Original Article

DOI: 103126/JNPS.V4113

Retinopathy of Prematurity: Incidence, Risk Factors & Outcome in North Indian Rural and Semi-urban population

Kamal Parihar,[1] Pradeep Kumar Gupta,[2] Vandana Singh,[3] Sanjay Sharma[4]

[1]Senior Resident, Department of Paediatrics, Netaji Subhash Chandra Bose Subharti Medical College, Swami Vivekanand Subharti University, Subharti Puram, NH-58, Delhi Haridwar Bypass Road, Meerut – 25005, Uttar Pradesh, India.
[2]Assistant Professor, Head of Department, Department of Paediatrics, Netaji Subhash Chandra Bose Subharti Medical College, Swami Vivekanand Subharti University, Subharti Puram, NH-58, Delhi Haridwar Bypass Road, Meerut – 25005, Uttar Pradesh, India.
[3]Assistant Professor, Department of Paediatrics,Netaji Subhash Chandra Bose Subharti Medical College, Swami Vivekanand Subharti University, Subharti Puram, NH-58, Delhi Haridwar Bypass Road, Meerut – 25005, Uttar Pradesh, India.
[4]Assistant Professor, Department of Ophthalmology, Netaji Subhash Chandra Bose Subharti Medical College, Swami Vivekanand Subharti University, Subharti Puram, NH-58, Delhi Haridwar Bypass Road, Meerut – 25005, Uttar Pradesh, India.

Article History
Received On : Aug 11, 2021
Accepted On : Apr 05, 2022

Funding sources: None

Conflict of Interest: None

Keywords:
Frequency; Outcome; Predisposing Factors; Retinopathy of Prematurity; Rural North India

Online Access

DOI: https://doi.org/10.3126/jnps.v42i1.39034

***Corresponding Author**

Pradeep Kumar Gupta
Assistant Professor,
Head of Department,
Department of Paediatrics,
Netaji Subhash Chandra Bose Subharti Medical College, Swami Vivekanand Subharti University, Subharti Puram, NH-58, Delhi Haridwar Bypass Road, Meerut – 25005, Uttar Pradesh, India.
Email: drgupta_jsr@rediffmail.com

Abstract

Introduction: ROP is a challenge due to better premature survival. It has an increasing trend and is a preventable cause of vision loss. Its occurrence, severity and outcome in rural population is poorly studied.

Methods: Ahospital based prospective observational longitudinal study was conducted on babies born at a tertiary care centre. Babies with gestation <32 weeks or birth weight < 1500 g were screened for ROP. Preterm babies of >32 weeks gestation with oxygen requirement, RDS, surfactant use, PDA, neonatal hyperbilirubinemia requiring phototherapy, septicemia, red cell transfusion due to anemia, need for inotropes were also included. Babies with ROP were assessed for severity as also need for intervention and were followed for12 months.

Results: Of the 211 neonates screened, 51 had ROP. Frequency was inversely related to both birth weight and gestational age with no gender difference. Oxygen therapy (p 0.001), RDS (p 0.005), mechanical ventilation (p0.003) and septicemia (p 0.005) were main risk factors. Neonatal hyperbilirubinemia requiring phototherapy was found to be protective (p 0.0005). 15.68% cases required laser photocoagulation. During follow up, ROP regressed in all patients.

Conclusions: Risk factors for ROP included oxygen usage, RDS, mechanical ventilation and septicemia. Blood products or inotropes use was not an independent factor. Neonatal hyperbilirubinemia was protective. When diagnosed early, outcome is good in ROP.

Introduction

Retinopathy of prematurity (ROP) or retrolental fibroplasia (RLF), as it was originally named by Terry[1] in 1942, is a disease seen in preterm babies due to proliferation of blood vessels in tissue behind the retina leading to retinal neovascularization, followed by detachment, fibrosis and scar tissue formation. ROP has been recognized as a major reason of partial or total blindness which to a large extent is preventable.

