

Original Research Article

A clinical study on retinopathy of prematurity in a tertiary care centre

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age. India shares 20% of the world childhood blindness. Besides congenital cataract, congenital glaucoma and ocular injuries, ROP is emerging as one of the important causes of childhood blindness in India.

Methods: This hospital based prospective study was undertaken during October 2016 to September 2018 in the Department of Ophthalmology, SCB Medical College. Authors included (a) all preterm infants weighing less than 1750gm or gestational age less than 34 weeks at birth, (b) infants with birth weight between 1750gm to 2000gm and gestational age more than 34 weeks (late preterm and term infants) those were considered as high risk.

Results: Among the 328 babies included in our study, the incidence of ROP was 29.57%. Bilateral ROP was found in 76.29% with nearly equal stages in both eyes and only 23 neonates showed unilateral involvement.

Conclusions: Low birth weight, lower gestational age, blood transfusion, Respiratory Distress Syndrome (RDS), apnoea, supplemental oxygen therapy, maternal anaemia and gestational diabetes mellitus (GDM) were strongly associated with development of ROP.

Keywords: Hyperoxia, Lasers, Retinopathy of prematurity, Risk factors

INTRODUCTION

Retinopathy of prematurity is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age.¹ Both eyes are affected but the severity of retinopathy may vary between the two eyes. Vascular endothelial growth factor (VEGF) signalling is important in both physiologic and pathologic developmental angiogenesis. Based on studies in animal models of oxygen-induced retinopathy (OIR), exogenous factors such as oxygen levels, "oxidative stress," inflammation, and nutritional capacity have been linked to severe ROP through dysregulated signalling pathways involving hypoxia inducible factors and angiogenic

factors like VEGF, oxidative species, and neuroprotective growth factors to cause "phases" of ROP.² The possible mechanism of injury suggested is vasoconstriction, increase in level of vasogenic factors and compensatory neovascularization leading to retinal and extra retinal fibrovascular proliferation and retinal detachment. ROP mostly affects to neonates with birth weight of under 1500gm as per AAP (American Academy of Pediatrics) and 1750gm as per NNF (National Neonatal Forum) and gestational age less than 30 weeks and 34weeks according to AAP and NNF respectively.³ In India, approximately, 1 in 1000 children is blind, and the incidence of ROP is reported between 24% and 47%.^{4,5} The aim of the study was to estimate the incidence, to

identify the risk factors which predispose to ROP, and to assess the outcome of these cases.

METHODS

This hospital based prospective study was undertaken during October 2016 to September 2018 in the department of Ophthalmology, SCB Medical College. All the patients examined were admitted to SNCU (Sick Newborn Care Unit) of SCB medical college, SNCU and NICU (Neonatal Intensive Care Unit) of Sardar Vallabh Bhai Post Graduate Institute of Pediatrics (SVPPGIP), Cuttack, were taken for study as per the inclusion criteria given below.

Inclusion criteria

- All preterm infants weighing less than 1750gm or gestational age less than 34 weeks at birth,
- Infants with birth weight between 1750gm to 2000gm and gestational age more than 34 weeks who were considered as high risk with risk factors such as anemia, sepsis or history of oxygen supplementation, blood transfusion were included.

Exclusion criteria:

- All patients more than or equal to 34 weeks of gestational age without any risk factors,
- Critically ill patients,
- Patients with major congenital malformations,
- Whose parents did not give consent for the study and
- Babies those lost to follow up for 6 months.

All the findings of the clinical examination were noted in a predesigned proforma.

Recording of findings

Screening of ROP was done by indirect ophthalmoscopy using +20 D lens. The findings were recorded using universally acceptable graphical representations and standard notation from the CRYO-ROP and STOP-ROP.

Initial screening

We followed initial screening of all preterm neonates born at or after 28 weeks; at 3-4 weeks after birth or at the time of discharge from the hospital whichever is earlier. Neonates born before 28 weeks were screened initially at 2-4 weeks of life or at the time of discharge from the hospital whichever is earlier.

The policy of early screening was followed to avoid missing any case of potentially dangerous aggressive posterior ROP and to create awareness among parents about this potentially dangerous, yet preventable cause of blindness and to enroll the babies for follow-up ROP screening in their subsequent hospital visits.

Follow-up eye examination

Follow-up examination intervals were based on retinal findings and these findings were classified according to the Revised International Classification of ROP (ICROP). For each infant who had ROP the maximum stage, site, therapy for ROP was recorded and the time for next examination fixed. Infants who had no ROP were followed-up every 2 weeks till retinal vascularization was complete or till disease was stable. Infants in whom ROP was detected were followed-up every week.

Statistical analysis

Statistical analysis was done using SPSS 20.0.1 and Chi-square calculator. A 'p value' of less than 0.05 was taken as statistically significant.

