Original Research Paper

Volume - 11 | Issue - 04 | April - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalmology

PREVALENCE, RISK FACTORS AND TREATMENT OUTCOMES IN NEONATES WITH RETINOPATHY OF PREMATURITY (ROP) WITH BIRTH WEIGHT <1750 GRAMS AND ≥ 1750 GRAMS

Dr Monisha SP	Junior Resident, Department of Ophthalmology, Government Medical College, Amritsar, Punjab, India.
Dr Prempal Kaur*	Professor, Department of Ophthalmology, Government Medical College, Amritsar, Punjab, India. *Corresponding Author
Dr Karamjit Singh	Professor, Department of Ophthalmology, Government Medical College, Amritsar, Punjab, India.
Dr Ashwani Kumar	Professor, Department of Pediatrics, Government Medical College, Amritsar, Punjab, India.
Dr Upasna Ajmani	Junior Resident, Department of Ophthalmology, Government Medical College, Amritsar, Punjab, India.

ABSTRACT Retinopathy of prematurity (ROP) is one of the major cause of the preventable childhood blindness worldwide. One year prospective interventional study was conducted in a tertiary care centre in Northern India. All neonates with birth weight ≤ 2000 grams with gestational age ≤35 weeks were screened for ROP and divided into two groups, infants with birth weight <1750 grams (Group A) and ≥1750 grams (Group B). Prevalence of ROP, risk factors and laser treatment outcomes were compared between two groups. Of 191 neonates screened, 61(31.93%) developed ROP, out of which Infants with very low birth weight were at significantly higher risk of developing severe ROP requiring treatment. In addition, high concentration and fluctuating oxygen administration, sepsis, shock, intravenous fluids >10 days were observed to be statistically significant risk factors in infants <1750 grams. Timely screening and early treatment of threshold ROP results in desirable structural and functional outcome.

KEYWORDS : low birth weight; Retinopathy of prematurity; Risk Factors; Treatment Outcomes

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the major cause of the preventable childhood blindness worldwide. It is a vision-threatening vaso-proliferative disorder affecting the retina 4-5 weeks after birth of premature infants who have avascular or incompletely vascularized retina at birth.[1] The incidence of ROP is increasing with increased survival of preterm infants due to advent of recent developments in resuscitation and improved neonatal care especially in middle income countries like India.[2]

Unrestricted oxygen use led to the first epidemic of ROP in 1940-1950s while the second epidemic in 1970-1980s was thought to be due to increased survival of very preterm babies in high-income countries. India and other middle-income countries are facing the "Third epidemic of ROP" related to various factors, such as increased survival of preterm babies, inadequate quality of neonatal care, and low coverage of screening and treatment services for ROP.[3,4]

Improvement in neonatal resuscitation methods over a last two decades in middle income countries like India has though improved survival of the preterm babies but the incidence of sight threatening ROP requiring urgent laser treatments has also increased. As a result ROP screening strategies are now integrated with many national newborn and child health services to ensure healthy newborn outcome.[5] Three major programs in India which cover the range of services for prevention of blindness due to ROP are Child Health, Ministry of Health and Family Welfare; Rashtriya Bal Swasthya Karyakram(RBSK)[6] and National Programme for Control of Blindness and Visual Impairment [7].

Incidence and prevalence of ROP in India has been reported to vary between 38%-51.9% and 19.2%-32.4% respectively[8,9]. ROP is a multifactorial disease and based on clinical and epidemiological studies, numerous risk factors contribute to the development of ROP in newborn babies. The low birth weight and gestational age are the most predictive risk factors for the development of ROP. Other contributing neonatal risk factors include fluctuating or uncontrolled oxygen therapy, respiratory distress syndrome, apnea, sepsis, anemia, multiple blood transfusions. Further varied maternal risk factors also show significant correlation with development and progression of ROP[10,11].

Effective screening of all the premature neonates by a trained ophthalmologist in collaboration with paediatrician and timely intervention can successfully result in better visual and structural outcome in ROP. [12,13]

METHODS

After taking approval from the institutional ethical committee a prospective interventional study was conducted in a tertiary care hospital in North India between January 2019 to December 2019 where all the neonates born with birth weight less than or equal to 2000 grams and below 35 weeks of gestational age were screened. Also neonates between 34 and 36 weeks of gestation but with risk factors were enrolled in the study. A written informed consent was taken from the parents of neonates before their examination. A detailed history including birth weight, gestational age at birth, mode of delivery, neonatal and maternal risk factors and treatment given during NICU stay were recorded in a pre-structured performa. The first examination was performed at 4 weeks of age or 28 days of life in infants born at > 28 weeks. For infants < 28 weeks or < 1200 g, the first examination was done by 2-3 weeks of age for early identification of aggressive posterior ROP.

