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Original Research Article

A study of risk factors affecting outcome of retinopathy of prematurity: a cross-sectional study at tertiary care centre

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ABSTRACT

Background: Retinopathy of prematurity (ROP) remains a significant cause of preventable blindness in premature infants. This study aimed to analyze various risk factors affecting ROP outcomes in a tertiary care setting.
Methods: A cross-sectional study was conducted at the Neonatal Care Unit of Guru Gobindsingh Government Hospital and Shri M.P. Shah Government Medical College, Jamnagar, over 10 months, enrolling 180 newborns with ROP. Risk factors were analyzed using descriptive statistics and Chi-square tests, with $p<0.05$ considered statistically significant.
Results: The study identified several risk factors significantly associated with progression to severe ROP requiring intervention: early gestational age, lower birth weight, neonatal sepsis, respiratory distress syndrome, oxygen requirement >7 days, and blood transfusion. Among these, neonatal sepsis, respiratory distress, and prolonged oxygen requirement were identified as preventable factors. Conversely, antenatal steroid administration, exclusive breastfeeding, and surfactant use were associated with decreased ROP severity.
Conclusions: While factors like sepsis, prolonged oxygen requirement, low birth weight, respiratory distress syndrome, and blood transfusions were associated with more severe ROP stages, protective factors included exclusive breastfeeding, antenatal steroids, and surfactant use. This understanding can help develop targeted preventive strategies and improve outcomes in premature infants at risk for ROP.

Keywords: Neonatal care, Premature infants, Prevention strategies, Retinopathy of prematurity, Risk factors

INTRODUCTION

Retinopathy of Prematurity (ROP) was first identified by Terry in 1942 as retrolental fibroplasia, based on his observation of proliferative changes in the embryonic hyaloid system.[1] Heath later coined the term "Retinopathy of Prematurity" in 1951. ROP is a vasoproliferative retinal disorder primarily affecting premature infants, characterized by abnormal retinal neovascularization and potentially leading to retinal detachment and blindness if left untreated.[2]

The pathogenesis of ROP is unique among proliferative retinopathies as it exclusively occurs in infants with immature, incompletely vascularized retina. Global estimates suggest that ROP accounts for 6-18% of childhood blindness in developed countries and up to 40% in middle-income countries. [3]

Contemporary research has identified multiple risk factors including gestational age, low birth weight, oxygen therapy, respiratory distress, sepsis, systemic inflammation, antenatal steroid exposure, blood

transfusions, and nutritional factors.[4] The improved survival of extremely premature infants, particularly those with very low birth weight (<1500g), has led to an increased population at risk for developing ROP.

Treatment modalities have evolved substantially. While cryotherapy was historically used, contemporary management primarily relies on laser photocoagulation and anti-vascular endothelial growth factor (anti-VEGF) therapy.[4] The critical nature of early detection and intervention has led to the development of comprehensive screening protocols, typically focusing on infants born at ≤34 weeks gestational age or with birth weight ≤1800g, though specific criteria may vary by region.[5]

This study aims to analyze various risk factors influencing the outcome of retinopathy of prematurity (ROP), including gestational age, birth weight, antenatal steroid use, sepsis, respiratory distress, oxygen requirement duration, neonatal jaundice, seizures, surfactant administration, exclusive breastfeeding, and blood transfusion. It examines the relationship between the duration of these risk factors and ROP severity. Additionally, the study evaluates different treatment modalities used at various ROP stages and their outcomes. By identifying preventable causes among these risk factors, the study seeks to contribute to early intervention strategies and improved neonatal care to reduce ROP incidence.

METHODS

A cross-sectional study with internal comparison. The present study was institute based and newborn patients were screened for Retinopathy of Prematurity in Neonatal Care Unit of Guru Gobindsingh Government Hospital and Shri M P Shah Government Hospital, Jamnagar. This study conducted from August 2023 to May 2024 (Approx. 10 months). This study included 180 patients.

