Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

Risk Factors for Developing Treatment-Requiring Retinopathy of Prematurity: A Retrospective Study from a Single Center

[1]Devi Prasad Sahoo, [2]Bhagyashree Mohapatra, [3]Payal Pradhan, [4]Bineet Panigrahi,

[1]Assistant Professor, Department of Paediatrics, IMS & SUM Hospital, Odisha, India

[2]Assistant Professor, Department of Neonatology, IMS & SUM Hospital, Odisha, India

[3]Assistant Professor, Department of Paediatrics, IMS & SUM Hospital, Odisha, India

[4]Assistant Professor, Department of Paediatrics, IMS & SUM Hospital, Odisha, India

Corresponding Author: Bineet Panigrahi, Assistant Professor, Department of Paediatrics, IMS & SUM Hospital, Odisha, India

(Received: 11 June 2024 Revised: 16 July 2024 Accepted: 10 August 2024)

KEYWORDS

Retinopathy of prematurity, Preterm infants, Neonatal risk factors, Treatment-requiring ROP, Antenatal steroids, Neonatal intensive care.

ABSTRACT:

Background: Retinopathy of prematurity (ROP) is a significant cause of childhood blindness, primarily affecting preterm infants. The condition's incidence and severity are influenced by various factors, including gestational age, birth weight, and neonatal care practices. Early identification of risk factors associated with treatment-requiring ROP is crucial for timely intervention and prevention of severe outcomes.

Aim: To identify the risk factors associated with the development of treatment-requiring ROP in neonates admitted to a tertiary care NICU, providing insights to enhance early detection and managements strategies.

Methods: A total of 52 neonates who developed ROP were included in the study. Data on maternal, perinatal, and neonatal characteristics were collected and analyzed to identify risk factors for treatment-requiring ROP. Statistical analyses were performed using SPSS version 16, with p-values less than 0.05 considered significant.

Results: Of the 52 neonates included, 18 (34.6%) required treatment for ROP. Lower gestational age (mean 28 ± 1.8 weeks) and lower birth weight (mean 1091 ± 246 grams) were significantly associated with treatment-requiring ROP. Antenatal steroid administration showed a protective effect, while prolonged non-invasive ventilation, total parenteral nutrition, and conditions such as respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC) were identified as significant risk factors. The majority of treated cases (72.2%) underwent laser photocoagulation.

Conclusion: Lower gestational age, lower birth weight, prolonged respiratory support, and certain neonatal comorbidities are significant risk factors for treatment-requiring ROP. Antenatal steroids were found to be protective. Early identification and management of these risk factors are essential to prevent the progression of ROP to severe stages requiring treatment.

Recommendations: The study recommends enhanced monitoring of neonates with identified risk factors, especially those with low birth weight and gestational age. Implementing strict oxygen therapy protocols and promoting the use of antenatal steroids in eligible mothers can help reduce the incidence of severe ROP.

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

INTRODUCTION

Retinopathy of prematurity (ROP) is a serious Vaso proliferative disorder affecting the retina of premature infants, and it remains one of the leading causes of childhood blindness worldwide. The incidence and severity of ROP are inversely proportional to gestational age and birth weight, making extremely preterm and low-birth-weight infants particularly vulnerable to this condition. Despite advances in neonatal care, the global burden of ROP continues to rise, particularly in middle-income countries where neonatal survival rates have improved, but screening and treatment protocols may not be uniformly implemented of ROP is complex and multifactorial, involving both prenatal and postnatal factors [1]. The initial phase of the disease is characterized by the arrest of normal retinal vascular development due to factors such as the interruption of placental vascular growth factors like VEGF and IGF-1, followed by a proliferative phase triggered by hypoxia-induced overproduction of VEGF as the immature retina becomes metabolically active. This neovascularization can lead to fibrovascular proliferation, retinal detachment, and ultimately, blindness if left untreated [2].

Recent studies several risk factors beyond low gestational age and birth weight, including the duration and fluctuations of oxygen therapy, mechanical ventilation, sepsis, and intraventricular hemorrhage. The use of supplemental oxygen, particularly when not carefully monitored, has been implicated in the development of severe ROP. Fluctuations in oxygen saturation levels have also been recognized as an independent risk factor, emphasizing the need for precise control of oxygen therapy in neonatal intensive care units (NICUs) [3].

