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Original Research Article

Determinants of Retinopathy of Prematurity: An Observational Study

Vinita Yadav[1], Prasad Nayak N[2], Shivani Bansal[3]

[1]PG Resident, Dept. of Pediatrics, Rohilkhand Medial College and Hospital, Bareilly, UP, India
[2]Professor, Dept. of Pediatrics, Rohilkhand Medial College and Hospital, Bareilly, UP, India
[3]Associate Professor, Dept. of Pediatrics, Rohilkhand Medial College and Hospital, Bareilly, UP, India

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Corresponding Author: Dr. Vinita Yadav
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Abstract:

Background: In the modern era of medical science, advancements in early diagnosis, interventions, and rehabilitation have significantly reduced neonatal mortality rates. Central to this progress is the use of oxygen, a crucial tool for saving the lives of preterm infants. However, the increased use of oxygen in neonatal care has introduced its own challenges. Retinopathy of Prematurity (ROP) is a severe consequence of oxygen therapy, leading to significant visual impairment and blindness in affected infants. ROP primarily affects premature infants, especially those weighing less than 2000 grams, and can be mitigated through timely screenings and interventions.

Objective: To study the risk factors leading to development of Retinopathy of Prematurity.

Method: The prospective observational study was conducted in the Department of Pediatrics at Rohilkhand Medical College and Hospital from November 2022 to October 2023. All participants were enrolled after obtaining informed consent from the guardians or parents, with clearance from the institutional ethics committee. Participants in the inclusion criteria were screened for ROP based on the protocol.

Result: The study sows positive association between Retinopathy of Prematurity and as gestational age, birth weight, oxygen exposure, blood transfusions, sepsis, and phototherapy with the following p values 0.001, 0.017, 0.0001, 0.006, 0.004 and 0.004 respectively.

Conclusion: Retinopathy of Prematurity (ROP) continues to be a significant challenge for the care of preterm infants, with its occurrence and associated risk factors extensively documented in the literature. The study provides valuable insights into the multifaceted nature of ROP. The study highlights the association between ROP and various factors such as gestational age, birth weight, oxygen exposure, blood transfusions, sepsis, and phototherapy.

Keywords: Retinopathy of Prematurity, Preterm Infants, Premature Infants, Determinants.

Introduction

In this golden age of medical science, where we all take pride in the declining trend of fatalities as a result of advancements in the areas of early diagnosis [1], more effective interventions, and rehabilitation, we are also confronted with an increase in the number of people living with morbidities that are left behind by a condition that has the potential to be fatal. This is essentially true down to every word when we talk about lowering down the age of viability of a fetus and reducing the neonatal death rate, for which the primary credit can be given to the practice of a more effective and successful resuscitation. This is because such a practice has been shown to be effective in reducing the mortality rate of neonates. A significant increase in the number of preterm births has occurred concurrently with an increase in the number of preterm babies that have been successfully resuscitated. Oxygen turns out to be the most important medicine that makes all of this possible [2]. The use of oxygen has greatly aided in rescuing premature infants, yet it comes with its own drawbacks, notably ROP, a condition that can lead to blindness. In the paediatric realm, ROP is a significant cause of vision impairment, particularly affecting premature infants and those weighing less than 2000 grams who require oxygen support. Timely screenings for preterm neonates receiving oxygen can substantially reduce and prevent ROP. However, in India, the prevalent practice often reflects negligence and a lack of resources, leading to insufficient guidance for families regarding preterm infants' eye examinations before discharge and during follow-ups [3]. This, in turn, attracts more people who have visual impairments and the increase in the number of medicolegal conflicts that are occurring. There is a wide spectrum of symptoms associated with ROP, which is a disease

process that is primarily described in preterm newborns. These symptoms range from moderate, temporary abnormalities in the retina with remission to severe progressive vasoproliferation, scarring, retinal detachment, and blindness. If detected at the beginning, it is possible to successfully cure it. In 1942, Terry [4] was the first person to report retrolental fibroplasia, and he suggested that oxygen therapy was the pathogen responsible for the condition. As a consequence, the administration of oxygen to premature infants was severely restricted, which directly contributed to a rise in mortality rates. It is well knowledge that oxygen therapy is not the only factor that contributes to the development of ROP; rather, oxygen therapy is just one of numerous risk factors that play a part in the pathogenesis of ROP [5,6].

