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Prospective Observational Study

Prospective Study to Compare and Determine Optimal Screening for Retinopathy of Prematurity

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Abstract

***Introduction**: ROP screening standards vary between nations and even between regions of the same nation. The study was done to find out the incidence of Retinopathy of Prematurity (ROP) in urban population of India and to compare various screening guidelines for ROP, to find the ideal screening guidelines.*

***Materials and Methods**: Government of India and National Neonatology Forum recommend ROP screening for infants delivered less than 34 weeks and birth weight < 2000 Gms. Many international guidelines have lowered screening guidelines to 32 weeks and < 1500 Gms. Underscreening and overscreening can have a negative impact on the babies as well as the healthcare system of our country. This prospective observational study was undertaken in a tertiary care setup in India to find incidence of ROP, treatable ROP and to compare the different screening guidelines.*

***Results**: A total 79 preterm infants were screened for ROP in the unit, in accordance with the RBSK –GoI guidelines: 5 developed ROP, out of which 2 required treatment. The overall incidence of ROP was 6.3% (5/79) while 2.5% of the babies required treatment for ROP. Following the RBSK-GoI guidelines, 31 more babies were exposed to uncomfortable procedure of ROP screening, which could have been avoided using other screening guidelines.*

***Conclusion**: Our study showed that no baby with ROP was missed using our criteria and we could avoid ROP screening for others. However, larger multi-centric studies are required to support our findings.*

***Keywords**: Retinopathy of Prematurity, screening guidelines, risk factors*

Introduction

Retinopathy of prematurity (ROP) is a disease condition of the growing retinal blood vessels, seen in preterm and low birth weight babies and is a major contributor to juvenile blindness, more often seen in middle-income countries in Asia and other parts of the world. The development of the retina in fetus develops peripherally from the optic nerve head during the course of gestation and is incomplete when babies are born premature. The extent of vascularization of the retina depends majorly on the extent of the level of prematurity at birth, creating the possibility for abnormal development. In embryological life, the blood vessels in the retina develop during two phases. While vascularization of retinal regions continues till 40 weeks gestational age (GA), which is known as angiogenesis phase, the development of major retinal vessels happens between 14 and 21 weeks, which is also called as the vasculogenesis phase. [1]

In India, better perinatal care has improved the survival of preterm and very low birth weight babies, especially in urban population, which has increased the incidence of ROP.[2] Several tertiary care facilities are currently screening high-risk newborns for ROP. There is a huge variation in the incidence of ROP among rural and urban NICUs. In urban NICU settings, incidence of ROP is significantly lower (14.8 – 26.6%) compared to the rural settings, where incidence of ROP varies from 22.4% to 41.5%. [3-8]

There is lot of heterogeneity in screening guidelines for ROP among different countries. Government of India has its own guidelines under Rashtriya Bal Swasthya Karyakram (RBSK) program, which is similar to that recommended by National Neonatology Forum of India (NNFI). Incidence of ROP varies with the level of care provided, as ROP is a disease with multi-factorial etiology (prematurity, low birth weight, use of high FiO_2, target oxygen saturations, use of blenders, different incidence of sepsis etc.). Better perinatal care is shown to decrease the incidence of ROP in the NICU. So, this study was done to find out the actual incidence of ROP and babies who require treatment for ROP in an urban tertiary care NICU setting. The study also compared pick-up rates of ROP using different screening protocols, so that none of the babies who might develop ROP are missed and over-screening of large number of babies can be avoided, thereby exposing them to uncomfortable procedure of multiple ROP screenings. A sub-group analysis of different risk factors involved in developed ROP was also done.

Materials and Methods

This was a prospective, observational study conducted in a tertiary level NICU in urban India.

The babies were enrolled using RBSK-GoI guidelines for ROP screening. NNFI has also issued similar guidelines for ROP screening. Babies who were eligible for enrollment were identified (those with gestation less than 34 weeks or birth weight less than 2000grams). The babies were screened for ROP by a Senior Ophthalmologist experienced in ROP screening, at 4 weeks of birth for first screening & for babies born less than 28 weeks or less than 1200 grams, screening was done at 3 weeks after delivery. Infants with gestation more than 34 - 36 weeks were screened only if they had any additional risk factors.

The results were compared with unit's existing ROP screening guidelines, ROP screening protocol by All India Institute of Medical Sciences (AIIMS) and United Kingdom ROP screening protocols.

RBS-GoI ROP Screening Protocol advises to screen babies with gestational age less than 34 weeks or Birth weight less than 2000g & gestational age between 34 - 36 weeks with risk factors and also infants with an unstable clinical course who are at high risk. [9] These guidelines are similar to National Neonatology Forum ROP screening guidelines. [10] As per our Unit's ROP screening protocol all neonates less than 32 weeks gestation and/or Birth weight less than 1800grams are screened. According to AIIMS ROP Screening Protocol, babies with gestational age less than 32 weeks OR Birth weight less than 1500g and those babies born with gestational age 32-34 weeks with risk factors are to be screened. As per UK ROP Screening Protocol, all babies less than 32 weeks GA (Upto 31 weeks 6 days) OR Birth weight less than 1501g are to be screened for ROP.[11]

The study was approved by the institutional ethics committee.

