The Incidence and Risk Factors of Retinopathy of Prematurity in Sick Newborn Care Unit in a Tertiary Care Hospital in Eastern India - A Cross-Sectional Observational Study

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ABSTRACT

BACKGROUND

Retinopathy of prematurity (ROP) is one of the leading causes of ocular morbidity and mortality throughout the world. Prematurity, low–birth, and oxygen therapy are considered to be the common risk factors. The maldeveloped retina in those affected are very much prone to develop refractive error, neo-vasculopathy, and neurosensory detachment. The purpose of our study was to find out the incidence and ascertain the risk factors of retinopathy of prematurity among the neonates attending the sick neonatal care unit and OPD of Calcutta National Medical College & Hospital.

METHODS

This is an institution based cross-sectional observational study conducted in the sick newborn care unit of a tertiary care hospital. Informed consent was obtained from the parents along with proper birth history. Indirect ophthalmoscopy with a + 20 dioptre (+ 20 D) lens with a paediatric scleral depressor was performed in each eye under the guidance of the neonatologist after pupillary dilatation. If either eye was found to have ROP, the baby was considered as an ROP case in the study and each eye was considered as a single case.

RESULTS

50.27 % babies (N = 91) were delivered by Lower Uterine Segment Caesarean Section (LSCS) and 55. 24 % babies were < 32 weeks of gestational age whereas 21.45 % (N = 39) babies were having < 1500 gm birth weight. Phototherapy was needed in 50 % of the babies (N = 92) whereas hyperbilirubinemia was present in 59.66 % of total babies. Bradycardia, apnoea, and sepsis were present in 29.83 % (N = 54), 25.41 % (N = 46), 41.98 % (N = 76) of the babies respectively. When compared in the two independent groups (ROP present and absent), low gestational age and low birth weight of the babies were found to be statistically significant (P < 0.05) for the development of ROP. After adjusting with different factors in the regression model we have found that low birth weight and oxygen therapy after birth were statistically significant with the development of ROP (P < 0.05).

CONCLUSIONS

ROP screening, specifically for those babies with low-birthweight, low gestational age, and those who received oxygen therapy for other systemic reasons, is mandatory to have an early diagnosis and treatment done.

KEYWORDS

ROP, Low-Birthweight, Gestational Age, Oxygen Therapy

BACKGROUND

Retinopathy of prematurity is a vasoproliferative condition affecting immature & underdeveloped retina of premature infants having low birth weight and young gestational age. It is a major cause of blindness among young children globally. ROP was previously known as retrolental fibroplasia, a term first coined by Terry in 1942. He described the disease as a membrane behind the retina.[1] Mainly babies with prematurity & low birth weight are affected by ROP with oxygen therapy as an associated factor. Prematurity is defined as birth before 37 weeks of gestation.[2] Low birth weight is defined as birth weight 2500 or less.[3] Low birth weight babies are further classified as very low birth weight that is < 1500 gms and extremely low birth weight that is < 1000 grams.[2] This low birth weight can be due to prematurity or due to intrauterine growth retardation (IUGR). ROP also affects the babies with IUGR through different mechanisms i.e. hypoxia in the intrauterine period, diminished antioxidant supply, altered growth factor level, and post-natal events.[4]
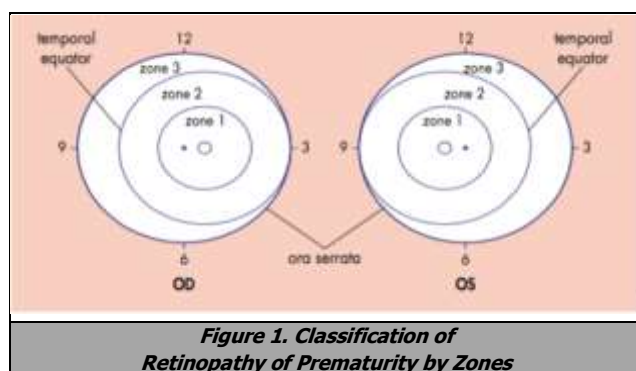

Figure 1. Classification of Retinopathy of Prematurity by Zones

The international classification of ROP[5] has made it possible to document and stage the disease accurately. ROP blindness can be prevented by treating the patients with Anti-VEGF (Vascular Endothelial Growth Factor) and laser therapy. It is thus a preventable cause among the several other causes of childhood blindness. The incidence of ROP has a wide variation in different studies. Among Indian studies, the incidence of ROP varies from 38 to 51.9 % among low-birth-weight babies.[6,7] In addition to low birth weight, several other risk factors such as oxygen therapy, anaemia, apnoea, and sepsis have also been linked to the development of ROP[6]. There is a paucity of data regarding incidence and risk factors in India. The present study is conducted not only to assess the magnitude of the problem in a neonatal care unit of an urban-based tertiary level hospital, but also to describe the possible systemic risk factors.

