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Original Article

Retinopathy of Prematurity and Neonatal Risk Factors: A Prospective Cohort Study

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Abstract

Background: *Retinopathy of Prematurity (ROP) is a disease process mostly reported in preterm and Low Birth Weight (LBW) neonates. Early detection of ROP in these groups and identification of associated neonatal factors and their prevention can prevent wide range of visual morbidity from impairment of vision to blindness in later life. The aim of this study was to determine prevalence of ROP and to identify neonatal risk factors for the development of ROP in preterm and LBW infants.*

Materials and methods: *A total of 105 LBW infants weighing <2000 gm and/or with a Gestational Age (GA) <35 weeks and more mature and heavier neonates with eventful neonatal period were enrolled in the study.Infants were subjected to eye examinations at 4 (±1) weeks after birthby experienced ophthalmologist trained in ROP.*

Results: *Out of 105 study population, ROP was found in 24 infants (22.9%):2 had stage 2 (25.0%), 17 had stage 3 (70.8%), 1 had stage 5 (4.2%) ROP. Two (8.4%) had Aggressive Posterior Retinopathy of Prematurity (APROP) and 3 (12.6%) had plus disease. On univariate analysis LBW, lower GA, female sex, apneic spell, sepsis, Prenatal Asphyxia (PNA) blood transfusion, longer duration of oxygen therapy and longer stay in hospital were found to be significant. On logistic regression analysis lower GA and female sex was found to be the independent factor for development of ROP.*

Conclusion: *To control blindness due to ROP the study suggested that all preterm infants weighing ≤1500gm and the GA of ≤32 weeks should be screened at 4 weeks post-natal age.*

Key words: Premature children; Retinopathy of prematurity; Risk factors.

INTRODUCTION

Retinopathy of Prematurity (ROP) is a disease in which retinal blood vessels of premature infants fail to grow and develop normally, sometimes resulting in visual impairment and blindness.[1] With the advent of new technologies and improved care for premature newborns, survival rates of Extremely Low Birth Weight (ELBW) neonates have jumped from 5% to 65 % and those of VLBW infants from 35 % to 90 % during the recent years.[2] Therefore, ROP is being increasingly diagnosed in these infants.

For the developing world ROP is an emerging problem.[3] According to earlier studies in Bangladesh, the incidence of ROP was variable ranges from as low as 4.4% to as high as 40%.[4-6] Studies are now focusing more on the identification of potentially modifiable factors associated with the development of ROP.[7] Numerous ophthalmic and nonophthalmic prognostic factors (Fluctuating FiO_2 of supplemental oxygen, sepsis, patent ductus arteriousus, anemia, intraventricular hemorrhage, blood transfusions and mechanical ventilation, apneic spells, exposure to light) have been identified to be associated with increased risk of unfavorable ROP outcome.[8]

Special Care Neonatal Unit (SCANU) of the Chittagong Medical College Hospital (CMCH) is dealing with a large number of high-risk neonates routinely. ROP is expected to be increasing as with the increased survival of these high-risk neonates. Therefore, it was important to document evidence-based frequency of ROP to find out the exact burden of ROP among the neonates admitted in SCANU of CMCH and the factors for development of ROP. The identification of such factors would be largely helpful for the prevention of ROP. Moreover, the risk factors would also help to anticipate at risk babies developing ROP and thus appropriate, timely intervention can be initiated which can prevent the development of this morbidity.With this context, this study aimed to determine the frequency and the predisposing factors of ROP in preterm and LBW infants hospitalize in the SCANU of CMCH and to compare the findings with other centers in Bangladesh and abroad.

MATERIALS AND METHODS

A prospective observational study was conducted during November 2018 to October 2019. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College and written informed consent was obtained from the parents of the participants.

Preterm and LBW neonates admitted into SCANU, with birth weight of <2000g, GA of 35 weeks or less, and infants with birth weight between 2000 g and 2500 g or GA of <37 weeks with unstable clinical course (RDS, sepsis, intraventricular Hemorrhage, multiple blood transfusions, apneic episodes, PNA) were included in the study.Infants with major congenital anomaly, with unilateral or bilateral retinal or choroidal disease (Other than ROP) and infants who died before the eye examination were excluded.

