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Original Article

Paediatrics Section

Retinopathy of Prematurity-Prevalence and High Risk Characteristics in a Rural Tertiary Care Hospital in Central India

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ABSTRACT

Introduction: Retinopathy of Prematurity (ROP), a disease characterized formation of a vascular barrier at junction of vascularized and non-vascularised retina is increasingly being common in developing countries due to increasingly improving neonatal fascilities. Various factors have been implicated in its causeation.

Aim: Present study aimed to find prevalence of ROP and associated risk factors in rural tertiary care hospital setting.

Materials and Methods: During study period, ROP screening and treatment was done by a trained retina specialist for neonates at 4-6 weeks after birth or at 31 weeks post menstrual age, whichever is later, using dilated indirect ophthalmoscopy with a 28 Dioptres condensing lens in Neonatal ICU. Risk factors including gestational age, birth weight and neonatal risk factors were noted and ROP, if present was classified and noted. Eligible babies were offered treatment.

Results: Prospective study to screen 50 premature babies was undertaken over the study period of 18 months in which 11 babies (22%) were found to have ROP. The birth weight of ROP babies ranged from 968-1650 grams with a mean weight of 1260.90 ± 215.52 gm, while that of non-ROP babies ranged from 900-2900 gm, with a mean weight of 1517.07 ± 419.04 grams. Similarly, the gestational age of ROP babies ranged from 28-36 weeks with a mean gestational age of 30.54 ± 2.54 weeks; while that of non-ROP babies ranged from 28-39 weeks with a mean age of 33.12 ± 3.05 weeks. The difference of mean weights between two groups was statistically significant with p-value of 0.0097 ($p< 0.05$). Also the difference of mean gestational age between two groups was significant with p-value of 0.0105 ($p< 0.05$). Low birth weight and low gestational age were identified as main significant risk factors.Apnoe, oxygen administration and respiratory distress were other risk factors noted.

Conclusion: ROP is a common issue in premature and low birth weight babies. ROP Screening should therefore be followed as standard protocol in paediatric NICU settings.

Keywords: Angiogenesis, Ophthalmoscopy, ROP screening

INTRODUCTION

Retinopathy of prematurity (ROP) is characterized by aberrant developmental retinal angiogenesis in preterm infants. It occurs in premature infants with or without certain risk factors of low birth weight and other physical comorbidities. ROP is seen only in premature babies, since in these babies angiogenesis of retina, which starts posteriorly from optic nerve head and progresses to anterior retina, is still incomplete [1]. This disorder usually develops in both eyes and is one of the most common causes of visual loss in childhood and can lead to lifelong vision impairment and blindness. In 1942, Terry first reported the disease as the retrolental fibroplasias [2]. The incidence of ROP in western developed countries seems to have declined incrementally over the last few decades. With advent of better neonatal care services in developing countries, survival rates and incidences of ROP both have been on rise [3]. In India also neonatal care has been improving but often with suboptimal standards of care resulting in not only an increase in survival of very low birth weight and premature babies but also an increased rate of ROP [4]. The most important determinant of any ROP management program is an effective screening strategy. As per western screening guidelines which include infants with gestational ages of 30 weeks, or 6/7 weeks post birth or less (irrespective of birth weight) and birth weights of 1250 g or less for screening, Indian scenario seems to have been missing on few babies as per these criteria [5].

Prompt and timely and adequate intervention in babies who require treatment, in form of laser photocoagulation with argon or diode lasers under topical anaesthesia

may prevent a baby going blind [6]. Moreover, in scenarios of better neonatal care in developing care, a good ROP screening facility with good follow-up may reduce the incidence of blinding stages of advance ROP. Recent advent of use of Anti VEGF agents in ROP as per recommendations of BEAT ROP study has opened new dimensions in management of ROP.

This prospective study aimed to determine prevalence of ROP in rural Indian tertiary paediatric neonatal ICU set up and associated factors promoting potential to reach threshold ROP. This was done by performing ROP screening in premature babies, stage the disease and document the risk factors.