Oxygen therapy is the most common cause of the vaso-proliferative disorder known as ROP, which typically affects premature newborns. There are around 50,000 children around the world who are affected by this significant cause of preventable blindness that occurs in both developed and developing countries [7, 8]. Although there was a rise in the number of premature infants that survived in the subsequent decades and improvements were made to monitoring procedures for oxygen supplementation, it was discovered that the number of ROP cases were increasing (a second epidemic) [9]. Over the past decade, there has been a surge in the number of cases of ROP blindness that have been reported in countries with low incomes. As a result of ROP, it is estimated that 500 children in India lose their vision each year [7]. Because of the increased survival rates among preterm neonates with very low birth weight or those with birth weights of less than 1500 grammes, who are the most susceptible to developing ROP, the condition has been subjected to a significant amount of research on a global scale. One possible explanation for these greater numbers is the improved quality of prenatal care.

The purpose of my research is to investigate the factors that put preterm infants who are born and admitted to RMCH, Bareilly at risk of ROP, as well as the ways in which we might prevent this condition by making prudent use of oxygen. As part of my research, we are focusing on both primary and secondary prevention of blindness. As we are all aware, there has been advancement of available treatment methods, which have proven to be useful in terms of raising the survival rate of preterm babies [10]. When we talk about dealing with the ever-increasing and diverse long-term difficulties that these youngsters face, paediatricians face a significant task. One such significant type of problem is ROP.

As part of this research project, I intend to conduct an in-depth investigation into the risk factors that are accountable for the development of ROP.

Material and Methods

The prospective observational study was conducted in the Department of Paediatrics at Rohilkhand Medical College and Hospital during November 2022 to October 2023. All preterm babies in born and out born both requiring oxygen support and babies with birth weight less than 2000g were included in the study after informed consent duly signed from the guardian or parents admitted in the Hospital during the study period were enrolled for this study after clearance from institutional ethics committee.

Inclusion Criteria:

- All preterm babies <34 wk of gestation requiring oxygen support.
- Babies with weight lesser than 2000g requiring oxygen support.
- Babies >34wk of gestation with ROP risk factors.

Exclusion Criteria:

- Babies of non-willing attendants
- Babies >34 wk of gestation with no ROP risk factors
- First screening for retinopathy of prematurity (ROP) was performed at 4 weeks postnatal age (PNA).
- In neonates <28 weeks of gestation or birth weight <1200g if gestation was not confirmed conclusively, the first screening was preponed to 2-3 weeks of postnatal age.

Combination of phenylephrine (5%), tropicamide (0.8%) was used diluted 1: 1 with pharmaceutically available methyl cellulose eye drops, so that the final drop had 2.5% phenylephrine and 0.4% tropicamide. One drop three times at 10 minutes interval.

A combination of topical anesthetic (TA) eye drops (0.5% proparacaine) 30 seconds prior to examination combined with oral 24% sucrose or 25% dextrose in the dose of 0.5 mL/kg just before the insertion of eye speculum was used for prevention of pain during screening for ROP. Follow-up examination for infants at risk was done 2–3 weeks intervals until the retina was fully vascularized or as frequently as the examining ophthalmologist recommended.

Statistical Analysis: The data was put into a Microsoft Excel spreadsheet, and the statistical analysis was performed using SPSS version 25.0, statistical software. The quantitative data, consisting of numerical factors, was displayed using the mean and standard deviation. On the other hand, the qual-

itative data, representing categorical variables, was presented using the frequency and percentage of each category.

Results

Among the subjects under investigation, a total of 8 newborns, accounting for roughly 11.27% of the sample, were found to have been diagnosed with ROP. This finding suggests a significant prevalence of ROP within the studied cohort. Among the cohort of infants born prior to 32 weeks, one individual (12.5%) exhibited ROP, while six individuals (9.52%) displayed normal ocular development. Collectively, this subset accounted for a relatively minor proportion (9.86%) of the entire cohort. The 32-34 weeks group exhibited a greater incidence of ROP with 4 (50.0%) cases, compared to 13 (19.05%) normal cases, constituting 22.54% of the total. In the group of infants aged 34-36 weeks, ROP was observed in one infant, accounting for 12.5% of the group. On the other hand, 19 infants (28.57%) were classified as normal, constituting 26.76% of the total population. Among infants who were older than 36 weeks, 2 individuals (equivalent to 25.0% of the sample) were diagnosed with ROP, while 27 individuals (representing 42.86% of the sample) exhibited normal ocular development.

