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Retinopathy of prematurity: Risk factors and associated co-morbidities

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ABSTRACT

Purpose: To estimate the prevalence of ROP and identify risk factors and co-morbidities associated with it.
Materials and Methods: This cross-sectional study was performed, enrolling all premature babies admitted to the NICU of Jawaharlal Nehru Medical College and Hospital, A.M.U., Aligarh, Uttar Pradesh over 18 months. Various risk factors and co-morbidities for ROP were assessed using univariate and multivariate analysis.
Results: Out of the studied 164 infants, 29 infants (17.68%) developed ROP in one or both eyes; 51.72% (15/29) had stage 1, 31.03% (9/29) had stage 2, 10.35 % (3/29) had stage 3, and 6.90% (2/29) babies had aggressive posterior retinopathy of prematurity (APROP). On univariate analysis, we observed a significant association between ROP and gestational age, low birth weight, multiple gestations, mechanical ventilation, history and duration of oxygen supplementation, history of blood transfusion, respiratory distress syndrome, apnea and sepsis. However, after multivariate analysis, only low birth weight, oxygen therapy, respiratory distress syndrome and apnea were found to have a significant association with ROP.
Conclusion: A prevalence of 17.68% emphasises the importance of neonatal screening in this region. Low birth weight, oxygen therapy, apnea, respiratory distress syndrome pose significant risk factors for ROP. Supplemental oxygen should be weaned off as early as possible,

1. Introduction

Retinopathy of prematurity (ROP) is a disorder of developing retinal vasculature mainly characterised by abnormal development of retinal vessels and is an important preventable cause of childhood blindness. The mechanism for ROP development is vasoconstriction and obliteration of the advancing capillary bed resulting in retinal oedema, retinal haemorrhage, extraretinal fibrovascular proliferation, traction, and eventually, detachment of the retina leading to blindness.[1] Theodore L. Terry, in 1942, first used the term "Retrolental Fibroplasia" for this suspecting prematurity as a predisposing factor for the disease. Further, Kinsey et al.,[2] in 1956, found that "the length of time premature babies are kept in an oxygen-enriched environment is an important factor in the development of retrolental fibroplasia. The aetiology of ROP is multifactorial, with three factors having a consistent and significant association with ROP: low gestational age LGA low birth weight LBW and prolonged exposure to supplementary oxygen following birth.

The World Health Organization identifies ROP as an important cause of preventable blindness in its Vision 2020 program, especially in middle-income countries,[3] and considers the control of childhood blindness a top priority for three main reasons. Firstly, the number of "blind

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years" is particularly high for a person blinded in infancy. Secondly, many causes of childhood blindness, including ROP are ether preventable or treatable. Hence they can be controlled if diagnosed and treated on time. Thirdly, many causes of childhood blindness are associated with increased child mortality (e.g. premature birth, congenital rubella syndrome, measles, meningitis and vitamin A deficiency). Thus, control of blindness in children is also closely linked to child survival.[3]

ROP is responsible for 0-16.9% of children's severe visual impairment/blindness in Asian countries.[4] It is emerging as one of the leading causes of preventable childhood blindness in India.[5] India accounts for the most preterm births in the world (3.5 million)[6] and has the third-highest incidence of L.B.W. being delivered every year, with about 1.7 million weighing <2500 g and about 0.4 million <1500 gm.[7] Crucially, premature birth and L.B.W. predispose a newborn to develop ROP, for which India is the hotbed.

However, subtle differences in the quality of neonatal care, genetic composition, infant mortality rate and incidence of premature birth limit their applicability and extrapolation in developing countries such as India. There is a need to find the prevalence and risk factors associated with ROP to understand the extent of the problem in our country for appropriate intervention to combat this disease. There is a paucity of studies in the northern parts of India, especially in Uttar Pradesh, the most populous state of the country with a population of 199,812,341 (16.51 % of India's population).

Therefore, this study was conducted to look for the prevalence and predisposing risk factors of ROP. We also tried to find out co-morbidities associated with ROP and study its pattern among preterm babies admitted to the NICU of our centre.

2. Materials and Methods

The study population was drawn from the NICU of Jawaharlal Nehru Medical College and hospital A.M.U., Aligarh. The study population included all the neonates with a gestational age of less than 36 weeks admitted to the NICU of our college from January 2018 to June 2019. Informed written consent was taken from each patient's guardian before participation in the study. Neonates whose guardians did not give consent, babies with hazy ocular media, and those who died before fundus examination were excluded from the study.