MATERIALS AND METHODS

After approval from institute ethical committee for conducting this prospective interventional; trial, the study was conducted in the Department of Ophthalmology, in a rural based hospital of Central India, during the period 2008 – 2011. This included babies referred from Pediatrics Department and those attending Ophthalmology OPD. All the relevant perinatal data including gestational age, post conceptional age and risk factors like exposure to oxygen, hyperoxia and hypoxia, sepsis, anemia and blood transfusion, acidosis, phototherapy, Aminophylline, apnoea, hypercarbia and hypocarbia, total parenteral nutrition, congenital cardiac defect (PDA), intraventricular hemorrhage, antenatal steroids was documented. Inclusion criteria included gestational age at birth of less than 36 weeks, birth weight equal to or less than 2000 gms and supplemental support of oxygen.

Babies with congenital anomalies of the eye, chorioretinitis as well as infants born after 36 weeks and whose birth weight was more than 2000 gms were considered as exclusion criteria for our study.

Screening

First examination was carried out in NICU prior to discharge at 4-6 weeks after birth, or at 31 weeks post menstrual age, whichever is later. Classification of ROP was done according to the International classification of ROP (ICROP). Neonatal and maternal risk factors were entered into the proforma.

Follow-up screening was done depending on disease severity and location as below [Table/Fig-1].

Babies were examined by dilating the pupils with diluted Tropicacyl Plus (0.5% Tropicamide + 2.5% Phenylephrine) eye drops in 1:2 dilution using distilled water. Eyes were examined 30 minutes after application of the first drop. Excess drops spilling over were wiped with sterile cotton to prevent systemic complications. Eyes were examined by indirect ophthalmoscopy with a condensing lens of +28 D. An infantile eye spectrum was used to keep the eyes open. Oculo-cephalic reflex was used to examine peripheral retina.

STAGE	ZONE I	ZONE II	ZONE III
Stage	Treat	<=1 week (if no plus)	Observe
Stage	<=1 week (if no plus)	1-2 weeks (if no plus)	2-3 weeks
Stage	<=1 week (if no plus)	1-2 weeks (if no plus)	2-3 weeks
Immature vascularization	<=1 week	2 weeks	2-3 weeks
Regressing ROP	1-2 weeks	2 weeks	2-3 weeks
Suspected APROP	<=1 week	-	-

[Table/Fig-1]: Stage-wise management protocol for ROP.

Screening was continued till term gestation and subsequent follow-up done in 3 to 6 months.

For risk factor analysis, all pertinent information about neonatal factors like sex, birth weight (in grams), gestational age (in weeks), details of respiratory support, blood transfusion, sepsis, apnoea, intraventricular hemorrhage, Indomethacin used for patent ductus arteriosus, aminophylline, acidosis (pH < 7.3), phototherapy, necrotizing enterocolitis, seizures and maternal risk factors, whether the baby was inborn or outborn type of delivery, twin pregnancy, premature rupture of membranes, maternal diabetes, pregnancy induced hypertension, antenatal steroids and oligohydramnios were recorded.

All infants receiving oxygen therapy had continuous monitoring with pulse oximetry and arterial blood gas analysis through umbilical or peripheral arterial blood sampling. Apnoea was defined as cessation of respiration for > 20 seconds which required resuscitation with Bag and Mask and Oxygen. Sepsis was diagnosed by clinical picture, changes in the leucocytes count, elevated C-reactive proteins and positive culture report. Follow-up screening and management of ROP was done as per guidelines given by AAP.

STATISTICAL ANALYSIS

Statistical significance testing for the nominal scaled data was performed using Chi-square test. Comparison of measurable parameters like birth weight and gestational period between ROP positive and ROP negative groups was performed using t-test of independent samples. Further, binomial exact test was used to study the significance of effect of intervention. The significance was tested at 5% level. The analysis was carried out using R programming (3.0.2) language.