Objectives
1. To find out the incidence of retinopathy of prematurity among the neonates attending sick neonatal care unit and Out Patient Department (OPD) of Calcutta National Medical College & Hospital.
2. To ascertain the risk factors of retinopathy of prematurity among the neonates attending the sick neonatal care unit and OPD of Calcutta National Medical College & Hospital.

METHODS

Institution based cross-sectional observational study was done at the sick newborn care unit (SNCU) and OPD in Calcutta National Medical College and Hospital (Kolkata) which included the neonates of the unit for a period of 1 year from March 2018 to February 2019. Informed consent was obtained from the parents of the neonates.

Sample Size
As the study was conducted to evaluate the different factors related to the development of ROP, the 'complete enumeration' technique was planned initially. So, all the babies attending SNCU in the hospital after applying inclusion and exclusion criteria were included in the study. Simple random sampling technique was used. Neonates were screened within 2 weeks of birth or gestational age below 35 weeks whichever comes earlier. Babies were followed up subsequently every 2 weeks till 50 weeks of gestational age or retinal vascular maturity i.e. complete vascular development up-to ora serrata. Babies with ROP were followed up at weekly intervals.

Inclusion Criteria
1. Birth weight < = 2000 grams' birth weight.
2. Babies born at < = 35 weeks of gestational age.
3. Premature babies with birth weight > 2000 grams with associated one or more risk factors (oxygen therapy etc.) for ROP.

Exclusion Criteria
1. Babies too sick for the examination or who died during follow up.
2. Babies diagnosed with any other systemic or congenital diseases.
3. Congenital ocular disease at birth.

Parameters Studied
Detailed history of the baby including birth weight and gestational age was taken. Thereafter fundus examination was done with binocular indirect ophthalmoscope using + 20 D lens along with documentation. Staging, zonal involvement, presence or absence of plus disease, and neo-vascular involvement (in clock hour) is documented in babies with ROP.

Study Tools
Indirect ophthalmoscope, + 20 D lens, paediatric eye speculum, paediatric scleral depressor, dilator drop (tropicamide 0.8 %), local topical anaesthetic - 0.5 %

proparacaine hydrochloride, Proforma for ROP screening, Informed consent from the parents.

Data Collection

History of gestational age, birth weight, mode of delivery, exposure to oxygen therapy, history of foetal distress, meconium staining, apnoeic spells, bradycardic spells were taken. Babies were screened within 2 weeks of birth or gestational age below 35 weeks whichever was earlier, then followed up every 2 weeks till 40 weeks of gestational age. Very sick babies and babies with congenital anomalies were excluded by the neonatologist.

Anterior segment examination was done with diffuse light and a hand-held slit lamp. Both eyes of the babies were dilated by dilating drops, instilled thrice at 10 min intervals. After dilatation of the pupil, anaesthetic drops were applied to both the eyes. An eye speculum was used for proper visualization. The babies were screened with the help of an indirect ophthalmoscope and a + 20 D lens. A scleral depressor was used to fix and rotate the eyeball. Documentation was done in the preformed proforma. Proper aseptic precautions were taken. All the examinations were done by a single vitreoretinal surgeon in presence of a competent neonatologist.

Any adverse event during examination of the babies was treated by standard management protocol. Examination of the anterior segment and fundus oculi was documented and further compiled in Microsoft excel.

Statistical Analysis

The clinical history, examination findings, and results were documented and tabulated. For statistical analysis, categorical variables were expressed as the number of patients and percentage of patients and compared across the groups using Pearson's chi-square test for independence of attributes / Fisher's exact test as appropriate. Continuous variables are expressed as mean, median, and standard deviation and compared across the 2 groups using the t-test. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5 % has been taken, i.e. P-value less than 0.05 was considered as significant. Linear regression was also used to test the significance.

RESULTS

181 babies were screened for ROP in our study, after systemic evaluation by a single competent neonatologist and under supervision of the same. Follow up done in the same setting and supervision. In the follow up period most important factor we noticed was the reduction in apprehension of the parents. The awareness of the parents, regarding the ophthalmological complications of premature birth were fully noticed during follow up visits, which were missing on the first screening day.

Among the babies screened, 97 were males (53.59 %) and 55.24 % babies (N = 100) were < 32 weeks of gestational age. 50.27 % of babies (N = 91) were delivered

by Lower Uterine Segment Caesarean section (LSCS) among the babies. 21.45 % (N = 39) of the screened babies were having < 1500 gm birth weight. Hyperbilirubinemia was present in 59.66 % of the babies (N = 108). After consultation with neonatologist, phototherapy was needed for 50.82 % of the babies (N = 92). Apnoea was present in 25.41 % (N = 46) of the babies and bradycardia was there in 29.83 % (N = 54) of the babies screened in our study. Sepsis was present in 41.98 % (N = 76) of the babies. All the systemic parameters were regularly monitored and treatment was provided according to standard management protocol. One of the most important factors noticed during examination of the babies was that topical 0.5 % proparacaine eye drops before applying paediatric eye speculum, helps us to examine the eye properly. Babies were handled and examinations were performed after standard hand washing technique.

