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Original Research Article

A study of risk factors and their correlation with severity of retinopathy of prematurity: a prospective study

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ABSTRACT

Background: Recent advances in neonatal care in the last decade and improved survival rates have resulted in an apparent increase in the incidence of retinopathy of prematurity (ROP), which is the most important cause of preventable blindness in infants. This study was done to identify the risk factors which predispose to ROP and to assess its correlation with severity of ROP.
Methods: A total of 140 neonates with gestational age ≤34 weeks, birth weight ≤2000 grams who were admitted at NICU, S. N. Medical College and HSK Hospital, Bagalkot from December 2018 to May 2019 were considered. Babies were assessed and recorded for the risk factors of ROP in a predesigned proforma. ROP screening was performed using wide-field digital imaging on a retcam shuttle (Clarity MSI, USA).
Results: A total of 140 babies were examined, and an overall incidence of ROP was 52 (37.1%). 17 (32.7%) had stage 3, 3 (5.8%) had stage 4, and 1 (1.9%) had stage 5. Among the 52 babies with ROP, 19 (51.3%) underwent laser photoablation. Risk factors like gestational age, birth weight, maternal risk factors, apnea, intrauterine growth restriction (IUGR), hypoglycaemia, respiratory distress syndrome (RDS), sepsis, coronary heart disease (CHD), blood transfusion and oxygen requirement duration were significantly associated with ROP. Delay in the establishment of feeds has been associated with ROP ($p<0.001$).
Conclusions: Screening should be intensified in the presence of risk factors which can reduce the incidence of severe stages of ROP as highlighted by this study.

Keywords: Retinopathy of prematurity, Blindness, Infants, Proforma, Screening

INTRODUCTION

Around 14 million children in the world are blind. The World Health Organization (WHO) defines blindness as a corrected visual acuity in the better eye of less than 3/60, and severe visual impairment as a corrected acuity in the better eye of less than 6/60. In accordance with global statistics of blind children, the control of blindness in children is a priority within the WHO's 'Vision 2020' programme.[1] Cerebral visual impairment and optic nerve anomalies remain the most common causes of blindness, while retinopathy of prematurity (ROP) and cataract are presently the most common avoidable causes.[2]

ROP is a common blinding disease in children in the developed world and is becoming increasingly prevalent. ROP, which was previously called as retrolental fibroplasia (RFL), is a vaso-proliferative disorder of the retina.[3] The manifestations of the disease can range from mild with no visual defects to severe with new vessel formation (neovascularization) and even progress to retinal detachment and blindness. Worldwide assessment in 2010 estimated that 36.5% incidence of ROP among preterm births.[4] Incidence of ROP and visual disability due to ROP might differ in various countries. Worldwide ROP accounts for 17.5% of visual impairment in prematurely born babies.[5]

As there are few studies showing a correlation of risk factors with the severity of ROP, and concerned on the high incidence of ROP globally, the present study was undertaken. The aim and objectives of this study are to identify the risk factors which predispose to ROP and to find its correlation with severity of ROP.

METHODS

This was a prospective study concerning 140 preterm infants (<34 weeks' gestation age and/or <2000 grams birth weight) who had been admitted to the neonatal intensive care unit of S. Nijalingappa Medical College and HSK Hospital, Bagalkot between December 2018 to May 2019 and all the babies were included in the study. The institutional ethical committee clearance was obtained. The study design and nature of the clinical study was explained to the babies' parents, and informed consent was obtained. Babies satisfying the inclusion criteria were included in the study.

The risk factors studied were gender, cesarean section, maternal age, single or multiple gestations, maternal hypertension, surfactant administration, birth weight (every <2000 grams), gestational age (every <34 weeks), postnatal weight gain (every 1 gram increase/day), respiratory distress syndrome (RDS) ≥III, patent ductus arteriosus (PDA), sepsis, cerebral hemorrhage, intrauterine fetal demise, apnea, exchange transfusion and duration of intubation days (≥10 days).

The babies were examined either in the neonatal intensive care unit if they were hospitalized for a prolonged period of time. Since ROP screening examinations can have short-term effects on blood pressure, heart rate and respiratory function, examinations were kept as short as possible. As per the American academy of pediatrics (AAP) 2013 guidelines precautions were taken to ensure that emergency situations were dealt with promptly and effectively.[6] Discomfort to the baby was minimized by pre-treatment of both eyes with a topical proparacaine and swaddling the baby. Babies were kept nil by mouth (NBM) for at least an hour before the examination to avoid vomiting and aspiration. All aseptic precautions were ensured.

