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Early-Stage treatment for Retinopathy of prematurity- A prospective study

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KEYWORDS

Oxygen Therapy, Prematurity, Risk Factors, Retinopathy of Prematurity

ABSTRACT:

Background: To investigate retinopathy of prematurity (ROP).is a serious complication of prematurity treatment and can lead to blindness unless recognized and treated early.

Materials and Methods: This prospective study was conducted in a private NICU hospital and center Shri Aurobindo Medical Research Centre Raipur Chhattisgarh, India. The study population included 182 neonates; all preterm infants admitted to the NICU from January 2017 to December 2019.

Results - Out of the 182 neonates; 89 (48.90%) were boys and 93 (51.09%) were girls. The mean gestational age was 33.02 ± 1.72 weeks; 28 (15.38%) were ≤ 32 weeks; and 154 (84.61) were >32 weeks. The birth weight ranged from 950 to 2100 grams. 63 (34.61%) were delivered vaginally and 110 (60.43%) cases were delivered by cesarean section, and 9 (4.94%) cases were delivered by instrumental. Around 98 (53.84%) cases are from urban areas and 84 (46.15%) from rural areas. Out of the 182 neonates; 59 (32.41%) cases developed ROP in one or both eyes classified as 28 (15.38%) cases Stage 1, 19 (10.43%) cases stage 2, and 12 (6.59%) cases Stage 3. Study shows the relationship between ROP and risk factors. There was a significant relationship between the occurrence of ROP and gestational age (P = 0.000), sepsis (P = 0.000), oxygen therapy (P = 0.000), and frequency of blood transfusions (P = 0.030).

Conclusion: The prevalence of ROP in this study was 59 (32.41%) When monitoring preterm newborns, clinicians should be aware that these additional risk factors exist. The examination of risk variables will aid in understanding and predicting ROP development in severely preterm newborns. Preventing the development of progressive ROP in high-risk preterm newborns requires prompt retinal screening. All efforts must be taken to prevent the development of advanced ROP by removing preterm infants, altering neonatal care, and improving the identification of dangerous ROP signs. This is because ROP can cause catastrophic sequelae up to full blindness.

1. INTRODUCTION

Retinopathy of prematurity (ROP) or who weigh less than three pounds at birth may develop an eye condition known as Retinopathy of prematurity (ROP). Another researcher provided a significant explanation for children's avoidable blindness. [1].

The growth of aberrant blood vessels in the retina, the light-sensitive layer of tissue in the back of the eye, results in ROP. Babies with mild symptoms of ROP sometimes recover without any medical intervention. The retina might become dislocated and scarred by these aberrant blood vessels, which are brittle and prone to

Journal of Chemical Health Risks
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leaking or bleeding. This causes a tractional retinal detachment, which is the main cause of visual impairment and blindness in ROP.[2]

ROP is divided into 5 stages. These phases are used by doctors to monitor the severity of ROP. Stage 1 (moderate) to Stage 5 (severe) are the various stages:
• Stages 1 and 2: Without medical intervention, babies in these stages typically recover and go on to have normal vision. Physicians will closely monitor infants to see if their ROP worsens.
• Stage 3: Some infants with stage 3 develop better and go on to have healthy vision without the need for treatment. However, some require medical attention to prevent aberrant blood vessels from producing retinal detachment, an eye condition that can result in visual loss.
• Stage 4: Babies at this stage require medical attention due to partially detached retinas.
• Stage 5: During this stage, the retina totally separates. Babies in stage 5 may go blind or lose their vision even with treatment.

A subtle demarcation line indicates Stage 1 of ROP, a raised ridge indicates Stage 2, extraretinal fibrovascular tissue indicates Stage 3, a partial retinal detachment indicates Stage 4, and a whole retinal detachment indicates Stage 5. The ophthalmoscopic features at the interface of the vascularized and avascular retina are described by the stages of ROP. Additionally, plus disease can appear at any stage and is defined by significant posterior retinal artery tortuosity and vascular dilatation, which reflect increased retinal blood flow. [3]

The disease has garnered significant international research attention due to the higher survival rates among very low birth weight preterm newborns (NBs), or those with birth weights (BW) of 1500 grams (3.3 pounds) or less—2000 grams (4.4 pounds) less than typical full-term infants, who are most at risk of developing ROP. These increasing numbers could be explained by improved prenatal care.

