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Incidence and risk factors of retinopathy of prematurity in extremely low birth weight babies in a tertiary neonatal care unit in northern India

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ABSTRACT

Purpose: To study the incidence and risk factors of Retinopathy of prematurity in extremely low birth weight babies in a tertiary neonatal care unit in northern India.

Materials and Methods: A prospective cohort study of all neonates born during January 1, 2015 to December 31, 2015, with birth weight less than 1000 grams. Demographic details, risk factors and incidence of ROP were studied.

Results: Sixty babies were enrolled for the study with mean birth weight of 892.983±112.933 (560 to 1000) grams and mean gestation age of 29.47±2.258 (25-35) weeks. The incidence of ROP in this cohort was 50% (30 infants), out of which 23% (7 infants) required treatment (laser photocoagulation). The statistical analysis of risk factors on univariate analysis revealed significant association for oxygen exposure, apnoea, surfactant use, anaemia, blood transfusion, intraventricular haemorrhage, sepsis and antibiotic use. On multivariate logistic regression analysis anemia and oxygen exposure > week were found to be independent risk factors for development of ROP.

Conclusion: The incidence of ROP was although high in this exclusive cohort of babies born <1000g but there is substantial decrease in incidence as compared to that reported in earlier studies. Gestational age <30 wks, being appropriate for gestation rather than small for gestation, anemia and oxygen exposure>1 week were found to be independent risk factors for development of ROP in this cohort.

1. Introduction

Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study reported an overall incidence of ROP of 65.8% in ≤1250 grams birth weight babies and 81.6% in infants with birth weight <1000 grams.[1] The Early Treatment of Retinopathy of Prematurity (ETROP) study reported 68% incidence of ROP in <1251 grams and 82.5% in infants with <1000 grams birth weight.[2] Later studies have reported incidence of ROP in extremely low birth weight babies (ELBW) ranging from 32.8% to 75.5%.[3–8]

Several risk factors have been reported for ROP in ELBW babies including anemia,[4,8,9] gestational age,[5,8] birth weight,[5,8] surfactant use,[6,9] apnoea,[6,10] pneumonia,[6] meningitis,[6] ventilation,[6,11] intraventricular hemorrhage,[6,8,9,11] respiratory distress syndrome (RDS),[6,8] patent ductus arteriosus (PDA)[6] necrotising enterocolitis (NEC),[6,8] intraventricular hemorrhage,[8] sepsis,[6,8–10] blood transfusion,[6,8,9] male sex,[9] serum bilirubin levels[9] and bronchopulmonary dysplasia (BPD).[9]

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Majority of reports have been retrospective in nature and there are, thus we conducted prospective study to determine the incidence and risk factors for ROP in ELBW (birth weight <1000g) babies.

2. Materials and Methods

This study was carried out at the level III NICU of a tertiary care referral institute in northern India after obtaining approval from institutional ethics committee. The study adhered to the tenets of the declaration of Helsinki. All babies born with a birth weight below 1000 grams irrespective of gestational age and admitted in the neonatal care unit during January 1, 2015 to December 31, 2015 were prospectively enrolled. Babies with lethal congenital malformations and those who died or were lost to follow up during the screening period were excluded. The initial examination started at 2-3 weeks after birth and/or at discharge whichever was earlier.

Indirect ophthalmoscopy was done using +20D lens after pupillary dilatation with topical 50% tropicamide. Anterior segment examination was carried out with magnification provided by the + 20 D lens. Retinal changes were recorded in accordance with the International Classification of ROP.[12] Follow up examinations were scheduled as per the ETROP study recommendations.[2,13] Examination was continued till either treatable stage of ROP was reached (type 1 ROP i.e. Zone I, stage3 without plus; zone I, any stage with plus; zone II, stage 2 or 3 with plus; APROP) or spontaneous regression or complete vascularisation of retina was observed and/or No ROP. "No ROP" term was used for temporal avascular retina, which ultimately ended to complete vascularisation of retina without going through any stage or plus disease. Appropriate for gestational age (AGA) newborns defined as whose birth weight was within the normal range or between 10th and 90th percentile for that gestational age and sex. Small for gestational age (SGA) defined as those newborns whose birth weight was less than normal or less than 10th percentile for that gestational age and sex. i.e. intrauterine growth retardation (IUGR) Babies.[14]