Many risk factors like low birth weight (LBW), prematurity, supplemental oxygen use, sepsis, hypoxic ischemic encephalopathy (HIE), necrotizing enterocolitis (NEC), apnea of prematurity, neonatal jaundice, use of phototherapy and frequent blood transfusions

have been reported to contribute to the causation of ROP[2,3] and 20% preterm infants worldwide have been reported to have ROP.[4] Better outcome of preterm babies as also routine screening have contributed to greater awareness.

However, ROP incidence varies from region to region, depending on the prevalence of preterm babies and quality neonatal care. While reports from large cities are available, none is with rural background. Hence, present study is an endeavor to have study the incidence of ROP as well as its risk factors, severity and outcome among rural and semi urban population.

Methods

This study is a hospital based prospective observational studycarried out in babies admitted to neonatal unit of a tertiary care centre catering to rural and semi-urban population. Study period wasfrom 1st January 2018 to 30th June 2021. Study was approved by institution's ethics committee. In every case, written informed consent was obtained from one or both the parents before baby was enrolled in the study. Babies with birth weight of less than 1500 g as well as babies having gestational age of less than 32 weeks were included. Preterm babies of more than 32 weeks gestation and without referenceto weight who had any apparent risk factors[5] (Oxygen requirement, RDS, surfactant use, PDA, neonatal hyperbilirubinemia requiring phototherapy, septicaemia, red cell transfusion due to anaemia,need for inotropes) were also screened. Babies were provided with oxygen support or mechanical ventilation if needed as per NICU protocol. If indicated, surfactant was instilled via endotracheal tube. Babies with HIE stage II or III, those with cranio- facial anomalies and babies of 32 to 37 weeks'gestation who had no risk factors were excluded. Cases of parental refusal for written consent were also excluded.

Babies were screened for ROP in Ophthalmology OPD.First screening was planned at four weeks of post-natal age or 32 weeks of post-menstrual age which ever was later and was done within three days of the scheduled date. Baby was pre-treated with topical proparacaine in eyes to reduce discomfort and if needed swaddled. Phenylephrine 2.5% and tropicamide 0.5% were used to dilate pupils.[5] Ophthalmological notes were prepared after examination of baby. Details of presence of ROP regarding zone, its stage and extent in terms of clock hours according to ICROP classification were noted and presence of pre-plus or plus disease, if any, was also recorded.[6] Any need for re- examination was also decided and communicated to parents. Data obtained was subjected to statistical analysis - Fischer Exact test, Chi Square test and multivariate regression analysis - using SPSS software.

Results

A total of 355 preterm neonates were admitted out of a total of 1523 admissions during the study period in NICU. Of these, 81 neonates were excluded due to non-fulfilment of inclusion criteria and 63 refused consent or expired. A total of 211 babies were enrolled in the study and 51 of these were positive for ROP (Fig 1). So, overall frequency of ROP was found to be 24.1%.