Anterior segment examination was done using a torchlight/direct ophthalmoscope to look for conjunctiva, cornea, lens/ media clarity, and the pupillary reaction. The pupil was dilated with mydriatic eye drop containing (tropicamide 0.4%, phenylephrine 2.5% and Cyclopentolate 0.5%), instilled every 15 minutes for 3-4 times, starting 1 hour before the posterior segment examination. The retinal examination was done using an indirect binocular ophthalmoscope and 28 dioptre lens, using Alfonso eye speculum and Schocket scleral depressor. Findings were drawn on a retinal diagram mentioning the zone, stage, the extent of disease in clock hours, and the presence of pre-plus or plus disease.

ROP staging was done as per ICROP classification, and further treatment was done according to guidelines laid by the ETROP study. Patients with non-vascularised peripheral temporal retina at 36 weeks were reviewed in retina clinic/NICU at a two-week interval until ROP requiring treatment developed or vascularisation of the retina reached the expected completion. Patients were treated using laser and intravitreal anti-VEGF injections as per the need. Their ocular condition was recorded, and follow-ups were scheduled for. The study was approved by the multidisciplinary research ethics and advisory committee, J.N. Medical College and hospital, A.M.U.

2.1. Statistical analysis

The data were entered and analysed using IBM SPSS© Version 20. The prevalence of ROP was described in percentage proportion. Chi-square test and Fisher exact test were used to analyse categorical variables, as applicable. For continuous variables, independent sample t-test and Mann-Whitney U test were used as appropriate. A p-value of < 0.05 was taken as statistically significant. Further, multivariate analysis was done to adjust for factors that were found significant in univariate analysis.

3. Results

The study population included 164 babies with a gestation age < 36 weeks. 87 (53.05%) were male, and 77 (46.95%) were female. The mean gestational age of babies enrolled was 32.43±2.18 weeks (26 weeks to 35.71 weeks). The mean birth weight was 1.55 kg±0.39 kg (range: 0.86 kg-2.76 kg). 92 (56.10%) babies were delivered normally, and 72 (43.90%) were delivered by caesarean section. Among 164 babies, 126 (76.83%) were born singleton, 33 (20.12%) were twins, and 5 (3.05%) were born as triplets.

3.1. Prevalence of ROP

The prevalence of ROP was 17.68% (29/164). Among those suffering from ROP, 29 babies 51.72% (15/29) had stage 1, 31.03% (9/29) had stage 2, 10.35 % (3/29) had stage 3 and 6.90% (2/29) babies had APROP. None of the babies progressed to stage 4 or 5. The disease was localised to zone 1 in two cases (6.9%), zone 2 in eight cases (27.59%), and in nineteen cases (65.51%) the disease was confined to zone 3.

Table 2 depicts the association between ROP and various risk factors and co-morbidities. A significant association was observed between ROP occurrence and gestational age,

Table 1: Demographic data of the respondents

Data		n (%) or mean±SD
Sex	Male	87 (53.05%)
	Female	77 (46.95%)
Mean Gestational Age		32.43±2.18 weeks
Mean Birth Weight (g)		1.55±0.39 kg
Mode of Delivery	Normal delivery	92 (56.10%)
	Caesarean section	72 (43.90%)
Type of Gestational	Singleton	126 (76.83%)
	Twins	33 (20.12%)
	Triplet	5 (3.05%)

Table 2: Risk factors associated with ROP

		Cases with ROP (n=29)	Cases without ROP (n=135)	p -value
Sex	Male (87)	17 (19.54%)	70 (80.46%)	0.508
	Female (77)	12 (15.58%)	65 (84.42%)	
Gesatational age (weeks)*	<28 weeks	3 (42.86%)	4 (57.14%)	<0.001
	28-32 weeks	15 (24.59%)	46 (75.41%)	
	>32 weeks	11 (11.46%)	85 (88.54%)	
Birth weight (kg)*	<1.00 kg	6 (50%)	6 (50%)	<0.001
	1.00-1.49 kg	18 (23.68%)	58 (76.32%)	
	1.50-2.49 kg	5 (6.58%)	71 (93.42 %)	
Multiple gestation*	Singleton	18 (14.28 %)	108 (85.72%)	0.004
	Twins	7 (21.21%)	26 (78.79%)	
	Triplets	4 (80%)	1 (20%)	
Mechanical ventilation* (n=12)		5 (41.67%)	7 (58.33%)	0.039
History of oxygen therapy* (n=55)		23 (41.82%)	32 (58.18%)	<0.001
Duration of oxygen therapy* (days)		6.45±5.62	0.88±2.37	<0.001
History of blood transfusion* (n=9)		5 (55.56%)	4 (44.44%)	0.009
Apgar score 1 min		5.97 ± 1.52	6.30 ± 1.17	0.193
Apgar score 5 min		7.55 ± 0.74	7.84 ± 0.81	0.075
Respiratory distress syndrome* (n=42)		16 (38.10%)	26 (61.90%)	<0.001
Neonatal jaundice (n=61)		8 (13.11%)	53 (86.89%)	0.238
Apnea* (n=11)		8 (72.73%)	3 (27.27%)	<0.001
Sepsis* (n=44)		13 (29.55%)	31 (70.45%)	0.016
Shock (n=5)		2 (40%)	3 (60%)	0.214
Hypocalcaemia (n=6)		2 (33.33%)	4 (66.67%)	0.287
Necrotising enterocolitis (n=8)		2 (25%)	6 (75%)	0.632
Thrombocytopenia (n=4)		2 (50%)	2 (50%)	0.144