The risk factors noted from the clinical records included: Oxygen exposure (>1 week), Respiratory distress syndrome (RDS), Meconium aspiration syndrome (MAS), Sepsis (culture negative/ culture positive), Blood transfusion (mostly whole blood used), Multiple births, Apnea, Intraventricular hemorrhage(IVH), Anemia (Hb<10gm), Neonatal jaundice, Seizures, Antenatal and Postnatal Steroid use, Surfactant use, Antibiotics use. Wherever indicated, risk factors were defined as per definitions given by the National neonatal perinatal database (NNPD) report 2002-2003.[15]

2.1. Statistical analysis

IBM SPSS 22 software version (2016) was used for data analysis. The incidence of ROP in different birth weight and gestational age categories was described by descriptive studies. Comparison of ROP incidence between various categories done by using Chi square test. Univariate analysis performed for the putative risk factors. Student't' test used to compare normally distributed numerical variables, Chi square test used for categorical variables. Relative risks with 95% confidence intervals calculated for all putative risk factors. Multivariate logistic regression analysis applied to multiple risk factors to identify the independent risk factors.

3. Results

During the study period, 184 babies were born with a birth weight of <1000 grams irrespective of gestational age. Sixty (32.61%) babies who fulfilled the inclusion criteria and those with complete records were enrolled for the study. The mean birth weight was 892.983 ± 112.933 grams (560-1000) while mean gestational age was 29.47 ± 2.258 weeks (25-35).

The incidence of any ROP was 50%. Maximum stage reached was stage 2 in 20(66.67%), stage 1 in 4(13.33%), stage 3 in 4(13.33%) and APROP in 2(6.67%) babies. Pre-plus developed in 9(30%), plus disease in 7(23.33%) and no plus in 14(46.67%). All 23 patients with no-plus and pre-plus disease showed spontaneous regression. Seven patients (23.3%) developed plus disease. Of all these 7, 5 developed type 1 ROP and 2 developed APROP requiring laser photocoagulation at a mean post menstrual age of 35 weeks (Table 1).

The demographic variables of gender and birth weight did not individually reveal statistically significant association with ROP within the study population. On further analysis of gestational age, there was statistically significant association between ROP and AGA babies ($p<0.01$). Among 30 AGA babies, 21(70%) developed ROP and among 30 SGA babies only 9 (30%) develop ROP. Out of 9 babies, 5 had gestational age ≤30 weeks and 4 had >30 weeks. Furthermore, gestational age was a significant risk factor for development of ROP ($p<0.01$). Twenty-six (66.7%) babies out of 39 with gestational age <30 weeks had ROP and 4 (19%) babies out of 21 with gestational age > 30 weeks had ROP. There was no statistically significant relation between mean birth weight at different stages of ROP ($p>0.05$) but there was statistically significant relation between mean gestational age at different stages of ROP ($p<0.01$) (Table 2). The statistical analysis of neonatal complications (Table 3) and interventions (Table 4) as risk factors revealed significant association for oxygen exposure, apnoea, surfactant use, anaemia, blood transfusion, intraventricular haemorrhage, culture proven sepsis, and antibiotic use. There was

significant (p<0.01) association of oxygen exposure (>1 week) with development of ROP with 16 (84.2%) babies with oxygen exposure (n=19) developing ROP. Sepsis was another major risk factor for development of ROP, however analysis did not reveal any association between sepsis and need for treatment or outcome in ROP (p=0.666). Further analysis revealed strong association between number of sepsis episodes and development of ROP and between sepsis and stage of ROP, thereby suggesting impact of sepsis on severity of disease as well as sepsis as dose dependent risk factor for ROP similar to exposure to oxygen. To compare between the risk factors in babies who required laser treatment and those who did not require treatment, no risk factor was found to be statistically significant.

