestational age >32 weeks (Bar diagram 1). Significant association was found between gestational age <32 weeks and occurrence of ROP (p=0.044). On univariate analysis Gestational age <32 weeks (OR=2.750) found to be significantly associated with ROP. In conformance to that Chaudhari et al (2009) [17] observed that the incidence of ROP rose as gestational age decreased (P=0.003). Chang-Yo Yang et al (2011) [18], Hakeem et al (2012) [19], Kumar et al (2011) [20] and Rao et al (2013) [21] also observed that low GA was associated with ROP. Further logistic regression demonstrated that gestational age was one of the most significant adjusted risk factors for ROP (odds ratio: 2.64, 95% confidence interval; 1.73 to 4.03. Regression analysis by Port et al (2014) [22] for the entire cohort revealed that gestational age at birth (OR: 0.563 per week; 95% CI: 0.454, 0.697) was an important risk factor for treatment-requiring ROP. Jothi et al (2016) [23] observed that gestational age was found to be autonomous risk factors for the development of ROP.

Among the 30 neonates with ROP, 24 (80%) had birth weight of <1500g and 6 (20%) had birth weight of >1500g (Fig. 2). Contrary to this, among the 130 neonates without ROP, 51 (39.2%) had birth weight of <1500g and 79 (60.8%) had birth weight of >1500g (Bar diagram 2). Significant association was found between birth weight of <1500g and occurrence of ROP (p<0.001). On univariate analysis Birth weight <1500g (OR=6.196) found to be significantly associated with ROP. Chaudhari et al (2009) [17] similarly observed that mean birth weight of the subjects was 1306 ±267g. Kumar et al (2011) [20] observed that Infants with severe ROP had mean birth weights of 1113± 438 g. Isaza et al (2013) [24] observed that Children with ROP had a mean birth weight of 840 g (500 to 1,890 g), which was considerably lower than the mean birth weight of infants without ROP, which was 1,191 g (470 to 2,460 g). Further, logistic regression demonstrated that birth weight was one of the most significant adjusted risk factors for ROP (odds ratio: 1.90, 95% confidence interval 1.34 to 2.69). Rao et al (2013) [21] also observed that low BW significantly associated with ROP. Regression analysis by Port et al (2014) [22] for the entire cohort revealed that birth weight (OR: 0.741 per 100 g; 95% CI: 0.606, 0.905) was an independent risk factor for treatment-requiring ROP. Jothi et al (2016) [23], Bassiouny et al (2017) [25], Abdel-Aziz et al (2021) [26] observed that low birth weight was found to be independent risk factors for the development of ROP.

Among all the 30 neonates with ROP, 12 (40%) had respiratory distress syndrome, while among the 130 neonates without ROP, 39 (30%) had respiratory distress syndrome (Table 3). This difference in proportion of RDS among neonates with and without ROP was not found to be statistically significant (p=0.400). Similar study by Hakeem et al (2012) [19] also observed that ROP incidence was not significantly correlated with respiratory distress syndrome. Kumar et al (2011) [20] however observed significant association of ROP with RDS. In

conformance to our study findings Hungi et al (2012) [27] observed that The ROP group had greater rates of respiratory distress syndrome but the differences were not statistically significant. Le et al (2016) [28] also observed respiratory distress syndrome as one of the most common postnatal risk factors.

Among the 30 neonates with ROP, 19 (63.3%) had sepsis, while among the 130 neonates without ROP, 40 (30.8%) had sepsis (Table 1). This difference in proportion of sepsis among neonates with and without ROP was found to be statistically significant (p=0.002) i.e sepsis was significantly associated with ROP. Yang et al (2011) [18] and Kumar et al (2011) [20] also found similar association of ROP with sepsis. Hungi et al (2012) [27] observed that the ROP group had greater rates of sepsis but the differences were not statistically significant.

Among the 30 neonates with ROP, only 1 (3.3%) had patent ductus arteriosus, while among the 130 neonates without ROP, only 2 (1.5%) had PDA (Table 3). This difference in proportion of PDA among neonates with and without ROP was not found to be statistically significant (p=0.926). Yang et al (2011) [18] and Hakeem et al (2012) [19] also concluded no significant association of ROP with patent ductus arteriosus. Kumar et al (2011) [20] however observed significant association of ROP with PDA.

Among the 30 neonates with ROP, 13 (43.3%) had shock requiring inotrop support, while among the 130 neonates without ROP, 20 (15.4%) had shock requiring inotrop support (Table 1). This difference in proportion of shock requiring inotrop support among neonates (p=0.002) was significantly associated with development of ROP. Gordon et al (2014) [29] also observed significant association with inotrope support. Among the 30 neonates with ROP, 26 (86.7%) received phototherapy, while among the 130 neonates without ROP, 118 (90.8%) received phototherapy (Table 3). This difference in phototherapy among neonates with and without ROP was however not found to be statistically significant (p=0.926). Sathar et al (2018) [30] observed that aside from low birth weight and short gestation, phototherapy found to be significant risk factor for ROP.