* Statistically significant

Table 3: Risk factors for ROP; Multivariate logistic regression analysis

	OR	95% C.I. for OR		p- value
Gestational age	.923	.707	1.206	0.558
Supplemental oxygen therapy*	5.530	1.609	19.005	0.007
Apnea*	7.139	1.144	44.565	0.035
RDS*	6.745	2.047	22.224	0.002
Birth weight*	.076	.009	.664	0.020
Multiple gestation	2.384	.696	8.170	0.167
Mechanical ventilation	1.498	.275	8.146	0.640
Blood transfusion	1.817	.199	16.578	0.597
Sepsis	.525	.148	1.864	0.319

* Statistically significant

Table 4: Association between oxygen supplementation and stages of ROP

Stage of ROP	Cases required oxygen therapy	Cases without oxygen therapy	p- value
Stage 1 (n=15)	10	5	
Stage 2 (n=9)	8	1	<0.001
Stage 3 (n=3)	3	0	

low birth weight, multiple gestation, mechanical ventilation, history and duration of oxygen supplementation, history of blood transfusion, respiratory distress syndrome, apnea, and sepsis. However, an insignificant association was found between ROP and sex, mode of delivery, Apgar score at 1 and 5 minutes, neonatal jaundice, shock, hypocalcaemia, necrotising enterocolitis, thrombocytopenia (all $p > 0.05$).

Factors that were statistically significant after univariate analysis were further analysed for multivariate analysis using multiple logistic regression. Birth weight, supplemental oxygen therapy, apnea and R.D.S. were significant even after multivariate analysis (Table 3). Further, a statistically significant association was found between oxygen supplementation and stages of ROP, as shown in Table 4.

4. Discussion

This study was conducted by the Institute of Ophthalmology in collaboration with NICU, Department of Paediatrics, J.N.Medical College, A.M.U, Aligarh, to find the prevalence of ROP and associated co-morbidities in preterm babies admitted to NICU of our Hospital.

The prevalence of ROP was found to be 17.68% (29/164). The prevalence of ROP in India is relatively high and ranges from 2.3%% to 47.2%.[8–14] Le et al. (Telangana, 2016) reported a prevalence of 2.3% (66/2910),[14] Parekh et al. (Maharashtra, 2016) 28.57% (44/154),[15] Ashwani Kumar et al. (Punjab, 2017) reported a prevalence of 40% (31/77),[11] while Mantri et al. (Rajasthan, 2017) reported a prevalence of 13.6 % (34/250).[13] This vast disparity is attributed to the fact that neonatal care is highly variable in different parts of our country.

4.1. Risk factors associated with ROP

We found prematurity to be significantly associated with ROP, which has been proven in many other studies.[14,16–22] It was observed that 42.86% (3/7) of extremely preterm babies developed ROP, 24.59% (15/61) of very preterm babies developed ROP and among remaining moderate to late preterm babies, only 11.46% (11/96) babies developed ROP A significant association was observed between prematurity and development of ROP after univariate analysis. This inferred that babies born at lower gestational age are more prone to develop ROP. The probable reason behind this association is incomplete vascularisation of the retina as vascularisation completes in 38-40 weeks of gestation. The immature retina is more susceptible to insults that disrupt vascular growth and leads to ROP.[23,24] Such an immature retina is also more likely to get oxidative damage hyperoxia or hypoxia, blood transfusions, and sepsis, which are known factors contributing to ROP development. In the CRYO-ROP cohort, it was observed that each additional week of gestational age decreases the odds of reaching threshold disease by 19%.[25] However, in multivariate analysis, no significant association was found between low gestational age and ROP occurrence. This may be because most preterm babies who did not have any other associated co-morbidities did not develop ROP. Similar findings were observed after multivariate analysis in many other studies conducted across the globe, indicating that gestational age does not independently determine the development of ROP[18,26,27]