On univariate analysis, gestational age <30 weeks, oxygen exposure >1 week, apnoea, surfactant use, intraventricular hemorrhage, anaemia(Hb <10gm), blood transfusion, culture proven sepsis, no. of sepsis episodes, antibiotic use found to be significant risk factors in present study(Table 5). Gestational age although significant but not entered into multivariate logistic regression analysis because of more number of small for gestational age babies and no cut off criteria for gestational age defined in present study.

Factors which were found significant on univariate analysis were entered into the Multivariate logistic regression analysis, forward stepwise model. Anemia and oxygen exposure >1 week were found to be independent risk factors for development of ROP.

4. Discussion

Retinopathy of prematurity is a leading cause of blindness affecting approximately 50,000 children worldwide.[16,17] The last decade has seen reemergence of ROP epidemic, in middle income countries and urban areas of low income countries where neonatal care is rapidly improving with survival of less mature and smaller babies.[18]

It has been difficult to compare results of different studies because data availability, screening criteria methods, ethnicity, geographical location, risk factors, survival rate and neonatal standards of care vary between studies.[16,19] The reported incidence of ROP in ELBW babies has varied widely across the studies with range of 32.8% to 82.5%.[2–8] We found the incidence of ROP to be 50% in our cohort of ELBW babies. The incidence of ROP was comparable to studies by Choo et al[11] (58.6%), Yau et al[20] (53.4%), Shah et al[21] (55.4%) and Dhingra et al[22] (44.4%). However much higher incidence was reported by CRYO-ROP[1] study (81.6%), ETROP[2] (82.5%), Charan et al[3] (90% among ELBW babies) and Rekha et al[4] (73.3%), which is perhaps a reflection on improved neonatal care in recent years compared to these studies which were conducted decades ago.

Low birth weight has been reported as a significant risk factor for ROP in various studies.[3,8,16,21] Birth weight <1000 grams was independent risk factor in studies by Rekhaet al,[4] Fortes filho et al[13] and Kumaret al.[6]

The mean birth weight and gestational age in our study was 892.983±112.933grams (range 560-1000) and 29.47±2.258 weeks (range 25-35) which is similar to previously reported series.[5,7,8,11]

Kumar et al[6] and Shah et al[21] have reported gestational age < 30 weeks as independent risk factor for ROP across all weight categories. We also found gestational age to be an important risk factor on univariate analysis for ROP within this cohort (p=0.000), as has been reported in other similar studies.[5–7,21,23] In present study, we also observed statistically significant (p=0.000) association of gestational age with different stages of ROP, however similar association was lacking for birth weight (p=0.281).

The requirement of laser treatment in 23.33% patients with ROP in current cohort is in general agreement with previously reported series (Borroni et al[24] 21.1%; Demir et al[7] 30.2% ; Celebi et al[8] 36.6%).

ROP is a disease of prematurity and associated with multiple risk factors. In present study, amongst the various risk factors gestational age <30 weeks, oxygen exposure (>1 week), sepsis, blood transfusion, apnoea, intaventricular hemorrhage, anemia, surfactant, antibiotic use and duration of antibiotic use were found as significant risk factors on univariate analysis.

On multivariate logistic regression analysis with forward step model, anemia and oxygen exposure >7 days were independent risk factors for ROP. Similar to earlier reports, duration of oxygen exposure[5,9,11,23] was significant risk factor for ROP in present cohort of ELBW babies. Moreover, duration of oxygen exposure > 1 week, reported as a significant risk factor by Choo et al.[11] Neonatal anemia and need for blood transfusions were significant risk factors in our study and similar observations have been made by several previous authors,[4,8,9,13] although few have failed to observe statistically significant association.[5,23] The anemia of prematurity reduces the oxygen carrying capacity of blood and predisposes neonates to development of ROP.[13] However interestingly, Fortes Filho reported significant association for transfusions in babies below 1250 gram (p=0.01)[13] but failed to observe the same in babies below 1000 gram (p=0.07).[5]

Sepsis, culture proven sepsis, number of sepsis episodes were found as significant risk factors for ROP. Sepsis[8–10,23] and culture proven sepsis[8] were significant in various studies. Weintraub et al[9] reported number of sepsis episodes as significant risk factor and sepsis as independent risk factor for ROP.

