Original Article

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Retinopathy of Prematurity (ROP): A Curse for Low Birth Weight Neonates

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Abstract

Introduction: Advances in neonatology and ventilator systems, results in exposure of preterm and low birth weight babies to high oxygen concentration there by leading to initiating ROP. This study was done to identify the incidence, risk factors, for the ROP formation in Neonatology ICU at a tertiary care hospital in South India. *Methods:* Pre term babies with gestational age less than 32 weeks and wright less than 1750 gm were included in the study. Babies were followed up till complete vascularization of retina. Risk factors and details of ROP were recorded in the proforma. *Results:* Seventy two babies were thus examined. The incidence of ROP is 8.33% in the study group and it peaks at 38.46% in babies ≤ 30 weeks gestation and/or ≤ 1250 gm birth weight. RDS, Apnea, Sepsis, oxygen administration, ventilation, hyperoxia and hypoxia are independent risk factors significantly associated with ROP ($p<0.05$). *Conclusion:* Ongoing ROP screening programme is recommended to all babies ≤ 32 weeks gestation age and/or ≤ 1750 gm birth weight at 4 weeks after birth by indirect ophthalmoscopy. Screening of babies ≤ 30 weeks gestation and /or ≤ 1250 gm birth weight would be more cost effective. It would detect the more severe stages of ROP easily enough to permit treatment, reduce unnecessary examinations and avoid wastage of time and manpower. Screening should be intensified in the presence of riskfactors.

Keywords: ROP; Pre-Mature Baby; Hyperbaric Oxygen; Cryotherapy.

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Introduction

Retinopathy of prematurity (ROP) is a proliferative disorder of the retinal vessels peculiar to premature infants. The disease is entirely asymptomatic in early phase and has the potential of progressing to severe visual impairment [1]. Long term morbidity have a spectrum ranging from mild myopia to blindness. 90% of cases of ROP go on to spontaneous regression with little or no visual loss, fewer than 10% of the involved eyes progress to significant visual loss [2]. Hence detection of ROP require on going screening programme.

Advances in neonatology and increased survival of preterms have increased population of babies at risk for developing ROP. Although there are other risk factors, the incidence of ROP is inversely related to gestational age and birth weight with the greatest at risk group being in the low birth weight babies under 1500 grams, and especially infants with very low birth weight of less than 1000 grams [3].

Oxygen exposure, apnea, septicemia ventilation, respiratory distress syndrome blood transfusion, hypoxia, hyperoxia, hypercarbia, hypotension and intracranial hemorrhage are well recognized risk factors of ROP [4].

Studies in the literature use a cutoff point for high risk prematurity of a birth weight of 1,251gm or 1,501gm a gestational age of 32 or 28 weeks or both. The incidence of ROP is going to be higher if

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a lower weight (i.e. 1250gm) is used as the cutoff point. Study by the cryotherapy for retinopathy of prematurity co-operative group found evidence of ROP in 65.8% infants weighing less than I251g and in 80% of infants weighing less than 1,000 gm [5].

Reports from developing countries indicate that although the trend in ROP is not similar in all the units, there is an overall decrease in the incidence of disease wherever there is on going surveillance programme. Aggarwal and co-workers noted a drop in the overall incidence of ROP from 32% to 20% over a period of 8 years (Table1) [2].

Table 1: Incidence of ROP

Indian Studies	Inclusion criteria		Incidence
	GA (wks)	BW (gm)	
Dutta [12], 2004	≤ 32	≤ 1700	21%
Gupta [13], 2004	≤ 32	≤ 1250	21.7%
Maheshwari [14], 1996	≤ 35	≤ 150	20.0%
Pati [l4], 1997	≤ 32	≤ 1250	17.5%
International studies			
Conrath [11], 2001	≤ 32	≤ 1500	9.4%
Fledelius [15], 2000	≤ 32	≤ 1750	10%
Chye [16], 1999	≤ 37	≤ 1250	15.0%
Nair [17], 2003	≤ 32	≤ 1500	25.4%

Risk Factors for Development of ROP

ROP is a multifactorial disease and based on clinical and epidemiological studies, numerous risk factors for ROP have been proposed. Prematurity and oxygen are well recognized and accepted while others are controversial [6].