Low birth weight was another significant risk factor for the development of ROP. Low birth weight was another significant risk factor for the development of ROP. Among extremely low birth weight babies(1.00 kg) 50% (6/12) babies developed ROP, 23.76%(18/76) babies with very low birth weight (1 to 1.49kg) developed ROP and among the

remaining Low birth babies(1.5 to 2.49 kg) only 6.58% (5/76) developed ROP. Similar results were observed in the multicenter trial of cryotherapy (CRYO ROP study), where it was concluded that lower the birth weight, greater the risk of developing ROP, especially in infants with birth weight less than 750 gm. It was also reported that for every 100 gm increase in birth weight, there is a 27% decrease in odds of reaching threshold ROP.[25] Our results were also supported by observations of many other studies which reported a significant relationship between ROP and birth weight.[19,28–33] This association can be explained by the fact that low birth weight is associated with prematurity and many other co-morbidities which have a direct association with ROP

This study also revealed a significant relationship between oxygen supplementation and ROP development (p-value<0.001). Our findings were also supported by many other studies conducted in India[10,13,14] and across the world.[17,22,34,35] This association can be explained by the fact that inside the uterus baby is in a hypoxic state after delivery, supplemental oxygen induces hyperoxia and suppresses normally produced growth factors (VEGF) which result in cessation of growth of retinal vasculature. Subsequently, the increasing metabolically active but poorly vascularised retina becomes ischemic. It leads to a surge of VEGF, further leading to the sudden proliferation of vessels and the development of ROP[36] On the other hand, in a study conducted by Palmer et al. (2005) and Alizadeh et al. (Iran, 2015), no significant association was found between ROP and supplemental oxygen. They also stated that ROP might develop in cases that did not have any history of oxygen supplementation.[37,38]

A significant association was observed between duration of oxygen supplementation on ROP development. This result was also supported by Norman Ashton et al., who, in their randomised controlled trial in 1956, reported that the severity of the vaso-obliterative effect of oxygen is directly proportional to the concentration and duration of oxygen administered.[39]

However, no significant relationship was observed between ROP and multiple gestations, mechanical ventilation, blood transfusion, Apgar score at 1 and 5 minutes, neonatal jaundice.

4.2. Co-morbidities associated with ROP

Many co-morbidities are linked with ROP. By reducing these morbidities or managing them properly, we can reduce the incidence of this disease.[40]

In our study, we observed a significant association between R.D.S. and ROP (p-value <0.001). Similar results have been reported by other previous studies. These results are unsurprising because R.D.S. requires supplemental oxygen, which induces hyperoxemia in the developing retina, thus arresting the retinal vascular growth. Consequently, the resulting hypoxia of the retina causes ROP[41]. However, Alajbegovic et al. (Europe, 2015) and Hakeem et al. (Egypt, 2012) reported an insignificant association between ROP and R.D.S.[20,42]

A statistically significant association between ROP and apnea (p-value<0.001) was also observed in this study. Similar findings were reported by Alizadeh et al.[43] Chattopadhyay et al. Le et al Kumar et al. Wu et al. Fluctuation of arterial oxygen tension (PaO2) occurs during apneic attacks, which has a more adverse effect on proliferative retinal diseases than hyperoxia alone, leading to neovascularisation and development of ROP[43,44]

Many other co-morbidities like neonatal jaundice, shock, hypocalcaemia, necrotising enterocolitis, sepsis and thrombocytopenia were also considered in this study. None of them showed any statistically significant association with the development of ROPs.

Almost all babies with stage 1 and stage 2 disease underwent spontaneous regression except for four babies, whose fate is unknown, as they were lost to follow up, whereas babies with stage 3 and APROP disease were treated with laser/ Anti- VEGF.

5. Conclusion

In a nutshell, a prevalence of 17.68% in this study from a tertiary centre in western Uttar Pradesh emphasises the importance of neonatal screening in this region. Low birth weight, oxygen therapy, apnea, respiratory distress syndrome pose a significant risk factor for ROP. Timely ROP screening of high-risk preterm babies is essential to prevent the development of advanced ROP None of the babies in our study developed stage 4 or 5 ROP, emphasising the importance of timely ROP screening in reducing the severity of the disease. Since ROP may produce serious sequelae leading to complete blindness, no stone should be left unturned to prevent the development of advanced ROP by reducing preterm births, improving neonatal care, proper monitoring of oxygen saturation. We should wean off supplemental oxygen as early as possible since it is detrimental to the occurrence and severity of ROP. An adequate number of trained retinal surgeons in ROP care is required as the magnitude of the problem is ever-increasing. Government programs are required in this field to make the patients aware regarding the complications of this disease and to emphasise on the importance of screening for close follow up of such neonates.

6. Conflict of Interest

The authors declare that they have no conflict of interest.

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