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THE INCIDENCE AND RISK FACTORS OF RETINOPATHY OF PREMATURITY

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ABSTRACT

Purpose: To study the incidence and risk factors of retinopathy of prematurity at Indira Gandhi Medical College Shimla and Kamla Nehru State Hospital For Mother & Child Shimla in the hilly terrain of Himachal Pradesh. **Methods:** A hospital based prospective observational study was conducted from July2014 to June2015at neonatal intensive care unit and ophthalmology unit at Indira Gandhi Medical College Shimla and Kamla Nehru State Hospital For Mother & Child Shimla. 92 babies admitted to the neonatal unit who were ≤ 1750gms or whose gestation was ≤ 34 weeks were examined by an ophthalmologist by indirect ophthalmoscope at 4 weeks postnatal age**. Results:** Out of 92 babies screened 22 babies developed ROP. The incidence of ROP was 23.92%.Out of 22 babies who developed ROP 8 (36.36%) had stage 1, 6 (27.27%) had stage 2, 7 (31.81%) had stage 3, 1 (4.54%) had APROP, 1 (4.54%) had preplus disease and 2 (9.09%) had plus disease. On univariate analysis birth weight, gestational age, oxygen administration, duration of oxygen exposure, respiratory distress syndrome, sepsis, anemia, blood transfusion, congenital cardiac defects, multiple birth, premature rupture of membranes were found to be significant risk factors. In the present study thrombocytopenia, neonatal jaundice, phototherapy, apnea, surfactant, hpoxic ischemic encephalopathy, antenatal steroid intake, gestational diabetes mellitus, pregnancy induced hypertension, antepartum hemorrhage were however not found as significant risk factor. **Conclusion**: Lower gestation age, lower birth weight, sepsis, apnea, blood transfusion, duration of oxygen are associated with a greater incidence of retinopathy prematurity. These factors must be prevented and more care for early detection of retinopathy should be conducted.

KEYWORDS: Retinopathy of Prematurity, Neonatal risk factors, Low birth weight, Preterm infant.

INTRODUCTION

Retinopathy of prematurity (ROP) which was previously called as retrolental fibroplasia is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age (GA). The possible mechanism of injury suggested is vasoconstriction, increase in level of vasogenic factors like vasculoendothelial growth factor and compensatory neovascularisation leading to severe extraretinal fibrovascular proliferation and retinal detachment.ROP was first described by Terry in 1942 as retrolental fibroplasia with implication of oxygen therapy as causative agent.[1] ROP is emerging as one of the leading causes of preventable childhood blindness in India.

Improved neonatal care has increased the survival of very low birth weight and premature babies and has consequently increased the incidence of ROP. Studies from India have reported ROP in 20% to 52% of screened neonates.[3-8] More recent studies reporting lower rates of ROP ranging from 20% to 30%.[9-10] It is estimated that out of 100 preterm infants, 20 to 40 develop ROP, out of which 3-7 become ultimately blind.[11] Many risk factors are associated with ROP like low GA, low birth weight, prolonged oxygen exposure, severity of neonatal illnesses, severe respiratory distress requiring mechanical ventilation, shock, sepsis, hypoxia, prolonged ventilatory support, need for blood transfusion, intraventricular hemorrhage, acidosis, anemia. The purpose of this study is to know the incidence and risk factors of ROP at IGMC Shimla and Kamla Nehru State Hospital for mother and child Shimla.

MATERIALS AND METHODS

A hospital based prospective observational study was conducted from July2014 toJune2015at neonatal intensive care unit and ophthalmology unit at Indira Gandhi Medical College Shimla and Kamla Nehru State Hospital For Mother & Child Shimla to study the incidence of ROP in preterm infants with less than or equal to 34 weeks of gestational age or ≤ 1750 grams birth weight and to determine the risk factors associated with ROP in the Preterm infants and Low Birth Weight babies. Ninety two babies with birth weight≤ 1750 gms or gestational age less than or equal to 34 weeks of gestational age were enrolled in the study.

