Association of infection, blood transfusion and other clinical factors with retinopathy of prematurity (ROP)

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Abstract

Background : In Bangladesh advancement of neonatal care has increased the survival of preterm very low birth weight (VLBW) neonates; thus the incidence of Retinopathy of prematurity (ROP) has also been increased.

Objective : To identify the cases of ROP and to observe the association of birth weight, infection and other clinical factors (recorded during hospital stay) with its occurrence.

Method : This was a prospective observational study at special care baby unit (SCABU) and Intensive care unit of Dhaka Shishu Hospital from July, 2006 to March, 2008 among premature (34 weeks) and/or VLBW (1500 gm) neonates. Neonates who fulfilled the inclusion criteria were followed up daily to record certain clinical factors and features suggestive of sepsis.Infants were divided into "No ROP group" that included newborns without ROP (n=35), and "ROP group" that included newborns with ROP (n=23). Comparative analysis of recorded clinical factors was done between the two groups.

Result : Among the study neonates rate of ROP occurrence is 40% (23 of 58). VLBW, culture proven septicaemia, mean total hours of oxygen inhalation, mechanical ventilation, cumulative volume of blood transfusion, and intra ventricular hemorrhage (IVH) grade II were significantly related with ROP. Stepwise logistic regression analysis revealed birth weight [p=.004, Odds Ratio (OR), .33; Confidence Interval (CI), 0.14 to.436], culture proven septicaemia (p=.005; OR, 4.0 CI, 2.50 to 9.99) and cumulative volume of blood transfusion (p=.013; OR,.43; CI, .028 to .653) to be most significant factors.

Conclusion : Rate of ROP occurrence in the current study is 40% and VLBW, culture proven septicaemia and large volume of blood transfusion are significant risk factors.

Introduction

Retinopathy of prematurity (ROP) is a disease of incomplete retinal vascularization in infants.[1] It has been considered as one of the major causes of blindness in infants and children in developed countries. It is now emerging as a problem in developing countries like ours also, due to the increased survival of premature and very low birth weight neonates with the blessings of modern advances in neonatology.[2]

Many recent studies have suggested causative association of low birth weight, low gestational age, high oxygen exposure, blood transfusion and many other factors with ROP.[3] It has also been found that infections, culture proven septicaemia and associated systemic inflammatory response are also responsible for ROP occurrence .[4]

Neonatal intensive care units (NICU) in developing countries have to face the giant problem of infection and septicaemia among premature infants despite of considerable progress in hygiene and introduction of new antimicrobial agents.[5] In a study of neonatal sepsis in NICU of the largest pediatric hospital, it has been found that 21% of neonates with a birth weight less than 1500 grams had septicaemia.[6] The correlation of septicaemia and other factors with occurrence of ROP in our set up, has yet not been observed.

The purpose of this study is to determine the association of gestational age, birth weight, septicaemia, and other factors with the development of ROP.

Methods

This prospective observational study has been conducted at Special Care Baby Unit (SCABU) and Intensive Care Unit (ICU) of Dhaka Shishu Hospital (DSH) from 1st July, 2006 to March, 2008. Neonates admitted to SCABU or ICU born at 34 or less weeks of gestation having birth weight 1500 gm were initially enrolled in the study. Neonates who died during hospital stay or could not complete the ophthalmoscope examination schedule were excluded during final data entry. Ophthalmological examinations were performed at Paediatric Ophthalmology Department of Bangladesh Eye Hospital.

At admission maternal history has been recorded from maternal recall and accompanying documents. Duration of gestation has been confirmed by assessing modified new Ballard score. Daily follow up has been documented regarding clinical course, investigations and culture reports if there was any. When the baby got oxygen inhalation its duration, maximum FiO_2 (Oxygen fraction of the inspired air, according to Guha DK[7]), highest SpO_2 (percent saturation of hemoglobin) was recorded daily.

Based on the presence of one or more clinical signs consistent with possible serious bacterial infection (including lethargy, feeding intolerance, abdominal distension, vomiting, groaning, respiratory distress, hypothermia, hyperthermia) neonates were diagnosed as suspected sepsis. Blood culture was taken in all

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cases of suspected sepsis and cerebrospinal fluid (CSF) culture was performed in cases of suspected meningitis.