RESULTS

During the study period of 18 months, 138 babies with gestational age less than 36 weeks and birth weight less than 2000 gm were born in the hospital. Out of these, 50 babies fulfilled all the inclusion criteria and were considered in the study; rests were either lost in the

follow-up or died and hence, excluded from the study. There were 30 male (10 with ROP) and 20 female (1 with ROP) babies. Male dominance was noted in the present study. Eleven of the 50 preterm (22%) developed ROP and all had bilateral disease.

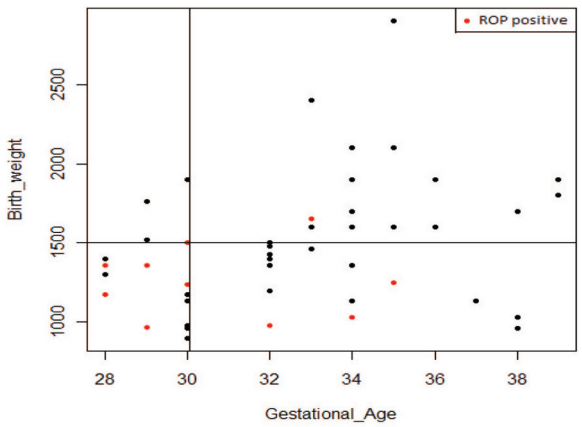
Impact of Birth Weight and Gestational Age on Incidence of ROP

The birth weight and the gestational period between ROP +ve and ROP –ve groups were compared. The results of comparison are shown in [Table/Fig-2]. The birth weight of ROP babies ranged from 968-1650 grams with a mean weight of 1260.90 ± 215.52 gm, while that of non-ROP babies ranged from 900-2900 gm, with a mean weight of 1517.07 ± 419.04 grams. Similarly, the gestational age of ROP babies ranged from 28-36 weeks with a mean gestational age of 30.54 ± 2.54 weeks; while that of non-ROP babies ranged from 28-39 weeks with a mean age of 33.12 ± 3.05 weeks. The difference of mean weights between two groups was statistically significant with p-value of 0.0097 (p< 0.05). Also the difference of mean gestational age between two groups was significant with p-value of 0.0105 (p< 0.05).

The relationship between gestational age and birth weight was studied and depicted through scatter plot in [Table/Fig-3]. The plot reveals that for a cut-off weight of 1500 gm, the incidence of ROP was statistically significant with p-value of 0.045 (p< 0.05). Nearly, 31% of the babies weighing less than 1500 gm were affected. Further, a cut-off gestational age of 30 weeks indicated significant number of ROP cases with a p-value of 0.04 (p< 0.05).

Characteristics	ROP positive (n = 11)	ROP negative (n = 39)	t-value	p-value
Birth weight (gms)	1260.90 ± 215.52	1517.07 ± 419.04	-2.7424	0.0097
Gestational age (weeks)	30.54 ± 2.54	33.12 ± 3.05	-2.8392	0.0105

[Table/Fig-2]: Comparison of Birth weight and gestational age on incidence of ROP.



[Table/Fig-3]: Scatter plot showing the distribution of cases according to gestational age and birthweight.

Neonatal Risk Factors for Prematurity

Various neonatal risk factors found in our study were septicemia, apnoea, oxygen administration, Respiratory Distress Syndrome (RDS) and phototherapy which were associated with an increased incidence of ROP. In our study 36 (72%) babies were exposed to oxygen and 14 (28%) infants out of 50 developed RDS and 21 (42%) babies received blood transfusion. Phototherapy was given to 23 (46%) infants and 23 (46%) infants developed sepsis. Among all the risk factors, sepsis and Intraventicular Hemorrhage (IVH) were most significantly associated with ROP with p-values 0.04 and 0.029 (p< 0.05) respectively.