All babies more than 34 weeks of gestational, or more than 1750 grams of birth weight, babies with suspected chromosomal anomalies clinically assessed and babies who died before they could be examined or before full vascularization of retina were excluded. Informed consent of parents was taken after explaining in detail about methods and procedures involved in the study in their own language. Ethical clearance was obtained. All eligible babies were screened at Neonatal Intensive Care Unit where temperature was well controlled and the place to handle any emergencies exists. One cabin in NICU was converted to dark room for indirect ophthalmoscopy. First screening examination was carried out at 4 weeks of postnatal age.Pupils were dilated with Phenylephrine 2.5% and Tropicamide 0.5% (1:1dilution with distilled water). One drop of Tropicamide and Phenylephrine was instilled every 10-15 minutes for 4 times starting 1 hour before the scheduled time for examination. Indirect ophthalmoscope and +20D lens were used for examination. 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 stage1-2 disease and twice weekly for stage 3 disease, till disease started resolving or progressed to threshold stage. Babies showing evidence of regression were followed up till vascularisation was complete.

STATISTICAL ANALYSIS

The data was analysed using statistical software IBM Microsoft SPSS version 20.0.Continuous variables were presented as means± standard deviations and their associations were analysed using Independent T-test and ANOVA.

The discrete data was analysed using Pearson Chi-square test of significance or Fischer exact test whichever was applicable. The association between potential related risk factors with ROP and without ROP were studied through an Univariate analysis. Odds Ratio (OR) and 95% Confidence Interval (CI) was calculated. In all the above test the "p" value of less than 0.05 was accepted as statistically significant and all the test used for analysis were two tailed.

RESULTS

Out of 92 babies, 22 babies developed ROP. Incidence of ROP in study group was 23.92%. Out of 22 babies who developed ROP, 8 (36.36%) had stage 1, 6(27.27%) stage 2, 7(31.81%) had stage3, 1(4.54%) had APROP (Aggressive posterior ROP). (Table 1.)

Table 1: Stages of ROP seen in study group.

ROP	ROP Stages						Total
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	APROP	
Yes	8	6	7	0	0	1	22
	36.36%	27.27%	31.81%	0%	0%	4.54%	100%

Out of 22 babies preplus disease was seen in 1(4.54%) baby and plus disease in 2(9.09%) babies. Out of 92 neonates screened for ROP 56 (60.86%) were male and 36 (39.13%) were females. Among male newborns 13 (23.21%) out of 56 developed ROP and in female newborns 9 (25.0%) out of 36 developed ROP. Sex was not a significant risk factor in development of ROP p=1.00.

Mean birth weight in ROP babies was 1159.09 ± 238.146 and mean birth weight in babies without ROP was1394.43 ± 264.49.Difference in mean birth weight between ROP and no ROP babies was statistically significant p=.000. (Table 2) Incidence of ROP among different birth weight groups was 58.80% ≤ 1050 grams, 28% in 1051-1300 grams, 14.81% in 1301 -1550 grams, 4.34% in 1551-1750 grams. The incidence was highest in ≤ 1050 grams and incidence of ROP decreases with increase in birth weight.

Table2: Comparison between mean birth weight in two groups.

ROP	Number	Mean Birth.Weight in Grams	Standard Deviation	P VALUE
YES	22	1159.09	238.146	.000
NO	70	1394.43	264.49	

Mean gestational age in ROP babies was 30.27 ± 2.529 and mean gestational age in babies without ROP was 32.27 ± 2.455.Difference in mean gestational age between ROP and no ROP babies was statistically significant p=.001.(Table 3) Incidence of ROP among different gestational age groups was 50.00% ≤ 28 weeks, 28.26% in 28≤ 32 weeks, 13.04% in 32≤ 34weeks, 7.69% in >34weeks.The incidence was highest in ≤ 28

weeks and incidence of ROP decreases with increase in gestational age.

Table 3: Comparison between mean gestational age in two groups.

ROP	Number	Mean Gestational Age Weeks	Standard Deviation	P VALUE
YES	22	30.27	2.529	.001
NO	70	32.27	2.455	

Post Conceptional Age at First Examination among ROP babies ranged from 32–36 weeks (mean35.09± 2.37weeks), while that of non-ROP babies ranged from 32-40 weeks (mean36.21±4.96weeks). Difference in mean post conceptional age at first examination among ROP babies and no ROP babies was not statistically significant (p=.309).