Definitive and well accepted

- Prematurity/ Gestational age (< 32 or 28weeks)/ Birthweight (< 1750gm)
- Oxygensupplementation

-Oxygen is the prime factor suspected of causing the initial insult leading to ROP. The concentration and fluctuation of oxygen are key factors. Sudden discontinuation of oxygen and duration of oxygen therapy are also incriminated in the pathogenesis of ROP [5].

-A definite safe range for arterial PaO_2 is not know, nor we know the critical duration of oxygen exposure. Until such guidelines are established, keeping PaO_2 < 100 m Hg is recommended preferably between 50 and 70 mm Hg and saturation between 90-95%.

Other associated risk factors

RDS	Hypercarbia/ Hypocarbia
Apnea of prematurity	Metabolic acidosis/ alkalosis
Septicemia	Ventilation
Blood transfusion	ICH
Hyperoxia/ Hypoxia	Hypotension
Asphyxia	Surfactant
	Vitamin E deficiency

Although ROP has been recognized as an important cause of blindness in developed countries for some years, it is now becoming more significant in developing countries. The world health organization's "vision 2020 programme" targets ROP as an avoidable disease requiring early detection and treatment to prevent blindness. As described by vision 2020, recent research has resulted in strategies that have been successful in reducing the incidence of ROP [7].

Current treatment options are expensive and can have potentially serious complications, thus prevention is still the best strategy available at present to avoid visual deficits caused by ROP [7]. Treatment options available are – retcam for follow up of the neonate, Cryotherapy, endolaser photocoagulation, pars planavitrectomy.

Aims

To identify the incidence and risk factors of ROP

Materials and Methods

-Informed consent of parents was taken after explaining in detail about the methods and procedures involved in the study in their own vernacular language. Institutional ethical committee clearance was taken.

- Prospective observational study , conducted in tertiary care hospital in South India
- 72 babies were included in the study
- The study period was one year

Inclusion Criteria

- Babies with gestational age 32 week orless.
- Babies with birth weight 1750gm orless.
- Babies with birth weight 1750-2000gm and 32-35 weeks of gestational age having sepsis, Apnea, Blood transfusion, respiratory distress syndrome and O_2 supplementation.

Methodology

Detailed history and risk factors were documented using a structured proforma. Sepsis was clinically suspected and confirmed by blood culture. Apnea is defined as cessation of respiration for ≤ 20 seconds or accompanied by bradycardia. Standard definitions were used to define other risk factors (Table 2). Gestational age was assessed by New Ballard Score.

Table 2: Risk factor definition

Metabolic acidosis	pH <7.25
Alkalosis	pH >7.45
Hypoxia	PaO_2< 50mm of Hg.
Hyperoxia	PaO_2 > 100 mm of Hg.
Hypercarbia	$PaCO_2$ > 50 mm of Hg.
Hypocarbia	$PaCO_2$< 25 mm of Hg.

Examination of eye for ROP was done by indirect ophthalmoscopy after dilating pupils with topical mydriatics (1% tropicamide + 2.5% phenylephrine) used twice or thrice at 15 minutes interval. The first indirect ophthalmoscopic examination was performed in NICU at 4-6 weeks of chronological age or 32 weeks of postconceptional age whichever was later by the same ophthalmologist and was not informed about the babies clinical details to eliminate the possibility of a biased examination. Feeding was avoided 30 minutes before examination neonatologist was present during examination of unstable babies. All aseptic precautions were taken and speculum used wherever necessary. If no ROP was detected at initial examination the infants were re-evaluated every 2 weeks until complete vascularization of retina. If ROP detected, frequency of follow up examination was decided by ophthalmologist based on stage of ROP. Details of ROP were recorded in the proforma as per International Classification of ROP [8].

Results

General Data

Seventy two (72) babies satisfying the inclusion criteria were included in the study. The incidence of retinopathy of prematurity is 8.33%. The mean gestational age of babies screened was 32.43 ≤ 1.89 weeks. The range of gestational age was 28 wks – 36 wks. Three fourth of them were more than 32 wks and 6.9% of them were below 29 wks. The mean birth weight of babies was 1544.48 ≤ 285.96 gm, 55.5% of them were above 1500 gm. Only 15.3% of them were below 1249 gm. The range of birth weight was 850 to 2000 gm. 61.2% of babies were inborn. 46 babies were males and 26 babies were females. Male: Female ratio is 2:1. No significant correlation of sex with ROP was found (p value =0.87)

Rop Profile

- 4 babies had stage I ROP (66.66%) and 2 babies had stage II ROP (33.33%). 4 (66.66%) babies had zone III ROP and 2 babies (33.33%) in zone II.

