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STUDY ON CORRELATION OF RETINOPATHY OF PREMATURITY AND CLINICAL STAGING

Neonatology

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ABSTRACT

BACKGROUND: Retinopathy of prematurity (ROP), a vasoproliferative retinal disorder, is an important cause of visual impairment in premature neonates and infants.

OBJECTIVES: The primary objective was to study the correlation of Retinopathy of Prematurity with gestational age, birthweight, oxygen delivery and clinical staging.

METHODS: Study was conducted at the neonatal intensive care unit of a private tertiary care hospital in Navi Mumbai from September 2015-September 2017 wherein 54 inpatients who were < 34 weeks of gestation and < 1500 grams birthweight were taken. A detailed history, clinical examination and an ophthalmological screening at 3 – 4 weeks of chronological age was undertaken and recorded

RESULTS: All neonates revealed ROP, with maximum in 28 -30 weeks of gestation, 1000 – 1500 grams birthweight and in Stage 2 ROP and Zone 2 ROP. Major risk factors were Respiratory Distress Syndrome, Anaemia, Metabolic Acidosis and Sepsis.

CONCLUSION: The duration of oxygen therapy and FiO2 delivered were directly proportional to the severity of ROP staging and judicious use of monitored oxygen therapy would be mandatory for the prevention of ROP.

KEYWORDS

Retinopathy of Prematurity, Low birth weight, gestational age

INTRODUCTION

Retinopathy of prematurity has been recognized as an important cause of childhood visual impairment and blindness since the 1940s where in improved facilities and treatment increased the survival rate of premature infants. Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder[1].

Prematurity being the important consistent risk factor for the development of ROP, along with other risk factors like – low birth weight (LBW), very low birth weight (VLBW), extremely low birth weight (ELBW), unmonitored oxygen therapy, sepsis, apnea, blood transfusion, babies on mechanical ventilation. Infants with birth weight <1,250 grams have 65% risk of developing ROP and 80% of those with birth weight <1,000g. Indian studies reveal incidence of ROP in LBW as 38% to 51.9%[2].

ROP is essentially asymptomatic in the early stages with paucity of clinical signs or symptoms. Hence it is essential to follow the guidelines in order to screen and perform regular retinal examination for changes of ROP in premature neonates. The present study envisages to associate the clinical staging of retinopathy of prematurity with the gestational age, birth weight and oxygen therapy at a tertiary care Hospital in Navi Mumbai.

MATERIALS AND METHODS

A Prospective, Randomized, Non-Interventional, Descriptive Study was conducted at Neonatal Intensive Care Unit, Department of Paediatrics, D. Y. Patil Medical College &Hospital, Nerul, Navi Mumbai, wherein inpatients fulfilling the inclusion criteria for a total duration of 2 years (2015 – 2017) were admitted. Sample size of the study was 54. Institutional ethics committee approval was taken, and an informed consent was obtained before enrolling patients into the study.

A detailed history, clinical examination with special reference to the Ophthalmological Examination of the neonates was recorded. The details of the same were entered in a predesigned proforma. A trained posterior segment ophthalmologist specialized in ROP evaluation screened the premature neonates at 3 – 4 weeks of chronological age. Threshold was usually reached by 37 weeks. After the initial screening, follow-up for ROP was done from 15 days after initial screen to 6 months intermittently determined by the severity of the staging of ROP.

INCLUSION CRITERIA

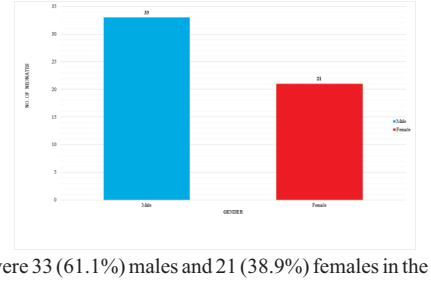
1) All neonates who were born between 28 - 34 weeks' period of gestation.
2) All neonates who were weighing <1500 g.