Procedure

One drop of tropicamide was instilled in both eyes every 10-15 minutes an hour before the examination. This was followed by phenylephrine (one drop) immediately before the ophthalmic examination. Phenylephrine (10% concentration) was diluted four times before its use. Repeated installation of phenylephrine was avoided for fear of hypertension. Screening of ROP was done with Retcam Shuttle (Clarity MSI, USA) by an experienced ophthalmologist in the NICU.

After instilling proparacaine, (topical anaesthetic), a wire speculum was inserted to keep the eye-lids apart. Firstly the anterior segment of the eye was examined. It was assessed for tunica vasculosalentis, pupillary dilation and lens/media clarity. Secondly, the posterior pole was assessed for the plus disease. This was followed by a sequential examination of all clock hours of the peripheral retina. A scleral depressor was used to indent the eye externally to examine, rotate and stabilize the eye. Each ROP examination was documented with regard to zone, stage and its extent (clock hours) and presence of any pre-plus or plus disease. After screening, the cases were classified as per international classification for retinopathy of prematurity (ICROP) on the basis of vascularization of the retina and characterized by its position (zone), severity (stage), and extent (clock hours).

Follow up was done as per the recommendation by ICROP.[7] Infants without ROP were examined monthly until there was complete vascularization of the retina. Those with stage 1 or 2 ROP were re-examined every two weeks until resolution or progression to a more advanced stage. All pertinent information, such as birth weight, gestational age, gender, details of respiratory support, blood transfusion, sepsis, intraventricular haemorrhage (IVH), and total parenteral nutrition (TPN) were recorded on proforma.

Statistical methods

ROP was considered as the primary outcome variable. Maternal and fetal parameters like gestational age, mode of delivery, birth weight and maternal risk were considered as primary explanatory variables.

All quantitative variables were checked for normal distribution within each category of an explanatory variable by using visual inspection. Shapiro-Wilk test was also conducted to assess normal distribution. Shapiro-Wilk test p value of >0.05 was considered as a normal distribution.

For normally distributed quantitative parameters, the mean values were compared between study groups using independent sample t-test (2 groups). Categorical outcomes were compared between study groups using chi square test. Association between quantitative explanatory and outcome variables was assessed by calculating the person correlation coefficient.

Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. Unadjusted odds ratio along with 95% confidence interval (CI), is presented. Variables with statistical significance in univariate analysis were used to compute multivariate regression analysis. Adjusted odds ratio along with their 95% CI is presented. P value <0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analysis.

RESULTS

The difference in maternal age, gender, birth asphyxia and birth order, and need of resuscitation between the ROP, was found to be insignificant with a p value >0.05. Among the people with ROP, majority of 29 (55.8%) children birth weight was 1000 to 1499 grams. The mean birth weight of children of people with ROP was 1394.62±332.546. The mean gestational age at birth of people with ROP was 30.40±2.427.

The mean difference between two groups was statistically significant about birth weight and gestational age (p value <0.05). The difference in intrauterine growth restriction (IUGR) between the ROP is found to be significant with a p value of 0.033

Table 1: Awareness about the management of dog bite case among the study population.