Neonates were divided into two groups, neonates with birth weight <1750 grams(Group A) and birth weight ≥1750 grams(Group B). Screening of infants was done by comprehensive retinal examination. Indirect ophthalmoscopy using 28 or 20 D lens was done after wide pupil dilation achieved with phenylephrine 2.5% and tropicamide 0.5% instilled 3 times at 10 minutes interval. Further babies with ROP were classified according to the international classification of retinopathy of prematurity (ICROP).[14]

Various neonatal risk factors like birth asphyxia, sepsis, apnea, shock, hypoxic ischemic encephalopathy (HIE), meningitis, hyaline membrane disease (HMD), neonatal jaundice, any use and duration of supplemental oxygen, phototherapy, surfactant, blood transfusion, duration of intravenous fluids and maternal risk factors like antepartum haemorrhage, Gestational diabetes mellitus, PIH, anemia, fetal distress in two groups were assessed.

Subsequent review was done as per the guidelines and severity of the disease until complete regression of the ROP. All the babies with threshold ROP or APROP were treated with double frequency Nd-YAG laser. The data thus collected was tabulated and statistically analysed.

Categorical variables were reported as count and percentage while continuous variables as mean ±standard deviation (SD). Univariate analysis was conducted using Chi square test. p value less than 0.05 was considered as statistical significant. To study the independent risk factors, multiple logistic regression analysis was performed among those risk factors which were significant in the univariate analysis. All data analysis was done with IBM SPSS Statistics for Windows (IBM Corp. Released 2011. Version 21. 0. Armonk, NY: IBM Corp).

RESULTS

During one year period of study between January 2019 to December 2019 out of total 900 preterm deliveries in our tertiary care hospital, 191 neonates fulfilled inclusion criteria for screening for ROP. The prevalence of ROP among the study population was 31.93%.(61/191) It was 23%(47) in Group A (<1750 grams) and 7.32%(14) in Group B (≥1750 grams).

Table 1: Showing relation of severity of ROP among birth weight groups

Stages of ROP	ROP		Total
	Group A (<1750 grams)	Group B (≥1750 grams)	
Stage 1	21 (67.7%)	10 (32.3%)	31
Stage 2	19 (82.6%)	4 (17.3%)	23
Stage 3	4 (100%)	0 (0.0%)	4
Stage 4/5	0 (0.0%)	0 (0.0%)	0
APROP	3 (100%)	0 (0.0%)	3
Pre plus disease	3 (100%)	0 (0.0%)	3
Plus disease	7 (100%)	0 (0.0%)	7
Pre threshold disease-type 1(stage 2/3 with plus disease)	4 (100%)	0 (0.0%)	4
Pre threshold disease-type 2(stage 3 without plus disease)	2 (100%)	0 (0.0%)	2

Out of 31 babies with stage 1ROP, 21(67.7%) were in Group A and 10(32.3%) were in Group B while of 23 babies with stage 2 ROP, 19(82.6%) were in Group A and four(17.3%) in Group B. The prevalence of the APROP and pre threshold type 1 ROP among our study population was 1.57%(3) and 2.09%(4) respectively and all these neonates belonged to Group A. (Table 1)

Table 2: Showing baseline characteristics of the study population:

		ROP				Total	p-value
		Group A (<1750 grams)		Group B (≥1750 grams)			
Mean Birth weight(grams)		47	1363.62 ±238.3	14	1983.57 ±253.5	61	<0.01
Mean gestational age (weeks)		47	30.94±3 .0	14	34.29±1 .7	61	<0.01
Gender	Male	22	64.7%	12	35.3%	34	0.810
	Female	25	92.6%	2	7.4%	27	
Mean mother age(years)		47	25.64±2 .4	14	26.93± 2.2	61	0.087
Birth order	Single	35	72.9%	13	27.1%	48	0.252
	Twins	12	92.3%	1	7.7%	13	
Mode of delivery	NVD	35	79.5%	9	20.5%	44	0.096
	LSCS	12	70.6%	5	29.4%	17	
Place of delivery	In born	46	78%	13	22%	59	0.581
	Out born	1	50%	1	50%	2	

Abbreviations: NVD: normal vaginal delivery; LSCS : lower segment cesarian section; ROP: retinopathy of prematurity.

