Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: https://ijooo.org/

Original Research Article

To study the significance of various risk factors in development of retinopathy of prematurity at a tertiary care center in Eastern Uttar Pradesh

Ram Yash Singh Yadav[1], Chiranji Rai[1], Nupur Srivastava[1], Aditi Jhunjhunwala[1,*]

[1]*Dept. of Ophthalmology, B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received 16-07-2022
Accepted 26-07-2022
Available online 08-11-2022

Keywords:
ROP
Prematurity
Oxygen
Low GA
Sepsis

ABSTRACT

Background: Retinopathy of prematurity is a multi factorial vaso-proliferative disease that is the most common cause of preventable childhood blindness worldwide.
This study aims to determine the frequency, clinical course and risk factors of ROP in premature infants treated in the Neonatal Intensive Care Unit (NNICU) of our hospital.
Materials and Methods: In this retrospective observational study the case records of 243 infants who visited our ROP clinic between January 2020 and august 2021 were reviewed.
Observation: The mean GA was 33.4 weeks and the mean birth weight was 1.3 kg. A total of 55 (22.82%) patients developed ROP. low birth weight (p value = <0.001), low gestational age (p value = <0.001), multiple pregnancy (p value 0.002), blood transfusion (p value = 0.033), sepsis (p value = 0.009, odds ratio = 2.29 at CI 95%), oxygen supplementation (p value = <0.001 odds ratio= 10.56 at CI 95%) and duration of oxygen (p value = <0.001, odds ratio =1.93 at CI 95%) were significant risk factor for development of ROP. 2 (3.63%) cases were zone I, 8 (14.54%) zone II, and 45 (81.81 %) in zone III. Out of which 8 had plus disease. Analysis of the risk factor for severity of disease was found to be statistically significant with multiple pregnancy (p value = 0.015).
Conclusion: Our study shows less gestational age, low birth weight and supplemental oxygen along with sepsis as biggest risk factor for development of ROP in our set –up and multiple pregnancy for severity.

1. Introduction

One of the most common cause of preventable childhood blindness in developed and developing countries is retinopathy of prematurity (ROP). ROP is a multifactorial vasoproliferative disease of vitreo-retina which occurs in incompletely vascularized retina of the preterm infants.[1–4] Clinical presentation can range from spontaneous regression in about 85% of the infants to complete bilateral detachment of the retina and complete blindness in nearly 50,000 infants each year.[5,6] Till date world has seen three ROP epidemics with third currently going on in low income countries like India due to improvement in the neonatal care which leads to survival of more preterm infants and varying level of neonatal care provided.[7] It was first described by Terry who named it Retrolental fibroplasia in 1942.[8]

It is a two phase disease with hyperoxia of premature infants in the first phase leads to reduced retinal vascular growth and loss of blood vessels due to a lack of growth factors like VEGF and IGF-1. Further development of peripheral avascular zone leads to a hypoxic state and in turn induces the second phase of ROP by increasing the expression of the vascular endothelial growth factor (VEGF) and uncontrolled neovascularization.[9,10]

Although the pathogenesis of ROP is incompletely understood multiple factors have been implicated in over

* *Corresponding author*.
E-mail address: aditijtw@gmail.com (A. Jhunjhunwala).

https://doi.org/10.18231/j.ijooo.2022.043

studies over year and it all started with Campbell who suggested association between supplemental oxygen and ROP. Major risk factors in the occurrence of ROP are gestational age, birth weight and oxygen therapy but development of ROP has also been described in the lack of oxygen therapy.[2] Many other factors, such as blood transfusions, intraventricular hemorrhage (IVH), apnea, sepsis, hypercarbia or hypocarbia, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD) and perinatal asphyxia has been reported in association with ROP.[2,3]

Although association of various factors and ROP is extensively studied and reported over years it varies in different setup especially in developing countries due to varying levels of NICU care given. Understanding the risk factors and mechanism which determine the onset and progression of disease helps in improving the screening and management.

The objective of the present study was to determine the frequency, clinical course and risk factors of ROP in premature infants treated in the Neonatal Intensive Care Unit (NNICU) of our hospital. We also examined the correlation between multiple risk factors and ROP incidence and analyzed which risk factors are more closely associated with severity of ROP in our setup.