EXCLUSION CRITERIA

1) All neonates who Gestational age was > 34 weeks' period of gestation.
2) All neonates whose Birth weight was >1500 gms.
3) Parents / Guardians of the neonates who refused to give consent.

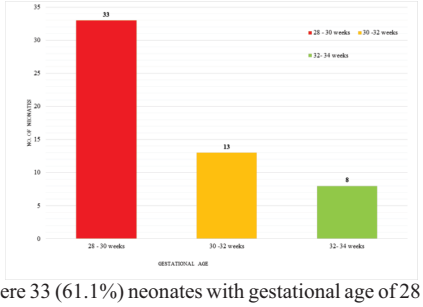
RESULTS

Figure 1. Gender Profile



There were 33 (61.1%) males and 21 (38.9%) females in the study.

Figure 2. Gestational Age

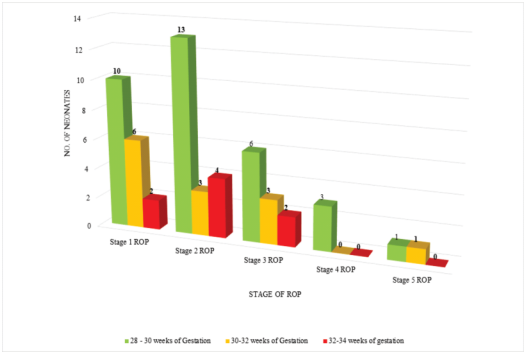


There were 33 (61.1%) neonates with gestational age of 28 - 30 weeks, 13 (24.1%) neonates with gestational age of 30 -32 weeks, 8 (14.8%) neonates with 32- 34 weeks.

Table 1. Relationship Between Gestational Age And Stages Of Retinopathy Of Prematurity

Stages of ROP	28 - 30 weeks of Gestation	30-32 weeks of Gestation	32-34 weeks of gestation	Total	P value
Stage 1 ROP	10	6	2	18	Chi square statistic – 3.45 P value – 0.896
Stage 2 ROP	13	3	4	20	
Stage 3 ROP	6	3	2	11	
Stage 4 ROP	3	0	0	3	
Stage 5 ROP	1	1	0	2	
Total	33	13	8	54	

Figure 3. Relationship Between Gestational Age And Stages Of Retinopathy Of Prematurity



There were 33 (61.1%) neonates with 28 - 30 weeks of gestation (ROP Stage 1 – 10, ROP Stage

2 – 13, ROP Stage 3 – 6, ROP Stage 4 – 3, ROP Stage 5 – 1), 13 (24.1%) neonates with 30 - 32

weeks of gestation (ROP Stage 1 – 6, ROP Stage 2 – 3, ROP Stage 3 – 3, ROP Stage 4 – 0,

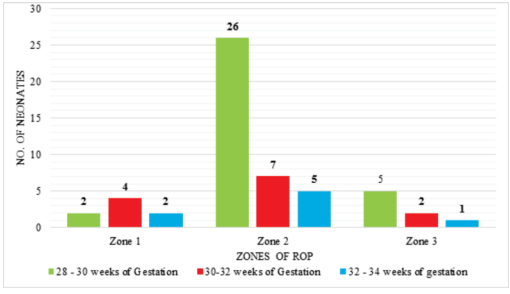
ROP Stage 5 – 1), 8 (14.8%) neonates with 32-34 weeks of gestation (ROP Stage 1 – 2, ROP

Stage 2 – 4, ROP Stage 3 – 2, ROP Stage 4 – 0, ROP Stage 5 – 0). There was no statistically significant difference between the groups.