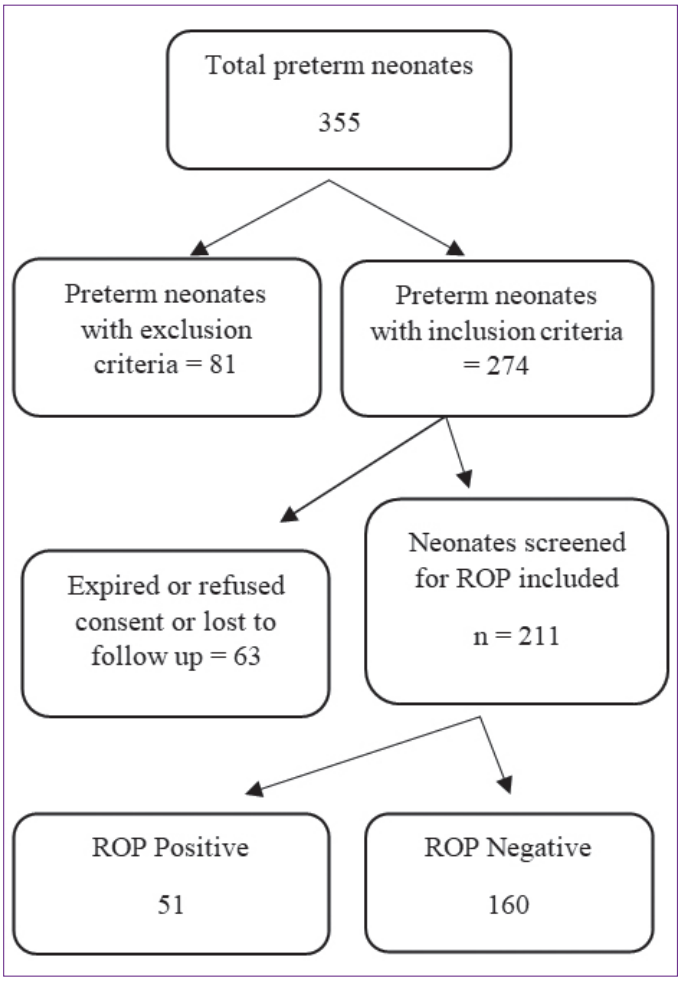

Fig 1. Distribution of cases

Mean gestational age (GA) and mean weight of neonates in study was 32.05 ± 1.86 weeks and 1434.75 ± 243 grams respectively. Only 35.5% cases were above 32 weeks GA. Mean GA and mean weight of new born babies with ROP were 30.55 ± 1.5 weeks and 1185.49 ± 177 grams respectively as compared to 32.52 ± 1.65 weeks and 1514.22 ± 291 grams respectively in babies without ROP. There was no gender bias with 24.7% of male babies and 23.2% of female babies developing the disease (P = 0.3954) and odds ratio 1.08 with 99% CI.

Most cases were of less than 32 weeks gestation and below 1500 g birth weight. Oxygen supplementation was found to be a major risk factor.Babies that developed ROP needed oxygen supplementation for 421 ± 27 hours as compared to 79 ± 23 hours with those who did not develop ROP. Other important risk factors were RDS and mechanical ventilation. It was found that babies with neonatal hyperbilirubinemia had significantly less risk of ROP. No significant associated between ROP and anemia or need for packed red cell transfusion as well as use of inotropes

could be elicited. Eight of the 51 babies who developed ROP required laser photocoagulation while the disease regressed on its own in all others. Of these, three cases were of ≤ 28 weeks gestation and in stage III at the time of 1st assessment. After the laser, ROP regressed in all the patients who underwent photocoagulation.

Tables 1 and 2 display cases distribution across gestation and weight groupsrespectively. Table 3 depicts ROP risk factors and Table 4 shows multivariate regression analysis.

Table 1. ROP in relation to Gestational Age (n = 211)

Group	GA (Weeks)	Without ROP	With ROP	Stage I	Stage II	Stage III	P value
1	27- 28	0 (0%)	5 (100%)	0	2	3	0.0001
2	29 – 30	9 (32.1%)	19 (67.9%)	7	12	0	0.0003
3	31 – 32	81 (78.6%)	22 (21.4%)	18	4	0	0.009
4	33 – 34	46 (92.0%)	4 (8.0%)	4	0	0	0.008
5	35 – 36	24 (96.0%)	1 (4.0%)	1	0	0	0.008
	Total	160 (75.8%)	51 (24.2%)	30 (58.8%)	18 (35.3%)	3 (5.9%)	

No cases of APROP (Aggressive Posterior Retinopathy of Prematurity) were found
GA = Gestational age
ROP = Retinopathy of prematurity. NS = not significant

Table 2. ROP in various Birth Weight groups*

Group	Birth weight (g)	With ROP	Without ROP	p - value
a	< 999	21 (80.8%)	5 (19.2%)	0.0026
b	1000 – 1499	24 (21.6%)	87 (78.4%)	0.0089
c	1500 – 1999	5 (9.6%)	47 (90.4%)	0.0001
d	> 2000	1 (4.5%)	21 (95.5%)	0.0001
	Total	51 (24.1%)	160 (75.9%)	