Blood was collected aseptically in a standard method. Using a sterile syringe and needle about 2 ml of blood was collected from a peripheral vein and was added to the culture media bottle supplied from the microbiology department.

According to the age of onset of clinical features study neonates were categorized as having early onset neonatal sepsis (EONS) (within 7 days of life) or late onset neonatal sepsis (LONS) (8 to 28 days of life). Daily clinical care was performed by attending neonatologist in accordance with hospital protocol.

At the end of the hospital stay all the parents were counseled for regular follow up and ophthalmological examination. First eye examination date was fixed at 4 to 6 weeks of chronological age of the baby.

One paediatric ophthalmologist has examined all the cases. After initial ophthalmological examination, neonates were advised for repeat examinations. Healthy eyes were examined 2-3 weeks interval, and diseased eyes were examined weekly After ophthalmological examinations neonates were divided into 'No ROP group' that had normal findings on examinations (No ROP) and 'ROP group' that included newborns with abnormal findings (any stages of ROP). Risk factors were compared between the two groups.

Procedure of eye examination

The ophthalmologist performed indirect ophthalmoscope. Pupils were made dilated with 1% phenylephrine and 0.5% tropicamide eye drop. Drops were instilled twice 1 to 5 minutes apart. The examination was performed about 20 to 25 minutes later using a binocular indirect opthalmoscope and + 20D lense. Lid speculum was used to view the retina properly.

Data analysis

Data managment and anlaysis was done using the Statistical Package for the Social Science (SPSS, version: 12). Comparative analysis of the variables was done between the "No ROP" and "ROP" groups. During univariate analysis the categorical variable were tested with Chi squire (c^2) and for continuous variables "Student's t test" was done. Multivariate analysis (of the variables which were found to be significantly related with the occurrence of ROP) was done by Stepwise logistic regression analysis.

Ethical approval

The Thesis and Dissertation Approval Committee, Bangladesh College of Physicians and Surgeons, approved the study. The parents were informed about the study, and their written informed consents were recorded.

Results

During the study period, 129 premature neonates fulfilled inclusion criteria of which 36 (28%) died. Screening could be completed in 58 neonates (from discharged 93, 62%). Among 58, "No ROP" group comprised of 35(60%) and "ROP" group comprised of 23(40%) neonates (Fig.1). Therefore in this study the rate of ROP occurrence is 40%.

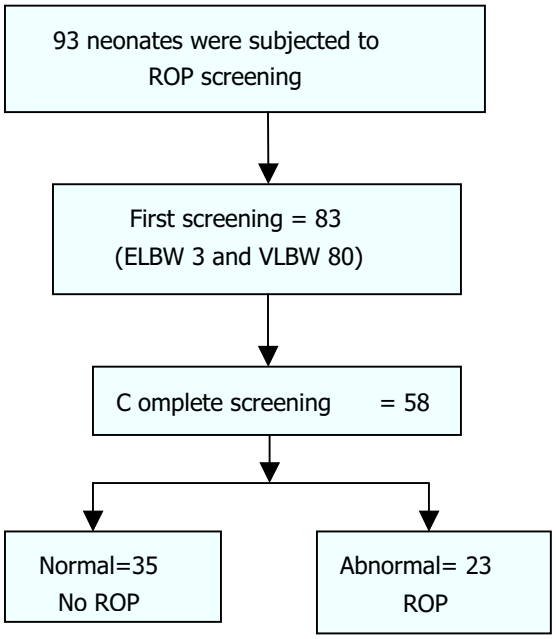

Fig 1: Study population

Characteristics of study neonates have been shown in table I. Among the study population, gestational age was ranging from 27 to 34 weeks and birth weight was ranging from 990 to 1500 gm. Twenty six percent of the neonates were delivered at home, 64% were delivered normally (NVD). Sixty percent of the neonates were admitted within 24 hours of age.