Table 2. Relationship Between Gestational Age And Zones Of Retinopathy Of Prematurity

Stages of ROP	28 - 30 weeks of Gestation	30-32 weeks of Gestation	32 - 34 weeks of gestation	Total	P value
Zone 1	2	4	2	8	Chi square statistic – 5.442 P value – 0.245
Zone 2	26	7	5	38	
Zone 3	5	2	1	8	
Total	33	13	8	54	

Figure 4. Relationship Between Gestational Age And Zones Of Retinopathy Of Prematurity

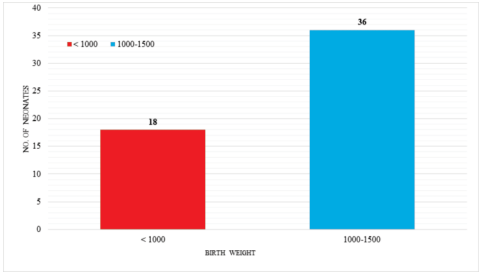


There were 8 (14.8%) neonates with zone 1, 38 (70.4%) neonates with zone 2, 8 (14.8%) neonates with zone 3. There was no statistically significant difference between the groups.

Table 3. Stage of ROP according to Birth weight

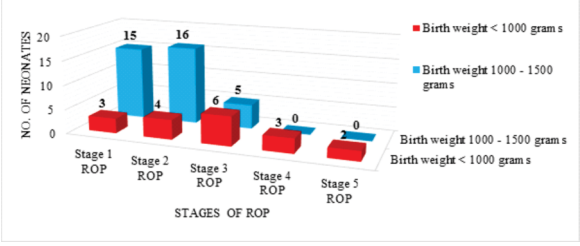
Stages of ROP	Birth weight < 1000 grams	Birth weight 1000-1500 grams	Total
Stage 1 ROP	3	15	18
Stage 2 ROP	4	16	20
Stage 3 ROP	6	5	11
Stage 4 ROP	3	0	3
Stage 5 ROP	2	0	2
Total	18	36	54
Chi square – 11.89 P value – 0.018			

Figure 5. Birth Weight



There were 18 (33.3%) neonates with < 1000 grams, 36 (66.7%) neonates with 1000-1500 grams.

Figure 6. Stage of ROP according to Birth weight



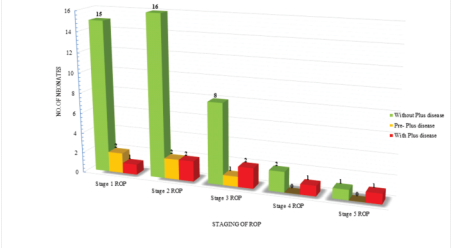
There were 3 (5.6%) neonates < 1000 grams, 15 (27.8%) neonates between 1000-1500 grams in Stage 1 ROP, 4 (7.4%) neonates < 1000 grams, 16 (29.6%) neonates between 1000-1500 grams in Stage 2 ROP, 6 (11.1%) neonates < 1000 grams, 5 (9.2%) neonates between 1000-1500 grams in Stage 3 ROP, 3 neonates < 1000 grams in Stage 4 ROP, 2 neonates < 1000 gms in Stage 5 ROP. There was statistically significant difference between the groups with respect to distribution of stages of ROP among birth weight < 1000 grams and Birth weight 1000-1500 grams.

Table 4. Staging of ROP

Stages of ROP	Without Plus disease	Pre- Plus disease	With Plus disease	Total	P value
Stage 1 ROP	15	2	1	18	Chi square – 4.65 P value – 0.794
Stage 2 ROP	16	2	2	20	
Stage 3 ROP	8	1	2	11	
Stage 4 ROP	2	0	1	3	
Stage 5 ROP	1	0	1	2	
Total	42	5	7	54	

*Chi square test

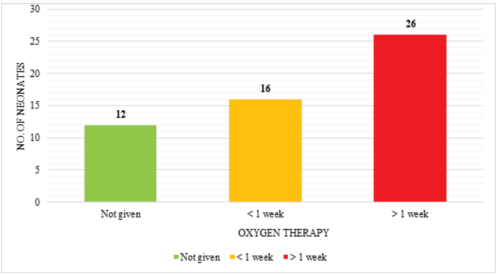
Figure 7. Staging of ROP



There were 15 (27.7%) neonates with Stage 1 ROP without plus disease, 2 (3.7%) neonates with Stage 1 ROP with pre-plus disease and 1 (1.8%) neonate with Stage 1 ROP with plus disease. There were 16