The most noteworthy discovery pertains to the notable prevalence of ROP among newborns with the lowest birth weight category, namely those weighing less than 1 kg. In this category, one infant (equivalent to 1.41% of the overall study population) was diagnosed with ROP, whereas the total number of infants in this weight category was only one (equivalent to 2.82% of the whole population). Consequently, the statistical analysis yielded a p-value of 0.017. This finding indicates a statistically significant association between infants with extremely low birth weight and the incidence of ROP.

Notably, within the cohort of infants who underwent blood transfusions, a total of 4 individuals (5.63%) were diagnosed with ROP, representing 22.54% of the overall population of 16 newborns who got transfusions. In comparison, the cohort that did not have blood transfusions had a comparable number of cases of ROP, specifically 4 or 5.63%, but within a significantly larger sample size of 55 newborns (77.46%). The p-value of 0.006 observed in the group that underwent blood transfusions is of special significance, as it suggests a statistically significant association between getting blood transfusions and an elevated likelihood of developing ROP.

Remarkably, the occurrence of ROP was observed in all 8 cases, representing 100.0% of the total ROP cases. These cases exclusively involved newborns who underwent oxygen therapy, accounting for 70.42% of the entire cohort, which consisted of 50 infants. In marked divergence, ROP did not manifest in any of the infants who were not administered oxygen therapy, despite comprising a significant proportion of 29.58% within the study population. The obtained p-value of 0.0001 in the group subjected to oxygen therapy provides compelling evidence of a statistically significant association between the administration of oxygen therapy and an elevated susceptibility to developing ROP. Among the infants who experienced sepsis, 5 (7.04% of the total cohort) developed ROP, out of 13 infants (18.31% of the total) who had sepsis. This is in contrast to the group without sepsis, where a smaller proportion of ROP cases (3 or 4.23%) were observed among a larger subset of 58 infants (81.69%). The p-value of 0.004 for the sepsis group is statistically significant, indicating a strong association between sepsis and an increased risk of ROP.

In the group that received phototherapy, 5 infants (7.04% of the total cohort) developed ROP, out of a larger group of 52 infants (73.24% of the total) who were given this treatment. Conversely, in the group that did not receive phototherapy, a smaller number of ROP cases (3 or 4.23%) were observed, despite this group comprising a smaller portion of the total cohort (19 infants or 26.76%). The p-value of 0.004 for the group that received phototherapy is statistically significant and suggests a strong correlation between phototherapy and an increased risk of developing ROP.

Table 1: Describing the study groups as per Prevalence of ROP

Prevalence	N	%
ROP	8	11.27
Normal	63	88.73
Total	71	100.0

Table 2: Describing the study groups as per Age

Age	ROP	Normal	Total	p-value
<32 wk	1 (12.5)	6 (9.52)	7 (9.86)	0.001
32-34 wk	4 (50.0)	12 (19.05)	16 (22.54)	
34-36 Wks	1 (12.5)	18 (28.57)	19 (26.76)	
>36wks	2 (25.0)	27 (42.86)	29 (40.85)	
Total	8 (100)	63 (100)	71 (100.0)	

Table 3: Describing the study groups as per Birth Weight (kg)

Birth Weight (kg)	ROP	Normal	Total	p-value
< 1 kg	1 (1.41)	1 (1.41)	1 (2.82)	0.017
1.01-1.49 kg	4 (5.63)	16 (22.54)	20 (28.17)	
1.5 -1.8 kg	2 (2.82)	18 (25.35)	20 (28.17)	
> 1.8 kg	1 (1.41)	28 (39.44)	29 (40.85)	
Total	8 (11.27)	63 (88.73)	71 (100.0)	

Table 4: Describing the study groups as per Blood Transfusion

Blood Transfusion	ROP	Normal	Total	p-value
Received	4 (5.63)	12 (16.90)	16 (22.54)	0.006
Not received	4 (5.63)	51 (71.83)	55 (77.46)	
Total	8 (11.27)	63 (88.73)	71 (100.0)	

Table 5: Describing the study groups as per Oxygen therapy

Oxygen Therapy	ROP	Normal	Total	p-value
Received	8 (100.0)	42 (59.15)	50 (70.42)	0.0001
Not received	0 (0.0)	21 (29.58)	21 (29.58)	
Total	8 (11.27)	63 (88.73)	71 (100.0)	