Table I : Distribution of the baseline characteristics among the study neonates (N =58)

Parameters	Categories	Number	Percentage	Mean
Ges tational age(weeks)	27 - 28	03	05	30
	29 - 30	19	33	
	31 - 32	23	40	
	33 - 34	13	22	
Birth weight (grams)	?999	03	06	1185±186
	1000 - 1250	17	30	
	1251 - 1500	38	64	
Place of delivery	Hospital	43	74	
	Home	1 5	26	
Mode of delivery	NVD	3 8	64	
	LUCS	2 0	36	
Sex	Male	28	48	

NVD-Normal vaginal delivery LUCS-Lower Uterine caeserian section

In this study suspected bacterial infection cases were 47. Among them 20 babies were in No ROP group and 27 were in ROP group.The most common clinical presentations of patients with suspected bacterial infection were feeding intolarence, (39/47), lethargy (32/47), fluctuation of SpO_2(13/47) and colour change (12/47) showed in table II. Of the 47 neonates with suspected septicaemia 21(45%) had culture positive septicaemia . Among 21 culture positive septicaemia 6

had EONS and the rest had LONS. Organisms revealed on blood culture have been narrated in table III. Commonest organism isolated form blood were Acinetobactor (12.7%), Klebsiella pneumoniae (11%), Serratia mercesence (8.5%), Escheriricia coli (8.5%) and Staphylococcus aureus (4.2%). None of the CSF culture was positive.

Table II : Clinical features in suspected sepsis cases (n=47)

Clinical features	Number	percentage
Feeding intolerance	39	83
Lethargy	32	68
Fluctuation of SpO_2	13	28
Color change/mottling	12	25
Apnoe a	08	17
Abdominal distension	08	17
Vomiting	07	15
Convulsion	07	15
Respiratory distress	06	13
Fever	04	09
Hypothermia	03	06

Table III : Organisms isolated on blood, CSF or other cultures (N=47)

Organism	Number	Percentage
Acinetobacter	06	13
Klebsiella Pneumoniae	05	11
Serratia marcescence	04	8.5
Escheriricia coli	04	8.5
Staphylococcus aureous	02	4.0
None	26	55
Total	47	100

An univariate analysis was done to see the relationship between investigated risk factors and No ROP and ROP groups. Among eleven risk factors, six were significantly related with the development of ROP (birth weight, culture proven septicaemia, total hours of oxygen inhalation, mechanical ventilation, volume of blood transfusion and IVH) (table IV). Logistic regression analysis showed three of them to be mostly significant. These are very low birth weight, culture proven septicaemia and large cumulative volume of blood transfusion (table V).

Table IV : Univariate analysis on association of risk factors with Ohthamoscopy findings (N=58)

Parameters	No ROP(35)	ROP(23)	p value	Odds ratio(95% CI)
Mean gestational age(weeks)	30±2	29±2	.329	-
Mean birth weight(gm)	1258	1070	.03	2.18(1,12 -5.95)
Mother had PET (11)	06	05	.573	-
Delivered by NVD (39)	20	19	.266	-
Mal e/Female	17/18	11/12	1.00	
Mean hour of O_2 inhalation	54.54	141.41	.001	10.2(4.85 -17.82)
Mechanical ventilation(06)	0	06	.001	3.36(2.05 -5.52)
Suspected septicaemia (47)	20	27	.243	-
Culture positive septicaemia(21)	05	16	.005	.05 (.010 -.248)
Blood tra nsfusion (ml/kg)	10.96	67.94	.005	2.79(1.65 - 4.41)
IVH grade II or more (12)	02	10	.08	3.75(2.794 -7.72)

Table V: Risk factors revealed in stepwise logistic regression analysis

Factors	*p value*	OR	95% CI
Birth weight	.004	0 .33	0.14 - .436
Culture positive septicaemia	.005	4.0	2.50 -9.99
Blood volume transfused	.013	0 .43	0 .028 -.653

Discussion

This prospective hospital based study identified the ROP cases and associated risk factors among the hospitalized preterm VLBW neonates. ROP has a well-known variation in the incidence as well as in associated risk factors among centers and among countries, related to differences in case ascertainment, sampling variability, and aspects of both obstetric and neonatal clinical practice.[2,4,8]

The same variables have been occasionally reported as associated with an increased risk of ROP by some single-centre, cohort studies, or on the contrary as not associated or even protective by some others. For example, many studies have confirmed the association of Oxygen supplementation with occurence of ROP.[2,4] On the contrary Shohat M et al[9] and Patil J et al[10] in their study did not demonstrate any significant association between ROP and length of time in supplemental oxygen or the mean maximum oxygen concentration required. Again, Gitalisa et al [11] showed that younger gestational age and low birth weight were not associated with the risk of ROP.