In addition to these risk factors, emerging evidence suggests that maternal factors such as hypertensive disorders, diabetes, and preeclampsia may contribute to the development of ROP. Moreover, the use of antenatal corticosteroids has been shown to reduce the incidence of severe ROP, likely due to its role in promoting fetal lung maturation and reducing the need for postnatal respiratory support [4].

The management of ROP has evolvingly, with early screening and timely intervention being crucial in preventing severe outcomes. Laser photocoagulation remains the gold standard for treating threshold ROP, while newer therapies, such as intravitreal anti-VEGF agents like bevacizumab, are being increasingly utilized for aggressive posterior ROP and in cases where laser treatment is not feasible [5].

This study aims to identify the risk factors associated with the development of treatment-requiring ROP in a tertiary care setting.

METHODOLOGY

Study Design

A retrospective observational study.

Study Setting

The research was carried out in the Department of Neonatology at IMS & SUM Hospital and College, under SOA (Deemed to be University) in Bhubaneswar, Odisha. The study was conducted over a period of two years, from September 2019 to August 2021.

Participants

Participants included all neonates who were admitted to the NICU and either developed ROP or were at risk for ROP and required screening. The study population comprised both inborn and outborn infants who met the inclusion criteria.

Inclusion Criteria

1. All inborn neonates who developed ROP.
2. All outborn neonates who developed ROP.
3. All neonates admitted to the NICU for receiving treatment for ROP.

Exclusion Criteria

1. Neonates with ROP who did not undergo follow-up ROP screening.
2. Babies who died before complete retinal maturation.

Bias

Potential biases were minimized by adhering to standardized ROP screening protocols and by ensuring

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

consistent data collection from NICU records and ROP screening cards. However, the retrospective nature of the study may introduce selection bias, as only those infants who survived long enough to be screened and treated were included.

Data Collection

Data were collected retrospectively from NICU records and the ROP screening cards maintained by the LV Prasad Eye Institute, Patia, Bhubaneswar. Maternal demographics, obstetric characteristics, neonatal characteristics, and details of ROP screening and treatment were recorded.

Maternal Demographics and Obstetric Characteristics

- Maternal age at conception
- Parity (primigravida or multigravida)
- History of consanguinity
- History of leaking per vaginum (PV)
- History of maternal illnesses (e.g., gestational diabetes mellitus, pregnancy-induced hypertension)
- Antenatal steroid exposure

Neonatal Characteristics

- Mode of delivery
- Gestational age (in completed weeks)
- Birth weight
- Immediate post-birth status (e.g., whether the baby cried immediately after birth)
- Need for resuscitation, delivery room CPAP, or oxygen support
- Type of pregnancy (single or multiple)
- Appropriateness of weight for gestational age (AGA, SGA, LGA)
- APGAR scores at 1 and 5 minutes
- Weekly weight gain from day 15 of life to 42 days or until discharge
- Respiratory support details (mode, duration, maximum FiO2)
- Administration of early or late rescue surfactant
- NICU course details (e.g., RDS, apnea, HsPDA, shock, sepsis, PPHN, IVH, NEC, BPD, PRBC transfusions, lowest hemoglobin, total duration of NICU stay)
- Other parameters (e.g., hypoglycemia, neonatal jaundice, type of feeding, spontaneous regression of ROP, treatment mode if required)

Procedure

ROP screening was performed according to national guidelines:

1. Infants with a gestational age of 34 weeks or less were screened.
2. Infants with a gestational age of more than 34 weeks were screened if they were exposed to risk factors.
3. Infants with unknown gestational age but a birth weight of 2000 grams or less were screened.
4. Other preterm infants were screened at the discretion of the neonatologist or pediatrician.

The first screening was conducted before discharge or before 30 days of life, whichever was earlier. Infants weighing less than 1200 grams and with a gestational age of less than 30 weeks underwent their first screening at 2 to 3 weeks of life to rule out aggressive posterior ROP (APROP). Indirect ophthalmoscopy was used for screening.

Discharged infants were advised to undergo follow-up ROP screening at LV Prasad Eye Institute. ROP was classified according to the International Classification of ROP, and screening continued until retinal maturation. The need for treatment and the mode of treatment were determined by the ophthalmologist.

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

Primary Outcome

The primary outcome of the study was to identify the risk factors associated with ROP requiring treatment.

Secondary Outcomes

1. Incidence of ROP among inborn babies in the NICU.
2. Incidence of ROP requiring treatment.
3. Descriptive epidemiology of patients with ROP.

