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Original Research Article

Prevalence and risk factors of retinopathy of prematurity among preterm neonates admitted to a tertiary care hospital

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ABSTRACT

Background: Retinopathy of prematurity is a multifactorial vaso-proliferative disorder of the retina affecting mainly premature neonates. We aimed to determine the prevalence of ROP as well as to find out the risk factors behind this.
Methods: This cross-sectional analytic study was conducted in the department of neonatology and obstetrics and gynecology of BSMMU, Dhaka, from April 2016 to September 2017. All stable term and stable preterm newborns of both sexes were enrolled. Hemodynamically unstable newborn babies, newborns with congenital anomalies, newborns of<30 weeks, and newborns admitted after 72 hours of age were excluded. 70 samples comprising into two groups, in preterm group 40 and in term group 30 samples were taken. Plasma tocopherol <500 mg/dl was used as a deficient vit-E level. ROP screening was done by an ophthalmologist using a binocular indirect ophthalmoscope.
Results: Among 40 pre-term neonates, 12 were diagnosed as ROP with a prevalence of 30%. Stage 1-3 ROP were present among 8, 2 and 2 cases, respectively. There were equal number of males and females (35 each). Deficient vit-E level and SGA were significantly associated with ROP (p=0.05 and p=0.01, respectively). Stepwise multiple logistic regressions of risk factors showed vitamin E deficiency as a significant risk of developing ROP when other risk factors are intercepted.
Conclusions: Prevalence of ROP was 30% among pre-term neonates. Deficient vit-E level and SGA were significantly associated with ROP. Vitamin E deficiency resulted significant risk of developing ROP when other risk factors are present.

Keywords: Retinopathy of prematurity, Neonate, Vitamin E, SGA

INTRODUCTION

Retinopathy of prematurity is one of the most important disabilities and it is a vasoproliferative retinopathy occurring primarily, but not exclusively, in premature infants.[1] Every year, fifteen million infants are born preterm, and this number is rising. Over one million children die every year due to complications of preterm birth, and millions more face lifetime disability.[2]

The condition is a major cause of Pediatric blindness in developed countries. Although acute retinopathy of prematurity regresses spontaneously for more than 90% of infants, a chronic or late proliferative phase follows in some eyes, whereby tractional retinal detachments, macula ectopia, scarring, and Significant visual loss occur. While retinopathy of prematurity was considered untreatable 10 to 20 years ago, the condition has become controllable in recent years. Cryopexy or laser is useful for arresting the progression of ROP to avoid vitreo-retinal complications.[3]

There are two phases of retinopathy of prematurity. The 1st phase of ROP in premature infants consists of

cessation of the normal retinal vascular growth, which would occur in utero, as well as loss of some of the developed vessels. As the infant matures, the resulting non-vascularized retina becomes increasingly metabolically active and increasingly hypoxic. The 2nd phase of ROP, retinal neovascularization, is hypoxia-induced. This occurs at about 34 weeks of postmenstrual age. The hypoxia-induced retinal neovascularization phase of ROP is similar to other proliferative retinopathies.[4]

Although many causative factors have been proposed for ROP, low birth weight and low gestational age have been consistently associated with the disease. Severe disease is seen especially in babies under 26 weeks of gestation. The immaturity of retinal vessels correlates with the birth Weight. The high incidence of ROP in very low birth weight (VLBW) infants appears to be related to these babies being more ill, and they are exposed to a greater concentration of oxygen, usually for longer durations.[4]

Plasma vitamin E levels are low in preterm neonates, and it has been suggested that the antioxidant properties of vitamin E may be important in protecting the developing retina from the harmful effects of oxygen-free radicals. The use of vitamin E supplementation as a means of reducing the incidence and severity of ROP remains controversial. Growth-restricted infants have increased mortality and morbidity rates. However, there have been reports on the impact of growth restriction on the development of ROP. There has been intensive research into the role of oxygen in the pathogenesis of this condition. The significance of oxygen saturation lies in the choroidal Circulation which is unique in that it fails to autoregulate to altered oxygen tension. Hyperoxic conditions may also interfere with the growth and maturation of spindle cells, causing gap junction formation between cells and disruption of normal migration and vasculogenesis.[5]