Low birth weight, Low gestational age, and prolonged exposure to more oxygen after delivery are the three traits that have been consistently and significantly associated with reduced oxygen pressure after birth (ROP). [4] The increased incidence of other preterm birth-associated comorbidities, such as blindness related to ROP, is significantly rising as a result of the heightened rates[5]. These comorbidities have major implications for society. In the world, 10% of births happen before 37 weeks of gestation.[6]
Sepsis, intraventricular hemorrhage, anemia [7], transfusions, infection, breathing problems, heart disease, mechanical ventilation [8], sepsis [9], intraventricular hemorrhage [10], surfactant therapy [11], frequent blood transfusions [7], and apnea are additional risk factors for ROP. The precise roles that each of these components plays in the progression of the illness are still unknown. [12] The present study aims to investigate retinopathy of prematurity (ROP).is a serious complication of prematurity treatment and can lead to blindness unless recognized and treated early.

2. Methods

This prospective study was conducted in private NICU hospital and centre Shri Aurobindo Medical Research Centre Raipur Chhattisgarh, India. The study population included 182 neonates; all preterm infants admitted to the NICU from January 2017 to December 2019, with a gestational age of 32 weeks or less at birth and a birth weight of 1500 grams or less. Infants whom gestational age was >32 weeks or birth weight was >1500 grams were included if they were exposed to oxygen therapy for more than 7 days. Also, infants who were born between 32- and 34-weeks gestational age were examined if they had a course of instability (like sepsis, asphyxia or ventilation). Neonates who died before the first ophthalmologic examination were excluded. Infants with congenital anomalies, chromosomal abnormalities, inborn errors of metabolism were excluded from the study.

All infants were examined regularly by the ophthalmologist at 1-2 weeks intervals. The eyes were dilated with a combination of cyclopentolate 0.1% and phenylephrine 0.1% eye drops applied one hour before the examination. Indirect ophthalmoscopy with a 28 diopter lens was performed with speculum and scleral de-pression. Retinal examination by the ophthalmologist with retinal drawing and RetCam 2 fundus imaging was done when indicated.

Journal of Chemical Health Risks

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JCHR (2023) 13(6), 1458-1466 | ISSN:2251-6727

ROP was defined as the incomplete or abnormal vascular proliferation of the retina. The ophthalmological examinations were initiated at the 4 week of life and were repeated weekly or biweekly, using the schedule for follow-up, until full vascularization of the retina reached zone 3 (the most peripheral temporal retinal zone), or until full remission of ROP after treatment. In this study we examined a series of suspected pre and postnatal risk factors for ROP to identify independent risk factors associated with the development of mild and severe forms of this disease in our NICU conditions. The pre-natal variables were gestational age, birth weight, sex, and mode of delivery. The post-natal variables, were respiratory distress syndrome, oxygen therapy, phototherapy for jaundice, frequency of blood transfusions, sepsis (by clinical diagnosis, with either C-reactive protein greater than 6.0 mg/dl, or blood culture positive cases), hypotension (as identified by the standard mean for age and weight), intraventricular hemorrhage (as identified by cranial ultra-sound), and patent ductus arteriosus (as identified by echocardiography).

Data was analyzed using computer IBM- SPSS Version 26 software for further statistical analysis. The descriptive analysis had done using frequency and proportion, mean, variance, paired t-test, and frequency tables used for presenting the information. The finding decided to use crude and adjusted or with a 95% confidence interval. were used to check for factors associated with glycemic control and a P-value < .05 was considered statistically significant

3. RESULT

The study subject included 182 neonates; all pre terms with a gestational age of 32 weeks or less at birth and a birth weight of 1500 g or less. This study also included infants whose gestational age was >32 weeks or birth weight was >1500 g with unstable condition during the duration from January 2015 to December 2019.

Table 1- Demographic data of the studied cases with frequency and percentage.

Variables	Categories	Frequency	Percentage
Sex	Boys	89	48.90%
	Girls	93	51.09%
Gestational Age	<32 Weeks	28	15.38%
	>32 Weeks	154	84.61%
Birth Weight	1500grams or Less	1	0.54%
	1000-1500 grams	98	53.84%
	>1500 grams	83	45.60%
Mode of Delivery	Vaginal Delivery	63	34.61%
	Casarean Section	110	60.43%
	Instrumental	9	4.94%
Residence	Urban	98	53.84%
	Rural	84	46.15%

Out of the 182 neonates; 89 (48.90%) were boys and 93 (51.09%) were girls. The mean gestational age was 33.02 ± 1.72 weeks; 28 (15.38%) were ≤ 32 weeks; and 154 (84.61) were >32 weeks. The birthweight ranged from 950 to 2100 grams. 63 (34.61%) were delivered vaginally and 110 (60.43%) cases were delivered by caesarean section, and9 (4.94%) cases were delivered by instrumental. Around 98 (53.84%) cases from urban areas and 84 (46.15%) cases are from rural areas. Out of the 182 neonates; 59 (32.41%) cases developed ROP in one or both eyes classified as 28 (15.38%) cases stage 1, 19 (10.43%) cases stage 2, and 12 (6.59%) cases stage 3. [Table 1]

Table 2- Relationship between retinopathy of prematurity and risk factors.