Statistical Analysis

Statistical analysis was performed using SPSS version 16 software. Associations with ROP requiring treatment were assessed using odds ratios with confidence intervals and chi-square tests for categorical data. Unpaired t-tests and Mann-Whitney U tests were used for continuous variables with normal and skewed distributions, respectively. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 52 neonates were included in the study, out of which 18 (34.6%) received treatment for ROP. The study population consisted of 23 male (44.2%) and 29 female (55.8%) neonates. The distribution between inborn and outborn infants was 41 inborn (78.8%) and 11 outborn (21.2%). The gestational age of the neonates ranged from 23 to 35 weeks, and the birth weight ranged from 690 grams to 1710 grams.

Table 1: Baseline Characteristics of Neonates (N = 52)

Characteristic	Total (N=52)	ROP without Treatment (N=34)	ROP Requiring Treatment (N=18)	p-value
Gestational Age (weeks)	28.7 ± 3.4	30.7 ± 2.2	28.0 ± 1.8	0.0001
Birth Weight (grams)	1128 ± 260	1268 ± 260	1091 ± 246	0.02
Male Sex	23 (44.2%)	16 (47.1%)	7 (38.9%)	0.573
Inborn	41 (78.8%)	29 (85.3%)	12 (66.7%)	0.118
Outborn	11 (21.2%)	5 (14.7%)	6 (33.3%)	0.118

Among antenatal factors, antenatal steroid (ANS) administration showed a significant protective effect against the development of treatment-requiring ROP, while small for gestational age (SGA) status was also associated with a lower risk. Other factors like primigravida status, gestational diabetes mellitus (GDM), leaking per vaginum (PV), and gestational hypertension (GHTN) did not show significant associations.

Table 2: Antenatal Risk Factors and ROP

Variable	ROP without Treatment (N=34)	ROP Requiring Treatment (N=18)	Odds Ratio (95% CI)	p-value
Primigravida	22 (64.7%)	11 (61.1%)	1.16 (0.35-3.79)	0.798
Gestational Diabetes Mellitus	1 (2.9%)	2 (11.1%)	4.12 (0.34-48.94)	0.229
Leaking PV	20 (58.8%)	8 (44.4%)	0.56 (0.17-1.77)	0.322
Gestational Hypertension	6 (17.6%)	2 (11.1%)	0.58 (0.10-3.23)	0.534
Antenatal Steroid (ANS)	25 (73.5%)	3 (16.7%)	0.07 (0.01-0.30)	0.000
Small for Gestational Age (SGA)	14 (41.2%)	2 (11.1%)	0.17 (0.03-0.90)	0.025

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

In the delivery room, factors such as mode of delivery, perinatal depression, APGAR scores, and the need for resuscitation, oxygen, or CPAP were analyzed. None of these factors showed a statistically significant association with the development of treatment-requiring ROP.

Table 3: Delivery Room Risk Factors and ROP

Variable	ROP without Treatment (N=34)	ROP Requiring Treatment (N=18)	Odds Ratio (95% CI)	p-value
Vaginal Delivery	15 (44.1%)	13 (72.2%)	0.30 (0.08-1.04)	0.053
Perinatal Depression	11 (32.4%)	5 (27.8%)	1.24 (0.35-4.37)	0.734
Oxygen at Resuscitation	20 (58.8%)	14 (77.8%)	2.45 (0.66-9.02)	0.172
Delivery Room CPAP	12 (35.3%)	7 (38.9%)	1.16 (0.35-3.79)	0.798
PPV Requirement	9 (26.5%)	5 (27.8%)	1.06 (0.29-3.85)	0.919
Apgar 1' (Median, IQR)	6 (5-7)	6 (5-7)		0.936
Apgar 5' (Median, IQR)	8 (7-8)	8 (7-8)		0.922

Neonatal factors during NICU stay were also analyzed, revealing that the need for respiratory support, particularly non-invasive ventilation (NIV), and longer duration of total parenteral nutrition (TPN) were significantly associated with the development of treatment-requiring ROP.