RESULTS

During the study period a total of 2320 newborns were screened. Out of these 514 babies were eligible for screening of ROP. A total of 186 babies were excluded from the study because they became critically ill or died or lost to follow-up before 6 months.

Only 328 babies who completed follow-up (including those who developed ROP) were taken for the study.

The incidence of ROP in our study was 29.6%. Authors observed no gender predilection (M: F: 1.01:1). Bilateral involvement was more common. More ROP cases were from rural areas. Babies of parents of low socioeconomic status were more affected than parents of middle or high economic status. (Table 1)

Most infants were in Stage I ROP and no infants were detected with stage V ROP. (Table 2)

With respect to birth weight the incidence of retinopathy was as follows-32(52.45%) of neonates weighing less than 1000, 55(24.77%) of the 222 neonates weighing between 1001-1500g and 10(22.22%) of infants weighing between 1500-2000 gm. developed ROP. Of the 79 infants who fell in the gestational age group <28 weeks 41(51.89%) developed ROP. Of the 176 infants in the 28-32 weeks group 32(18.18%) developed ROP. (Table 3)

In 32-34 weeks gestational age group 18(31.03%) out of 58 neonates and 6 out of 15 infants who fell in gestational age group >34 weeks developed ROP. In this study, out of 217 babies, who received oxygen therapy for at least 5 days, 78 babies (35.94%) developed ROP. Of the 126 (38.4%) infants who had apnea attacks, 54(42.9%) developed ROP and of the total 202 (61.64%) infants who had no apnea attacks 43(21.3%) developed ROP. Babies who received packed cell transfusion 33 38.37% developed ROP.

Table 1: Incidence of ROP in different categories.

Sex	No. of infants observed	Infants with ROP	ROP									
			%	Laterality			Habitat			Socioeconomic status		
Male	172	51	29.6	UL	BL	T	U	R	T	*BPL	**APL	T
Female	156	46	29.4	23	74	97	31	66	97	61	36	97
Total	328	97	29.57	23.71%	76.29%	100%	31.95%	68.05%	100%	62.88%	37.22%	100%

BPL-below poverty line, **APL- Above poverty line, UL-unilateral, BL-bilateral, T-total, U-Urban, R-Rural.

Table 2: Distribution of stages of ROP.

Stages	Number of infants	% of ROP
STAGE I	48	49.48
STAGE II	35	36.08
STAGE III	12	12.37
STAGE IV	2	2.06
STAGE V	0	0
TOTAL	97	100

Table 3: Incidence of ROP with reference to different parameters.

Parameter	ROP		Total	%	p value	
	Present	Absent				
Birth weight	<1000	32(52.45%)	29(47.54%)	61	18.59	0.0001
	1001-1500gm	55(24.77%)	167(75.22%)	222	67.6	
	>1500gm	10(22.22%)	35(77.77%)	45	13.71	
Gestational age	<28weeks	41	38	79	24.08	<0.00001
	28-32weeks	32	144	176	53.65	
	32-34weeks	18	40	58	17.69	
	>34weeks	6	9	15	4.57	
Oxygen therapy (more than or equal to 5 days)	yes	78	139	217	66.15	0.0004
	no	9	92	111	33.85	
Blood transfusion	yes	33	53	86	26.21	0.0374
	no	64	178	242	73.78	
Apnea	yes	54	72	126	38.4	<0.00001
	no	43	159	202	61.6	
Sepsis screen positive*	yes	61	122	183	55.79	0.0937
	no	36	109	145	44.21	
PDA	yes	13	21	34	10.37	p=0.242
	no	84	210	294	89.63	
RDS	yes	26	30	56	17.08	0.0024
	NO	71	201	272	82.92	

*culture proven / clinical suspicion with positive sepsis screen or culture negative sepsis treated with antibiotics for >5-7 days.

The association was found to be significant (p=0.0374). ROP was found in 13 neonates (38.23%) of 34 PDA patients and 84 (28.57%) of 294 neonates without PDA. Out of the total 57 (17.07%) neonates who developed RDS 26(46.42%) developed ROP while of the 272(82.92%) neonates without RDS 71(26.10%) developed ROP. The association was found statistically significant (p=0.0024).

There was significant association between GDM and ROP. In this study 45.1% babies with maternal anemia, developed ROP while 26.71% developed ROP with no history of maternal anemia. The association was statistically significant. Association of ROP was significantly high in babies whose mothers were not given antenatal dexamethasone. (Table 4)

Table 4: Maternal risk factors and ROP.