Mean birth weight (1363.62 ±238.322 grams) and mean gestational age (30.94±3) in Group A was significantly lower than in Group B (1983.57 ±253.578 g) and (34.29±1.7) respectively (p value <0.01) (Table 2)

Table 3: Showing neonatal risk factors in newborns with ROP:

Neonatal risk factors		ROP				Total	p-value
		Group A(<1750 Grams)		Group B(≥1750 Grams)			
HMD	Present	12	80%	3	20%	15	0.754
	Absent	35	76.1%	11	23.9%	46	
Apnea	Present	11	91.7%	1	8.3%	12	0.179
	Absent	36	73.5%	13	26.5%	49	
Sepsis	Present	34	85%	6	15%	40	0.042
	Absent	13	61.9%	8	38.1%	21	
Intracranial haemorrhage	Present	1	100%	0	0%	1	0.582
	Absent	46	76.7%	14	23.3%	60	
HIE	Present	0	0%	1	100%	1	0.065
	Absent	47	78.3%	13	21.7%	60	
Meningitis	Present	5	100%	0	0%	5	0.203
	Absent	42	75%	14	25%	56	
Anemia of prematurity	Present	7	87.5%	1	12.5%	8	0.451
	Absent	40	75.5%	13	24.5%	53	
Birth Asphyxia	Present	14	70%	6	30%	20	0.360
	Absent	33	80.5%	8	19.5%	41	
Shock	Present	16	94.1%	1	5.9%	17	0.049
	Absent	31	70.5%	13	29.5%	44	
Neonatal jaundice	Present	18	72%	7	28%	25	0.435
	Absent	29	80.6%	7	19.4%	36	
Oxygen therapy	Present	38	80.9%	9	19.1%	47	0.117
	Absent	9	64.3%	5	35.7%	14	
Oxygen duration	<10 days	14	73.6%	5	26.3%	15	0.023
	>10 days	24	85.7%	4	14.2%	32	
IVF duration	<10 days	11	91.6%	1	8.3%	12	0.010
	>10 days	22	81.4%	5	18.5%	27	
Blood transfusion	Present	8	88.9%	1	11.1%	9	0.360
	Absent	39	75%	13	25%	52	
phototherapy	Present	18	69.6%	7	30.4%	25	0.435
	Absent	29	81.6%	7	18.4%	36	

Abbreviations: HMD : hyaline membrane disease; HIE : hypoxic ischemic encephalopathy; IVF : intravenous fluids; ROP: retinopathy of prematurity .

Fluctuating oxygen administration >10 days (p value=0.023), sepsis (p value=0.042), shock (p value=0.04), intravenous fluids >10 days (0.010) were statistically significant neonatal risk factors in Group A. After multiple logistic regression analysis the fluctuating oxygen administration > 10 days was found to be independently significant (p=0.021). (Table 3)

Table 4: Showing maternal risk factors in newborns with ROP:

Maternal risk factors		ROP				Total	p-value
		Group A(<1750 grams)		Group B(≥1750 grams)			
PIH	Present	14	87.5%	2	12.5%	16	0.247
	Absent	33	73.3%	12	26.7%	45	
GDM	Present	0	0%	0	0%	0	
	Absent	47	77%	14	23%	61	
Antenatal hemorrhage	Present	2	100%	0	0%	2	0.433
	Absent	45	76.3%	14	23.7%	59	
MSL	Present	4	80%	1	20%	5	0.870
	Absent	43	76.8%	13	23.2%	56	
Fetal distress	Present	3	75%	1	25%	4	0.920
	Absent	44	77.2%	13	22.8%	57	
Antenatal Steroids	Present	1	100%	0	0%	1	0.582
	Absent	46	76.7%	14	23.3%	60	
Anemia	Present	4	80%	1	20%	5	1.870
	Absent	43	76.8%	13	23.2%	56	

Abbreviations: GDM: gestational diabetes mellitus; MSL : meconium stained liquor; PIH: pregnancy induced hypertension.

Table 5: Showing results of laser treatment given and final outcome in ROP babies:

ROP Present		Birth Weight group		Total
		Group A(<1750gms)	Group A(>1750gms)	
Laser treatment required		7(14.89%)	0(0.0%)	7
Laser treatment not required		40(85.10%)	14(100.0%)	54
Final outcome	TR	47 (100.0%)	14 (100.0%)	61

Abbreviations: ROP, retinopathy of prematurity; TR, total regression.