(29.6%) neonates with Stage 2 ROP without plus disease, 2 (3.7%) neonates with Stage 2 ROP with pre-plus and plus disease respectively. There were 8 (14.8%) neonates with Stage 3 ROP without plus disease, 1 (1.8%) neonate with pre-plus disease and 2 (3.7%) neonates with plus disease. 2 (3.7%) neonates with Stage 4 ROP without plus disease, 1 (1.8%) neonate with plus disease 1 (1.8%) neonate with stage 5 ROP with plus disease and 1 (1.8%) neonate without plus disease. There was no statistically significant difference between the groups.

Figure 8. Relationship Between Retinopathy Of Prematurity And Oxygen Therapy



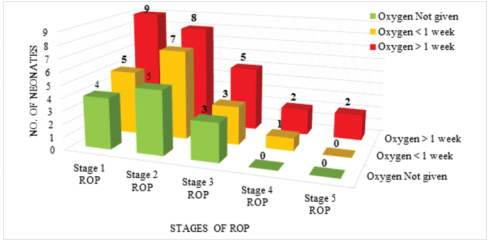
There were 16 (29.6%) neonates who received oxygen for < 1 week and 26 (48.2%) neonates who received oxygen for > 1 week.12 (22.2%) neonates not received oxygen therapy.

Table 5. Correlation between Stage of ROP and duration of Oxygen therapy

Stages of ROP	Duration of Oxygen therapy			
	Not given	< 1 week	> 1 week	Total
Stage 1 ROP	4	5	9	18
Stage 2 ROP	5	7	8	20
Stage 3 ROP	3	3	5	11
Stage 4 ROP	0	1	2	3
Stage 5 ROP	0	0	2	2
Total	12	16	26	54
Chi square – 2.081 P value – 0.97				

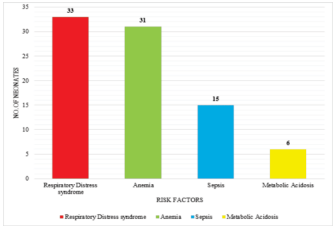
*Chi square test

Figure 9. Correlation between Stage of ROP and duration of Oxygen therapy



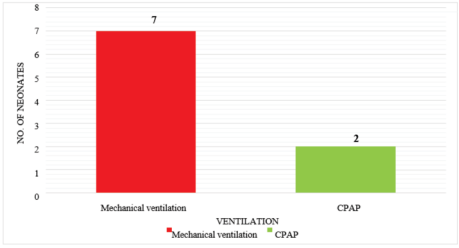
Amongst Stage 1 ROP, 4 (7.4%) neonates were not given oxygen, 5 (9.2%) neonates were given oxygen < 1 week, 9 (16.7%) neonates were given oxygen > 1 week. Among Stage 2 ROP, 5 (9.2%) neonates were not given oxygen,7 (13%) neonates were given oxygen < 1 week, 8 (14.8%) neonates were given oxygen > 1 week. Among Stage 3 ROP, 3 neonates were not given oxygen, 3 neonates were given oxygen < 1 week, 5 neonates were given oxygen > 1 week. Among Stage 4 ROP, 1 neonates were given oxygen < 1 week, 2 neonates were given oxygen > 1 week. Among Stage 5 ROP, 2 neonates were given oxygen > 1 week. There was no statistically significant difference between the groups with respect to distribution of stages of ROP and duration of oxygen therapy.

Figure 10. Relationship between retinopathy of prematurity and Risk factors



There were 33 (61.1%) neonates with Respiratory Distress Syndrome, 31 (57.4%) neonates with Anaemia, 30 (55.6%) neonates with Metabolic Acidosis, 15 (27.8%) neonates with Sepsis.