With a pretested, structured case record form, data regarding GA of the child, Sex of the child, Body weight, clinical events (RDS, Apnea, Sepsis, Perinatal Asphyxia, Intraventricular Hemorrhage, Blood transfusion, Mechanical ventilation, CPAP treatment, Oxygen therapy and relevant perinatal data) including the hospital course up to the time of discharge and the results of the eye examination were as recorded in a structured questionnaire.

Eye examination was carried out at 4 (±1) weeks after birth or 31 to 34 weeks postmenstrual age, which ever was later. Ophthalmologic examination was done by a single experienced ophthalmologist in accordance with the recommendations of the American Academy of Pediatrics, using binocular indirect ophthalmoscope (Brand:HIENE, Model: Omega500, made in Germany) with a 20D + lens in a Private Specialized Eye Hospital in Chattogram, Bangladesh. Examination was done with an infant speculum and a Kreissig scleral depressor, under topical anesthesia using 2% proparacaine drops. The pupils were dilated by using 0.4% tropicamide +1.25% phenylephrine eye drops two or three times, till full dilatation occurred. Retinopathy was graded into stages and zones as per the ICROP classification.[9]

Data were analyzed using SPSS 23.0. Infants were divided into two groups according to the stage of ROP (ROP stage <2 and ROP stage ≥2). Continuous data were expressed either as mean and standard deviation or median and Interquartile Range (IQR) according to distribution of data. Between groups differences of mean or median were tested by either independent sample t test or Mann-Whiteny U test. Categorical data were expressed as frequency (Percentage) and compared between groups by Chi-square test or Fisher's exact test. To detect independent risk factors for ROP logistic regression analysis was performed and Odds Ratio (OR) with 95% Confidence Interval (CI) was calculated. p-values less than 0.05 were considered statistically significant.

RESULTS

ROP was found in 24 of the 105 infants included in the study (22.9%): 6 had stage 2 (25.0%), 17 had stage 3 (70.8%), 1had stage 5 (4.2%). Out of 24 ROP cases 2 (8.4%) had APROP and 3 (12.6%) had plus disease (Figure 1).

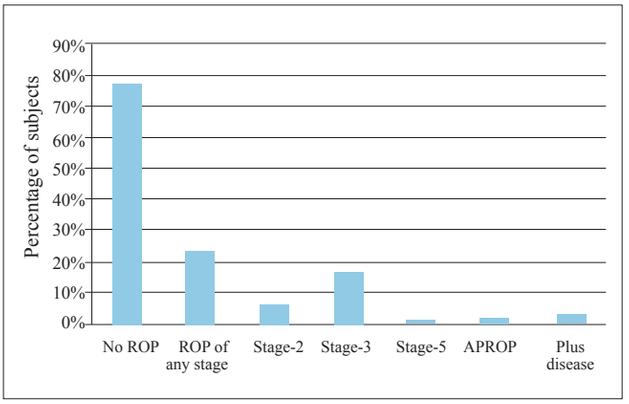

Figure 1 Staging of ROP among 105 studied neonates

The incidence of ROP was more in lower GA group and all of the 3 out of 105 included infants with GA <30 weeks had ROP. On the other incidence of ROP in infants from the GA group of 33-34 weeks and ≥35 week's group was 8.1% (3/37) and 11.4% (4/35) respectively. These differences among groups were statistically significant (Figure 2).

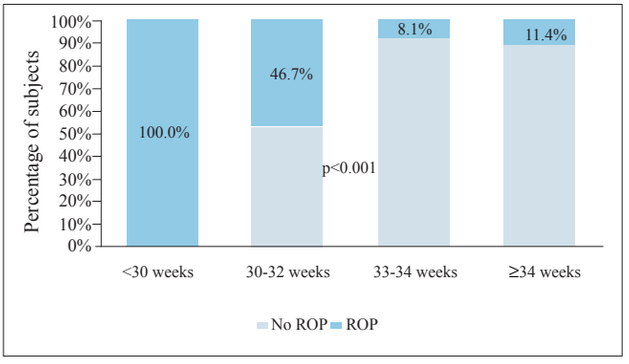

Figure 2 Distribution of ROP in infants with different Gestational Age (n=105)

The incidence of ROP was more in infants with lower birth weight group and none of the infants having birth weight >2000 gm (0/16) had ROP. On the otherhand incidence of ROP in infants from the birth weight group of <1500 g and 1500g to 2000 g group was36% (9/25) and 23.4%(15/64) respectively. These differences among groups were statistically significant (Figure 3).