Table 4: Neonatal Risk Factors and ROP

Variable	ROP without Treatment (N=34)	ROP Requiring Treatment (N=18)	Odds Ratio (95% CI)	p-value
NICU Support	27 (79.4%)	18 (100%)	1.66 (1.31-2.11)	0.039
Invasive Ventilation	8 (23.5%)	5 (27.8%)	1.25 (0.34-4.59)	0.736
Duration of Invasive Ventilation (Median, IQR)	0 (0-0.5)	0 (0-30)		0.561
NIV Support	27 (79.4%)	18 (100%)	1.66 (1.31-2.11)	0.039
Duration of NIV (Median, IQR)	120 (21-331.5)	600 (162-912)		0.002
Max FiO2 (%)	28	33		0.21
Respiratory Distress Syndrome (RDS)	24 (70.6%)	17 (94.4%)	7.08 (0.82-60.65)	0.045
Surfactant	7 (20.6%)	6 (33.3%)	1.92 (0.53-6.97)	0.313
Caffeine	21 (61.8%)	18 (100%)	1.85 (1.38-2.48)	0.002
Shock	7 (20.6%)	7 (38.9%)	2.45 (0.69-8.65)	0.157
Inotrope Requirement	7 (20.6%)	6 (33.3%)	1.92 (0.53-6.97)	0.313
TPN	20 (58.8%)	16 (88.9%)	5.60 (1.10-28.32)	0.025
Duration of TPN (Median, IQR)	84 (0-198)	204 (144-330)		0.003
Expressed Breast Milk (EBM)	21 (61.8%)	9 (50%)	1.61 (0.50-5.12)	0.414
Intraventricular Hemorrhage (IVH)	4 (11.8%)	4 (22.2%)	2.14 (0.46-9.83)	0.320
Hypoglycemia	4 (11.8%)	0 (0%)	0.62 (0.50-0.778)	0.130
Bronchopulmonary Dysplasia (BPD)	8 (23.5%)	8 (44.4%)	2.60 (0.76-8.82)	0.120

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Sepsis	10 (29.4%)	8 (44.4%)	1.92 (0.58-6.29)	0.278
Necrotizing Enterocolitis (NEC)	0 (0%)	2 (11.1%)	0.32 (0.21-0.47)	0.047
PRBC Transfusion	9 (26.5%)	10 (55.6%)	3.47 (1.04-11.55)	0.038
Lowest Hemoglobin during NICU stay (g/dL)	11.7 ± 4.8	8.8 ± 2.2		0.018
Apnea	16 (47.1%)	12 (66.7%)	2.25 (0.68-7.38)	0.177
Pneumonia	1 (2.9%)	2 (11.1%)	4.12 (0.34-48.94)	0.229
Patent Ductus Arteriosus (PDA)	5 (14.7%)	5 (27.8%)	2.23 (0.54-9.06)	0.255
Weight Gain (g/day) in 15 to 21 days	21.6 ± 10.2	17.3 ± 9.6		0.15
Weight Gain (g/day) in 22 to 28 days	23.9 ± 9.6	20.1 ± 5.9		0.128
Weight Gain (g/day) in 36 to 42 days	26 ± 11.9	28.1 ± 9.5		0.56
Duration of NICU stay (days)	40 ± 20	69 ± 51		0.005

Out of the 18 neonates who required treatment for ROP, the majority (72.2%) underwent laser photocoagulation. A smaller proportion (22.2%) received both laser photocoagulation and intravitreal bevacizumab, while only one neonate (5.5%) required surgery for retinal detachment.

Table 5: Types of Treatment Administered for ROP

Treatment Type	Number of Neonates (N=18)	Percentage (%)
Laser Photocoagulation	13	72.2%
Laser Photocoagulation + Bevacizumab	4	22.2%
Surgery (Retinal Detachment)	1	5.5%

DISCUSSION

The study analyzed 52 neonates who developed retinopathy of prematurity (ROP), focusing on identifying risk factors associated with the need for treatment. Among these, 18 neonates (34.6%) required treatment, while 34 (65.4%) experienced spontaneous regression of ROP. The study found significant associations between lower gestational age and birth weight with the development of severe, treatment-requiring ROP. Specifically, neonates who required treatment had a mean gestational age of 28 weeks compared to 30.7 weeks in those who did not require treatment, and a mean birth weight of 1091 grams versus 1268 grams in the non-treatment group. This reinforces the well-established understanding that extreme prematurity and low birth weight are major risk factors for severe ROP.

Antenatal factors were also examined, revealing that the administration of antenatal steroids (ANS) significantly reduced the risk of developing treatment-requiring ROP. This finding aligns with previous research suggesting that ANS reduces the incidence of respiratory distress syndrome (RDS) and other morbidities, thereby decreasing the oxygen and ventilation requirements after birth, which are critical in the pathogenesis of ROP. Interestingly, being small for gestational age (SGA) appeared to offer some protective effect against severe ROP, with 14 out of 16 SGA neonates experiencing spontaneous regression. However, this might be due to the small sample size and needs further investigation.