Parameters	ROP		Total	%	p-value	
	Present	Absent				
Mode of delivery	NVD	76	187	263	80.1	0.693
	LSCS	21	44	65	19.9	
PIH	YES	8	33	41	12.5	0.131
	NO	89	198	287	87.5	
GDM	YES	19	23	42	12.8	0.0172
	NO	78	208	286	87.2	
Anemia*	YES	23	28	51	15.54	0.0082
	NO	74	203	277	84.46	
Antenatal dexamethasone	YES	27	119	146	44.51	0.0001
	NO	70	112	182	55.48	

*Hb less than 10g% or hematocrit value < 30%. NVD – Normal Vaginal Delivery, LSCS –lower (uterine) segment Caesarean section.

Table 5: management of ROP.

Management	Number of neonates	Percentage (%)
Spontaneous regression	69	71.13
Laser photocoagulation only	18	18.55
Laser photocoagulation and Intravitreal Bevacizumab	8	8.24
Vitreoretinal surgery	2	2.06
Total	97	100

Spontaneous regression occurred in 69 babies (71.13%). Diode red 810 nanometer wavelength laser was used at strength of 250 milliwatts for 150 milliseconds and number of shots varied from 1500 to 2000 depending upon the area extent of retina involvement. Babies (8.24%) those diagnosed as aggressive posterior retinopathy of prematurity (APROP) were first treated with intravitreal anti Vascular endothelial growth factor (VEGF) Bevacizumab to reduce the dilatation and tortuosity of vessels at posterior pole followed by laser photocoagulation after 1 week. Here the number of shots required was higher (ranging from 2500 to 3500 shots) than for any stage of ROP requiring treatment. Two babies (2.06%) with stage 4 plus disease underwent vitreoretinal surgery. The laser photocoagulated babies and babies who had undergone vitreoretinal surgery were followed first after 2 weeks and then at monthly intervals. All the laser photocoagulated babies showed signs of regression of ROP in subsequent visits and the disease became stable in babies who underwent surgery. The final outcomes of these babies were still under study as they are prone for complications of ROP like refractive error, amblyopia, glaucoma and retinal detachment which may develop later.

DISCUSSION

The sex incidence in this study was supported by CRYO-ROP study (66.4% male and 65.3% female; M: F: 1.01:1).⁶ Although there are some reports indicating a male predilection of ROP, the CRYO-ROP study

revealed no difference based on sex. The incidence in this study is comparable to the 29.2% incidence in Shah et al study, 25.45% incidence in Adhikari S et al, study, 31.9% in Teoh et al, study and 22.3% incidence in Chaudhary S et al, study. A total of 97 patients were diagnosed to be ROP out of 328 patients.^{4,5,7} Thus the incidence of ROP in this study was 29.57%. The present study however shows lower incidence of ROP in comparison to many other studies like 60.1% in Ng et al, (U.K), 40.4% in Holmstrom et al, 46% in Rekha S et al, 45.57% in Sood V et al 41.5% in Hungi B et al and 38% in Gopal L et al.⁹⁻¹⁴ The possible causes may be: I. High dropout rate from my study (36.18%) due to illiteracy, ignorance of the disease, less child care mentality. II. Poverty, low education and poor awareness among the parents and lesser knowledge by the treating physician about the potential but preventable cause of blindness. III. Critically ill babies or those with major anomalies usually succumb or loss to follow-up before full vascularization of the retina. Hence comparison among studies must be made cautiously because a number of associated factors such as difference in inclusion criteria, variable methods of assessment, level of education of the general population influence the outcome of a study. Though this hospital is a tertiary care hospital people from different places come for treatment; there are also private hospitals exists in this locality. So, many families living in urban area prefer for private hospitals to avoid the crowd and long waiting time. Hence this study shows babies of parents living in rural area were more affected than urban area. Low awareness about the disease, poor antenatal

care of the mother and poor availability of basic needs are the possible causes of high incidence of ROP in babies of parents belonging to below poverty line. Stage I ROP was found in 48 babies, 35 had stage II ROP, 12 babies had stage III ROP, 2 had stage IV and no babies had stage 5 ROP. Out of these, 22 babies had plus disease.

