



Incidence and Risk Factors of Retinopathy of Prematurity (ROP) in Neonates of Weight 1.5 to 2 kg

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Abstract

Objective :- To find incidence and risk factors of ROP in neonates of birth weight 1.5-2 kg.

Methods: - All the neonates admitted in NICU at GMC, Amritsar from August 2014 to July 2015 with birth weight 1.5-2 kg were enrolled and followed up for all neonatal problems and interventions and screened for ROP by indirect ophthalmoscope at 4 weeks of postnatal age and followed up till retinal vascularization was complete. Neonatal risk factors including diseases and various interventions and treatment given to them were noted and data was analyzed statistically.

Results: - A total of 70 children were screened for ROP, 12 of them were diagnosed with retinopathy of prematurity. Thus, incidence of ROP was 17.1%. 11 of them had stage 1 ROP, 1 had stage 2 ROP with plus disease. On univariate analysis, sepsis and oxygen duration of more than 7 days were significantly associated with development of ROP. None of the risk factor was independent predictor of ROP on logistic regression analysis.

Conclusion: - Neonates with birth weight upto 2 kg having sepsis and oxygen therapy duration of more than 7 days and having other risk factors should be screened for ROP as they can develop ROP including threshold ROP.

Keywords: Retinopathy, prematurity, sepsis

Introduction

Retinopathy of prematurity is a fibro vascular proliferative disorder, affecting the peripheral retinal vasculature in premature infants. It is a preventable cause of childhood blindness.¹ It was first identified by Terry in 1942 who termed it Retrolental Fibroplasia. The term ROP was coined by Health in 1951.² The control of blindness is given a high priority in WHO Vision 2020 (Right to sight) program.³ Globally there are estimated 1.4 million children blind due to any cause.⁴ Retinopathy of prematurity is one of several factors causing childhood blindness. First epidemic was reported in 1940 -1950 in Europe and North America occurring primarily in larger and more mature babies with unmonitored supplemental oxygen being the major risk factor.⁵ At present, in developed countries the majority of babies getting severe ROP weigh less than 1000 g at birth so the cause of ROP is prematurity rather than unregulated oxygen which is termed a "second epidemic."⁶ India, like other middle-income countries is experiencing the 'third epidemic' of blindness due to ROP which is a mixture of the first two epidemics meaning that both premature and relatively mature babies are being affected⁷. The number of babies with ROP in India will be equal to number of babies having ROP in rest of world put together.

Many studies have reported ROP occurring in relatively bigger and more mature babies with birth weight > 1500 gm and GA > 34 weeks in our country. The population of 1500 gm to 2000 gm is unique and less well studied in the past in terms of incidence and risk factors for developing ROP in this population. Present study was undertaken to address this issue.

Materials and Methods

This prospective cohort study was conducted in Neonatal Intensive Care Unit(NICU), Govt. Medical College, Amritsar, on infants with birth weight of 1.5 -2 kg from August 2014 to July

2015. Total one hundred and sixty three neonates of birth weight 1.5-2 kg were admitted. 93 babies could not be screened due to death, exclusion due to congenital malformations and loss to follow up. 70 infants were followed up as per protocol and included in the study. On admission, babies were examined and managed as per existing medical conditions and as per unit protocol. The babies were weighed at birth, other demographic information obtained and entered in the study questionnaire which included the gender, mode of delivery, neonatal risk factors i.e. birth asphyxia, sepsis, apnea, NEC, HIE, pneumonia, hyperbilirubinemia, seizures, meningitis, HMD and treatment modalities given to babies documented in questionnaire i.e. any use and duration of supplemental oxygen, phototherapy, surfactant, exchange transfusion, blood transfusion, IVF, type of feeding.

Detailed Eye examination of all the babies were conducted by a single ophthalmologist at 4 weeks postnatally. Pupillary dilatation was achieved with a mixture of 2.5% phenylephrine and 0.5% tropicamide instilled 3 times before the scheduled examination. Topical anaesthetic 2% proparacaine was used. The examination protocol included examining the fundus using an indirect ophthalmoscope with 20 D lens or 28 D lens. The retinal findings were documented carefully in examination sheets as per guidelines of ICROP. Follow-up examinations were conducted until full vascularization of retina reached zone 3 or until full remission of ROP after treatment.

Data was analyzed statistically. The incidence rate of ROP was described in simple proportion. By using the chi-squared test, Univariate analysis of risk factors between 2 groups i.e. with and without ROP was done. A logistic regression model was performed and the adjusted OR (95% CI) was obtained for the risk factors which had been shown to be significant in univariate analysis. A probability (p) of less than 0.05 was considered significant.