Table 6: Describing the study groups as per Sepsis

Sepsis	ROP	Normal	Total	p-value
Yes	5 (7.04)	8 (11.27)	13 (18.31)	0.004
No	3 (4.23)	55 (77.46)	58 (81.69)	
Total	8 (11.27)	63 (88.73)	71 (100.0)	

Table 7: Describing the study groups as per Phototerapy

Phototherapy	ROP	Normal	Total	p-value
Given	5 (7.04)	47 (66.20)	52 (73.24)	0.004
Not Given	3 (4.23)	16 (22.54)	19 (26.76)	
Total	8 (11.27)	63 (88.73)	71 (100.0)	

Discussion

ROP is a vaso-proliferative illness that affects the still growing retina of premature neonates. It was first reported by Terry in 1942 [7]. The primary cause of visual loss in preterm newborns is ROP, which is often associated with the need for oxygen administration due to the preterm development of the lung.

The initial instance of the outbreak was observed on February 14, 1941, when a preterm infant in Boston was diagnosed. The initial outbreak of ROP occurred in the 1940s and 1950s, primarily in developed nations as a result of unregulated administration of oxygen to preterm infants. Due to advancements in neonatal intensive care, an increasing number of newborns with low Birth Weight (BW) and low Gestational Age (GA) are now able to survive. As a result, a 'Second Epidemic' of ROP emerged during the 1970s and 1980s.

The third epidemic of ROP primarily began in middle-income countries from a global standpoint [17]. The current global population of blind individuals is estimated to be over 45 million, with approximately 30% of them residing in Asia. Childhood blindness is 4% of all cases of complete blindness. The prevalence of ROP in poor nations such as India has been documented to range from 24% to 47% among preterm newborns at high risk. The study, conducted over a period of one year from November 1, 2022, to October 31, 2023, had the objective of identifying and analysing the risk factors that contribute to the development of ROP in premature newborns. The inquiry entailed a methodical analysis of multiple potential risk variables, encompassing, among others, the gestational age at delivery, birth weight, the severity of neonatal sickness, and exposure to supplementary oxygen.

A study was conducted to examine the occurrence of ROP in a group of 71 neonates. Out of the participants being studied, a total of 8 neonates, which makes up approximately 11.27% of the sample, were diagnosed with ROP. This discovery indicates a notable occurrence of ROP among the group that was examined. On the other hand, the majority of the neonates, specifically 63 individuals (which accounts for 88.73% of the total), did not show any signs of ROP and were classified as having a normal condition. The data distribution indicates that while ROP is present in a significant

proportion of instances, the bulk of the sample population does not show signs of this condition. In a study conducted by Gupta et. al., [15] the point prevalence of ROP was determined to be 12.5%, which aligns with the findings of our own study. The low occurrence of ROP in the study conducted by Gupta et. al. [15] may be attributed to the lack of access to ventilatory assistance, resulting in a limited number of preterm/very ELBW newborns surviving until the first ROP evaluation at 4-6 weeks of post-conceptional age. Paranjpe et. al. [18] found that out of the 83 infants admitted, 35.63% were diagnosed with ROP. In another study by Ramirez et. al., [16] 44.7% of the 452 neonates included developed ROP.

The current study conducted a thorough examination of the prevalence of ROP across different gestational age groups. Additionally, the study compared the occurrence of ROP in a group of 71 newborns categorised as normal. Out of the group of babies delivered before 32 weeks, one baby (12.5%) had ROP, while six babies (9.52%) had normal eye development. Together, this subgroup represented a relatively small percentage (9.86%) of the whole group. The group of infants born between 32-34 weeks had a higher occurrence of ROP with 4 cases, accounting for 50.0% of the cases in this group. In comparison, there were 13 cases of normal development, which constituted 19.05% of the total. Among the group of infants that were between 34 and 36 weeks old, one newborn was found to have ROP, which represents 12.5% of the total. However, 19 infants (28.57%) were categorised as normal, making up 26.76% of the entire population. Out of the newborns that were older than 36 weeks, 2 individuals (25.0% of the sample) were found to have ROP, while 27 individuals (42.86% of the sample) had normal ocular development. Significantly, the latter group comprised the majority, making up 40.85% of the whole population being examined. The study documented 8 cases (100%) of ROP and 63 cases (100%) classed as normal.