- Mean gestational age at which complete vascularization of retina was evident is 39.15 wks. 37.5% of babies had mature retina at 40 wks of gestational age.

- Mean gestational age of babies with ROP is 29.83 ≤ 1.33 wks. 83.3% i.e., 5 out 6 babies were below 30 wks of gestational age. Range is 28-32 wks. The incidence of ROP was found to be significantly inversely proportional to the gestational age of babies (p = 0.001).

- Mean birth weight of babies with ROP is 1228.33 ≤297.34 gm range is 900 gm to 1600 gm. 83.3% were below 1250 gm and one baby was 1600 gm. The incidence of ROP was found to be significantly inversely proportional to birth weight (p=0.004). Observation noted in our study that ROP was most common in babies less than 1250 gm and 32 wks of gestational age was also statistically significant (p=0.001).

- All six babies who developed ROP needed respiratory support and received oxygen. Four babies were ventilated. Two third of them had sepsis and apnea. 50% developed RDS, hypoxia and hypotension. Hyperoxia (PaO_2 > 100 mm Hg) was seen in all babies where as 50% of babies had hypoxia (PaO_2 < 50 mmHg). Half of them received blood transfusion and one baby had grade II intraventricular hemorrhage. Surfactant was administered in 33% of babies To establish association of ROP with risk factors, we proceeded to analyze data with univariate and multivariate analysis. (Tables 3,4). From univariate analysis, risk factors significantly associated with ROP are apnea, sepsis, oxygen, ventilation, hyperoxia, hypoxia and RDS. On multiple logistic regression analysis, none of the risk factors had statistically significant association with ROP.

Table 3: Univariate analysis of risk factors

Risk factors	Total babies	Babies with Rop	P value	Significance
BW (<1750 gm)	72	6	0.004	S

GA (<32 wk)	72	6	0.001	S
Sepsis	20	4	0.08	S
Apnea	20	4	0.08	S
Blood transfusion	0	3	0.87	NS
RDS	8	3	0.024	S
Oxygen	34	6	0.022	S
Ventilation	11	4	0.002	S
Hyperoxia	22	6	0.001	S
Hypoxia	06	03	0.002	S
Hypercarbia	03	00	0.913	NS
Metabolic acidosis	08	0	0.8921	NS
ICH	01	01	0.83	NS
Hypotension	14	03	0.151	NS
Surfactant	06	02	0.123	NS

Table 4: Multivariate analysis of risk factors

Risk	No. of factor	ROP cases	Estimation of parameter	Standard error	p. values
Sepsis	20	4	-5.810	307.335	0.985
Apnea	19	4	-5.816	307.335	0.985
RDS	08	3	0	2	1.000
Oxygen	34	6	0.10	491.901	1.000
Ventilation	11	4	0	2	1.000
Hyperoxia	22	6	22.865	449.332	0.959
Hypoxia	06	3	32.024	1055.432	0.976

Discussion

ROP is likely to become a significant problem in India with improving standards of neonatal care. A review of the literature showed a scarcity of data on the epidemiology of ROP from the Indian sub-continent [2]. Reports from developed countries indicate that although the trend in ROP is not similar in all the units, there is an overall decrease in the incidence of the disease wherever there is an ongoing surveillance programme [9].

Screening of babies with ≤30 wks of gestational age and/or ≤ 1250 gm birth weight in this study would have increased the incidence of ROP to 38.46%. This is comparable with results of Blair [10] (38%) and Conrath [11] (33%).

A question may be asked regarding absence of threshold disease in the present study. ROP is difficult to detect in its early stages but threshold disease is very obvious and cannot be missed by a trained examiner. Similar findings were noted by Patil and co-workers who reported only stage I and stage IIROP [4].

Risk Factors

Though accumulating evidence indicates that ROP is a multifactorial disease, immaturity of retina and a period of hyperoxia are the main contributing etiological factors in the pathophysiology of ROP [12]. In our study, the incidence of ROP was significantly inversely proportional to both birth weight and gestational age (p=0.001).