In the study by palmer et al as part of the CRYO-ROP study, 38.29% babies were found with stage 1, 32.97% in stage 2 and 27.81% in stage 3. No babies were detected in stage 4 or 5 ROP.³ The incidence of ROP in children <1000g is comparable to Gupta VP et al, with incidence of 75% and Rekha S et al, with incidence of 73.3%.^{10,15} The babies who developed ROP in the study had significantly lower birth weight ($p=0.00077$) comparable to Maheswari R et al, study, Gopal L et al, study, Shah V et al, study, Charan R et al and Fielder AR et al study.^{4,10,14,17,18} The association of gestational age to incidence of ROP was found to be significant ($p<0.00001$) in this study. This is supported by Hussain N et al, study, Shah VA et al, study, Charan R et al study, Nødgaard H et al, study, Ng YK et al, study and Yang CS et al, study.^{9,19-21} However, there was higher incidence of Retinopathy in larger babies (>34 weeks) with established risk factors. 6 out of 9 larger babies with risk factors screened, developed ROP (40%), which was significantly higher. This is supported by Kim HY et al, study who conducted study on term babies with retinopathy similar to retinopathy of prematurity.²² Chen LN et al, found an incidence of ROP in 29.3% of full term babies and Ratra D et al, found stage I and II ROP in 21.7%, threshold disease, plus disease in 26% and stage IV, V in 30.4%, which is comparable to this study.^{23,24} Significant association between oxygen therapy and development of ROP was noted in many studies. In this study, out of 217 babies, who received oxygen therapy for at least 5 days, 78 babies (35.94%) developed ROP. The association was found to be statistically significant ($p=0.0004$), which is supported by Chaudhary S et al, Rekha S et al, Patz et al, and Saugstad OD et al.^{8,11,25,26} Apnea and mechanical ventilation are well known factors for ROP development. The association was found to be extremely statistically significant ($p<0.00001$) which is supported by Simth J et al, and Chaudhary S et al.^{8,27} In this study 33 out of 86 babies (38.37%), who received packed cell transfusion, developed. The incidence of ROP was higher in babies without anemia, probably due to associated factors such as blood transfusion, prematurity, low birth weight, etc.; this was supported by several studies such as Englert JA et al, which found that anemia did not affect the severity of ROP as an independent risk factor, however, the number of transfusion were associated with highest stage of ROP.²⁸ Similar finding were suggested by Bifano et al, Brooks et al, Dani et al, and Sullivan et al.²⁹⁻³² Yang CS et al, concluded that sepsis in the low birth weight premature infants is frequently accompanied by hypotension which will impair tissue perfusion with local hypoxia to render retina under the risk of development of ROP.²¹ Recent studies such as Maheswari et al, Shah VA et al,

Varughese S, et al, etc on ROP in India had showed significant association between these factors.^{4,16,33} However, in this study, no significant association was found between sepsis and development of ROP. In this study, the association between PDA and development of ROP was not found to be statistically significant ($p=0.242$), like the study of Sood V et al.¹² ROP in RDS was supported by Teoh SL et al, study, Murthy et al, study, Sood et al, study and Chou YH et al.^{7,34,35} There was significant association between GDM and ROP ($p=0.0172$), which was supported by study Tunay ZO et al.³⁶ However, a study by Sumru Kavurt et al, found no association between GDM and ROP ($p=0.622$) ROP and mode of delivery which was not statistically significant ($p=0.693$) similar to the study by Hungi B et al. Holmstrom G et al. found in their study by multiple regression analysis, apart from gestational age and birth weight, only essential hypertension prior to pregnancy was a predicting risk factor.^{10,13,37} Sood V et al, found PIH to be a significant risk factor ($p=0.006$) for development of ROP.¹² However, in this study 8 out of 41 babies (19.59%) with maternal history of PIH developed ROP. There was no association between maternal PIH and ROP ($p=0.131$), similar to the study of Murthy et al. There was significant association between GDM and ROP ($p=0.0172$), which was supported by study Tunay ZO et al.³⁶ In this study, 23 out of 51 babies (45.1%) with maternal anemia developed ROP while 74 out of 277 babies (26.71%) developed ROP with no history of maternal anemia.³⁴ The association was statistically significant ($p=0.0201$), which is supported by Hammer et al, study and Sood V et al, this result of ROP and dexamethasone use was statistically significant which was supported by Rosemary D Higgins et al, and Sobel DB et al.^{12,38-40}

CONCLUSION

In this study, incidence of ROP was found to be greater with lesser birth weight and showed significant statistical correlation with prematurity, supplemental oxygen therapy, apnea, blood transfusion and RDS. Maternal risk factor such as GDM and maternal anemia were found as significantly associated with ROP. There exists a statistically significant correlation between administration of dexamethasone to mother and reduce risk of developing ROP. Spontaneous regression was in 71.13% neonates, 28.87% patients required treatment either as laser only or laser with intravitreal Bevacizumab injection or vitreoretinal surgery. After treatment all neonates showed regression of ROP during follow up period.

So, this study can be taken as a reference study for further studies in future. Still it requires a larger sample size and longer period of study and measures must be taken to reduce drop-out rates so that a clearer picture of actual incidence and associated risk factors of the infants can be extrapolated to entire population in this country.

Limitation of this study due to small sample size authors cannot reach in a conclusion about the significance of these associations. Further studies with large number of samples are required to draw any inference about gender predilection.

What this study adds to the existing knowledge?

The present study contributes to the knowledge of development of ROP in preterm infants as well as late preterm and term infants with risk factors.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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