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"A PROSPECTIVE STUDY OF INCIDENCE OF RETINOPATHY OF PREMATURITY IN PRETERMS LESS THAN 35 WEEKS OF GESTATION AND BABIES WEIGHING LESS THAN 2000 GRAMS"

Paediatrics

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KEYWORDS

Introduction:
Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative disorder affecting developing retina. ROP occurs in premature infants who have immature and incompletely vascularised retina. It is an important and preventable cause of blindness in children, accounting for 6 to 18 % of blindness in developed countries. It is estimated that in India ROP accounts for about 0.2% of childhood blindness.[1,2,3]

Currently no definitive methods are available for the prevention of ROP. Since most of the risk factors associated with ROP arise in the neonatal intensive care unit (NICU) itself and most of them are avoidable, cautious monitoring of the risk factors, early screening, follow up and surgical interventions have shown to reduce the incidence and improve the outcome of ROP.[4]

This study aims to:

- To find out the incidence of ROP in preterm less than 35 weeks gestation and babies weighing less than 2000 grams attending the Department of Paediatrics, J.L.N. Hospital & R. C, Bhilai, Chhattisgarh.
- To evaluate the various maternal and neonatal risk factors associated with Retinopathy of Prematurity.
- As there is a paucity of published reports in this part of India, this study was undertaken to evaluate the incidence and risk factors of ROP with our ultimate aim being "NOT ONLY SURVIVAL, BUT THE QUALITY OF SURVIVAL".

Material and methods:
The present study was conducted at Department of Pediatrics and Department of Ophthalmology, Jawaharlal Nehru Hospital & Research Centre, Bhilai, Durg, Chhattisgarh between1st November 2015 to 31st October 2017. This was a prospective observational study.

INCLUSION CRITERIA:
All preterm neonates of less than 35 weeks gestation and birth weight less than 2000 grams, surviving at the postnatal age of 3 weeks and attending the neonatal development follow up clinic were referred to Department of Ophthalmology for ROP screening and further management.

EXCLUSION CRITERIA
Preterm with gestation less than 35 weeks but birth weight more than 2000 grams, those born outside this hospital, babies who fulfilled the criteria but did not survive till first eye examination for ROP, babies with gross congenital malformation and those lost during follow-up were excluded from the study.

The gestational age was assessed by mother's last menstrual period/first trimester ultrasound scan and new Ballard score after birth. All infants were managed according to the standard NICU. The survivors were advised to attend neonatal development follow-up clinic at discharge.

For ROP screening, binocular indirect ophthalmoscopy was done with +20 D condensing lens and pediatric wire speculum was used to open the eyes.

If ROP was detected, then patients were examined weekly till threshold ROP reached or regression of disease occurred. If threshold ROP was present, treatment in the form of Laser Photocoagulation was done and patient followed up till regression of the disease occurred.

For each infant screened for ROP, a number of factors were prospectively recorded on a predesigned Performa. All pertinent information such as name, date of birth, birth weight and sex were obtained. Gestational age was assessed within 24 hrs of birth using the new Ballard score. Maternal dates and ultrasound scans were also used where available. Severe birth asphyxia was defined as APGAR score ≤3 at 5 minutes of life. Apnea was defined as cessation of respiration for more than 20 seconds or less if accompanied with bradycardia and/or cyanosis. Respiratory Distress Syndrome (RDS) was diagnosed on the basis of clinical presentation and radiological findings. Intra Cranial Hemorrhage (ICH) was diagnosed by ultrasound scan of the brain. Sepsis was diagnosed on the basis of clinical presentation substantiated by a positive sepsis screen and/or blood culture for bacteria/fungus. Necrotizing Enterocolitis (NEC) was diagnosed when typical clinical finding and radiological changes were present and staged according to modified Bell's Staging.

Relevant patient data were tabulated and analyzed using the software SPSS 18 for windows.

Results:
During the study period, 4215 number of neonates were admitted in NICU, of them 926 were preterm.

Of 926 number of premature babies admitted in NICU, 318 were screened for ROP, 43 were excluded from the study according to the exclusion criteria mentioned before, after which 275 preterm were left for study. Patient characteristics are shown in table 1.