As reported in earlier studies apnoea,[4,6,10] surfactant use[6,20,21] and intraventricular hemorrhage,[6,9,11,13,21] were also found to be significant risk factors for ROP in our

Table 1: Stage of ROP and outcome

	Stage 1	Stage 2	Stage 3	APROP	Total
Spontaneously regressed	4(17.39%)	18(78.26%)	1(4.35%)	0	23
Regressed with laser	0(0%)	2(28.57%)	3(42.86%)	2(28.57%)	7
Total	4	20	4	2	30

Table 2: Mean birth weight and gestational age in different stages of ROP

Stages	Mean birth weight(grams) Mean±SD	Mean Gestational age(weeks) Mean±SD
NO ROP	908.87±114.26	30.67±2.07
Stage 1	958.75±50.72	29±1.15
Stage 2	858.95±119.57	28.33±1.71
Stage 3	888±87.86	27.40±2.30
P value	0.281	0.000

Table 3: Showing risk factors (neonatal complications and interventions) studied

Neonatal complications	N(%)
Neonatal jaundice	48(80%)
Respiratory distress syndrome	13(21.7%)
Apnoea	29(48.3%)
Multiple births	11(18.3%)
Anemia	18(30%)
Sepsis	42(70%)
Thrombocytopenia	3(5%)
Patent ductus arteriosus	10(16.7%)
Intraventricular hemorrhage	10(16.7%)
Necrotising enterocolitis	3(5%)
Seizures	0
Meconium aspiration syndrome	3(5%)

Table 4: Showing risk factors (neonatal complications and interventions) studied

Interventions	N(%)
Phototherapy	47(78.3%)
Oxygen exposure	19(31.7%)
Antibiotic use	37(61.7%)
Blood transfusion	18(30%)
Surfactant	10(16.7%)
Double volume exchange transfusion	2(3.3%)
Steroid use	4(6.7%)

Table 5: Showing all the statistically significant risk factors for ROP on univariate logistic regression analysis

S No.	Risk factor	ROP	No ROP	P value
1	Oxygen exposure (>1week)	16(84.2%)	3(15.8%)	0.000
2	Gestational age (<30 weeks)	26(66.67%)	4(19%)	0.000
2	Apnoea	19(65.5%)	10(34.5%)	0.020
3	Surfactant use	8(80%)	2(20%)	0.038
4	Anemia	16(88.9%)	2(11.1%)	0.000
5	Blood transfusion	15(83.3%)	3(16.7%)	0.001
6	Intraventricular hemorrhage	8(80%)	2(20%)	0.038
7	Culture proven sepsis	8(100%)	0(0%)	0.000
8	No. of sepsis episodes	4(80%)	1(20%)	0.004
9	Antibiotic use	25(67.57%)	12(32.43%)	0.001

study. This study reports the incidence of ROP in babies with birth weight <1000 g from a level III NICU in northern India. The incidence rate is lower in comparison to other studies done decades ago and comparable to that reported from the west and from south India done years ago. Our study results are comparable to study done by Dhingra et al[22] from northern India, recently published. They also reported decrease in incidence of ROP in ELBW babies (16 ROP/36 ELBW babies i.e 44.4%) due to substantial changes in NICU protocols like use of blended oxygen, regular monitoring of oxygen saturation targets, use of continuous positive airway pressure (CPAP) and other non invasive modes of ventilation, lower sepsis rate, better monitoring equipments and changed blood transfusion policies. This decrease in incidence of ROP may be due to improvement in NICU protocols in tertiary care centers and dedicated ROP screening programs.

5. Conclusion

There is decrease in overall incidence of ROP in ELBW babies due to improved neonatal care and better ROP screening services or programs under Rashtriya Bal Swasthya Karyakram in developing countries like India.

6. Source of Funding

None.

7. Conflict of Interest

None.

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