Figure 11. Relationship Between Retinopathy Of Prematurity And Oxygen Therapy

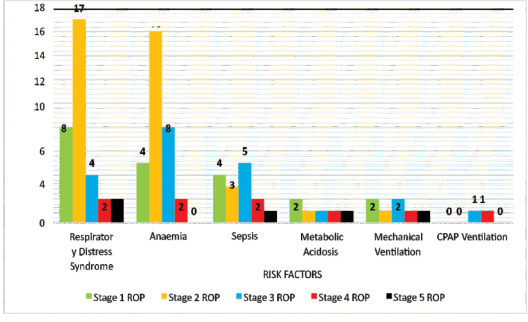


There were 7 (13%) neonates who was on Mechanical Ventilation and 2 (3.7%) neonates who was on Continuous Positive Airway Pressure (CPAP) ventilation.

Table 6. Univariate Analysis For Risk Factors

Risk Factors	Respiratory Distress Syndrome	Anaemia	Sepsis	Metabolic Acidosis	Mechanical ventilation	CPAP ventilation
Stage 1 ROP	8	5	4	2	2	0
Stage 2 ROP	17	16	3	1	1	0
Stage 3 ROP	4	8	5	1	2	1
Stage 4 ROP	2	2	2	1	1	1
Stage 5 ROP	2	0	1	1	1	0
Total	33	31	15	6	7	2
Chi-square Statistic- 17.55, P value – 0.62						

Figure 12. Univariate Analysis For Risk Factors



There were 33 neonates with Respiratory distress syndrome {ROP Stage 1 – 8 (24.2%), ROP Stage 2 – 17 (51.5%), ROP Stage 3 – 4, ROP Stage 4 – 2, ROP Stage 5 – 2}, 31 neonates with Anaemia {ROP Stage 1 – 4 (12.9%), ROP Stage 2 – 16 (51.6%), ROP Stage 3 – 8 (25.8%), ROP Stage 4 – 2, ROP Stage 5 – 0), 15 neonates with Sepsis {ROP Stage 1 – 4 , ROP Stage 2 – 3, ROP Stage 3 – 5 (33.3%), ROP Stage 4 – 2, ROP Stage 5 – 1}, 6 neonates with Metabolic Acidosis {ROP Stage 1 – 2, ROP Stage 2 – 1, ROP Stage 3 – 1, ROP Stage 4 – 1, ROP Stage 5 – 1}, 7 neonates with Mechanical ventilation {ROP Stage 1 – 2, ROP Stage 2 – 1, ROP Stage 3 – 2, ROP Stage 4 – 1, ROP Stage 5 – 1} and 2 neonates {ROP Stage 1 – 0, ROP Stage 2 - 0, ROP Stage 3 – 1, ROP Stage 4 – 1, ROP Stage 5 – 0} who were on CPAP ventilation. There was no statistically significant difference between the groups.

DISCUSSION

Retinopathy of prematurity is a leading cause of visual impairment in pre-mature neonates. Our study assesses the relationship between the incidence of Retinopathy of Prematurity and various contributory factors like Gestational age, Birth weight, Oxygen therapy and risk factors.

We observed male preponderance (61.1% males) in our study.
There were 33 (61.1%) neonates with gestational age of 28 - 30 weeks, 13 neonates with gestational age of 30 -32 weeks, 8 neonates with 32-34 weeks. Mean gestational age was 29.4 ± 2.4 weeks.

In a study by Wang et al, they found, 11 (68.75%, 11/16) neonates born at ≤28 weeks had ROP and only 10 (10.42%, 10/96) neonates born at >28wk ($\chi2$=30.632, P<0.001). Amongst the neonates born at ≤28 weeks, 6 (37.50%) had severe ROP requiring treatment and only 2 (2.08%) neonates born at >28 weeks had severe ROP requiring treatment ($\chi2$=20.807, P<0.001). In the same study, univariate analysis of all the neonates showed that the mean gestational age of the 21 neonates with ROP was 28.56 weeks (SD 1.82) and was significantly lower than those with no ROP (31.35 ± 1.54 weeks, P<0.001)[3].

