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Neonatal Risk factors and retinopathy of prematurity among preterm infants

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Abstract

Introduction: To study the incidence and to identify neonatal risk factors which could influence the development and progression of ROP. **Materials and methods:** A hospital-based, prospective observational study was conducted at neonatal intensive care unit and ophthalmology unit of Amrita Institute of Medical Sciences and Research Centre during period of May 2008 to December 2009 in which babies <32 weeks and <1500gms were included. Preterm infants were screened by pediatric ophthalmologist using indirect opthalmoscopy and retinopathy was graded following the International Classification of ROP. Neonatal risk factors for ROP were assessed by univariate and multiple logistic regression analysis. **Results:** Seventy four infants entered in this case study. Incidence of ROP was 35.1%. In univariate model lower birth weight , lower gestational age , Hypotension requiring ionotropic support , hemodynamically significant patent ductus arteriosus requiring treatment , Anemia , septicemia ,Intraventricular hemorrhage ,apnea, blood transfusion, RDS, oxygen, was associated with a higher incidence of retinopathy of prematurity. In multiple regression gestational age and duration of oxygen found significant. **Conclusion:** Lower gestatinal age, lower birth weight, sepsis, apnea, blood transfusion, duration of oxygen are associated with a greater incidence retinopathy of prematurity. These factors must be prevented and more care for early detection of retinopathy should be conducted.

Keywords: Incidence, Neonatal risk Factors, Preterm Infants, Retinopathy of Prematurity, Screening

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina, which principally occurs in premature children. It was first identified by Terry in 1942 and named retrolental fibroplsia. In many cases it may undergo spontaneous regression or may progress to blindness.

If detected early and timely intervention done, the blindness is preventable [1].

There are approximately 50 million blinds in the world today out of them 30% in Asia. Of the total blindness 4% account for childhood blindness which comes to 2 million. 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. It is estimated that out of 100 preterm infants, 20 to 40 develop ROP, out of which 3-7 become ultimately blind [2].

Improved neonatal care has increased the survival of very low birth weight and premature babies and has consequently increased the incidence of ROP [3]. Of several risk factors lower birth weight, younger gestational age and exposure to oxygen are well studied and there are reports from both developed and newer neonatal centers [3-9]. While some risk factors like septicemia, blood transfusions, apnea and anemia have been investigated in Indian centers [7-9],others like , respiratory distress, hyaline membrane disease, icterus, intraventricular hemorrhage and seizure disorder need further study [3,8,9]. The purpose of this study is to know the incidence of ROP in our tertiary neonatal unit, the risk factors and their correlation with retinopathy of prematurity.

Objective

To know the incidence and to identify prenatal factors which could influence the development and progression of ROP.

Materials and Methods

A hospital-based, prospective observational study was conducted at neonatal intensive care unit and ophthalmology unit of Amrita Institute of Medical Sciences and Research Centre during period of May 2008 to December 2009.

Source of Data:

Premature and/or low birth weight babies admitted to neonatal intensive care unit or attending neonatal follow-up clinic at amrita institute of medical sciences.

Inclusion Criteria:

1. Babies born ≤ 32 weeks of gestation.
2. Babies whose birth weight is ≤ 1500 gms.

Exclusion Criteria:

1. Babies who did not complete follow up up to complete vascularisation of retina.
2. Babies with ocular disorder which interfere with fundus examination.
3. Babies with congenital retinal abnormalities

All eligible babies were screened at Neonatal Intensive Care Unit where temperature is well controlled and the place to handle any emergencies. The pupils were dilated using 2.5% phenylephrine and 0.5% tropicamide eye drops instilled three times into each eye at intervals of 15 minutes about one hour before the scheduled examination. Indirect ophthalmoscopy was performed by Pediatric Ophthalmologist well trained in ROP screening using a 20D lens and all infants were screened by same ophthalmologist.

First examination:

For babies born before 28 weeks, the first examination was at 4 weeks postnatal age (PNA: age in weeks after birth) or 32 weeks post-conceptional age (PCA: gestational age at birth plus the PNA), whichever was earlier. For this purpose, gestational age was calculated from the last menstrual period, where available, or based on New Ballard score. Babies born after 28 weeks of gestational age were seen at two weeks after birth.

Follow up protocol:

If no ROP was detected at initial examination, the infants were re-evaluated once every two weeks until vascularisation was complete. If ROP was detected, the examinations were performed weekly for stage 1-2 disease and more frequently for stage 3 disease, till the disease started resolving or progressed to threshold stage. Babies showing evidence of regression were followed up till vascularisation was complete.

Demographic and clinical data including sex, gestational age, birth weight and neonatal risk factors were collected by administrating a predetermined check list.