Parameter	ROP		P value
	With ROP (n=52)	Without ROP (n=88)	
	N (%)	N (%)	
Maternal age (mean±standard deviation)	22.04±2.368	21.80±1.763	0.49
Gender			
Male	32 (61.5)	58 (65.9)	0.602
Female	20 (38.5)	50 (34.1)	
Birth weight			
<1499 grams	31 (59.6)	39 (44.3)	0.08
1500-2000 grams	21 (40.4)	49 (55.7)	
Birth weight (mean±standard deviation)	1394.62±332.546	1547.22±273.827	0.004
Mean gestational age at birth (mean±standard deviation)	30.40±2.427	31.76±2.040	0.001
Intrauterine growth restriction (IUGR)	22 (42.3)	22 (25.0)	0.033
Pregnancy induced hypertension (PIH)	14 (26.9)	2 (2.3)	<0.001
Preterm premature rupture of the membranes (PPROM)	8 (15.4)	5 (5.7)	
Antepartum haemorrhage (APH)	3 (5.8)	2 (2.3)	
Anemia	4 (7.7)	3 (3.4)	
No illness	23 (44.2)	76 (86.4)	
Birth order			
Single	38 (73.1)	60 (68.2)	0.541
Twin	14 (26.9)	28 (31.8)	
BMV	1(1.9)	7 (8.0)	0.331
Intubation	2 (3.8)	3 (3.4)	
Oxygen	44 (84.6)	13 (14.8)	<0.001
Birth asphyxia			
Stage 1	1 (1.9)	7 (8.0)	0.331
Stage 2	2 (3.8)	3 (3.4)	
Apnea	18 (34.6)	1 (1.1)	<0.001
Hypoglycaemia	24 (46.2)	3 (3.4)	<0.001
RDS	27 (51.9)	4 (4.5)	<0.001
Sepsis	26 (50.0)	4 (4.5)	<0.001
CHD	19 (36.5)	13 (14.8)	0.003
Pneumonia	3 (5.8)	1 (1.1)	0.145
Polycythaemia	4 (7.7)	3 (3.4)	0.424
Phototherapy	26 (50.0)	30 (34.1)	0.063
Blood transfusion	22 (42.3)	10 (11.4)	<0.001
Day of establishment of feed (mean±standard deviation)	3.17±1.855	1.99±0.719	<0.001
Gestation age at 1st ophthalmological evaluation (mean±standard deviation)	32.75±2.334	34.19±2.094	<0.001
Gestation age at complete vascularizatio-n of retina (mean±standard deviation)	48.81±3.459	45.41±3.464	<0.001

The difference in maternal risk factors between the ROP was found to be significant with a p value of <0.001. The difference in oxygen between the ROP was found to be significant with a p value of <0.001. The difference in apnea, hypoglycaemia, respiratory distress syndrome

(RDS), coronary heart disease (CHD) and sepsis between the ROP was found to be significant with a p value of <0.001. The difference in pneumonia, polycythemia and phototherapy between the ROP is found to be insignificant with a p value as >0.05. The difference in blood transfusion between the ROP is found to be significant with a p value of <0.001. The mean day of establishment of feed of people with ROP was 3.17±1.855. The mean gestation age at 1st ophthalmological evaluation of people with ROP was 32.75±2.334. The mean gestation age at complete vascularization of the retina of people with ROP was 48.81±3.459. The mean difference between two groups was statistically significant with respect to the day of establishment of feed of people, gestational age at 1st ophthalmological evaluation and at complete vascularization (p value <0.001) (Table 1). There was no statistically significant difference in birth weight across stages of ROP with p value of 0.595. There was no statistically significant difference in oxygen across stages of ROP with p value of 0.100. There was no statistically significant difference in gestation age at 1st ophthalmological evaluation across stages of ROP with p value of 0.315. There was no statistically significant difference in gestation age at complete vascularization of retina across stages of ROP between with p value of 0.270 (Table 2).

Table 2: Comparison of demographic and clinical parameters across stages of ROP (n=52).

Parameter	Stage of ROP					P value
	Stage I (n=7)	Stage II (n=24)	Stage III (n=17)	Stage IV (n=3)	Stage V (n=1)	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Zone of ROP						
Zone 1	1 (14.3)	1 (4.2)	6 (35.3)	2 (66.7)	1 (100)	
Zone 2	5 (71.4)	18 (75.0)	6 (35.3)	1 (33.3)	0 (0)	*
Zone 3	1 (14.3)	5 (20.8)	5 (29.4)	0 (0)	0 (0)	
Gender						
Male	7 (100)	13 (54.2)	9 (52.9)	2 (66.7)	1 (100)	*
Female	0 (0)	11 (45.8)	8 (47.1)	1 (33.3)	0 (0)	
Birth weight						
<1000	0 (0)	0 (0)	2 (11.8)	0 (0)	0 (0)	
1000-1499	5 (71.4)	13 (54.2)	9 (52.9)	2 (66.7)	0 (0)	*
1500-2000	2 (28.6)	11 (45.8)	6 (35.3)	1 (33.3)	1 (100)	
Birth weight (mean±standard deviation)	1295.71±291.93	1468.96±331.70	1325.88±356.61	1360.0±350.42	1575±0	0.595
IUGR	3 (42.9)	7 (29.2)	9 (52.9)	2 (66.7)	1 (100)	*
Maternal risk						
PIH	2 (28.6)	6 (25.0)	5 (29.4)	0 (0)	1 (100)	
PPROM	0 (0)	4 (16.7)	3 (17.6)	1 (33.3)	0 (0)	
APH	0 (0)	2 (8.3)	1 (5.9)	0 (0)	0 (0)	*
Anemia	3 (42.9)	1 (4.2)	0 (0)	0 (0)	0 (0)	
No illness	2 (28.6)	11 (45.8)	8 (47.1)	2 (66.7)	0 (0)	
Birth order						
Single	5 (71.4)	19 (79.2)	11 (64.7)	2 (66.7)	1 (100)	*
Twin	2 (28.6)	5 (20.8)	6 (35.3)	1 (33.3)	0 (0)	
Mode of delivery						
Normal	5 (71.4)	18 (75.0)	10 (58.8)	3 (100)	1 (100)	
Instrument assisted	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	*
LSCS	2 (28.6)	6 (25.0)	6 (35.3)	0 (0)	0 (0)	
Apena	2 (28.6)	8 (33.3)	7 (41.2)	0 (0)	1 (100)	*
Hypoglycemia	3 (42.9)	10 (41.7)	9 (52.9)	1 (33.3)	1 (100)	*
RDS	4 (57.1)	11 (45.8)	10 (58.8)	2 (66.7)	0 (0)	*
Sepsis	5 (71.4)	11 (45.8)	8 (47.1)	2 (66.7)	0 (0)	*
Blood transfusion	3 (42.9)	8 (33.3)	9 (52.9)	1 (33.3)	1 (100)	*
Gestation age at 1st ophthalmological evaluation (mean±standard deviation)	32.43±1.718	33.04±2.255	32.06±2.410	34.0±3.464	36±0	0.315
Gestation age at complete vascularization of retina (mean±standard deviation)	*	48.25±5.188	47.78±2.489	50.86±3.185	46±0	0.270