Results

In our study, out of 70 neonates, 12 developed ROP as shown in Table no.1.

Table No 1: Incidence of ROP

No. of Neonates	ROP Present	ROP Absent
70	12 (17.1%)	58 (82.9%)

The incidence of ROP was 17.1% and 11 of them were having stage 1 ROP, 1 of them was having stage 2 ROP with plus disease. No one had stage 3 or stage 4 ROP. Out of 12 cases, 11 of them were having regressive ROP, which did not required treatment.

Table no. 2 shows various neonatal diseases as risk factors for ROP. Sepsis was statistically significant risk factor for ROP development on univariate analysis.

Table no.2 : Neonatal diseases as risk factors for ROP

S. No.	Risk factors	ROP Present(12)	ROP Absent(58)	χ^2 p value
1.	Shock	1	5	0.974
2.	PNA	3	17	0.764
3.	Anemia	3	5	0.105
4.	Apnea	1	1	0.211
5.	Sepsis	10	24	0.008
6.	NNJ	5	17	0.401
7.	HMD	4	7	0.065
8.	NEC	1	1	0.211
9.	Pneumonia	1	4	0.860
10.	Hypoglycemia	0	3	0.421

Table no. 3 shows comparison of treatment modalities between 2 groups with ROP and without ROP. Although surfactant administration (OR = 2.545, 95% CI 0.212 – 30.578 ; p = 0.461), Blood Transfusion (OR = 2.625, 95% CI 0.737 – 9.344 ; p = 0.136), Exchange Transfusion (OR = 2.545 ; 95% CI 0.212 – 30.578 ; p= 0.461), Invasive procedures (OR = 5.182 ; 95% CI 0.301 – 89.222 ; p = 0.257), intravenous fluids (IVF)

(OR = 4.5; 95% CI = 0.860 - 23.547 ; p = 0.075), hood oxygen (OR = 3.286 ; 95% CI 0.659 – 16.385, p = 0.147) were likely to be associated with development of ROP but association was not significant. This data showed that on univariate analysis oxygen administration for more than 7 days was a statistically significant risk factor for development of ROP.

Table no.3 Treatment modalities as risk factors for ROP

S. NO.	TREATMENT	ROP Present(12)	ROP Absent(58)	X ² p value	
1	Resuscitation	2	11	0.852	
2	Phototherapy	3	19	0.598	
3	Surfactant	1	2	0.447	
4	Blood Transfusion(BT)	6	16	0.128	
5	Exchange Transfusion (ET)	1	2	0.447	
6	Invasive procedures(UVC)	1	1	0.211	
7.	Oxygen>7days	7	8	0.001	
8.	IVF>7 days	3	4	0.057	
9.	Mode of delivery of oxygen	Hood	10	35	0.130
		CPAP	6	24	0.583
		Ventilator	1	8	0.607

Table no 4 shows logistic regression analysis of risk factors found significant on univariate analysis and found that oxygen duration >7 days, sepsis were likely to be associated with ROP but

association was not statistically significant ($p>0.05$). Thus, they were not independent predictors of development of ROP.

Table no.4 : Logistic regression analysis of risk factors

S. No.	Risk Factors	p value	Adjusted Odd ratio	Confidence interval
1.	Oxygen>7 days	0.059	4.667	0.945-23.039
2.	Sepsis	0.228	3.187	0.484-21.000

Discussion

Incidence of ROP varies in different neonatal units.^{8,9} Incidence reported by Jalali et al in babies <2000 gm and GA <36 weeks was 11% and by Hungi et al in babies < 2000 gm and GA < 34 weeks was 10.2 %^{10,11}. Vivekar et al reported incidence as high as 44.9% in babies with birth weight >1250 gm¹². Higher incidence of severe ROP in more mature and bigger babies (mean birth weight 1488 gm for threshold ROP) has been reported by Shah et al¹³. Sanghi et al reported aggressive posterior ROP (APROP) in infants more than 1500 gm in our country¹⁴. Although supplemental oxygen therapy has been considered the main risk factor in the past, several recent studies have suggested a multifactorial basis for ROP development. The risk factors reported in different studies^{15,16,17} are very low birth weight, prolonged mechanical ventilation, repeated blood transfusion, septicemia, hyperoxia/hypoxaemia, hypotension, acidosis, apnea treated by bag and mask ventilation,

oxygen duration for more than 7 days, respiratory distress syndrome, anemia, patent ductus arteriosus, phototherapy , type of feeding.