ROP may develop in premature infants who have received little or no supplemental oxygen, and it is not known what determines which infants progress to retinal detachment. The hypothesis put forward that genetic factors may contribute to the development of ROP is supported by variation observed between ethnic groups. Blood transfusion has been identified as an important causative factor for ROP. A potential role for blood transfusions or anemia in the pathogenesis of ROP has been suggested by several investigators. Some previous studies have suggested sepsis as a risk factor for ROP. In some studies, sepsis increased the risk of ROP, but it was not independently significant when BW was controlled. Steroids thought to prevent endothelial cell migration had minimal effect on normal retinal development but greatly reduced neovascularization in rat ROP.[5]

The high incidence of ROP in patients using ventilator care for >48 h may be correlated with prolonged exposure to high oxygen pressure, which may influence the development of ROP.A significant association between the presence of IVH and the development of ROP in many studies.[6]

In these perspectives, the present study aimed to determine the prevalence of ROP as well as to find out the risk factors behind this at Bangabandhu Sheikh Mujib Medical University, Bangladesh.

METHODS

This cross-sectional analytic study was conducted in the department of neonatology and the department of obstetrics and gynaecology of BSMMU, Dhaka, from April 2016 to September 2017. Ophthalmoscopic examinations were performed in the department of ophthalmology of this institution.

All stable term newborns (38-42 weeks of gestation) and stable preterm (30-37 weeks of gestation) newborns of both sexes were enrolled.

Hemodynamically unstable newborn babies, newborns with congenital anomalies, newborns of<30 weeks, and newborns admitted after 72 hours of age were excluded.

The sample size was calculated by using the following formula.

$N=Z^2 P(1-P)/d^2$

$=(1.96)^2\times0.25(1-0.25)^2/(0.05)^2=192$

Where, n=sample size, P=expected prevalence or proportion. As the proportion of vita E status is about 25% (p=0.25), and d=precision (In proportion of one; if 5%, d=0.05). Z: For the level of confidence of 95%, which is conventional, the Z value is 1.96.

Due to time and financial constraints, 70 samples comprising into two groups, in preterm group 40 and in term group 30 samples were taken. In the preterm group, the sample size was larger to minimize dropout.

After taking informed written consent from parents of the selected neonates, a detailed maternal history was taken, birth weight was collected, or admission weight was taken by a digital weighing scale (SALTER, model-914). Blood Sample for vitamin E estimation was collected between 72 hours and 120 hours of age. When the baby got oxygen inhalation for respiratory distress or cyanosis due to any cause, its flow rate and duration were also noted daily.

There are several ways to determine vitamin E sufficiency, such as vitamin E/ total lipid, cellular vitamin E concentrations, and plasma tocopherol. In our study, we used plasma tocopherol because of the ease of using this test, and it has a clear cutoff for deficiency according to the WHO criteria, i.e., tocopherol <500 mg/dl.[7]

The date of the first ROP examination was fixed at 4 to 6 weeks of chronological age of the baby, and the repeat examination was addressed accordingly. ROP screening was done by an experienced ophthalmologist of the department of ophthalmology of BSMMU using a binocular indirect ophthalmoscope. Pupils were dilated with 1% phenylephrine and 0.5% tropicamide eye drops. Drops were instilled twice, 5 minutes apart, with the excess drops immediately blotted from the lids by clean tissue paper to minimize systemic side effects. The examination is performed about 30 minutes later using a binocular indirect ophthalmoscope and 20D lenses. If necessary, scleral indentation was done to see the periphery of the retina. The investigator made a phone call to every parent one day before the ROP screening schedule to give a reminder to minimize drop-out.

After counseling and obtaining consent, 3ml free flow venous blood was drawn in a red-top test tube supplied by the laboratory with all aseptic measures. Then the tube was wrapped in aluminum foil to protect from sunlight and kept in a cool box with ice and transported to the local office of the testing lab within 30 minutes. Vitamin E estimation was done by an HPLC system with a UV detector from Waters Pvt. Ltd., USA.

Data analysis was done using the statistical package for the social sciences (SPSS) version 20.0. Mean and standard deviation were calculated for the continuous variables, and the proportion was calculated for the categorical variables. Level of significance was tested by independent t test, Chi-squared test, odds ratio, or Relative risk, and Stepwise multiple logistic regression test, where applicable. Ethical clearance was obtained from the institutional review board of BSMMU.