Sampling technique

The sampling technique used is Consecutive sampling. In this study we have enrolled the new born patients admitted in neonatal ICU from August 2023 to May 2024 (10 months) who fulfilled the eligibility criteria.

Inclusion criteria

Inclusion criteria were prematurely delivered babies having gestational age less than 34 weeks and birth weight less than 1.8 kilograms who underwent screening for ROP and found to have some form of ROP; newborns whose parents have given consent for the study were included in the study.

Exclusion criteria

Exclusion criteria were Newborns screened for retinopathy of prematurity who are found to be negative; parents who have not consented for the study.

Newborns who could not be followed up till a definitive outcome, due to premature death/insufficient clinical data's, were excluded from the analysis.

NOTE: Out of the 180 newborn patients which were enrolled in study, the parents of 24 patients did not give consent for the study, and approx. 15 patients were lost to follow up, therefore the data of 141 newborn patients, which were having positive findings of ROP on examination are analyzed.

Study methodology

Statistical Analysis: Categorical variables were described in frequency and percentage, numerical variables were described with mean and standard deviation (sd) and median and inter quartile range (IQR). CHI square test was used to test statistical significance among categorical variables. All tests had 2 tailed hypothesis, and the probability value ($p<0.05$) was used to determine statistical significance.

Screening protocol

Screening protocol are babies born before 34 weeks of gestation. Babies born with birth weight less than 1.8 kgs; baby born >28 weeks of gestation, ROP screening were be conducted at 4 weeks after birth; baby born <28 weeks of gestation or birth weight <1.2 kgs, should be screened at 3 weeks after birth.

The neonatal ophthalmological examination

Place of examination

ROP screening was done in a dedicated room for screening of ROP within the NICU premises.

Pupillary dilatation

Phenylephrine 2.5% and tropicamide 0.5% were used for pupillary dilatation. The latter was instilled one drop each, every 15 minutes, up to a maximum of 4 times, 1 hour prior to examination. 1 drop of phenylephrine just before examination is usually enough, since its repeated administration can lead to increased systemic absorption leading to hypertension.

Procedure

Screening was done by a binocular indirect ophthalmoscopy using 20 D or 28/30 D condensing lens, by an experienced ophthalmologist. A topical anaesthetist (proparacaine) and antibiotic (diluted povidone iodine) was instilled prior to examination. First, a wire speculum is used to keep the eye-lids apart and the anterior segment of the lens is looked for tunica vasculosa lentis, pupillary dilatation and lens/media clarity. Next, the posterior pole is examined for presence of plus disease and sequential examination of all clock hours of retina peripherally. This

is done by scleral depressors that indent the eye externally, thus rotating and stabilizing the eye.

Recording the findings

The study recorded ROP zones and stages, including the presence or absence of plus or pre-plus disease, in the Neonatal Intensive Care Unit by expert vitreoretinal surgeon Dr. Ruchir Mehta, following Rashtriya Bal Swasthya Karyakram (RBSK) guidelines. The follow-up schedule was documented, and infants were monitored until a definitive outcome was reached either spontaneous regression or ROP requiring treatment. Treatment options included laser therapy or intravitreal anti-VEGF injection. Post-treatment follow-up was conducted to assess outcomes. Risk factors were analyzed, and collected data were transferred into an Excel sheet for statistical analysis to identify significant associations with ROP progression and treatment response.

Use of wide field digital camera (RetCam) for screening

A mobile self-contained RetCam system with a portable fundus camera as an alternative to routine indirect ophthalmoscopic examination can take pictures of retina that can be stored, transmitted to expert, reviewed, analyzed and sequentially compared over time. We captured and stored some of the images taken on RetCam in Pediatrics department.

RESULTS

This study enrolled total 141 breastfeeding mothers. Mean gestational of the mothers was 31.6±1.3 years.