Mean gestational age of stage1was 29.910 ± 2.702 weeks (range 25.714-32.857weeks) and mean birth weight was 1090 ± 170.461(range 860-1300) grams. Mean gestational age of stage 2 was 29.809 ± 3.128 (range 26.285-35.285) weeks and mean birth weight was 1060 ± 283.901(range 800-1500) grams. Mean gestational age of stage 3 was 30.428 ± 2.223(range 28-33.857) weeks and mean birth weight was 1331.428 ± 189.774(range 1030-1600) grams. There was no correlation between birth weight, gestational age and different stages of ROP. (Table 4)

Table 4: Mean gestational age and birth weight in different stages of ROP.

Stages	Mean Gestational Age(weeks)± SD	Mean birth weight(grams)± SD
Stage 1	29.910 ± 2.702	1090 ± 170.461
Stage 2	29.809 ± 3.128	1060 ± 283.901
Stage 3	30.428 ± 2.223	1331.428 ± 189.774
APROP	33	1400
P value	0.906	.058

On univariate analysis(Table5) birth weight(p<.000), gestational age(p<.001), oxygen administration(p=0.019), duration of oxygen exposure(p=0.000) respiratory distress syndrome (p=0.015), sepsis(p=0.007),anemia(p=0.013), blood transfusion(p=0.013), congenital cardiac defects(p=0.041) multiple birth(p=0.003), premature rupture of membranes (p=0.027) were found to be significant risk factors. In the present study thrombocytopenia (p=1.0), neonatal jaundice (p=0.10), phototherapy (p=0.06), patent ductusarteriosus (p=0.4), antenatal steroid intake (p=1.0), gestational diabetes mellitus(p=0.4), pregnancy induced hypertension (p=0.4). Antepartum hemorrhage (p=0.3) were however not found as significant risk factor.

Table 5: Univariate analysis of various risk factors (N=92).

Risk factor	Total Babies	Babies With Rop	Odds Ratio	95% CI	P Value	SIGNIFICANCE S=significant NS=nonsignificant
Oxygen	78	22	1.393	1.212-1.601	.019	S
Surfactant	11	3	1.224	.295-5.078	.721	NS
Respiratory distress syndrome	62	20	6.667	1.443-30.79	.015	S
Apnea	55	17	2.863	.951-8.623	.095	NS
Sepsis	34	14	4.375	1.591-12.03	.007	S
Anemia	32	13	3.877	1.426-10.538	.013	S
Thrombocytopenia	9	2	.900	.173-4.686	1.0	NS
Blood transfusion	32	13	3.87	1.426-10.538	.013	S
Neonatal jaundice	76	21	5.727	.711-46.108	.105	NS
Phototherapy	74	21	6.736	.842-53.71	.062	NS
Congenital cardiac defects	4	3	10.895	1.071-110.79	.041	S
Patent ductus arteriosus	2	1	3.286	.197-54.823	0.42	NS
Hypoxic ischemic encephalopathy	2	1	3.286	.197-54.823	0.423	NS
Multiple birth	6	5	20.294	2.223-185.301	.003	S
Antepartum hemorrhage	5	0	.747	.661-.844	0.333	NS
Gestational diabetes mellitus	2	1	3.286	.197-54.823	0.423	NS
Antenatal steroid intake	3	0	.753	.668-.848	1.00	NS
Pregnancy induced hypertension	9	3	1.68	.384-7.380	0.442	NS
Premature rupture of membranes	34	13	3.370	1.25-9.087	.027	S

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**. It is one of the major cause of blindness in children in developed countries and is emerging as a problem in developing countries as well.

The overall incidence of ROP in the present study was 23.92%. Various Indian studies had reported overall incidence ranging from 17.5% to 51.9% and International studies ranging from 10.0% to 45.4%.

Patil et. al[12] 1n 1997 reported overall incidence as 17.5% and no severe ROP. They studied 40 babies with <32wk or < 1250gms. Maheshwari et. Al[3] in 1996 reported overall incidence as 20% and severe ROP as 7%. They studied 66 babies with <35wk or < 1500gms. Gupta et. Al[13] in 2003 reported overall incidence as 21.7% and severe ROP as 5%. They studied 60 babies with < 35wk or <1500gms. Dutta S et. al[6] screened 108 babies of ≤32 wk or ≤1700 grams and reported overall incidence as 21%.