*No statistical test was applied due to 0 subjects in the cells

Table 3: Bivariate and multivariate logistic regression for identifying independent risk factors associated with occurrence of ROP (n=140).

Factors	Univariate		Multivariate	
	OR (95%CI)	P value	OR (95% CI)	P value
Oxygen (baseline=no)	31.7 (12.2-82.6)	<0.001	18.5 (2.5-135.3)	0.004
Hypoglycemia (baseline=no)	24.3 (6.8-86.8)	<0.001	139.9 (9.7-2021.5)	<0.001
RDS (baseline=no)	22.7 (7.2-71.0)	<0.001	15.8 (1.9-130.3)	0.010
Sepsis (baseline=no)	5.7 (2.4-13.5)	<0.001	53.3 (5.4-522.9)	0.001

Table 4: Correlation between severity of ROP and day of establishment of feeds (n=140).

	Pearson correlation	P value
Day of establishment of feeds	0.136	0.337

The univariate and multivariate logistic regression analysis had shown statistically significant association with ROP with all explanatory factors, as presented in Table 3. There was a weak positive correlation between the severity of ROP and day of the establishment of feeds (r-value=0.136, p value=0.337) (Table 4).

DISCUSSION

Significance of ROP screening lies in the fact that ROP is the most common preventable cause of childhood blindness. In middle-income countries like South American and Asian countries, ROP is emerging as a major cause of blindness (also referred to as the third epidemic).[9]

Possible reasons for this epidemic are: birth rates and the rate of premature births is increasing, and neonatal care may be compromised as a result of the limitation of resources.

These reasons result in higher rates of severe ROP not only in extremely premature infants but also in term infants. Less nationwide implementation of screening and treatment programs for ROP due to the lack of awareness, skilled personnel and/or financial resources.[10]

The primary prevention of ROP can be done by limiting the exposure to antenatal, natal and postnatal risk factors which contribute to the increased incidence and severity of ROP. Secondary prevention of ROP is done by timely screening and early treatment to prevent blindness. Therefore, secondary prevention of ROP is given utmost importance in the WHO 'Vision 2020' programme.[11] Studies from developed countries have reported the overall decrease in the incidence of ROP wherever there is an ongoing surveillance programme.[12] So timely screening is a very important aspect in the management of ROP.

The overall incidence of ROP in the present study is 37.1%. Hungi et al reported the overall incidence of ROP as 41.5% and treatable ROP was 26.4%.[13] Their study included 118 babies of ROP with ≤34 weeks gestation or ≤2000 grams. Maheshwari et al in 1996 reported an overall incidence of ROP as 20% and severe ROP as 7%.[14] Their study included 66 babies with <35 weeks or <1500 grams. However, in most instances, it is not possible to compare studies, as the inclusion criteria are different. Screening of babies with a gestational age of <34 weeks and/or <2000 grams birth weight in this study have made the incidence of ROP comparable to other Indian studies. Recent reports from India and other Asian countries have suggested that babies heavier and more mature than their western counterparts are at risk of developing ROP.[15-18] This would be missed if western guidelines were used to assess ROP. Most of the studies consider stage 3 and above as severe ROP. In our study, there was 40.4% of severe ROP, which was similar to the study conducted by Austeng et al.[19] Nineteen babies (36.5%) required treatment for ROP. This higher severity of ROP can be explained because, in the present study, a higher proportion of infants were born in the earliest weeks of gestation (40.3% in ≤29 weeks).