Impact of Neonatal Risk Factors on ROP

The impact of some of the key factors of interest was studied on ROP. The factors identified were either singleton or in combination with the 'inborn' or 'out born' category, as shown in the [Table/Fig-4]. The objective was to assess the significance of effect of intervention on the incidence of ROP. In other words, interest is to test whether the intervention has significant effect on the success (non-occurrence of ROP). Accordingly, Binomial exact test was used for each of the above factors/factor combinations, and the results obtained are as shown in [Table/Fig-4].

S. No.	Risk factors/ Factors combinations	Number of cases (N=50)	No. of successes (No ROP)	p-value	Signi-ficance
1	Steroids	21	18	0.0014	S
2	Inborn + Steroids	13	12	0.003	S
3	Outborn + Steroids	8	6	0.239	NS
4	Inborn + Oxygen exposure	17	14	0.0127	S
5	Outborn + Oxygen exposure	19	14	0.063	NS

[Table/Fig-4]: Statistical significance of impact of factors on ROP.

In this study, there were 21 premature deliveries who received antenatal steroids, out of which 18 cases were not having ROP which is a significant occurrence with p-value of 0.0014 (p< 0.05). The 13 inborn cases in which steroids were administered, 12 had no ROP, which was also found significant with p-value of 0.003 (p< 0.05). Due to judicious use of oxygen in NICU as compared to outside deliveries, we found significantly reduced occurrence of ROP in babies managed in our NICU with a p-value of 0.0127 (p< 0.05).

DISCUSSION

ROP is getting increasing common due to betterment in healthcare facilities in Paediatric Neonatal ICUs, better survival of high risk babies. This poses a serious

blinding issue in this age group [7]. The incidence of prematurity has increased over the few years. With increasing incidence of prematurity and better survival of smaller babies, the incidence of ROP was expected to increase. In the current study an attempt was made to study the incidence of ROP in a rural based hospital where the standards of care for premature babies are suboptimal. For the present study, 50 babies admitted to NICU and satisfying the inclusion criteria during the study period were screened for ROP. First examination was carried out between 4-6 weeks postnatally for neonates weighing less than 2000 grams and gestation age less than 36 weeks. ROP screening undertaken earlier than 4-6 weeks of birth may miss out on babies potentially at risk to develop ROP in future, since angiogenesis of retina progresses anteriorly in timely fashion. At the same time, if the examination is too late any acute changes may have regressed and no sequel can be detected [8]. According to American Academy of Ophthalmology guidelines, the first examination should normally be performed between 4 and 6 weeks of chronologic (postnatal) age or, alternatively, within the 31st to 33rd week of post-conceptional or postmenstrual age (gestational age at birth plus chronological age), whichever is later, as determined by the infant's attending pediatrician or neonatologist. Post conceptional age is a better followed criteria in ROP screening which allows screening beyond 4 weeks of birth.

The incidence of ROP in the present study is 22% which is very much similar to the observations made in other studies. An Indian study by Gupta et al., in 2004 reported incidence of 21.7% [9]. Maximum numbers of ROP cases were seen in birth weight between 1000-1500 grams. The incidence of ROP in various Indian studies has been reported to vary from 17.5% to 51.9%. Rekha et al., reported ROP in 46% infants weighing less than 1500 grams and less than 34 weeks [10]. We reported seven ROP positive cases (63.63%) between 28-30 weeks of gestation which forms the maturity group of ROP. Hence, lower gestational age was significantly associated with increased incidence of ROP. In a study by Patil et al., they have reported incidence of 17.5% in babies with gestational age less than 32 weeks and birth weight less than 1250 gm.

In some studies the inclusion criteria for patients was less gestational age and/or weight while in some other studies either gestational age or only weight was considered as inclusion criteria. In order to include all ROP positive cases, we have included all babies with gestational age less than 36 weeks and /or birth weight less than 2000 gm as suggested by Jalali et al.,[11]. In our setup we have found ROP positive cases both above and below the gestational age of 32 weeks and birth weight of 1500 grams. As the inclusion criteria are different it's not possible to compare results fully. Thus, the screening criteria should be less rigid than described in reports from long established centers. Therefore, every country and particularly, different regions should make guidelines based on current and local data.