Among the 30 neonates with ROP, 23 (76.7%) required oxygen therapy, while among the 130 neonates without ROP, 55 (42.3%) required oxygen therapy, showing no statistically significant (p=0.001) association with development of ROP (table 1). Similar to our findings Hakeem et al (2012) [19], Kumar et al (2011) [20] and Khalesi et al (2015) [31] also observed that ROP incidence was significantly correlated with oxygen therapy. Bassiouny et al (2017) [25] also observed that regarding oxygen therapy there were statistically significant differences (P≤0.05) between the ROP group and the non-ROP group.

Among the 30 neonates with ROP, only 5 (16.7%) received mechanical ventilation, while among the 130 neonates without ROP, only 14 (10.8%) received mechanical ventilation (Table 3). This difference in proportion of mechanical ventilation among neonates with and without ROP was however not found to be statistically significant (p=0.557). Similar to our findings Hakeem et al (2012) [19] also observed that ROP incidence was not significantly associated with mechanical ventilation. Kumar et al (2011) [20] however observed significant association of severe ROP with positive pressure ventilation.

Among the 30 neonates with ROP, 9 (30%) received CPAP, while among the 130 neonates without ROP, only 16 (12.3%) received CPAP (Table 1). This difference in CPAP among neonates with and without ROP was found to be statistically significant (p=0.033). Kumar et al (2011) [20] and Azami et al (2018) [32] also observed significant association of severe ROP with CPAP. Among the 30 neonates with ROP, 7 (23.3%) received oxygen for 21-25 days, 7 (23.3%) for 16-20 days, 4 (13.3%) for 11-15 days, 9 (30%) for 6-10 days and only 3 (10%) for <6 days. While among the 130 neonates without ROP, most received oxygen for<6 days (36.9%) and 6-10 days (31.5%) followed by 11-15 days (16.9%), 16-20 days (10.8%) and only 5 (3.8%) for 21-25 days (Table 2). This difference in duration of oxygen among neonates with and without ROP was found to be statistically significant (p<0.001) i.e. higher duration of oxygen was significantly associated with development of ROP. Hakeem et al (2012) [19] however observed that ROP incidence was not significantly correlated with duration of oxygen therapy. Abdel-Aziz et al (2021) [26], Kalyani et al (2022) [33] observed that the incidence of ROP dramatically rises as oxygen exposure time increases.

Among the 30 neonates with ROP, 18 (60%) received blood transfusion, while among the 130 neonates without ROP, only 24 (18.5%) received blood transfusion (Table 6). This difference

in blood transfusion among neonates was significantly associated with development of ROP (p<0.001). Similarly, Kumar et al (2011) [20] and Akkawi et al (2019) [34] observed significant association of severe ROP with packed cell transfusion.

Among the 30 neonates with ROP, 17 (56.7%) had hypoglycemia, while among the 130 neonates without ROP, 34 (26.2%) had hypoglycemia (Table 1). This difference in hypoglycemia among neonates with and without ROP was found to be statistically significant (p=0.003). Among the 30 neonates with ROP, 15 (50%) had anaemia, while among the 130 neonates without ROP, 27 (20.8%) had anaemia (Table 1). Statistically significant association was noted (p=0.002) between incidence of anaemia with development of ROP. Akkawi et al (2019) [34] also observed similarly.

Among the 30 neonates with ROP, 5 (16.7%) had received surfactant, while among rest without ROP, 12 (9.2%) had received surfactant (Table 3). This difference in surfactant among neonates with and without ROP was however not found to be statistically significant (p=0.736). Sathar et al (2018) [30] also observed that surfactant use was substantially linked with the severity of ROP. Among the 30 neonates with ROP, 7 (23.3%) had apnea, while among the 130 neonates without ROP, 27 (20.8%) had apnea (Table 3). This difference in apnea among neonates with and without ROP was however not found to be statistically significant (p=0.951). Sundar et al (2018) [35] observed that 35 infants (21%) had birth asphyxia, which was one of the risk factors for ROP.

CONCLUSION

Retinopathy of prematurity is an avoidable cause of retinal blindness. Prematurity, low birth weight, inadvertent use of oxygen therapy blood transfusion, sepsis and hypoglycemia were found to be remarkable risk factors for ROP. Thus, judicious use of oxygen and blood products and better perinatal management with special focus on sepsis and hypoglycemia can prevent or reduce the occurrence of ROP. Further prospective studies are required in order to evaluate the magnitude of the cause-effect relationship of the risk factors described in the study with the development of ROP.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Mamta Choudhary collected data, interpreted the statistical values. She along with Nisha Dulani and Harish Dulani designed the study and contributed in drafting and editing the manuscript. Meghna Solanki contributed in manuscript writing and processing the collected data. She also contributed in compiling the data, interpretation of data and wrote final draft of manuscript. The final manuscript was read and approved by all authors.

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