The 275 babies enrolled for study had mean birth weight: 1648.70gm ± 275.51gms and mean gestational age: 33.21 ± 1.70wks. 130 were male (47.3%) and 145 (53%) were females, 112 (40.7%) babies were delivered by LSCS and 163 (59.3%) vaginally. 27 (9.8%) were ≤1250 grams, 48 (17.5%) between 1250-<1500 grams and 200 (72.7%) had birth weight between 1500- <2000 grams. In the study population (n=275), 89 were small for gestation while 186 were appropriate for gestation. 5 (1.8%) were <28 weeks 47 (17.09%) between >28- 32 weeks and 223 (81.09%) were between >32 but <35 weeks of gestation. Only 8 out of 275 babies required NICU stay beyond 2 weeks. A total of 210 babies out of 275 had some degree of respiratory distress. Oxygen therapy was received by 209 babies, Mechanical ventilation was required by 19 babies and 35 babies received FiO_2 >40% for more than 24 hours.

Out of 275 babies 17 had culture proven sepsis, multiple blood transfusions were received by 46 babies, 163 babies received phototherapy, and 36 babies had multiple apnoeic episodes. Of 275 babies in the study, 5 required surfactant therapy and 27 babies developed necrotising enterocolitis of any stage. (See table 2)

Mean post conception age for first ROP screen was 36.55 ± 2.12 weeks. Total 63 babies out of 275 developed ROP of any stage and in the cohort of 550 eyes 116 eyes developed ROP with the incidence rate of 21.09%. Of 116 eyes 56 had stage 1, 33 stage 2 and 27 stage 3 ROP. No stage 4 or 5 cases were seen.

14 cases required laser therapy and all the cases had regression on follow-up. Birth Weight <1500 grams were significantly associated with ROP. 3 babies were of < 28 weeks gestation, 28 with gestation between 28-32 weeks and32 were >32 but less than 35 weeks. Gestation less than 32 weeks was found to be significantly associated with ROP. Out of 8 babies who had NICU stay of more than 2 weeks 6 developed ROP with significant statistical association p =0.0004.

Among 210 babies who had respiratory distress 61 developed ROP. 60 out of 63 babies, who developed ROP, received oxygen therapy. Out of 19 babies requiring Mechanical ventilation 13 developed ROP. FiO_2 >40% was required by 35 babies and of them 15 developed ROP. (See Table 2)

Statistically significant association was found with sepsis, multiple blood transfusions, phototherapy, apnoea, surfactant and necrotising enterocolitis. While statistically insignificant association was found with mode of delivery, gender and multiple pregnancies. (See table 3)

Discussion:

In our study 63 out of 275 subjects (22.9 %) developed ROP. This is much greater than that reported from developed nations were the incidence is 5-8 %.[4, 5, 6] The reason for lower incidence of ROP in developed might be that mothers receiving good antenatal care, vigilant monitoring of high risk mothers, routine administration of ante-natal steroids where-ever indicated. Other important finding noticed in our study was that there was absence of ROP Stage IV and Stage V. The absence of the advanced and severe stages of ROP may be explained by the early timing of first eye examination.

Birth Weight <1500 grams showed strong association with the disease with the p value=0.0001($p<0.05$).This association can be explained by the fact that in most instances premature babies are already compromised from intra-uterine period which continues postnatal leading to a large number of problems, increased exposure to supplementary oxygen therapy, sepsis, blood transfusion and a vicious cycle of hypoxia-hyperoxia sets in which, leads to development of ROP.

In our study, infants with gestational age <32 weeks were significantly associated with ROP. This association again was due to the fact that low gestational age leads to even more immature retina, poorly developed vascularization, poor development of body's innate protective mechanisms as well as low birth wt. and its associated problems. [7,8,9]

Mechanical ventilation was found to be significantly associated with ROP. FiO_2>40% was also significantly associated with ROP. This result can be explained by the fact that most of the infants in our study were critically ill having multiple problems and as part of line of treatment oxygen therapy was provided under stringent control which saved the lives of such babies but simultaneously also increased the chances for development of ROP. Oxygen therapy should not be deemed as the sole culprit for ROP. [1,5,9,]

A significant association was seen between ROP and sepsis. Prolonged preterm rupture of membranes in the mother leads to both maternal sepsis/chorio-amnionitis and preterm delivery. The baby develops early onset sepsis needing NICU interventions to save lives.[10,11]

Our study revealed that those critically ill preterm with NICU stay >14 days had higher chances of development of ROP. The association with ROP is probably a reflection on the severity of illness of these infants. We could not trace any reference study for comparison of this observation. In our view, this is an important parameter for identifying preterm survivors needing ROP screening.

Multiple Blood transfusions was significantly associated with development of ROP. Critically ill preterm infants commonly have multi organ dysfunction, bleeding, abnormal coagulogram, thrombocytopenia etc. In order to prevent acute bleeding in vital organs and to ensure survival, blood component therapy becomes life saving [9,10,and11]

Our patients with ROP had a significant higher frequency of apnea which is in agreement with other studies. This can be explained by hypoxemia, fluctuating level of oxygen and hyperoxemia following therapy for apnea. It is possible that presence of apnea simply represents a marker for the presence of severe systemic illness [12,13]

In our study, 14 patients out of 63 required Laser Photocoagulation to prevent progression of the disease (table 22). All these patients received Laser therapy.