Statistical analysis was performed using SPSS software. The analysis depends upon independent factor assessment and adjustment with other factors in regression model.

ROP have been found in 60 babies (33.14 %) screened in our study in that particular period of 1 year. This is one of the warning sign for the future of our country. Gestational age and birth weight of the babies were found to be statistically significant (P < 0.05) when compared in two independent groups (ROP present and absent).

Risk Factor	ROP	N	Mean (± SD)	Test Applied	P-Value
Gestational age (in week)	Present	60	30.1 (± 2.1)	Independent sample t-test - 5.0 (- 2.1, - .96)	0.000
	Absent	121	31.6 (± 1.9)		
Birth weight (in grams)	Present	60	1446.6 (± 249.5)	Independent sample t-test - 9.5 (- 371.9, - 244.6)	0.000
	Absent	121	1754.9 (± 177.8)		

Table 1. Independent Group (ROP Present and Absent) Comparison of Gestational Age and Birth Weight

Epidemiological Correlates		ROP No (%)	ROP Yes (%)	AOR	P-Value
Gestational age (in weeks)	< 32	56 (56.0)	44 (44.0)	1	0.31
	≥ 32	65 (80.2)	16 (19.8)	1.5 (0.64, 3.9)	
Gender	Male	63 (64.9)	34 (35.1)	1	0.47
	Female	58 (69.0)	26 (31.0)	1.3 (0.57, 3.2)	
Birth weight	< 1500 gram	6 (15.4)	33 (84.6)	1	0.00
	≥ 1500 gram	115 (81.0)	27 (19.0)	22.4 (6.6, 75.6)	
Mode of delivery	Normal/ vaginal delivery	66 (73.3)	24 (26.7)	1	0.60
	LSCS	55 (60.4)	36 (39.6)	0.79 (0.34, 1.8)	
Indirect hyperbilirubinemia	Present	70 (64.8)	38 (35.2)	1	0.82
	Absent	51 (69.9)	22 (30.1)	0.83 (0.17, 4.0)	
Phototherapy	Yes	57 (62.0)	35 (38.0)	1	0.43
	No	64 (71.9)	25 (28.1)	1.8 (0.40, 8.5)	
Apnoea	Present	20 (43.5)	26 (56.5)	1	0.43
	Absent	101 (74.8)	34 (25.2)	.47 (0.07, 3.0)	
Bradycardia	Present	24 (44.4)	30 (55.6)	1	0.11
	Absent	97 (76.4)	30 (23.6)	3.5 (0.73, 17.4)	
Sepsis	Present	46 (60.5)	30 (39.5)	1	0.59
	Absent	75 (71.4)	30 (28.6)	1.4 (0.38, 5.3)	
Oxygen use	Yes	64 (53.8)	55 (46.2)	1	0.01
	No	57 (91.9)	5 (8.1)	8.1 (1.5, 44.0)	
	Total	121 (66.9)	60 (33.1)		

Table 2. Regression Model after Adjusting with Other Factors and Adjusted Odds Ratio (AOR) and Their Significance Level (P)

Linear regression model, after adjustment with different factors, failed to show any significant correlation between

mode of delivery (P = 0.60) and occurrence of ROP. No gender predilection (P = 0.47) was found among the ROP babies. Many systemic factors were studied to correlate with the incidence of ROP. We found that indirect hyperbilirubinemia had no significant (P = 0.82) effect on the incidence of ROP. Apnoea of the new-born had not shown any significant correlation with occurrence ROP (P = 0.43). Bradycardia and sepsis of the new-born did not significantly increase the incidence of ROP in our study (P = 0.11 and P = 0.59 respectively).

In the regression model after adjusting with different factors, we have found that birth weight and oxygen therapy after birth became statistically significant with the development of ROP (P < 0.05) in neonates.

DISCUSSION

The study was conducted primarily to find out the incidence and risk factors of Retinopathy of Prematurity in the sick new born care unit of a tertiary care hospital in Kolkata.