2. Materials and Methods

We performed a retrospective observational study on 243 preterm infants that presented to us at our ROP clinic between January 2020 and august 2021. The demographic and clinical data were collected with the consent of the patient's parents. GA was calculated based on the last menstrual period and BW was measured during the first postnatal minutes. The first examination was done at a postnatal age of 4 weeks, but in infants with gestational age <27 weeks first examination was postponed until a postnatal age of 31 weeks. All preterm infants who presented to our clinic were included in this study. History of maternal pre-eclampsia and multiple delivery, sex, birth weight, gestational age, oxygen therapy and its duration, mechanical ventilation and its duration along with all associated systemic findings including blood culture-proven sepsis, clinical sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and blood product transfusion were recorded for each infants.

Pupils were dilated using 2 drops of tropicamide 0.5% and phenylephrine 2.5% at 10-min intervals. Once pupils were dilated, ROP screening was performed using a binocular indirect ophthalmoscope with a pan-retinal 2.2 lens, pediatric eye speculum and pediatric scleral depressor under topical anesthesia. The ROP status of each infant was classified according to the International Classification of ROP, including stage, zone, and extent of disease, and presence or absence of plus disease.[11] Accordingly, patients were referred for treatment. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as numbers and/or percentages. Univariate analysis was performed using the Student's t-test and χ^2 test to examine continuous and dichotomous variables, respectively. The level of statistical significance was set at P<0.05.

3. Results

During the study period a total of 243 neonates meeting the inclusion criteria for our study were screened out of which 2 neonates had congenital cataract and were planned for cataract surgery. The mean GA at birth was 33.4 weeks and the mean birth weight was 1.3 kg. Majority were singleton, 163 out of 241 (67.63%), 65 were twins (26.97%), 11 were triplets (4.56%) whereas 2 were surviving babies of quadruple pregnancy. A total of 55 (22.82%) patients developed any stage ROP, and 9 (3.7%) patients developed severe ROP.

Analysis of gestational age indicates that patients who developed active ROP were significantly (p value <0.001) (Table 1) born earlier (50.9% neonate in our study had GA between 30-33 weeks) compared to those who did not develop active ROP. Also, birth weight was statistically significantly (p value <0.001) (Table 2) lower in patients (60% neonate in our study has birth weight between 1-1.5kg) who developed active ROP compared to patients who did not develop active ROP.

Using univariate analysis, low birth weight, low gestational age, multiple pregnancy (p value 0.002), history of blood transfusion (p value = 0.033) (Table 3), history of sepsis (p- value = 0.009) (Table 4), oxygen supplementation (p value = <0.001) (Table 5) and duration of oxygen supplementation (p value = <0.001) were significant risk factor for development of ROP.

All the following covariates were significantly associated with ROP development on statistical level (all with p value of <0.05). In order to determine the conditions that increase ROP incidence, a logistics regression analysis was performed. Besides the gestational age, birth weight, oxygen supplementation and its duration which all are strongly correlated to ROP incidence, sepsis was found to be the most important risk factor in our study. Retinopathy incidence was multiplied by 2.29 (odds ratio at 95% confidence interval) in neonates with sepsis. Whereas, odds ratio for each day of oxygen supplementation and each blood transfusion was 10.56 and 1.93 respectively at 95% confidence interval.

Analysis of patients according to zones revealed the following: 2(3.63%) cases were zone I, 8(14.54%) zone II, and the largest number of 45(81.81%) in zone III. Out of which 8 had plus disease, 1 in zone 3, 5 in zone 2 and 2 in zone 1. Most of the patient belonged to stage 1 in

Table 1: Relation of birth weight to development of ROP

Birth weight	No ROP		ROP		p value
	Frequency	%	Frequency	%	
<1kg	9	4.8%	10	18.2%	
1-1.5kg	90	48.4%	33	60.0%	
1.5-2kg	52	28.0%	5	9.1%	<0.001
>2kg	35	18.8%	7	12.7%	
Total	177	95%	55	100%	

Table 2: Relation of Gestational age to development of ROP

GA	No ROP		ROP		p value
	Frequency	%	Frequency	%	
27-30 weeks	27	14.5%	19	34.5%	
30-33 weeks	88	47.3%	28	50.9%	<0.001
>33 weeks	71	38.2%	8	14.5%	
Total	186	100%	55	100%	

Table 3: Relation of blood transfusion and development of ROP

Blood transfusion	No ROP		ROP		p value
	Frequency	%	Frequency	%	
No	121	65.1%	27	49.1%	
Yes	65	34.9%	28	50.9%	0.033 Odds ratio 1.93 CI = 1.05-3.55
Total	186	100%	55	100%	