Statistical analysis:

The student ‘t’ test was used to determine whether there was a statistical difference between two means. The association between potential related risk factors with ROP and without ROP were studied initially through an Univariate analysis. The categorical variables were assessed using Pearson chi-square. To estimate the independent effect of the factors that were significantly associated with ROP and without ROP the confounding effect they may have on each other, logistic regression analysis was done. In all the above test the “p” value of less than

0.05 was accepted as indicating statistical significance. Data analysis was carried out using Statistical Package for Social Science (SPSS, V 16) package. The study was approved by Ethical committee of Amrita Institute of Medical Sciences and Research.

Results

Out of 556 babies admitted to NICU only 74 babies fulfilled all criteria for screening and among these 26(35.1%) had ROP. The incidence of ROP in the study group was 35.1%.

Out of 74 babies screened 44 were male and 30 were female. Among 44 male babies 19 (43.2%) developed ROP and out of 30 female babies 7(23.3%) had ROP.

Distribution by Birth weight:

The birth weight of the ROP babies ranged from 850-1350 gm (mean 1116 ± 231.7 gms), while that of non-ROP babies ranged from 1350-1500 gm (mean 1371 ± 175gms). Lower birth weight was significantly associated with increased incidence (p=.0001)(Table 1) of ROP. Out of 26 babies who had ROP, 19(72.8%) were below 1250 gms.

Distribution by Gestatation age:

The gestational age of the ROP babies ranged from 28 -32 weeks (mean 29.7±1.58weeks), while that of non-ROP babies ranged from 30-32weeks (mean 31.5 ± 1.25 weeks). of these cases of ROP , 4(15.3%) were below 28 weeks , 16(61.5%) were between 28-30 weeks of gestation , 6 (23.1%)cases were above 30 weeks Lower gestational age was significantly associated with increased incidence of ROP (P<0.0001) (Table 1).

Neonatal risk Factors

Clinical Characteristics

These data are summarized in table 2. Babies with ROP had higher incidence of Hypotension requiring ionotropic support, hemodynamically significant patent ductus arteriosus requiring treatment, Anemia (p<0.01). Babies who developed ROP also developed more septicemia (P<0.002), Intraventricular hemorrhage P (<0.0001), apnea (P<0.001).

Blood transfusion used in 21(80.7%) in group with ROP compared to 9(18.8%) in group without ROP (P<0.0001). DVET used in 8(30.8%) in group with ROP compared to 2(4.2%) in group without ROP (P<0.01). No of Blood transfusion & DVET transfusion used in ROP group is more compared to no ROP group which was statistically significant (P<0.01). The incidence of necrotizing enterocolitis, chronic lung disease, hyperbilirubinemia was not statistically different in group with ROP and without ROP.

Respiratory Data:

Severity of respiratory disease, reflected by babies with RDS/HMD (P<0.001), need for surfactant, need for oxygen therapy and also prolonged duration of oxygen requirement and respiratory support in the form of mechanical ventilation requirement were significantly greater in those who developed ROP (P<0.001). Average Fio2 used was 40±10% in ROP group compared to 23.6±3.11% in group without ROP which was statistically significant (P<0.001). Duration of CPAP and airleaks were not significantly difference between ROP and without ROP group.

Multiple logistic Regression analysis

As most of risk factors were functions of immaturity, Multiple logistic Regression model was designed with neonatal risk factors inclusive of, Birth weight, gestational age, RDS, Oxygen therapy, duration of oxygen, Average fio2, mechanical ventilation, apnea, septicemia, hypotension, DVET and blood transfusion .

Table 1: Birth weight , Gestational age and ROP

Risk Factors	ROP (n=26)(%)	No ROP (n=48) (%)	P value
Birth weight in gms (mean +/- SD)	1116+/- 231.7	1371+/- 175	0.0001†
Gestational age in weeks (mean +/- SD)	29.7+/- 1.58	31.5+/- 1.25	0.0001†

ROP - retinopathy of prematurity,† indicates P <0.05 , significant ,Univariate analysis

Distribution of stages of ROP by postconceptional age:

Stage 1 ROP occurred at a median age of 33.8wk. PCA (Post Conceptional Age). Stage 2 was seen at a median age of 35.19 wk PCA. Similarly stage 3 was noticed at median age of 35.86 wk. PCA

Table 2: Neonatal Risk factors and ROP

Risk Factors	ROP (n=26)(%)	No ROP (n=48) (%)	P value
Birth weight in gms (mean +/- SD)	1116+/- 231.7	1371+/- 175	0.0001†
Gestational age in weeks (mean +/- SD)	29.7+/- 1.58	31.5+/- 1.25	0.0001†
Hyaline membrane disease	26(100)	37(77.0)	0.008†
Surfactant given	15((57.6)	3 (6.25)	0.0001†
Oxygen given	26(100)	35 (72.9)	0.003†
Hyperbilirubinemia	26(100)	47(97.9)	0.459
Anemia	20(76.9)	12 (25.0)	0.0001†
Septicemia	13 (50.0)	8(16.6)	0.002†
Patent ductus arteriosus	14(53.8)	3(6.25)	0.0001†
Apnea	13(50.0)	4(8.3)	0.0001†
Hypotension	8 (30.8)	4(8.3)	0.01†
Acidosis	8(30.8)	6(12.5)	0.06
Blood transfusion	21(80.7)	9(18.8)	0.0001†
DVET	8(30.8)	2(4.2)	0.001†
No of Blood transfusion	4.38+/- 6.23	0.58+/- 1.44	0.0001†
No of DVET	0.96+/- 1.48	0.15+/- 0.71	0.01†
Duration of Oxygen in days	20+/- 34.2	1.48+/- 1.37	0.0001†
Average FiO2	40.65+/- 10.75	23.60+/- 3.11	0.0001†