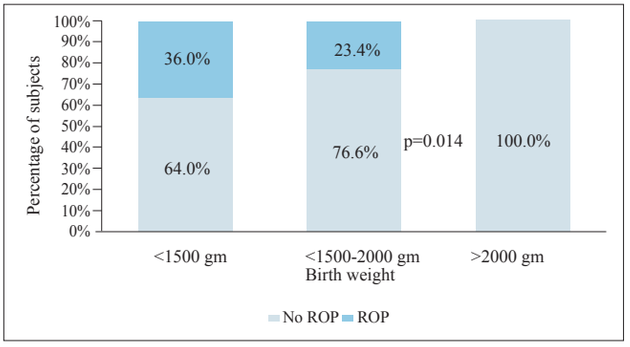

Figure 3 Distribution of ROP in infants with different birth weight (n=105)

Newborn who developed ROP had a significantly lower BW and GA than the non-ROP counter part. Female sex, Apneic spell, sepsis, anemia, BT, higher amount of BT and longer duration OT, CPAP treatment, phototherapy and longer LOS were found to be associated with ROP. However, maternal age, twin or triplet pregnancy, RDS, seizure, PNA, oxygen therapy and mechanical ventilation could not demonstrate a significant difference between both the groups (Table I). The median cumulative volume of transfused blood was 20ml in no ROP group. On the contrary it was 60 ml in the ROP group. The relationship of volume of transfused blood and ROP was significant (p=.006; reached from Mann-Whiteny U test). Duration of oxygen inhalation has very significant relationship (p= <0.001) with occurrence of ROP. The median days of oxygen inhalation was 3 days in no ROP group in contrast to 6 days in ROP group.

Table I Univariate analysis of factors contributing to the development of ROP

Characteristics	No ROP (n=81)	ROP (n=24)	p value
Gestational age (Weeks)	34.1±1.5	32.0±1.9	<0.001*
Birth weight (grams)	1707±310	1491±230	0.002*
Male sex	42 (51.9%)	6 (25.0%)	0.020
Maternal age (Years)	26.3±4.9	25.4±5.3	0.443*
Twin pregnancy	22 (27.2%)	6 (25.0%)	0.985*
Triplet pregnancy	6 (7.4%)	0 (0%)	0.333*
RDS	8 (9.9%)	4 (16.7%)	0.358†
Apneic spell	9 (11.1%)	11 (45.8%)	<0.001†
Sepsis	57 (70.4%)	24 (100%)	0.002†
Seizure	4 (4.9%)	0 (0%)	0.572†
Anaemia	21 (25.9%)	14 (58.3%)	0.003†
PNA(HIE-II)	11 (13.6%)	1 (4.2%)	0.289†
Blood transfusion	23 (28.4%)	15 (62.5%)	0.002†
Oxygen therapy	77 (95.1%)	24 (100%)	0.572†
CPAP treatment	1 (1.2%)	3 (12.5%)	0.037†
Mechanical ventilation	1 (1.2%)	1 (4.2%)	0.407†
Phototherapy	38 (46.9%)	21 (87.5%)	<0.001†
LOS (Days)	9 (6-15)	21 (10-30)	<0.001‡

*p values were reached from independent sample t test; †p values were reached from Chi-square or Fischer's exact test, ‡p value were reached from Mann-Whiteny U test, Significant values were in bold face.

Total 12 factors were found to be related with occurrence of ROP in univariate analysis (p=<0.05). Later, a binary logistic regression analysis was done including all of these factors (Table II). Finally,GA and sex of the neonate was revealed as an independent factor for ROP in the present study. The risk of ROP increased about 2 (1/0.478) times for every 1 week lower of GA. In other words, for each 1 week increase in GA there 52.2% (1-0.478=0.522) less chance to develop ROP. Regarding sex, female neonates were about 5 times more likely to had ROP compared to male neonates.