Table 4: Relation of sepsis and development of ROP

Sepsis	No ROP		ROP		p value
	Frequency	%	Frequency	%	
No	98	52.7%	18	32.7%	
Yes	88	47.3%	37	67.3%	0.009 Odds ratio 2.29 CI = 1.22-4.31
Total	186	100%	55	100%	

Table 5: Relation of oxygen supplementation and development of ROP

O2	No ROP		ROP		p value
	Frequency	%	Frequency	%	
No	53	28.5%	2	3.6%	
Yes	133	71.5%	53	96.4%	<0.001 Odds ratio 10.56 CI = 2.48-44.9
Total	186	100%	55	100%	

zone 3 (32 patients) whereas, 7 patients in zone 2 belonged to stage 3 and both the patients in zone 1 were stage 3. Analysis of the risk factor for severity of disease was found to be statistically significant with multiple pregnancy only in our study where twins showed more severe disease than singleton (p value of 0.015). While low birth weight, low gestational age, duration of oxygen supplementation, sepsis and blood transfusion showed more severe disease in our study the difference was statistically insignificant. It was not possible to perform the logistic regression for severe ROP due to the reduced number of this outcome.

4. Discussion

ROP is a major cause of potentially preventable blindness. According to guidelines published by the American Academy of Ophthalmology, infants weighing less than 1500 g or GA ≤ 30 weeks, and infants weighing between 1500 and 2000 g or GA > 30 weeks with an unstable clinical course should receive dilated ophthalmoscopy examinations for ROP screening.[12]

In this retrospective observational study including 243 babies, 55 developed ROP. While considering gestational age as a factor in ROP, prevalence decreases from 41.3% in 27-30 weeks gestation age to 24.13% in gestation age 30-33 weeks in our study which shows a direct role of gestational age in development of ROP and is consistent with the findings reported by Azami M et al.,[13] yau et al.,[14]

study by EXPRESS group[15] and others[16–18] None of the babies in our study had gestational age of less than 27 weeks which can be contributed to non-survival of such babies in our setup.

ROP is a multifactorial disease, in our study less GA, low birth weight, longer duration of oxygen supplementation (more for babies who are intubated), sepsis, blood transfusion and multiple pregnancy are the risk factors for development of ROP which is consistent with an 18-year study in Australia[18] and other studies published over years.[13–15,19] Invasive mechanical ventilation is an independent risk factor in our study where 6 out of 11 (54.54%) babies who were intubated developed ROP, whereas, only 32 babies out of 131 who were on nasal prong developed ROP with p value of <0.001.

While multiple pregnancy had been related to increased risk of ROP development in various studies over the years like bossi et al,[20] its association with severity of disease is highly debatable as some studies, like by Shaffer et al[21] and yau et al[14] found an association whereas other studies by Shohat et al[22] and Friling et al[23] did not find any. We found a significant association between multiple pregnancy and severity of disease. Our study is limited by being retrospective in nature and lack of digital photographic documentation.