*Data shows number of babies and percentage in parenthesis

Table 3. Occurrence of ROP vis a vis various risk factors*

Risk factors	With ROP (n=51)	Without ROP (n=160)	p value	Odds ratio
GA (weeks) 32, (n =136)	46 (90.19%)	90 (56.25%)	0.0001	7.16
Birth weight <1500g, (n =137)	45 (88.24%)	92 (57.5%)	0.0002	5.54
Oxygen supplementation required (n =114)	42	72	0.0018	5.704
Oxygen supplementation not required (n = 97)	9	88	0.0001	
RDS present (n = 75)	40	35	0.0056	12.98
RDS absent (n = 136)	11	125	0.0001	
Mechanical ventilation needed (n = 45)	24	21	0.0036	5.88
Mechanical ventilation not needed	27	139	0.0002	
Neonatal hyperbilirubinemia Requiring phototherapy (n = 112)	16 (14.3%)	96 (85.7%)	0.0005	0.3048
Neonatal hyperbilirubinemia absent	35	64		
Blood transfusion (n = 65)	17 (26.2%)	48 (73.8%)	.654	1.17
Septicemia (n = 82)	11 (13.4%)	71 (86.6%)	.005	0.345
Inotropes (n = 59)	12 (20.3%)	47 (79.7%)	.419	0.739
Anemia (n = 48)	16 (33.3%)	32 (66.7%)	.094	1.828

*Four babies had Patent Ductus Arteriosus but none developed ROP

Table 4. Independent risk factors for ROP by multivariate logistic regression analysis

Variables	OR	95% CI	p value
GA	7.24	2.70-18.96	0.001
Birth weight	5.60	2.24-13.74	0.007
Oxygen supplementation	5.77	2.60-12.49	0.009
RDS	13.03	6.04- 27.92	0.0056
Mechanical ventilation needed	5.98	2.88- 12.04	0.003

Discussion

Incidence of ROP from reports of last two decadesis highly variable. Both, incidence and severity vary considerably geographically in different studies.The overall occurrence of ROP in the present study was 24.1%. Different studies in the past from Northern India have shown variable incidences like 11.9%, 21.87% and 44.6%.[7-9]Another study from Turkey found ROP in 32.1% cases.[10] Such variability is expected as developing of ROP depends on the survival rates of preterm neonates, the quality of neonatal care provided by the unit and level of ophthalmic assessment of the discharged neonates. In contrast to Europe and America, ROP has often been reported in larger Asian babies.[12] But data is sketchy and there are not many large reports from our region.

Relation of gestational age (GA) was significant with development of ROP. We found 100% occurrence for 27- 28 weeks GA, 67.9% for 29 - 30 weeks and 21.4% for GA of 31- 32 weeks. It decreased to ≤ 8% after 32 weeks and none required treatment. This pattern in relation to gestational age was well documented in European and American studies.[10,11,14] Difference is in incidence as Austeng[13] reported 55% at 26 weeks and we found 100% at 28 weeks. Difference could probably be due to difference in exposure to oxygen both as duration as well as concentration. Many studies have not reported GA wise incidence.[7,9,15,16] Gupta et al[14] reported 30%, 27.3% and 13.8% incidence of ROP in gestational age 28 - 30 weeks, 30 - 32 weeks and 32 - 37 respectively. However, our rates of occurrence are almost twice in 29 - 30 weeks GA and were similar to those reported by Singh[8] from Gujrat. We could not find Indian reports for 27- 28 weeks gestation to compare.