Table 1 presents the distribution of various risk factors and the diagnosis of retinopathy of prematurity (ROP) among 141 neonates. Birth weight categories include extremely low birth weight (ELBW), very low birth weight (VLBW), and low birth weight (LBW). History of antenatal steroid administration, sepsis, respiratory distress, oxygen requirement duration, surfactant use, exclusive breastfeeding, and blood transfusion status are recorded. The table also categorizes neonates based on ROP diagnosis, including aggressive posterior ROP (APROP), hybrid ROP, and stages 1-3 ROP. The data highlight the prevalence of these risk factors and their potential association with ROP severity.

A strong correlation between ROP stage and both gestational age and birth weight is found. Infants below 30 weeks gestation showed higher risk of stage 3 ROP (Table 2).

Infants with very low birth weight and extremely low birth weight had higher chances of getting severe ROP (Table 3).

Sepsis presence not significantly associated with ROP stages despite higher percentages in severe cases (Table 4).

Table 1: Distribution of risk factors and ROP diagnosis in the study population (n=141).

	Frequency (N)	Percentage (%)
Birth weight		
ELBW	7	4.96
VLBW	89	63.12
LBW	45	31.91
H/o antenatal steroid		
Yes	27	19.15
No	114	80.85
Sepsis		
Yes	73	51.77
No	68	48.23
Respiratory distress		
Yes	128	90.78
No	13	9.22
O_2 Requirement		
<7 days	70	49.65
>7 days	59	41.84
No	12	8.51
Surfactant		
Yes	69	48.94
No	72	51.06
Exclusive breastfeeding		
Yes	65	46.10
No	76	53.90
Blood transfusion		
Yes	32	22.70
No	109	77.30
Diagnosis		
APROP	22	15.60
Hybrid ROP	6	4.26
Stage 1 ROP	50	35.46
Stage 2 ROP	52	36.88
Stage 3 ROP	11	7.80

Table 2: Association between stage of ROP and gestational age.

Diagnosis	Gestational age category		Total
	≤30 (%)	>30 (%)	
APROP	12 (36.4)	10 (9.3)	22
Hybrid ROP	1 (3)	5 (4.6)	6
Stage 1 ROP	2 (6.1)	48 (44.4)	50
Stage 2 ROP	10 (30.3)	42 (38.9)	52
Stage 3 ROP	8 (24.2)	3 (2.8)	11
Total	33 (100)	108 (100)	141
Value of χ^2 = 38, df = 4 and p value <0.001**			

*p value <0.05-Significant, **p value <0.001-Highly Significant

Findings of the current study suggest significant association between stage of ROP and respiratory distress as well as requirement and duration of oxygen support. Infants with respiratory distress had higher chances of getting severe or stage 3 ROP compared to infants who did not have respiratory distress (Table 5).

Table 3: Association between stage of ROP and birth weight.

Diagnosis staging	Birth weight			Total
	LBW (%)	VLBW (%)	ELBW (%)	
APROP	0 (0)	20 (22.5)	2 (28.6)	22
Hybrid ROP	0 (0)	6 (6.7)	0 (0)	6
Stage 1 ROP	31 (68.9)	19 (21.3)	0 (0)	50
Stage 2 ROP	14 (31.1)	37 (41.6)	1 (14.3)	52
Stage 3 ROP	0 (0)	7 (7.9)	4 (57.1)	11
Total	45 (100)	89 (100)	7 (100)	141
Value of χ^2 = 62.9, df = 8 and p value <0.001**				

*p value <0.05-Significant, **p value <0.001-Highly Significant

Table 4: Association between sepsis and stage of ROP.

Diagnosis staging	Sepsis		Total
	Yes (%)	No (%)	
APROP	21 (28.8)	1 (1.5)	22
Hybrid ROP	4 (5.5)	2 (2.9)	6
Stage 1 ROP	13 (17.8)	37 (54.4)	50
Stage 2 ROP	24 (32.9)	28 (41.2)	52
Stage 3 ROP	11 (15.1)	0 (0)	11
Total	73 (100)	68 (100)	141
Value of χ^2 = 2.24, df = 4 and p value = 0.692			

*p value <0.05-Significant, **p value <0.001-Highly Significant

Table 5: Association between stage of ROP and respiratory distress.