ROP is an emerging child health problem in our country. The incidence of ROP has increased in the last decades because of the increased frequency of premature births relevant to the developments in assisted reproduction techniques and the advances in neonatology that allows a great improvement in survival rate of more immature neonates.

It has a well known variation in the incidence as well as in associated risk factors among centers and among countries, related to difference in case selection, sampling variability and aspects of both obstetric and neonatal clinical practice¹⁸. Although recent studies have reported increased incidence of ROP in babies >1.5 kg, most of the studies have not suggested their inclusion in the screening program.

The incidence of ROP in our study was 17.1%. Our incidence was similar to 19.2% reported by Hakeem et al¹⁹, 18.5% reported by Aggarwal et al²⁰. Similarly Jalali et al and Hungi et al reported incidence of 11% and 10.5 % respectively^{10,11}. Shah et al and Sanghi G et al reported threshold ROP and APROP in infants more than 1500 gm babies respectively^{13,14}. The incidence in our study was much lower than 35.1% reported by Bettegowda et al²¹ and 47.2% reported by Adedayo et al²². These differences may be due to differences in gestational age, birth weight, quality of infant survival and health care activities and other related factors such as ethnicity and race, limited sample size, loss to follow up. In our study, out of total ROP (12 cases), we found stage 1 ROP in 11 (91.7%), stage 2 ROP with plus disease in 1 (8.3%). No case was diagnosed with ROP stage 3, 4. Our result was comparable to as reported by Adeodyo et al²² who found 84% stage 1, 12 % stage 2 with no plus disease, 4% with threshold disease, none had stage 3,4. Out of total ROP cases in our study, 91.7 % were having regressive ROP and recovered without treatment and 8.3% were having progressive ROP and required laser treatment, which was similar to as reported by Sariyadin et al.²³

The presence of sepsis in our study was a significant risk factor for ROP on univariate analysis but not an independent predictor of ROP on logistic regression analysis. In the literature, this association has already been described by Shah et al²⁴, Babei et al²⁵, Bassiouny et al¹⁵, Bettegowda et al²¹. Sepsis is frequently accompanied by hypotension, which may impair tissue perfusion and release of angiogenic factors (VEGF, IGF-1) secondary to hypoxic stress resulting in ROP.

In our study, the duration of oxygen administration for more than 7 days was a significant risk factor on univariate analysis for development of ROP and this agreed with Shah et al²⁴, Ikeda et al²⁶.

In our study, the mechanical ventilation and CPAP were non-significant risk factors for ROP and this was in agreement with Hakeem et al¹⁹, Abrishami et al²⁷. However, Shah et al²⁴ in their

study observed significant association between mechanical ventilation, CPAP and ROP. In summary different studies have shown some differences in risk factors for ROP.

So in India we are facing third epidemic due to more preterm births, increased survival of preterms, unregulated and unblended oxygen, less awareness in pediatricians about saturation targets, ROP screening and lack of trained ophthalmologists. In India large and more mature babies are being affected due to above reasons and different studies may come with different incidences and different risk factors but we need to screen larger and more mature babies as well. So NNF has recommended screening for babies less than 1750 gm and or <34 weeks Gestation. Also babies with gestation of 34-36^{6/7} weeks and who remained sick (sepsis, shock) and received ventilation and prolonged oxygen should also undergo ROP screening. In view of the current scenario RBSK guidelines of 2015 has recommended ROP screening of babies upto 2000 gm, >34 weeks with risk factors and any baby considered at risk by Pediatrician. There should be focus on prevention with target saturation in babies <28 weeks as 90-95% and in more mature babies in range of 88-93%.

Conclusion

Hence the study concluded that neonates with birth weight 1.5-2 kg do develop ROP, which may require treatment. Neonates having sepsis and/or received oxygen for more than 7 days or having other risk factors are at high risk for development of ROP including threshold ROP and APROP. Thus, screening for ROP is also recommended in neonates with birth weight up to 2000 gm and or gestation >34 weeks if they were exposed to one or more risk factors. Judicious use of oxygen in low birth weight babies, following the guidelines on target saturations and prevention and effective treatment of sepsis is recommended to avoid the development of ROP so as to reduce the burden of blindness.

Abbreviations

ROP:Retinopathy of prematurity
 VEGF:Vascular Endothelial Growth Factor
 IGF1:Insulin Growth Factor 1
 NNF:National Neonatology Forum
 CPAP:Continuous Positive Airway Pressure
 NEC:Necrotising Enterocolitis
 HIE:Hypoxic Ischemic Encephalopathy
 WHO:World Health Organisation
 HMD:Hyaline Membrane Disease

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