There were 23 (69.7%) premature neonates with gestational age between 28 – 30 weeks revealed Stage 1 & 2 ROP and 10 cases had stage 3 – 5 ROP. There were 10 cases (30.3%) who had severe stages of ROP showing the importance of preventing birth of low gestation neonates. However, the silver lining was that the 23 cases who revealed Stage 1 & 2, which could regress spontaneously to the tune of 86% for stage 1 and 57% for stage 2 on follow up. Further on with increasing gestational age (30 – 34 weeks) the severity of ROP diminished considerably 15/21 cases (71.4%) exhibited Stage 1 & 2 and 6 cases (28.6%) exhibited Stages 3 to 5.

As regards to Zones, majority 31/33 (93.9%) cases were in Zones 2 & 3 and only 2 (5.1%) cases were in Zone 1 in the age group of 28 – 30 weeks gestational age. Also 15/21 (71.4%) cases were in Zones 2 & 3 and only 6 cases (29.6%) were in Zone 1.

There were 18 (33.3%) neonates with <1000 grams, 36 neonates with 1000 - 1500 grams. In the multicenter CRYO-ROP trial, study reported 81.6% incidence in neonates <1000 grams birth weight. The early treatment for retinopathy of prematurity cooperative group (ETROP) reported an incidence of ROP of 89.0% among neonates who born at ≤28 weeks[4].

Neonates who had a birth weight of <1000 grams had more propensity to develop Stage 3 to 5 ROP 11/18 (61.1%) as compared to neonates with a birth weight between 1000 – 1500 grams 7/18 (38.9%). Majority of the neonates 31/36 (86.1%) cases weighing between 1000 – 1500 grams at birth developed Stages 1 & 2 ROP as compared 5/36 (13.9%) cases who developed Stages 3 to 5 ROP. There was statistically significant difference between the groups with respect to distribution of stages of ROP among birth weight < 1000 grams and 1000-1500 grams

In our study, out of the 18 neonates with Stage 1 ROP, 15 (27.7%) were without plus disease, 2 (3.7%) were with pre-plus disease and 1 (1.8%) with plus disease. Out of the 20 neonates with Stage 2 ROP,16 (29.6%) were without plus disease, 2 (3.7%) with pre-plus and plus disease respectively. Of the 16 neonates between Stages 3 - 5 ROP, 10 (62.5%) were without plus disease, 1 (6.25%) with pre-plus disease and 4 (25%) with plus disease. Our study revealed that Stage 3 to 5 had greater severity of disease (with plus disease) as compared to Stages 1 & 2. This reinforces the fact that every patient needs weekly follow up, irrespective of the Stage of ROP. The distribution of stages of ROP was consistent with other studies[5].

Oxygen plays a very important role in the development of ROP. Our study unveiled that prolonged oxygen therapy (>1week) had higher incidence of ROP, 26 (48.1%) cases as compared to 16 (29.6%) cases in oxygen therapy given for < 1 week and 12 (22.2%) cases who did not receive any oxygen. Amongst the 26 cases who received prolonged oxygen therapy for > 1 week, majority 17 (65.4%) cases were in Stage 1 & 2 ROP, whereas 9 (34.6%) cases were in Stage 3 to 5 ROP. Similar trends were observed in neonates receiving oxygen therapy for <1 week and who did not receive any oxygen therapy at all. The duration of oxygen therapy was directly proportional to the severity of ROP staging.

In a meta-analysis of studies, Minghua et. al found that low oxygen saturation (70%–96%) in the first several postnatal weeks was associated with a reduced risk of severe ROP (risk ratio [RR]: 0.48 [95% confidence interval (CI): 0.31–0.75]). High oxygen saturation (94%–99%) at ≥32 weeks' PMA was associated with a decreased risk for progression to severe ROP (RR: 0.54 [95% CI: 0.35–0.82])[6].