Duration of CPAP	1.54+/-3.31	1.77+/- 2.20	0.719
Duration of Mechanical ventilation	17.23+/-34.31	0.81+/- 2.36	0.001†
Chronic lung disease	1(3.8)	0(0.0)	0.17
Intraventricular hemorrhage	10(38.4)	2(4.2)	0.0001†
Necrotizing enterocolitis	3(11.5)	3(6.25)	0.426
Airleaks	1(3.8)	0(0.0)	0.17

ROP - retinopathy of prematurity,CPAP –Continuous positive airway pressure
DVET – Double Volume exchange Transfusion ,† P <0.05 , significant

Gestational age and duration of oxygen were identified to be factors predictive of ROP(table 3).

Table-3 :Stepwise multiple Logistic Regression of factors related to ROP

Risk Factors	**Odds ratio**	**95%confidence interval**	**P value**
Gestational age	0.054	0.006 – 0.499	P<0.01
Duration of Oxygen	0.007	0.001 – 0.067	P<0.001

Discussion

Retinopathy of prematurity is a bilateral vasoproliferative retinopathy affecting preterm or low birth weight babies which sometimes progresses to cause visual impairment or blindness. It is an avoidable cause of childhood blindness and its control is given priority in WHO's VISION 2020 programme [10].

The incidence of ROP in the present study 35.1 %. V AShah [11], et. al screened babies of ≤32 wk or ≤1500gms and reported overall incidence as 29.2%. Hernandez [12], et. al reported overall incidence as 32.1%. Sudha Chaudrietal [13], in 2008 screened babies of <32 weeks and < 1500gms along with >32 weeks or >1500gms requiring cardiopulmonary support and reported incidence of 22.3%.Mean birth weight of ROP babies was 1116 ± 231.7 gms in our study was similar to mean birth weight of 1118gms in V AShah [11]et. al. Mean gestational age of ROP babies was 29.7±1.58weeks in our study was similar to mean gestational age of 29.7 weeks in V AShah [11] et. al.

Neonatal risk factors and ROP

ROP incidence and severity increases as birth weight and gestational age decreases [14]. In our study both birth weight and gestational age was associated ROP, and gestational was independent risk factor in causing ROP. Both in Gupta [15] et al and VA shah [11] et al ROP was significantly associated with birth weight and gestational age .

RDS, Surfactant, Oxygen administration, IVH, sepsis, anemia was significantly associated with ROP group in our study. Oxygen, IVH (18.8%), sepsis (25.5%), RDS (58.2), surfactant (24.9%) were comparable with VA shah [11] et al study, in significant association with ROP.

The causal link between ROP and supplemental oxygen has been confirmed by controlled trials and clinical studies [16].

In our study Blood transfusion and DVET and number of times given transfusion were significantly associated ROP, In Dutta [17] et al study blood transfusion(49%) and DVET(45.5%) was significantly associated with ROP ,which is comparable to our study. It has been hypothesized that the adult hemoglobin, being more capable of

releasing oxygen to tissues, causes tissue-level hyperoxia. The hyperoxia in the tissues leads on to free oxygen radical release and reflex vasoconstriction leading on to the familiar cascade of events that causes ROP [18].

In our study, duration of oxygen was independent risk factor in causing ROP. Also average FiO2 and duration of mechanical ventilaton was significantly associated with ROP group.

In VA Shah et al study also, duration of oxygen, average FiO2 and duration of mechanical ventilaton was significantly associated with ROP group which was comparable with our study. The concentration and fluctuation of oxygen are key factors. Sudden discontinuation of oxygen and duration of oxygen therapy are incriminated in the pathogenesis of ROP [19].

Mechanical ventilation may potentiate the effects of a given oxygen concentration as it is forced in to lungs under high pressure [20].

Conclusion

Lower gestational age , lower birth weight, , Anemia, septicemia with ionotropic support, Intraventricular hemorrhage, apnea, blood transfusion, DVET, RDS/HMD, need for surfactant, need for oxygen therapy and also prolonged duration of oxygen requirement and respiratory support in the form of mechanical ventilation requirement and average Fio2 were significantly associated with ROP. Gestational age and duration of oxygen were identified to be factors predictive of ROP. Our study concluded that ROP is an important complication of prematurity Screening should be intensified in the presence of factors associated with ROP. There is need for the obstetricians, neonatologist and ophthalmologist to work in close co-operation to prevent blindness due to ROP.

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