RESULTS

Among 40 pre-term neonates, 12 were diagnosed as ROP with a prevalence of 30% (Figure 1). Stage 1 ROP was present among 8 neonates, stage 2 and stage 3 ROP were present among 2 cases each, respectively (Figure 2). Out of 40 pre-term neonate 18 (25.7%) were born in 30-32 weeks and 22 (31.4%) were born in 33-37 weeks. There were equal number of males and females (35 each). 53 (75.7%) babies were born by LUCS, and the remaining 17 (24.3%) by NVD. The 15 (21.4%) neonates were SGA (Table 1). Among 40 pre-term neonates, 17 needed O_2 therapy. Majority of them (12, 30%) required O_2 at 1-2 L/min, 3 (7.5%) required 3-5 L/min and 2 required >5 L/min O_2. 5 (12.5%) babies required O_2 <24 hours,

another 5 (12.5%) required 25-72 hr, 4 (10%) needed 73-120 hr and rest 3 (7.5%) needed >120 hr O_2 (Table 2). Deficient vit-E level, SGA, lower gestational ages, sepsis, necessity of O2 therapy, and blood transfusion were assessed for causative risk factors of ROP among pre-term neonates. Deficient vit-E level and SGA were significantly associated with ROP (p=0.05 and p=0.01, respectively), while lower gestational ages, sepsis, necessity of O_2 therapy, and blood transfusion had no statistically significant association with ROP (Table 3). Stepwise multiple logistic regressions of risk factors showed vit E deficiency as a significant risk of developing ROP when other risk factors are intercepted Table 4.

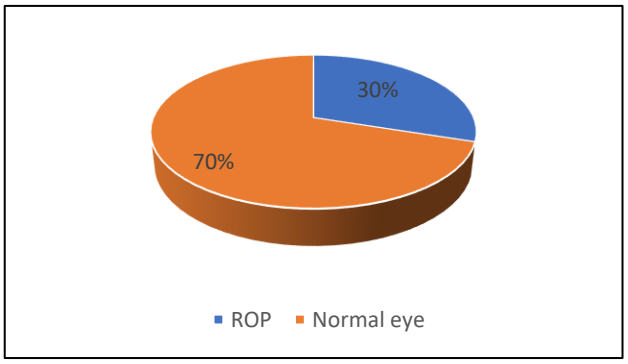

Figure 1: Prevalence of ROP among pre-term neonates.

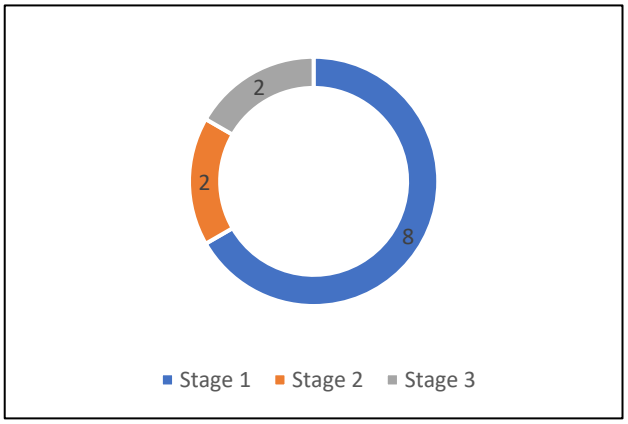

Figure 2: ROP according to stages.

Table 1: Baseline characteristics of study subjects, (n=70).

Parameters	N	Percentage (%)
Gestational age (in weeks)		
Pre-term (30-32)	18	25.7
Pre-term (33-37)	22	31.4
Term (38-42)	30	42.9
Gender		
Male	35	50
Female	35	50

Continued.

Parameters	N	Percentage (%)
Mode of delivery		
LUCS	53	75.7
NVD	17	24.3
Body wight		
SGA	15	21.4
AGA	47	67.1
LGA	08	11.5

Table 2: O_2 necessity with rate and duration among pre-term neonates.

O_2 necessity	N	Percentage (%)
No	23	57.5
Yes		
Rate		
1-2 L/min	12	30
3-5 L/min	3	7.5
>5 L/min	2	5
Duration		
<24 hr	5	12.5
25-72 hr	5	12.5
73-120 hr	4	10
>120 hr	3	7.5

Table 3: Association between ROP and various risk factors.