Paired Samples Test

	Paired Differences						
				95% Confidence Interval of the Difference			
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	Sig. (2-tailed)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(6), 1458-1466 | ISSN:2251-6727

Pair 1	Male	Cases with ROP	.23	.426	.050	-.855	-.652	-14.832	.000
		Cases without ROP	.99	.117	.014				
Pair 2	Female	Cases with ROP	.25	.438	.051	-.836	-.631	-14.265	.000
		Cases without ROP	.99	.115	.013				
Pair 3	Vaginal Delivery	Cases with ROP	.42	.499	.074	-.707	-.405	-7.416	.000
		Cases without ROP	.98	.149	.022				
Pair 4	Cesarean Section	Cases with ROP	.22	.419	.042	-.851	-.680	-17.785	.000
		Cases without ROP	.99	.101	.010				
Pair 5	<32 Weeks	Cases with ROP	.50	.512	.109	-.357	-.007	-2.160	.042
		Cases without ROP	.68	.477	.102				
Pair 6	>32 Weeks	Cases with ROP	.22	.416	.037	-.846	-.698	-20.635	.000
		Cases without ROP	.99	.089	.008				
Pair 7	1000-1500	Cases with ROP	.30	.462	.053	-.791	-.577	-12.748	.000
		Cases without ROP	.99	.115	.013				
Pair 8	>1500	Cases with ROP	.27	.449	.055	-.824	-.600	-12.680	.000
		Cases without ROP	.98	.123	.015				
Pair 9	Respiratory	Cases with ROP	.37	.488	.063	-.738	-.482	-9.528	.000
		Cases without ROP	.98	.130	.017				
Pair 10	Sepsis	Cases with ROP	.41	.495	.051	-.676	-.473	-11.205	.000
		Cases without ROP	.99	.103	.011				
Pair 11	Hypotension	Cases with ROP	.43	.501	.076	-.699	-.392	-7.183	.000
		Cases without ROP	.98	.151	.023				
Pair 12	Phototherapy	Cases with ROP	.37	.484	.042	-.710	-.542	-14.750	.000
		Cases without ROP	.99	.087	.008				
Pair 13	Oxygen Therapy	Cases with ROP	.47	.504	.066	-.640	-.377	-7.746	0.00
		Cases without ROP	.98	.130	.017				
Pair 14	Duration of Oxygen Therapy	Cases with ROP	.63	.490	.083	-.508	-.177	-4.212	.0000
		Cases without ROP	.97	.169	.029				
Pair 15	Mechanical	Cases with ROP	.58	.502	.090	-.569	-.205	-4.353	.0000
		Cases without ROP	.97	.180	.032				

Journal of Chemical Health Risks

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JCHR (2023) 13(6), 1458-1466 | ISSN:2251-6727

Pair 16	Ventilation	Cases with ROP	.43	.507	.111	-.757	-.291	-4.690	.000
		Cases without ROP	.95	.218	.048				
Pair 17	CPAP	Cases with ROP	.55	.510	.109	-.632	-.186	-3.813	.001
		Cases without ROP	.95	.213	.045				
Pair 18	Blood Transfusion	Cases with ROP	.16	.374	.061	-.943	-.678	-12.421	.000
		Cases without ROP	.97	.164	.027				
Pair 19	Blood Transfusion more than one	Cases with ROP	.56	.504	.089	-.586	-.226	-4.605	.000
		Cases without ROP	.97	.177	.031				

Table 2 shows the relationship between ROP and risk factors. There was a significant relation-ship between the occurrence of ROP and gestational age (P = 0.000), sepsis (P = 0.000), oxygen therapy (P = 0.000), and frequency of blood transfusions (P = 0.030). On the other hand, there was no significant relationship between the occurrence of ROP and sex, mode of delivery, birthweight, respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, hypotension, phototherapy, and duration of oxygen therapy, mechanical ventilation, and CPAP at >0.05 level.