A total of 181 neonates were screened in the study after taking informed consent from the parent of the infant. Here we have found that incidence of ROP to be 33.14 % (N = 60) among the screened newborns. As far as the incidence of ROP is concerned it varies widely in the literature. Among Indian studies, there is a wide variation of incidence of ROP. Gopal et al. reported a 38 % incidence of ROP of infants < 2000 gm.[6] Another study by Gupta et al. shows the incidence of retinopathy to be 21.7 %.[8] As the wide variability regarding the incidence of ROP according to the gestational age, birth weight, and oxygen therapy is frequent, it would be difficult to draw any conclusion regarding the incidence. The incidence of ROP in our study has similarity with the result of a multicentre prospective cohort study done in turkey.[9]

43.33 % (N = 26) neonates having ROP were females and 56.66 % (N = 34) were males in our study. Though among ROP babies' male babies were more in this study, a study about the epidemiology of ROP conducted in the United States had concluded that female gender was one of the predictors of ROP.[10,11] Regression analysis after adjusting with other risk factors, indirect hyperbilirubinemia (I-HBl) showed no statistically significant correlation with the development of ROP in our study (P = 0.82). In a study conducted in Alexandria, Egypt it was concluded that I-HBl was not a risk factor for the development of ROP.[12]

In this study, we have found that, among the ROP babies, 36 babies (60 %) were delivered by LSCS compared to 24 (40 %) by normal delivery. Though it is not statistically significant, a study conducted in Ghana has concluded that there was a statistically significant decrease in incidence of ROP in the babies delivered by LSCS.[11]

In our study, we have found that apnoea was present in 43.33 % of ROP babies (N = 24), and bradycardia was present in 30 ROP babies (50 %). No serious adverse events were faced by the babies during examination due to apnoea and bradycardia. Wade KC et al. in a study have concluded that apnoea and bradycardia are key responsible factors for the adverse events during examination.[13]

A study by Padmani Karna et al. stated that neonates of lower gestational age (≤ 25 weeks and 26 – 28 weeks) had an increased odds ratio of 8.49 and 3.19 for the development of severe retinopathy of prematurity, respectively, compared to those 29 weeks and older.[14] In our study we have found that the mean gestational age of ROP babies was 30.1 (± 2.1) weeks and No-ROP babies was 31.6 (± 1.9) weeks. Independent group comparison was statistically significant (P = 0.000). A study conducted in Kenya has concluded that the most significant risk factor for the development of ROP is low gestational age.[15]

In the study conducted, here we have found the mean birth weight of the ROP babies was 1446.6 (± 249.5) gm whereas in No-ROP babies it was 1754.9 (± 177.8) gm. Comparison by independent sample t-test showed d a statistically significant difference between those groups (P = 0.000). In the regression model after adjustment with other factors shows that < 1500-grams birth weight is a potential risk factor (P = 0.00) for the development of ROP. A meta-analysis done in Iran using 42 studies, has concluded convincingly that low birth weight is one of the most important risk factor for the development of ROP.[16]

According to our study, 91.66 % (N = 55) of ROP babies had received oxygen supplementation, whereas 5 (08.33 %) babies with ROP had not received oxygen therapy. This shows statistical significance (P = 0.01) which corresponds to the results of Askie LM et al. concluding that monitored oxygen therapy has potential harms, without clear benefits.[17]

In our prospective study, gestational age at birth, low birth weight, and oxygen use have been found to be important risk factors for the development of ROP. Awareness of the parents regarding the disease and its management were very much definite at the end of our study.

CONCLUSIONS

ROP is a disease that is increasing in incidence, not only in India but also worldwide. As ROP is one of the important cause of visual disability along with ocular mortality, prevention, early diagnosis, and treatment is our goal. This global increase in incidence of ROP of today will ultimately be reflected in the future as the baby grows. Social and educational growth of a country is dependent on todays' new-borns. Increased knowledge and skill for the screening of neonatal fundus and timely intervention is important.

ROP was found to be significantly related to low birth weight and low gestational age, and oxygen therapy. Among the medical illnesses, apnoea, jaundice, and sepsis were studied as risk factors in our study. They are not to be found significant in the regression model. Timely screening of low birth weight, preterm gestational age babies, and babies with risk factors within 4 weeks of birth were the key to their detection, as the babies we had examined were from different parts and different socio-economic status of our state. So, parents' awareness regarding the importance of ROP screening and its impact on further development of the baby in the subsequent follow-up examination was clearly

reflected which was missing initially. Follow-up and timely intervention can reduce the unfavourable outcome.

Limitations

The present study was limited in the fact that it was not a multicentre study, and the study population group was not large enough as the duration of the study was one year. Large multicentre studies with larger popularized sizes were required to solve these limitations. We can also include the effects of blood transfusion, mechanical ventilation, apnoea jaundice, and sepsis on the development of ROP. No issues related to maternal health in ante-natal period was dealt within our study which may be very much related to the results. As the study was conducted in sick new born care unit, premature but otherwise healthy babies who had been discharged after initial resuscitation measures, were not screened.

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