54 babies with ROP showed spontaneous regression while seven babies developed pre threshold type1 disease and APROP. All these

babies were in Group A .The double frequency Nd YAG laser was used to treat these babies. Mean number of laser spots given were 1689±802.6(R/E) and 1463±1018.3 (L/E) and the range of intensity set was 280-320 mw. The babies who underwent laser treatment showed complete regression after three months of follow up. (Table 5)

DISCUSSION

The prevalence of ROP reported in India varies between 19.2% and 32.4% while the incidence of ROP lies between 38% - 51.9%.[8,9] In a prospective study conducted in our tertiary care hospital between January 2019 to December 2019, out of total 900 preterm deliveries 191 babies were screened for ROP. 61(31.93%) babies were observed to developed ROP. Similar to our study 30% infants were diagnosed to have ROP by Dwivedi et al .[20] whereas another study in 2012 and Milad Azami et al reported prevalence of 19.2% and 23.5% respectively.[9,16]

Prevalence of ROP in Group A (<1750 grams) was 23%(47) and in Group B (≥1750 grams) was 7.32%(14), the difference was statistically significant. The prevalence of the plus disease, pre plus disease and APROP among our study group was 3.66% (7), 1.57% (3) and 1.57% (3) respectively and all these neonates were in Group A. Mean birth weight (1363.62 ±238.322 grams) and mean gestational age (30.94±3) in Group A was significantly lower than in Group B (1983.57 ±253.578 g) and (34.29±1.7) respectively (p value <0.01).(Table 2) It is in accordance with studies in literature which suggest that prevalence and severity of ROP are strongly associated with low birth weight .[13,15]

Prevalence of severe ROP observed by Dwivedi et al was 14.2%, out of which 55.5% infants had a classic ROP, eighteen (16.6%) were diagnosed as advanced ROP (stage IV and V) and 27.7% infants had a APROP. Mean gestational age (GA) and birth weight (BW) of severe ROP babies was 31.05 weeks and 1.34 kg respectively.[20] Similarly in our study also of 61 babies with ROP, 21 babies (67.7%) with stage 1ROP and 20(83.3%) with stage 2 ROP were in Group A. All four babies with stage 3 ROP and 10 babies with pre plus, plus disease and APROP were also seen in Group A only (<1750 g).(Table 1) Brazilian study also confirmed that threshold disease in 17% of the infants were in the ELBW group (825.34□±128.3g) and 2.3% in the VLBW group (1329.05±191.5□ g)(*P*<0.001).[17] However on the contrary severe ROP has also been reported in babies born with BW≥1500□g.[18,19]

The oxygen supplementation and prolonged mechanical ventilation have frequently been identified as risk factors for severe and threshold ROP. In 1951, Campbell was the first to suggest supplemental oxygen as the cause for the sudden increase in the numbers of infants developing retrolental fibroplasia(RLF) in the early 1940's.[21,22] Fluctuating oxygen therapy has also been identified as the most significant contributing factor. Hence appropriate monitoring of actual PaO2 in infants at risk of developing ROP is essential. It is recommended to keep PaO2 <100mm Hg (50-70mmhg) and saturation between 90-95%. We also observed that high concentration and fluctuating oxygen administration for >10 days was a statistically significant risk in Group A (birth weight <1750 grams) (p value=0.023). (Table 3)

In addition sepsis (p value=0.042), shock (p value=0.04), intravenous fluids for >10 days (0.010) were also observed as statistically significant risk factors in Group A (birth weight <1750 grams). Azami et al screened infants weighing less than 1500 g or GA□≤□30 weeks and observed that many potential risk factors like low BW, prematurity, sepsis, high concentration of oxygen as important risk factors for ROP.[16] Similarly another studyshowed that gestational age, sepsis, oxygen therapy, and frequency of blood transfusions remained significant variables among the babies with birth weight 1500 g or less.[9]

Among 61 babies with ROP in the current study, laser treatment was indicated in seven (11.47%) babies in Group A .Total regression was observed in all the seven babies after treatment with double frequency Nd-YAG laser and follow up as per guidelines .(Table 5) Contrary to this J B Fortes et al, found that out of 15 babies with threshold disease in ELBW group and 6 babies in VLBW group when treated with laser photocoagulation, 19 babies regressed completely and two showed a progression of the disease to stage 4A and stage 5 ROP.[17]

CONCLUSION:

ROP is a multifactorial disease, various risk factors contribute to the development of ROP in newborn babies. The low birth weight and gestational age are the most predictive risk factors for the development of ROP. Infants with very low birth weight are at significantly higher risk of developing severe ROP requiring treatment. By following proper screening strategies and initiating early treatment in threshold ROP or APROP better structural and functional outcome can be achieved.