The p-value of 0.001 seen in the group of infants born before 32 weeks of gestation indicates a substantial level of statistical significance in relation to the occurrence of ROP in this specific age group, when compared to the other groups. This discovery indicates that extremely preterm infants are at a higher risk of getting ROP. Based on Ramirez et. al.'s research [16], it is well-established that Low Gestational Age (GA) and Birth Weight (BW) are the most influential risk factors for the development of ROP (ROP) [19]. The study found that the average gestational age (GA) was 27.69 ± 2.32 weeks for newborns who developed ROP and 26.39 ± 1.95 weeks for infants who experienced ROP advancement. These values were considerably lower compared to infants who did not develop or progress in ROP. Furthermore, it was shown that newborns with ROP progression had significantly lower gestational age (GA) and weight at the time of ROP diagnosis. Gupta et. al. [15], also observed similar findings regarding the relationship between gestational age and the risk of developing ROP. Babies with a gestational age of up to 28 weeks had a higher likelihood of developing ROP compared to those between 29 and 30 weeks (OR 63; 95% CI 4.86-17.79 and OR 49; 95% CI 13.09-196.84 respectively). Gupta et al. [20] discovered that a decrease in gestational age significantly raised the occurrence of ROP.

This study demonstrates a statistically significant correlation between newborns that have an exceptionally low birth weight and the occurrence of ROP. ROP is shown to be reasonably scattered in weight categories over 1.01 kg, specifically within the ranges of 1.01-1.49 kg, 1.5-1.8 kg, and larger than 1.8 kg. Paranjpe et. al. [18] conducted a study and found that low gestational age and LBW are the primary risk variables that determine the development of ROP [21]. Out of the newborns weighing less than 1.501 kg, a total of 71 (85.54%) developed ROP. All the neonates in our study that got ROP had a weight of less than 1.501 kg. All eight newborns that underwent laser photocoagulation had a birth weight below 1,500 kg. The research conducted by Choudhary et. al. [22] shown that there is a significant association between low birth weight ($p<0.001$) and the likelihood of developing ROP. This finding is consistent with the research conducted by Shah et al. [14], Filho et al. [23], and Flores-Santos et al. [23].

The study additionally examined the relationship between blood transfusions and the development of ROP in a sample of 71 neonates. Among the group of infants who had blood transfusions, 4 individuals (5.63%) were diagnosed with ROP, accounting for 22.54% of the total population of 16 neonates who received transfusions. By contrast, the group of individuals who did not get blood transfusions had a similar incidence of ROP, precisely 4 cases or 5.63%, however this was observed in a substantially larger group of 55 babies (77.46%). The significance level (p-value) of 0.006 observed in the group that received blood transfusions is particularly noteworthy, as it indicates a statistically significant correlation between receiving blood transfusions and an increased probability of developing ROP. Gupta et. al. [15] conducted a study that found blood transfusion to be a significant risk factor for the development of ROP, with an odds ratio of 12.96 and a 95% confidence interval of 4.22-40.62. Previous investigations undertaken by Nair et al. [25], Ballard et al. [26], and Bonotto et al. [27] have also demonstrated a comparable correlation.

Studies have demonstrated that adult haemoglobin, which is better at delivering oxygen to tissues, might result in tissue-level hyperoxia and hence contribute to the development of ROP [28-30]. The study conducted by Choudhary et. al. concluded that there was no significant association (p=0.46) between blood transfusion and the development of ROP. In contrast to the study conducted by Chawla et al. [20], which identified blood transfusion as a risk factor for the development of ROP. The present investigation establishes a statistically significant association between the application of oxygen therapy and the occurrence of ROP in a sample of 71 neonates. Interestingly, ROP was identified in all 8 cases, accounting for 100.0% of the total ROP cases. The cases in question solely pertained to babies who received oxygen therapy, making up 70.42% of the overall group, which comprised 50 infants. Interestingly, none of the infants who did not get oxygen therapy showed any signs of ROP, even though they made up a considerable fraction of 29.58% of the research sample. The p-value of 0.0001 found in the group receiving oxygen therapy shows strong evidence of a statistically significant link between the use of oxygen therapy and an increased vulnerability to developing ROP. A study conducted by Gupta et. al. [15] found that among 56 neonates who received oxygen therapy, 30.3% (17 out of 56) developed ROP, while only 4.8% (8 out of 144) of newborns who did not get oxygen therapy developed ROP. The overall risk of developing ROP in newborns undergoing oxygen therapy was 7.41 (odds ratio) with a 95% CI of 2.75-20.44. The statistical significance of this discovery was extremely strong ($p < 0.000$). The factors that were most commonly shown to increase the likelihood of ROP were the use of oxygen therapy, high oxygen concentration, longer duration of oxygen supplemetation, and prolonged mechanical ventilation [19]. In 1956, the first randomized-controlled experiment on ROP, which was based on the preclinical research conducted by Ashton and Patz [31,32], discovered that exposure to more than 50% oxygen resulted to a higher occurrence of ROP compared to a group that received limited oxygen. In 1992, Flynn and colleagues [12] discovered that the risk of severe ROP increased by almost twofold for each 12-hour period where the transcutaneous partial pressure of oxygen (tcPO2) was equal to or greater than 80mmHg. Fluctuations in oxygen saturation, together with high levels of oxygen, have been identified as a separate risk factor for severe ROP [32].