5. Conclusion

Our study shows less gestational age, low birth weight and supplemental oxygen along with sepsis as biggest risk factor for development of ROP in our set –up and multiple pregnancy for severity of disease.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Tasman W, Patz A, Mcnamara JA, Kaiser RS, Trese MT, Smith BT, et al. Retinopathy of prematurity: the life of a lifetime disease. *Am J Ophthalmol*. 2006;141(1):167–74. doi:10.1016/j.ajo.2005.07.034.
2. Karna P, Muttineni J, Angell L, Karmaus W, Pediatr B. Retinopathy of prematurity and risk factors: a prospective cohort study. *BMC Pediatr*. 2005;5(1):18. doi:10.1186/1471-2431-5-18.
3. Chang JW. Risk factor analysis for the development and progression of retinopathy of prematurity. *PLoS ONE*. 2019;14(7):e0219934. doi:10.1371/journal.pone.0219934. eCollection 2019.
4. Maurya R. Retinopathy of prematurity: An update. *Ind J Clin Exp Ophthalmol*. 2018;4(3):1–2.
5. Dogra MR, Katoch D, Dogra M. An Update on Retinopathy of Prematurity (ROP). *Indian J Pediatr*. 2017;84(12):930–6. doi:10.1007/s12098-017-2404-3.
6. Saugstad OD. Oxygen and retinopathy of prematurity. *J Perinatol*. 2006;26(1):46–50. doi:10.1038/sj.jp.7211475.
7. Mehmet S, Fusun A, Sebnem C. One-year experience in the retinopathy of prematurity: frequency and risk factors, short-term results and follow-up. *Int J Ophthalmol*. 2011;4(6):634–40. doi:10.3980/j.issn.2222-3959.2011.06.12.
8. Terry T. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens I. preliminary report. *Am J Ophthalmol*. 1942;192:28. doi:10.1016/j.ajo.2018.05.024.
9. Hellström A, Hård AL. Screening and novel therapies for retinopathy of prematurity. A review. *Early Hum Dev*. 2019;138:104846. doi:10.1016/j.earlhumdev.2019.104846.
10. Smith LEH. Pathogenesis of retinopathy of prematurity. *Growth Horm IGF Res*. 2004;14(A):140–4. doi:10.1016/j.ghir.2004.03.030.
11. The International Classification of Retinopathy of Prematurity revisited, International Committee for the Classification of Retinopathy of Prematurity. *Arch Ophthalmol*. 2005;123(7):991–9. doi:10.1001/archopht.123.7.991.
12. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131(1):189–95. doi:10.1542/peds.2012-2996.
13. Azami M, Jaafari Z, Rahmati S, Farahani A, Badfar G. Prevalence and risk factors of retinopathy of prematurity in Iran: a systematic review and meta-analysis. *BMC Ophthalmol*. 2018;18(1):83. doi:10.1186/s12886-018-0732-3.
14. Yau GSK, Lee JWY, Tam VTY, Liu CC, Wong I. FCOphthHK Risk Factors for Retinopathy of Prematurity in Extremely Preterm Chinese Infants. *Medicine*. 2014;93(28):e314. doi:10.1097/MD.0000000000000314.
15. Austeng D, Blennow M, Ewald U. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Paediatr*. 2010;99(7):978–92. doi:10.1111/j.1651-2227.2010.01846.x.
16. Isaza G, Arora S. Incidence and severity of retinopathy of prematurity in extremely premature infants. *Can J Opthalmol*. 2012;47(3):296–300. doi:10.1016/j.jcjo.2012.03.027.
17. Hwang JH, Lee EH, Kim EA. Retinopathy of prematurity among very-low-birth-weight infants in Korea: incidence, treatment, and risk factors. *J Korean Med Sci*. 2015;30(1):88–94.
18. Gunn DJ, Cartwright DW, Gole GA. Incidence of retinopathy of prematurity in extremely premature infants over an 18-year period. *Clin Exp Ophthalmol*. 2012;40(1):93–9. doi:10.1111/j.1442-9071.2011.02724.x.
19. Austeng D, Källen KB, Ewald UW. Incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol*. 2009;127(10):1315–9. doi:10.1001/archophthalmol.2009.244.
20. Bossi E, Koerner E. Ocular Circulation and Neovascularization. Documenta Ophthalmologica Proceedings Series. In: BenEzra D, Ryan SJ, Glaser BM, Murphy R, editors. Influence of Statistical Methodology and Composition of Patient Populations on the Correlation of Risk Factors with Retinopathy of Prematurity. vol. 50. Springer, Dordrecht; 1987.
21. Shaffer DB, Palmer EA, Plotsky DF, Metz HS, Flynn JT, Tung B, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Rethinopathy of Prematurity Cooperative Group. *Opthalmology*. 1993;100(2):230–7. doi:10.1016/s0161-6420(93)31665-9.
22. Shohat M, Reisner SH, Krikler R, Ben-Sira I, Yassur Y, Nissenkorn I, et al. Retinopathy of prematurity: incidence and risk factors. *Pediatrics*. 1983;72(2):159–63.
23. Friling R, Rosen SD, Monos T. Retinopathy of prematurity in multiple-gestation, very low birth weight infants. *J Pediatr Ophthalmol Strabismus*. 1997;34(2):96–100. doi:10.3928/0191-3913-19970301-08.

Author biography

Ram Yash Singh Yadav, Professor

Chiranji Rai, Assistant Professor

Nupur Srivastava, Junior Resident

Aditi Jhunjhunwala, Resident

Cite this article: Yadav RYS, Rai C, Srivastava N, Jhunjhunwala A. To study the significance of various risk factors in development of retinopathy of prematurity at a tertiary care center in Eastern Uttar Pradesh. *IP Int J Ocul Oncol Oculoplasty* 2022;8(3):190-194.