In a US national survey, 56 neonates with a birthweight of less than 1500 g who had a maximum SpO2 greater than 98% in the first 2 postnatal weeks had severe retinopathy in 5.5% of cases, compared with 3% in those with a maximum SpO2 of 98% or less (p< 0·0001). Stage 3 or higher disease was seen in 5.5% of cases from among the neonates with the higher saturation target, and in 2.4% of cases from among those with the lower target[7].

Although no individual study has been conclusive as to the best SpO2 target, targets should be different in different stages of development and in the different phases of retinopathy of prematurity. Strict management of oxygen in terms of FiO2 delivery to minimize alternating hypoxia and hyperoxia and avoidance of undesired high oxygen saturations in phase 1 seem to be the most promising strategies to prevent retinopathy of prematurity.

Respiratory distress syndrome was one of the highest contributory factors of ROP in our study, 33 (61.1%) neonates, majority of whom 17 (51.5%) cases were Stage 2 ROP. This was followed by anaemia 31 (57.4%) neonates, majority of whom 16 (51.6%) cases were Stage 2 ROP, sepsis 15 (27.8%) neonates, majority of whom 5 (33.3%) cases were Stage 3 ROP, acidosis 6 (11.1%) neonates, majority of whom 2 (33.3%) cases were Stage 1 ROP, mechanical ventilation 7 (13%) neonates and CPAP ventilation 2 (3.7%) neonates. CPAP ventilation showed the least contribution towards development of ROP emphasizing the fact that minimal invasive ventilation and optimally controlled FiO2 delivery is necessary to reduce the incidence of ROP in preterm neonates.

In a study by Neeraj Gupta et al, amongst neonates diagnosed with ROP, 148 (79%) of them had risk factors namely prematurity 53 (28%) and anaemia 15 (8%) were the common risk factors 78.

In a study by Pardeep et al, significant risk factors were gestation ≤30 weeks, birth weight <1000 grams, respiratory distress syndrome (RDS), use of surfactant, apnea, hypotension, patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis, pneumonia, meningitis, intraventricular hemorrhage, packed cell transfusion, use of oxygen, continuous positive airway pressure and positive pressure ventilation[8]. In a study conducted in Aga Khan University, they found, low gestational age, sepsis and RDS were found to be independent predictors of ROP development. ROP is an important emerging cause of preventable childhood blindness in urban areas[9].

CONCLUSION

Retinopathy of prematurity has been recognized as an important cause of childhood visual impairment and blindness. The study concluded that related to the gestational age, the staging and zones of ROP may differ emphasizing the need for mandatory screening of all preterm neonates at 3 and/ 4 weeks post-natal age for Retinopathy of Prematurity, irrespective of the gestational age and birth weight. There is a need for initiation of prompt screening and a stringent follow-up thereby in order to observe for spontaneous regression of ROP or initiate early treatment. The birth weight has a significant impact on the development of ROP in the neonates. We concluded that the duration of oxygen therapy was directly proportional to the number of affected neonates as well as the severity of ROP staging. Administration of oxygen therapy to be critically monitored with respect to the route of administration, rate of oxygen delivery, FiO2 delivered and target SpO2 levels and unmonitored oxygen therapy to be strictly avoided. There are other risk factors like respiratory distress syndrome, anaemia, sepsis, metabolic acidosis, mechanical and CPAP ventilation that contribute to the development of ROP in premature neonates. It is imperative that we strive to improve maternal health in terms of regular antenatal check-ups and monitoring, to enhance maternal nutrition and prevent antenatal illnesses in our clinical setting in order to enable each pregnancy to reach its full term. The pediatrician, neonatologist and a paediatric vitreoretinal surgeon must work in tandem and screen the premature and high-risk neonates in order to prevent blindness due to ROP.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee

FUNDING

None

CONFLICT OF INTEREST

None

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