A total of 84 babies were enrolled for screening of ROP, following the RBSK guidelines as in Figure 1.

Babies who expired, or left against medical advice or were lost to follow up were excluded. A sub-group

analysis was done to see the rates of ROP among different gestational ages and birth weight categories. The data was compiled and analyzed using Fischer's exact test and independent samples t-test was used to analyze the continuous data. A p-value of < 0.05 was considered as statistically significant.

Results

A total of 79 babies completed the ROP screening process and appropriate follow up. The average mean birth weight was 1700.20 $\pm$ 374.64 grams and mean gestational age was 33.2 $\pm$ 2.39 weeks. 5 babies out of the 79 developed any stage of ROP, overall incidence of ROP being 6.3% in the unit. 2 babies out of the total screened babies developed treatable ROP (2.5%). 1 baby developed Aggressive posterior ROP and required Intra-vitreal anti-VEGF injection and 1 baby required Laser treatment.

The baby who required Laser treatment was born at 24 weeks gestation and was extremely low birth weight (750 grams at birth). The baby was mechanically ventilated at birth and required oxygen for more than 24 hours. The baby developed culture positive sepsis and required inotropic support for some time due to septic shock. The baby also received blood transfusion during NICU stay.

The baby who required laser was born at 28 weeks gestation and was also extremely low birth weight (890 grams). The baby did not require mechanical ventilation, but required oxygen support through Nasal CPAP for > 24 hours. The baby did not develop Sepsis and did not have episodes of apnea. The baby did require blood transfusion due to anemia of prematurity. The baby did not require any inotropic support during the NICU stay.

3 babies developed Stage 1 ROP (Demarcation line) in Zone 2 and spontaneously regressed in subsequent follow up visits.

There were 2 babies who required treatment of ROP, both being less than 1000 grams (Table 1). Another baby who developed Stage 1 ROP was also between 1000 - 1500 grams. 2 babies above 1500 grams developed Stage 1 ROP, which resolved spontaneously. Incidence of ROP in babies less than 1000 grams was 33.3% and

incidence of ROP requiring treatment was also 33.3% babies in this subgroup. Incidence of treatable ROP decreased to 0% in babies born > 1000 grams.

Similarly, the babies who developed ROP requiring treatment were less than 30 weeks (Table 2). 1 baby who developed ROP and regressed spontaneously was below 30 weeks. 1 baby in each group from 30 – 32 weeks and > 32 weeks developed ROP, but did not require any intervention. The incidence of ROP requiring treatment in babies born less than 30 weeks was 22.2%. In higher gestations (> 30 week), incidence of babies requiring ROP treatment was 0%. The mean birth weight and gestational age was significantly lower for infants developing ROP compared to those babies who did not develop ROP.

When using the unit's existing screening protocol, none of the babies who developed ROP (any stage and ROP requiring treatment) were missed when compared with babies enrolled as per RBSK-GoI screening protocol (Table 1). When the babies were screened using the AIIMS ROP screening protocol and UK ROP screening protocol, 1 baby who developed ROP would have been missed, although the ROP had spontaneously regressed in that baby and did not require any treatment.

While following ROP screening using RBSK-GoI guidelines, 31 more babies were screened compared to unit's existing ROP screening protocol, thereby subjecting them to repeated ROP screening examination (Table 3).

All babies who developed ROP required Nasal CPAP for respiratory distress (p value = 0.029). Table 4 shows the various risk factors among those babies who developed ROP. Oxygen is an important risk factor involved in the development of ROP. 4 out of the 5 babies who developed ROP of any stage, required oxygen support (p = 0.051). 52 babies did not require oxygen after birth and 1 baby went on to develop any stage ROP but not requiring treatment, while 22 babies required oxygen for more than 6 hours after birth and 4 out of these babies developed ROP, p value being 0.038.

Only 2 babies out of the babies who developed ROP required oxygen for more than 24 hours duration. 2 babies

who developed ROP had culture positive sepsis. 3 babies out of them required Blood transfusion during their NICU stay.