Distribution of different stages of ROP in our study, stage1accounted for 36.36% and stage 2 for 27.27%, stage3 for 31.83%, APROP 4.54% in the study group. Out of 22 babies preplus disease developed in 1(4.54%) baby and plus disease developed in 2(9.09%) babies.

Lieu[14] et al retrospectively studied 1864 preterm infants from January 2009-November 2012 in Southwest China with gestational age <37 weeks and birth weight≤2000 grams and found ROP in 12.8% of the babies.Stage1,2,3, and 4were seen in 64.6%,29.6%,3.4%and 0.5% of the infants respectively.

Study on incidence of ROP in a neonatal care unit in 1995 from Chandigarh by Charan[5] R determined the incidence of ROP in a prospective manner. One hundred sixty-five preterm babies of birth weight less than or equal to 1700 gm were examined over a period of 1 year. An incidence of 47.27% of ROP was detected. The maximum stage reached was stage 1 in 28 (16.97%), stage 2 in29 (17.58%), stage 3 in19 (11.52%) and stage 4b in 2 (1.21%) babies. Plus disease was present in 17 (10.3%) babies. Niranjan[15] et al reported incidence of 27% among 248 babies with gestational age <34 weeks and /or birth weight of <2000 grams. The incidence of stage1 was 10.5%, stage2 58.2% and stage 3 was 31.3%.

CONCLUSION

Our study concluded that ROP is an important complication of prematurity. Meticulous fundus examination with indirect ophthalmoscopy in all preterm babies is essential non invasive method for early detection of ROP and its progression.

In our study incidence of ROP among different birth weight groups was 58.80% ≤ 1050 grams, 28% in 1051-1300 grams, 14.81% in 1301 -1550 grams, 4.34% in 1551-1750 grams. In our study the incidence was highest in ≤ 1050 grams and incidence of ROP decreases with increase in birth weight. Incidence of ROP among different gestational age groups was 50.00% ≤ 28 weeks, 28.26% in 28 ≤ 32 weeks, 13.04% in 32 ≤ 34weeks, 7.69% in >34weeks.In our study the incidence was highest in ≤ 28 weeks and incidence of ROP decreases with increase in gestational age. Reisner[16] et al found ROP in 20% of all survivors with a birth weight ≤ 2500gms admitted to a tertiary neonatal intensive care unit between 1977 and 1983. They found reciprocal relation with birth weight and the incidence of the disease, with an incidence of 72% in infants weighing ≤ 1000 gms at birth, 35% in 1001-1250 grams, 21% in infants weighing between 1251-1500 gms and 10% in infants between 1501-2000 grams. They found that mean birth weight and gestational age of the affected new borns were significantly lower than in unaffected infants. More premature the child, more immature the retinal vasculature; thus much more larger retinal area at risk for insults like hyperoxia[17,18] and its interplay with various factors like VEGF[19] and IGF.

Mean duration of oxygen exposure was 16.64±6.793 days in babies who developed ROP and 8.89±9.168 in babies who had no ROP. There was statistically significant difference in duration of oxygen exposure p = (.000) in present study. Feghhi et al in their study in south western region of Iran reviewed all neonates with low birth weight ≤2000 grams and/or less than 32 weeks gestational age who had been hospitalized in the neonatal intensive care unit (NICU) from 2006 to 2010 and reported ROP in 32% of infants. Duration of oxygen administration was found as significant risk factor.[20]

On univariate analysis birth weight, gestational age, oxygen administration, duration of oxygen exposure,respiratory distress syndrome, sepsis, anemia, blood transfusion, congenital cardiac defects, multiple birth, and premature rupture of membranes were found to be significant risk factors.

In the present study apnea, surfactant, thrombocytopenia, hypoxic ischemic encephalopathy, neonatal jaundice, phototherapy, patent ductus arteriosus, antenatal steroid intake, gestational diabetes mellitus, pregnancy induced hypertension, antepartum hemorrhage were however not found as significant risk factor.

Screening should be intensified in the presence of factors like RDS, oxygen administration, anemia, blood transfusion, sepsis. Timely referral of detected ROP cases for early treatment prevents blindness. 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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