Diagnosis staging	Respiratory distress		Total
	Yes (%)	No (%)	
APROP	22 (17.2)	0 (0)	22
Hybrid ROP	6 (4.7)	0 (0)	6
Stage 1 ROP	38 (29.7)	12 (92.3)	50
Stage 2 ROP	51 (39.8)	1 (7.7)	52
Stage 3 ROP	11 (8.6)	0 (0)	11
Total	128 (100)	13 (100)	141
Value of χ^2 = 20.3, df = 4 and p value <0.001**			

*p value <0.05-Significant, **p value <0.001-Highly Significant

Table 6: Association between stage of ROP and oxygen support.

Diagnosis staging	O_2 requirement			Total
	<7 days (%)	>7 days (%)	No (%)	
APROP	1 (1.4)	21 (35.6)	0 (0)	22
Hybrid ROP	1 (1.4)	5 (8.5)	0 (0)	6
Stage 1 ROP	30 (42.9)	8 (13.6)	12 (100)	50
Stage 2 ROP	37 (52.9)	15 (25.4)	0 (0)	52
Stage 3 ROP	1 (1.4)	10 (16.9)	0 (0)	11
Total	70 (100)	59 (100)	12 (100)	141
Value of χ^2 = 75.7, df = 8 and p value <0.001**				

*p value <0.05-Significant, **p value <0.001-Highly Significant

Infants who required oxygen support for more than 7 days had higher chances of getting severe or stage 3 ROP compared to infants who required oxygen for less than 7 days. All infants who did not require oxygen were having stage 1 ROP (Table 6).

Surfactant use significantly associated with severe ROP stages (Table 7).

Table 7: Association between stage of ROP and surfactant injection.

Diagnosis staging	Surfactant		Total
	Yes (%)	No (%)	
APROP	20 (28.99)	2 (2.78)	22
Hybrid ROP	3 (4.35)	3 (4.17)	6
Stage 1 ROP	14 (20.29)	36 (50)	50
Stage 2 ROP	22 (31.88)	30 (41.67)	52
Stage 3 ROP	10 (14.49)	1 (1.39)	11
Total	69 (100)	72 (100)	141
Value of χ^2 = 33, df = 4 and p value <0.001**			

*p value <0.05-Significant, **p value <0.001-Highly Significant

Table 8: Association between exclusive breastfeeding and stage of ROP.

Diagnosis staging	Exclusive breastfeeding		Total
	Yes (%)	No (%)	
APROP	1 (1.5)	21 (27.6)	22
Hybrid ROP	0 (0)	6 (7.9)	6
Stage 1 ROP	39 (60)	11 (14.5)	50
Stage 2 ROP	23 (35.4)	29 (38.2)	52
Stage 3 ROP	2 (3.1)	9 (11.8)	11
Total	65 (100)	76 (100)	141
Value of χ^2 = 44.4, df = 4 and p value <0.001**			

*p value <0.05-Significant, **p value <0.001-Highly Significant

Table 9: History of blood transfusion and stage of ROP.

Diagnosis staging	Blood transfusion		Total
	Yes (%)	No (%)	
APROP	8 (25)	14 (12.8)	22
Hybrid ROP	4 (12.5)	2 (1.8)	6
Stage 1 ROP	5 (15.6)	45 (41.3)	50
Stage 2 ROP	11 (34.4)	41 (37.6)	52
Stage 3 ROP	4 (12.5)	7 (6.4)	11
Total	32 (100)	109 (100)	141
Value of χ^2 = 14.8, df = 4 and p value = 0.005*			

*p value <0.05-Significant, **p value <0.001-Highly Significant

This study found significant association between exclusive breast feeding and stage of ROP. Proportion of severe ROP was found among infants who were not exclusively breastfed. So, breastfeeding was protective factor against development of severe ROP (Table 8).