The analysis of delivery room factors such as mode of delivery, APGAR scores, and the need for resuscitation or oxygen did not show significant associations with treatment-requiring ROP. This suggests that while these factors are critical for overall neonatal outcomes, they

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

may not directly influence the progression of ROP to a stage that requires treatment.

Neonatal risk factors during NICU stay were more telling. The need for respiratory support, especially prolonged non-invasive ventilation (NIV), and longer durations of total parenteral nutrition (TPN) were significantly associated with treatment-requiring ROP. This indicates that the prolonged need for respiratory support and nutrition via TPN in extremely premature infants might reflect underlying severity of illness that predisposes them to severe ROP. Additionally, conditions like RDS and necrotizing enterocolitis (NEC) were linked with higher incidences of treatment-requiring ROP, highlighting the role of systemic illness in the progression of ROP.

In terms of treatment, laser photocoagulation was the most common intervention, used in 72.2% of cases, with some neonates also receiving intravitreal bevacizumab. Only one case required surgery for retinal detachment, indicating that while severe, most cases of treatment-requiring ROP could be managed with less invasive interventions.

Overall, these results underscore the importance of close monitoring and early intervention in neonates with low birth weight, extreme prematurity, and other identified risk factors. The findings suggest that strategies to reduce the duration of respiratory support and improve early postnatal care could be crucial in preventing the progression of ROP to stages that require treatment.

An extensive analysis was conducted identifying different risk factors for ROP development and progression. The study found that prenatal steroid use, gestational age, duration of mechanical ventilation, and respiratory distress syndrome significantly contributed to the initial development of ROP. However, factors like bronchopulmonary dysplasia, the number of red blood cell transfusions, intraventricular hemorrhage, and periventricular leukomalacia were more closely associated with the progression to severe ROP, necessitating treatment [6].

A study developed a risk calculator to predict the need for ROP treatment based on specific clinical factors. The study highlighted that a larger temporal avascular area of the retina and extended periods of mechanical ventilation significantly increased the likelihood of developing ROP that requires treatment. This predictive model aims to improve early intervention strategies by identifying high-risk infants during their initial screenings [7].

A study focused on hematologic factors, finding that lower platelet mass indexes measured on the first day of life were modestly predictive of early-stage ROP. Although these hematological markers were not strong predictors, their association with ROP development suggests that platelet counts could be a factor in the disease's onset, particularly in premature infants [8].

Another study analyzed data from preterm infants admitted to a tertiary care center, identifying sepsis, blood transfusions, and the need for inotropes as significant risk factors for ROP development. The study also found that the use of prongs for oxygen therapy posed a substantial risk, further emphasizing the importance of careful oxygen management in premature infants to prevent ROP [9].

A study evaluated the recurrence of ROP following treatment with laser photocoagulation or intravitreal anti-VEGF therapy. The study identified early postmenstrual age at initial treatment, involvement of Zone I, low Apgar scores, and multiple births as key risk factors for ROP recurrence, indicating that close monitoring and long-term follow-up are essential for infants at risk of recurrence [10].

A retrospective cohort study in a tertiary care unit was conducted, examining the incidence and associated risk factors of ROP. The study found significant correlations between ROP and conditions like patent ductus arteriosus, sepsis, bronchopulmonary dysplasia, respiratory distress syndrome, as well as the use of postnatal steroids and blood transfusions, highlighting the complexity of managing these vulnerable infants [11].

Research explored the impact of maternal diabetes mellitus on the severity of ROP, concluding that maternal diabetes is an independent risk factor for severe ROP, particularly in neonates weighing less than 1500 grams. The study's findings suggest that the risk of severe ROP increases with the presence of maternal diabetes, further complicating the management of preterm infants [12].

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JCHR (2024) 14(5), 01-08 | ISSN:2251-6727

CONCLUSION

Lower birth weight and gestational age were significantly associated with the development of treatment-requiring ROP. Antenatal steroid administration was found to be protective, while factors such as prolonged duration of NIV support, TPN, and specific comorbidities like RDS and NEC were linked to a higher risk. These findings underline the importance of vigilant monitoring and early intervention in neonates with these risk factors to prevent severe ROP outcomes.

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