Lower gestational age and low birth weight are the most important risk factors for the etiology for ROP in our study and it is well recognized that the incidence and severity of ROP are inversely proportional to gestational age and birth weight.

In our study mean gestational age of infants who developed ROP (30.54 ± 2.54 weeks) was lower than those who did not develop ROP (33.12 ± 3.05 weeks) and was statistically significant with p = 0.0105. Incidence was more in lower gestational age and lower in higher gestational age. The mean birth weight pf babies who developed ROP (1260.90 ± 215.52 grams) was lesser that those who did not develop ROP (1517.07 ± 419.04 grams) and was statistically significant with p = 0.0097. Other studies have reported the same.

Various neonatal risk factors for ROP in our study were oxygen exposure, blood transfusion, Respiratory Distress Syndrome (RDS), apnoea, Patent Ductus Arteriosus (PDA), phototherapy, sepsis, Intra Ventricular Hemorrhage (IVH), Fetal distress and Hyaline Membrane Disease (HMD). Out of all premature babies (n=50) we reported 23 babies (46%) with sepsis and eight babies (34.75%) among them developed ROP which was statistically significant (p = 0.04). Six out of these eight premature babies were outborn i.e. they were delivered outside our hospital and were referred here, which explains the high incidence of sepsis in these cases. Sepsis may act through cytokines and endotoxins or by oxidative burst in the neutrophils consequent to infection. Its prevention and early control may reduce the incidence of ROP. Another important risk factor in our study was IVH. We reported ROP in three (75%) out of four babies of IVH and so correlation of ROP was statistically significant (p-value = 0.029).

Antenatal use of steroids to mothers at 24-34 weeks gestation in cases at high risk for respiratory distress syndrome, guards against development of ROP. The same has been observed in the present study as well [12,13].

In our study, history of antenatal steroids was found in 21 premature cases. Out of these, 18 premature babies did not develop ROP and showed that use of antenatal steroids helps in non-occurrence of ROP and was statistically significant (p=0.0014). Antenatal steroids administration to reduce the incidence of ROP was also reported by Higgins et al.,[14]. The casual link between ROP and supplemental oxygen has been confirmed by controlled trials and clinical studies. However, a safe level of oxygen usage has not been defined clearly in literature. Controlled and monitored oxygen therapy too helps in reducing prevalence of ROP. In our NICU, oxygen administration, its flow rate and duration are not

based solely on clinical findings like cyanosis, respiratory distress or heart rate, but are closely monitored by pulse oxymetry and oxygen saturation is kept between 88-94%. Although oxygen administration was a significant independent risk factor of ROP, but in our study, 14 out of 17 inborn babies (i.e. babies born in our hospital) were given oxygen judiciously and so they did to babies delivered and managed outside our hospital (outborn) who showed increased incidence of ROP. The same was reported in literature by Palmer et al., and Schaffer et al., that multiple births outside a study hospital were associated with an increased risk of severe disease [15,16].

The management of ROP basically depends on findings of ROP screening and follow up screening once ROP is detected. The prevalence of ROP is relatively less in our set up probably due to monitored oxygen therapy and proper screening protocols. The reduced incidence could also be due to low survival of extreme premature babies and limited sample size.

CONCLUSION

ROP is preventable blinding complication of prematurity to be looked for in all premature infants less than 36 weeks and weighing less than 2000 gm. According to our study, the risk factors contributing to the development of ROP are low birth weight, low gestational age, exposure to oxygen, sepsis and intra ventricular hemorrhage. Use of antenatal steroids helps in prevention of ROP. Guidelines for ROP screening in Indian scenario should be gestational age of less than 36 weeks and birth weight less than 2000 gm to avoid missing ROP cases. Judicious use of oxygen (saturation between 88-94%) and mechanical ventilation will decrease the incidence of ROP. Our study concluded that ROP is an important complication of prematurity for which screening should be started at 4 weeks postnatal age.

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