There was significant association between history of Blood transfusion and stage of ROP according to the findings of the study. Infants who received blood transfusion had higher chances of getting severe ROP (Table 9).

DISCUSSION

The present study investigated various factors associated with Retinopathy of Prematurity (ROP) in 180 low birth weight infants. Low birth weight remains a significant public health concern globally, with 15-20% of newborns classified as low birth weight. South Asia accounts for approximately 50% of all LBW births worldwide.[9] In India, recent data shows 18.24% of newborns are classified as low birth weight, with higher prevalence in rural (18.58%) compared to urban areas (17.36%).

In our study population, 31.9% were LBW, 63.1% VLBW, and 5% ELBW. The higher proportion of VLBW cases compared to general population statistics (approximately 2.28%) may be attributed to increased ROP risk in premature and low birth weight infants. The survival rates of these infants have improved due to better healthcare accessibility.

Antenatal corticosteroids play a crucial role in reducing neonatal complications. However, only 19.15% of mothers in our study received antenatal steroid injections. Previous research indicates that antenatal steroids are associated with lower rates of severe ROP, particularly in infants born between 23 and 29 weeks.[12,13]

Sepsis was observed in 51.77% of infants, significantly higher than rates reported in comparable studies.[9] Meta-analysis has shown that sepsis increases the likelihood of developing any stage of ROP by 57% and severe ROP by 133%.[7] The inflammatory response triggered by sepsis can disrupt normal retinal angiogenesis.[7,8]

The present study's findings were compared with other studies regarding key risk factors for ROP. For gestational age less than 30 weeks, our study found 23.4% prevalence, which was higher than finding of 6.25%.[9] Regarding blood transfusion, our study's rate of 22.7% was higher than 6.7% in another study.[9] For longer exposure to oxygen therapy, our study showed 41.8% of cases, which was notably lower than 93.7% in previous study.[9] Finally, regarding sepsis, our study's rate of 51.77% was significantly higher than 6.3% in previous study.[9]

Respiratory distress was present in 90.8% of infants, with 41.8% requiring oxygen therapy for more than a week. Research indicates that respiratory distress syndrome significantly increases ROP risk (OR=2.49). Both hyperoxia and hypoxia contribute to ROP pathogenesis.

The study revealed significant correlations between ROP severity and multiple factors, showing that infants under 30 weeks gestational age experienced more severe ROP forms, aligning with Zong Hua Wang et al.'s findings.[10] Additionally, VLBW and ELBW patients demonstrated higher proportions of severe ROP, while sepsis was linked to increased stage 3 ROP risk.[10-12] Blood transfusions, especially multiple ones, were also associated with severe ROP.

Regarding treatment, most patients required no intervention. APROP cases primarily received anti-VEGF injections, while stage 3 ROP patients typically underwent laser therapy. Some APROP cases required both treatments.[15,16]

The study's limitations include its cross-sectional nature, absence of a control group, and inability to consider biochemical factors like IGF-1 and VEGF due to resource constraints. The current screening guidelines, while highly sensitive, may result in over-screening of infants who never develop clinically significant disease.

Studies show ROP in low-birth-weight infants is influenced by gestational age, sepsis, oxygen therapy, and blood transfusions, requiring standardized screening and management.

These results contribute to the growing body of evidence regarding ROP risk factors and management strategies. Future research should focus on developing more specific screening protocols while maintaining high sensitivity, particularly in resource-limited settings.

CONCLUSION

The study emphasizes crucial neonatal factors linked to severe ROP, including sepsis, respiratory distress, extended oxygen needs, and blood transfusions. Preventive strategies like antenatal steroids, strict asepsis, respiratory management, and limited oxygen therapy can reduce ROP severity. Expanded screening beyond VLBW and extreme prematurity is recommended. While both LASER and anti-VEGF treatments are effective, LASER remains the gold standard, especially in cases requiring intervention after anti-VEGF. Further research with larger, balanced groups is needed to improve risk prediction and outcomes.

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