Table II Binary logistic regression analysis to determine the independent factors for ROP (n=105)

Risk factors	p value	Odds ratio	95% CI for OR	
			Lower	Upper
Gestational age	0.007	0.478	0.279	0.817
Female sex	0.040	4.872	1.077	22.045
Birth weight	0.355	0.490	0.108	2.222
Apnoeic spell	0.093	3.968	0.794	19.822
Anaemia	0.556	2.455	0.124	48.692
BT	0.992	0.985	0.053	18.325
CPAP	0.634	0.461	0.019	11.231
Phototherapy	0.324	2.735	0.370	20.213
LOS	0.795	1.014	0.913	1.127
Duration of OT	0.402	1.109	0.870	1.414
Amount of BT	0.470	0.988	0.955	1.021
Sepsis	0.110	9.537	0.601	151.302

OR: Odds Ratio, CI: Confidence Interval, BT: Blood Transfusion, OT: Oxygen Therapy, LOS: Length of Stay in Hospital, CPAP: Continuous Positive Airway Pressure, Significant values were in bold face.

DISCUSSION

About one in every four infants screened (22.9%) were found to have ROP in the present study. Due to the limitation of logistic support, eye examination could not be performed in CMCH during hospital stay. However, during follow up of the recruited patients there was huge drop out [159 neonates were subjected to screening, but examinations were completed by 105 (66%) neonates]. As the dropout rate was high this incidence of ROP may not be the exact figure what we ought to get.A higher prevalence (40%) was reported by Akter et al. from Bangladesh but this study was conducted more than a decade ago and there has been an improvement in neonatal care practice since then.[5] However, our finding agreed with a more recent study where the overall frequency of ROP was 23.5% among high-risk premature infants.[9,10] ROP incidence varies considerably (20.4%–44.4%) reflecting the differences in screening criteria, neonatal care and population heterogeneity.[4-6,11-13]

The mean GA was significantly lower in the ROP group when compared with the non-ROP group in the present study and it was revealed as a significant factor for ROP in univariate and multivariate analysis. On the other hand, though the mean birth weight was lower among infants who developed ROP, than the non-affected infants, the difference was not significant in multivariate analysis. Present study results were consistent with other studies that suggested that the incidence and severity of ROP are inversely related to birth weight and GA, with a few diagnoses of severe ROP being identified among infants with a birth weight >1500g or GA >32 weeks.[14,15] In the present study, female infants were more likely to develop ROP than male infants and the association persisted in the multivariate analysis. Studies on gender and ROP risk have also been conflicting.[16-18]

The presence of anaemia, blood transfusion and amount of transfused blood all were significant risk factors for ROP development in univariate analysis in the present study and this was similar to other studies.[5,19] The total duration of oxygen supplement was found to be significant risk factors for ROP on univariate analysis which agreed with previous studies.[5,6].

Longer length of initial hospital admission has been found to be significantly associated with higher rates of ROPin univariate analysis in the present study. The finding agrees with other studies.[7] The association between length of hospital stay and ROP, however, may arise because length-of stay is a proxy for cumulative illness burden, with the most ill infants requiring the longest hospital stays.

Neonatal sepsis is among the most frequently identified risk factors for any ROP and severe ROP.[7] However, conflicting evidence were noted from previous Bangladeshi studies.[6,10] In agreement with the present study, Bhuiyan et al. observed a significant association between sepsis and ROP in univariate analysis only but Shahidullah et al. reported no such association.[10,6]

The prevalence of some risk factors like apnoeic spell, RDS, PNA, CPAP treatment, mechanical ventilation was very low in the present study (11.4%, 11.4%, 3.8% and 1.9% respectively). Though these factors increase the risk of ROP, due to very low prevalence it was not possible to make any comment from the present study.[7]

LIMITATIONS

The present study was based on a small sample size from a single institution. Maternal risk factors were not studied in this study.

CONCLUSION

Univariate analysis showed from the included 20 factors, 12 factors (Lower GA, low BW, female sex, Apneic spell, sepsis, anemia, BT, higher amount of BT and longer duration OT, CPAP treatment, phototherapy and longer LOS) were found to be associated with ROP. Multivariate analysis revealed only two factors (Lower GA and female sex) to have an independent association with ROP.

RECOMMENDATIONS

To control blindness due to ROP we suggest that all preterm infants weighing 1500gm or less and the GA of 32 weeks or less should be screened at 4 weeks post-natal age. Studies in larger scale (Multi centre study) with larger sample size should be undertaken to find out the real picture of ROP and associated risk factors among the preterm LBW newborns in Bangladesh.

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DISCLOSURE

The authors declared no conflicts of interest.

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