Table 1: Incidence of ROP in relation to birth weight

Birth weight (gms)	No of babies screened	Incidence of ROP	Incidence of ROP requiring treatment	P value
<1000	6	2 (33.3%)	2 (33.3%)	0.017
1000 -1500	16	1 (6.25%)	0 (0%)	
>1500	57	2 (3.5%)	0 (0%)	

Table 2: Incidence of ROP in relation to gestational age

Gestational age	No of babies screened	Incidence of ROP	Incidence of ROP requiring treatment	P value
< 30 weeks	9	3 (33.3%)	2 (22.2%)	0.001
30-32 weeks	13	1 (7.69%)	0 (0%)	
> 32 weeks	57	1 (1.75%)	0 (0%)	

Table 3: Babies enrolled into ROP screening using different guidelines and developed ROP of different stages

	Unit Protocol	**RBSK**	**AIIMS**	**UK**
No. of babies screened	48	79	42	29
No. of babies developed ROP – any stage	5	5	4	4

Babies developed ROP requiring treatment	2	2	2	2
Babies developed ROP Stage 1	3	3	2	2
Babies developed ROP Stage 2	0	0	0	0
Babies developed ROP Stage 3	2	2	2	2
Babies requiring Laser treatment	1	1	1	1
Babies requiring Intra-vitreal anti-VEGF	1	1	1	1

Table 4: Risk factor in babies who developed ROP

	Gestation	Birth weight	O_2* > 6 h	O_2* > 24 h	Sepsis	Blood Tx	Inotropes	Apnea	Ventilation	Antenatal Steroids
1	34+6	1610	YES	Yes	YES	YES	NO	No	No	YES
2	28+2	890	YES	YES	NO	YES	NO	No	No	YES
3	24+1	750	YES	YES	YES	YES	YES	Yes	Yes	NO
4	27+1	1045	YES	YES	NO	NO	NO	Yes	Yes	YES
5	30+1	1725	NO	NO	NO	NO	NO	No	No	YES

** O2 – Oxygen requirement*

Discussion

In our study, the incidence of ROP was 6.32% and the incidence of ROP requiring treatment was 2.53%. It is comparatively lesser as compared to previous studies done in urban centres of India. The incidence of ROP was 16.5% and treatable ROP was 6.17% as per a study conducted by Murthy et al.[6] A study done in an urban NICU in Chandigarh quoted the incidence of ROP was 21.8% and treatable ROP was 6.2%. [12] All the babies in our study who developed treatable ROP were < 1000 Gms.

UK ROP screening guidelines enroll babies less than 32 weeks and less than 1500 gms. By using these

screening criteria, none of the treatable ROP would have been missed, however 1 baby who developed ROP, which spontaneously regressed would be missed. Similarly using the AIIMS ROP screening guidelines to our study cohort, 1 baby who developed ROP would have been missed but the baby did not require any treatment for ROP. UK and AIIMS ROP screening protocol did not miss any baby requiring treatment for ROP. Following the unit's protocol, all the babies who developed any stage ROP or ROP requiring treatment were picked up.

Babies who receive good neonatal care immediately after birth and maintain target oxygen saturations levels by pulse oximetry have a lower chance of developing ROP. Babies who are subjected to higher oxygen concentrations, especially in rural neonatal units, where monitoring and care of these neonates might be sub-optimal may have higher rates of ROP. In that context, not to miss any baby, it might be prudent to follow the RBSK guidelines for ROP screening, so that none of the babies are missed. But in tertiary care neonatal units in urban settings, where care and monitoring of the preterm babies is adequate, we can modify the screening guidelines, so that many extra babies are not subjected to uncomfortable procedure of ROP screening multiple times.

The main risk factors seen in study for ROP included lower gestational age (< 30 weeks), Extremely low birth weight (< 1000 gms), oxygen requirement (especially for more than 24 hours). Other important risk factor for development of ROP in Indian setting includes Sepsis and Blood transfusion. Gestational age and birth weight are non-modifiable risk factors while other factors contributing to the development of ROP can be controlled to some extent. Use of antenatal steroids, delayed cord clamping, strict handwashing, use of Total Parenteral Nutrition (TPN) filters, adherence to strict asepsis guidelines, blending of oxygen in the NICU as well as in the delivery room, optimal target oxygen saturation levels can help reducing the modifiable risk factors, to a great extent. Strict infection control policy should be in place and strictly followed. Judicious use of blood transfusion, use of non-invasive ventilation can also help decreasing the rates of ROP. The sample size in our

study is relatively small and bigger studies would be required to substantiate the finding of our study.

Conclusion

ROP screening guidelines can be individualized based on the level of perinatal and neonatal care being provided in a setting. The ROP screening guidelines for tertiary care NICUs in urban centres can be different from a single universal national guideline, which may subject many babies to multiple ROP screening procedures, which might be painful and uncomfortable. In urban settings like ours, the majority of babies who developed ROP and especially ROP requiring treatment were born at gestation age less than 32 weeks and amongst those babies who were extremely low birth weight. In urban settings, the ROP screening can be individualized to screen babies born at lower gestational ages and lower birth weights. Also strict adherence to prevent modifiable risk factors would help mitigate the chances of ROP among the babies in this cohort. Long-term studies with larger sample size would be required to substantiate our findings.

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