Risk factors for retinopathy of prematurity in a district in South India: A prospective cohort study

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Abstract:
PURPOSE: The purpose of this study was to determine the incidence, severity, and associated risk factors of retinopathy of prematurity (ROP) in a district in South India.

METHODS: This was a prospective, observational, cohort study involving babies at risk of ROP conducted in five Neonatal Intensive Care Units in a district in Tamil Nadu, South India. All babies with gestational age at birth of ≤36 weeks and a birth weight (BW) of ≤1900 g with a follow-up period of at least 6 months were enrolled for the study. Neonatal and maternal risk factors were assessed and univariate and multivariate logistic regression analysis performed to examine the predictors of ROP.

RESULTS: A total of 325 infants were screened. ROP was identified in 210 eyes of 106 (32.6%) babies with severe ROP (stage ≥3 ROP) occurring in 14 (13.2%) babies. Low BW (LBW) was the only significant risk factor for ROP on multivariate logistic regression analysis. The mean BW was 1285 and 1452 g for babies with and without ROP, respectively. Treatment was indicated in 22 eyes of 14 (13.2%) infants.

CONCLUSIONS: The incidence of ROP was fairly high and strongly associated with LBW. A relatively low incidence of severe ROP was, however, observed. More effort is, therefore, required towards the prevention of preterm births while the present gains in neonatal care should be sustained to reduce the incidence of ROP and thus childhood blindness in the country.

Keywords:
Gestational age, low birth weight, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a leading cause of potentially avoidable childhood blindness worldwide. It is a vision-threatening disease associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina. ROP in high-income countries now occurs, mostly in extreme low birth weight (LBW) infants. In those countries, the incidence of ROP seems to have declined incrementally over the last few decades. In middle-income countries, however, high rates of premature birth and increasing resuscitation of premature infants, often with suboptimal standards of care, have resulted in a third epidemic of ROP.

Short gestation and LBW have been identified as the most important risk factors responsible for ROP and other recognized risk factors being sepsis, intraventricular hemorrhage (IVH), mechanical ventilation, oxygen therapy, blood transfusion, and exposure to light. Most cases of ROP are mild and resolve spontaneously without treatment. A small proportion progress to...
more severe ROP, which, if untreated, can result in retinal detachment or scarring and distortion of the retina with irreversible vision loss.\[9\]

Recently, a rise in the number of children admitted to Neonatal Intensive Care Units (NICUs) across India has been observed with an increase in the number of preterm babies with ROP due to variable neonatal practices.\[6\] This emerging epidemic of ROP blindness is the result of high birth rate, high rate of preterm births, and survival of LBW children due to the advanced and expanded provision of medical care.\[7\] A growing interest in pediatric ophthalmology and vitreoretinal subspecialty in the country has also led to ROP becoming increasingly recognized.\[8\] This study was, therefore, designed to determine the current incidence and severity of ROP in preterm infants and to analyze the neonatal and maternal risk factors for its development in a district in South India.

**Methods**

This was a prospective, observational, cohort study involving babies at risk of ROP conducted in five hospitals equipped with NICUs in Tirunelveli district, Tamil Nadu. The hospitals also serve as referral centers for hospitals in two other surrounding districts; Tuticorin and Kanyakumari. All babies with gestational age (GA) at birth of ≤36 weeks and a BW of ≤1900 g with a follow-up period of at least 6 months were eligible for the study. Exclusion criteria included incomplete hospital documentation of pre- and perinatal comorbidities and incomplete follow-up. All babies were enrolled over a period of 18 months from November 2011 to April 2013.

The study followed the tenets of the Declaration of Helsinki, and ethical approval was obtained from the institutional review board of the hospital. A written informed consent was obtained from the parents for necessary investigations and treatments. Complete documentation of hospital records including details regarding other factors that could increase the risk of ROP was done. Screening was carried out in premature babies with the following risk factors: oxygen therapy, respiratory distress syndrome (RDS), sepsis, history of blood transfusion, surfactant therapy, multiple gestations, phototherapy, and IVH. All relevant comorbid conditions and risk factors, both maternal and neonatal, were recorded from the patient’s chart. Infants receiving oxygen therapy had continuous monitoring with pulse oximetry and arterial blood gas analysis through umbilical or peripheral arterial blood sampling. Sepsis was diagnosed by clinical picture, changes in the leukocyte count, elevated C-reactive protein, and positive culture report.