On univariate analysis, Oxygen administration, sepsis, apnea, RDS, ventilation, hypoxia and hypoxia are significantly associated with development of ROP. This is in comparison to findings of Agarwal [2] and Gupta [13]. In contrast, blood transfusion, which was a significant factor in both studies, is not associated with ROP in our study.

Oxygen

Oxygen administration is an independent risk factor for development of ROP (p=0.02). The causal link between ROP and supplemental Oxygen has been confirmed by controlled trials and clinical studies [14,15]. 17.2% of babies who received oxygen therapy developed ROP in the present study, whereas nearly half of the babies on oxygen therapy developed the disease in other studies [2,13]. Though hyperoxia was seen in 64.7% of babies who received oxygen, only 27.2% of them developed ROP in our study. This difference is due to close monitoring of babies on oxygen therapy by pulse oxymetry and arterial blood gas analysis in ourunit.

Sepsis

Sepsis is an independent risk factor for ROP in the present study (p=0.08) and corroborates with findings of other studies [2,13]. Gupta [13] in his study reported 52% sepsis among babies with ROP. In the present study too, 66% of babies with ROP have sepsis. Its prevention and early treatment may reduce the incidence of ROP.

RDS

RDS is significant independent risk factor in the present study (p=0.02). Of 8 babies who suffered from RDS in the study group, 37.5% developed any stage of ROP. Gupta [13] and associates reported ROP in 33.3% of babies with RDS, comparable to the present study. Surfactant used to treat hyaline membrane disease has been shown to reduce the risk of ROP. 75% of RDS babies received surfactant and only one fourth of them developed ROP. Surfactant did not significantly reduced the incidence of ROP

in the present study (p=0.12).

Apnea

ROP is known to be associated with apnea [2,13]. Two third of babies with ROP have apnea in the present study and is a significant risk factor (p=0.08). This can be compared to 54.1% and 54.5% as reported by Agarwal [2] & Gupta [13] respectively. Its appropriate management may reduce the incidence of ROP.

Ventilation

The present study is in agreement that mechanical ventilation significantly increases the risk of ROP (p=0.002) [2]. It may potentiate the effects of a given oxygen concentration as it is forced into the lungs under high pressure [16]. Agarwal and co- workers [2] reported that 52% of babies who were ventilated developed ROP. In contrast, only 36.4% of ventilated babies have ROP in the present study. This difference may be due to less number of babies we haveventilated.However on multivariate analysis by multiple logistic regression models, none of the factors were significantly associated with ROP.

The limitation of the study is that the sample size is small and may not represent all premature babies in the region. Hence, a large multicentric study is required to establish the true incidence and causal relationship of risk factors associated withROP.

Conclusion

The incidence of ROP is 8.33%. ROP group had mean birth weight of 1228gm and mean gestational age of 29.83wk. Mean gestational age at which complete vascularization of retina was evident is 39.15 week. Using a birth weight ≤ 1750g or a gestational age of ≤ 32wk, or both as criteria for inclusion in this study explains low incidence of ROP. Two third of them had stage I disease in zone III and remaining babies had stage II disease in zone II.

Incidence of ROP was inversely proportional to birth weight (p=0.004) and gestational age (p=0.001) which is statistically significant. 83.3% of babies were below ≤ 1250 gm and ≤ 30 wk of gestation age. Observation made that ROP is more common in babies ≤ 1250 gm ≤ 30 wk gestational age was also statistically significant (p=0.001). Hence, screening of babies with lower birth weight and gestational age would be more cost effective.

The present study clearly highlights the magnitude of the problem due to ROP in Indian preterm babies. The incidence is likely to increase as smaller babies survive, unless a parallel reduction in other risk factors occurs. By preventing prematurity, controlling or minimizing risk factors, and meticulous management sick babies, it may be possible to reduce the incidence of ROP. As the roles of the obstetrician, neonatologist and ophthalmologist are vital; they should work in close co-operation to reduce the incidence and morbidity associated with ROP. We suggest that indirect ophthalmoscopy should be perform edina preterm babies weighing ≤ 1750 gm and ≤ 32 wk gestational age, beginning first at 4 weeks of post natal age. Screening should be intensified in the presence of factors like oxygen administration, sepsis, apnea, ventilation RDS, hyperoxia and hypoxia.

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