REFERENCES:

1. Shah, P. K., Prabhu, V., Karandikar, S. S., Ranjan, R., Narendran, V., & Kalpana, N. (2016). Retinopathy of prematurity: Past, present and future. *World journal of clinical pediatrics*, *5*(1), 35.
2. Gilbert, C., Rahi, J., Eckstein, M., O'Sullivan, J., & Foster, A. (1997). Retinopathy of prematurity in middle-income countries. *The Lancet*, *350*(9070), 12-14.
3. Kiranmayee, P. S., & Kalluri, V. (2019). India to gear up to the challenge of "third epidemic" of retinopathy of prematurity in the world. *Indian journal of ophthalmology*, *67*(6), 726.
4. Gilbert, C. (2008). Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early human development*, *84*(2), 77-82.
5. Shukla, R., Murthy, G. V. S., Gilbert, C., Vidyadhar, B., & Mukpalkar, S. (2020). Operational guidelines for ROP in India: A Summary. *Indian journal of ophthalmology*, *68*(Suppl 1), S108.
6. Sangeetha, J. (2019). Rashtriya Bal Swasthya Karyakaram (RBSK). *TNNMC Journal of Community Health Nursing*, *7*(2), 34-37.
7. Jose, R., & Sachdeva, S. (2009). School eye screening and the National Program for Control of Blindness. *Indian pediatrics*, *46*.
8. Charan, R., Dogra, M. R., Gupta, A., & Narang, A. (1995). The incidence of retinopathy of prematurity in a neonatal care unit. *Indian journal of ophthalmology*, *43*(3), 123.
9. Hakeem, A. H., Mohamed, G. B., & Othman, M. F. (2012). Retinopathy of prematurity: a study of prevalence and risk factors. *Middle East African journal of ophthalmology*, *19*(3), 289.
10. Chang, J. W. (2019). Risk factor analysis for the development and progression of retinopathy of prematurity. *PloS one*, *14*(7), e0219934.
11. Shah, V. A., Yeo, C. L., Ling, Y. L., & Ho, L. Y. (2005). Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. *Ann Acad Med Singapore*, *34*(2), 169-78.
12. Banach, M. J., & Berinstein, D. M. (2001). Laser therapy for retinopathy of prematurity. *Current opinion in ophthalmology*, *12*(3), 164-170.
13. Early Treatment for Retinopathy of Prematurity Cooperative Group. (2005). The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. *Pediatrics*, *116*(1), 15-23.
14. International Committee for the Classification of Retinopathy of Prematurity. (2005). The international classification of retinopathy of prematurity revisited. *Archives of ophthalmology (Chicago, Ill.: 1960)*, *123*(7), 991-999.
15. Isaza, G., Arora, S., Bal, M., & Chaudhary, V. (2013). Incidence of retinopathy of prematurity and risk factors among premature infants at a neonatal intensive care unit in Canada. *Journal of pediatric ophthalmology and strabismus*, *50*(1), 27-32.
16. Azami, M., Jaafari, Z., Rahmati, S., Farahani, A. D., & Badfar, G. (2018). Prevalence and risk factors of retinopathy of prematurity in Iran: a systematic review and meta-analysis. *BMC ophthalmology*, *18*(1), 1-14.
17. Fortes Filho, J. B., Eckert, G. U., Procianoy, L., Barros, C. K., & Procianoy, R. S. (2009). Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil. *Eye*, *23*(1), 25-30.
18. Jalali, S., Matalia, J., Hussain, A., & Anand, R. (2006). Modification of screening criteria for retinopathy of prematurity in India and other middle-income countries. *American journal of ophthalmology*, *141*(5), 966-968.
19. Fang, P. C., Kuo, H. K., Ko, T. Y., Chen, C. C., Hwang, K. P., & Chung, M. Y. (2006). Retinopathy of prematurity in larger preterm infants. *American journal of perinatology*, *23*(05), 273-278.
20. Dwivedi, A., Dwivedi, D., Lakhtakia, S., Chalisgaonkar, C., & Jain, S. (2019). Prevalence, risk factors and pattern of severe retinopathy of prematurity in eastern Madhya Pradesh. *Indian journal of ophthalmology*, *67*(6), 819.
21. Campbell, K. (1951). Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach. *Med. J. Aust*, *2*, 48-50.
22. Ashton, N., Ward, B., & Serpell, G. (1953). Role of oxygen in the genesis of retrolental fibroplasia: a preliminary report. *The British journal of ophthalmology*, *37*(9), 513.