One of the apparent risk factors for ROP is birth weight. But birth weight often corresponds to gestational age which makes it difficult to assess as an independent risk factor. Among babies with birth weight ≤ 999 g, 80.8% developed ROP; risk gradually reduced to 4.5% in babies who had birth weight of 2000 g or more.While similar findings with reference to birth weight have also been reported,[8-11,15] it is difficult to compare studies. Inclusion criteria are often different, some centres had only selective age groups in their studies and at times differently classified weight groups of babies do not allow comparison between the studies.

We found relationship between oxygen supplementation and ROP was highly significant and only nine infants out of 88 who were not given oxygen developed ROP ($p < 0.0001$). In these babies, other risk factors were present which predisposed them to ROP. Various authors have also reported statistically significant correlation between supplemental oxygen and development of ROP[8,10,14,17]. More importantly, a negative correlation of baby not likely to develop ROP without oxygen supplementation in absence of other risk factors was significantly high. RDS has been reported as a significant risk factor.[8,10,17] In the present study also about half the cases of RDS developed ROP. However, more significant in our study was a correlation that only 10% of those without RDS developed ROP. This aspect has been new and not reported to our knowledge in other studies. Similarly, we found that babies not requiring mechanical ventilation also had significantly reduced risk of ROP ($P = 0.0002$). Apparently, reduced exposure to use of oxygen in these babies is the underlying factor for correlation between absence of RDS and non occurrence of ROP. There was no significant difference between the two genders in developing ROP which has been shown in other studies too.[10,18]

Among the other reported risk factors like jaundice,[9] blood products,[6,8,10,18] septicemia,[8,9,17,18] use of inotropes,[19] blood products,inotropes and anemia[20] were not found to be risk factors. Septicaemia was a risk factorbut hyperbilirubinemia necessitating use of phototherapy was found to be a protective factor ($P = 0.0005$). There have been conflicting reports about role of bilirubin.[9,18,21] It is well known that bilirubin acts as an antioxidant and as ROP is related to free oxygen radicals, such a finding is not unexpected.

In the present study maximum number of cases found were in stage I ROP. Thisis probably due to regular and early screening and also due to judicious use of oxygen. The three preterm babies with stage III ROP were of < 30 weeks, < 999g and were also hemodynamically unstable. They could be screened after four weeks post- natal age only. Similar findings have been supported by others also.[9,14] Apparently, if babies are screened early and oxygen is used judiciously, more babies may be picked up early. More severe disease in more preterm may be due to difficulty in screening early as well as inability to restrict use of oxygen. In our study, eight preterm babies required laser photocoagulation and ROP regressed in all of them. So, timely screening and prompt referral for its treatment is utmost important for the prevention of blindness due to ROP.

Conclusions

ROP is an important complication of prematurity in rural and semi urban populations. Most important predisposing factor, other than prematurity, was use of oxygen. Use of surfactant was not protective against ROP. Screening should be intensified in the presence of factors like oxygen administration, RDS and septicemia. Early screening and management may reduce the chances of progression to vision threatening disease.

References

1. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report. Am J Ophthalmol. 1942; 25:203 - 4. DOI:https://doi.org/10.1016/s0002-9394(42)92088-9

2. Chen M, Citil A, McCabe F, Leicht KM, Fiascone J, Dammann CE, et al. Infection, Oxygen, and Immaturity: Interacting Risk Factors for Retinopathy of Prematurity. Neonatology. 2011; 99: 12532.
DOI: https://doi.org/10.1159/000312821

3. Shah PK, Prabhu V, Ranjan R, Narendran V, Narendran K. Retinopathy of Prematurity: Clinical Features, Classification, Natural History, Management and Outcome. Indian Pediatr. 2016. 53: S (2) 118-123.PMID 27915319

4. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013; 74 Suppl 1: 3549.
DOI: https://doi.org/10.1038/pr.2013.205

5. Chawla D, Agarwal R, Deorari A, Paul VK, Chandra P, Azad RV. Retinopathy of prematurity,symposium on AIIMS protocols in neonatology. Indian J Pediatr. 2012. 79: 501-509.
DOI: https://doi.org/10.1007/s12098-010-0279-7

6. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-999Find all citations in this journal (default).
DOI: https://doi.org/10.1001/archopht.123.7.991

7. Pardeep K, Sankar MJ, Deorari A, Azad R, Chandra P, Agarwal R, et al. Risk Factors for Severe Retinopathy of Prematurity in Preterm Low Birth Weight Neonates. Indian J Pediatr. 2011; 78:812–6.
DOI: https://doi.org/10.1007/s12098-011-0363-7

8. Singh PH, Surana AU, Shah AN. Retinopathy of prematurity in neonatal care unit. Int J Contemp Pediatr.2016;3:234-9.
DOI: https://doi.org/10.18203/2349-3291.
ijcp20160166

9. Maini B, Chellani H, Arya S, Guliani BP. Retinopathy of prematurity and role of antenatal betamethasone in Indian preterm newborn babies. J Cl. Neonatol. 2014; 3: 20-24.
DOI: https://doi.org/10.4103/2249-4847.128724

10. Alpay A, U urba SH. Incidence and risk factors for retinopathy of prematurity in the West Black Sea region, Turkey. Turk J Pediatr. 2012;54(2): 113-8.
PMID 22734296

11. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB,et al. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity.Ophthalmology 1991;98(11):1628-1640.
DOI:10.1016/s0161-6420(91)32074-8

12. Vedantham V. Retinopathy of prematurity screening in Indian population: It's time to set our own guidelines! Indian J. Ophthalmol. 2007; 55: 329-330.
DOI: https://doi.org/10.4103/0301-4738.33816

13. Austeng D, Källen KB, Ewald UW, Jakobsson PG, Holmström GE. Incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. Arch Ophthalmol 2009;127(10):1315-1319.
DOI:https://doi.org/10.1001/archophthalmol.2009.244

14. Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of prematurity – risk factors. Indian J Pediatr 2004;71:887-892.
DOI: https://doi.org/10.1007/bf02830827

15. Crystal Le, Basani LL, Zurakowski D, Ayyala RS, Agrahran, SG. Retinopathy of prematurity: incidence, prevalence, risk factors, and outcome at a tertiary care center in Telangana. J clin Ophthalmol Res.2016; 4: 19-22.
DOI: 10.4103/2320-3897.190785

16. Dwivedi A, Dwivedi D, Lakhtakia S, Chalisgaonkar C, Jain S. Prevalence, risk factors and pattern of retinopathy of prematurity in eastern Madhya Pradesh. Indian J Ophthalmol. 2019: 67: 819-23.
DOI: https://doi.org/10.4103/ijo.ijo_1789_18

17. Kumar N, Kaushik SL, Grover N, Sharma RL. Retinopathy of prematurity: incidence and risk factors: a hospital-based study from Shimla, Himachal Pradesh, India. Int J Res Med Sci 2017; 5:56-61.
DOI: https://doi.org/10.18203/2320-6012.
ijrms20164400

18. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center – incidence, risk factors and outcome. Indian Pediatr.2009;46:.219-24.
PMID 19179740

19. Wong J, Shah PS, Yoon EW, Yee W, Lee S, Dow K. Inotrope use among extremely preterm infants in Canadian neonatal intensive care units: variation and outcomes. Am J Perinatol. 2015 Jan; 009-014.
DOI: 10.1055/s-0034-1371703

20. Lundgren P, Athikarisamy SE, Patole S, Lam GC, Smith LE, Simmer K. Duration of anemia during the first week of life is an independent risk factor for retinopathy of prematurity. Acta Paediatrica. 2018: 759-766.
DOI: https://doi.org/10.1111/apa.14187

21. DeJonge MH, Khuntia A, Maisels MJ, Bandagi A. Bilirubin levels and severe retinopathy of prematurity in infants with gestational age of 23- 26 weeks. J Pediatr 1999; 135: 102-04.
DOI: https://doi.org/10.1016/s0022-3476(99)70336-7