Risk factors	ROP		RR	P value
	+ve	-ve		
Vit-E level				
Normal	1	11	4.71 (1.07-32.5)	0.05
Deficient	11	17		
Birth weight				
SGA	6	4	3.0 (1.25-7.21)	0.01
AGA/LGA	6	24		
Gestational age (in weeks)				
30-32	5	13	0.87 (0.33-2.29)	0.78
33-37	7	15		
Sepsis				
Present	8	14	1.64 (0.59-4.57)	0.33
Absent	4	14		
O_2 therapy				
Needed	7	10	1.89 (0.72-4.95)	0.18
Not	5	18		
Blood transfusion				
Needed	3	8	0.88 (0.29-2.66)	0.82
Not	9	20		

Table 4: Stepwise multiple logistic regression of risk factors.

ROP intercept	P value	95% CI	
		Lower	Upper
Vitamin E	0.000	4.08	4.09
Birth weight	0.063	0.008	1.13
Gestational age	0.115	0.023	2.54
Sepsis	0.261	0.015	3.13
Oxygen therapy	0.097	0.635	238.39
Blood transfusion	0.097	0.006	1.52

DISCUSSION

Several previous studies documented variable prevalence of ROP among study subjects. Hakeem et al conducted a study comprising 172 pre-term neonates at Egypt and documented 19.2% prevalence of ROP. In their study, 18 cases (54.5%) had stage 1, 9 (27.3%) had stage 2, and 6 (18.2%) had stage 3 ROP. There were no stage 4 and stage 5 cases.[8] Our study had a higher prevalence rate but similar ROP staging among cases. Three other Asian studies conducted in Pakistan, Singapore, and India by Taqui et al, Shah et al and Murthy et al reported the prevalence of ROP to be 32.4%, 29.2%, and 24%, respectively, close to our finding.[9-11]

Hakeem et al reported female to male ratio of 1.04:1, which was almost similar to the current study (1:1). They also documented more LUCS among the babies, but with a lower percentage (58.1%) than our finding (75.7%).[8]

Baydas et al found a weak but statistically significant correlation between the serum vitamin E levels and gestational age (r=0.324, p=0.05). They found that premature infants have lower levels of serum vitamin E than term infants (p=0.05).[12] However, another study reported that there was no significant difference between the vitamin E levels of preterm and term babies.[13]

Many studies have confirmed the association of oxygen supplementation with the occurrence of ROP.[14-16] The current study showed there was no significant relationship between ROP and the duration of oxygen and the mean concentration of oxygen.

Several studies have demonstrated that sepsis has a close relationship with the occurrence of ROP.[17-19] However, Sabzehei et al and Lin et al reported that sepsis was not significantly associated with premature infants with and without threshold ROP (p>0.05), which is consistent with the current study.[20,21]

We found significantly lower serum vitamin E levels in the premature newborn infants with ROP then who didn't develop ROP, that is agreement with Edward et al.[22]

In this study, 6 confounders could contribute to the development of ROP, like vit-E level, SGA, low gestational age, sepsis, oxygen therapy, and blood transfusion. In many studies of ROP, younger gestational age is a significant risk factor.[23] This study did not show any significant relationship of gestational age with the occurrence of ROP. Many studies have confirmed the association of oxygen supplementation with the occurrence of ROP.[14,15] On the contrary, Shohat et al 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.[24] The current study did not find any relationship between ROP and oxygen therapy, which may be due to the small sample size.

Transfusion may adversely influence the retina, not only by increasing oxygen delivery to the retina, but also by overloading iron, which in turn increases free oxygen radicals. The transfused adult haemoglobin increases oxygen delivery to the retina, which may increase the risk of ROP. In this study, no significant correlation was found between ROP and blood transfusion, but Shaheen et al and Yang found a significant correlation between ROP and BT.[25,26]

In this study, among the 40 premature neonates 10 (25%) were small for gestational age (SGA). A significant relationship was observed between SGA and ROP. There have been reports on the impact of growth restriction on the development of ROP.[27]

Limitations

It was a single-center study comprising a smaller sample size. During the study period serum vitamin E estimation facility was not available in the country; the specimen was sent to a neighboring country. A retinal camera was not available in BSMMU as well to delineate retinal vessels accurately. Further multi-center study comprising a larger sample size and long-term follow-up is recommended.

CONCLUSION

The prevalence of ROP was 30% among pre-term neonates. Deficient vit-E level and SGA were significantly associated with ROP. Stepwise multiple logistic regressions of risk factors showed Vitamin E deficiency as a significant risk of developing ROP when other risk factors are intercepted.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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