Among the infants who had sepsis, 5 of them (7.04% of the total cohort) developed ROP. This occurred in 13 infants (18.31% of the total) who had sepsis. In comparison to the group without sepsis, a lesser percentage of ROP cases (3 or 4.23%) were detected among a larger selection of 58 newborns (81.69%). The p-value of 0.004 for the sepsis group is statistically significant, suggesting a robust correlation between sepsis and a heightened susceptibility to ROP. This discovery indicates that sepsis is a notable determinant for the occurrence of ROP, emphasising the significance of efficiently preventing and treating sepsis in newborns to decrease the likelihood of this severe ocular illness. Gupta et. al. [15] conducted a study which found that 36% of preterm neonates with septicaemia acquired ROP, while only 4.6% of those without septicaemia had ROP. The difference in these percentages was statistically significant, with a p-value of less than 0.0000. Several studies have also shown septicaemia as a separate risk factor for ROP [20, 25, 34]. Studies have demonstrated that sepsis can cause ROP either by activating cytokines and endotoxins or by triggering an oxidative burst in the neutrophils following an infection [13]. Kim et. al. [19] found that Neonatal sepsis is a common risk factor for occurrence of ROP. New York State found that the occurrence of newborn sepsis was linked to a higher likelihood of developing ROP [35]. The ELGAN study found that late bacteraemia is a risk factor for pre-threshold/threshold ROP in extremely low gestational age neonates [36].

The current study also demonstrated a noteworthy correlation between the application of phototherapy and the occurrence of ROP in a group of 71 newborns. Among the cohort of 52 newborns who underwent phototherapy, 5 infants (7.04% of the entire cohort) had ROP. In contrast, the group that did not get phototherapy had a lower number of ROP cases (3 or 4.23%), even though this group represented a smaller proportion of the overall cohort (19 infants or 26.76%). The p-value of 0.004 for the group that underwent phototherapy is statistically significant, indicating a robust association between phototherapy and a heightened susceptibility to developing ROP. The study conducted by Gupta et. al. [15] found a strong and statistically significant connection ($p < 0.0000$) between ROP and phototherapy. Nair et al. [25] have identified phototherapy as a risk factor for causing ROP. Yeo et al. [11] found that phototherapy, which decreases bilirubin levels, increases the risk of illnesses like ROP by promoting free radical mediated harm.

Conclusion

In conclusion, ROP remains a significant concern for preterm infants, with its occurrence and risk factors well-documented in literature. The study conducted at Rohilkhand Medical College and Hospital adds valuable insights into understanding ROP's multifaceted nature. It highlights the association between ROP and factors such as gestational age, birth weight, oxygen exposure, blood transfusions, sepsis, and phototherapy. The

study's findings underscore the importance of early identification and management of preterm infants at risk for ROP, particularly those with extremely low gestational age and birth weight. Additionally, it emphasizes the impact of interventions like oxygen therapy, blood transfusions, sepsis, and phototherapy on ROP development, providing crucial information for healthcare professionals involved in neonatal care. Overall, the study contributes to our understanding of ROP and informs strategies for prevention, early detection, and management, ultimately aiming to reduce the burden of this severe ocular condition in preterm neonates. Continued research and implementation of targeted interventions are essential in addressing the challenges posed by ROP and improving outcomes for vulnerable neonates.

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