Table 3- Relationship between gestational age and stages of retinopathy of prematurity.

			Mean	Std. Deviation	Std. Error Mean	P VALUE
	ROP 1	<32 Weeks with ROP	.42	.507	.116	
Pair 20		>32 Weeks with ROP	.95	.229	.053	.082
Pair 21	ROP 2	<32 Weeks with ROP	.67	.492	.142	
		>32 Weeks with ROP	.92	.289	.083	
Pair 22	ROP 3	<32 Weeks with ROP	.75[a]	.463	.164	
		>32 Weeks with ROP	.75[a]	.463	.164	

Table 3 shows the relationship between gestational age and stages of ROP. There was no significant relationship between the gestational age and stages of ROP (P = 0.082).

Table 4- Relationship between Oxygen therapy and stages of ROP.

			Mean	Std. Deviation	Std. Error Mean	t value
Pair 23	ROP 1	Oxygen Therapy	.87	.352	.091	.168
		Without Oxygen Therapy	.60	.507	.131	
Pair 24	ROP 2	Oxygen Therapy	.85	.376	.104	
		Without Oxygen Therapy	.62	.506	.140	
Pair 25	ROP 3	Oxygen Therapy	.70	.483	.153	
		Without Oxygen Therapy	.50	.527	.167	

Table 4 shows the relationship between oxygen therapy and stages of ROP. There are no significant relation between oxygen therapy and stages of ROP (P = 0.168).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 1458-1466 | ISSN:2251-6727

Table 5- Outcome of ROP in Studied cases. (n=59)

Stages	n %	Outcome
Stage 1 ROP	28 (47.45%)	Spontaneous Regression on Follow-up
Stage 2 ROP	19 (32.20%)	Spontaneous Regression on Follow-up
Stage 3 ROP	12 (20.33%)	These cases needed laser and improved

Table 5 shows the outcome of ROP in studied cases. Intervention with laser was necessary for the six cases diagnosed as stage 3, and patients showed improvement on follow-up.

4. DISCUSSION

In premature babies, a condition of the retinal vascular development is known as retinalopathy of prematurity. It continues to be a significant complication in preterm neonates, it remains a major cause of childhood blindness globally and a severe problem in preterm neonates.

ROP is a complex illness that is caused by numerous variables. The incidence of respiratory distress syndrome, low birth weight, sepsis, oxygen therapy, short gestational age, and blood transfusion have all been linked to possible risk factors for ROP. Numerous studies have demonstrated that Low birth weight and gestational age were found to be the most important risk factors for the development of ROP. [12,14], According to Aydemir O .et al. showed very low birth weight infants in a Turkish NICU found that weight gain in the first 4 weeks of life was not a significant predictor of ROP [15]. Even other researcher explained by the retina's immaturity of vascularization, which increases its vulnerability to oxidative damage and several perinatal events such as sepsis, blood transfusions, and hyper- and hypoxia. [11,**16,17**,18] Current study noted that demonstrated a significant associated between lower gestational age and severe ROP, In current study no significant association between gestational age and the severity of ROP.

In current study showed that low gestational age, sepsis, oxygen treatment, and blood transfusion frequency were independent risk factors for the development of ROP. Supported study also noted oxygen therapy, respiratory distress syndrome (RDS), intrauterine infection, sepsis, and postnatal blood transfusion contribute to the development of ROP. [19,20,21] In the meantime, factors include birth weight, sex, patent ductus arteriosus, respiratory distress syndrome, and intraventricular Using univariate analysis, hemorrhage, hypotension, phototherapy, length of oxygen therapy, mechanical ventilation, and continuous positive airway pressure were found to be nonsignificant risk variables. Other several study had reported [22,23,24,25] that gestational age, birth weight, maternal preeclampsia, anemia, septicemia, oxygen therapy, and mechanical ventilation were the risk factors of the predisposition to ROP.

In current study showed that short gestational age is the primary risk factor for ROP in terms of its impact on its occurrence. This was consistent with research findings by Karna et al.[11], Fortes et al.[16], and Shah et al.[17] they explained that retina's immaturity of vascularization, which increases its vulnerability to oxidative damage and several perinatal events such as sepsis, blood transfusions, and hyper- and hypoxia. Current study noted that demonstrated a significant associated between lower gestational age and severe ROP, In current study no significant association between gestational age and the severity of ROP.