Standard ROP screening guidelines were used to determine which babies required screening. All preterm infants were initially screened at 4 weeks postnatally. Babies were examined by dilating the pupils with 0.5% tropicamide and 2.5% phenylephrine eye drops. An infantile eye speculum was used to keep the eye being examined open. All babies were examined by a retina specialist experienced in ROP using indirect ophthalmoscopy with a +20D condensing lens and scleral depression. The severity and extent of ROP was recorded in the chart. The international classification of ROP was used to document all retinal examination findings.\[8\] Neonatal and maternal risk factors were entered into a prepared pro forma.

Babies diagnosed with ROP were given further appointments, i.e., schedule for screening. This was once in 2 weeks in stage I zone III disease, once a week in stage 2 disease in the posterior pole, and once in 3 days if it was zone I with plus disease. Screening was continued till term gestation, and subsequent follow-up was done over a period of 6 months. Babies who reached the criteria for treatment as per the guidelines of the American Academy of Pediatrics were treated as clinically necessary.\[9\] If no ROP was noted, eye examinations were continued every 2 weeks until vascularization had reached zone 3.

Statistical analysis was performed using a commercially available statistical software package (STATA, version 11.0, Texas, USA). Univariate comparison of risk factors between eyes with and without ROP was done using Chi-square test and Fisher’s exact test. Multivariate analysis was performed with binary logistic regression to compare the incidence of ROP as response variable and various risk factors. A p-value < 0.05 was considered to indicate a statistically significant association between a risk factor and the risk of developing ROP.

**Results**

Three hundred and twenty-five babies who satisfied the inclusion criteria were included in the study. There were 175 (54%) males and 150 (46%) females. ROP was seen in 210 eyes of 106 babies giving an incidence of 32.6% with 100 (94.3%) babies having bilateral disease. Ninety-five (45%) eyes had stage 2 ROP or worse with aggressive posterior disease occurring only in 2 (0.9%) babies [Figure 1].

The mean BW for the cohort was 1420 g (standard deviation [SD]: 300, range: 850–1900 g). Babies with ROP had a mean BW of 1285 g (SD: 0.27, range: 0.86–1.8 g) while the mean for babies without ROP was 1452 g (range: 0.85–1.9 g, SD: 0.24). This difference was statistically significant with P < 0.001 [Table 1]. The incidence of ROP was inversely related to BW with
babies weighing <1000 g having the highest incidence of 71.78%.

The mean GA for the babies screened was 30.68 weeks (SD: 2.84, range: 26–36 weeks). Babies with ROP had a mean GA of 29.71 weeks (range: 26–36 weeks, SD: 2.64) while babies without ROP had a mean GA of 31.14 weeks (range: 26–36 weeks, SD: 2.80). This difference was statistically significant (P < 0.001). Babies with a GA of <28 weeks had the highest incidence of ROP (62.8%).

Seventy-two (68%) out of 106 babies with ROP and 142 (65%) of 219 babies without ROP had mothers ≤25 years of age. This difference was not statistically significant with P = 0.13. Table 2 shows the association between ROP and other risk factors on univariate analysis. There was a significant association between the occurrence of ROP and oxygen therapy as well as RDS. The remaining risk factors including IVH, surfactant therapy, blood transfusion, sepsis, multiple gestations, gestational diabetes, maternal hypertension, and antepartum hemorrhage did not show any significant association with the development of ROP. On multiple logistic regression analysis, only LBW remained a statistically significant and independent risk factor for ROP [Table 3].

Treatment was indicated in 22 eyes of 14 (13.2%) babies with ROP. Treatment modalities included laser therapy, intravitreal antivascular endothelial growth factor injection, and surgery. Laser treatment was done in 10 babies with 2 babies receiving unilateral treatment while 8 were treated in both eyes. All treated babies were followed up till regression of ROP occurred in all the eyes. Two babies with unilateral stage 5 ROP had scleral buckling with vitrectomy, and 1 baby with bilateral closed funnel total retinal detachment did not have any surgical intervention. All babies with initial presentation of stage 1 ROP regressed without treatment.