Among other risk factors studied, birth weight has been termed as the most significant sign of maturity.[12] The immaturity of retinal vessel correlate with birth weight.[10,13] A good number of studies have proven the relationship between very low birth weight and occurrence of ROP.[2,4,9] This study demonstrated the increased incidence of ROP in very low-birth weight babies which is comparable with most studies. Mean birth weight in the ROP group was 1070 gm where as in the normal findings group it was 1258 gm (p=.03; OR , 2.18; 95% CI 1.12-5.95). Bassiouny et al[3] in Indonesia and Shah et al[14] had similar findings of mean birth weight.

Though many studies of ROP[2,12,14] have shown that younger gestational age has a causative relationship with development of ROP, this study could not reveal any significant relationship. In this study mean gestational age of ROP group was 29.0 ± 2 weeks and No ROP group was 30±2 weeks. Only 03 (05%) neonates were in the high risk gestational age group (<28 weeks) and 62% of the neonates had >30 weeks of gestation. Unlike developed countries only few very premature extremely low birth weight neonate could be saved who fortunately had a smooth clinical course and short duration of hospital stay. These factors may be responsible for gestational age not to be significant. There are other studies in developing countries who did not find significant relationship between gestational age and ROP.[9,11,15] Gitallisa et al[11] in Indonesia have found that mean gestational age in Normal and ROP group is 33.3 and 32.0 weeks consecutively. Lam et al[15] in their study at Hong Kong also could not show the relationship of younger gestational age and ROP.

Infections and sepsis are frequent complications among preterm infants.[2-3, 8-11] Many previous studies of ROP have suggested sepsis as a risk factor. Bacterial, fungal and any other (non-specified) sepsis are significant risk factors in preterm newborns, both for threshold and all

degrees of ROP.[2,16,17] Sepsis is frequently accompanied by hypotension, which may impair tissue perfusion and release of angiogenic factors secondary to hypoxic stress. Part of this effect might be due to direct exposure of the developing retina to circulating products of infection and/or inflammation. Another potential mechanism that deserves exploration is that inflammation and/or oxidative stress can modify the known increased risk of oxygen-associated ROP. Taken together, accumulating evidence suggests that prenatal, perinatal, and postnatal systemic inflammation contribute to the occurrence of ROP.[4,18]

In the present study, of 21 culture positive septicaemic neonates, 16 had abnormal retinal examination. Suspected sepsis or culture negative sepsis did not show significant correlation. In premature neonates many diseases are manifested with the features of sepsis. All suspected sepsis with differential diagnoses might not be case of septicaemia till last. This may be the explanation why only the culture proven sepsis became significant. This finding has similarity to that of Bassiouny et al[3] and Minghua et al[16].

Like other studies of ROP, our study revealed prolong duration of oxygen inhalation were significantly associated with abnormal eye examination findings. We had 8(11.1%) neonates who got mechanical ventilation support and eight of them developed at least stage II- ROP. Bassiony et al[3] ,Shah et al[14], Lam et al[15] and Minghua et al[16] have got the similar result.

Transfusion may adversely influence the retina, not only by increasing oxygen delivery to the retina by adult hemoglobin, but also by overloading iron, which in turn increases free oxygen radicals.[18] In our study we found >37 ml /kg of cumulative blood transfusion has significant association with causation of ROP. We had two neonates who undergone double volume exchange transfusion and both of them developed significant ROP. The authors in their previous report Dani C et al[19] and Dutta et al.[20] observed that administration of packed cell and double volume exchange transfusions in the neonatal period is a major risk factors for the development of threshold ROP.

Conclusion

Our study demonstrates the incidence of ROP in low-birth weight babies which is comparable with most Western reports.

The data of our study showed that culture proven septicaemia, very low birth weight and blood transfusion are independent risk factors in the development of ROP. Further prospective and multicentre studies are needed to estimate the true incidence and risk factors of ROP in Bangladesh

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