In rest ROP cases i.e., 49 cases which did not require Laser Photocoagulation, follow up was done till full maturation of their retina or regression of neo-vascularization.

In Laser done ROP cases follow up was done first after a week, then after 2 weeks and then monthly to screen for regression or any neo-vascularization after treatment. All the treated cases had good results on follow up. There was regression of ROP on follow up and no further neo-vascularization. (See Table 4) We found Laser as treatment modality, extremely satisfactory which is in accordance to the studies in review of literature. [14,15,16]

Conclusion:

On the basis of this study, following conclusions were drawn.

Incidence of ROP in Jawahar Lal Nehru Hospital & Research Centre Bhilai is 22.9%. Statistically significant risk factors associated with ROP in our study were gestational age ≤32 weeks, birth weight ≤1500gms, sepsis, apnea, respiratory distress, phototherapy, blood component therapy, oxygen therapy, (FiO_2>40%),ventilator support, NICU stay >14 days while mode of delivery, gender and multiple births were not statistically associated with ROP.

In contrast to western data, 26 infants with >1500gram of birth weight were having ROP, this suggests screening criteria of western countries is not applicable in our scenario.

In our study 14 patients were treated with laser photocoagulation and followed up for 3 months. There was gradual regression of ROP and no further neo-vascularization.

Table :1 Patient characteristic (n=275)

Birth weight (in Grams)	1648.70±275.51
Gestational age (in weeks)	33.21± 1.70
Post conceptional age for ROP screening (in weeks)	36.55 ± 2.12
Male : Female	1:1.05
Pregnancy Single Multiple	82.2% 17.8%
Mode of Delivery LSCS Vaginal	40.72% 59.27%
Birth weight (in grams) Less than 1250g 1250 to 1499g 1500 to 1999g	9.8% 17.5% 72.7
Weight for Gestation AGA SGA	67.63% 32.36%

LSCS-lower segment caesarean section, AGA- Appropriate for gestational age, SGA- Small for gestational age.

Table:2 Patient and risk factors (n=275)

Risk factor	Percentage
NICU stay more than 2 weeks	2.91%
Oxygen therapy	76%
FiO2 > 40% for >24 hours	12.72%
Mechanical ventilation	6.9%
Sepsis	6.2%
Blood transfusion	16.7%

Phototherapy	81.1%
Respiratory distress	76.4%
Apnea	13.1 %
Surfactant Therapy	1.8%
Necrotising enterocolitis	9.8%

FiO2-Fraction of inspired Oxygen.

Table 3: Relationship between retinopathy of prematurity and risk factors

Variable		Cases with ROP (n=63)	Cases without ROP (n=212)	p Value (significant <0.005)
Gestational age (weeks)		31.68 ±1.98	33.54 ±1.18	0.000
Birth Wt (gm)	<1500	23(56.1%)	37(28.9%)	0.002
	≥1500	18(43.9%)	91(71.1%)	
Total days on supplementary O_2	6.47 ±7.1 0	2.6 ±2.74	0.002	
ICU stay (days)	6.44 ±7.1	2.37 ±2.46	0.001	
Total Hospital Stay	10.68 ±7.2	6.51 ±3.45	0.001	
Antenatal steroid	No	10 (24.4%)	69(53.9%)	0.001
	Yes	31(75.6%)	59(46.1%)	
Proven sepsis	No	31(75.6%)	124(96.9%)	0.000
	Yes	10 (24.4%)	4(3.1%)	
Blood Transfusion	No	24(58.5%)	116(().6%)	0.**000**
	Yes	17(41.5%)	12(9.4%)	
Respiratory Distress	No	1(2.4%)	32(25.0%)	0.000
	Yes	40((97.6%)	96(75.0%)	
Apnea	No	25(61.0%)	116(90.6%)	0.000
	Yes	16(39.0%)	12(9.4%)	

Table 4: ROP and treatment outcome

STAGES	NO.	%	INTERVENTION(LASER)	OUTCOME
STAGE 1	56	48.27%	FOLLOW-UP	REGRESSION
STAGE 2	33	28.44%	FOLLOW-UP+LASER(2 cases)	REGRESSION
STAGE 3	27	23.27%	FOLLOW-UP+LASER(12 cases)	REGRESSION
STAGE 4	0	0%	-	
STAGE 5	0	0%	-	
TOTAL	116	100%	LASER -14 cases	REGRESSION

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