**Discussion**

Despite current treatments, ROP remains a major cause of blindness in premature infants, and the incidence is increasing with increased survival of infants born at very early GAs.[10] The incidence of ROP in this study was 32.6% which falls within the range of 15.6%–47.3% reported from previous studies in India.[11–13] ROP is a multifactorial disease with risk factors such as low GA, LBW, sepsis, oxygen therapy, RDS, and blood transfusion shown to influence its incidence.[14] Of these LBW, low GA and oxygen therapy are considered the most important risk factors for ROP with LBW being the greatest predictor of severity.[16,17] LBW was found to be a significant and independent risk factor for ROP on multivariate analysis in this study. This is in agreement with Hungi et al.[18] The incidence and severity of ROP show an inverse relationship with BW and GA, with few cases diagnosed in babies weighing over 1500 g or babies whose GA is >32 weeks at birth.[15,19] There have,
However, been several reports of ROP in bigger and more mature babies in India. \cite{14,18,20-22} The onset and progression of the disease is also earlier and more rapid in Indian babies. \cite{21} Seventeen percent of babies with ROP in this present study weighed >1500 g which is much lower than 65% reported by Hungi et al. \cite{18} The mean BW of ROP babies in this series (1285 g) compares with the report by Charan et al. \cite{13} but is lower than figures from other India studies. Hungi et al. \cite{18} reported a mean BW of 1556 g, Ashok et al. \cite{14} reported a mean BW of 1370 g, while Murthy et al. \cite{11} reported a mean BW of 1344 g and 1375 g for babies in urban and semiurban NICUs, respectively.

Low GA was not found to be a significant risk factor on multivariate logistic regression analysis in this present cohort. This is in agreement with the study by Chaudhari et al. \cite{13} but contrasts with finding by Murthy et al. \cite{14} We obtained a mean GA of 29.71 weeks for ROP babies in this series. This is lower than findings from previous reports which range from 30.8 to 32 weeks. \cite{11,12,14,15,18} The lower GA, lower BW as well as the lower proportion of babies weighing >1500 g with ROP in this series are a reflection of improved neonatal care.

Increasing maternal age has recently been reported as a risk factor for the development of ROP in Taiwan. \cite{23} We did not observe this trend in this present cohort. Most cases (68%) of ROP in our series occurred in babies with mothers ≤25 years of age. Uchida et al. \cite{24} in Japan also reported an inverse relationship between maternal age and incidence of ROP. They suggested that younger mothers having premature infants probably had critical events which disrupted the pregnancy, and the event may have adversely affected the infant’s development, increasing the incidence of ROP. In contrast, infants with high maternal age might not have survived, and infants who overwhelmed the risk of pregnancy failure in spite of the high maternal age and were born alive might have less biological problems and therefore succeeded in vessel development in the retina, avoiding ROP. \cite{24}

Treatment for ROP was carried out in 14 (13%) babies in this series. This is lower than 26%–75% reported in previous studies. \cite{11-13,18} This reveals the lower incidence of severe ROP (13%) in this cohort. This study, therefore, shows that despite the high incidence of ROP, there is a decline in the severe forms of the disease. This can also be attributed to improvements in neonatal care and monitoring of oxygen therapy in the NICUs where the babies were screened. Studies have demonstrated a significant reduction in severe ROP and ROP requiring laser treatment with changes in clinical practice such as the introduction of specific target values of arterial oxygen saturation, the introduction of new technology using pulse oximeters, and education of staff on the potential risks due to exposure to oxygen. \cite{25} It is possible though that this observed decline in severe ROP may not necessarily reflect what is happening in the entire district. Our study was conducted in hospitals located within the city which are more likely to have better facilities and probably a lower incidence of severe ROP compared with NICUs in rural areas. However, in a recent prospective study on the incidence and profile of ROP babies in urban and rural NICUs in another region of South India, the authors surprisingly observed a comparable incidence (over 30%) of severe ROP. \cite{11}

A limitation of our study was the exclusion of NICUs in the rural areas of Tirunelveli district. This was as a result of limited workforce and other logistic reasons. Further studies incorporating these NICUs are, however, being planned.

**Conclusions**

Our findings show that the incidence of ROP was 32.6% and was strongly associated with LBW in Tirunelveli district. Compared with previous Indian studies, it was found in babies with a lower mean GA and BW. These along with a reduction in the severe forms of the disease are evidences of improved neonatal care. More, therefore, needs to be done in the area of prevention of preterm births while the present gains observed in neonatal care delivery should be sustained to reduce the incidence of this preventable cause of childhood blindness.

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**Conflicts of interest**

There are no conflicts of interest.

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