Malnutrition is common in preterm and critically ill infants, and likely amplifies the effect of hyperoxia on the pulmonary vasculature , systemic blood flow might result in retina hypoxia [26], sepsis [27,28] ,chronic hypoxia (increased erythropoietin concentrations) which were highly associated with elevated amniotic fluid markers of oxidative and nitrosative stress [29,30].

In current study noted that birth weight had not a significant factor on the development of ROP. Other research like Movsas TZ et al., and Cleary Goldman J et al. they found a significant associated between lower birthweight and the development of ROP. [31,32] These studies also explained why lower birthweight children were more susceptible to oxygen therapy, extended breathing, sepsis, and blood transfusion. The small number of patients (1 out of 172 instances) in this work

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JCHR (2023) 13(6), 1458-1466 | ISSN:2251-6727

whose birth weight was less than 1000 g may be the reason for this.

In current study found that there was a significant associated between sepsis and the onset of ROP. Many studies have demonstrated that sepsis has a close relationship with the occurrence of ROP. According to Al-Essa *et al*. [33] the incidence of ROP in preterm infants with sepsis was 3.5 times as high as in those without sepsis. Araz *et al*. [34] found that sepsis was independently associated with the development of severe ROP in infant inpatients. Other study conducted by Sabzehei *et al*. [35]and Lin *et al. [36]* they found not significantly different between premature infants with and without threshold ROP ($p>0.05$).

One separate risk factor for the development of ROP was oxygen therapy. In current study found significant relationship between the use of oxygen therapy and the incidence of ROP, but no significant correlation was established between oxygen therapy and the stages of ROP. Conversely, oxygen therapy was found to be a nonsignificant risk factor for ROP incidence by Palmer et al. They stated that in circumstances when oxygen therapy was not significant, ROP may occur. According to other research, receiving oxygen therapy for longer than seven days significantly increased the likelihood of developing ROP.[37] In current study found that it was not significant.

The Current study found that the frequency of blood transfusions is a separate risk factor for the development of ROP. Though preferential streaming occurs via the persistent foramen ovale, blood from the placenta returns via the ductus venosus and mixes with blood from the inferior vena cava/superior vena cava in the right atrium before flowing to the left atrium and mixes once more with less oxygenated blood returning from the pulmonary veins before reaching the ascending aorta, the brain, and the eyes. However, asserted that the development of ROP may be more likely to be caused by iron overload than by the quantity of transfusions.

There was no significant correlation seen between the occurrence of ROP and other risk factors, such as phototherapy, intraventricular hemorrhage, respiratory distress syndrome, patent ductus arteriosus, and hypotension. Other study found a significant relationship between respiratory distress syndrome and the development of ROP and linked it to the fact that systemic hypoxia causes retinal hypoxia and an increased need for oxygen therapy, they also reported an insignificant relationship between ROP and patent ductus arteriosus and intraventricular hemorrhage. [38]

Following logistic regression analysis, multivariate analysis verified that sepsis, oxygen therapy, low gestational age, and frequent blood transfusions were important risk factors for the development of ROP.

Regressing ROP was found to be highly effective with laser photocoagulation. In current study found that after regular follow-up, ROP regressed and the 12 patients that needed laser intervention improved, which is consistent with Coats et al.'s findings. Since laser treatment is easier to administer than cryotherapy for the most severe types of the condition, laser has become the modality of choice.

which is consistent with Good WV. et al. found Visual outcomes reported after laser are better than those after cryotherapy.[39] When the laser is unavailable, cryotherapy may be investigated under general anesthesia to prevent needless blindness, according to Azad RV et al. [40]

5. CONCLUSION

We acknowledge that the modest number of patients in this study is one of its limitations. The data from this investigation indicate that low gestational age, sepsis, oxygen therapy, and frequency of blood transfusions are independent risk factors in the development of ROP. In conclusion, the prevalence of ROP in this study was 59 (32.41%) When monitoring preterm newborns, clinicians should be aware that these additional risk factors exist. Understanding and predicting ROP development in severely preterm newborns will be aided by the examination of risk variables. Preventing the development of progressive ROP in high-risk preterm newborns requires prompt retinal screening. All efforts must be taken to prevent the development of advanced ROP by removing preterm infants, altering neonatal care, and improving the identification of dangerous ROP signs. This is because ROP can cause catastrophic sequelae up to full blindness.

Journal of Chemical Health Risks

www.jchr.org

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6. STRENGTHS AND LIMITATIONS

It's a short-term and area-based study to study the long-term Effects Early-Stage treatment for Retinopathy of prematurity

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Journal of Chemical Health Risks

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