Though accumulating evidence indicates that ROP is a multifactorial disease, immaturity of the retina and a period of hyperoxia are the main contributing etiological factors in the pathophysiology of ROP.[2] In our study, the incidence of ROP was significantly inversely proportional to both birth weight ($p<0.05$) and gestational age ($p<0.006$). The duration of oxygen administration, need for oxygen supplementation, clinical sepsis, apnea, RDS, hypoglycemia, CHD, IUGR, antenatal steroids and administration of blood products were significant risk factors associated with the development of ROP. The prevalence of ROP was more among very low birth weight (VLBW) neonates, and the risk is inversely proportional to birth weight, and gestational age in a study conducted by Maheshwari et al study confirmed that the incidence of ROP increased as the birth weight decreased.[14] The duration of oxygen administered was associated with the development of ROP ($p=0.001$). 84.6% of babies who received oxygen therapy developed ROP in the present study. Different studies showed that 50% of the babies on oxygen therapy developed ROP.[21,22]

The causal link between ROP and supplemental oxygen has been confirmed by controlled trials and clinical studies.[22,23] However, a safe level of oxygen usage has not been defined. Preliminary work has suggested that continuous oxygen monitoring may reduce the incidence of ROP.

A study conducted by Rosemary et al showed that antenatal steroid administration for the mother had a protective effect against ROP development in the neonates.[24] In our study, it was a significant risk factor associated with ROP (p=0.04). A study by Hammer et al showed the association between a maternal risk factor and ROP due to hypoxia and acidosis.[25] A study was done by Purohit et al found that pregnancy-induced hypertension (PIH) to be a significant risk factor.[26] This was found to be significant in our study. RDS is a significant risk factor in the present study and an independent risk factor on multivariate analysis. Gupta et al reported ROP in 33.3% of babies with RDS.[21] In our study, 51.9% of babies with ROP had RDS, which is almost comparable to the other studies mentioned. It has been hypothesized that the adult haemoglobin, being more capable of releasing oxygen to tissues, causes tissue-level hyperoxia and result in ROP.[27] Exchange transfusion has been identified as a risk factor for the development of ROP by Rekha et al and Maheshwari et al.[14,28] The hyperoxia in the tissues leads to free oxygen radical release and reflex vasoconstriction leading to the familiar cascade of events that causes ROP.[8,29] In our study, blood transfusion was found to be associated with the development of ROP.

Clinical sepsis is associated with ROP and considered an independent risk factor in the present study (p=0.001). This association corroborates with the findings of other studies.[21,22] Its prevention and early treatment may reduce the incidence of ROP. The risk of ROP was independently proportional to the presence of bacterial and fungal sepsis only in extremely low birth weight (ELBW) babies and those with threshold ROP. This is shown in the study of Manzoni et al.[30] ROP is known to be associated with apnea in the present study as compared to other studies.[21,31] Appropriate management of apnea may reduce the incidence of ROP. Apnea was also found to be a risk factor for ROP in studies conducted by Shohat et al, Gunn and coworkers.[32,33] Human milk is a positive predictor of ROP, indirectly implying that prolonged parenteral nutrition is a risk factor for ROP. Porcelli and coworkers studied that ROP cases had a late onset of enteral feeds compared to non ROP.[34] Also, the delay of initiation of feeds was a risk factor of ROP.

We suggest that more detailed studies for the contribution of neonatal illness, for example, the effect of changes in blood pressure and oxygenation, on the occurrence of ROP. This may require continuous measurements of these variables. This will depend on the availability of appropriate equipment in sufficient number. Since severe ROP (stage 3, 4 and 5) seems to develop only in a small number of infants, future clinical studies will probably require to be carried out on a multicentre basis.

CONCLUSION

Improving neonatal care and survival in semi-urban and rural areas by meticulous monitoring and follow up is essential for early detection of ROP. The timely institution of treatment helps to avoid the complications. Screening should be intensified in the presence of risk factors which can reduce the incidence of severe stages of ROP, as shown by this study.

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